Chapter 1

Introduction

1.1. Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by high blood sugar that has become a global health concern with increasing global incidence since 1980 (ADA, 2009; WHO, 2022). The chronic DM condition causes long-term dysfunction, damage, and failure of organs (ADA, 2010). One of the common diabetes complications is diabetic foot ulcer, which has a global prevalence of 6.3% and may result in amputation (Zhang et al., 2017; Oliver & Mutuloglu, 2022). DM condition causes inflammatory dysregulation, which can manifest as the imbalance of anti- and pro-inflammatory cytokines response that dysregulates the skin function in tissue remodeling and granulation that impairs wound healing (Theocharidis & Veves, 2020).

Current treatment for diabetic wounds includes wound dressing which is ideally non-toxic, non-allergic, non-adherent, sterile, easy usage, and cost effective. It must provide a moist wound environment, absorb excess debris, protect wounds from microorganism infections, allow gas exchange, and insulate the wound temperature (Kavitha et al., 2014). These features can be found in biocellulose (BC) which is synthesized from a membrane of biosynthetic microfibrillar cellulose made by *Acetobacter xylinum* or other bacterias (Naomi & Fauzi, 2020). It is safe, able to retain moisture, absorb exudates, and improve the granulation process to promote wound closing (Portela et al., 2019; Alhajj & Goyal, 2021). However, BC does not have any antimicrobial activity; therefore, studies suggested the impregnation of BC with antimicrobial agents (Junka et al., 2019).

Diabetic wound is more prone to infection due to reduced blood flow; hence leukocytes cannot reach the wound, which lessens the immune protection of the wound (Dumville et al., 2017; Spampinato et al., 2020). To treat the chronic wound infection, antibiotics are commonly prescribed, however, diabetic wound infection is caused by polymicrobial pathogens (i.e. *Staphylococcus aureus,*

Pseudomonas aeruginosa, and *Salmonella typhii*) and can develop resistant mechanisms to antibiotic treatment. Thus, an alternative approach to antimicrobial treatment is to utilize plant extracts, which are reported to have multiple and/or more complex phytochemicals that can prevent the bacteria from developing resistance easily (Gupta & Birdi, 2017). A previous study found that certain plant extracts have antimicrobial and anti-inflammatory properties against the skin bacteria to improve wound healing (Abid et al., 2022), including tamanu nuts oil (Raharivelomanana et al., 2018). Tamanu or *Calophyllum inophyllum* L. (Caryophyllaceae) can be commonly found in Asia, Africa, and Pacific countries. The oil produced from its nuts has been traditionally used in topical application to treat dermal conditions, i.e. diabetic sores. The proven biological activity of Tamanu includes antimicrobial, anti-inflammatory, wound healing, and promoting the protein expression in extracellular matrices in the skin (Raharivelomanana et al., 2018). As they age, the Tamanu nuts become darker (Emilda, 2019), thus it is called black tamanu, which is extracted as black tamanu oil. Hence, black tamanu oil is an appealing candidate to be impregnated into BC to provide antimicrobial properties.

In studying wound healing activity, animal study is suggested as the predictive models. Commonly used models are mice and rabbits. Mice is a suitable model due to their loose skin, good availability, and small size. Rabbit has advantages of being bigger in size, as well as having more similar skin thickness and viscoelasticity to humans (Wei et al., 2017), thus it can be used as an interspecies study before clinical trial. Thus in this study, the wound healing and antimicrobial activity of BC-black tamanu oil was studied on wounds in diabetic mice and non-diabetic rabbits.

1.2. Objectives

This study aimed to investigate the wound healing and antimicrobial activity of BC-black tamanu oil to diabetic and non-diabetic wounds on mice and rabbits, respectively.

1.3. Hypothesis

It was hypothesized that BC-black tamanu oil is able to improve wound reduction and lower microbial count compared to BC-only treatment and gauze covered wounds to both diabetic mice and non-diabetic rabbit wound models.