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Utilization of mangosteen peel extract (*Garcinia Mangostana* Linn) as an alternative control of endothelial cell degeneration in pregnant mice with hypertension

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Abstract
Background: Maternal Mortality Rate (MMR) in Indonesia is still quite high and ranks second in Southeast Asia, this shows that there is an increase in maternal health problems. One of the highest causes of maternal and fetal mortality and morbidity is the result of hypertension. Besides hypertension is caused by oxidative stress which triggers the emergence of free radicals in the body of pregnant women. Compounds that can prevent or inhibit damage caused by free radicals are antioxidants. Fruits contain a lot of antioxidants, one of which is mangosteen peel, because mangosteen peel has a very high antioxidant content that exceeds vitamin E and vitamin C which has been known as the highest antioxidant.
Objective: Knowing the use of mangosteen peel extract (*Garcinia Mangostana* Linn) as an alternative to controlling endothelial cell degeneration in pregnant mice with hypertension.
Method: The type of research used is Tru-Experimental with Posttest only control group design. This study arranged five groups: three treatment groups were given mangosteen peel extract at doses of 100 mg, 200 mg and 300 mg, while the two control groups were mice that were normal pregnant without treatment and pregnant mice with hypertension without treatment. Technique Probability sampling with method simple random sampling is used to obtain 25 mice (Musmuculus) were divided into five groups of 5 mice each.
Results: The test results One Way Anova and Post hoc Multiple Comparisons showed a p value = 0.000 which means that there was an effect of giving mangosteen peel extract (*Garcinia Mangostana* L) to Malondialdehyde (MDA) levels in pregnant mice with hypertension.
Conclusion: Mangosteen peel extract (*Garcinia Mangostana* L) at doses of 100 and 200 mg/Kg weight /day given for 10 days can affect oxidative stress (MDA) in mice (Mus Musculus) pregnant with hypertension model.

Keywords: mangosteen peel extract (*Garcinia Mangostana* Linn), endothelial cell degeneration, pregnant mice, hypertension

1. Introduction
Maternal Mortality Rate (MMR) in Indonesia is still quite high and ranks second in Southeast Asia. From the 2012 IDHS data, the maternal mortality rate (MMR) of 359 / 100,000 live births is more than the results of the 2007 IDHS, which stands at 228 / 100,000 live births. While the target of MDG'S reduction in Maternal Mortality Rate (MMR) in 2015 was 102 / 100,000 live births, this has not been achieved, and currently has been announced again in SDG'S regarding the achievement target of reducing Maternal Mortality Rate (MMR) in 2030 by 72 / 100,000 live births, where one of the goals of SDG'S is to ensure a healthy life and improve well-being for all ages. Maternal Mortality Rate (MMR) in Central Java Province in 2014 was 126.55% / 100,000 live births, and in 2016 109.65% / 100,000 live births were caused by 27 circulatory disorders, 08, bleeding as much as 13.29%, metabolic disorders as much as 0.33%, infections as much as 4.82% and 33.22% due to others. This shows that there is an increase in maternal health problems [1, 2]. One of the highest causes of maternal and fetal mortality and morbidity is the result of hypertension. Hypertension in pregnancy is 5-15% complicating pregnancy. In cases of pregnancy with hypertension, preeclampsia syndrome, both isolated and overlapping with chronic hypertension, is the most dangerous. Impacts for pregnant women with hypertension are at greater risk of experiencing placental abruption and preeclampsia. Meanwhile, the impact on the fetus / neonate is an obstacle to fetal growth. The cause of hypertension in pregnancy until now has not been clearly known. Many theories have been put forward about the occurrence of hypertension in pregnancy, but none of the theories is considered absolutely correct. Current theories widely adopted are theories of placental vascularization abnormalities, placental ischemic theory, free radicals and endothelial dysfunction, theories of immunologic intolerance between mother and fetus, theories of genetic cardiovascular adaptation, theories of nutritional deficiency, inflammatory theories [3, 4]. Abnormal development of the placenta (infarction, sclerosis) can cause placental insufficiency resulting in the release of some placental material into the maternal circulation, this can cause endovascular cytotrophoblast changes. This change was accompanied by a failure in the remodeling of the spirals and the decidua basalis, so that utero placental circulation could be disrupted. With this disturbance the activation of nitric oxide synthase decreased, causing oxygen flow through the placenta to be low, this could lead to free radicals and reactive oxygen species of development. increased, if this continues it can result in chronic inflammation in the placenta. Endothelial cell degeneration can occur because the process of inflammation can release cells that have died and inflammation factors in the arteries, besides that apoptosis will continue to occur, free radicals,

lipid oxides and cytokines are released, this can cause vasoconstriction and increased blood pressure [5, 6]. Heper tensi is often accompanied by systematic disorders including protenuria, impaired liver function and pulmonary swelling. In addition, there are also symptoms of cerebral disorders such as seizures and visual disturbances originating from pathological changes in maternal endothelium vascularization resulting in endothelial dysfunction in the placenta, where there is endothelial dysfunction. is that endothelial cells cannot adapt adequately to stimulation, this is due to exposure to inflammatory cytokines and increased expression of VCAM-1 resulting in oxidative stress [7, 8]. In conditions of oxidative stress there will be an increase in the production of lipid peroxidation which is thought to play an important role in causing impaired endothelial function so that endothelial cell degeneration can occur. The increase in lipid peroxidation can be measured by various measurements of blood lipid peroxidation markers, one of which uses Malondialdehyde (MDA) which has been recognized as a clinical marker of lipid peroxidation [9]. Compounds that can prevent or inhibit damage caused by free radicals by working to bind the activation of free radicals and bypass the chain of oxidation reactions caused by free radicals are antioxidants, so antioxidants are needed by the body, especially in pregnant women.[8] Free radicals play a key role in oxidative stress in hypertension, because in high concentrations radicals form oxidative stress. Free fatty acids and cell membranes when attacked by free radicals will produce lipid peroxide, this can result in endothelial dysfunction and increased sensitivity to vasopressors in hypertension, causing free radicals can develop sustainably in all cells during normal aerobic metabolism [5, 6, 10]. Oxidative stress in hypertension is controlled by administering antioxidants and anti-inflammatory drugs. Fruits contain lots of antioxidants. Jowet fruit (syzygium cumimi) contains anthocyanin, phenolics and polyphenols as antioxidants that have been studied to reduce the expression of VCAM-1 in preeclampsia [7]. Mangosteen peel has the same content as jowet fruit where mangosteen peel contains anthocyanin, phenolics, and the typical polyphenols, xanton [11, 12]. The results of the research of several other researchers stated that mangosteen rind can function as cardiotonic, anti-inflammatory and antioxidant in the body, on mangosteen skin there is a very high antioxidant content exceeding vitamin E and vitamin C which has been known as the highest antioxidant. Antioxidants also work specifically on the central nervous system and can eradicate cell-damaging free radicals in the body, this can inhibit degeneration (damage) of body cells [5, 6, 13]. From the description above, a study was carried out on the use of mangosteen peel extract as an alternative to control endothelial cell degeneration in mice (Mus musculus) pregnant with hypertension. In this study using experimental animals namely mice (Mus musculus) because research with human placental samples cannot be done related to ethical issues, there are other considerations also that these animals have the advantage that regular estrus can be detected, pregnancy is short and has many children, has the ability to adapt life to the environment and have genetic similarities with humans so that it is expected to be used as a comparison in humans [8, 14].

2. Methods

This type of research uses an experimental research design (True Experiment) with a posttest only control group design. Researchers arranged five groups consisting of three treatment groups and two control groups. In the first treatment group was given mangosteen peel extract at a dose of 100 mg / Kg weight / day, the second treatment was given mangosteen peel extract at a dose of 200 mg / Kg weight / day and the third treatment was given mangosteen peel extract at a dose of 300 mg / Kg weight / day, while the two groups control was not given mangosteen peel extract. The administration of mangosteen peel extract was carried out for 10 days, after which the were measured levels of Malondialdehyde (MDA) in the treatment and control groups. Then do a comparison of the five groups in both the treatment group and the control group. Measurement oflevels was Malondialdehyde (MDA) carried out at the Anatomical Pathology Laboratory of Gadjah Mada University (UGM) in Yogyakarta using a spectrophotometer and a microscope digital. The population in this study were mice (Musculus normal pregnant) obtained from the Anatomical Pathology Laboratory of Gadjah Mada University (UGM) as a place for the maintenance of test animals. Determination of the minimum sample size using a technique probability sampling with a method simple random sampling and is based on inclusion and exclusion criteria of 25 mice (Mus musculus) divided into five groups namely 15 mice (Mus musculus) in the treatment group and 10 mice (Mus musculus) in the group control with 5 mice each group. In this study, researchers conducted data collection by observation, identification and filling in the observation sheet. The collected data was analyzed through the IBM SPSS program version 24.0, and continued with a different test, namely the parametric (test One Way Anova test andtest Post hoc Multiple Comparisons). The processed data is used as a basis for discussing statement matters, which are then presented in tabular form so that conclusions can be drawn.

3. Results

Table 1: Frequency distribution MDA levels of (Malondialdehyde) pregnant mice in the treatment group and control group

No.	Group	Sample	Amount of Melondialdehyde (MDA)	Minimum MDA level (nmol / ml)	Maximum MDA level (nmol / ml)
1	K (-)	K(-).1	38	38	80
		K(-).2	40		
		K(-).3	54		
		K(-).4	46		
		K(-).5	50		
2	K (+)	K(+).1	136	80	110
		K(+).2	114		
		K(+).3	116		
		K(+).4	132		

		K(+).5	115		
3	P1	P.1.1	78	44	80
		P.1.2	77		
		P.1.3	89		
		P.1.4	74		
		P.1.5	82		
4	P2	P.2.1	72	40	64
		P.2.2	71		
		P.2.3	69		
		P.2.4	70		
		P.2.5	68		
5	P3	P.2.1	67	63	100
		P.2.2	64		
		P.2.3	63		
		P.2.4	69		
		P.2.5	60		

Description: K (-) (negative control group), K (+) (positive control group), P1 (treatment group 1), P2 (treatment group 2) and P3 (treatment group 3).

Based on the table above, the results of the study showed the amount of Malondialdehyde (MDA) maximum in pregnant mice with hypertension, namely in the positive control group (+) of 110 nmol / ml, while the minimum MDA levels in pregnant mice with hypertension were found in the positive control group that was as much as 38 nmol / ml.

Table 2: Analysis differences in the amount of Malondialdehyde (MDA) in pregnant mice with hypertension between the treatment group and control group

No	Groups	p value	p value (PH Test)
1	K(-) (Negative control group)	0.000	K(-) against K(+) with pvalue 0.001 K(+) against P1 with p value 0.015 K(+) against P2 with p value 0.001 K(+) against P3 with p value 0.240
2	K(+) (Positive control group)		
3	P1 (Treatment group 1)		
4	P2 (Treatment group 2)		
5	P3 (Treatment group 3)		

* P value and Pos Hoc Tests: significant (<0.05)

Based on the table above, it shows that there is an effect of giving mangosteen peel extract (*Garcinia Mangostana* L) to Malondialdehyde levels (MDA) in pregnant mice with hypertension, this is evidenced by the results of p value 0,000 (p<0.05).

4. Discussion

4.1. Analysis difference in the amount of Malondial dehyde (MDA) in pregnant mice with hypertension between the treatment group and control group

Measurement of average Malondialdehyde levels (MDA) after administration of mangosteen peel extract at different doses to 3 groups for 10 days resulted in a significant effect on the treatment group where there were significant differences between the treatment groups. The lowest average number of measurements of melondialdehyde of mice in the intervention group based on Table 3 is shown by the treatment group K (-) against K (+) with p value 0.001, K (+) against P1 with p value 0.015, K (+) against P2 with p value of 0.001. While on K (+) with respect to P3 with a p value of 0.240 it means that it is not significant.

The results of this study indicate that the intervention group (P1) and intervention (P2) have an effect on reducing MDA levels in pregnant mice with hypertension, this is because in the mangosteen peel extract it has antioxidant content which we know that antioxidants play an important role in preventing radicals free so that it can reduce levels of MDA. The ability to reduce levels of MDA is thought to be from the content of flavonoids and phenols [15, 16].

Flavonoids are phenolic components found in fruits, vegetables that act as good reservoirs against hydroxyl radicals and super oxides, by protecting membrane lipids against damaging oxidation reactions. Flavonoids, peliphenol and tannins are compounds that function as antioxidants because the three compounds are phenol compounds, which are compounds with the -OH group attached to carbon aromatic rings, functioning as effective antioxidants. The free radical products of these compounds are resonant stabilized and are therefore not reactive compared to most other free radicals. Apart from the flavonoid compounds there are also alkaloid compounds and saponin which are also allegedly having activity in reducing MDA levels. Alkaloid compounds can act as free radical scavengers and can prevent lipid peroxidation in microsomal hepatic. Alkaloid compounds, especially indols have the ability to stop free radical chain reactions efficiently [17, 18]. The results of the study in the treatment group (P1) and (P2) with doses of 100 and 200 mg / KgBB / day, respectively, have significant effects on decreasing levels of Malondialdehyde (MDA), then in further analysis to see between the two doses, dosage which one has a stronger effect on decreasing levels of Malondialdehyde (MDA) and results at a dose of 100 mg / KgBB / day which has a stronger effect. This is in line with previous research which states that antioxidants with ideal doses are very optimal to inhibit the process of lipid peroxidation which has been statistically tested to reduce oxidative stress, where the flavoniod compounds contained in mangosteen peel are included in the group of phenol compounds found in almost all plants having negative effects as well so that allegedly cannot be used in large quantities [19, 20].

Oxidative stress is a condition of imbalance between the production of free radicals and antioxidants in the body so that it will trigger pathological conditions such as

inflammation, inflammation, cardiovascular disease, neorogenerative and cancer [22]. Free radicals also cause cell death through the process of apoptosis by stimulating the release of cytochrome c and then activating the caspase 3. Malondialdehyde (MDA) is one of the most commonly used indicators of lipid peroxidation, Malondialdehyde (MDA) is also a lipid peroxidation product a constant relative to the proportion of lipid peroxidation, therefore is an appropriate indicator for measuring the level of oxidative stress. Free radicals play a key role in oxidative stress which can cause endothelial dysfunction in preeclampsia [8, 21].

5. Conclusion

Based on the results of research and discussion that has been described related to the influence of mangosteen peel extract (*Garcinia Mangostana* L) on the amount of Malondialdehyde (MDA) andarterial diameterof Malondialdehyde (MDA) andarterial diameter villi chorialisvilli chorialiscan be formulated several conclusions, namely: can be formulated several conclusions, namely:
Mangosteen peel extract (*Garcinia Mangostana* L) with a dose 100 and 200 mg / kg weight / day given for 10 days can affect oxidative stress (MDA) in mice (Mus Musculus) pregnant with hypertension model.

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