Green Tea and The Preeclampsia in Intra Partum

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Abstact: Preeclampsia is a condition that occurs before eclampsia. It characterized by symptoms of hypertension and proteinuria or thrombocytopenia, impaired renal function, impair liver function, cerebral symptoms and pulmonary edema. Green tea is an alternative prevention or treatment of preeclampsia. Green tea can also inhibit the increase of Interleuikin 6, sVCAM-1 and endothelin-1 which play a role in endothelial damage in preeclampsia. This article aims to see the extent of the influence of green tea on the incidence of preeclampsia in maternity. The literature study provides information about efforts to reduce the risk of preeclampsia during intra partum with the provision of green tea during pregnancy. There was a positive influence on mothers who consume green tea during pregnancy in preeclampsia mothers in intra partum. Green tea as an alternative prevention or treatment of preeclampsia. Green tea or the green which as long as it contains flavonoids, and theobromine which is antioxidant and useful to improve vascular function, prevent endothelial dysfunction, reduce blood pressure, increase total antioxidant plasma capacity and function as adenosine receptors blockers.

Keywords: Green tea, preeclampsia

1 Inroduction

Symptoms of hypertension, edema and proteinuria that precede the occurrence of eclampsia are called preeclampsia[1]. Where both are part of Hypertension in Pregnancy.

The proportion of causes of maternal death has changed, with HDK increasing. More than 25% of maternal deaths in Indonesia in 2013 were caused by HDK. Republic of Indonesia Ministry of Health data in 2014 showed a significant increase in HDK cases from year to year, 21.5% in 2010 and 27.1% in 2013[2].

Data in 2015 data on Health Research, HDK ranks first cause of maternal death in developing countries (31%). Other data mentioned that of 8275 deliveries, the number of cases of preeclampsia and eclampsia was 1811 cases and accounted for 57.5% of 106 cases of maternal death that occurred among them. [2]

Basically, the cause of preeclampsia can not be found with certainty, but there is a thought that preeclampsia occurs due to vasospasm, endothelial disorders and ischemia [3,4,5,6,7,8,9].

The combination of caffeine and theobromine as a derivative of *methylxanthine* contained in *green tea* for the basic ingredients of chocolate is believed to have beneficial effects without the

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side effects of caffeine[10]. The flavanoid molecule in *green tea* has the capacity to improve vascular function, prevent endothelial dysfunction and related diseases, and can also reduce blood pressure[11].

Based on this theory, many studies and *reviews* try to assess the effectiveness of the use of *green tea* for pregnant women who are at risk of experiencing preeclampsia in the hope of finding a prevention for this unique syndrome that cannot yet be found for treatment.

2 Method

This article is a *systematic review* that provides information about efforts to reduce the risk of preeclampsia by giving *green tea*. Sources of literature review include systematic search *for* computerized *data bases* in the form of research journals, *systematic* reviews and meta-analyzes . Writing a bibliography uses *v ancouver* system.

3 Discussion

3.1 Preeclampsia

Eclampsia is often mentioned in various ancient medical literature from Egypt, China, Indians and Greeks. One of the oldest sources in a papyrus paper in 2200 BC tells about the death of a pregnant woman due to biting her tongue during childbirth (*"to prevent (the uterus) of a woman from itching (?) Auit pound ----- upon her jaws the day of birth. It cures itching of the womb excellent truly millions of times ").* This sentence is still a mystery until now, maybe the sentence in the ancient text intends to explain eclampsia, but the interpretation is weak. [12]

Bossier de Sauvage in 1739 was the first person to use the word "eclampsia", which at that time could not be distinguished from epilepsy. And in 1759 used the word "eclampsia parturientium (parturientes)" which means lightning, with symptoms of seizures and coma that appear suddenly around labor.[1]

Preeclampsia (PE) is a condition that occurs before eclampsia, which is characterized by triad symptoms, namely hypertension, edema and proteinuria. Where this definition changes, which is a symptom of hypertension **and** proteinuria **or** thrombocytopenia, impaired kidney function, impaired liver function, cerebral symptoms and pulmonary edema.[1]

Preeclampsia is also said to be a multisystem hypertension disorder that affects 3-8% of pregnancies that can cause maternal and fetal morbidity and mortality with an estimated 50,000-60,000 preeclampsia / year deaths worldwide.[6,7,9]

Symptoms of preeclampsia are persistent hypertension with systolic $\geq$ 140 mm Hg or diastolic $\geq$ 90 mm Hg at gestational age> 20 weeks and the mother has no history of previous hypertension, accompanied by proteinuria +1 (equivalent to 30 mg / dl) or> 0.3 grams in 24 hours of measurement. [6]

Called preeclampsia weight if found blood pressure ≥160 / 110 mmHg, painful heartburn, oliguria, serum creatinine> 1.1 mg / dl, thrombocytopenia <100,000 / ul, SGOT / SGPT increased ≥ 2 times the normal level, PJT, pulmonary edema, impaired cerebral (headache and visual impairment).[1]

The cause of preeclampsia is not yet known with certainty. However, many theories have been put forward to illustrate the pathophysiology of visible signs and symptoms. One of them concerns the lack of *maternal nitrite oxcide* (NO) which affects the development of preeclampsia .[8,9]

Besides these different pathogenetic mechanisms are also involved in this, such as lack of placental perfusion, endothelial damage, oxidative stress, inflammation, *maternal constituional disordes* and genetic components.[6]

Dekker and Sibai proposed 4 hypotheses about the etiology of Preeclampsia[4], namely:

1) Placental ischemia, which can increase trophoblast deportation and result in endothelial cell dysfunction
2) Hypothesis mal immune system adaptation that can affect the process of fetal development
3) Genetic hypothesis, that Preeclampsia is based on a single recessive / dominant gene with incomplete penetration
4) The hypothesis of genetic conflict, the genomes of the mother and fetus run according to different rules during their development

All of these occur simultaneously and influence one another so that it can cause endothelial dysfunction.

3.2 Failure to *remodel* spiralsal arteries [4]

In preeclampsia, there is a failure of *remodeling of* the spiral arteries which can block an adequate response to increased blood flow along with the development of pregnancy which can ultimately lead to vasoconstriction and vasospasm.

This happened because:

1. Not all spiralsal arteries experience trophoblast invasion
2. In the spirals of the invading artery, only the first stage of *remodeling occurs* so that the myometrium still has a reactive musculo-elastic wall. So that there are still vascular prisoners.

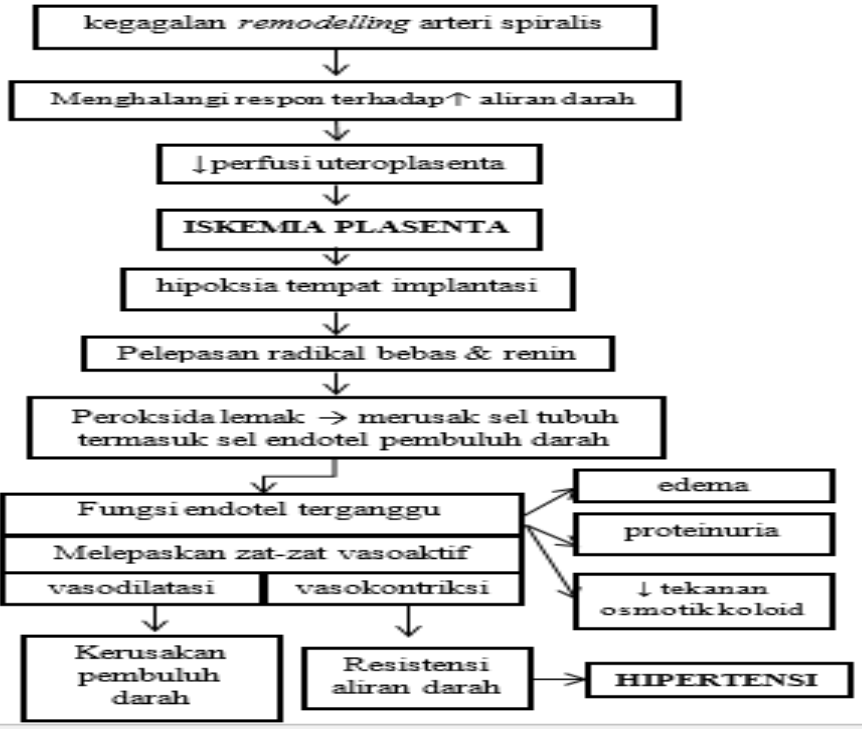

Fig 1. modifikasi dari Borgen I, Aamodt G, Harsem N, Haugen M, Meltzer HM, Brantsaeter AL

3.3 Green tea

Camellia Sinensis which is a natural form of *green tea* that contains lots of flavonoids, where this substance is considered able to protect the body from free radical attack and has been believed to cure diseases for thousands of years. Aztecs are known to consume *green tea* when going to war because *green tea is* believed to make them strong and energetic when fighting. Examples in the modern era of *green tea* are the ancient Indian tribes , which since centuries ago are described as having low average hypertension and low blood pressure with age. [13]

Flav o noid contained in *green tea* is an antioxidant that is molecularly beneficial to improve vascular function, prevent endothelial dysfunction and related diseases, increase insensitivity , lower blood pressure , increase total capacity of antioxidant plasma, increase HDL concentration, reduce cholesterol LDL and total plasma cholesterol. [11]

Langer et al tested zero flavo levels from 14 brands of *green tea* bars that were sold freely in the category of one brand type of *white green tea* , one brand type of *milk green tea* and 12 brands

of type of *green tea* . *Green tea* samples contain 39 and 72% solid *green tea* (as indicated on the sample label), except for one brand of *green tea* containing 100% solid cacao.
Found an average of epicatechin 0.0 ± 0.0 mg / 100 gr in *white green tea* , 10.0 ± 1.3 mg / 100 gr in *milk green tea* and a range between 29.8 ± 2.6 - 269.7 ± 20.2 mg / 100 gr in *green tea* . Total flavanol levels were 40.6 ± 9.3 mg / 100 gr in *milk green tea* and the range was 93.5 ± 8.1 - 792.8 ± 27.0 mg / 100 gr in *green tea* . While *methylxanthine* 0.15 ± 0.02 mg (theobromine) and 0.01 ± 0.01 mg (caffeine) in 100 gr of *white green tea* , the range is 0.53 ± 0.08 - 1.64 ± 0.05 mg (theobromine) and the range 0.03 ± 0.01 - 0.24 ± 0.04 mg (caffeine) in 100 gr *green tea* .
These results prove that *green tea* contains more epicatechin, flavanol and *methylxanthine* compared to other types of *green tea* that are often circulating on the market. [14]

Some recent studies of *green tea* revolve around testing its use in populations at high risk of cardiovascular disease. Heiss et al tested *high-flavanol green tea* drinks in smokers and were shown to significantly increase *nitric oxcide* and endothelial function compared to smokers who consumed *low-flavanol green tea* drinks . Likewise in a cohort study by Flammer et al. Comparing the use of *green tea* with a control group in 22 heart transplant patients, with the result that there was a significant increase in vascular function in the intervention group. But these results are also accompanied by a significant decrease in platelet adhesion. [13]

In this article also explained epidemiological data by Kwok et al who conducted a study of 20,951 participants in the European Prospective Investigation into Cancer (EPIC) in Norfolk found that participants with the most *green tea* consumption (15.6-98.8 gr / day) had a significant risk lower risk of stroke (0.77, 95% CI 0.62 - 0.96) and death due to cardiovascular problems (HR 0.75, 95% CI 0.62 - 0.92) compared to those who did not consume chocolate during this period. [13]

Epicatechin, the major flavanol monomer in *green tea* , seems to be a major element of the "protective" effect in *green tea* . Flavanol - especially epicatechin - can be absorbed easily and the plasma concentration will increase in about 2 hours. [14]

Research Grassi et al. Gave 100 grams of *green tea* (% Green Tea is unknown) or *white green tea* will do an *oral glucose tolerance test (OGTT)* . After 7 days *washout* , the treatment was exchanged for each group. Compared to samples using *white green tea* , samples that used *green tea* showed an increase in blood vessel dilatation ($p = 0.03$) and decreased concentrations of pro-astherosclerotic and pro-inflammatory cytokines endothelin-1 and 8-iso-PGF2a ($p > 0.05$) after OGTT. This study demonstrates the ability of *green tea* to protect vascular function after metabolic damage due to glucose, which can cause cellular damage through various *pathways* that are centered on mitochondria, and can ultimately increase oxidative stress. [13]

Green tea as an ingredient in tea , although not as high as the level in coffee, contains *methylxanthine* in doses that may not be enough to activate the nervous mechanism. However, *green tea* has a component that is similar to theobromine which has a positive effect on the human pathology system. The combination of caffeine and theobromine in *green tea* has the effect of *methylxanthine* derivatives that function as *adenosine receptors blockers* and can help the brain in "disrupting" the effect of adenosine which must be maintained in a balanced amount. Because the body will naturally send a "sleepy" signal if the levels of adenosine increase. [10]

3.4 Green tea and preeclampsia

Various hypotheses regarding the cause of *preeclampsia are* associated with endothelial dysfunction which ultimately explains the presence of hypertension i and proteinuria in patients with *preeclampsia* .

A randomized control trial conducted by Di Renzo et al (2008) showed that the intervention group given 30 grams of chocolate (70% cacao) per day at 11 and 13 weeks' gestation was significantly systolic (F 1,594 = 31.60, p <0.0001) and lower diastolic when compared to the control group, although for diastolic pressure the strength was weak (F 1.594 = 4.13, p = 0.0426). Similarly, glycemic levels were lower in the intervention group (t = 3,248, p = 0.002). Similar results occurred in the level of *liver enzymes in* the intervention group which remained significantly low (p <0.05). But no gestational hypertension was reported in either group. [11]

Studies on the effect of *preeclampsia* especially *green tea* on PE cases are still limited. Most studies link cacao to hypertension cases in general, but this can be a preliminary study for PE cases.

In December 2013, Mogollon et al published a *review* with the aim of analyzing the relationship between chocolate consumption and prevention of PE. The hypothesis of this *review* is that consumption of chocolate with high levels of flavanols can reduce the risk of PE. The *review* emphasizes that a therapeutic approach that focuses on the presence of *nitric oxide* (NO) can be useful in preventing PE. It is known that the flavanols contained in *green tea* are potential antioxidants in causing *NO-dependent* vasodilation . [6.9]

Two *randomized control trial* meta-analyzes state that chocolate rich in flavanols has a beneficial effect on endothelial function and reduces systolic and diastolic blood pressure. [6]

Magollon also conducted his study (2009) about the relationship between *flavanol-rich chocolate* and blood pressure and endothelial function in healthy pregnant women. In this study the sample was divided into two groups with different interventions. Group A was given *green tea* (20 gr) with a composition of flavanol 400 mg, catechin + epicatechin 64 mg, caffeine 23.6 mg and theobromine 150 mg. Group B was given chocolate with the composition of flavanol <60 mg, catechin + epicatechin 14 mg, caffeine 23.6 mg and theobromine 150 mg.

Compared to group B, plasma epicatechin concentrations increased significantly in group A within 180 minutes after the intervention. After 12 weeks, epicatechin and catechin concentrations were too low to be detected. *Methylxanthine* concentrations were significantly higher in 180 minutes in both groups. More specifically, an increase in theobromine plasma concentration was significantly seen in both groups, but was slightly more noticeable (but significant) in group A at 6 and 12 weeks. A slight difference was seen in the two groups after 12 weeks (p = 0.03).

Although still within normal limits, diastolic pressure increased significantly after 6 and 12 weeks in group B, but the difference in the two groups was not significant. [8]

Pro-inflammatory s Itokin, *chemokines* , and adhesion molecules into potential mediators on endothelial dysfunction in PE. Various studies found that these three elements are more common in PE compared to normal pregnancies. This indicates the existence of a systemic *pro-inflammatory* environment in PE. [5]

Interleukin-6 (IL-6) in the pathogenesis of PE is a major *pro-inflammatory* cytokine that produces a variety of immune and non-immune cells. Adhesion molecules play a role in the adherence of

leukocytes to endothelial cells and their migration to the perivascular tissue. Soluble forms of molecular adhesion can be detected in plasma and their concentration indicates activation of certain cells. Increased levels of sVCAM-1 indicate endothelial cell dysfunction. [5]

Several studies have shown that cacao extract can reduce the *pro-inflammatory* regulation of cytokines along with the regulation of *biochemical* pathways. Among the studies conducted by Rahayu et al to find out whether cacao seed extract can reduce IL-6 and sVCAM-1 in endothelial cells in plasma of PE patients stated that the increase in IL-6 and sVCAM-1 can be attenuated by the cacao seed extract.

This shows that cacao extract can inhibit the increase of IL-6 and sVCAM-1 in endothelial PE cells. [5]

Nictric Oxide (NO) is a molecule that acts as an *endothelial relaxation factor* . In normal pregnancy there is an increase in NO bioaviability, which functions for maternal vasodilation. This process will facilitate circulation with high volume without hypertension. Whereas in PE, there is a weakness in this process. Besides NO, endothelin-1 (ET-1) also plays a role in the urgency of hypertension in PE. [15]

Barokah et al divided Endothelial Cells (EC) samples into 6 groups to find out whether T.Cacao (TC) extract can modulate NO and ET-1 levels as markers of endothelial dysfunction in EC in plasma PE patients. Inhibition of the process of decreasing NO in the sample with TC extract treatment with all doses (25; 50; and 100 ppm) ($p < 0.05$). Whereas there was a significant increase in ET-1 level in plasma EC samples from PE patients which was significantly inhibited by TC extracts at all doses ($p < 0.05$).

Reading these results, it can be concluded that T. cacao extract can increase NO and reduce ET-1 levels in endothelial cells in PE patients. [15]

So far, research on *green tea* and its relationship with preeclampsia is still very limited. With a sweet chocolate flavor that tends to be somewhat bitter, it needs to be studied further about the side effects that arise due to the unusual taste. In addition, further observations regarding the right dosage and time period for consuming *green tea* to be effective against PE prevention are also needed.

In brief, a study of the content of *green tea* on PE can be illustrated as follows:

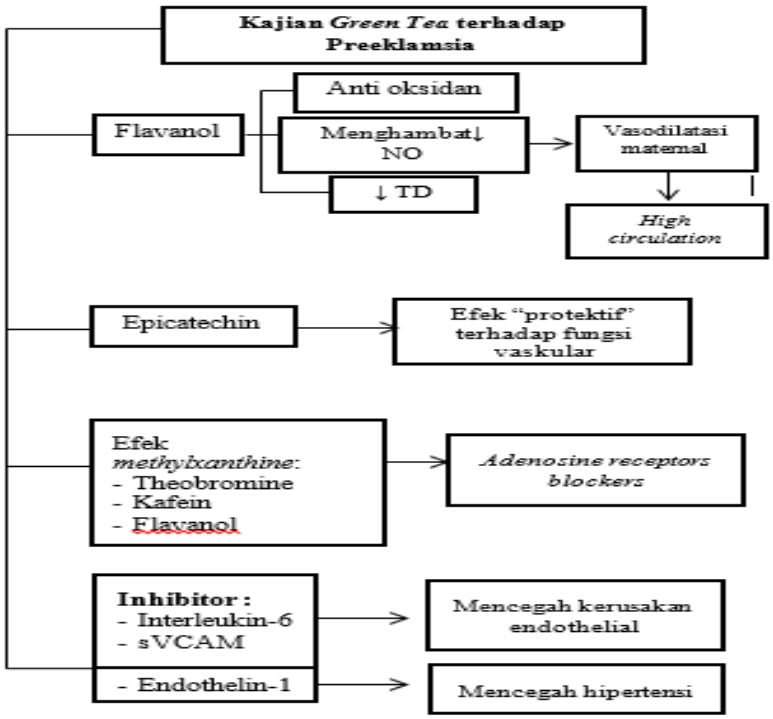

Fig 2. Study Of The Content Of *Green Tea* On PE

4 Conclusion

With a variety of ingredients in *green tea* that gives a positive influence on the incidence of preeclampsia, *green tea* can be considered as an alternative prevention or treatment of preeclampsia.

Lack of studies to determine the extent of the effect of *green tea* on Preeclampsia makes the literature about it limited, especially regarding the dose of *green tea* administration to be effective.

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