Chapter 1

Introduction

1.1 Background

Inflammation is a natural defense mechanism of the body that aims to fight pathogens, recognize harmful stimuli, and fight any irregularities in our body, such as fight against cancer cells (Institute for Quality and Efficiency in Health Care, 2023). Its primary function is to maintain the body's homeostasis. However, when this balance is disrupted, it can lead to the development of various diseases. If left untreated, inflammation can progress into various diseases and chronic pain, such as skin diseases, type-2 diabetes, cancer, cardiovascular diseases, metabolic disorders, autoimmunity, allergies, headaches, sleep disorders, and hormonal imbalances (Chavda et al., 2024).

In the United States, the prevalence of chronic diseases is expected to rise significantly over the next 30 years (Pahwa et al., 2023). Similarly, in Indonesia, chronic obstructive pulmonary disease (COPD), a condition linked to inflammation, accounts for approximately 60% of deaths caused by chronic illnesses (Aprilen & Indratama, 2022). Globally, three out of five deaths are attributed to chronic inflammatory diseases, including stroke, chronic respiratory diseases, heart disease, cancer, obesity, and diabetes (Pahwa et al., 2023).

Chronic inflammation is also related to the delay of wound healing, which can lead to various diseases, such as infection and prolonged inflammation. Wound healing is crucial since lack of wound care can cause prolongation of treatment, which can cause an economic burden to the patient and can make the patient more susceptible to infections (Criollo-Mendoza et al., 2023). Wound healing is one of the most expensive treatments for patients, in which surgical wounds and diabetic ulcers are the most expensive (Sen, 2021).

The prevalence of herbal medicine has been seen as an appealing treatment option for anti-inflammation and wound healing-related diseases compared to using conventional therapies.

This is due to the perception that herbal treatments are considered safe, more accessible, and a cheaper alternative to people (Criollo-Mendoza et al., 2023).

Propolis is a natural, resinous substance produced by bees to protect their nests and has been valued throughout history in various cultures such as the Egyptians, Greeks, and Persians. Today, propolis is widely recognized for its diverse biological activities, including antibacterial, antiviral, antifungal, antiparasitic, antioxidant, and anti-inflammatory effects (Zulhendri et al., 2022).

Research has demonstrated the potential of propolis in promoting anti-inflammatory effects and enhancing wound healing, as evidenced by findings from *in vitro*, *ex vivo*, and *in vivo* studies (Zulhendri et al., 2022). Previous research has demonstrated the anti-inflammatory effects of flavonoids found in propolis, highlighting their ability to downregulate the expression of COX-2 (cyclooxygenase-2) and TNF-a, which are key enzymes involved in the inflammatory pathway (Jalali et al., 2020). Propolis has also been shown to play a significant role in wound healing by reducing scar formation and promoting tissue repair by the stimulation of VEGF (vascular endothelial growth factor) and reduction of MMP-9 (metalloproteinase-9), which is a component that prolongs the wound healing process (Sungkar et al., 2021). Understanding the mechanisms involved in inflammation and wound healing can provide therapeutic insight.

In silico methodologies present a robust framework by exploring propolis's anti-inflammatory and wound-healing properties. These computational techniques yield critical insights into the specific compounds responsible for their biological effects by assessing the binding affinities and molecular interaction of their bioactive components (Emon et al., 2021). This knowledge not only enhances our understanding of the propolis's therapeutic potential but also lays the groundwork for targeted experimental studies and innovative medical applications.

Given the rise in the prevalence of inflammatory diseases and wound healing diseases, the use of propolis presents a promising alternative to conventional therapies. *In silico* approaches can further

enhance the understanding of its bioactive components, providing a foundation for future experimental studies and therapeutic applications.

1.2 Objective

This study aims to utilize *in silico* methods to identify and analyze the bioactivity of lead compounds from propolis against key inflammatory markers (TNF-a and COX-2) to evaluate their anti-inflammatory potential and wound healing effect (VEGF-a and MMP-9). The computational pipeline includes bioactivity prediction using PASS server, obtaining binding affinity through molecular docking, molecular dynamics simulations, drug-likeness, pharmacokinetics and toxicity analysis.

1.3 Hypothesis

Propolis bioactive components with predicted activity scores (Pa values) between 0.3 and 0.7 will demonstrate favorable binding affinities to inflammatory (TNF-a, COX-2) and wound healing (VEGF-a, MMP-9) targets through molecular docking, and the top-performing ligands will form stable protein-ligand complexes as demonstrated by molecular dynamics simulations with RMSD values ranging between 1 and 3 Å.