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ORIGINAL RESEARCH

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## EFFECT OF *CARICA PAPAYA L* LEAF ON MENSTRUAL PAIN AND PROSTAGLANDIN LEVEL IN ADOLESCENT WITH PRIMARY DYSMENORRHEA: A TRUE EXPERIMENT

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### ABSTRACT

**Background:** Primary dysmenorrhea occurs because of the excessive amount of prostaglandins in the blood. Papaya leaf extract is considered to be able to reduce prostaglandin and menstrual pain.

**Objective:** This study aims to prove that papaya leaf extract (*Carica Papaya L.*) can decrease the level of menstrual pain and prostaglandin levels in primary dysmenorrhea.

**Methods:** A true experimental study with randomized pretest posttest control group design. There were 32 samples recruited using simple random sampling, with 16 each assigned to an experiment group and a control group. Numerical Rating Scale (NRS) was used to measure menstrual pain, and the level of prostaglandin was measured using the enzyme-linked immunosorbent assay (ELISA) method. Independent t-test and paired t-test were performed for data analysis.

**Results:** There was statistically significant difference of menstrual pain and prostaglandin level before and after intervention with p-value 0.000 (<0.005), which indicated that papaya leaf extract had a significant effect on reducing menstrual pain. The decrease of menstrual pain in the experimental group was -3.375 and in the control group was -3.438; while the decrease of prostaglandin level in the experimental group was -56.971 and in the control group was -57.557.

**Conclusion:** Provision of papaya leaf extract (*Carica Papaya L.*) significantly decreased the level of menstrual pain and prostaglandin levels in primary dysmenorrhea. Papaya leaf extract can be used as a safe and effective herbal medicine for primary dysmenorrhea which has almost the same efficacy as mefenamic acid.

**Keywords:** *Carica Papaya L.*, primary dysmenorrhea, menstrual pain, prostaglandin level

## INTRODUCTION

Dysmenorrhea is a medical condition that occurs during menstruation characterized by pain in the abdominal or hip area.<sup>1</sup> Adolescents with dysmenorrhea will affect academic and social activities.<sup>2</sup> Primary dysmenorrhea is a menstrual pain that occurs not because of a physical disorder but because of the excessive amount of prostaglandins in menstrual blood resulting in uterine hyperactivity.<sup>3</sup> Prostaglandins are hormone-like components that act as mediators of various physiological responses such as inflammation, muscle contraction, blood vessel dilation, and platelet aggregation.<sup>3</sup> Prostaglandin F2 $\alpha$  is the result of metabolism of arachidonic acid by cyclooxygenase enzyme, causing vasoconstriction and contraction of the myometrium, which causes ischemia and pain.

If prostaglandins are released in excessive amounts into the bloodstream, systemic effects such as diarrhea, nausea, vomiting will occur.<sup>4</sup> Studies that have been done to measure PGF2 $\alpha$  levels in menstrual blood present in tampons, suggest that PGF2 $\alpha$  levels are twice as high in women with menstrual pain as compared with those without menstrual pain.<sup>5</sup>

The incidence of dysmenorrhea differs largely worldwide. On average, over 50% of women in every country have dysmenorrhea. In the United States the percentage is about 60% and in New Zealand is around 66.5%.<sup>6</sup> The primary dysmenorrhea rate in Indonesia is about 54.89%, while the rest are patients with secondary type.<sup>7</sup> The incidence of dysmenorrhea in Central Java reaches 56%.<sup>8</sup>

Dysmenorrhea however can have an impact on daily activities, school attendance, and limitations in social or functional activities.<sup>9</sup> The study showed

that those who have mild to severe dysmenorrhea had an impact on daily activities (92.4%), were absent in the class (25.3%), and were self-treated using analgesics 1-6 times per cycle (39.9%).<sup>10</sup>

Non-pharmacological therapies are ways to decrease menstrual pain in addition to pharmacological treatment. Medicinal plant is an alternative treatment, which is increasingly in demand today and widely accepted in almost all countries around the world.<sup>11</sup> One of the most commonly used is papaya (*Carica Papaya* L.). Papaya leaves contain flavonoids that have anti-inflammatory activity that can inhibit the enzyme cyclooxygenase I, which is the first path of pain mediation synthesis such as prostaglandin that affects the decrease in the intensity of menstrual pain.<sup>12</sup>

Study stated that analgesic activity of papaya leaf extract is proportional to aspirin.<sup>13</sup> Papaya methanol extract has anti inflammation activity due to the contain of flavonoids which act as anti-inflammation by inhibiting prostaglandin synthesis.<sup>14</sup> Thus, this study aimed to examine the effect of papaya leaf on menstrual pain and prostaglandin level in adolescent with primary dysmenorrhea.

## METHODS

### *Design*

A true experimental study with randomized pretest posttest control group design.

### *Population and sample*

The study was conducted in the dormitory of Midwifery and Nursing of Ngudi Waluyo University between August and October 2016. The number of samples was measured using unpaired numerical analytic formula.<sup>15</sup> There were 32 samples recruited using simple random sampling, with 16 each assigned to an experiment and control group. The inclusion criteria

of the sample were: 1) regular menstrual cycle seen from the last 3 months, 2) adolescent females who experienced primary dysmenorrhea on the first day of menstruation, 3) easy to communicate and willing to participate, and 4) willing not to use either pharmacological or nonpharmacological therapies during the study. The exclusion criteria were: 1) women who had other complaints in the womb, 2) undergoing treatment with painkillers (analgesics) and performing techniques to reduce other pain such as compress, massage, exercise etc., and 3) experiencing premenstrual syndrome (PMS).

#### *Instruments*

Numerical Rating Scale (NRS) was used to measure menstrual pain as a substitute for the word descriptor tool about how severe the pain felt by respondents with a scale of 0-10, the greater the number the more severe the pain rate.<sup>16</sup> The level of prostaglandin was measured using the enzyme-linked immunosorbent assay (ELISA) method, which is a technique of immunological screening that utilizes specific bonds between antibodies and antigens. Blood collection was performed but not simultaneously because of different menstrual cycles in each person. Each blood collection was stored in a vacutainer and then centrifuge and stored in a refrigerator of -80 °C, while waiting for the total number of blood samples completed according to the specified number of samples.

#### *Intervention*

Papaya leaf extract (*Carica Papaya* L.) was given in the experimental group with dose of 350 mg given as much as 3 times per day for 3 days before menstruation and on the first day of menstruation, with consideration of menstrual cycle backward or forward. The time of the treatment was based on the estimated menstrual cycle based on the previous

menstrual cycle. Papaya leaf was extracted using maceration or immersion technique. The drug is inserted in the capsule with same color, and the administration of the drug was done by the aid of the enumerator with double blind. The control group was given mefenamic acid 500 mg in the same time with the intervention group.

On the first, second and third day of menstruation, respondents were asked about side effects after taking the medicine and recorded. After undergoing treatment for 3 days, before menstruation until the first day of menstruation, blood was collected on the first day of the second cycle of menstruation in each group. In addition, the respondents were also asked about the intensity of menstrual pain and was measured using NRS.

Measurement of prostaglandin levels and intensity of menstrual pain was performed 12 hours after menstruation. After the total blood sample completed, then the measurement of PGF2  $\alpha$  with ELISA (Enzyme-linked immunosorbent assay) method was performed in collaboration with GAKI laboratory of Diponegoro University, Semarang.

#### *Data analysis*

Data analysis was performed using dependent t-test to compare mean of two data (before and after intervention) in the experiment and control group, and using independent t-test to identify differences of menstrual pain level and prostaglandin level in the experiment and control group.

#### *Ethical consideration*

This research has been approved by the Health Research Ethics Committee (K.EP.K) of Health Polytechnic of Ministry of Health (Poltekkes) of Semarang No. 103/KEPK/ Poltekkes-SMG/ EC/ 2016. The researchers ensured that all respondents have obtained the appropriate informed consent.

## RESULTS

Table 1 shows that there was statistically significant difference of menstrual pain before and after intervention with p-value 0.000 ( $<0.005$ ), which indicated that papaya leaf extract had a significant effect on reducing menstrual pain. The decrease of menstrual pain in the experimental

group was -3.375 and in the control group was -3.438. It is also said that there was no difference of the effect of papaya leaf in the experimental group and the effect of mefenamic acid in the control group to reduce menstrual pain with p-value 0.612 ( $>0.05$ )

**Table 1** Difference of menstrual pain in the experiment and control group

Variable	Group		P-value
	Experiment (n = 16)	Control (n = 16)	
Before intervention Mean±SD Min-max	4.688±1.078 4-8	5.438±1.263 4-8	0.061 <sup>1</sup>
After intervention Mean±SD Min-max	1.313±0.602 0-2	2.000±0.894 1-3	0.031 <sup>1</sup>
Mean difference of before and after intervention P-value	0.000 <sup>2</sup>	0.000 <sup>2</sup>	
Difference of menstrual pain level Mean±SD Min-max	-3.375±0.957 (-6)-(-2)	-3.438±0.814 (-5)-(-2)	0.612 <sup>1</sup>

<sup>1</sup>Mann-Whitney Test <sup>2</sup>Wilcoxon Rank Test

**Table 2** Difference of prostaglandin levels in the experiment and control group

Variable	Group		P-value
	Experiment (n = 16)	Control (n = 16)	
Before intervention Mean±SD Min-max	184.895±71.622 63.60-333.81	260.240±134.356 53.80-478.41	0.060 <sup>1</sup>
After intervention Mean±SD Min-max	127.924±44.172 59.96-249.12	202.68±114.455 44.76-387.47	0.025 <sup>1</sup>
Mean difference of before and after intervention P-value	0.001 <sup>2</sup>	0.001 <sup>2</sup>	
Difference of prostaglandin level Mean±SD Min-max	-56.971±54.132 (-226.15)-(-3.64)	-57.557±57.643 (-224.38)-(-7.28)	1.000 <sup>3</sup>

<sup>1</sup>Independent t-test <sup>2</sup>Paired t-test <sup>3</sup>Mann-Whitney

Table 2 shows that there was statistically significant difference of prostaglandin level before and after intervention with p-

value 0.001 ( $<0.005$ ), which indicated that papaya leaf extract had a significant effect on reducing prostaglandin level. The

decrease of prostaglandin level in the experimental group was -56.971 and in the control group was -57.557. It is also said that there was no difference of the effect of papaya leaf in the experimental group and the effect of mefenamic acid in the control group to reduce menstrual pain with p-value 0.612 ( $>0.05$ ). It is also said that there was no difference of the effect of papaya leaf in the experimental group and the effect of mefenamic acid in the control group to reduce prostaglandin level with p-value 0.612 ( $>0.05$ )

## DISCUSSION

The aim of this study was to examine the effect of papaya leaf extract on menstrual pain and prostaglandin levels in primary dysmenorrhea. Findings of this study showed that papaya leaf extract statistically had significant effect on reducing menstrual pain and prostaglandin levels. This finding however confirmed the previous study, which stated that papaya leaf extract has a flavonoids contents that provide analgesic activity similar to aspirin,<sup>13</sup> which the cause of pain and inflammation is prostaglandin, by blocking the effects of cyclooxygenase (COX) enzymes to reduce the production of prostaglandin and pain will be decreased.<sup>17</sup>

In addition, Sudarko, et al<sup>18</sup> mentioned that papaya leaf extract contains anti-inflammatory, which able to inhibit the enzyme cyclooxygenase and lipoxygenase that can reduce the effects of pain. Similar with Nindya, et al<sup>19</sup> who stated that papaya leaves as herbal plants contain high flavonoids work through the process of inhibition of arachidonic acid metabolism in the cyclooxygenase pathway which is a mediator of prostaglandin formation so that by blocking the metabolism prostaglandins can be suppressed so as to reduce menstrual pain. Thus, this study proved that the papaya leaf was effective to

decrease pain in primary dysmenorrhea. The content of flavonoids in papaya leaf in this study was 2.4964 mg/g.

On the other hand, the result of the mean analysis of the difference of menstrual pain level in the experimental group and the control group obtained p-value 0.612 and the mean of prostaglandin level obtained p-value 1.000, which indicated that there was no mean difference of menstrual pain level and prostaglandin level between the experimental group and the control group. Thus, it can be concluded that giving papaya leaf extract has the significant effect similar to mefenamic acid in decreasing the level of menstrual pain and prostaglandin level. As seen from pharmacodynamics, mefenamic acid with papaya leaf extract have the same working mechanism, which is to inhibit Cyclooxygenase (COX).

The results of this study can be used as non-pharmacological alternative therapy, which is processed naturally to reduce menstrual pain without side effect, affordable, and relatively safer to use in long-term.

### *Limitation of the study*

The measurement of menstrual pain and prostaglandin levels in one cycle might be the limitation of this study. In addition, this study did not examine other factors that affect the occurrence of primary dysmenorrhea such as leukotriene and anxiety levels, and the selection of the sample was just based on anamnesis and palpation examination alone, not using ultrasound examination.

## CONCLUSION

Provision of papaya leaf extract (*Carica Papaya L.*) significantly decreased the level of menstrual pain and prostaglandin levels in primary dysmenorrhea. Papaya leaf extract can be used as a safe and effective herbal medicine for primary



dysmenorrhea which has almost the same efficacy as mefenamic acid. Therefore, it is advisable to adolescent females who have primary dysmenorrhea to consume papaya leaf extract. The finding of this study also can be a part of midwifery care to deal with primary dysmenorrhea.

#### Declaration of Conflicting Interest

None declared.

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#### Authorship Contribution

Authors have equal contribution in this study.

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