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APPLICATION OF PAPAYA LEAF AND HONEY EXTRACT ANALGESIC TESTS IN MALEMICE TO REDUCE MENSTEM PAIN IN ADOLESCENTS IN THE NGAWEN II PUSKESMAS AREA, GUNUNG KIDUL DISTRICT

K. H. Endah Widhiastuti[1], Sih Rini Handajani[2], Wiwik Setyaningsih[3] and Rustam Aji*[4]

[1]Midwife Professional Study Program, Surakarta Indonesia Health Polytechnic.
[2]Department of Midwifery Profession Study Program, Surakarta Indonesia Health Polytechnic.
[3]Speech Therapy Department of Health Polytechnic Surakarta Indonesia.
[4]Diploma III Study Program Department of Nursing Curup Bengkulu Indonesia.

***Corresponding Author: Rustam Aji**
Diploma III Study Program Department of Nursing Curup Bengkulu Indonesia.

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ABSTRACT
Background: Menstruation Complaints of menstrual pain can occur ranging from mild to severe complaints Menstrual pain can be treated with pharmacological and non-pharmacological therapy. One of the traditional methods made from natural ingredients that are used as medicine to reduce pain during menstruation, namely papaya leaves (carica papaya) and honey, many papaya tree plants grow around us. Papaya leaves contain vitamin E which can reduce menstrual pain. Honey contains glucose and fructose, which function to control the smooth muscles of the uterus, so that the uterine muscles can relax, so there will be a reduction in pain during menstruation. Research objective: To test the effectiveness of the analgesic reaction of honey and papaya leaves. Research Methods: This study used the Experiment method with a post test design only approach conducted at the Pharmacy Laboratory of Gajah Mada University, Yogyakarta. Healthy male white mice as experimental animals. A total of 25 male Wistar mice were divided into 5 groups to test the effectiveness of analgesics on papaya leaves and 5 groups to test the effectiveness of honey analgesics. Data processing was carried out by one way Anova statistical test. Results: The optimal analgesic effect can be shown by the less amount of writhing at the intervals observed, namely per 10 minutes (stretching inhibition 48.83%) and still persists at 60 minutes (stretching inhibition 75.79%). Post hoc KVII (3 mg/0.125 mL papaya leaf extract suspension and 56.7 mg/20 gram rat body weight (25:75)) proved significantly different from KIV (honey 75.6 mg/20 gram rat body weight). KVII when compared to KIV is much better able to provide pain protection in the form of decreased writhing in mice because judging from the % inhibition of KVII stretching it is much higher. Conclusion: The combination of papaya leaf decoction and honey has a higher effect than honey and papaya leaf decoction. Keywords: papaya leaf, honey, menstrual pain, young women.

KEYWORDS: Knowledge, attitude and ovitrap.

INTRODUCTION
Menstrual pain is pain that is characterized by brief pain before or during menstruation, lasting one to several days during menstruation. Menstrual pain is usually characterized by a feeling of cramps and is concentrated in the lower abdomen. Complaints of menstrual pain can occur ranging from mild to severe complaints. Menstrual pain has an impact on daily activities. The impact of menstrual pain can be in the form of activity disturbances such as high rates of absence from school, limitations in social life, decreased academic performance and sports activities. Menstrual pain can also cause depression and infertility if not treated immediately (Reeder, 2011; Prawirohardjo, 2014).

Menstrual pain can be treated with pharmacological and non-pharmacological therapy. Pharmacological therapy includes administration of non-steroidal anti-inflammatory drugs /NSAIDs and combined contraceptive pills. Whereas non-pharmacologically it can be done with warm compresses, rest, exercise, relaxation techniques, massage, and in a traditional way made from natural ingredients that are used as medicine to reduce pain during menstruation, namely papaya leaves (carica papaya) and honey.(Prawirohardjo, 2014).

Papaya leaves contain vitamin E which can reduce menstrual pain. Papaya leaves contain the enzyme papain, alkaloids karpaina, pseudokarpaina, glycosides, carposid, saponins, saccharose, dextrose, levulose. Karpaine alkaloids have effects similar to digitalis, the

content in papaya leaves is efficacious for increasing appetite and reducing menstrual pain. Honey contains glucose and fructose which function to control the smooth muscles of the uterus, so that the uterine muscles can relax, so there is a reduction in pain during menstruation(Mirbagher and Aghajani, 2016).

Health workers who have the responsibility to provide care throughout the life cycle of women and one of them for adolescents are midwives. Midwives have standardized independent authority in obstetrics to teach young women appropriate interventions for menstrual pain. In accordance with the decision of the Minister of Health of the Republic of Indonesia number 369/MENKES/SK/III/2007 concerning the ninth competency midwife professional standard, namely carrying out midwifery care for women/mothers with reproductive system disorders. Menstrual pain is a disorder of the female reproductive system, so midwives have the authority to provide care to women who experience menstrual pain (Ministry of Health RI, 2015).

From the results of a preliminary study conducted by researchers on January 24 2020 on 10 class X students at SMA N 1 Wedi Klaten, the results showed that 5 students slept, 2 students took medication, 3 students answered that they were left alone. Of the number of students who experienced menstrual pain said that they rarely exercised because they only once a week, 75% of students who experienced menstrual pain had an irregular eating pattern with unhealthy foods such as fast food, and 3 students answered that they had a historyof mothers who also experienced menstrual pain when they were young.

Based on this background, it encouraged researchers to conduct research to see the effect of giving papaya leaf boiled water and honey to reduce menstrual pain in adolescents at the Ngawen II Gunung Kidul Health Center. In the second year, the focus will be on examining analgesic tests on honey and papaya leaves whichhave been tried in the first year's research.

FORMULATION OF THE PROBLEM

Based on the description above, the formulation of the problem is "How is the effectiveness of the Analgesic Test of Papaya Leaf Extract and Honey in male mice to reduce menstrual pain in adolescents in the Ngawen Health Center, Gunung Kidul Regency?"

OBJECTIVE

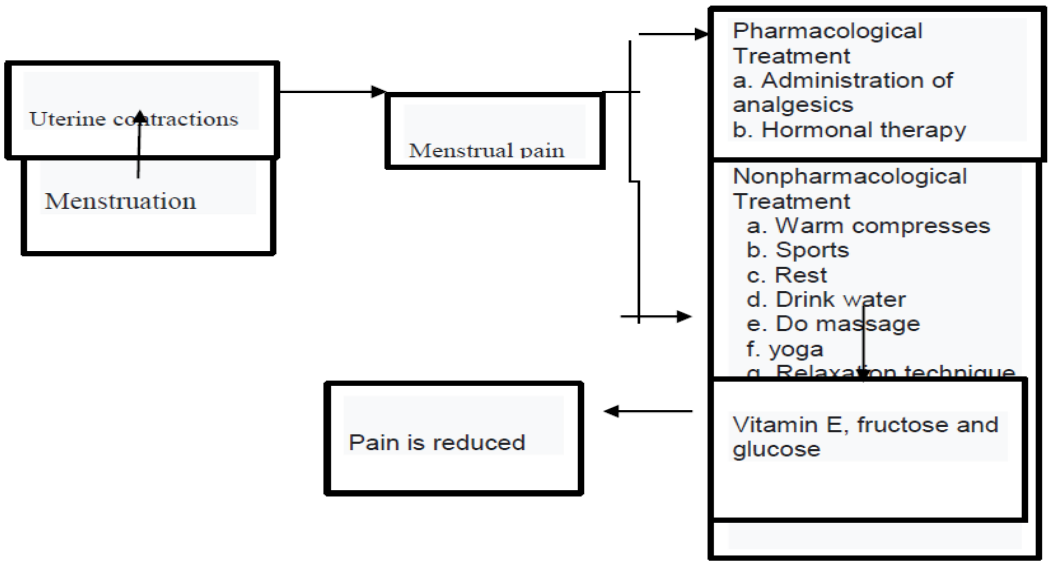
To find out the analgesia activity of honey and papaya leaf extract, To find out the analgesia activity of honey, To find out the analgesia activity of papaya leaf extract, To find out the analgesia activity of papaya leaf extract and honey, To analyze the most optimum dose of papaya leaf extract and honey in reducing menstrual pain.

BENEFIT

Theoretically

1. It becomes the basis for further similar research related to papaya leaves and honey and menstrual pain inadolescents.
2. Can contribute to the scope of midwifery in the field of adolescent health to provide health promotion related to traditional medicine for menstrual pain in adolescents.

THEORETICAL FRAMEWORK



Source: Modification Wiknjosastro (2007). Wiknjosastro (2009). Komalasari (2011). Anurogo (2011). Layla (2011). Stella (2014).

METHODOLOGY

This study aims to test the analgesic effectiveness of honey and papaya leaf ethanol extract. This research is an experimental study with a post test only control group design and a completely randomized design with one

way pattern. The subjects used were male Swiss galus mice aged 2-3 months with a body weight of 20-30grams as many as 35 mice and divided into 7 groups. The division of the groups was carried out randomly andthere were control and treatment groups. The one-way pattern indicates that it only examines one variable, namely the variation in administration of analgesic compounds (papaya leaf extract and/or honey) given to thedependent variable, namely analgetic power in mice in the form of percent writhing inhibition. The test group can be seen in the design as follows:

Table of Research Design Analgesic Test of Papaya Leaf Extract and Honey

Treatment	Number of minute stretches								
	5	10	15	20	25	20	35	dst	60
K I									
K II									
K III									
K IV									
K V									
K VI									
K VII									

Information

K I = positive control of paracetamol dose of 65 mg/kg BWKII = negative control CMC NA 0.5% suspension
K III = papaya leaf extract dose of 600 mg/kg BW mice
KV = combination of papaya leaf extract with a dose of 600 mg/kg BW mice K IV = honey at a dose of 378 mg/kgBB and honey (50:50)
K VI = combination of papaya leaf extract and honey (75:25) K VII = combination of papaya leaf extract and honey (25 :75)

TIME AND PLACE OF RESEARCH

The time for conducting the research is from January to August 2022 and this research was conducted at theLPPT Gadjah Mada University, Jogjakarta.

POPULATION AND SAMPLE

The population in this study were 35 healthy male mice of the Swiss strain aged 2-3 months with a body weight of 20-30 grams. The samples in this study were 35 healthy male mice of the Swiss strain aged 2-3 months with a body weight of 20-30 grams divided into 7 treatment groups.

RESEARCH VARIABLE

The variables in this study consist of:

1. Independent variable Variations in giving analgesic compounds, namely papaya leaf extract, honey and a combination of papaya-honey leaf extract.
2. Dependent variable Analegtic power, which is a number in percent indicating the strength of a certain substance in causing ananalgesic effect so that it can inhibit the stretching response.
3. Controlled variable

a. The strain of male mice which was the test subject was from the Swiss line
b. The mice tested were 2-3 months old
c. The body weight of the tested mice was 20-30 g
d. The honey used in the test comes from 1 particular brand
e. Papaya leaf extract used.

Methods of Data Processing and Data Analysis.

The data obtained is in the form of the amount of stretching which is then converted into the percentage of stretching inhibition with the following equation:

Percentage of writhing inhibition = 100-((the cumulative number of stretches of the test animals after treatment)/(the average number of stretches of the test animals in the negative control group) x 100).

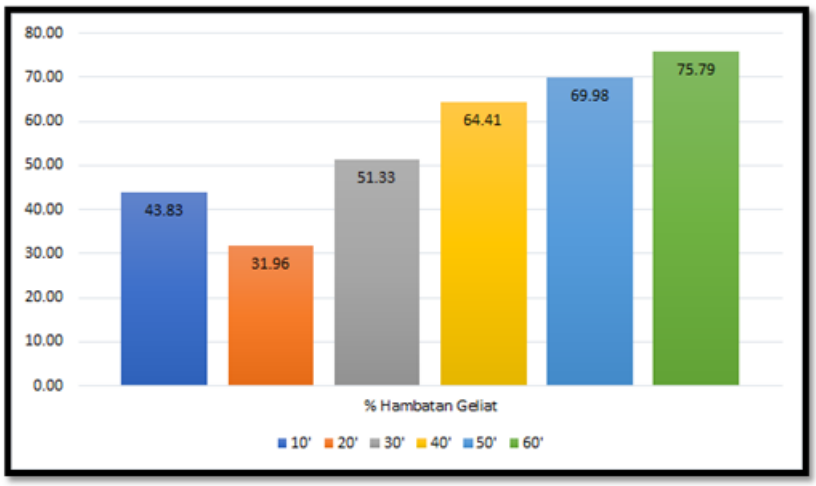
Furthermore, the data were analyzed statistically using the One sample Komolgorov-Smirnov test to determine the normality of the data. If normally distributed data is obtained, it is followed by a parametric test, namely the Oneway Anova Test, to determine whether there is a significant difference between the test groups, which is declared significant if the p value <0.05. If a significant difference is obtained, then it is continued with the Post-Hoc Test with a 95% confidence level.

RESULTS

Determination of the time interval between paracetamol and acetic acid stimulation.

Determination of the time interval for administering paracetamol and acetic acid aims to determine the time needed to provide optimal analgetic effects. Optimal analgesic effect can be shown by the less amount of stretching at the intervals observed, namely per 10 minutes. The test used paracetamol 1.3 mg/0.5 mL, CMC NA 0.5% 0.5 mL and papaya leaf extract suspension 6 mg, 9 mg and 3 mg and honey 75.6 mg/ 20 grams. the cumulative amount of stretching from each treatment (group) compared to the negative control group to determine the percentage of stretching inhibition. As for the results obtained in the table as follows:

Delivery Time(Minute)	The cumulativeamount of stretching	% StretchInhibitor	Sig
10	33,14 ± 12,13	48,83	0,089
20	40,14 ±13,67	31,96	
30	28,71 ± 17,70	51,33	
40	21,00 ± 20,40	64,41	
50	17,71 ± 21,29	69,98	
60	14,29 ± 21,18	75,79	



Based on the description in the table above, the statistical analysis results obtained the value of Sig. of 0.089 (Sig. > 0.05), it means that there is no difference between groups seen from the dosing time interval. This shows that the time interval for stimulation does not make a difference to stretching. So that the initial interval of 10 minutes the dose given has an effect on inhibition of stretching. However, the optimal time interval occurs at 60 minutes, where the stretching response is considered a little, when compared to other time intervals. Where the dose given can provide an analgesic effect with the highest % value of stretching inhibition.

2. Testing the analgesic power of giving suspension of papaya leaf extract and honey

Data on the amount of stretching and % inhibition of stretching in the stretching group of suspension ofpapaya leaf extract and honey are as follows:

Delivery Time(Minute)	The cumulativeamount of stretching	% StretchInhibitor	Sig
KI	17,20 ± 8,17	75,71	0,000
KII	70,8 ±8,10	0	
KIII	21,62 ± 25	64,69	
KIV	39,20 ± 18,55	44,63	
KV	24,40 ± 11,46	65.54	
KVI	19,80 ± 5,45	72,03	
KVII	20,60 ± 3,78	70,90	

Information

Treatment Test solution given

K I Paracetamol suspension 1.3 mg/0.5 mL K II CMC NA 0.5 % 0.5 Ml

K III Papaya leaf extract suspension 12mg/0.5 mL K IV Honey 75.6 mg/20 gram body weight of mice

K V Papaya leaf extract suspension 6 mg/0.25 mL and 37.8 mg/20 gram BW mice (50:50) K VI Papaya leaf extract suspension 9 mg/0.75 mL and 18.9 mg/20 gram BW mice (75:25)

K VII Papaya leaf extract suspension 3 mg/0.125 mL and 56.7 mg/20 gram body weight of mice (25:75) Based on the table above, it can be seen that the amount of stretching is inversely proportional to the % ofstretching inhibition. The more stretching, the smaller the % inhibition of stretching. The negative control group has a lot of stretching that is more dominant than the other groups. This indicates that it does not have pharmacological activity to reduce pain due to the induction of 1% acetic acid. Meanwhile, the positive control group and the treatment group with the concentration of papaya leaf extract and honey experienced a decrease in the amount of stretching when compared to the negative control. This means that there is pharmacological activity in reducing carnation race seen from the reduced intensity of stretching. From the results of statistical analysis, the value of Sig. 0.05 (Sig. <0.05), meaning there is a difference. This means that there are differences in each treatment group, so it is continued in the LSD post hoc analysis to see more clearly the differences in each group. The following are the results of the LSD post hoc analysis.

Dosis	KI	KII	KII	KIV	KV	KVI	KVII
KI		BB	BTB	BB	BTB	BTB	BTB
KII	BB		BB	BB	BB	BB	BB
KIII	BTB	BB		BTB	BTB	BTB	BTB
KIV	BB	BB	BTB		BTB	BB	BB
KV	BTB	BB	BTB	BTB		BTB	BTB
KVI	BTB	BB	BTB	BB	BTB		BTB
KVII	BTB	BB	BTB	BB	BTB	BTB	

BB Description: Significantly Different ($p<0.05$) and
BTB: Not Significantly Different ($p>0.05$)

Based on the tests above, it was found that KI (positive control) proved to be significantly different from KII (negative control) and KIV (Honey 75.6 mg/20 grams), while the other treatments were not significantly different (significant). KI when compared to KII and KIV is more able to provide pain protection in the formof decreased writhing in mice because judging from the % inhibition of writhing KI is much higher.

Then the KII (Control -) test proved to be significantly different for all treatments. This means that KI (control-) provides the lowest protective effect when compared to the other groups, this can be seen that the % writhing inhibitor has a 0 reaction, so there is no effect on changing pain in mice.

Then the KIII test (12 mg/0.5 mL papaya leaf extract suspension) proved to be significantly different from KII (negative control), while the other treatments were not significantly different (significant).

KIV (Honey 75.6 mg/20 gram BW mice) proved to be significantly different from KII (Control -) and KVI (Suspended papaya leaf extract 9 mg/0.75 mL and 18.9 mg/20 gram BW mice (75:25)). KIV when compared to KVI is far more able to provide pain protection in the form of decreased writhing in mice because judging from the % inhibition of KVI stretching it is much higher.

KVII (suspension of papaya leaf extract 3 mg/0.125 mL and 56.7 mg/20 gram body weight of mice (25:75)) proved to be significantly different from KIV (honey 75.6 mg/20 gram body weight of mice). KVII when compared to KIV is much more able to provide pain protection in the form of decreased writhing in mice because if seen from the % inhibition of stretching KVII is much higher

DISCUSSION

A. Determination of the time interval between paracetamol and acetic acid stimulation.

This study showed that there were differences between groups in terms of the dosing interval. After 10 minutes, the initial dose given has an effect on inhibition of stretching. However, the optimal time interval occurs at 60 minutes, where the stretching response is considered a little, when compared to other time intervals. Where the dose given can provide an analgesic effect with the highest % value of stretching inhibition, namely 75.79%.

B. Testing the analgesic power of giving suspension of papaya leaf extract and honey

In this study it was found that the amount of stretching was inversely proportional to the % of stretching inhibition. The more stretching, the smaller the % inhibition of stretching. The K II negative control group stretched more than the other groups because it did not have pharmacological activity to reduce pain. In the treatment group the concentration of papaya leaf extract and honey experienced a decrease in the amount of stretching when compared to the negative control.

From the results of the analysis there was a difference in the seven then proceed to post hoc analysis with the result that the KI (positive control) proved to be significantly different from KII (negative control) and KIV (Honey 75.6 mg/20 gram), while the other treatments were not different real (meaningful). This shows that K1is able to protect against pain compared to KII and KIV.

In the KIII group (12 mg/0.5 mL papaya leaf extract suspension) was found to be significantly different from KII (negative control), while the other treatments were not significantly different (significant). This shows that the KIII group was able to reduce pain but had the lowest protective effect when compared to the others.

In the KIV group (Honey 75.6 mg/20 gram BW mice) there was a significant difference in KII (Control -) and KVI (Papaya leaf extract suspension 9 mg/0.75 mL and 18.9 mg/20 gram BW mice (75: 25)). This means that KIV is more able to reduce stretching in the KII group, but compared to KVI it is still lower.

In the KVII group (suspension of papaya leaf extract 3 mg/0.125 mL and 56.7 mg/20 gram body weight of mice (25:75)) the test showed a difference in the KIV group (honey 75.6 mg/20 gram body weight of mice). Therefore, group VII was more able to provide pain protection compared to K IV and K II when seen from the % KVII stretch inhibition was much high.

The results of the analysis showed a decrease in pain levels from the highest in the KVI group (72.03%), KVII (70.90%), KV (65.69%), KIII (64.69%) and the lowest KIV (44.63%). The papaya leaf extract and honey group

had a higher effect on reducing stretch marks (pain) than the papaya leaf extract group with a significance value of 0.000 <0.005. The results of this study indicate that the combination of papaya leaf suspension and honey is significantly beneficial in reducing the level of primary dysmenorrhea pain. The results of this study were supported by previous research that boiled papaya leaves was only 1.72 and the reduction in pain in zinc tablets was 1.73.

Papaya leaves have a myriad of benefits. In parts of Asia, the young papaya leaves are steamed and eaten like spinach. Additional Benefits of Papaya Leaves: As an acne medication, Increase appetite, Relieve menstrual pain and Relieve nausea (Yogiraj et al., 2014). The results of this study are supported by previous research that the results of the analysis showed a decrease in pain levels from the three treatments between boiling papaya leaves and zinc tablets and the combination of boiled papaya leaves and zinc tablets showed very beneficial results with a significance value of 0.000 <0.005 (Mundarti et al., 2020) . Supported by research that has previously stated that the average intensity of dysmenorrhea decreased after being given papaya leaf decoction, this indicates that the effectiveness of papaya leaf decoction is very significant in young women who experience dysmenorrhea during menstruation (Putri & Nelis, 2021).

Papaya leaf cooking water can reduce the level of pain in primary dysmenorrhea respondents. Vitamin E contained in papaya leaves (Carica Papaya Linn) can reduce menstrual pain, through inhibition of prostaglandin biosynthesis besides calcium and vitamin C content can be used to affect contractility, stress and relax uterine smooth muscle or calm nerves. Based on previous research, the dose used in this study is considered safe because the maximum zinc dose for women aged 17-21 years is 150 mg/day (Akhila & Vijayalakshmi, 2015).

Previous studies have shown that giving papaya ethanol extract to mice can reduce pain in mice. Papaya ethanol extract (dose 0.5 ml/kg BW) showed an analgesic effect in the 20th minute after treatment and continued to show its analgesic effect until the 90th minute. The analgesic effect of ethanol extract (dose 1 ml/kgBB) reached its peak at 30 minutes. By 90 minutes, the analgesic effect had disappeared. pain responseof mice before treatment. Papaya leaf extract has an effective analgesic content in rats because of the flavonoid content. Flavonoids act as analgesics whose mechanism of action is to inhibit the action of the cyclogenase enzyme. Thus it will reduce the production of prostaglandins by arachidonic acid thereby reducing pain (Prabandari, 2019).

Papaya leaf extract has a statistically significant effect on reducing menstrual pain and prostaglandin levels (Hasimun et al., 2014). Papaya leaf extract contains flavonoids which provide analgesic activity similar to aspirin,13 which cause pain and inflammation are prostaglandins, by blocking the effect of cyclooxygenase (COX) enzymes to reduce prostaglandin production and reduce pain. Thus, this study proved that papaya leaves are effective for reducing pain (Abidah et al., 2017).

Honey can provide an analgesic effect on women who feel menstrual pain. The results of previous studies showed that honey and mefenamic acid capsules have the same effect in reducing pain. Pure honey significantly relieves menstrual pain (Harianja & Septyani, 2021).

According to the assumptions, the study showed that the group that received paracetamol positive control experienced less stretching than the group that received boiled papaya and honey. However, papaya and honey decoction has no difference with paracetamol which is an anti-pain drug. The analgesic effect given by honey and papaya leaf decoction has no side effects in long term use. Papaya extract and honey experienced less writhing pain compared to the negative control group and only papaya decoction. The conclusion based on the results of an analysis of the six treatments showed that they were effective in reducing pain levels in mice given papaya leaf and honey boiled water, and K V, K VI, and K VII these treatments had effectiveness in reducing dysmenorrhea pain levels. The results of this study are expected to be an alternative to reduce dysmenorrhea pain

CONCLUSION

A. Conclusion

1. The optimal analgesic effect can be shown by the less amount of writhing at the intervals observed, namelyper 10 minutes (stretching inhibition 48.83%) and still persists at 60 minutes (stretching inhibition 75.79%).
2. The result of the highest writhing inhibition was in the positive control group 1 (1.3 mg/0.5 mL), which was 75.71%. then in the KVI group (suspension of papaya leaf extract 9 mg/0.75 mL and honey 18.9 mg/20 gram body weight of mice (75:25), namely 70.90%
3. In the KVII post hoc test (suspension of papaya leaf extract 3 mg/0.125 mL and 56.7 mg/20 gram body weight of mice (25:75)) proved to be significantly different from KIV (honey 75.6 mg/20 gram body weight of mice). KVII when compared to KIV is much more able to pro pain protection in the form of decreased writhing in mice because if seen from the % KVII stretch inhibitor ismuch higher

B. Suggestion

1. Theoretical

a. It is recommended to see the long-term effects of using papaya extract and honey in reducing pain
b. It is recommended to conduct human trials with adjusted doses in people with dysmenorrhea

2. Practical

a. It is recommended that health workers can provide

alternative treatments to reduce dysmenorrhea in women It is recommended for menstruating women to consume papaya leaf decoction and honey to reduce menstrual pain

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