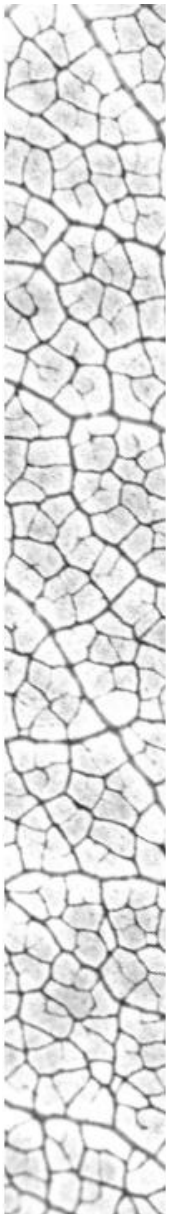

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Antiinflammation effect of *garciana mangostana* pericarp extract in albino mice skin induced by 12-0-tetradecanoylphorbol-13-acetate

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Abstract

Background: Mangosteen (*Garciana mangostana Linn.)* is a tropical fruit that is most commonly found in Southeast Asia. Mangosteen skin has been reported to contain various beneficial bioactive components such as anti-inflammatory effects. The skin not only serves as a physical and chemical barrier but also as a competent immune system that elicits both innate and adaptive immune responses to pathogens or other inflammatory damages. 12-O-tetradecanoylphorbol-13-acetate (TPA) is a protein kinase activator that induces inflammatory skin reactions. In this study, we investigated the effect of mangosteen pericarp extract as an inhibitory agent for acute inflammatory responses on TPA-induced albino mice skin inflammation.
Materials and Methods: Hematoxylin & Eosin staining histopathology was used to analyze neutrophil infiltration, epidermal thickness, edema, and vascular permeability.
Results: *Garciana mangostana* pericarp extract cream showed reduced TPA-induced neutrophil infiltration and epidermal thickness. The best concentration is both at 20% and 10%, respectively.
Conclusion: Our study suggests that the naturally derived *Garcinia mangostana* pericarp extract cream provides an acute anti-inflammatory effect on the skin.

Keywords: *garciana mangostana*, histopathology, TPA-induced acute inflammation

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INTRODUCTION

Natural products are traditionally utilized as a therapeutic agent against many conditions. *Garcinia Mangostana* (GM) is one of those naturally derived medications that have been used to treat gastrointestinal infection, urinary tract infection, anti-scorbutic, laxative, and as an antipyretic. In recent times, mangosteen is believed to be able to treat an assortment of infectious diseases, such as inflammation, diarrhea, abdominal pain, fever, acne, food allergy, and arthritis. (Ovalle-Magallanes et al., 2017, Maione et al., 2016) Secondary metabolites from mangosteen, especially on the skin, have been reported to possess extensive pharmacological properties, such as anti-inflammatory, antioxidant, anti-proliferative, anti-microbial, anti-cancer, hepatoprotective, cardioprotective, and neuroprotective on Alzheimer's disease. (Pedraza-Chaverri et al., 2008, Chen et al., 2018) In dermatological use, a slew of inflammatory conditions, both acute and chronic, requires medication associated with several side effects.

Mangosteen, also known as *Garcinia mangostana Linn*. is a tropical plant belonging to the *Clusiaceae* family that has been widely cultivated as food in Southeast Asia (Indonesia, Malaysia, Thailand, the Philippines, and India). This fruit, known as the "*Queen of fruits*", consists of white-colored fruit divided into septa and covered by dark purple skin. The mangosteen tree grows very slowly and is in the shape of a pyramidal crown. The tree can reach a height of between 20 and 82 feet (6-25 m), dark brown or almost black peeling bark with the inner bark containing a lot of rubbery, yellow, and bitter sap. The leaves are green with short stalks. Mangosteen skin is reported to contain various bioactive components that have potential as therapeutic agents such as xanthones, tannins, flavonoids, saponins, quinines, and other bioactive components. (Anwar et al., 2016, Suttirak et al., 2014) *Xanthone,* as a

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significant component is a hydrophobic compound composed of a tricyclic aromatic ring system, which is a mixture of isoprenyl, hydroxyl, and methoxy substitution. *α-mangostin and γ-mangostin* are the most common *xanthone* found and has the most prominent therapeutic role. Other *xanthones* include *β-mangostin, gartanin, 8-deoxygartanin, garcinones A, B, C, D and E, mangostinone, 9-hydroxycalabaxanthone,* and *isomangostin* consistently show that *xanthones* have antioxidant, anti-proliferative, proapoptotic, anti-microbial, anti-cancer, and anti-inflammatory activities. (Gutierrez-Orozco et al., 2013)

Acute inflammation is the initial immune response to maintain tissue homeostasis against trauma or infection by eliminating potential pathogens.(Loynes et al., 2018) The inflammatory process in the skin occurs due to a tissue reaction that elicits cell defense mediators and proteins to the site of infection and damaged tissue.(Abbas et al., 2015) Inflammatory mediators such as cyclooxygenase-2 (COX-2), interleukin-1 beta (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) play a role in inflammatory diseases. (Lee et al., 2012). The release of inflammatory mediators such as nitric oxide and prostaglandins also increases the permeability of blood vessels, allowing the migration of leukocytes, especially neutrophils, to inflamed tissues. Cyclooxygenase 2 (COX-2) is an enzyme that regulates the prostaglandin/eicosanoid pathway induced by proinflammatory cytokines in an *NF-κß-dependent* manner.(Wei et al., 2011)

Phorbol esther, 12-O-tetradecanoylphorbol-13-acetate (TPA) also known as tetradecanoyl phorbol acetate, or phorbol 12-myristate 13-acetate (PMA) is a protein kinase-C (PKC) activator. TPA is a potent phorbol diester and tumor promoter often used in biomedical research. TPA is also used to induce other

biological effects in low concentrations such as skin irritation (Madsen et al., 2016)

We conducted a study assessing the anti-inflammatory effect of *Garcinia mangostana Linn* skin extract on *TPA-induced* mice skin. The histopathological analysis will be conducted based on neutrophil infiltration, epidermal thickness, edema, and increased tissue permeability.

MATERIAL AND METHODS

GM skin extract was made in the Phytochemical Pharmacognosy Laboratory of the Hasanuddin University Faculty of Pharmacy. The method used is the maceration method with 96% ethanol as a solvent, a ratio of 1:2, and evaporation time of 20 hours. GM skin extract cream was formulated and made at the Laboratory of the Faculty of Pharmacy, University of Surabaya, Surabaya, East Java. The TPA substance used is made by Sigma-Aldrich, USA. The empirical formula for TPA is $C_{36}H_{56}O_{8,}$ with a molecular weight of 616.83 g mol^{-1}. Each glass bottle packaging contains 5 mg of TPA, 5 mg of TPA is dissolved in 50 ml of acetone as a solvent to become homogeneous. The dose of TPA required in this study is 2 µg dissolved in 20 µl acetone.

Table 1. Anti-inflammatory effect of GM skin extract

Component	Concentration	Mean (SD)	
		Neutrophil Infiltration	Epidermal Thickness
Control	-	1,40 (0,548)	56,571 (23,766)
TPA	-	3,40 (0,548)	107,907 (48,734)
TPA + Base Cream	-	3,80 (0,447)	155,807 (31,573)
TPA + GM	2,5%	2,80 (0,447)	64,830 (25,985)
TPA + GM	5%	2,40 (0,548)	67,994 (11,059)
TPA + GM	10%	1,40 (0,548)	62,994 (18,701)
TPA + GM	20%	1,20 (0,447)	67,591 (11,019)

Animal

The Samples used were female albino mice, aged 6-9 weeks, weighing 20-30 grams, healthy and derived from one brood. Animals are housed in a veterinary care facility in the veterinary laboratory of Hasanuddin University Faculty of Medicine with a light-dark cycle of 12/12 hours (dark from 8 PM to 8 AM and light from 8 AM to 8 PM). Animals were given free access to their food and water and were left in this state for 1 week prior to the study. Mice were divided into 7 groups. Mice ears were smeared with 2 µg TPA dissolved in 20 µl acetone, then 12 hours and 24 hours later after TPA application, the mice ears were applied topical cream base, GM skin extract in four different concentrations, namely 2.5%, 5%, 10% and 20%.

Group A: The control group was 5 mice without treatment.

Group B: 5 mice with TPA applied on the outer ear.

Group C: 5 mice that were applied with base cream after inflammation induced by TPA.

Group D: 5 mice were applied with a 2.5% GM extract cream after inflammation induced by TPA.

Group E: 5 mice were applied with 5% GM extract cream after inflammation induced by TPA.

Group F: 5 mice were applied with 10% GM extract cream after inflammation induced by TPA.

Group G: 5 mice were applied with 20% GM extract cream after inflammation induced by TPA.

The mice were then biopsied 6 hours after the application of the second GM skin extract cream. Indicators of inflammation include neutrophil infiltration in the epidermal dermis, epidermal thickness, edema, and vascular permeability through a microscope (Olympus, Japan). Epidermal thickness was measured using ImageJ software.

Histology

Tissue samples were fixed in a 10% formalin buffer. All tissues were placed in paraffin blocks and cut to a

Table 2. Effect on edema and increased vascular permeability by Garciana Mangostana in TPA-induced mice

Group	N	Edema[a]			Vascular Permeability[a]		
		Yes	No	*Asymptotic Significance*[b]	Yes	No	*Asymptotic Significance*[b]
Control	5	0	5	0.000	0	5	0.000
TPA	5	5	0		5	0	
TPA+Base Cream	5	5	0		5	0	
TPA+GM 2.5%	5	5	0		5	0	
TPA+GM 5%	5	5	0		5	0	
TPA+GM 10%	5	5	0		5	0	
TPA+GM 20%	5	5	0		5	0	

[a]Edema and increased vascular permeability were examined histologically and categorized into scores, namely: loose stroma and erythrocyte extravasation (present), dense stroma and no erythrocyte extravasation (absent)
[b]Statistical test was performed with Crosstab. The reading is based on the Chi-Square Tests, where 14 cells (100%) are estimated to have a count less than 5. The minimum expected count is 0.71.

thickness of 4 - 5 µM. Each part that was cut was deparaffinated with *xylene* and divided to scale with serial alcohol to water then stained with *hematoxylin-eosin* (HE) for standard evaluation using an Olympus CX21 microscope.

Histopathological preparations were obtained from excisional biopsy, the ear tissue of mice. Each specimen was fixed with a buffer of formalin, placed on a flat plane. The slide was taken from the middle area then cut perpendicularly with a thickness of 4 µM then stained with HE.

Statistical Analysis

The data is collected from all the results of the research, then edited, tabulated, and entered into a computer program, then a descriptive and analytic analysis is carried out. The results of the analysis will be presented in tables or graphs accompanied by an explanation using SPSS version 25. A normality test is conducted from the seven treatment groups. Due to the small sample size (5 mice) per group, One way ANOVA and Crosstab tests were used as statistical tests. Kruskal-Wallis test is performed If the data distribution is not normal. The test result is significant if the p-value <0.05.

RESULT

Anti-inflammatory effect of GM extract cream against TPA-induced neutrophil infiltration

Acute inflammatory processes are measured through a set of parameters, such as Increased neutrophil infiltration, epidermal thickness, vascular permeability, and edema. Neutrophil infiltration is calculated using a microscope, with neutrophils measured as scores, such as single neutrophil infiltration/sparse 1-1 cells (score 1), focal neutrophil cell infiltration (score 2), group of neutrophil cell infiltration (score 3), and diffuse neutrophil cell infiltration (score 4). Measurements were carried out 6 hours after interventions had been performed, including the second GM extract application. TPA exposure was found to increase neutrophil infiltration at 12 o'clock position. More neutrophil infiltration was seen after the base cream application. However, GM extract cream application reduces the neutrophil infiltration, and the greater the concentration, the lower the neutrophil infiltration.

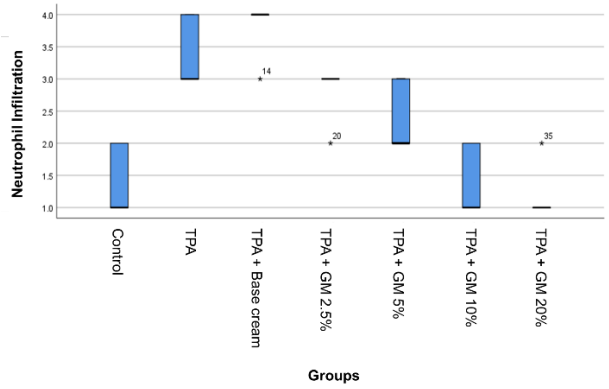

Fig. 1. Neutrophil infiltration on all groups

The ability of GM extract cream to reduce neutrophil infiltration is evident in this study, with the best result obtained with a concentration of 20%.

Anti-inflammatory effect of GM extract on epidermal thickness induced by TPA

Epidermal thickness is the first sign of local inflammation. The thickness of the epidermis was measured from the basal cell layer up to the stratum corneum using ImageJ software. The data is then reported in micrometers. Based on the measurement results, the thickness of the epidermis was found to be the thickest in group C with a TPA-induced inflammation and given base cream afterward. Meanwhile, the application of GM skin extract cream is decreased in the GM group with a concentration of 5%, then 20%, 2.5%; the best result was in the group with a concentration of 10%. A concentration of 10% GM skin extract cream had the best anti-inflammatory effect compared to other formulations.

Anti-inflammatory effect of GM extract cream against edema and TPA-induced vascular permeability improvement

Histopathological examination did not show GM extract cream to have any effect on edema and vascular permeability. This can be seen in the Kruskal-Wallis test, where there is no significant difference. Furthermore, Post Hoc test with Mann-Whitney, showed that there

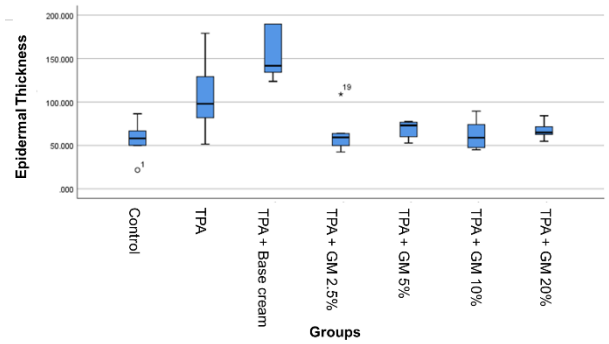

Fig. 2. Epidermal thickness on all groups

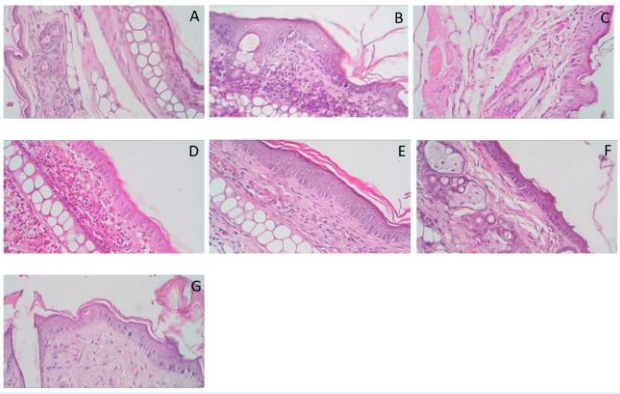

Fig. 3. Histopathology of the skin of albino mice with 100x magnification. Slides of Hematoxylin and Eosin staining on normal mouse skin (A), TPA-induced inflammation (B), Base cream applied to the skin of albino mice after being inducted to TPA 24 hours prior (C), GM skin extract cream with 2.5% concentration Applied to the skin of albino mice after being inducted to TPA 24 hours prior (D), 5% concentration of GM skin extract cream that was applied to the skin of albino mice after being inducted to TPA 24 hours prior (E), 10% concentration GM skin extract cream which Applied to the skin of albino mice after being inducted to TPA 24 hours prior (F), 20% concentration of GM skin extract cream was applied to the skin of albino mice after being inducted to TPA 24 hours prior (G). The picture shows a representative of 7 mice from each group

was no edema and increased vascular permeability in the untreated group. Whereas in the TPA-induced or on groups treated with GM extract cream, edema, and increased vascular permeability were found.

DISCUSSION

The skin is the largest organ of the human body; it forms a protective barrier, which is essential in protecting individuals from the external environment. The skin not only serves as a physical and chemical barrier but also as a competent immune system that elicits both innate and adaptive immune responses to various pathogens and inflammatory damages. Due to the presence of exogenous factors such as foreign pathogens, ultraviolet radiation, and chemical irritants, the innate immune cells (granulocytes, mononuclear phagocytes, natural killer cells, keratinocytes) elicit various types of immune responses such as (1) release of anti-microbial agents; (2) induction of inflammatory mediators such as cytokines, chemokines, neuropeptides, and eicosanoids; and (3) initiation and modulation of adaptive immune responses. (Xie et al., 2015, Modlin et al., 2012)

Acute inflammation is a rapid response to infection or tissue damage that lasts only for a short time, ranging from a few minutes to several days. Excessive inflammation or inadequate immune response in the skin may cause various skin diseases such as allergic reactions, psoriasis, and skin cancer.(Wei et al., 2011) TPA-induced inflammatory responses in mouse models have been widely used in several studies to test the effectiveness of various drugs or natural substances as anti-inflammatory agents. TPA application results in the recruitment of inflammatory cells and the massive production of proinflammatory cytokines.(Khan et al., 2013) Multiple studies have used TPA to assess the effects of inflammation in mouse models.(Lee et al., 2012, Park et al., 2016, Choi et al., 2009, Wei et al., 2011, Huang et al., 2006, Yasukawa et al., 2009) Epidermis exposure to TPA causes keratinocytes and Langerhans cells to be stimulated to activate protein kinase C (PKC), resulting in the activation of P13K/Akt, Erk and NF-κB signaling transduction pathways. Akt and NF-κB play an essential role in activating key inflammatory enzymes such as inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2). One study showed that COX-2 and iNOS expression was detected in the epidermis after TPA stimulation, indicating that COX-2 and iNOS are released from epidermal cells (keratinocytes).(Wei et al., 2011)

Along with the development of science and technology, naturally derived products are continuously being developed. The anti-inflammatory effect of *Garciana mangostana* is one of them. Our study shows that the anti-inflammatory capabilities of *Garciana mangostana* can suppress the TPA-induced inflammation in the skin of a mouse model. *Garciana mangostana*'s anti-inflammatory mechanism of action is by inhibiting the cyclooxygenase (COX) enzyme in the arachidonic acid pathway, which results in decreased inflammation. Xanthone also inhibits inflammation through the NF-κB signaling cascade. This inhibition is due to the inactivation of cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) cyclase in vascular endothelial cells due to the absence of prostanoid production, thus inhibiting inflammatory reactions. Other studies have found that mangosteen contains several identical components as nonsteroidal anti-inflammatory drugs, an anti-inflammatory agent that targets the COX enzyme. (Marzaimi and Aizat, 2019)

It is evident in *in vivo* studies that α- and γ-mangostin inhibit histamine release and PGE2 induction. Previous

in vitro studies also showed that *Garciana mangostana L*. could inhibit COX-1 and COX-2. (Nakatani et al., 2002) Furthermore, α-mangostin shows effectiveness as an antimetastatic agent against the expression of TPA-induced matrix metalloproteinase-2 (MMP-2) and MMP-9 on lung adenocarcinoma cells A549. Data indicate that α-mangostin can inhibit the activation of αvβ3 integrin, focal adhesion kinase (FAK), extracellular signal-regulated kinase ½ (ERK ½); all of these are involved in the downregulating activity of enzymes and NFκB.(Shih et al., 2010) In vivo effect of isogarcinol (mangosteen) using xylene on acute inflammation in the animal model result in the reduction of edema in the ear of the mouse. Oral administration of 100 mg kg^{-1} of isogarcinol has an aspirin-like effect on xylene-induced ear edema. Meanwhile, in vitro studies have shown that isogarcinol inhibits COX-2 mRNA and iNOS expression; Isogarcinol also suppresses NO production in supernatant RAW 264,7 cells. The investigators concluded that isogorcinol significantly reduced serum levels of IL-1β, TNF-α, IL-6, and IL-17. (Fu et al., 2014) α-mangostin exhibits a significant effect in inhibiting lipopolysaccharide production and cytotoxicity in mice stimulated by monocyte macrophage cell line (RAW 264.7 cells). At 3 to 25 μM of α-mangostin, the amount of NO production was measured continuously and the IC50 value was found to be 12.4. Production of lipopolysaccharide-activated PGE2 in RAW 264.7 cells was also significantly reduced by α-mangostin, with an IC50 value of 11.08 μM. The concentration of α-mangostin was found to reduce the induction of iNOS. 1 μg mL^{-1} lipopolysaccharide was used to activate RAW 264.7 cells for 12 hours, iNOS activity in activated macrophages was inhibited after treatment with 5 μg mL^{-1} α-mangostin in 24 hours. Carrageenan-induced edema in mice was used to evaluate the anti-inflammatory effect of α-mangostin, which showed potent inhibition 3 hours after treatment. (Ibrahim et al., 2016)

Histopathological examination showed that topical administration of TPA induces inflammation, as evidenced by the increase of epidermal thickness, leukocyte infiltration, vascular permeability, and edema. The release of mediators such as nitric oxide and prostaglandins raises vascular permeability, resulting in fluid accumulation in the vicinity of inflammation (edema) and allows the migration of leukocytes, especially neutrophils, in the inflammatory tissue. Epidermal hyperplasia is the result of increased inflammatory mediators. (Wei et al., 2011) Based on our preliminary study, the administration of 2 μg topical TPA has shown increased signs of inflammation at 12 hours after TPA induction as evidenced by increased neutrophil infiltration, vascular permeability, and edema. Inflammatory markers are significantly increased in a linear correlation with more prolonged TPA exposure. Histopathological examination was performed using an Olympus microscope, where the thickness of the epidermis was measured vertically from the basal cell layer to the corneum layer using ImageJ software. Neutrophil infiltration was assessed using histopathological scores.

In this study, the group induced by inflammation and given base cream showed higher inflammation than the group that was only exposed to TPA. This may be caused by the base cream components such as alcohol, propylene glycol, sorbitan oleate esters, cetylene stearyl alcohol, and isopropyl myristate, all of which have the potential to cause allergic contact dermatitis. (Goossens and Clinics, 2014) Our study showed that GM skin extract cream could inhibit neutrophil infiltration and hamper epidermal thickness in all groups. Meanwhile, based on edema measurements and increased vascular permeability, it appears that GM cream extract did not show any anti-inflammatory effect on both categories.

CONCLUSION

Topical application of GM skin extract cream with concentrations ranging from 2.5%, 5%, 10%, and 20% can inhibit TPA-induced inflammatory reactions in the skin of mice. The topical anti-inflammatory effect of GM skin extract cream is evident by the decrease in neutrophil infiltration and epidermal thickness. In comparison, edema and increased vascular permeability were unchanged. The group treated with a topical administration of 20% GM skin extract cream exhibit the most significant effect on neutrophil infiltration. Meanwhile, a concentration of 10% provides an anti-inflammatory effect, as shown by the lowest epidermal thickness compared to other groups. The results of this study indicate that GM skin extract cream can be developed as an alternative topical treatment for inflammatory skin diseases.

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