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The Effects of *Apium graveolens* and *Eucalyptus globulus* in Decreasing Stress and Protecting Folliculogenesis Marker on Woman Reproductive Health during COVID-19 Pandemic

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ABSTRACT

Stress during Coronavirus disease-2019 (COVID-19) pandemic affects the physiological and immunological response to women's reproductive health. Meanwhile, *Apium graveolens* and *Eucalyptus globulus* are immunomodulators related to women's reproductive health. This investigation had a goal to examine the effectiveness of *A. graveolens* and *E. globulus* towards the expression of Heat Shock Protein-70 (HSP70) as the primary biomarker of stress, Tumor Necrosis Factor-Alpha (TNF-α) as a pro-inflammatory protein, along with Luteinizing Hormone (LH) and Growth Differentiation Factor 9 (GDF-9) as folliculogenesis markers. An experimental randomized controlled trial was utilized by using a pre-test and post-test control group design. Sixty women, who had stress based on DASS-21 questionnaire, were divided into two groups in Nusukan Health Center, Indonesia. The intervention group was orally administered with 300 mg *A. graveolens* capsules and *E. globulus* essential oil for 14 days, while the control group was given a placebo. Blood samples and stress levels were then evaluated before and after the intervention. No significant difference was found in the stress levels of the control and treatment groups at the pre-test. Meanwhile, the intervention group had the decreased HSP70, TNF-α, and stress levels ($p<0.001$). In contrast, increased LH and GDF-9 levels were displayed in the intervention group compared to the control group ($p<0.001$). These findings revealed that *A. graveolens* supplementation and *E. globulus* essential oil have the ability to decrease stress and are able to protect folliculogenesis markers on women's reproductive health due to stressful conditions during pandemic COVID-19.

Keywords: *Apium graveolens*, *Eucalyptus globulus*, folliculogenesis, immunomodulator, woman reproductive health

INTRODUCTION

Coronavirus disease-2019 (COVID-19) pandemic is part of the ongoing worldwide pandemic, including Indonesia. Positive cases of COVID-19 initially were indicated in Indonesia on March 2, 2020, and by April 9, it had spread rapidly to 34 provinces, including Jakarta, East Java, and West Java as the most highly exposed provinces. As of February 14, 2022, Indonesia has reported 4.807.778 positive cases (Dong *et al*., 2020).

Beyond the medical risks, pandemics have enormous psychological and social impacts. In this unprecedented situation, any prediction of COVID-19's psychological and emotional consequences accurately was very difficult. Previous investigations from the first affected country, China, stated that mental disorders such as anxiety, depression, stress, and destructive behaviors such as increased consumption of alcohol and cigarettes can be provoked by the fear of the uncertainty and the unknown (Shigemura *et al*., 2020). A study of 1210 people in China using the Depression, Anxiety, and Stress Scale (DASS-21) pointed out that 16.5% of the sample had mild depressive symptoms, while 28.8% with moderate anxiety symptoms, and 8.1% with severe stress levels. Poor health status was significantly associated with a more significant psychological impact, as measured by levels of stress, depression, and anxiety (Wang *et al*., 2020). Indeed, women are more easily exposed to stress and become its targets than men. Furthermore, stress can also affect many cellular processes and is essential in physiological and immunological responses (Mayor, 2015). This condition may lead to several metabolism activities in the body, such as menstrual problems (Rafique and Al-Sheikh, 2018). Stressors influence the brain, whether physical or biological receive a response from the body. Stress also increases stress hormones, including cortisol (Maduka *et al*., 2015; McEwen *et al*., 2016). Various types of stress inhibit ovarian steroidogenesis and follicular development creating follicular atresia in rats' ovaries.

Moreover, stress is a stimulus that affects the entire system and causes a biological response, including harmful effects on health. Molecular changes due to stress are thought to affect folliculogenesis as well. As the hypothalamic-pituitary-adrenal (HPA) axis' activation will be triggered by stress, as a result, the hormone release and ovarian function will be affected by it (Zhu *et al*., 2016). Thus, the psychological stress makes some impacts to the women's reproductive health through the immune pathway, such as an increase in the hormone cortisol and Heat Shock Protein-70 (HSP-70), in which HSP-70 plays an important role in oocyte maturation (Novika *et al*., 2019). Meanwhile, natural products have a potential as the novel therapeutic drugs for various diseases. *Eucalyptus globulus* which belongs to the *Myrtaceae* family is one of the medicinal plant products (Hayat *et al*., 2015). It has been widely benefited to treat upper respiratory conditions (Her *et al*., 2022) and other diseases such as diabetes, gastritis, and knee pain (Jun *et al*., 2013). The existing studies also reported that *E. globulus* has analgesic and anti-inflammatory properties (Nakamura *et al*., 2020). Its anti-inflammatory property in the leaf extract works by performing the production inhibition of IL-6 and TNF-α from LPS-induced peripheral mononuclear cells (PMNC) (Landau *et al*., 2014; Qabaha *et al*., 2016). The solid anti-inflammatory abilities of *E. globulus* extract are commonly found in the main phenolic compound, which is Gallic acid (Lin *et al*., 2015). Similarly, *Apium graveolens* or celery is an herbal therapeutic plant with many health advantages, such as an anti-inflammatory effect (Kooti *et al*., 2015). Celery has enormous bioactive compounds such as antioxidants, carotene, cellulose, essential oils, flavonoids, protein, and vitamins (Li *et al*., 2018; Nagella *et al*., 2012). Additionally, *A. graveolens* has been reported to be able to help increase appetite, prevent iron deficiency anemia, and is a good source of fiber. *A. graveolens* has also the ability to affect the hormonal system. At specific doses, it can expand or lower follicle-stimulating hormone (FSH) along with luteinizing hormone (LH). Changes in FSH can affect other hormone mechanisms such as estrogen and progesterone. Previous studies revealed that *A. graveolens* contains phytoestrogens which can positively impact the reproductive physiology (Khairullah *et al*., 2021). Anti-inflammatory, antiviral, and antimicrobial effects have also been spotted (Rondanelli *et al*., 2018).

In line with this, LPPM (Unit of Research and Community Development) of Sebelas Maret University has strategic business research plans covering various strategic issues like climate change and biodiversity, which includes the superiority of local biological resources in the international level. Thus, this study was one of the strategic plans' implementations in promoting the ideal conditions for future research as the way of solving the potential problems faced nationally and globally by people due to various trends (environmental changes). This study would like to investigate women of reproductive age during COVID-19 pandemic related to their level of stress. Additionally, it also assessed the effectiveness of *A. graveolens* and *E. globulus* on HSP-70 level as the primary biomarker of stress, expression of TNF-α

as a pro-inflammatory protein, LH, and GDF-9 as biomarkers of oocyte growth factor.

MATERIALS AND METHODS

Study design

A single center randomized clinical experiment along with a pre-post-test control group design was applied to this study. This work was approved by the ethics board of the Regional Development, Planning, and Research Agency, Surakarta, Indonesia with Reference Number: 070/0454/IV/2021.

Participant

The randomized control trial method was applied for measuring the sampling determination. Sixty women of reproductive health age at Nusukan Health Center, Surakarta, Indonesia were grouped into two: the control group and intervention group from May until July 2021, with a ratio of 1:1 with the inclusion criteria as follows: aged between 19-30 years old with mild until severe stress according to DASS-21 screening, voluntarily participated in the research, and were able to establish verbal communication. The exclusion criteria were women with hormonal and mental disorders.

Intervention Group

As the study was conducted with two groups, the intervention and control groups, each group contained of 30 women aged around 19-30 years old. In the intervention group, for 14 days the administration of *A. graveolens* capsule supplementation orally for the pregnant women was conducted at a 300 mg dosage per day and *E globulus* essential oil was topically applied to the skin after bath time, twice a day during the similar duration, 14 days. Meanwhile, the control group had a placebo without containing any active substances and any effect on health.

Herbal Intervention

Two herbal ingredients were utilized as an intervention. First, *A. graveolens* capsules *were* purchased from the existing products that had received BPOM approval. The dosage was determined based on the instructions derived from the supported reputable journal publications. The application of *E. globulus* essential oil was given at the dosage of 300 mg per day for 14 days in total which referred to the prior study (Naki *et al*., 2018).

Stress Measurement

The stress level was measured using DASS-21. DASS-21 was identified as a self-report scale with the purpose of measuring the negative emotional states of anxiety, depression, and stress. There are five scales of DASS-21 measurement (Table I).

Table I. DASS-21 Scale

	Depression	Anxiety	Stress
Normal	0-9	0-7	0-14
Mild	10-13	8-9	15-18
Moderate	14-20	10-14	19-25
Severe	21-27	15-19	26–33
Extremely Severe	28+	20+	37+

Metabolite assay

Metabolite changes in serum like HSP-70, TNF-α, LH, and GDF-9 were assessed by applying Enzyme-Linked Immunosorbent Assay (ELISA) guided by the instructions from the manufacturer (Multi-sciences, Biotech Co., Ltd).

Statistical analyses

By utilizing SPSS version 21.0. The normality test was then assessed by the independent-group t-tests, while the Levene test examined the homogeneity test. Friedman test was applied to conduct the different tests and then the examination was proceeded to a post hoc test. All data were presented with mean±standard deviation (SD) with a significantly difference occurred with the value of $p < 0$.

RESULT AND DISCUSSIONS

Patients' Characteristics

Most respondents are aged around 19-25 years old, working women with university degree as their last educational level working women (Table II). No significant differences were found in age, education level, and occupation both in control and intervention groups.

Stress Level Result

For the stress level, no significant difference was exhibited in the control and intervention groups at baseline (pre-intervention). Contrastingly, a significant difference occurred at the stress level results between the control and intervention groups after receiving treatment of *A. graveolens* capsules and *E. globulus* essential oil.

Table II. Demographic characteristics of hospitalized schizophrenia patients

Characteristics	All patients (n=60)	Control (n=30)	Intervention Group (n=30)	p-value
Age (years)[a]				
19-25	37	21	16	0.188[b]
26-30	23	9	14	
Educational Level[s]				
Primary	28	16	12	0.305[b]
University	32	14	18	
Occupation [a]				
Student	28	16	12	
Housewives	2	2	-	0.190[b]
Working	30	12	18	

Table III. The stress levels at pre and post intervention of *A. graveolens* and *E. globulus* supplementation

Items	All patients (n=60)	Control Group (n=30)	Intervention Group (n=30)	p-value
Baseline (Pre-intervention)				
Normal	0	0	0	
Mild	10	5	5	
Moderate	19	10	9	0.839[b]
Severe	31	15	16	
Extremely severe	0	0	0	
after intervention				
Normal	8	0	8	
Mild	12	3	9	
Moderate	21	14	7	0.0001[b*]
Severe	19	13	6	
Extremely severe	0	0	0	

[a] frequency (percentage), [b] Mann Whitney, * p-value

Stress Marker Result

The evaluation of both HSP-70 and TNF-α levels in serum between the intervention and control groups was completed pre and post intervention. No significant difference was displayed between HSP70 ($p = 0.084$) and TNF-α ($p = 0.755$) levels in the serum (Figure 1) prior to the treatment with *A. graveolens* supplementation and *E. globulus* essential oil. On Day 14, the significant decrease was found on HSP-70 and TNF-α levels especially in the intervention group than the control group ($p < 0.001$).

Folliculogenesis Markers

LH and GDF-9 levels as folliculogenesis markers was examined in serum samples from both the intervention and control groups pre and post the intervention. No significantly difference was exhibited differences in folliculogenesis markers prior to the treatment of *A. graveolens* capsule supplementation and *E. globulus* essential (Figure 2). Furthermore, there were significant increases within the intervention group than the control group ($p < 0.001$ and $p < 0.001$) on the stress markers and LH and GDF-9 levels on Day 14.

HSP-70 and TNF-α have been used as markers to detect stress. They regulate cellular responses to stressful conditions related to cortisol. Cortisol also regulates heat shock proteins (HSP) expression in somatic cells such as adipocytes (Dhama *et al*., 2018). Meanwhile, heat shock proteins are a group of proteins related to stressors. High plasma cortisol levels along with chronic stress are able to reduce the suppressive effect of myocyte proteins and stimulate hepatocytes to synthesize HSP-70 and HSP-90 (Uchimura *et al*., 2018; Rastogi and Haldar, 2020).

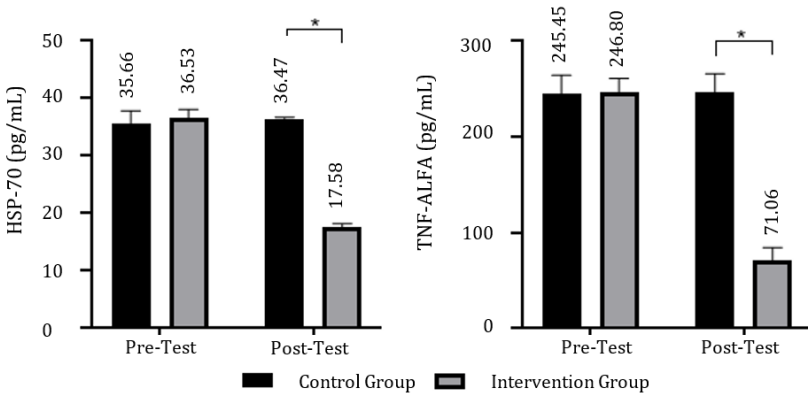

Figure 1. Stress markers on reproductive health women. The control group had a placebo, while the intervention group was treated with *A. graveolens* capsule supplementation orally and *E. globulus* essential oil for 14 days.

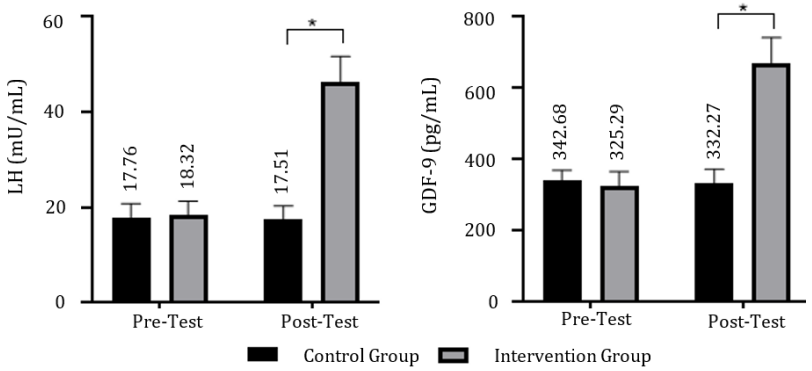

Figure 2. Folliculogenesis markers in relation to the reproductive health women. The control group had a placebo, while the intervention group was administered with *A. graveolens* capsule supplementation and *E. globulus* essential oil for 14 days.

Correspondingly, in this study, the results showed, within the intervention group, the considerably decreased HSP-70 and TNF-α levels compared to the control group. This investigation displayed that HSP-70 level was deficient in woman's reproductive health under the stressing conditions. Stress has some effects on functional pathways in all organs and tissues. Although the results were not significant, the accumulation of stressors in prenatal and postnatal periods contributed to the more elevated inflammatory fed back levels, such as CRP, IL-6, and TNF-α levels (Pedersen *et al*., 2018). This study presented a statistically considerable decrease in HSP70 and TNF-α levels in the intervention group after the combination of treatment between *A. graveolens* and *E. globulus*. Furthermore, stress triggers reactive oxygen species (ROS) and produces a pro-oxidant state. The increased oxidative stress in woman with stress may affect the ovary, hormonal imbalance, oocyte quality, and follicular growth (Pandey *et al*., 2018). An inhibitory effect was exerted by chronic stressors activated HPA axis on the female reproductive system. The chronic restraint stress (CRS) rat model found that the rats' estrus cycle became irregular due to being exposed by these stressors (Heck and Handa, 2019). Additionally, the follicle count's result revealed that CRS did influenced ovulation identifying the considerably decreased number of corpus luteum post chronic stress exposure. Also, the reduced number of secondary follicles suggested that the further development of primary follicles was delayed by the stress (Xu *et al*., 2018).

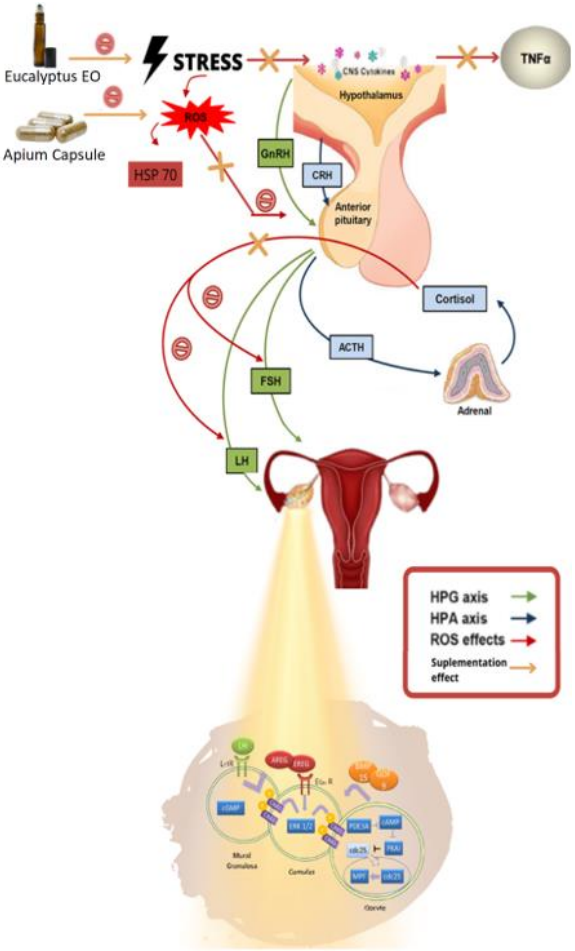

Figure 3. The novelty and schematic diagram related to the negative effect of stress on immunological response and ovary. *Apium graveolens* capsule supplementation and *Eucalyptus globulus* essential oil are able to decrease stress and protect folliculogenesis markers on women's reproductive health as the result of stressing conditions during pandemic COVID-19.

Moreover, *A. graveolens* and *E. globulus* are determined as photogenic products (Akbarian-Tefaghi *et al*., 2018). *A. graveolens* contains various bioactive compounds such as saponins, lipase, flavonoids, flavo-glucoside (apiin), tannins, apigenin, phytosterols, choline, phthalides, essential oils, asparagine, vitamins (A, B, and C), and volatile oil (Cho *et al*., 2020). Administering *A. graveolens* supplements in experimental animals in previous investigation revealed its beneficial effects on health. *A. graveolens* act as an antistress and immunostimulant on both humans and animals (Dean *et al*., 2018). The flavonoid content in herbal medication is proven to suppress free radicals (ROS) with antioxidant bioactivities in human blood monocytes (Li *et al*., 2018; Wahidah *et al*., 2020), which includes halting the generation and the capture of ROS directly, or the increase enzymes indirectly (Shigemura *et al*., 2020).

This examination displayed the increase on LH and GDF-9 levels within the intervention group leading to the protection of folliculogenesis markers from the combination treatment of *A. graveolens* and *E. globulus*. Thus, *A. graveolens* have shown contribution in affecting the hormonal system. It has the capability in influencing both FSH and LH (Khairullah *et al*., 2021).

During folliculogenesis, oocyte maturation, and embryogenesis, ROS physiological level of ROS is very valuable (Prasad *et al*., 2016). However, stress during a pandemic increases ROS level leading to the activation of. HPA axis as an adaptive stress response (Leistner and Menke, 2020). In this case, the triggered activation of HPA axis by stressors can provoke paraventricular nucleus of the hypothalamus in discharging corticotropin-releasing hormone (CRH) by the. Moreover, it stimulates the production of adrenocorticotropic hormone (ACTH) which will stimulate the synthesis of glucocorticoids in the adrenal cortex. This may affect all levels of hypothalamic-pituitary-gonadal (HPG) axis and inhibit the reproductive hormones in the follicular phase in hindering GnRH. This condition blocks the anterior pituitary to secrete FSH and LH. Furthermore, the diminishing estradiol production influences the decline in GnRH/LH secretion as the result of follicles which grow slower (Valsamakis *et al*., 2019). This condition can be seen in the appearance level of GDF-9. The antioxidant activity of *A. graveolens* plays a crucial role in protecting cells from the increased oxidative injury. *A. graveolens* play major role in the immune response because it has vitamins, biochemical compounds, and essential minerals (Kooti *et al*., 2017). This investigation revealed that LH level increased after *A. graveolens* intervention. The flavonoid content in *A. graveolens* shows this condition suppresses ROS as the result of stress in a reproductive aged woman. *A. graveolens* has an antioxidant effect and inhibits oxidative stress. By suppressing ROS in the limbic response, GNRH gives the anterior pituitary through the arcuate nucleus to stimulate the release of LH.

Additionally, FSH reduces the effects of oxidative stress. An intervention of methanol extract can lower malondialdehyde (MDA), which is an indicator of cellular defects done by the free radicals (ROS) (Boonruamkaew *et al*., 2017). On the other hand, *E. globulus* oil also has the ability to drop HSP-70 level by lowering the molecular stress due to anxiety and another stressor. The improved GDF-9 level in the intervention group presents that *E. globulus* oil indeed has an association with the growth factor of oocyte. GDF-9 is the transforming growth factor β superfamily and contribute greatly in the development of ovarian follicular and ovulation rate (Sanfins *et al*., 2018). *E. globulus* oil has also antioxidant, anti-inflammatory, anti-proliferative, and antibacterial activities. Due to its function, *E. globulus* provokes oocyte growth by suppressing molecular stress. In an experimental study with mice, the inhibition of follicular growth, the development of follicular atresia and the suppression of GDF-9 expression can be triggered by unpredictable chronic stress. Moreover, GDF-9 stimulates granulosa cell differentiation, including LH receptors and steroidogenesis (Richards *et al*., 2018). Therefore, *A. graveolens* and *E. globulus* simultaneously play an essential role in decreasing stress and modulating HPA axis function to protect folliculogenesis.

The limitation of this investigation only focuses on the Follicullogenesis marker as a reproductive health indicator in women. Further study is warranted to evaluate the estrogen-progesterone level, FSH, and inflammatory parameters such as ROS, MDA, and cortisol to provide a better understanding of the effect of *A. graveolens* and *E. globulus*.

CONCLUSION

A. graveolens supplementation and *E. globulus* essential oil have proven their abilities in decreasing stress and protecting folliculogenesis markers on women's reproductive health due to the stressful conditions during pandemic COVID-19.

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