



The Effect of Ginger Candy (*Zingiber Officinale Rosc.*) on $\text{PGF2}\alpha$ Levels in Adolescents with Primary Dysmenorrhea

Eka Tri Wulandari^{1*}; Desi Kumalasari¹

^{1*)} Program Studi Kebidanan Universitas Aisyah Pringsewu

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ABSTRACT

Primary dysmenorrhoea is a common complaint that is commonly experienced by women around the world, especially teenagers. One of the causes of primary dysmenorrhea is the hyperactivity of the myometrium which is modulated by the synthesis of prostaglandins, especially $\text{PGF2}\alpha$. Some herbs are known to work as prostaglandin inhibitors, one of them are ginger. Giving ginger in adolescents who experience dysmenorrhea is expected to lower the levels of $\text{PGF2}\alpha$ so that dysmenorrhea pain can be reduced. Generally ginger can be developed in a variety of food and beverage products such as jelly candy. The purpose of this study was to analyze the effect of ginger candy to decrease the level of $\text{PGF2}\alpha$ in adolescents with primary dysmenorrhoea. This research is an analytic research which used randomize pre post group design experimental approach. The object of the research is 38 adolescents with primary dysmenorrhoea. The object is divided into two groups, 19 treatment group and 19 control group. The treatment group was given jelly candy containing 100 mg of ginger extract, while the control group was given jelly candy without ginger. The candy was given on the first day of menstruation until the second day of menstruation. The measurement of $\text{PGF2}\alpha$ level was on the second day of menstruation after the candy was given to the groups. The results showed that after administration of candy, the last average levels of $\text{PGF2}\alpha$ in the treatment group decreased from 482,9 ng/ml to 370,5 ng.ml or down by 11%. Whereas in the control group, the $\text{PGF2}\alpha$ level 483,3 become 409,2. The difference in the percentage of decreasing in the levels of $\text{PGF2}\alpha$ using mann whitney test showed significant result ($p=0,002$). The conclusion of this research is ginger candy can reduce levels of $\text{PGF2}\alpha$ in adolescents with primary dysmenorrhoea.

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Kata kunci:

$\text{PGF2}\alpha$

Dismenorea Primer

Permen Jeli Jahe

^{*)} corresponding author

Eka Tri Wulandari

Program Studi Sarjana Terapan Kebidanan

Fakultas Kesehatan, Universitas Aisyah

Pringsewu

Email: fatihnyaumi@gmail.com

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ABSTRAK

Dismenorea primer merupakan keluhan umum yang biasa dialami oleh wanita di seluruh dunia terutama remaja. Salah satu penyebab terjadinya dismenorea primer adalah hiperaktivitas miometrium yang dimodulasi oleh sintesis prostaglandin, terutama $\text{PGF2}\alpha$. Beberapa herbal diketahui dapat bekerja sebagai prostaglandin *inhibitors*, salah satunya jahe. Pemberian jahe pada remaja yang mengalami dismenorea diharapkan akan menurunkan kadar $\text{PGF2}\alpha$ sehingga nyeri dismenorea yang dirasakan akan berkurang. Secara umum jahe bisa dikembangkan dalam berbagai produk makanan salah satunya permen. Tujuan penelitian ini adalah untuk menganalisa pengaruh pemberian permen jahe terhadap penurunan kadar $\text{PGF2}\alpha$ pada remaja yang mengalami dismenorea primer. Penelitian ini merupakan penelitian analitik dengan pendekatan eksperimental *randomize pre post group design*. Objek penelitian berjumlah 38 orang remaja yang mengalami dismenorea primer, objek dibagi menjadi 2 kelompok, yaitu 19 kelompok perlakuan dan 19 kelompok kontrol. Pada

kelompok perlakuan diberikan permen jeli yang mengandung 100 mg ekstrak jahe, sedangkan pada kelompok kontrol diberikan permen jeli tanpa kandungan jahe. Pemberian permen dilakukan pada hari pertama menstruasi sampai hari ke dua menstruasi. Untuk pengukuran kadar PGF 2α dilakukan pada hari ke 2 menstruasi setelah pemberian permen. Hasil penelitian menunjukkan bahwa setelah pemberian permen, rerata kadar PGF 2α pada kelompok perlakuan turun dari 482,9 ng/ml menjadi 370,5 ng/ml atau turun sebesar 11,5%, sedangkan pada kelompok kontrol dari 483,3 ng/ml menjadi 490,2 ng/ml. Perbedaan presentase penurunan kadar PGF 2α pada kedua kelompok penelitian dengan menggunakan uji *Mann Whitney* menunjukkan hasil yang bermakna ($\rho=0,002$). Simpulan dalam penelitian ini adalah permen jahe dapat menurunkan kadar PGF 2α pada remaja yang mengalami dismenorea primer.



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INTRODUCTION

Dysmenorrhea is pain associated with the menstrual process, and is a common gynecological complaint in women of reproductive age. (Proctor & Murphy, 2001), (Bettendorf, Shay, & Tu, 2008), (Wallace, Keightley, & Gie, 2010) Dysmenorrhea can be divided into two types, namely primary and secondary. Primary dysmenorrhea is a pain during normal menstruation and is not associated with any pathological conditions (MY., 2006), (Lindeque BG, 2015) while secondary dysmenorrhea is a menstrual pain due to pathological conditions. (Wallace et al., 2010), (Lindeque BG, 2015).

Primary dysmenorrhea is a common complaint experienced by women all over the world, especially teenagers. In a study, it was reported that almost 90% of adolescents experienced dysmenorrhea and more than 50% of adult women also reported experiencing it, 10-20% of them complained of being very suffering and anxious about their condition. (Berkley, 2013) The data of dysmenorrhea case and the impact of dysmenorrhea on daily activities days on adolescents in Indonesia it self is not definite. In a preliminary study conducted at AISYAH Pringsewu University Lampung on 61 nursing students, it was found that 58 people or 95% experienced dysmenorrhea, using the VAS (Visual Analog Scale) scale for pain measurement, the results were obtained; 22% experienced mild pain, 47% moderate pain, 29% severe pain and 2% severe pain.

Primary dysmenorrhea is not a life-threatening disease, but dysmenorrhea pain can have an impact on a person's quality of life, even in severe conditions that will affect daily activities, being absent from school or work, mental and psychological disturbances, and even the choice of the desired type of baby delivery. (Liu et al., 2013) A study reported that dysmenorrhea is the reason for 34-50% of adolescent girls to be absent from school. (Mahvash et al., 2012).

One of the causes of primary dysmenorrhea is an increase in uterine prostaglandins derived from cyclooxygenase (COX)-2. The COX enzyme consists of 2 iso-enzymes, namely COX-1 and COX-2. COX-1 enzyme is constitutive to maintain normal physiology and homeostasis, while COX-2 is an enzyme that is induced in inflamed cells by cytokines, endotoxins, and growth factors (Zukhrullah & Aswad, 2012) COX-1 is found in most tissues that functions to catalyze prostaglandin E-2 (PGE-2) which has a cytoprotective function and helps in maintaining the integrity of the

gastrointestinal mucosa. While COX-2 is induced by pro-inflammatory cytokines and produces prostaglandins (PGF 2α) which mediate the inflammatory response, vasoconstriction (reduced oxygen flow), ischemia and the onset of pain. (Connolly, 2003) Clinical evidence also shows that women with severe dysmenorrhea have PGF 2α . (Sriyakul, Kietinun, Pattaraarchachai, & Ruang rungsi) If excessive amounts of prostaglandins are released into the bloodstream, systemic effects such as diarrhea, nausea, vomiting will occur (MY., 2006).

The use of prostaglandin inhibitors, NSAIDs (Non Steroidal Anti-Inflammatory Drugs), and birth control pills are commonly used to treat dysmenorrhea, but are not recommended for routine use because there are concerns about side effects, namely stomach irritation (with symptoms of chest pain, nausea and vomiting), headache, and fluid retention. In addition, the use of birth control pills in unmarried adolescents is less accepted by culture in society. (Proctor & Murphy, 2001), (MY., 2006). There fore, it is very important to find a new type of therapy that is simpler and more acceptable by society for management of dysmenorrhea in adolescents.

Traditional medicine to reduce dysmenorrhea has been passed down from generation to generation by the people of Indonesia. In a preliminary study conducted by researchers, several teenagers used herbal medicine to reduce the pain of dysmenorrhea they felt. The traditional medicine itself according to Law No. 36/2009 concerning Health covers ingredients or potions in the form of plant ingredients, animal ingredients, mineral ingredients, preparations of extracts or mixtures of these ingredients which have been used for generations for treatment. In accordance with Article 100 paragraphs (1) and (2), sources of traditional medicines that have been proven to be efficacious and safe to use will be preserved and guaranteed by the Government for the development and maintenance of their raw materials. (Gunawan, 2015).

Some herbal spices are known to be effective for treating dysmenorrhea pain and other symptoms that accompany dysmenorrhea. Several compounds in herbs have anti-spasmodic and prostaglandin inhibitor effects, one of which is ginger (*Zingiber officinale* Rosc.) (Mirabia, Alamolhodab, Esmaeilzadeha, & Mojabc, 2013), (Terry, Posadzki, Watson, & Ernst, 2011).

The use of ginger for dysmenorrhea therapy is widely practiced. The compounds contained in ginger can inhibit the cyclooxygenase (COX) pathway in the process of

prostaglandin synthesis (van Breemen, Tao, & Li, 2011), (Chrubasik, Pittler, & Roufogalis, 2005) There fore, ginger can reduce prostaglandin levels that cause hyperactivity myometrium causing uterine ischemia causing pain. In an RCT (randomized clinical trial) study of 150 adolescents, it was stated that there was a significant difference in pain levels between the groups which were given ginger and those which were given a placebo. (Rahnama, Montazeri, Huseini, Kianbakhta, & Naseri, 2012) Another study that compared the use of ginger, tamarind mefemanat, and ibuprofen for the treatment of dysmenorrhea in 150 students found that ginger was as effective as mefemanic acid and ibuprofen for relieving dysmenorrhoea pain. (Ozgoli, Goli, & Moattar, 2009).

Ginger has anti-inflammatory properties. The main compounds of ginger that are anti-inflammatory are gingerol and zingerone, but in vivo almost all components of ginger have anti-inflammatory effects. Ginger works by influencing the modulation of leukotrienes and prostaglandin synthesis. (Lakhan, Ford, & Tepper, 2015) In one study, the administration of [6] gingerol (25 mg-50 mg/kg) intraperitoneally could inhibit inflammation in the paws of animals that were given carrageenan. (Singh, Duggal, Singh, & Katekhaye, 2010) It is well known that excessive production of prostaglandins (especially PGF2) will stimulate abnormal myometrial contractions which will reduce blood flow to myometrial cells, causing pain. (MY., 2006).

In some literature it is stated that the use of ginger dosage for the treatment of dysmenorrhea is 1000-2000 mg with variations in the administration of 2x per day, 3x per day, and 4 times per day, and in the form of a powder or capsule. (Lakhan et al., 2015) Other dosage forms that are simpler and more acceptable by the public, such as in the form of candy, or biscuits, have not been found in many literature studies. In general, ginger can be developed in various food and beverage products. Domestic products made from ginger include dried ginger, ginger candy, ginger powder, ginger oil and oleoresin. (Supriadi, Yusron, & Wahyudi, 2011).

In a preliminary study conducted by research hers nationally on adolescents in several provinces to find out which form of processed ginger was preferred by adolescents, it was found that adolescents preferred processed ginger in the form of candy preparations.

METHOD

The research subjects were 38 Diploma 3 Midwifery students at Aisyah Pringsewu University who experienced dysmenorrhea. subjects will be divided into 2 groups. 19 people in the control group and 19 in the treatment group, who met the inclusion criteria and were willing to become respondents by signing the consent form after the explanation.

The research sample was taken by simple random sampling. Inclusion criteria were patients with primary menstrual pain aged 18-21 years, no organic abnormalities were found through ultrasound examination, experienced menstrual pain on a VAS scale of 4-6, had never been married and gave birth, had regular menstrual cycles for the last 3 months (28-30 days), and volunteered to participate in this study.

The exclusion criteria in this study were adolescents who had other complaints in the uterus and pelvis, adolescents who were undergoing treatment with painkillers, adolescents who had undergone surgery on the abdomen and pelvis, and adolescents who used contraceptives and other drugs.

The process of this research is to give ginger jelly candy and jelly candy without ginger for 2 days, namely the first day and the second day of menstruation to adolescents who are menstruating and experiencing primary dysmenorrhea. The dose used in this study was 100 mg of ginger extract which was made in 1 package of 6 pieces of candy which was given twice a day with 3 pieces of candy per serving. Subsequently, blood samples were taken to measure PGF2 α levels. The data were collected directly by the researcher. Data collecting was conducted by using questionnaires, checklists and blood collection. PGF2 α examination was carried out in the Molecular Genetics Laboratory, Faculty of Medicine, Unpad, using the ELISA method. The data collected were analyzed descriptively and analytically to analyze the effect of ginger candy on decreasing PGF2 α levels.

The design used in this research is true experimental. The approach used in this study was a randomized pretest-posttest group design. Data analysis used Wilcoxon test and Mann-Whitney test.

RESULTS

Table 1
Characteristics of Subjects in Both Research Groups

Characteristic	Group		p
	Treatment (n=19)	Control (n=19)	
Age (year)			
x (SD)	19,0(1,20)	19,0(0,88)	0,795*
Median	19,0	19,0	
Range	18-21	18-21	
Menarche			
x (SD)	12,2(0,78)	13,3(0,94)	0,001*
Median	12,0	13,0	
Range	11-13	11-15	
Weight			
x (SD)	51,6(7,49)	58,0(25,25)	0,644*
Median	50,0	50,0	
Range	40-66	43-157	
Height			
x (SD)	156,(4,54)	146,9(30,41)	0,644*

Median	157,0	156,0	
Range	150-165	59-169	
PGF2α			
x (SD)	482,9(509,76)	483,3(443,51)	0,506*
Median	378,9	347,2	
Range	293,47-2543,08	253,16-2215,06	

*test used: Mann Whitney**

Based on the table. 1 In this study, the characteristics of the research subjects were equal between the control and

treatment groups, including in terms of age, height, weight, and PGF2 α levels.

Table 2
Differences in PGF2 α Levels Before and After Dysmenorrhea Adolescents Given Ginger Candy

Description	Treatment (n=27)		Score ρ	Control (n= 27)		ρ
	Pre test	Post test		Pre test	Post test	
PGF2α level						
x (SD)	482,9(509,76)	370,5(190,34)	0,002*	483,3(443,51)	490,2(433,6)	0,601*
Median	378,9	308,41		347,2	334,8	
Range	293,47-2543,08	253,16-1090,76		253,16-2215,06	302,9-2153,3	
Δ PGF2α level						
x (SD)	112,3((327,81)			6,9(42,62)		0,003**
Median	-23,79			2,9		
Range	-1452,32 – 35,27			-61,76 – 94,02		
PGF2α percentage						
x (SD)	11,5 (15,11)			2,6(12,20)		0,002**
Median	-7,34			0,67		
Range	-57,11 – 10,33			-14,55- 34,83		

Test used: Wilcoxon, Mann Whitney***

DISCUSSION

Ginger is a type of herb that has many benefits, cheap and relatively safe to use. One systemic review reported that subjectively ginger can be used for pain relief in certain conditions, one of which is dysmenorrhea. (Terry et al., 2011)

In a randomized clinical trial (RCT) study of 150 adolescents, it was stated that there was a significant difference in pain levels between the groups that were given ginger and those who were given a placebo. (Rahnama et al., 2012) The use of ginger for dysmenorrhoea therapy is widely practiced. Compounds contained in ginger such as gingerol, shogaol and their derivatives can inhibit the cyclooxygenase (COX) pathway in the process of prostaglandin synthesis, (van Breemen et al., 2011). In addition, they can also inhibit the synthesis of pro-inflammatory cytokines such as IL-1, TNF- α , and IL-8. (Mashhadi et al., 2013) Therefore, ginger can reduce prostaglandin levels which cause myometrial hyperactivity which results in uterine ischemia causing pain.

Table 2 shows that at the beginning of the study the mean of serum PGF2 α level in the treatment group was higher (378.9 ng/ml) than the control group (347.2 ng/ml), but statistically there was no significant difference between the control and treatment groups. This shows that the initial serum PGF2 α level before candy administration was homogeneous. This condition is probably due to the fact that the research respondents have almost the same characteristics. Meanwhile, at the end of the study, the mean of serum PGF2 α level in the treatment group was lower (308.41 ng/ml) than the control group (334.8 ng/ml). This average value indicates the success of giving ginger candy to reduce PGF2 α levels. This table also shows that in the treatment group there was a significant decrease in PGF2 α levels before and after the study ($\rho=0.002$) and the decrease

in PGF2 α levels in the group given ginger candy therapy was greater than in the group given candy without ginger ($\rho<0.05$).

Giving ginger to reduce pain has been mentioned in several studies. Research by Amritpal Singh et al 2010 on experimental pharmacology for gingerol compounds and their derivatives showed that ginger is considered to have an anti-inflammatory effect because it inhibits cyclooxygenase and 5-lipoxygenase, thereby reducing the synthesis of prostaglandins and leukotrienes. (Singh et al., 2010) Research by Richard et al. about Cyclooxygenase-2 inhibitors in ginger also show the results that by using liquid chromatography-tandem mass spectrometry (LC-MSMS) compounds 10-gingerol, 8-shogaol, and 10 shogaol are compounds in ginger that may be responsible for the anti-inflammatory process by inhibiting COX-1 and COX-2. (van Breemen et al., 2011)

The existence of a correlation between prostaglandins and menstrual pain is supported by the research of Fortier et al., in their research it was found that prostaglandins and leukotrienes cause an inflammatory response, which will cause uterine muscle spasm and systemic complaints such as nausea, vomiting, flatulence and headaches. (Fortier, Krishnaswamy, Danyod, Boucher-Kovalik, & Chapdalaine, 2008). A study conducted by Dawood and Khan-Dawood, by measuring the levels of PGF2 α in menstrual blood contained in tampons, it was found that PGF2 α levels were twice as high in women who experienced menstrual pain compared to those who experienced no menstrual pain. Giving ginger to adolescents who experience dysmenorrhea is expected to reduce PGF2 α levels so that the perceived dysmenorrheal pain will be reduced. (MY., 2006), (Ozgoli et al., 2009)

Based on the table, it is observed that there are respondents who experience a decrease in PGF2 α levels in

the control group and conversely there is an increase in PGF₂ α levels in the treatment group. Many factors can influence this, including hormone levels, nutritional status, stress, and physiological conditions of the body, sports activities and diet. (Mayo, 1997) Besides that, humans are unique individuals and have different biological characteristics so that their response to stimuli are also different.

During the luteal phase, there is excessive production of endometrial prostaglandins. Prostaglandins (especially PGE₂ and PGF₂ α) diffuse into the endometrial tissue which then stimulates abnormal uterine/myometrial muscle contractions, this excessive contraction will reduce blood flow resulting in ischemia in myometrial cells resulting in spasmodic pain. PGF₂ α levels are highest in the first 2 days of the menstrual period. (GUIDELINE, 2005)

Based on the explanation above, it can be concluded that there is an effect of giving ginger jelly candy to the decreasing of serum PGF₂ α levels in adolescents with primary dysmenorrhea.

CONCLUSION

In the ginger candy group there was a decreasing of PGF₂ α levels before and after the study and the decreasing of PGF₂ α levels in the group which was given ginger candy therapy was greater than in the group which was given candy without ginger.

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