Chapter 1

Introduction

1.1 Background

The coronavirus disease (COVID-19) outbreak was caused by highly infectious single-stranded enveloped RiboNucleic Acid (RNA) viruses known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Rahimi et al.,2020). Until 31 May 2023, COVID-19 has lead to approximately 767,364,883 confirmed cases and 6,938,353 deaths worldwide, whereas approximately 6,807,085 confirmed cases and 161,762 deaths were reported in Indonesia (WHO, 2023). This has encouraged many studies worldwide to search for a novel and effective medications for COVID-19. A prospective target for creating COVID-19 medications is the 3C-like protease (3CLpro), which has an important role in the replication of coronaviruses by aiding the production of SARS-CoV-2 essential proteins (Zhu et al., 2022).

Currently, there are several drugs that are used to treat the disease. Paxlovid, which is a 3CLpro inhibitor, is one of the recommended drugs for COVID-19 treatment. However, these FDA approved drugs may induce undesirable side effects and hypersensitivity reactions (Lam & Patel, 2023). Furthermore, COVID-19 vaccines have been successfully developed as an effort to prevent the disease. However, there is still a possibility of contracting the COVID-19 disease post-vaccination (Antonelli et al., 2022). Thus, it is necessary to continuously search for an alternative treatment to treat COVID-19.

Over time, many studies were conducted to search for naturally derived 3CLpro inhibitors (Guijarro-Real et al., 2021; Mandal et al., 2021; Yang et al., 2022). This phenomenon may be due to the increase in demand for alternative medicine in developing nations. The perceived health benefits of herbal medications and the perception that herbal medicines are safer and more

affordable than synthetic medicines contributes to the phenomenon (Bareetseng, 2022). Moreover, natural product compounds, such as kaempferol, quercetin, and its derivatives, were reported to have potential 3CLpro inhibitory properties (Mouffouk et al., 2021; Septembre-Malaterre et al., 2022; Jo et al., 2020).

The bitter ginger plant is a member of the *Zingiberaceae* family and was reported to contain high amounts of flavonoids, such as kaempferol, quercetin, and its derivatives (Silalahi, 2018; Yob et al., 2011). This makes the bitter ginger plant an attractive target for the creation of an alternative medication for COVID-19. The part of the plant containing the highest amounts of flavonoids are the rhizomes (Koga et al.,2016). To this date, the inhibitory properties of the rhizome of bitter ginger against 3CLpro of SARS-CoV-2 have not been studied. Therefore, this study was performed to examine whether bitter ginger rhizome extract possesses inhibitory effects on 3CLpro.

1.2 Objective

The objective of this research was to identify potential 3CLpro inhibitor compounds, such as kaempferol, quercetin, and its derivatives in the bitter ginger rhizome ethanolic extract and assess the SARS-CoV-2 inhibitory activity of the bitter ginger rhizome ethanolic extract.

1.3 Hypothesis

The ethanolic extract of bitter ginger rhizome and its flavonoid phytoconstituents are expected to have inhibitory activities against SARS-CoV-2 3CLpro.