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Original Article

THE EFFECTS OF HONEY ADMINISTRATION ON SOLUABLE *FMS-LIKE TYROSINE KINASE (SFLT-1), SOLUBLE ENDOGLIN (S-ENG), VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF)* SERUM LEVELIN THE RAT MODEL OF PREECLAMPSIA

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ABSTRACT

Objective: To find out the effect of honey administration on changes in antiangiogenic and proangiogenic serum levels in the rat model of preeclampsia. This study is the first research that examines the effect of honey on preeclampsia especially on proangiogenic and antiangiogenic factors

Methods: This study uses analytic research with a quasi-experimental design in laboratory rats (*Rattus Norvegicus*) pregnant females given honey with concentration. The treatment of all samples was carried out simultaneously and during the treatment it was observed using the type of postest only control group design.

Results: Honey administration significantly reduced sFlt-1 levels in preeclampsia rats, and a greater dose of honey had an effect on strengthening the effect of honey in reducing sFlt-1 levels. Honey administration significantly increased VEGF levels in preeclampsia mice ($p = 0.034$). Honey administration significantly decreased s-Eng levels in preeclampsia mice, and administration of a larger dose of honey had an effect on strengthening the effect of honey in reducing s-Eng levels ($p = 0.012$).

Conclusion: The honey administration on rat's model of preeclampsia may reduce the antiangiogenic level sFlt-1 and sEng dan increase VEGF level as the pro-angiogenic.

Keywords: Honey, Soluble FMS-Like Tyrosine Kinase (sFlt-1), Soluble Endoglin (s-Eng),Vascular Endothelial Growth Factor (VEGF), Preeclampsia

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INTRODUCTION

Pregnancy is a normal physiological phenomen with many biochemical changes ranging from changes in electrolyte concentrations to more complex changes in cortisol and calcium metabolism. Pregnancy is associated with normal physiological changes that help in maintaining and sustaining the fetus. Biochemical parameters reflect adaptive changes and are clearly different from non-pregnant countries [1].

Preeclampsia is a systemic syndrome that occurs during pregnancy and after pregnancy, and affects 3-8% of pregnancies. It is one of the main causes of maternal mortality and morbidity throughout the world. The diagnosis of preeclampsia is based on the presence of specific hypertension caused by pregnancy accompanied by disorders of other organ systems at gestational age above 20 w. Preeclampsia, previously always defined by the presence of hypertension and proteinuria that only occurs in pregnancy (*new onset hypertension with proteinuria*) [2, 3].

The strong role of sFLT-1, sEng, PlGF in the pathogenesis of preeclampsia was also developed as a biomarker for both diagnostic and prognosis [4-6]. It is an angiogenic factor that plays a role in inhibiting TGFB1 binding to its receptors, resulting in a disruption in the production of nitric oxide (NO), vasodilation, and capillary formation by endothelial cells *in vitro*. In patients with preeclampsia, blood levels tend to increase [7].

Honey has long been documented as having healing properties and more recent research has shown that honey can be effective for clearing infections in various wounds, including abscesses, surgical wounds, trauma wounds, burns, and ulcers of various etiologies. So that it is done to confirm the angiogenic potential honey and to study its effect on VEGF expression [8].

To date there has been no research on the effects of honey on preeclampsia, this study is the first research that examines the effect of honey on preeclampsia especially on proangiogenic and antiangiogenic factors as pathogenesis and pathophysiology of preeclampsia.

MATERIALS AND METHODS

Research has performed examination *of soluble fms-like tyrosine kinase (sFlt-1), soluble soluble endoglin (sEng) and vascular endothelial growth factor (VEGF),* with a quasi-experimental design in laboratory rats (*Rattus Norvegicus*) pregnant females given honey with *concentrationbyELISA* method on 4 groups of rats, each group consisting of 6 rats subject to research conducted in January-October 2019. The research sample is part of the study population that meets the inclusion and exclusion criteria by using the Postest Only Control Group Design.

RESULTS

This study used 24 *Rattus norvegicus* rats which were divided into 6 rats in each study group. Each group was then referred to as group A which is a negative control group, group B was a positive control group, group C was a group of mice given honey with a concentration of 0.015% v/v, and group C was a group of mice given honey with a concentration of 0.06% v/v.

Table 1: The differences in sFlt-1 levels

	n	sFlt-1, mean (SD)	p [a]	Post Hoc		
				Group B	Group C	Group D
Group A	6	5.52 (1.47)	0.002	0.004 [b]	0.1150 [b]	0.025 [b]
Group B	6	11.07 (1.49)			0.006 [b]	0.006 [c]
Group C	6	7.17 (1.45)				0.1150 [b]
Group D	6	8.17 (1.37)				

[a]Kruskal Wallis, [b]Mann Whitney, [c]T Independent

The mean levels of sFlt-1 in group A was 5, 52 (SD = 1.47). No significant difference in sFlt-1 was found between group A and group C. The mean sFlt-1 level in group C was 7, 17 (SD = 1.45). The mean sFlt-1 level in group B was 11,07 (SD = 1.49). The mean sFlt-1 levels between group B and group A, group B and group C as well as group B and group D showed significant differences ($p<0.05$). The mean of group C and group D did not show a significant difference in mean ($p = 0.150$).

Table 2: The differences in VEGF levels

	n	VEGF, mean (SD)	p [a]	Post Hoc [b]		
				Group B	Group C	Group D
Group A	6	15 (3.42)	0.021	1,000	0.747	.166
Group B	6	13.64 (3.42)			.185	0.034
Group C	6	18.04 (3.22)				1.000
Group D	6	19.51 (3.10)				

[a]Anova, [b]Bonferroni

The lowest mean VEGF levels were in group B with a mean of 13,64 (SD = 3.42) and the highest VEGF mean were in group D with a mean of 19,51 (SD = 3,10). Only the mean VEGF in group B and group D had a significant difference ($p = 0.034$). There was no significant difference in mean VEGF between group B and group D ($p = 1.000$).

Table 3: The difference in s-eng levels

	n	s-Eng, mean (SD)	p [a]	Post Hoc [b]		
				Group B	Group C	Group D
Group A	6	5.94 (1.86)	.001	<0.001	1,000	.183
Group B	6	11.25 (1.79)			0.012	.100
Group C	6	7.43 (1.89)				1.000
Group D	6	8.44 (1.92)				

[a]Anova, [b]Bonferroni

Mean s-Eng content was lowest for the group A with a mean 5, 94 (SD = 1.86) and the mean of the highest s-Eng contained in the B group with a mean of 11.25 (SD = 1.79). Only the mean *s-Eng* in group B and group C had a significant difference ($p = 0.012$). There was no significant difference in s-Eng between group B and group D ($p = 1.000$).

DISCUSSION

The administration of honey can reduce sflt-1 levels in mice preeclampsia models, honey plays a role in suppressing sFlt-1 bonds so that levels in the blood decreases and causes improvement of endothelial dysfunction. Honey can improve the endothelial tubular seminiferous tissue in immunohistochemical observation [9].

sFlt-1 levels should increase in pregnancy compared to non-pregnancy conditions. The placenta is known as the main source of sVEGFR1 although endothelial tissue can produce a small amount of sVEGFR. In normal pregnancy there is an increase in sVEGFR1 20 times the normal value, this is caused by hypoxia in the placenta in early pregnancy, but in preeclampsia, sVEGFR1 levels can increase up to 43 times [10].

Hypoxia states is a major trigger for increased expression of VEGFR1 in the placenta as well as an increase in sVEGFR1, and higher doses show a better suppressing effect [10].

Soluable endoglin (sENG) is another anti-angiogenic biomarker that is regulated in preeclampsia with a pattern similar to sFLT-1. ZINC is a truncated form of endoglin (CD105), a cell surface receptor to change the β-growth factor (TGF-β), which binds to and opposes TGF-β. ZIN strengthens vascular damage mediated by sFLT-1 in pregnant mice, inducing syndromes such as severe preeclampsia with features of HELLP syndrome. Like sFLT-1, circulating ZY levels increase several weeks before the onset of preeclampsia, and an increase in ZY levels is observed in a mouse model of reduced uterine perfusion pressure from preeclampsia [3].

The mechanism that explains the high expression of endoglin in the presence of placental hypoxia is based on the fact that the endoglin gene promoter has hypoxic responsive element (HRE) regions. HIF-1, in collaboration with Sp1 and CBP/P300 coactivators bound to this region stimulates endoglin expression. This stimulating effect is further enhanced when the HIF-α/Sp1 complex collaborates with the TGF β/Smad signaling pathway. On the other hand, there are data showing that the increase in Eng expression observed in pre-eclampsia can also be mediated, at least in part, by HIF-1 α, perhaps through activation of the TGF-β3 pathway. Tal R. *et al.* Have demonstrated the effect of overexpression of HIF-1 in pregnant mice using adenoviruses that express constitutively active and stable HIF-1 [11, 12].

Honey has an anti-inflammatory-inducing effect on cells, through intervention in the angiogenesis process that relies on VEGF [13]. As we know, hypoxia occurs in preeclampsia, this will cause the process of angiogenesis induced by HIF-α in the placenta.

CONCLUSION

Honey administration significantly reduced sFlt-1 levels in rat model of preeclampsia, and a greater dose of honey had an effect on strengthening the effect of honey in reducing sFlt-1 levels. Honey

administration significantly increased VEGF levels in preeclampsia mice (p = 0.034). Honey administration significantly decreased s-Eng levels in preeclampsia mice, and administration of a larger dose of honey had an effect on strengthening the effect of honey in reducing s-Eng levels (p = 0.012).

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The authors declare that this research was conducted without any commercial offinancialrelationship that could be seen as a potential conflict of interest.

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