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Antifertility effects of mangosteen peel extract (*Garcinia Mangostana L*) on the amount, diameter and layer thickness of the Teka *Folikel De Graaf*

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Abstract
Background: Mangosteen peel extract is a drug that has been widely consumed with various products and various dosage forms by many women because it has been believed to have benefits that can cure various diseases. The study of the administration of ethanol extract of papaya seeds can reduce the number of tertiary follicles and de follicles in which the ethanol extract of papaya seeds has some of the same compounds with mangosteen peel extract but there is no study of mangosteen peel extract against female reproductive folliculogenesis processes. The final process of folliculogenesis is producing de graaf follicles where de graaf follicles play an important role in the pregnancy process.
Objective: To determine the effect of mangosteen peel extract on the number, diameter and thickness of de graaf theca follicular layer in female mice.
Methods: Experimental studies with post-test only with control group design were carried out in 20 female mice which were divided into 4 groups. Giving mangosteen peel extract for 21 days. Data analysis using ANOVA and continued with post hoc multiple comparisons.
Results: There was no difference in the number and thickness of the deafra follicle theca layer between the treatment groups and there was a difference in the mean diameter of de graaf follicles with a p value of 0.002 ($p<0.05$) after the administration of mangosteen peel extract.
Conclusion: Mangosteen peel extract did not affect the amount and thickness of the theca follicle de graaf layer but had an influence on de graaf follicle diameter in female mice.

Keywords: mangosteen peel extract, folliculogenesis, de graaf follicle

1. Introduction
Mangosteen (*Garcinia Mangostana* L) is a plant that is known as a raw material for the color of food and the textile industry. This fruit is naturally found in Southeast Asia and Indonesia and is endemic to the Malay Peninsula, Myanmar, Thailand, Cambodia, Vietnam and Maluku. Mangosteen has been cultivated in the tropics (for example, India, Honduras, Brazil, and Australia) for the past two centuries. This species thrives in warm, humid, or tropical climates. Thailand is the world's main producer of mangosteen, producing around 240,000 trees every year. Different parts of mangosteen like bark, fruit skin or pericarp, and roots have been used for hundreds of years as medicine. Mangosteen peel extract contains alkaloids, flavonoids, saponins, triterpenoids, tannins, polyphenols and xantons [1, 2].

Mangosteen rind extract (*Garcinia Mangostana* L) is a drug that has been widely consumed with various products and various dosage forms such as capsules, herbal powders, gels that contain mangosteen rind extract which has been widely circulated in the market and consumed by many women because it is believed to have benefits can cure various diseases. 3 Mangosteen peel extract is also a high level of antioxidants that are most needed by the body to be able to balance prooxidants. Various benefits of mangosteen have been proven by various studies including being used to stop diarrhea and dysentery, cardioprotective, anti-inflammatory, antioxidant, antiallergic, antibacterial, antifungal, cytotoxic, antidepressant, anti- Alzheimer's, and antiglaucoma. Mangosteen has the potential to be used as therapy in cancer treatment and has good potential as an antioxidant preparation. The mangosteen pericarp is an abundant source of natural antioxidants and phenolics including xantons and their derivatives, benzophenone, flavonoids, anthocyanins, and tannins [4, 11].

On the other hand their assessment of the ethanol extract of papaya seeds can decrease the number of tertiary follicles and follicular de graaf onprocess folliculogenesis in which the ethanol extract of papaya seeds have some compounds similar to the mangosteen peel extract such as saponins, tannins and flavonoids. Compounds contained in ethanol extracts of papaya seeds such as Saponin have the effect of causing abortions in farm animals and tannins haveeffects toxic on developing cells such as eggs [12]. flavonoids can disrupt the endocrine system by inhibiting the release of GnRH (Gonadotropin-Releasing Hormone), which causes disruption in the release of FSH (Follicle Stimulating Hormone) and LH (Luteinizing Hormone). FSH and LH play a role in stimulating the ovaries to release the hormones estrogen and progesterone which play an important role in the process of folliculogenesis. End ofprocess folliculogenesis that produces follicle de graaf [13, 14].

From this background, in addition to considering the various benefits of mangosteen peel extract (*Garcinia Mangostana* L) which have been proven for its usefulness, further study is needed regarding the effect of mangosteen peel extract (*Garcinia Mangostana* L) as an antifertility that can

interfere with the process of folliculogenesis. Therefore, this study will analyze the effect of mangosteen peel extract (*Garcinia Mangostana* L) on de graaf follicles by measuring the amount, diameter and thickness of the theca layer.

2. Method

The method in this study uses true experiments with experimental laboratories. Determination of the research sample both the control group and the treatment group were randomly determined using a simple random sampling technique that each element or member of the population has the same opportunity to be selected into a sample which is then divided into 4 treatment groups the total number of mice used in this study is 20 mice divided into 4 groups: 1 control group (mice that were only given food and drink) and 3 treatment groups giving mangosteen peel extract with different doses of 49 mg / 20 grBW, 98 mg / 20 grBW and 196 mg / 20grBW. Providing mangosteen peel extract for 21 days. Data analysis used ANOVA and continued withtest post hoc multiple comparisons.

2.1 How to make mangosteen peel extract (*Garcinia Mangostana* L)

Mangosteen peel extract is obtained from mangosteen peel powder which is the product of superior commodity processed products from the Center for Research and Development of Traditional Medicinal and Medicinal Plants (B2P2TOOT) Tawangmangu Karanganyar Regency, Central Java Province which has obtained a permit products from the local health department and have been consumed by the community.

In this study, mangosteen peel was refluxically extracted, following the mangosteen peel extraction flow can be seen in Figure 2.1.

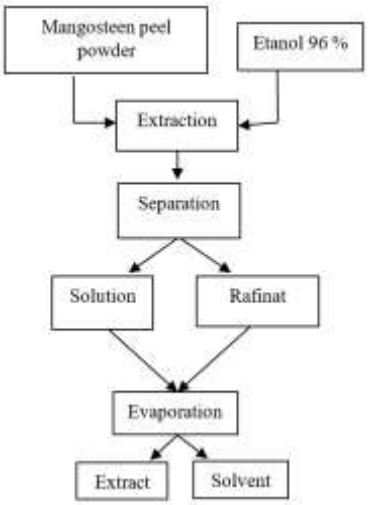

Fig 1: Chart of how mangosteen peel extracts

2.2 Research Design

The design in this study used a post-test only-control design to look for the effect of the administration of mangosteen peel extract (*Garcinia Mangostana* L) on the number, diameter and thickness of the thecalayer follicular de graaf. This study will use 4 groups divided into 1 control group who were given food and drinks only, and 3 treatment groups with different doses of mangosteen peel extract, namely P1 at a dose of 49 mg / 20 grBW, P2 at a dose of 98 mg / 20grBW and P3 at a dose of 196 mg / 20grBW.

2.3 Test Animals

In this study mice were placed in cages made of wire with a size of 30x30 cm. The mice used are female, virgin mice, aged around 3-4 months with a body weight of 20-30 grams obtained from the Laboratory of Biology, Semarang State University (UNES).

2.4 Provision of Test Materials

Provision of mangosteen peel extract by feeding (orally) using a syringe with a blunt tip and given a small rubber pipe given every morning around 09.00 - 10.00 WIB in the treatment group consisted of 4 groups which were divided into control groups ie those that were not mangosteen peel extract (*Garcinia Mangostana* L) and 3 treatment groups were given mangosteen peel extract (*Garcinia Mangostana* L) with different doses of 49 mg / kgWeight as P1, 98 mg / kgBW as P2, and 196 mg / kgBW as P3, where before treatment the test animals are equalized in the estrous phase. The treatment group was given extracts for 21 consecutive days each afternoon.

2.5 Surgery

After mice were treated for 21 days, then termination was done on day 22 of the 4 groups by researchers who were assisted by laboratory assistants with ketamine (100 mg / ml) as much as 0.75 ml with xylazine (20 mg / ml) added 0.75 ml is added again acepromazine (10 mg / ml) as much as 0.25 ml and the last is added aquades water as much as 8.25 ml until the total volume becomes 10 ml where for anesthetic injection intraperitonially at a dose of 0.1 -0, 2 ml / 25 grBW while for euthanasia the dose is given twice the anesthesia dose. After the mice in euthanasia are monitored by observing the eye is still blinking or not when given light stimulation and looks no longer breathing after confirmed mice have died put into a container which is then prepared for surgery on mice to take the ovaries. Ovaries that have been cut are fixed with buffer 10% formalinin a bottle which is then made histological preparations by the paraffin method, 8 µm incision thickness andstaining Hematoxylin Eosin. Ovaries were taken from both right and left ovaries of mice and then given coding and labeling to each group to facilitate researchers and laboratory assistants when making preparations to distinguish between groups.

The preparation process requires up to 15 days. After the process of making the preparations then the ovary preparations that have been made onobjects are glass analyzed to measure the number and diameter and thickness of the theca layer by taking pictures of de graaf follicles using a digital microscope with magnification 10 and 40 times. After taking an image or image of de graaf follicles from each group then an analysis of the number of de graaf follicles in both left and right ovaries was then analyzed the number of follicles using a digital microscope. Determination of the number of de graaf follicles in each sample of female mice was calculated by summing the number of de graaf follicles in both ovaries, left and right.

After analyzing the number of de graaf follicles, then analyzing the diameter of the de graaf follicles in each follicle, where the determination of the average length ofdiameter the de graaf follicle in each group was measured by calculating all the mean lengths ofdiameter the de graaf follicle in each mouse. Determination of the mean lengthdiameter of de graaf follicle is by measuring from the outer layer of the theca cell passing through the same center

to the outer cell layer of the theca cell by measuring on all sides of the de graaf follicle to determine the longest and shortest diameter, then determining the size of the diameter by adding the longest and shortest diameter sizes then the division is obtained the diameter size results, the next step is to measure the thickness of thethickened layer follicle de graaf by measuring the distance of the internal theca layer to the external theca layer of each group, then determine the thickness of the theca layer by adding up the thickness of the layer thickness. The longest and the shortest puzzle is then divided to get the measurement of the thickness of the puzzle layer.

2.6 Data Processing and Analysis Data

processing in this study is in accordance with statistics, starting from editing, namely by checking the results of monitoring / observation sheet that is filled every day during the treatment of mangosteen peel extract given. Coding is changing data in the form of letters into numbers / numbers to facilitate data analysis and entry data continued Cleaning is to check again on the observation sheet that has been filled in and the data that has been entered whether there is an error or not from the results of recording after that Tabulating is to make data in the form of tables to then be processed into frequency distribution data. Then the data that has been obtained is tested for distribution patterns and homogeneity where the data that is normally distributed and homogeneous is tested with ANOVA to find out the differences between treatment groups, if the ANOVA test results show differences between treatment groups then further tests will be carried out with thetest Duncan. However, for data that are not normally distributed and non-homogeneous, atest is performed non-parametric kruskal wallis to determine the differences between the treatment groups and then a further test using Mann-Whitney, all analyzes are carried out with a significance level of 5% (α = 0.05). Then the data is analyzed using a computer program.

3. Results

The reproductive function of female mice has a cycle called folliculogenesis. Folliculogenesis is the process that is responsible for the development of ovulatory follicles and the release of one or more oocytes at certain intervals throughout the reproductive cycle of female animals. The development of follicles starts from primordial follicles which undergo histological and physiological changes into de graaf follicles. Follicles that are easily observable and easily distinguished from other follicles are de graaf follicles because they have a large size compared to other follicles and there are cavities (antrum) of large follicles [15, 16].

Measurement of mean number, diameter and thickness of the thecalayer of de graaf follicle ovarianmice after mangosteen skin extract (*Garcinia Mangostana* L) for 21 days using a digital microscope with magnification of 10 and 40 times. After taking an image or image of de graaf follicles from each group then an analysis of the number of de graaf follicles in both left and right ovaries was then analyzed the number of follicles using a digital microscope. The measurement results are presented in table 3.1.

Table 1: Mean number, diameter and thickness of female mice (Mus Musculus) follicle de graaf lining after follicle mangosteen skin extract (*Garcinia Mangostana* L) for 21 days.

Parameter	Treatment				
	Control	Treatment 1	Treatment 2	Treatment 3	P value
	(Mean±SD)	(((Mean±SD)	(Mean±SD)	(Mean±SD)	
Total *folikel de graaf*.	2.00±0.00	2.20±130	2.00±1.22	1.60±1.32	0.49[a]
Diameter *folikel de graaf* (µm).	222.80±58.01	359.40±61.99	425.20±99.59	379.40±41.35	0.02[b]
Layer thickness teka *folikel de graaf* (µm).	14.00±1.22	14.80±1.30	14.20±3.96	13.95±2.35	0.29[a]

Note: a (Kruskal Wallis Test results), b (Anova Test results).

The mean number of de graaffollicles of ovarianmice in the lowest intervention group based on the table above is shown by treatment group 3 (P3 1.60), and the highest is the treatment group 1 (P1 2.20). These results indicate that treatment group 3 and treatment group 1 have different numbers of follicles. The average difference in the number ofde graaf follicles ovarianin this study can be caused by the development of ovarian follicles that have undergone ovulation because they have reached maturity and have ovulated as for images of follicles found when ready for ovulation are shown in Figure 3.1. that is.

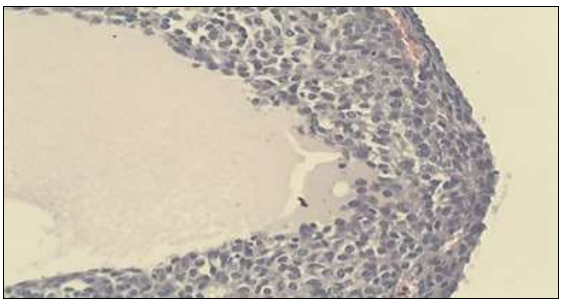

Fig 2: de graaf follicles ready for ovulation.

An example of the measurement results of the number of de graaf follicles is shown in Figure 3.2.

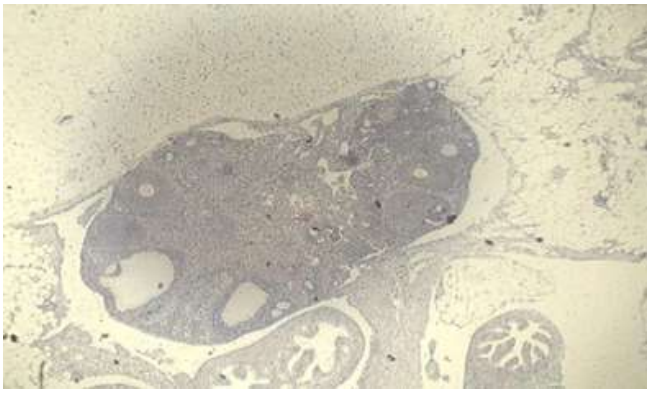

Fig 3: Calculation of the number of follicles de graaf

4. Discussion

Saponin content in mangosteen peel extract was also not proven to interfere with the process of folliculogenesis as mentioned in previous studies regarding the antifetility

effect of saponin compound content has a mechanism of damaging cell membranes by increasing permeability resulting in cell leakage followed by interacellular material release. Saponins form complex bonds with membrane sterols. Sterol membrane that has been bound will be separated from the cell membrane, causing interference with ion transport and cell membrane permeability. This causes the cell to rupture so that it can cause a significant decrease in the number of de graaf follicles [15, 16].

The mean mean number of follicular de graaf in this study can be assumed to have the same amount in this treatment group because of the content of xanton compounds in mangosteen peel extract (*Garcinia Mangostana* L) which is an antioxidant. Antioxidants are electron-giving compounds (donor electrons) or reductants. This compound has a small molecular weight, but is able to inactivate the development of oxidation reactions, by preventing the formation of radicals. Antioxidants are also compounds that can inhibit oxidation reactions, by binding to free radicals and highly reactive molecules. As a result, cell damage can be inhibited so that the de graaf follicles can develop better so as to make the egg mature according to the reproductive cycle so that the average difference in the number of de graaf follicles has no significant effect as evidenced by the results of the Kruskal Wallis Tests 0.49 (p value>0.05) which means there is no effect of mangosteen peel extract (*Garcinia Mangostana* L) on the number of follicles de graaf [14, 15, 16, 20].

Accurate assessment of follicular diameter size is important because the timing of oocyte (egg cell) maturation and subsequent egg collection is based on the principle that follicles are more likely to contain mature oocytes when they have large diameter sizes, egg maturity depends on many factors that cannot be explained in detail. In the oocyte follicle are coated granulosa cells and theca layers to maintain nutrition and egg maturity by providing metabolic functions, hormones and growth factors. Based on the above description follicle diameter is the factor that is rated and can be visualized during the procedure so that the research can be used in assessing the maturity of the oocyte nucleus, where the maturity of the oocyte nucleus has an impact on the process of conception(fertilization).

The mean size ofdiameter follicular de graafof lowesteach group was in the control group (K1) 222.80 µm and the highest mean was shown by treatment group 2 (P2) 425.20 µm. An example of the measurement results of the diameter of the de graaf follicle is shown in Figure 4.1.

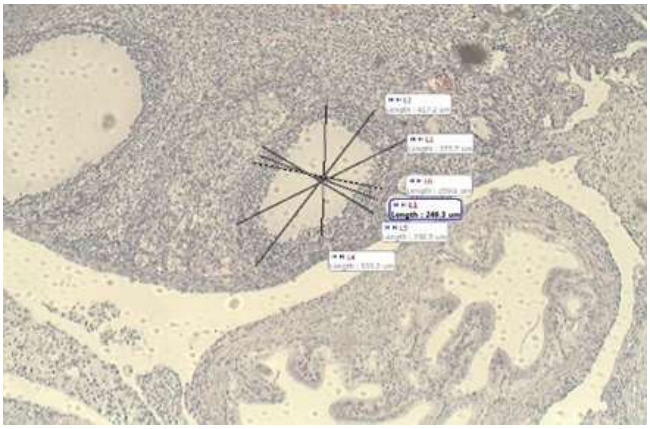

Fig 4: Example of the measurement resultsdiameter of de graaf follicle

Based on these results, it can be assumed that the exposure of mangosteen peel extract (*Garcinia Mangostana* L)influences the size ofdiameter the de graaf folliclesignificantlyas evidenced by thetest results Anova showing that the size ofdiameter the de graaf follicle there is a significant difference wherevalue p 0.002 (p<0,05) so it can be assumed that no effect of mangosteen peel extract(GarciniamangostanaL)to the diameter of follicles degraaf. The results showed that administration of skin extract of mangosteen (Garcinia Mangostan L) with a range of doses that have been tested on a low dose to a high dose in mice significantly influence thediameter folliclede graaf this is due to the provision of antioxidants from skin extract of mangosteen(*Garcinia Mangostana* L) allegedly can repair cell damage in the ovary caused by other toxic compounds while in the ovary so that it does not interfere with the processes that occur in the ovary, including does not interfere with the process of folliculogenesis, instead repairing cells so that the support of oocyte nucleus to become mature [16, 20, 24].

Besides the flavonoid content, in addition to being a cytotoxic material, it can also be used as an ingredient that can help restore ovarian work where the ovary works as a place for egg production. In this study kult mangosteen extract (*Garcinia Mangostana* L) caused the mean diameter of de graaf follicles to grow larger when compared to the control group from 222.80 µm to 425.20 µm at the first dose intervention where the follicle was more likely to contain mature eggs when has a large diameter, and the maturity of the egg is crucial in the success of the fertilization process.

The mechanism of flavonoids in treating ovarian dysfunction is by inhibiting oxidation reactions caused by compounds containing toxins that enter the body. Flavonoids also inhibit oxidation reactions by acting as an antidote to free radicals so as to protect lipid membranes from various damaging reactions so that they cannot cause damage to the reproductive organs and other organs that are interrelated so as to maintain the function of the ovaries for the process of folliculogenesis and other reproductive organs. in the body.[24 An] example of the measurement results of the thickness of the thecalayer thickness is follicle de graaf shown in Figure 4.2.

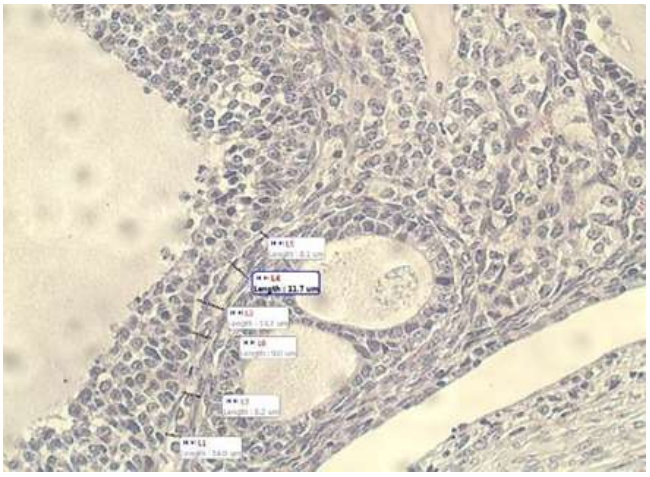

Fig 5: Example measurement of the thickness of the thecalayer thickness follicle de graaf.

The mean thickness of thelayer of de graaf follicle mice of the ovarianmice is as follows K1 (14.00 µm), P1 (14.60

μm), P2 (14.20 μm) and P3 (13.00 μm). These results indicate the mean thickness of the puzzle layer between treatment groups has a number that is not much different. Based on this, it can be assumed that the exposure of mangosteen peel extract (*Garcinia Mangostana* L) does not affect the thickness of the follicle de graafevidenced by the results of the kruskal wallis testthickened layer ason the thickness of the thecalayer thickness follicle de graaf showing insignificant resultsp value 0, 29 (p> 0.05) which means that there is no effect of giving mangosteen peel extract (*Garcinia Mangostana* L) in the treatment group.

The results showed the mean thickness oftheca layer the de Graaf follicular in all treatments ranged from 13.00-14.00 μm. These results indicate that the thickness oftheca layer is the de Graaf follicular not much different from the control group, thus the mangosteen peel extract given does not affect the thickness ofthecalayer thickness of the de Graaffollicle female mice. Previous research stated that the decrease in thickness of the theca layer is caused by asiatic acid. Asiatic acid is part of the triterpenoid that causes apoptosis in cells by damaging the mitochondria of the cell so that the theca layer is depleted. Impaired secretion of FSH and LH also causes thinning of the theca layer due to disruption of follicular development. The proliferation and differentiation of the theca layer is also influenced by several other factors, namely Insulin, IGF (Insulin-like Growth Factor), SCF (Stem Cell Factor), GDF9 (Growth Differentiation Factor 9) and KGF (Keratinocyte Growth Factor). Based on this, it is thought that the compounds contained in mangosteen peel extract did not affect the proliferation and differentiation factors of the theca layer, so the treatment of the mangosteen kult extract could not affect the thickness of the thecalayer follicular de Graaf.

5. Conclusion

The results of the study related to the antifertility effect of mangosteen peel extract (*Garcinia Mangostana* L) on the amount, diameter and thickness oflayer the de graaf follicular showed no effect of mangosteen peel extract on the amount and thickness of the mangosteenshell layer follicular but there was an influence of mangosteen peel extract on the diameter follicles de graaf, so it needs further study related to the effect of mangosteen peel extract on other variables related to theprocess folliculogenesis.

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