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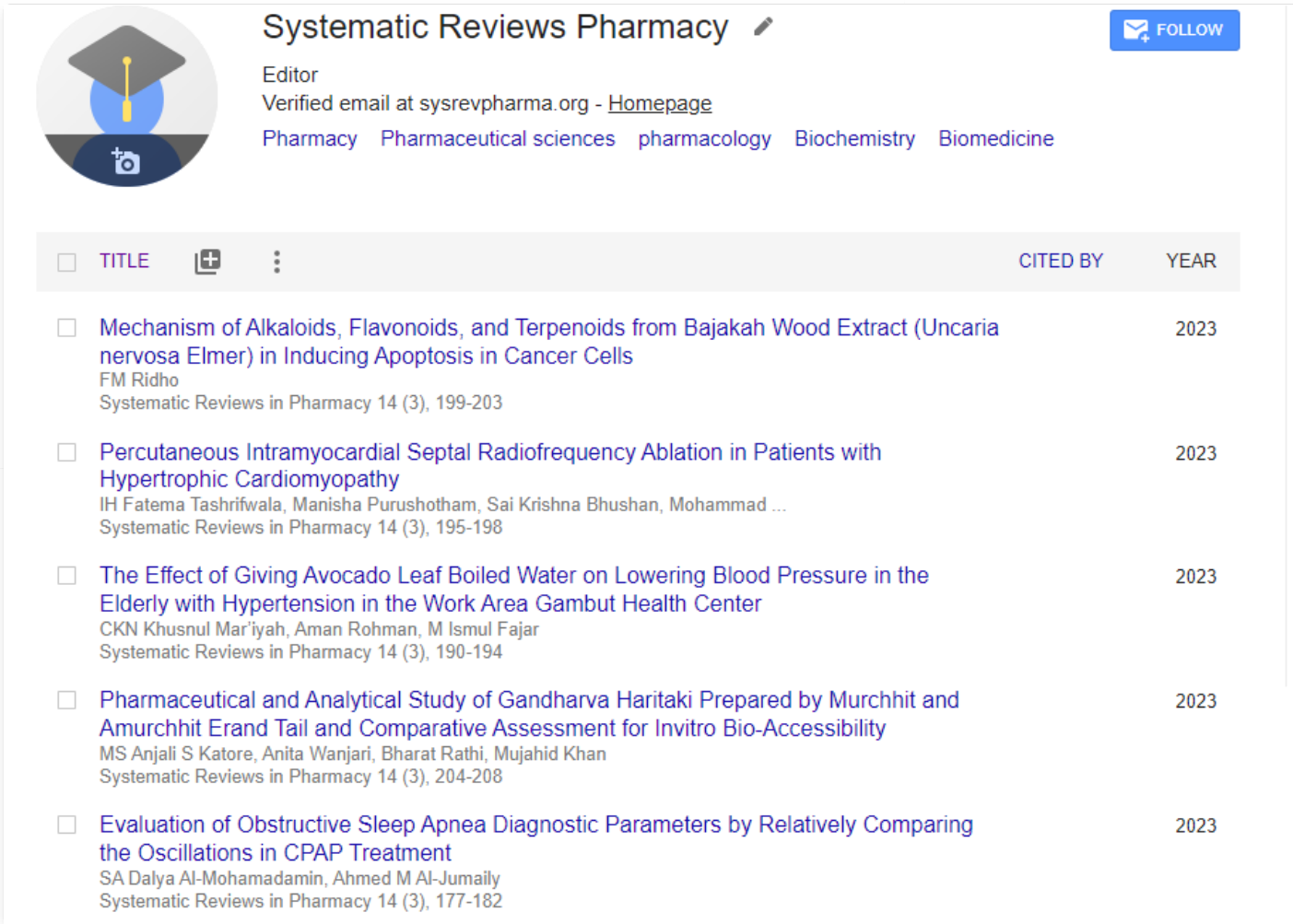

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EFFECT OF ZINGIBER OFFICINALE EXTRACT AND INSULIN ADMINISTRATION TOWARDS SOLUBLE FMS-LIKE TYPES OF TYROSINE KINASE-1 IN DIABETES MELLITUS PREGESTASIONAL RATTUS NORVEGICUS MODELS

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ABSTRACT

The perinatal mortality rate increases 20 times in pregestational diabetes mellitus (PGDM) women with preeclampsia complications associated with changes in soluble fms-like tyrosine kinase-1 (sFlt-1) levels. The study analyzed the differences of effect of Zingiber officinale extract and insulin administration on the sFlt-1 level of Rattus norvegicus PGDM models. Rattus norvegicus were divided into five groups. The sFlt-1 level concentration was examined by ELISA. There was statistically significant increase of sFlt-1 levels in all groups (1.24±0.16, 1.58±0.12, 1.73±0.30, 1.98±0.47, 2.34±0.23, p = 0.001 for negative control, positive control, insulin treatment, Z. officinale extract treatment, insulin and Z. officinale extract combination respectively). There was significant difference of sFlt-1 between negative control and treatment groups and between positive control and treatment groups. The most different group was the negative control group with the insulin and Z. officinale extract combination with p = 0.001 in MD = -1. The presence of Z. officinale extract can be used as a single therapy or a combination with insulin for PGDM for decreased risk factor of PGDM, such as preeclampsia.

Keywords: Pregestational diabetes mellitus, insulin, Zingiber officinale, sFlt-1.

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INTRODUCTION

Diabetes mellitus (DM) in pregnancy is classified into two forms, namely DM that precedes pregnancy, pregestational DM (PGDM), and DM that occurs during pregnancy, gestational DM (GDM) (1,2). This situation has great impacts when it occurs during pregnancy, such as increased morbidity and mortality both in mother and fetus. Maternal complications that often occur in DM during pregnancy are gestational hypertension, preeclampsia, preterm labor, hydramnios, diabetic nephropathy, diabetic retinopathy, diabetic neuropathy, infection, and increased labor with caesarean section (1,3).

The prevalence of hyperglycemia in pregnancy increases rapidly. Estimated 223 million women (20-79 years) live with diabetes. About twenty millions of live births have some forms of hyperglycemia in pregnancy. An estimated 84% are due to gestational diabetes. The vast majority of hyperglycemia cases in pregnancy is in low- and middle-income countries, where access to maternal care is often limited (4).

One of maternal complications of pregestational diabetes is hypertension, which subsequently becomes preeclampsia. The perinatal mortality rate increases twenty times in women with PGDM with preeclampsia. The previous study investigated that pregnant women with type 1 diabetes who had preeclampsia associated with hyperglycemia were associated with changes in levels of angiogenic factors, one of which was an increase in levels of soluble fms-like tyrosine kinase-1 (sFlt-1) and decreased levels of placental growth factor (PIGF) (5). In a study of 151 women with type 1 diabetes, an increase in sFlt-1 and a decrease in PlGF were found previously at the onset of preeclampsia (6).

Hyperglycemia causes endothelial dysfunction, resulting in vasoconstriction and vasospasm of the blood vessels (7). Exposure to hyperglycemia conditions for too long is known to cause an increase in oxidative stress that will affect the number of trophoblastic cell decrease and trigger the occurrence and condition of hypoxia (8,9). This condition will facilitate the occurrence of angiogenesis disorders, namely increased anti-angiogenic (sFlt-1) and decreased pro-angiogenic (PlGF). Increased plasma or serum sFlt-1 levels causes impaired vasculogenesis and angiogenesis in the fetomaternal circulation while increased sFlt-1 in the maternal circulation results in low circulating free PlGF concentrations. This results in impaired placental signaling of angiogenesis (10).

The American College of Obstetricians and Gynecologists do not recommend oral antidiabetic drugs to PGDM because they cross the placenta. The use of insulin injections is a therapy that can be given to pregnant women with DM, but people also use the plant as a therapy. WHO estimates 80% of the population in the world using medicinal plants for health, including in DM (11). Research on the utilization of herbs to treat DM has been widely practiced, one of which is using ginger (*Zingiber officinale*). Ginger has a variety of uses, such as spices, essential oils, or as a medicine (12). Ginger does not cause toxicity to the fetus and is safe for the mother. Ginger has been proven as an antidiabetic agent and helps in reducing the condition of hyperglycemia (13). This study analyzed the differences of effect of *Zingiber officinale* extract and insulin

administration on the sFlt-1 level of *Rattus norvegicus* PGDM models.

METHODS

This study was a true experimental research using post-test only control group design. The population used was pregnant *Rattus norvegicus* aged 3-4 months. The sampling technique was simple random sampling. The independent variables were insulin and *Zingiber officinale* extract, and the dependent variable was sFlt-1 level.

Thirty rats were selected and divided randomly into five groups. Each group consisted of 6 rats. Group A was not used as a DM model because it would be a negative control group, while the other groups being DM with type 1 DM model using injection streptozotocin (STZ). Rats were injected with STZ dose of 50mg/kgBW intraperitoneal. The injection material was prepared in a 0.05 M buffer solution with a pH of 4.5. Forty-eight hours after STZ induction, the rats were checked for their blood sugar. Rats were said to have DM and sampled when the glucose level was > 200mg/dL, then all groups were cut off. The process of twisting was done using PMSG and HCG injection and monomatting mated, then the vaginal plug was checked. Treatment began on the 1st day of pregnancy. Group B was given with distilled water 1 cc and being positive control. Group C was given with 1 IU insulin which was injected per IM after meals. Group D was given with ginger extract 500 mg/kgBB via sonde before meals, and the Group E was given with insulin and ginger. Rats'b lood was taken in day 17 to examine sFlt-1 concentration using ELISA and comparing to control group.

All data were processed using SPSS for descriptive test, Shapiro Wilk for normality test, and Levene test for homogenity test. If data were normally distributed and homogeneous, the data were examined using One Way Anova. Furthermore, a post hoc test was performed to compare the results of the research in each test group. The test results showed significant with $p < 0.05$.

RESULTS

Tabel 1 shows sFlt-1 level result. There was an increase from group A to E. The negative control group had the lowest average than the positive control. However, after good treatment using insulin (Group C), *Z. officinale* extract (Group D) and the combination of insulin and *Z. officinale* extract (Group E), increased improvement was shown. The statistical test results using the One way ANOVA test showed $p = 0.001$ ($p < 0.05$) so that there were differences in levels of sFlt-1 between insulin given with those given with *Z. officinale* extract. To determine the difference in which group was significant, the Post-hoc test and LSD were carried out because they had the same variant. Table 2 shows that there is significant difference of sFlt-1 between Group A and Group B ($p = 0.045$), Group A with Group D ($p = 0.001$), Group A and Group E ($p = 0.001$), Group B with Group C ($p = 0.001$), Group B with Group D ($p = 0.026$), Group C and Group E ($p = 0.001$), and Group C and Group D ($p = 0.038$). The most different group was the negative control group A with the group E given with insulin and ginger with $p = 0.001$ in MD = -1.

Table 1. Different test results sFlt-1 in five groups

Groups	Mean±SD (nm/ml)	P value
A	$1.24^{a} \pm 0.16$	
B	$1.58^{b} \pm 0.12$	
C	$1.73^{b} \pm 0.30$	0.001
D	$1.98^{b} \pm 0.47$	
E	$2.34^{c} \pm 0.23$	

A: negative control; B: positive control; C: insulin; D: ginger; E: insulin and ginger combination
Note: Different superscripts show significant differences

Table 2. The result of Post-hoc test

Groups	A	B	C	D
B	0.045			
C	0.007	0.374		
D	0.001	0.026	0.157	
E	0.001	0.001	0.001	0.038

A: negative control; B: positive control; C: insulin; D: ginger; E: insulin and ginger combination

DISCUSSION

The sFlt-1 level increased in the group receiving insulin therapy and a combination of insulin and ginger rather than the negative control group. The presence of *Z. officinale* extract can be a single or combination therapy with insulin for PGDM to reduce the risk factor of PE. The ginger can reduce blood glucose levels. Besides, ginger itself has anti-inflammatory and antioxidant effects. It should reduce reactive oxygen species (ROS) and oxidative stress which results in decreased cell hypoxia and decreases sFlt-1 levels (14).

Several in-vitro and ex-vivo studies showed that high glucose exposure in diabetes causes maternal problems. Female mice that were injected with STZ and were pregnant showed increased plasma sFlt-1 levels which caused vascularity and angiogenesis in the fetomaternal circulation (15). Besides, other reports found mice treated by STZ caused atherosclerosis accompanied with increasing blood glucose and cholesterol level (16).

This is consistent with other studies that the condition of diabetes in pregnancy also induces an antiangiogenic environment in endothelial cells. This environment occurs due to oxidative stress (17). The presence of hyperglycemia causes glucose to increase, thereby stimulating cytochrome P450 such as NADPH oxidase to be the main source of ROS generation. Overproduction of NADPH oxidase-dependent from ROS plays an important role in increasing oxidative stress (18). This improves hypoxia marked by an increase in HIF-1 α. This situation causes an angiogenic imbalance. This antiangiogenic environment is represented by sFlt-1 levels in serum in the maternal circulation (19), both in diabetes with preeclampsia or preeclampsia alone. Levels of sFlt-1 in the bloodstream are associated with decreased levels of free vascular endothelial growth factor (VEGF) and PlGF. This is why sFlt-1 levels increase in the STZ-induced group than in the group without the STZ.

However, this is not in accordance with some studies where the administration of insulin is the main therapy that can be given in diabetes to reduce blood sugar levels. Previous study proved that the administration of exogenous insulin prepared in various doses from the long acting insulin analogue group reduced blood glucose and HbA1C in STZ induced mice (20). Hyperglycemia can be reduced by the correct insulin therapy protocol. The type of insulin, number of doses, time of administration, and method of administration must be considered. Normal blood glucose condition due to insulin action is expected to suppress various effects of hyperglycemia such as increased ROS, the presence of oxidative stress which will reduce sFlt-1 levels (21).

ROS signals are also an important stimulus from dangerous enzymatic catalyzed by the protein kinase B/Akt. The insulin significantly increases intracellular superoxide production (22). The increase in ROS ultimately improves the hypoxic condition which will ultimately disturb the angiogenic balance

marked by an increase in antiangiogenic, namely sFlt-1 levels (23).

Another interesting opinion is that sFlt-1 is a variant of the VEGF receptor that loses the transmembrane and cytoplasmic domains. SFlt-1 is a VEGF 1 receptor (VEGFR-1) that is soluble in the bloodstream (24). SFlt-1 is produced in large quantities by the placental trophoblast and released into the maternal circulation. SFlt-1 acts as an antiangiogenic protein molecule that binds VEGF and free PlGF in circulation. The results of measurements of high sFlt-1 levels indicate that high flt-1 in cells dissolves and moves to the maternal circulation. The existence of this transfer can be a good compensation because sFlt-1 does not gather more in the cell.

High serum sFlt-1 levels and low free VEGF and PlGF levels have been known to occur before and during the clinical manifestations of DM with complications of preeclampsia. However, a study in 2011 stated that low levels of sFlt-1 may be due to compensatory mechanisms because the placenta might produce more VEGF and soluble VEGFR-1 levels that are not bound to VEGF levels are reduced (24). In patients who later miscarried, both VEGF and their receptors are both reduced so that sFlt-1 levels are also reduced. In pregnancy, sFlt-1 levels increase 20-fold, proving that the feto-placental unit is the main source of this protein. Good trophoblast cells indicate that the synthesis of Flt-1 in placenta also increases, and eventually, adaptation will occur to the maternal circulation.

Ginger contains high antioxidants and has anti-inflammatory properties (25). Ginger also has an antiangiogenic effect which means that ginger will increase VEGF. The high state of VEGF causes VEGFR to also increase, and the VEGFR-1 present in the cell will decrease. The VEGF receptor which loses its transmembrane domain increases in the maternal circulation. This increase provides better compensation to the cell nucleus because sFlt-1 moves and dissolves in the circulation of (26). However, VEGF and sFlt-1 levels in cells were not measured in this study, so the certainty on how VEGF levels and sFlt-1 levels in cells were still unknown.

Another research says that ginger and its components, gingerols and shogaols, can work on pancreatic β cells so that they can increase insulin production and reduce glucose in the blood. Ginger extract, 6-gingerol, is an effective antidiabetic agent through its ability to increase insulin sensitivity and reduce hyperglycemia (27). 6-gingerol also can decrease inflammatory mediators, such as inflammatory cytokines (28). Ginger and its constituents show important effects in controlling tumor development through regulation of tumor suppressor genes, induction of apoptosis and inactivation of the VEGF pathway. VEGF inhibition is an important step in preventing the development/management of tumors (26). VEGF inhibition can also be seen from high levels of VEGFR or sflt-1. This increase has a good effect and does not mean this effect is detrimental as in preeclampsia. That pathway explains why in this study the use of ginger finally can increase sFlt-1. The explanation above is also the basis for how the combination of both insulin and ginger increases sFlt-1 levels.

CONCLUSION

The presence of *Z. officinale* extract can be a single or combination therapy with insulin for PGDM to reduce the risk factor of preeclampsia.

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