Effect of Combination of Dark Chocolate and Herbal Ingredients for Dysmenorrhea in Late Adolescents

Rika Nurlaili Putri Azizah*, Putri Anggreini, Fajar Prasetya

Study Program of Clinical Pharmacy, Faculty of Pharmacy, Mulawarman University, Samarinda, Indonesia
*Corresponding author: rikaanurlailip@gmail.com

Abstract

About 55% of women experience dysmenorrhea. One of the foods that can reduce menstrual pain is dark chocolate. Other herbal ingredients such as turmeric, red ginger, moringa, sambiloto, and honey are also known to reduce pain. However, research on combination of dark chocolate with herbal ingredients has not been conducted. Therefore, this study aims to determine the effectiveness of dark chocolate with herbs in reducing menstrual pain. This test was conducted on 30 respondents who were divided into three groups, namely the positive control group (K), dark chocolate (C), and a combination of dark chocolate with herbs (C+H). Dark chocolate was combined with herbal ingredients consisting of turmeric, red ginger, moringa, sambiloto extract, and honey as a beverage 250 mL. The study is quantitative research with quasi-experimental method. Pain measurement using the Numeric Rating Scale (NRS) sheet was given before and 2 hours after treatment. The data was analyzed using paired t-test. State the results of the values obtained the combination of dark chocolate and herbs showed a significant reduction in pain before and after treatment ($p<0.05$). Based on these results, it was concluded that the combination of dark chocolate with herbs could be one of the therapies for dysmenorrhea.

Keywords: Dark Chocolate, Herbal, Dysmenorrhea, Menstruation

J. Trop. Pharm. Chem. 2023. Vol 7. No. 1.
p-ISSN: 2087-7099; e-ISSN: 2407-6090

1

1   Introduction

Dysmenorrhea is a cramp or pain experienced during menstruation, and it is one of the common causes of menstrual disorders [1]. In addition to pain, other symptoms can also be felt such as headaches, lethargy, sleep disturbances, disturbed appetite, nausea, vomiting, diarrhea, and stress [2]. According to the World Health Organization (2010), the prevalence of dysmenorrhea in women is about 90% and 55% in Indonesia [3]. Dysmenorrhea is subclassified as primary or secondary dysmenorrhea. Primary dysmenorrhea is menstrual pain due to prostaglandin levels from the ovulatory cycle, while secondary dysmenorrhea is menstrual pain due to diseases such as endometriosis, adenomyosis, fibroids (myomas), and pelvic disease [4]. Dysmenorrhea occurs due to increased secretion of prostaglandin F2α (PGF2α) and prostaglandin E2 (PGE2) in the uterus during endometrial sloughing, then increasing uterine tone, and also cause uterine contractions [5].

Therapy for dysmenorrhea can be done pharmacologically and non-pharmacologically. Drugs that can overcome dysmenorrhea are paracetamol, hormonal contraceptives and NSAIDs. NSAIDs are known to be drugs that are often used because they can reduce the concentration of prostaglandins in menstrual fluid, decrease uterine contractility, and menstrual volume. Although effective, long-term use of NSAIDs can cause effects on the gastrointestinal system to the point of bleeding [2]. Non-pharmacological management of dysmenorrhea can be done with warm compresses, light exercise such as muscle stretching, and adequate rest [6]. Some food are known to reduce menstrual pain such as dark chocolate, honey, turmeric and other herbal ingredients such as red ginger, Moringa and sambiloto.

Dark chocolate from cocoa beans is rich in vitamins and minerals. Cocoa beans contain high flavonoid polyphenol compounds, especially catechins, epicatechins, anthocyanidins and proanthocyanidins which are considered as compounds with anti-inflammatory and anti-nociceptive effects. Polyphenols have an analgesic effect by inhibiting the activity of the cyclooxygenase enzyme so that it can reduce prostaglandins and reduce pain [7, 8]. Dark chocolate is also high in magnesium which is able to have an effect on blood vessels and will contain calcium into smooth muscle cells in the body, so that it can affect the contraction, stress and relaxation of uterine muscles [9]. In a previous study, giving 72% dark chocolate at a dose of 35 grams could reduce the level of menstrual pain in Banda Aceh Midwifery Students in 2 hours [10]. Another similar study also found that giving 70% dark chocolate dose 45.7 grams could reduce menstrual pain in Lampung Medical Students [11].

The combination of several phytochemicals from the same or different foods can provide a synergistic anti-inflammatory effect [12]. A research study found that the combination of cocoa with omega 3 fatty acids can inhibit inflammation and reduce cardiovascular risk factors in humans [13]. Another similar study also showed that the combination of dark chocolate with carrot boiled water produced a good anti-inflammatory effect [14]. Taken together, the combination of dark chocolate with other herbal might increase the pharmacological effect, especially in antiinflamatory effect. Some herbal plants that well known as antiinflamatory agent

J. Trop. Pharm. Chem. 2023. Vol 7. No. 1.
p-ISSN: 2087-7099; e-ISSN: 2407-6090

2

are red ginger, turmeric, Moringa, sambiloto and honey. This plant can be used as an ingredient or mixture as traditional medicine. Red ginger contains gingerol and shogaol substances which are able to inhibit prostaglandins so that they can reduce menstrual pain during menstruation [15]. Turmeric contains curcumin compounds that are able to modulate the inflammatory response by regulating the activity of the enzymes cyclooxygenase-2 (COX-2) lipoxygenase, and nitrite oxygenase (iNOS) so that it will reduce and inhibit uterine contractions [16]. Moringa leaves are known to contain alkaloid compounds, glycosides, phenols, saponins and tannins so that they have analgesic properties in inhibiting cyclooxygenase-2 (COX-2) activity it can reduce pain [17]. Sambiloto contains andrographolide and 14-deoxy-11,12-didehydroandrographolide compounds which show analgesic and antipyretic activity [18]. Honey can inhibit cyclooxygenase synthesis due to the presence of flavonoid compounds and Vitamin E. The flavonoid can inhibit prostaglandin synthesis and can control uterine smooth muscle so that it can reduce pain during menstruation [19]. While vitamin E can suppress the activity of phospholipase A and cyclooxygenase enzymes through inhibition of post-translational activation of cyclooxygenase, so that it will inhibit the production of prostaglandins [20]. Information regarding the anti-inflammatory effect of these ingredients is already known. However, information about the combining of dark chocolate and herbal ingredients is still lacking. Thus, the present study aims to investigate the effect of combination dark chocolate with herbal ingredients as a beverage in late adolescence with dysmenorrhea.

2 Methods

The study is quantitative research with quasi-experimental method using purposive sampling technique. The study population was adolescents aged 19-21 years. The study was conducted on 30 respondents who were divided into three treatment groups: Positive Control Group (K); Dark Chocolate 35 grams (C); and the Combination of Dark Chocolate and Herbs (C+H). The ingredients of the combination dark chocolate and herbs as a beverage are 35 grams

of dark chocolate, 3 grams of turmeric, 2 grams of red ginger, 2.5 grams of Moringa leaves, 0.0057 grams of Sambiloto extract and 60 mL of honey. The pain measurement using the Numeric Rating Scale (NRS) sheet given before and 2 hours after treatment. The data was analyzed using the Paired T-Test to know the potential combination of dark chocolate and herbal ingredients and using the One Way Anova to determine the comparison in decreased menstrual pain between treatment groups.

3 Results and Discussion

Table 1 shows the percentage of characteristic data from 30 respondents. The characteristic data obtained include family history, age of menarche, menstrual length, body mass index (BMI), physical activity and hemoglobin levels (anaemia).

Table 1 Characteristics of Late Adolescent with Dysmenorrhea

Characteristic	Amount (n = 30)	Percentage (%)
Family History (dysmenorrhea)		
Yes	21	70%
No	9	30%
Age of Menarche		
<12 years	6	20%
12 years	9	30%
>12 years	15	50%
Menstrual Length		
<7 days	12	40%
7 days	9	30%
>7 days	9	30%
Body Mass Index		
Underweight	5	16,7%
Normal	14	46,6%
Overweight	5	16,7%
Obesity	6	20%
Physical Activity		
Yes	6	20%
No	24	80%
Anaemia		
Hb ≥ 12 (normal)	24	80%
Hb < 12 (anaemia)	6	20%

Based on the results between family history and the incidence of dysmenorrhea showed that the respondent who had a family history of dysmenorrhea were 21 respondents (70%) and did not have a family history of dysmenorrhea were 9 respondents (30%). According to Ehrenthal (2010), a family history that comes from a mother or sister who has dysmenorrhea is related to the condition

J. Trop. Pharm. Chem. 2023. Vol 7. No. 1.
p-ISSN: 2087-7099; e-ISSN: 2407-6090

3

anatomy and physiology are the same so there is a relationship of family history with the incidence of dysmenorrhea [21, 22]. This study similar to the results of [21] in young women in Sangihe Islands regency who had a family history of 61 respondents (100%), it can be said that family history has a significant relationship with the incidence of dysmenorrhea.

The results between the age of menarche with the incidence of dysmenorrhea showed in the age category of menarche < 12 years were 6 respondents (20%) , the age of menarche 12 years were 9 respondents (30%) and the majority of menarche age > 12 years were 15 respondents (50%). This is not similar to the results of Qomarasari (2021) which showed 89 respondents who had menarche age <12 years (84.8%) the majority suffered from dysmenorrhea with p-value = 0.022 which means there is a relationship between menarche age and the incidence of dysmenorrhea. The age of menarche is the age when the first menstruation begins. The age of menarche varies between the ages of 10 to 16 years, but the normal age of menarche occurs at the age of 12 to 14 years. If the age of menarche occurs at an earlier age than normal, the reproductive organs are not ready to undergo changes and there is still a narrowing of the cervix so pain will arise during menstruation [23, 24]. In this study there was no relationship between the age of menarche with dysmenorrhea because the majority of respondents had menarche age > 12 years.

The results between the menstrual length with the incidence of dysmenorrhea showed 12 respondents had menstrual length <7 days (40%), 9 respondents with menstrual length 7 days (30%) and 9 respondents with menstrual length >7 days (30%). This is not similar to the results of Worung et al. (2020) which showed that 62 respondents (96.9%) had normal menstrual length and 2 respondents (3.1%) had abnormal menstrual length. The normal time of menstruation is 3-7 days and if more than the normal time, it is possible to experience more severe dysmenorrhea. Menstruation longer than the normal time will cause the uterus to contract more often and more prostaglandins are secreted. Excessive production of prostaglandins is what causes pain. Meanwhile, continuous uterine contractions cause the blood supply to the uterus to stop and dysmenorrhea

occurs [24]. In this study, there was no relationship between the length of menstruation and dysmenorrhea because the majority of respondents had normal menstrual length.

The results between body mass index with the incidence of dysmenorrhea showed 5 respondents with underweight BMI (16.7%), 14 respondents with normal BMI (46.6%), 5 respondents with overweight BMI (16.7%) and 6 respondents with obese BMI (20%). This study similar to the results of Wahyuni dan Oktaviani (2018) at SMP PGRI Pekanbaru who found 34 of 53 respondents had a normal BMI (89,5%). However, this study not similar to the results by Nuraini et al. (2021) who found that the majority of respondent dysmenorrhea with overweight BMI. Obese is one of the factors for dysmenorrhea because of the presence of excess fat tissue resulting in pressured blood vessels by fatty tissue in the female reproductive system so that the blood flowing during menstruation will be disrupted and cause the pain. In addition, a person with a BMI of overweight and obese has higher levels of prostaglandins [27]. In this study there was no relationship between body mass index and dysmenorrhea because the majority of respondents had normal BMI.

The results between physical activity and the incidence of dysmenorrhea showed there were 6 respondents (20%) who did physical activity and 24 respondents (80%) who did not physical activity. These results similar with the research of Tsamara et al. (2020) which showed there was a relationship between physical activity and the incidence of dysmenorrhea (*p-value* = 0.012) [28]. Someone who rarely or never does physical activity is more at risk of experiencing dysmenorrhea than someone who is diligent in physical activity. This is because when dysmenorrhea oxygen cannot be channeled properly to the blood vessels, it causes vasoconstriction uterus [23]. If someone have a rutinity of doing physical activity, it can increase blood flow to the reproductive organs, reduce stress, and provide relaxation so that will relieve menstrual cramps [22]. In this study, there is a relationship between physical activity and the incidence of dysmenorrhea because the majority of respondents do not do physical activity.

J. Trop. Pharm. Chem. 2023. Vol 7. No. 1.
p-ISSN: 2087-7099; e-ISSN: 2407-6090

4

The results between anaemia and the incidence of dysmenorrhea, it shows that 6 respondents (20%) experienced anaemia and 24 respondents (80%) not experienced anaemia. This results not similar with the research of Machmud et al. (2018) which shows there was relationship between anaemia and dysmenorrhea which the majority of dysmenorrhea that were 37 respondents experienced anaemia (82.2%) and 19 respondents did not experience anaemia (32.2%). Anemia is a condition in which the levels of hemoglobin and erythrocytes are lower than normal. Hemoglobin functions to bind oxygen in the blood to be circulated throughout the body. If the level of hemoglobin in the blood is low, it will result in decreased blood flow and stimulation of the myometrium [29]. Decreased blood flow will cause oxygen cannot be delivered to the blood vessels in the reproductive organs and cause vasoconstriction in the uterus then causing pain [30]. In this study there was no relationship between anemia and dysmenorrhea because the majority of respondents not experienced anaemia.
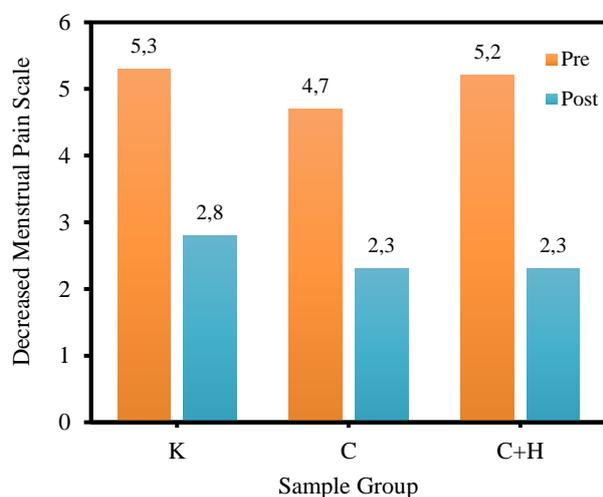

Figure 1 Results of Decreased Menstrual Pain Scale in the Positive Control Group (K); Dark Chocolate Group (C); and Combination Dark Chocolate with Herbs Group (C+H).

Based on these results (Figure 1) it showed that the positive control group has an average pretest pain scale was 5,3 and average posttest pain scale was 2,8. In the dark chocolate group, the pretest average pain scale was 4,7 and the posttest average was 2,3. Meanwhile, in the test group, the combination of dark chocolate and herbal ingredients had an average pretest pain scale was 5,3 and average posttest was 2,3. Therefore, it concluded that all of treatments group had a significant or potential effect in reducing dysmenorrhea pain in late adolescence.

Table 2 The Decrease of Menstrual Pain Between Groups

Group	Mean SD	Mean Difference	Max - Min	P-value
K				
Pre-Test	5,3 ± 1,703	2,5	8 – 3	0,000
Post-Test	2,8 ± 2,201		7 – 0	
C				
Pre-Test	4,7 ± 1,337	2,4	6 – 3	0,000
Post-Test	2,3 ± 2,163		6 – 0	
C+H				
Pre-Test	5,2 ± 1,476	2,9	8 – 3	0,000
Post-Test	2,3 ± 1,767		5 – 0	

Based on table 2, it showed that the mean menstrual pain of dark chocolate group before intervention was 4.7 and decreased to 2.3 after intervention. Meanwhile, the combination of dark chocolate and herbs before the intervention group was 5.3 and decreased to 2.3 after the intervention. Based on the results of the paired t-test, it showed that the results before and after intervention of dark chocolate 35 grams showed a p-value of 0.000 (p<0.05). The combination group of dark chocolate with herbal ingredients also showed a p-value of 0.000 (p<0.05) before and after treatment. This means that there is a relationship between giving a combination of dark chocolate with herbal ingredients in reducing menstrual pain in late adolescence.

This study similar to the results by Febriansyah (2020) on Midwifery Student Saleha Banda Aceh which showed a significant difference between giving dark chocolate before treatment (4.13) and after treatment (1.33) with a difference of 2.8 decreases. This study is also similar to the results of other studies which stated that giving 40 grams of dark chocolate per day was able to reduce the intensity of menstrual pain [14]. Therefore, in this study it can be concluded that 35 grams of dark chocolate can reduce the pain scale of dysmenorrhea in late adolescence.

J. Trop. Pharm. Chem. 2023. Vol 7. No. 1.
p-ISSN: 2087-7099; e-ISSN: 2407-6090

5

Table 3 Significance of Menstrual Pain Reduction Between Groups

Group	STDEV		Meann	Sig. One Way ANOVA
	pretest	postest		
K (n=10)	1.484	1.925	2.5	
C (n=10)	5.07	2.47	2.4	0.677*
C+H (n=10)	(mean)	(mean)	2.9	

Based on Table 3 significance of One Way Anova test showed p-value of 0.677 (p>0.05) which means there is no significant difference between the three treatment groups in reducing dysmenorrhea pain. However, when viewed from the decrease in pain scale on the combination dark chocolate and herbs group, the difference was 2.9 which is greater than in the dark chocolate group with a difference of 2.4 and a positive control group with a difference of 2.5. This showed that the combination of dark chocolate and herbs had better analgesic and anti-inflammatory potential compared to the test group of dark chocolate and paracetamol, although the differences were not very different.

Dark chocolate 70% high in phenol antioxidants and flavonoids. The content of antioxidants in dark chocolate is known to be 3 times more than in green tea. The mechanism of phenols and flavonoids as analgesics is able to reduce prostaglandins by inhibiting cyclooxygenase synthesis so as to reduce pain. In addition, Dark Chocolate also contains high magnesium which have a relaxing effect on smooth muscles and provide vasodilatory effects of blood vessels, so that the nerves become less tense and pain is reduced. By consuming 40 grams dark chocolate 69% a day can increase the amount of magnesium in the body and reduce pain during menstruation. A dose of 69% dark chocolate as much 40 grams contains enough magnesium, which is approximately 115 mg will help increase the amount of magnesium in the body obtained from food and can be used as a menstrual pain reliever. Menstrual pain can be overcome by taking a maximum of 300 mg of magnesium during pain [9].

In this study, the combination of dark chocolate with herbs had more potential analgesic and anti-inflammatory effect than the test group of dark chocolate and paracetamol drugs although the difference did not differ much. According to Zhang et al. (2019), the combination of several phytochemicals from the same or different foods can provide synergistic anti-inflammatory effects. This is appropriate because dark chocolate in this study combined with herbal ingredients that also act as anti-inflammatory, namely turmeric, red ginger, moringa, sambiloto and honey. This herbs can be used as a decoction or mixture as a traditional therapy.

Table 4 Beverage Composition of Combination Dark Chocolate with Herbal Ingredients

Ingredients
Dark Chocolate
Turmeric Extract
Red Ginger Extract
Moringa Extract
Sambiloto Extract
Honey

Red ginger contains gingerol and shogaol substances to relieve pain and nausea during menstruation. The chemical content of gingerol in red ginger is higher than other ginger variants, so red ginger is suitable for consumption by women with dysmenorrhea because it is able to inhibit prostaglandins so that it can reduce menstrual pain during menstruation. In addition, the content of essential oils and oleoresin in red ginger which is higher than other ginger variants also plays a role in reducing dysmenorrhea pain [15]. Turmeric has phenolic compounds as antioxidants, analgesics, and anti-inflammatory. Turmeric contains curcumin which has anti-inflammatory effects by inhibiting inflammatory mediators including phospholipase, lipooxygenase, COX-2, leukotrienes, thromboxane, prostaglandins, nitric oxide, collagenase, elastase, hyaluronidase, MCP-1, interferon-inducible protein, tumor necrosis factor, and interleukin-12. Turmeric can inhibit cyclooxygenase (COX) reaction so that it can inhibit uterine contractions that cause menstrual pain [16]. Moringa leaves also contain flavonoids that can provide an anti-inflammatory effect by inhibiting the activity of the cyclooxygenase enzyme. In addition, the presence of quercetin in Moringa leaves which also belongs to the flavonoid group is the main bioactive

J. Trop. Pharm. Chem. 2023. Vol 7. No. 1.
p-ISSN: 2087-7099; e-ISSN: 2407-6090

6

component of Moringa which has anti-inflammatory activity [17]. Sambiloto that also known as bitter leaf contains andrographolide and 14-deoxy-11,12-didehydroandrographolide compounds which have analgesic and antipyretic activity. [18]. Sambiloto has a strong anti-inflammatory effect that reduces the manifestation of pro-inflammatory agents, including COX-2, IL-6, IL-1β, iNOS, and NF-kB. Dehydroandrographolide and neo-andrographolide compounds also exhibit anti-inflammatory activity by affecting cyclooxygenase (COX)-1 and -2 and downregulating the expression of genes associated with the inflammatory response, including cytokines and cytokine receptors, chemokines, and NF-κB [31]. Honey can reduce pain due to the presence of flavonoids and vitamin E. Flavonoids can inhibit cyclooxygenase synthesis and inhibit neutrophil degranulation so that will inhibit the release of cytokines, free radicals and enzymes in inflammation [8]. Vitamin E can suppress the activity of phospholipase A and cyclooxygenase enzymes through inhibition of post-translational activation of cyclooxygenase, so that it will inhibit the production of prostaglandins [20]. Due to anti-inflammatory effect of these herbal ingredients, the combination of these ingredients have a pain-reducing effect in women with dysmenorrhea.

4   Conclusions

Based on the results of the study showed that the combination of dark chocolate with herbal ingredients such as turmeric, red ginger, moringa, sambiloto and honey had activity and potential in decreasing menstrual pain scale in late adolescents ($p<0.05$), so it could be as alternative therapies for dysmenorrhea.

5   Declarations

5.1   Author Contributions

Rika Nurlaili Putri Azizah: conducting research, collecting data and compiling manuscripts. Fajar Prasetya and Putri Anggreini: director, supervisor and final coordinator of manuscript.

5.2   Funding Statement

Not Available.

5.3   Conflicts of Interest

The authors declare no conflict of interest.

5.4   Ethic

Ethical has been approved by the Commission on Health Research Ethics Faculty of Pharmacy, University of Mulawarman No.56/ KEPK-FFUNMUL/EC / EXP/08/2022.

6   References

[1] Bernardi, M., Lazzeri, L., Perelli, F., Reis, F. M., & Petraglia, F. (2017). Dysmenorrhea and related disorders. *F1000Research*, 6, 1–7. https://doi.org/10.12688/f1000research.11682.1

[2] Itani, R., Soubra, L., Karout, S., Rahme, D., Karout, L., & Khojah, H. M. J. (2022). Primary Dysmenorrhea : Pathophysiology , Diagnosis , and Treatment Updates. *Korean Journal of Family Medicine*, 43, 101–108.

[3] Anggriani, A., Mulyani, Y., & Pratiwi, L. D. (2021). Pengaruh Terapi Farmakologi Dan Non-Farmakologi Terhadap Penurunan Nyeri Menstruasi Pada Mahasiswi Fakultas Farmasi Universitas Bhakti Kencana Bandung. *Jurnal Riset Kefarmasian Indonesia*, 3(3), 174–188. https://doi.org/10.33759/jrki.v3i3.156

[4] Lacovides, S., Avidon, I., & Baker, F. C. (2015). What we know about primary dysmenorrhea today: A critical review. *Human Reproduction Update*, 21(6), 762–778. https://doi.org/10.1093/humupd/dmv039

[5] Barcikowska, Z., Rajkowska-Labon, E., Grzybowska, M. E., Hansdorfer-Korzon, R., & Zorena, K. (2020). Inflammatory markers in dysmenorrhea and therapeutic options. *International Journal of Environmental Research and Public Health*, 17(4), 1–14. https://doi.org/10.3390/ijerph17041191

[6] Asih, S. N., Yuviska, I. A., & Astriana. (2020). Pengaruh Dark Chocolate Terhadap Pengurangan Nyeri Haid. *Jurnal Kebidanan*, 6(4), 499–501. http://jks.fikes.unsoed.ac.id/index.php/jks/article/download/680/408%0Ahttps://docplayer.info/42489606-Dark-chocolate-dan-nyeri-dysmenorrhea.html

[7] Toker, O. S., Konar, N., Palabiyik, I., Rasouli Pirouzian, H., Oba, S., Polat, D. G., Poyrazoglu, E. S., & Sagdic, O. (2018). Formulation of dark chocolate as a carrier to deliver eicosapentaenoic and docosahexaenoic acids:

J. Trop. Pharm. Chem. 2023. Vol 7. No. 1.
p-ISSN: 2087-7099; e-ISSN: 2407-6090

7

Effects on product quality. *Food Chemistry*, 254, 224–231. https://doi.org/10.1016/j.foodchem.2018.02.019

[8] Syamsul, E. S., Andayani, F., & Soemarnoe, Y. B. (2016). Analgesic Activity Study Of Ethanolic Extract Of Callicarpa longifolia Lamk. In Mice. *Traditional Medicine Journal*, 21(2), 99–103.

[9] Maharani, S. I., Pramono, N., & Wahyuni, S. (2017). Dark Chocolate's Effect on Menstrual Pain in Late Adolescents. *Belitung Noursing Journal*, 3(6), 686–692. https://belitungraya.org/BRP/index.php/bnj/article/download/292/pdf

[10] Febriansyah, E. (2020). Dismenore Primer Pada Mahasiswi Akademi Kebidanan Saleha Banda Aceh the Effect of Dark Chocolate To Decrease P Rimary Dysmenorrhea Pain Intensity in Saleha Midwifery Academy. *SEL Jurnal Penelitian Kesehatan*, 8(2), 96–105. https://doi.org/10.22435/sel.v8i2.5108

[11] Khairunnisa, N., Sukohar, A., Hanriko, R., & Septa, T. (2018). Hubungan Pemberian Dark Chocolate Terhadap Penurunan Skala Nyeri Menstruasi (Dismenorea Primer) Yang Dipengaruhi Dengan Kondisi Stres Pada Mahasiswi Kedokteran Universitas Lampung The Correlation of Dark Chocolate on Decreasing Pain Scale from Primary D. *Majority*, 7(3), 81–89.

[12] Zhang, L., Virgous, C., & Si, H. (2019). Synergistic anti-inflammatory effects and mechanisms of combined phytochemicals. *Journal of Nutritional Biochemistry*, 69, 19–30. https://doi.org/10.1016/j.jnutbio.2019.03.009

[13] Davinelli, S., Corbi, G., Righetti, S., Sears, B., Olarte, H. H., Grassi, D., & Scapagnini, G. (2018). Cardioprotection by cocoa polyphenols and ω-3 fatty acids: A disease-prevention perspective on aging-associated cardiovascular risk. *Journal of Medicinal Food*, 21(10), 1060–1069. https://doi.org/10.1089/jmf.2018.0002

[14] Siregar, R. D., Veri, N., Harahap, M. S., Alchalidi, A., & Usrina, N. (2021). Efektivitas Dark Chocolate Dan Wortel Dalam Menurunkan Intensitas Disminorea Primer. *Jurnal Kebidanan Malahayati*, 7(4), 642–646. https://doi.org/10.33024/jkm.v7i4.4418

[15] Ramayanti, E. D., Etika, A. N., & Jayani, I. (2020). Perbedaan Efektivitas Pemberian Perasan Air Wortel dan Jahe Merah Terhadap Nyeri Haid Pada Remaja. *Jurnal Penelitian Perawat Profesional*, 1(1), 61–70. http://jurnal.globalhealthsciencegroup.com/index.php/JPPP/article/download/83/65

[16] Utami, R. B., Damayanti, D. F., & Rodiah, D. (2020). The effectiveness of curcuma longa drink in decreasing the intensity of dysmenorrhea. *Biomedical and Pharmacology Journal*, 13(4), 2055–2060. https://doi.org/10.13005/BPJ/2085

[17] Hamdiyah, & Sukarta, A. (2019). Pengaruh Pemberian Teh Daun Kelor (Moringa Oleifera Leaves) Terhadap Penurunan Dismenore Pada Remaja Putri Anemia Di Panti Asuhan Sejahtera Aisyiyah Kabupaten Sidrap. *Jurnal Antara Kebidanan*, 2(4), 283–292.

[18] Ilmi, H., Pamungkas, I. R., Tumewu, L., Hafid, A. F., & Widyawaruyanti, A. (2021). Analgesic and Antipyretic Activities of Ethyl Acetate Fraction Tablet of Andrographis paniculata in Animal Models. *Evidence-Based Complementary and Alternative Medicine*, 2021, 1–8. https://doi.org/10.1155/2021/8848797

[19] Silaban, T. D. S., Amir, A., & Defrin. (2019). Pengaruh Pemberian Madu Murni Kaliandra Terhadap Perubahan Derajat Dismenorhea pada Remaja Putri di Poltekes Kemenkes Padang Tahun 2019. *Jurnal Kesehatan Andalas*, 8(4). http://jurnal.fk.unand.ac.id

[20] Kharaghani, R., Rahbari, M., Keramat, A., Mirmohammadkhani, M., & Yallanghach, M. (2014). The effect of vitamin E on ameliorating primary dysmenorrhea: A systematic review and meta-analysis. *Journal of Basic and Clinical Reproductive Sciences*, 3(2), 79. https://doi.org/10.4103/2278-960x.140037

[21] Horman, N., Manoppo, J., & Meo, L. N. (2021). Faktor-Faktor Yang Berhubungan Dengan Kejadian Dismenore Primer Pada Remaja Puteri Di Kabupaten Kepulauan Sangihe. *Jurnal Keperawatan*, 9(1), 38. https://doi.org/10.35790/jkp.v9i1.36767

[22] Worung, Y. V. F., Wungouw, H. I. S., & Renteng, S. (2020). Faktor-Faktor Yang Berhubungan Dengan Persepsi Nyeri Haid Pada Remaja Putri Di Sma Frater Don Bosco Manado. *Jurnal Keperawatan*, 8(2), 79–86. https://doi.org/10.35790/jkp.v8i2.32324

[23] Qomarasari, D. (2021). Hubungan Usia Menarche, Makanan Cepat Saji (Fast Food), Stress Dan Olahraga Dengan Kejadian Dismenorea Pada Remaja Putri Di Man 2 Lebak Banten. *Bunda Edu-Midwifery Journal (BEMJ)*, 4(2), 30–38. https://doi.org/10.54100/bemj.v4i2.53

[24] Indarna, A. A., & Lediawati, L. (2021). Usia Menarche dan Lamanya Menstruasi dengan Kejadian Dismenore Primer pada Siswi Kelas X Di SMK Kesehatan Bhakti Kencana Subang. *Journal of Nursing and Public Health*, 9(2), 1–7.

[25] Wahyuni, R. S., & Oktaviani, W. (2018). Hubungan Indeks Massa Tubuh dengan Dismenore pada Remaja Putri SMP PGRI Pekanbaru. *Jurnal Endurance*, 3(3), 618. https://doi.org/10.22216/jen.v3i3.2723

J. Trop. Pharm. Chem. 2023. Vol 7. No. 1.
p-ISSN: 2087-7099; e-ISSN: 2407-6090

8

[26] Nuraini, S., Sa'diah, Y. S., & Fitriany, E. (2021). Hubungan Usia Menarche, Status Gizi, Stres dan Kadar Hemoglobin Terhadap Kejadian Dismenorea Primer pada Mahasiswi Fakultas Kedokteran, Universitas Mulawarman. *Jurnal Sains Dan Kesehatan*, 3(3), 443–450. https://doi.org/10.25026/jsk.v3i3.398

[27] Juliana, J. (2018). Determinan Dismenorea Di Sman 2 Bagan Sinembah Kabupaten Rokan Hilir. *Jurnal Endurance*, 3(1), 61. https://doi.org/10.22216/jen.v3i1.1664

[28] Tsamara, G., Raharjo, W., & Putri, E. A. (2020). Hubungan Gaya Hidup dengan Kejadian Dismenore Primer pada Mahasiswi Program Studi Pendidikan Dokter Fakultas Kedokteran Universitas Tanjungpura. *Nasional Ilmu Kesehatan (JNIK)*, 2(3), 130–140. https://journal.unhas.ac.id/index.php/jnik/article/view/8543

[29] Machmud, A., Sharrif, S. A., & Thamrin, H. (2018). Kejadian Dismenorhoe Pada Mahasiswi Dengan Anemia. *Jurnal Kesehatan*, 1(3), 179–185.

[30] Kusumawardani, P. A., & Cholifah. (2018). The Relations Between Anemia and Female Adolescent's Dysmenorrhea. *Universitas Ahmad Dahlan International Conference on Public Health*, 190–195. https://osf.io/7698n/download

[31] Intharuksa, A., Arunotayanun, W., Yooin, W., & Sirisa-ard, P. (2022). A Comprehensive Review of Andrographis paniculata (Burm. f.) Nees and Its Constituents as Potential Lead Compounds for COVID-19 Drug Discovery. *Molecules*, 27(14). https://doi.org/10.3390/molecules27144479

J. Trop. Pharm. Chem. 2023. Vol 7. No. 1.
p-ISSN: 2087-7099; e-ISSN: 2407-6090

9