Chapter 1

Introduction

1.1 Background

Atopic Dermatitis (AD) is a chronic skin disease characterized by itching, and intense pruritus leads to skin trauma and can decrease the quality of patient life (Tamagawa-Mineoka & Katoh, 2020; Urban et al., 2021). Globally, AD affects more than 20% of children and 3% of adults (Hadi et al., 2021). Each country has a different prevalence of AD and it can occur at any age (Hadi et al., 2021). A high risk of AD can be found in people who have a family history of atopic dermatitis. The dysfunction of the gene can also lead to the development of AD (Thomsen, 2014; Nutten, 2015). Another risk factor for AD is environmental and immunological factors. Environmental factors such as Ultraviolet (UV) radiation, climate change, pollutants, stress, microbes, and allergens can affect the skin barrier integrity and inflammatory response (Pribowo et al., 2021). Aside from that, the overproduction of inflammatory cytokines (IL-33, IL-4, IL-25, IL-13, and thymic stromal lymphopoietin (TSLP)), are included in the immunological factor that can influence the severity of AD (Kantor & Silverberg, 2017).

In healthy humans, the skin plays a crucial function in protecting the body from harmful substances originating from the external environment (Boer et al., 2016). While in patients with AD, the skin loses the integrity of the stratum corneum (SC) which is the skin's outermost layer that has function as a skin barrier. This makes the susceptibility to environmental factors of AD patients decrease and can lead to inflammatory responses that make the severity of AD increase (Yang et al., 2020). Genes that contribute to the skin barrier are *Filaggrin* (*FLG*) and *Involucrin* (*IVL*). Both these genes are related to and contribute to the integrity of the skin barrier which has an important role in AD patients. Besides that, AD is also related to the inflammatory response. Several genes are associated with inflammatory responses of AD, such as *TSLP, TARC, IL-25, MDC, IL-33*, and *CTACK*. *IL-25, TSLP,* and *IL-33* is the gene that encodes important cytokines in the pathogenesis of AD (Cianferoni & Spergel,

2014; Cayrol & Girard, 2017; Deng et al., 2021). At the same time, TARC, MDC, and CTACK is the gene that is responsible encode chemokine which was also included in the pathogenesis of AD (Homey et al., 2002; Hashimoto et al., 2006; He & Geha, 2010; Vestergaard et al., 2004).

Currently, the treatment of AD already exists from topical to systemic treatments. Several topical treatments of AD is calcineurin inhibitors and corticosteroid, while systemic treatment such as azathioprine, cyclosporine A, methotrexate, and oral corticosteroids (Thomsen, 2014). However, Both skin barrier dysfunction and skin inflammation can lead to AD which makes the treatment of AD complicated. A good indication of treatment for AD is a therapeutic agent that can treat both skin barrier dysfunction and skin inflammation (Leung & Guttman-Yassky, 2014). The problem with the current treatment is the unwanted side effects. Topical corticosteroid has side effect such as epidermal thinning, rosacea, atrophy, perioral dermatitis, and purpura (Coondoo et al., 2014). Thus, calcineurin inhibitors are being used to overcome these side effects but the use of these treatments can cause the potential of carcinogenesis for long-term use, transient burning, erythema, and pruritus (Silverberg, Nelson & Yosipovitch, 2016). Because of the difficulty, there are efforts in research to find alternative treatments for AD.

Tamanu Oil, extracted from the nuts of Calophyllum inophyllum L. has been reported to be a potential treatment for AD. Tamanu nuts contain around 75% of oil and commonly being used as a medication for various diseases such as venous ulcers, to prevent skin infections, eczema, skin cracks, and rheumatisms (Pribowo et al., 2021). The oil of Tamanu is reported to have numerous properties such as anti-microbial, antioxidant, cytoprotective, and anti-inflammatory to treat various diseases such as (Cassien et al., 2021; Pribowo et al., 2021). Ethanolic extraction of tamanu oil has been found to have a high yield of bioactive compounds that has benefit in anti-bacterial, anti-inflammatory, anti-fungal, and antioxidant activities (Ginigini et al., 2019).

This research has the purpose to investigate the skin barrier repair effect and inflammatory response of Calophyllum inophyllum extracts using Human Keratinocyte Skin Cells (HaCaT) that are already

being induced by TNF-α and IFN-γ as an AD model by evaluating the *FLG, IVL, TSLP, TARC, IL-33, IL-25, MDC*, and *CTACK* gene expression level.

1.2 Objective

This study has aim to investigate the skin barrier repair and anti-inflammatory effects of *C. Inophyllum* EME by evaluating the gene expression level of skin barrier genes (*FLG*, and *IVL*) and Inflammation genes (*TSLP, TARC, IL-33, IL-25, MDC,* and *CTACK*) which are known to be upregulated and downregulated in AD patients, respectively in the HaCat cells induce by TNF-α and IFN-γ as an AD model.

1.3 Hypothesis

EME of *C. Inophyllum* oil increases the gene expression level of skin barrier genes (*IVL* and *FLG*) and decrease the gene expression of Inflammation gene (*TSLP, TARC, IL-33, IL-25, MDC*, and *CTACK*) which are related to AD using HaCaT induce with TNF-α and IFN-γ as AD model.