Chapter 1

Introduction

1.1 Background

Influenza, often referred to as the flu, is a highly infectious respiratory illness caused by influenza viruses. It significantly contributes to the global burden of infectious disease, frequently resulting in seasonal epidemics and annual mortality related to respiratory failure. Current antiviral therapies focus on interfering with the viral replication cycle, targeting viral components, such as the usage of neuraminidase inhibitors to prevent the release of progeny virions or polymerase inhibitors to disrupt RNA polymerase activity during the synthesis of new viral RNA. Furthermore, influenza vaccines—composed of inactivated or attenuated viral components—are provided annually, targeting high-risk demographics such as pregnant individuals, the elderly, and children between six months and five years of age. Nevertheless, the RNA-based genomic structure of influenza viruses promotes rapid mutation rates, triggering antigenic drifts that facilitate the development of drug-resistant strains and reduce vaccine efficacy (Chan et al., 2021). This predicament highlights the need to develop novel antiviral agents, including bacterial metabolites derived from various sources, such as plants.

One such plant is the *Piper crocatum*, otherwise known as the red betel vine or sirih merah. Widely cultivated across Indonesia for its traditional medicinal properties, the plant demonstrates significant therapeutic potential—specifically its anti-inflammatory and antibacterial effects—primarily attributed to its content of flavonoids, essential oils, and other organic compounds (Pratiwi et al., 2025). Additionally, it houses endophytes in the form of bacteria and fungi that reside within the plant's leaves, stem, and roots. In particular, these endophytes maintain a mutualistic symbiosis with the plant and have been shown to produce bioactive metabolites that have demonstrated antioxidant and antibacterial properties (Amrullah et al., 2018; Raisyadikara et al., 2025).

Previous studies on the antiviral capability of these endophytes have highlighted their activity in protecting their host plants from viral diseases alongside inhibitory activity against certain human viruses like SARS-CoV-2 (Akter et al., 2022; Fadiji & Babalola, 2020). However, the majority of these studies primarily focused on endophytic fungi, overlooking the possible contributions of endophytic bacteria. In regards to *Piper crocatum*, the few existing studies have mainly addressed antibacterial, antioxidant, and minor cytotoxic activity, again with a notable emphasis on the fungal endophytes rather than their bacterial counterparts.

Modern bioinformatics, with some coming in the form of accessible web-based platforms such as Galaxy and antiSMASH, provide new opportunities to uncover antiviral agents from those less characterized bacterial endophytes. Through analysis and reconstruction of genomic data from bacterial sequences, biosynthetic gene clusters (BGCs) that encode for potentially novel antiviral compounds, such as secondary metabolites, can be uncovered as a means of overcoming the variability of influenza viruses and provide a baseline for alternative, sustainable treatment options, supporting the potential of natural antiviral agents.

1.2 Objective

The objective of this study is to utilize bioinformatic methodologies to process genomic sequence data from endophytic bacteria isolated from *Piper crocatum*; to uncover Biosynthetic Gene Clusters (BGCs) that may demonstrate antiviral capabilities against influenza virus (such as via metabolites).

1.3 Hypothesis

The genomes of endophytic bacteria isolated from *Piper crocatum* contain distinct Biosynthetic Gene Clusters (BGCs) that encode for novel compounds, such as secondary metabolites, that show antiviral capability against the influenza virus.