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EFFECT OF CIPLUKAN EXTRACT (Physalis angulata L.) TO THE NUMBER OF FIBROBLASTS IN IMIQUIMOD INDUCES PSORIASIS MICE MODEL

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ABSTRACT

Imiquimod induces activation of Th17 cells and dendritic cells that play a role in psoriasis. Ciplukan extract (*Physalis angulata* L.) contains steroid compounds, flavonoids, alkaloids, and saponins such as Physalin B, Physalin F, Physalin G which have anti-inflammatory activity in psoriasis pathophysiology. This research is an experimental research with *post test only with control group design*. Thirty five female mice were divided into 7 groups. Group A: negative control, group B: positive control, group C induced by imiquimod and given with ciplukan extract 400 mg/kg BW for 7 days, group D induced by imiquimod and given with ciplukan extract 800 mg/kg BW for 7 days, group E induced imiquimod and given with ciplukan extract 1,200 mg/kg BW for 7 days, group F induced by imiquimod and given with methotrexate 1 mg/kg BW for 7 days, and group G induced by imiquimod and given with a combination of ciplukan extract 1,200 mg/kgBW and methotrexate 1mg/kgBW for 7 days. 7 days. The number of fibroblast cells was counted on the fifteenth day by taken a sample of mouse skin and made histological preparations and then counted manually used a microscope. The mean number of fibroblast cells in groups A, B, C, D, E, F, and G were 21.6±2.3, respectively; 39.2±5.5; 30.6±1.3; 24.0±2.8; 24.8±2.9; 28,4±3,0;28,2±3,2 . The results of the test *One Way* ANOVA showed a value of p = 0.000 (p < 0.05), so that the results are significant.

Keywords: ciplukan extract, fibroblast, methotrexate , *Physalis angulata*

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INTRODUCTION

Psoriasis is a chronic skin inflammation characterized by reddish patches on which there are rough, thick, multi-layered, transparent white scales [Cantika, 2012]. The prevalence of psoriasis sufferers worldwide according to the *World Health Organization* (WHO) in 2016 was 0.09 % -11.4 % with different figures in each country. The prevalence of psoriasis in Indonesia reaches 2.5% of the total population [Krisnarto *et al.*, 2016]. The number of psoriasis sufferers in Purwokerto based on the records of the Medical Record section of the Prof. Dr. Margono Soekarjo, Purwokerto, in 2016 reached 562 patients and from January to August 2017 reached 705 patients [Ernawati, 2017]. Patients with psoriasis often have an increased risk of suffering from comorbid diseases, including systemic lupus erythematosus and type 2 diabetes mellitus [Christophers, 2017]. Psoriasis has an emotional, social and physical impacts on sufferers. Psychological impacts are also frequently reported on psoriasis sufferers such as sexual dysfunction, depression, low self-esteem, plans to commit suicide [Ramsey, 2018].

The exact cause of psoriasis is not fully understood, but available research evidence suggests that the interleukin 17 (IL-17) and interleukin 23 (IL-23) axis play an important role in the pathophysiology of psoriasis [Menter, 2018]. Interleukin 17 (IL-17) is produced by T Helper 17 (Th17) cells and Interleukin 23 (IL-23) is produced by myeloid dendritic cells [Cai *et al*, 2018]. Th17 itself will be activated by IL-23 which is released by myeloid dendritic cells due to an increase in the number of Nuclear factor-κB (Nf-κB) in dendritic cells due to the binding between Cathelidin ligand (LL-37) of keratinocytes or imiquimod with *Toll-like Receptor receptors.* 7/8 (TLR 7/8) [Gottlieb *et al*., 2018]. IL-17 released by Th17 cells will bind to receptors on keratinocyte cells which will have an effect on keratinocyte cells themselves to produce AMP (*Anti Microbial Peptide*) as a neutrophil chemo-attractant to migrate to skin tissue and TGF-β1 (*Transforming Growth Factor Beta 1*) which plays a role in fibroblast cell proliferation and extracellular matrix production. Fibroblast cells will proliferate caused by increase in the number of mitochondria in the cell which causes an increase in the number of *reactive oxygen species* (ROS) in fibroblast cells. The increase amount of ROS will cause fibroblast cells to differentiate to form *NADPH Oxidase* 4 (NOX4) on the cell surface in excess amounts than normal. NOX4 plays a role in the release of ROS from within and out of fibroblast cells and into keratinocyte cells which causes activation of the p38 gene in the nucleus of keratinocytes. The activation of the p38 gene causes an increase in protein synthesis and proliferation of keratinocytes [Erraki *et al*, 2019]. The proliferation of keratinocytes will give a clinical picture of thickening of the skin and the formation of scales in psoriasis patients.

Current psoriasis treatment is more directed at decreasing the effect of inflammation on the skin. Psoriasis treatment can be divided into 3 types, that are topical treatment, *light therapy*, and systemic treatment. The treatment that is often used is systemic treatment using methotrexate because it causes cell apoptosis by inhibiting protein synthesis in cells. Methotrexate works as a suppressor of keratinocyte cells, fibroblasts by inhibiting dihydrofolate reductase and will inhibit DNA synthesis so that there will be a decrease in the proliferation of keratocytes, fibroblasts, and the formation of inflammatory cytokines [Elango *et al*., 2014]. Another advantage of using methotrexate is that it is easy to obtain and low cost compared to other pharmacological treatments [Feldman,2019]. Methotrexate has side effects that can occur, namely redness of the skin, fever, diarrhea and in 10% of cases bone marrow suppression occurs, causing pancytopenia in psoriasis patients undergoing treatment [Ohbayashi *et al*., 2010].

Ciplukan (*Physalis angulata L.*) is a plant that is often found in Indonesia and is used to by the usual people to treat diabetes, respiratory tract inflammation, and hypertension [Dalimartha,2006]. The active substances in Ciplukan (*Physalis angulata L.*) which are clinically proven are Pysalin G, Physalin B, and Quercetin which have anti-inflammatory and antiproliferative effects on cells [Huong *et al.*,2016]. Choi's research in 2018 showed that the content of Physalin B and Physalin G in ciplukan extract (*Physalis angulata L.*) at a dose of 400 mg/kg BW had an anti-inflammatory effect in rats induced by atopic dermatitis and inhibited the

production of inflammatory mediators through a binding mechanism with glucocorticoid receptors on lymphocytes and keratinocytes in mice. The process of developing drugs or substances for therapy requires complicated steps, issues, and takes a long time and is related to *ethical clearance*. The research of Na Takuathung *et al* in 2018 and Luo in2016 stated that the use of Balb/c mice induced by Aldara® imiquimod gave the most optimal results for the formation of psoriasis models compared to the use of Vaseline® and Likejie®. The aim of this study is to examining the anti-inflammatory's effectiveness of ciplukan extract (*Physalis angulate L.)* by measuring the number of fibroblasts in histopathologically staining with Haematoxylin Eosin (HE).

MATERIALS AND METHODS

This research is a type of *true experimental* with *randomized post-test only with control group design.* Simplisia ciplukan (*Physalis angulata L.*) was macerated using ethanol (95%) (binding to polar substances), n-hexane(binding to semi-polar substances), and etyl acetate (binding to non-polar substances) in gradually stages. We used ciplukan extract from ethyl acetate solution. The experimental animal were female mices (*Mus musculus*) which had been shaved on the back with a razor and the size area is 2 cm x 2 cm Then, psoriasis-like was induced with imiquimod cream at a dose of 62.5 mg for 7 days in the positive control group (A) and the negative control group (B). and 13 days in the ciplukan extract group at a dose of 400 mg/ kg BW (C), 800 mg/kg BW (D), 1,200 mg/kg BW (E), and methotrexate 1 mg/kg BW (F), combination of ciplukan extract 1,200 mg/ kg BW plus methotrexate 1 mg/ kgBW (G). Groups A and B were terminated on the eighth day for skin tissue sampling. Groups C, D, E, F, G were terminated on the fifteenth day to collect skin samples. The histopathological preparations were made after the previous ciplukan extract was administered on the eighth to the fourteenth day. The preparations were read using a microscope with 400x magnification in 10 different fields of view. Data analysis used SPSS IBM® 28.0.1 software with Shapiro-Wilk *test* and continued with One Way Anova test . The degree of significance limits if $p \leq 0.05$. This study used experimental animals by applying animal ethics, which had obtained by submitting approval to the Ethics Commission of the Faculty of Medicine, Jenderal Soedirman University with number 205/KEPK/IX/2020.

RESULTS

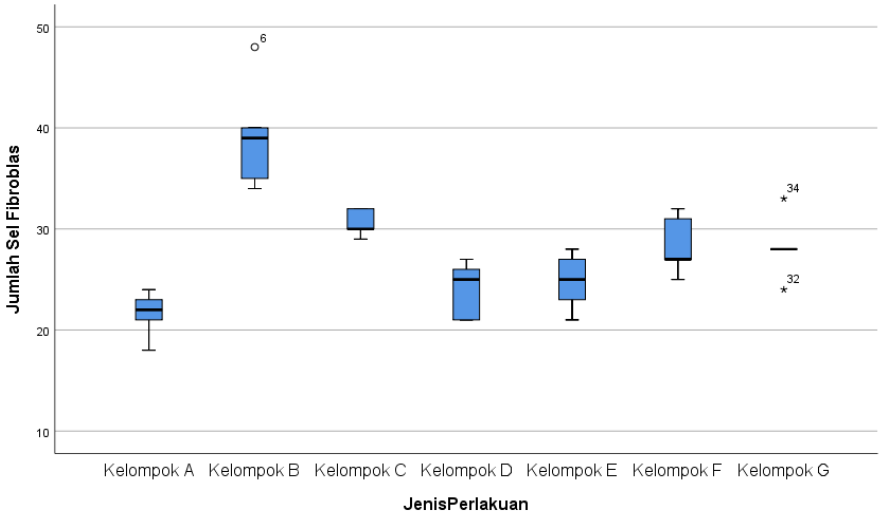
Based on the results, the number of fibroblasts in each treatment groups is shown in table 1.

Table 1 Description of the number of fibroblasts of mice per treatment group

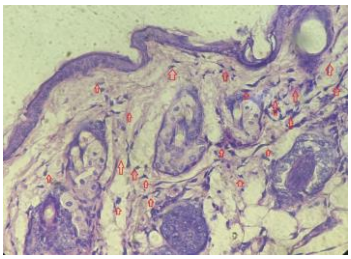
Group	N	Minimum (Cell/s)	Maximum (Cell/s)	Median (Cell/s)	Mean (Cell/s)	Deviation (Cell/s)
A	5	18	34	22.00	21.60	2.302
B	5	34	48	39.00	39.20	5.541
C	5	29	32	30.00	30.60	1.342
D	5	21	27	25.00	24.00	2.828
E	5	21	28	25.00	25.80	2.864
F	5	25	32	27.00	28.40	2.966
G	5	24	33	28.00	28.20	3.194

Note : Group A: negative control group; Group B: positive control group; Group C: the group that was given ciplukan extract 400 mg/kg BW; Group D: the group that was given ciplukan extract 800 mg/kg BW; Group E: the group that was given ciplukan extract 1,200 mg/ kgBW; Group F: the group that was given methotrexate 1 mg /kgBW; Group G: the group that was given a combination of ciplukan extract 1,200 mg/kgBW and methotrexate 1 mg/kgBW (Source: processed primary data)

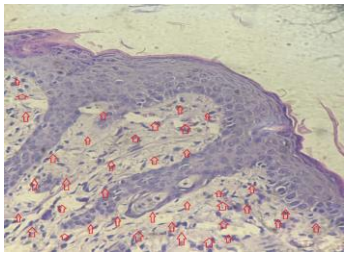
(a)


Jumlah Sel Fibroblas
50
40
30
20
10
6
34
32
Kelompok A
Kelompok B
Kelompok C
Kelompok D
Kelompok E
Kelompok F
Kelompok G
JenisPerlakuan

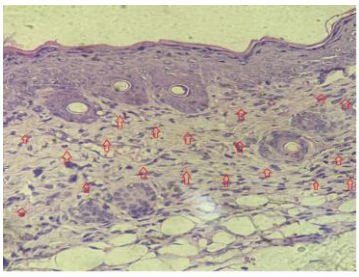
(b)



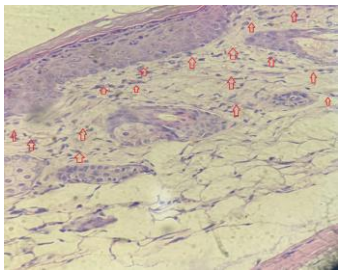
(b)



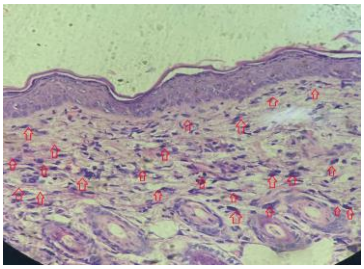
(c)



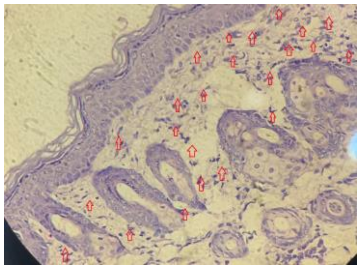
(d)



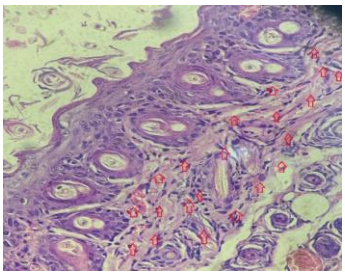
(e)



(f)



(g)



(h)

Figure 1. Graph of the number of fibroblast cells in each treatment groups (a), histological preparations for each group (fibroblast cells are indicated by red arrows), group A (b), group B (c)), group C (d), group D (e), group E (f), group F (g), group G (h).

The results of the normality test for the data on the number of fibroblasts in the treatment group using Saphiro-Wilk showed that 7 groups had data normally distributed (p>0.05). Then in the homogeneity test of the data using the Levene test, homogeneous data were obtained (p>0.05). The data on the number of fibroblasts were normally distributed and homogeneous so that they met the requirements of theparametric test One Way ANOVA. The results of thetest One Way ANOVA on the number of fibroblast cells in each treatment group showed a value of 0.000 (p ≤0.05). The results of One Way ANOVA test shown on table 2.

Table 2. Results of the One Way ANOVA test mean the number of skin fibroblasts in the imiquimod induced psoriasis like model

Group	N	Mean ± Deviation Standard (g/dL)	p value	Note
A	5	21,6±2,3	0,000	There is a significant difference
B	5	39,2±5,5		
C	5	30,6±1,3		
D	5	24,0±2,8		
E	5	24,8± 2,9		
F	5	28,4±3,0		
G	5	28,2±3,2		
Total	35			

Note : Group A: negative control group; Group B: positive control group; Group C: the group that was given ciplukan extract 400 mg/kg BW; Group D: the group that was given ciplukan extract 800 mg/kg BW; Group E: the group that was given ciplukan extract 1,200 mg/ kgBW; Group F: the group that was given methotrexate 1 mg /kgBW; Group G: the group that was given a combination of ciplukan extract 1,200 mg/kgBW and methotrexate 1 mg/kgBW (Source: processed primary data)

DISCUSSION

The difference in the number of fibroblast cells was significant. The number of fibroblast cells in group C, group D, and group E were less than group B due to the content of Physalin B, Physalin G, and Quercetin in ciplukan extract that was macerated with ethyl acetate. Selection of maceration results of ciplukan extract using ethyl acetate has the basis that ethyl acetate is a non-polar compound and will bind to semi-polar active compounds, namely seco-steroids (Physalin B, Physalin G) and flavonoids (Quercetin) in ciplukan extract (Pinto et al., 2011). Physalin B and Physalin G are seco-steroids that play a role in reducing levels nitric oxide (NO) released by lipopolysaccharide or interferon from plasmacytoid dendritic cells (Choi, 2018). Physalin B is known to have a chemical molecular group that can significantly reduce TNF- α, Interleukin-6 , and Interleukin-12 in mice with inflammation and stabilize tissue macrophages (Chen *et al*, 2017). Scientific evidence states that macrophages have the most important role in the activation of lymphocyte cells in the pathophysiology of psoriasis. Inhibition of activation of plasmacytoid

dendritic cells into dermal dendritic cells by Physalin B and Physalin G has another effect, namely a decrease in the cyclooxygenase enzyme (Laskin, 2020). Cyclooxygenase enzymes play a role in metabolizing arachidonic acid released by keratinocytes and vascular endothelial cells into prostaglandin PGE2 . Inhibition of prostaglandin PGE synthesis2 causes a decrease in the production of Interleukin 23 which is produced by dermal dendritic cells to induce nave T cells to become T helper 17 cells and an increase in TGF-β production (Ninnemann, 2018). TGF-β itself plays a role in the formation of collagen complexes and extracellular matrix, but on the other hand it also reduces the activation, differentiation, and proliferation of nave dendritic cells and nave T cells into mature dendritic cells and mature T cells (Matsumo, 2021).

Yang et al in 2018 sentenced that Physalin B and Physalin G have anti-inflammatory effects by inhibiting the activation of the NF-B cascade in the nucleus of dermal dendritic cells and helper T cells 17. The ability of Physalin B and Physalin G to inhibit this process is due to the molecular structure of Physalin B and Physalin G which is similar to Physalin B and Physalin G. glucocorticoid molecular structure. Glucocorticoids themselves have a strong anti-inflammatory effect in suppressing the inflammatory response (Masaki, 2017). Nf-κB is a major transcriptional activator in the cell nucleus that plays a role in transcription of proinflammatory cytokine molecules and cell differentiation by breaking away from the IκBα promoter. IκBα is an important regulator of gene transcription. Physalin B and Pysalin G specifically inhibit the degradation of IκBα in the cell cytoplasm and the cleavage of the IκBα-Nf-κB complex in the nucleus of dermal dendritic cells and nave T cells. This inhibition results in the absence of the cytokine Interleukin 23 by dermal dendritic cells and the transformation of naive T cells into helper T cells 17 which play a role in the activation of keratinocytes and dermal fibroblast cells (Solt, 2018).

Quercetin is one of the flavonoid compounds contained in ciplukan. The study of Chen *et al* in 2017 showed that Quercetin was able to reduce Nf-κB levels in the nucleus of leukocytes, keratinocytes, and fibroblasts in imiquimod induces psoriasis mice model. Quercetin has a similar mechanism of action to Physalin B and Physalin G in inhibiting the Nf-κB cascade but through a different pathway. Quercetin inhibits Nf-κB activation via the non-canonical Nf-κB and Mitogen Activated Protein Kinase (MAPK) pathways. MAPK plays an important role in the phosphorylation of Nf-κB by TNF-α in the process of inflammatory reactions in psoriasis. Inhibition of MAPK by quercetin also causes an increase in the number of Tumor Necrosis Factor Receptor (TNFR) expressed by keratinocytes and fibroblast cells. TNFR complex works by activating P100 / RelB in the cell cytoplasm via proteolytic pathway P100 *to* p52 resulting in increased expression of the gene encoding IκBα and TNFR associated factor *3* (TRAF3) which plays a role in cell necrolysis (Chen, 2017).

According to Huong in 2016 statement which explains that the number and speed of cascades are influenced by the number of receptor and ligand bonds where the number of ligands is affected by the concentration of a substance until a certain saturation point is reached. Chen's research in 2017 showed that thedose of ciplukan extract (*Pysalis angulata* L.) to provide an anti-inflammatory effect in female mices were a dose of 200 mg/kgBW to 800 mg/kgBW. The anti-inflammatory effect will increase with the level/concentration of the given extract and will experience saturation/no increase in effect at concentrations above 850 mg/kgBW. The saturation point of a substance is strongly influenced by the number of receptors on the cell surface and the affinity of a substance (Zhang, 2018).. The ligand will bind to the receptor by theprinciple *lock and key* . If all the receptors are occupied by ligands, the cascade will not occur even if the number of ligands exceeds the number of receptors. The affinity of Physalin B and Physalin G for glucocorticoid receptors on the cell surface was 0.5 nM and 0.3 nM at corticosteroid receptors types 1 and 2 (James, 2019)

The number of fibroblast cells in group F and group G were more than in group C, group, D, and group E, although statistically, the results were not significant, suggesting that there are differences in the inhibitory pathway of inflammation in the pathophysiology of psoriasis in the imiquimod induces psoriasis mice model. Group F and group G were the treatment groups that were given methotrexate and a combination of methotrexate and ciplukan extract. Chen *et al* in 2017 stated that methotrexate is one of the systemic drugs of choice for psoriasis. Methotrexate is well

absorbed in the proximal jejunum with a bioavailability of 70-80%. The bioavailability of methotrexate decreased within 1 week due to an increase in the saturation of reduced folate carrier (RFC) as a methotrexate transporter in blood serum. In the liver, methotrexate is conjugated to 7-hydroxymethhotrexate which then binds to albumin and has an affinity of 35-50%. Methotrexate works by inhibiting the action of the enzyme dihydrofolate reductase (DFHR) which plays a role in the synthesis of purines and pyrimidines in macrophage cells and lymphocyte cells. The effectiveness of methotrexate in group F and group G is influenced by various factors, one of which is the level of folic acid in the blood. Folic acid is the main ingredient in the formation of purines and pyrimidines through the DHFR enzyme in the cell nucleus. Methotrexate changes its form to *methotrexate polyglutamates* in the liver and inhibits *5-amino-1-β-D-ribofuranosyl-imidazole-4-carboxamide* (AICAR) causing an increase in the concentration of adenosine in the blood. Adenosine will bind to A2b and A3 receptors on leukocytes, keratinocytes, and fibroblasts, thereby inhibiting the release of proinflammatory cytokines, namely TNF- and cell proliferation. The higher number of fibroblast cells in group F and group G compared to group C, group D, and group E was due to the concentration of folic acid contained in the mice's diet, thereby reducing the bioavailability of methotrexate in reducing the inflammatory process. Group G gave more fibroblast cell counts than the other treatment groups due to the inhibition of Physalin B, Physalin G, and Quercetin by methotrexate. Elango in 2014 explained that methotrexate has interactions with steroids and flavonoids. Methotrexate will inhibit steroid and flavonoid transporter proteins on the basolateral surface of the small intestine by binding to Multidrug resistance-related proteins 2 & 4 (MRP 2 and MRP 4) in the liver. The binding of methotrexate to MRP 2 and MRP 4 results in inhibition of the release of steroid and flavonoid transporter proteins from the liver to the blood vessels so that the compounds Physalin B, Physalin G, and Quercetin will not be absorbed into the blood and will be excreted directly through the process of defecation. From the above statement can conclude that the higher number of fibroblast cells in group G was caused by the interaction between methotrexate and ciplukan extract.

CONCLUSION

There is a significant effect of ciplukan extract (*Physalis angulata* L.) on the number of fibroblast cells in the *imiquimod induces psoriasis mice model* and there is a significant difference in the number of fibroblasts in groups that were given with ciplukan extract (*Physalis angulate* L.) at doses 400 mg/kgBW, 800 mg/kg. kgBB and control groups.

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