Chapter 1

Introduction

1.1 Background

Diabetes mellitus represents a significant global public health challenge, affecting approximately 537 million adults, or 10.5% of the world population, as estimated by the International Diabetes Federation (Magliano et al., 2021). Among the various complications of diabetes, foot ulcers are particularly significant and become the primary cause of morbidity and hospitalization, affecting approximately 30% of diabetic patients (Chang & Nguyen, 2021). Unfortunately, the wound healing process in diabetic patients is impaired as hyperglycemia triggers the excessive production of reactive oxygen species (ROS) (Deng et al., 2021). The resulting oxidative stress hinders the proliferation and migration of keratinocytes, which is essential for the re-epithelialization of wounds through the production of various growth factors and cytokines, interaction with fibroblasts and endothelial cells, and initiating immune responses (Liu et al., 2023; Rybkowska, 2024). Consequently, inadequately managed or untreated diabetic foot ulcers can result in serious infections and potential amputations, significantly reducing the quality of life for diabetic patients. Therefore, to improve wound healing in diabetic foot ulcers, it is imperative to find treatments that promote the migration and proliferation of hyperglycemic fibroblasts and suppress the formation of ROS.

Due to the complex nature of the wounds and their underlying causes, current treatments for diabetic foot ulcers involve a multidisciplinary approach (Naves, 2014). Standard treatments may include surgical debridement, infection control with antibiotics, improving blood flow through vascular interventions, glycemic management, and wound dressings to maintain a moist environment surrounding the wound (Everett & Mathioudakis, 2018). In addition, advanced therapies such as stem cell therapy, growth factors, platelet-rich plasma, and antibiotics-loaded bone cement have also shown promise in promoting wound healing by enhancing antibacterial effects, angiogenesis, and

tissue repair (Hage et al., 2022; Mastrogiacomo et al., 2022). Despite these advances, a significant limitation remains as current treatments do not adequately address the oxidative stress caused by hyperglycemia, which might contribute to persistent wound chronicity, high recurrence rates, and complications such as infection and amputation (Spampinato et al., 2020; Yang et al., 2022). Thus, addressing oxidative stress more effectively remains a critical unmet need in improving diabetic foot ulcer outcomes.

Research indicates that antioxidant therapies can reduce oxidative damage and improve wound healing by restoring redox balance and suppressing ROS-induced inflammation (Deng et al., 2021; Song et al., 2022). Such capabilities could be derived from bioactive compounds that are available in nature. A potential source is *Moringa oleifera* (*M. oleifera*) leaves, which are easily found and grow in tropical climates, including Indonesia. Often called "the miracle tree," *M. oleifera* leaves offer a host of health advantages, mainly their antioxidant capacities, which demonstrate significant radical scavenging activity against 1,1-diphenyl-2-picrylhydrazyl (DPPH) radicals (Kashyap et al., 2022; Santos et al., 2012). Additionally, in animal models, it has been shown to effectively promote fibroblast migration, viability, and proliferation in addition to wound healing (Lambole & Kumar, 2012; Muhammad et al., 2013). However, research on the specific application of *M. oleifera* leaves for treating diabetic foot ulcers remains limited. Therefore, this research explores the potential of M. oleifera leaves extract to enhance the migration and proliferation of hyperglycemic keratinocytes while inhibiting the production of reactive oxygen species, with the ultimate goal of improving wound healing outcomes in diabetic foot ulcers.

1.2 Objective

This research aims to investigate the capabilities of *M. oleifera* leaves extract in enhancing the migration and proliferation of hyperglycemic keratinocytes, as a representation for diabetic foot ulcer wound healing.

1.3 Hypothesis

It is hypothesised that *M. oleifera* leaves extract will effectively enhance the migration and proliferation of hyperglycemic keratinocytes while inhibiting the production of reactive oxygen species.