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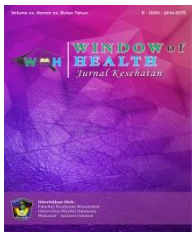

ARTICLE RESEARCH
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The Effect of Aloe Vera Tea on Constipation Management And Safety of Fetal Growth

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ABSTRACT

Constipation is one of the 60% of gastrointestinal discomforts in pregnancy. WHO (2018) states that 11-38% of pregnancies will experience constipation. It takes laxative substances that stimulate peristaltic movement of the intestinal wall, such as aloe vera. However, it contains a teratogenic component for pregnant women, namely aloin. The study aims to determine the effect of aloe vera tea as a treatment for constipation and test fetal weight growth's safety during organogenesis. Methods: This research is an experimental study, a laboratory pre-clinical study using a pre-post test randomized control group design in-vivo method. Against 24 pregnant mice constipated by induced oral extract of gambier 1 ml. Results: The control group intervention (Dulcolax 0.1 ml/20grBB) had a higher mean frequency than the aloe vera tea treatment. The results of the ANOVA test of 0.013<0.05 showed a significant difference between the four groups after five days. The category of the fastest onset of action of laxatives was shown in K3 (aloe vera tea dose of 0.2gr/20grBB) at 03:08 minutes compared to the control group (Dulcolax 0.1gr/20grBB) at 04:35 minutes. The ANOVA test of 0.000<0.05 showed a significant difference between K1, K2, K3 and K4. Based on the weight of the fetuses from the four groups was not significantly different (0.764>0.05). Conclusion: Dulcolax 0.1 ml and aloe vera tea 0.2gr/20grBB effectively increased the frequency of defecation in mice. Aloe vera tea 0.2gr/20grBB was very effective, with the fastest onset of laxative action compared to the control group. Aloe vera tea affects fetal growth in the form of a decrease in body weight at the highest dose of 0.4gr/20grBB. Suggestion: A dose of 0.2 grams of aloe vera tea is recommended to be converted to a human dose as an effective measure for treating constipation in pregnant women.

Keywords: Aloe vera; Aloin; Constipation; Fetus; Laxatives

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INTRODUCTION

Constipation is one of the gastrointestinal discomforts in pregnancy, 60% of pregnant women experience it, especially in the first and third trimesters. Ojieh (2012) defines constipation as difficulty emptying the intestines, slow peristalsis, and dry feces in the descending colon that accumulate due to excessive fluid absorption. [1] Based on WHO (2018), 11-38% of all pregnancies will experience constipation. Only 43.5% can be resolved, and the remainder will continue into the postpartum period. It is estimated that 27% of pregnant women experience constipation in the first trimester, 19.6% in the second trimester, and 41.8% in the third trimester. [2] The risk of constipation is greater if you have a previous history of constipation. [3] The incidence of constipation in pregnant women in Indonesia is 20-35%, with the prevalence reaching around 2-4%. [4]

Pregnancy constipation is classified as functional constipation. Therefore, many pregnant women allow it to continue, resulting in complications during labor and postpartum. [5] Pregnancy has an impact on anorectal function, especially the effect of hormones on intestinal motility, physical pressure on the intestines by the uterus, level of physical activity, diet patterns, increasing fetal growth, less than perfect defecation position and posture, causing delays in the digestive system. [6] Laxatives are substances that stimulate the peristaltic movement of the intestinal wall by increasing water in the lumen of the small intestine, which causes the stool to expand and become softer. [7] Some plants that can be used to treat constipation are those that have laxative activity. [8]

Practically speaking, laxative substances are easily found in the community or are known as laxatives. Traditional medicine has been proven empirically, one of which is aloe vera. According to SW Hong (2020), Many types of plants have been identified as having a laxative effect. Still, aloe vera is the most effective plant in treating constipation, with the shortest activation period, 1-3 hours. [9] The laxative effect of aloe vera is more easily absorbed and stronger than other herbs, including senna, cascara, or rhubarb root. [10] However, aloe vera contains teratogenic components for certain groups that are less publicized, namely " *aloin.* " [11] Aloin is a cytotoxic compound that can stimulate contractions and severe stomach cramps and inhibit the growth and development of cells or the fetus, so it is not recommended for pregnant women, breastfeeding mothers, and women during menstruation. [12] Onainor (2019) stated that the mildest form of the effects of a dangerous compound is a decrease in the weight and body length of the fetus compared to congenital malformations and death. [13] . Because fetal growth parameters are sensitive enough to determine the effect of toxic compounds, it is characterized by a decrease in weight. [14,15] Aloe vera will be harmless, or without teratogenic effects for pregnancy and lactation as long as the "aloin" content in the latex layer has been removed by processing. [16] Aloe vera is one of the plants that can be developed into herbal tea products. The presence of preparations in the form of tea is an excellent opportunity for pregnant women to get the good benefits of aloe vera. Making aloe vera tea products takes a long process, including removing the yellow sap (latex).

The benefits of using aloe vera as a constipation medicine for the general public have been widely studied. However, no one has conducted research on the laxative properties of aloe vera tea for pregnant

women. The difference from previous research is the development of aloe vera preparations in tea form has special implications for pregnant women. Health scientists say that the existence of medicinal plants for pregnant women cannot be equated with modern medicine if they have not been tested and only empirical data has been passed down from generation to generation. [17] The implication of this research for midwifery practice is to develop and prove the safety of traditional medicine (aloe vera) in responding to the needs of pregnant women to overcome discomfort (constipation) based on science through research. Therefore, it is important in this research to test the safety of aloe vera tea as a treatment for constipation during fetal growth using pre-clinical (in-vivo) methods in pregnant mice. This research aimed to determine the effect of aloe vera tea on treating constipation and safe fetal growth in pregnant mice *(Mus Musculus. L.)*.

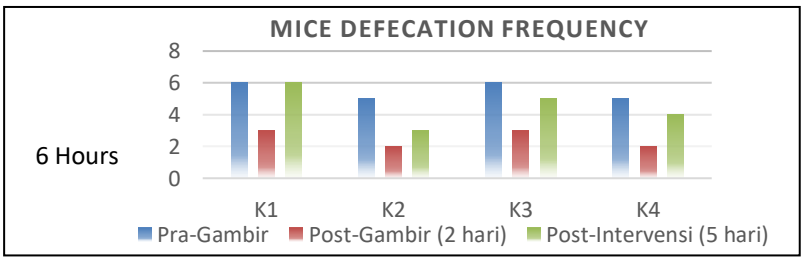
METHOD

Quantitative research True Experimental Pre-Clinical Study Laboratory *Pre-Post Test Randomized Control Group Design* with in-vivo method. They were carried out at the Phytochemical Laboratory of the Faculty of Pharmacy and Entoanimals, Faculty of Medicine, Hasanuddin University on 24 May-17 June 2022. The population in this study were mice *(Mus Musculus.L* .) from the Sudiang golden mice farm, the samples used female mice *(Mus Musculus.L* .) pregnant 24 birds aged 2-3 months weighing 20-25 grams, divided randomly (random sampling) into four intervention groups of 6 birds/group, namely three groups were given aloe vera tea at a dose of 0.1 grams, 0.2 grams and 0 .4 gr while the comparison group was given Dulcolax syrup 0.1 ml/day. The constipation induction agent was influenced by gambier extract 1 ml/head for two days. Constipated pregnant mice were then given the test substance once a day orally for five days at the same time, based on the theory of Yulianadevianti (2017) that providing tea within five days affects treating constipation.

Data collection was carried out by directly observing the frequency of defecation, the start of laxative action, and measuring the fetus's weight (weight and length). Data were analyzed using the one-way ANOVA test, which was presented in the form of diagrams and tables.

RESULTS

The following is a graph and table showing the average frequency of defecation in pregnant mice for 6 hours after being given treatment.



Graph 1 Average Frequency of Defecation in Pregnant Mice in a Time Span of 6 Hours After being given treatment for five days

Information :
K1 : Dulcolax syrup group 0.1 ml/head/day K3 : aloe vera tea group 0.2 gr/head/day
K2 : aloe vera tea group 0.1 gr/head/day K4 : aloe vera tea group 0.4 gr/head/day

Table 1. Mean frequency of defecation in pregnant mice in 6 hours After Being Given Treatment

Group	Average Frequency of Mice Defecation (first 6 hours)			P-value
	Pre-Gambier	Post-Gambir (2 days)	Post-Intervention (5 days)	
K1	6 times	3 times	7 times [a]	
K2	5 times	2 times	3 times [b]	0.033*
K3	6 times	3 times	6 times [a]	0.013**
K4	5 times	2 times	4 times [b]	

Note: [ab] different letter signs indicate different probability values
* Post Hoc test, sig value. Δ Water content of feces post gambier and post intervention
**Oneway Anova test sig value between the four treatment groups

Graph and table 1 show that the average frequency of defecation in mice before being given gambier was 5-6 times and there was a decrease after 2 days of being given gambier water to 2-3 times in the first 6 hours. There was a significant change in the mean frequency after each group was given the test material with a p-value of 0.033<0.05. This shows that there is a real difference in general in the difference in defecation frequency values between before and after being given the test material in constipated mice. Based on the data above, after 5 days of intervention the control group (dulcolax 0.1 ml/20grBB) had a higher average frequency of 7 times in the first 6 hours compared to the other groups. Apart from that, treatment with K2 (aloe vera tea dose 0.2gr/20grBB) had a higher frequency than other aloe vera tea doses. The ANOVA test obtained a probability value of 0.013<0.05, indicating a significant difference between the four groups after being given the test material for five days.

Average Working Start of Test Materials

Data was obtained regarding the start of action of the test material after being given intervention for 5 days:

Table 2. Average start of action of test materials (in time) after intervention

Dosage Group	N	Average start-up time of test material	P-value
K1 (Dulcolax 0.1 ml)	6	Minute 4:35	0.14
K2 (0.1 g tea)	6	Minute 8:12	
K3 (0.2 g tea)	6	Minute 3:08	
K4 (0.4 g tea)	6	Minute 4:38	

Source: Spss statistics ver.26

The start of action of the test substance is determined by calculating the difference between the time of first defecation after the time of administration of the test substance. Based on table 2, it shows that K3 (Aloe vera tea dose 0.2 gr) is the test material with the fastest start of laxative action, namely the average time for mice to defecate at 3:08 minutes, compared to the control group (dulcolax 0.1 ml) namely at 4:35 minutes with a difference of 1 minute 30 seconds. Based on the results of the Anova test, probability values were obtained 0.014 <0.05, so this shows that there are significant differences between the four groups.

Effect of Aloe Vera Tea on Fetal Growth

Data was obtained regarding the effect of the test material on fetal weight after 5 days of intervention:

Table 3. Effect of Test Material Work on Fetal Weight

Group number of parents)	Parameters (fetal birth weight) Length (mm) Mean ± SD	Weight (mg)
K1 (6 tails)	32.66±14.15	12.50±1.64
K2 (6 tails)	31.50±13.50	13.33±1.03
K3 (6 tails)	29.83±12.76	12.83±1.16
K4 (6 tails)	27.66±12.48	10.50±4.76
(P-Value)	0.276	0.913

Source: Oneway Anova Test

Based on table 3, it shows that the fetal body length of the four groups was highest in K1 with an average length of 32.66 mm, and from all groups there was no significant difference (0.276>0.05). Meanwhile, the highest average fetal body weight was in K2, with an average body weight of 13.33 mg, and was not significantly different from all groups (0.913>0.05).

DISCUSSION

The Effect of Giving Aloe Vera Tea on the Frequency of Defecation in Mice

The average frequency of defecation of mice in the graph and Table 1 shows a value that is not much different between the control group and the aloe vera tea treatment group because aloe vera tea and Dulcolax have the same type of stimulant laxative, working to stimulate the mucosa, intramural nerves or smooth muscles, increasing peristalsis and secretion. intestinal mucus synthesizes prostaglandins and cyclic AMP, consequently increasing electrolyte secretion. [18] The difference in the frequency of defecation in mice between the K2 K3 and K4 aloe vera tea intervention groups could be caused by the tea preparations having different sizes, as shown in the following picture:

Source: Personal Documentation

Figure 1. Difference in size of aloe vera tea after drying and crushing
(a) Smooth preparation and small surface, (b) Slightly rough preparation and wide surface

According to Kingston (2015), drying small powders will dissolve easily because the surface area is larger for the substance to dissolve with water so that powder extraction is more perfect and optimal. [19] . Supported by the results of research by Keraru (2017) which showed that fine Manggarai Robusta coffee grounds had a greater influence on the frequency of defecation in constipated rats than coarse Robusta coffee grounds. [20] The less laxative substances are extracted in the water, the less laxative substances enter the mice's bodies, the weaker the relaxation of the smooth muscles in the digestive tract. [21] . The reaction caused can be in the form of the number of events, namely the frequency of mouse defecation in the observed time period. This results in different defecation frequencies between the doses of K2, K3, and K4 aloe vera tea.

There are chemical groups in the laxative group, such as sugars, polysaccharides, inorganic salts, fat hydroxides, molecules with an anthracoid structure, and diphenylmethane derivatives. [22] The results of Sari's research (2020) show that the ability of aloe vera tea as a laxative is the influence of anthraquinone and glucomannan derivatives alone. [23] Meanwhile, dulcolax contains a laxative reinforced with sucrose and not lactose in each package, which is in the daily dose recommended by experts and doctors for treating constipation in humans. [24] So this is what causes the frequency of defecation in the aloe vera tea group to be lower than in the control group (Dulcolax).

The mice in this study varied in weight between 20-25 grams. One hour before treatment, mice were fasted from food. The aim is to ensure that food residue in the body does not affect the absorption process of the test material. [25] Because the presence of food residue in digestion can interfere with the bioavailability of the test substance from an oral medicinal product, bioavailability is the degree to which a drug or substance can be absorbed and circulated in the body. [26] The normal consumption of food for mice in a day, according to Veterinus (2020), is 4-5 gr/day/head. [27]

Source: Personal Documentation

Figure 3. Weighing the Amount of Mice Feed

Researchers give the same amount of feed every day, but the ability of mice to consume food will be different because the body's metabolic processes are different, so the amount of feces stored in the large intestine and rectum of each mouse is different. So, mice that consume a lot of food will empty their rectal contents more often by defecation. [19]

Starting Work on Test Material

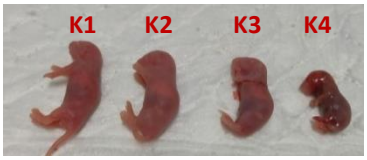
Keraru (2017) explains that laxatives begin to show effects 15-20 minutes after consumption. [20] . This is proven by the research results in Table 2, showing that K3 (Aloe vera tea dose 0.2 gr) is a laxative content test material with the fastest start of the action, namely the average time for mice to defecate at 3:08 minutes, compared to the control group (Dulcolax 0 .1 ml) namely at minute 4:35 with a difference of 1 minute 30 seconds.

The start of action indicates that the stimulation of laxatives in the defecation process predominantly occurs at 15-20 minutes, and then defecation time begins to decrease. It was proven in this study that between the first defecation and the second and subsequent defecation, there was a long time lag, namely around 1-3 hours. This is in line with the results of research by Devianti (2017), which identified that laxatives continue to have an effect on the digestive system for 4-6 hours. [28] Based on the results of the ANOVA test, probability values were obtained at 0.014 <0.05, which indicates there is a real difference between the four groups.

Dulcolax contains bisacodil, research conducted by Rahmani (2018) reported emptying of the ascending colon significant after being given bisacodyl. [29] Metabolism Bisacodil is converted into bis (*p-hydroxyphenyl*) *pyridyl-2-methane* (BHMP) in the digestive tract by enzymes or bacteria found in the intestine. The absorption of bisacodyl is very minimal in the gastrointestinal tract, which is around 6-12 hours, and only less than 5% is dissolved. Different from aloe vera, according to SW Hong (2020), Many types of plants have been identified as having a laxative effect, but the most effective type of plant in treating constipation is aloe vera, with the shortest activation period, namely 1-3 hours. [9] The laxative effect of aloe vera is more easily absorbed and stronger than other herbs, including senna, cascara, or rhubarb root. [10] Giving the right dose will increase the softness of the mass and speed up transit in the intestine, resulting in accelerated excretion of feces. [30] This could underlie the significant difference in starting time of action between the control group (Dulcolax 0.1 ml) and aloe vera tea 0.2 gr.

The Effect of Giving Aloe Vera Tea on Fetal Weight

Based on the ANOVA test, the length and body weight of the fetuses from the four groups were not significantly different. Table 3 shows the average length and weight of all groups which are still in the normal size category for mouse fetuses according to Veterinus (2020), namely PB 2-3 cm and BB 1-1.5 gr. [27] However, the data shows a decrease in weight at higher doses. K4 is the group treated with aloe vera tea at a dose of 0.4 gr/20 grBB. This shows that the higher the dose of aloe vera tea, the lower the average length and weight of the fetus, so giving aloe vera tea has an effect on the weight of the fetus in mice.



Source: Personal Documentation

Figure 6. Differences in Fetal Weight. (K1): dulcolax 0.1 ml (K2): aloe vera tea 0.1 gr, (K3): 0.2 gr aloe vera tea and (K4): 0.4 gr aloe vera tea

The degenerative effect on cell development is thought to cause a decrease in fetal weight and a general response due to aloin contamination in aloe vera which has a degenerative effect on cell proliferation, reduction of nucleic acids, cell interactions and proteins during embryogenesis. [31, 32] Supported by the opinion of Soenardirahardjo (2017) who states that there are many chemical substances that affect the replication and transcription of nucleic acids or RNA translation, the various properties of teratogenic substances involve several specific mechanisms, including interference with nucleic acids.[33]

If mother mice are exposed to teratogenic substances (aloin) from aloe vera which can enter through an absorption mechanism, this can have an impact on the safety of normal fetal growth. [34] . Embryos in their development are divided into 3 stages, namely pre-implantation, organogenesis stage and fetogenesis stage, all stages have sensitivity to teratogenesis.[13] Organogenesis is a stage of fetal

development on days 6-12 of pregnancy, this stage the cells begin to show significant morphological differences, if at this stage they are exposed to active teratogenic substances it can cause growth disorders that are observed at birth. [31, 35]

In this study, the intervention was carried out on days 8-12 of pregnancy, so it was proven, based on research data, that there were teratogenic substances that entered the maternal body and had an impact on the embryo in the form of decreasing fetal weight at increasingly higher doses. This is thought to be due to the presence of aloin, which degrades connective tissue. According to Dillasamola (2018), aloin shows hydrolytic activity in connective tissue, especially towards collagen, compared to other myofibrillar proteins. Aloin collagenase activity by hydrolyzing collagen is thought to be through the accumulation of hydroxyproline. [36] Collagen hydrolyzed by aloin makes the fetus's body very soft. Collagen is a form of protein that is found in many animal and human bodies. About 30 percent of the total protein in the body is collagen. Collagen is found in all connective tissues, such as the dermis, bones, tendons, and ligaments, providing structural integrity to all internal organs and normal tissues.[37] One of the important components of the body's connective tissue, which contains a lot of collagen, is blood, which specifically transports oxygen and nutrients throughout the body for growth and makes up about a third of the body's total weight. [38] Therefore, collagen degradation by aloin in aloe vera tea can reduce fetal body weight. This is supported by the results of research by Rubiyati (2016) showing that exposure to hydroquinone in pregnant mice tends to cause a decrease in body weight, number of lives, number of dead, morphology, and ochronosis in the fetus. [39] Onainor (2019) stated that a decrease in fetal weight and body length is the mildest form of dangerous compound effect compared to congenital malformations and death. [13] Because fetal growth parameters are sensitive enough to determine the effect of toxic compounds, it is characterized by a decrease in weight. [14, 15]

Even though there was a decrease at higher doses in this study, the weight and length limits for all fetuses were still in the normal category. Supported by journals “Pharmacognosy and Phytochemistry. The Miracle Plant (aloe vera) Its Medicinal and Traditional Uses in India 2016”. Aloe vera will be harmless or without toxic effects for pregnancy and lactation as long as the "aloin" content in the lower layer of the skin has been removed by processing; no carcinogenicity data has been found for the gel (flesh) part of aloe vera so it is safe for consumption by anyone. [16]

Aloe vera gel contains 1.14 – 0.38 mg/g of aloin compounds, while the outer skin contains 10 – 30%. [40] Fresh aloe vera contains the highest aloin, namely 23791.97 ppm, commercial drinks 735.17 ppm, and homemade drinks 1427.51 ppm. Various processing and heating processes are thought to influence the reduction in aloin levels. [41] Swami Hulle's research (2017) states that the activity of aloin will decrease in the high-temperature heating process; during heating, the degree of temperature affects the decrease and/or loss of the physicochemical properties of aloe vera. [42] The ideal temperature for processing aloe vera is around 50-90 ^{o} C. Supported by research by Fatimah (2020) identifying the instability of aloin compounds due to the impact of high temperature and long heat processes. The research also stated that the reduction in aloin levels was due to the hydrolysis of some of the aloin,

which was hydrolyzed into aloe-emodin, and most of it moved to other unknown substances, and it was not possible to detect aloin content in heated aloe vera because the amount was very small. [43] . The average reduction in aloin content in processed aloe vera is 10-30%. [(41)]

The process of making aloe vera tea in this research was made by the researcher himself in the phytochemical laboratory by applying the principle of clean aloin by removing the yellow sap that sticks between the skin and the gel. maximally through 3 washing stages, then dried and heated in a simple oven at a temperature of 50-60 ^{o}C for seven days.

In accordance with previous research and supported by the opinion of Agustina (2013), the content of a substance can be reduced to zero after going through the processing and heating stages. [(44)] So, it is suspected that in this study, the aloin content in aloe vera tea has been reduced or even disappeared. Therefore, no effect on weight reduction below normal limits was found in all fetuses in the aloe vera tea groups K2, K3, and K4.

CONCLUSIONS AND RECOMMENDATIONS

Based on the research results, it can be concluded that dulcolax 0.1 ml and aloe vera tea at a dose of 0.2g/20gBW are effective in increasing the frequency of defecation in pregnant mice with constipation and aloe vera tea at a dose of 0.2g/20gBW is very effective with the fastest onset of laxative action compared to the group. control (dulcolax 0.1 ml). Giving aloe vera tea at the embryogenesis stage has an effect on fetal growth in the form of reducing body weight at the highest dose, namely 0.4gr/20grBB. It is recommended that health workers provide education to women during pregnancy in dealing with discomfort with steps that focus on the use of medicinal plants and herbal medicinal products that are science-based, accountable, and risk-free. And future researchers can continue this research by testing the phytochemical substance aloin to determine the teratogenic effects affecting fetal growth, as well as using broader and more complex variables regarding the histopathology of mouse fetal organs.

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