1. Introduction

1.1 Background

The 2019 Coronavirus Disease (COVID-19) began in Wuhan, Central China, and has since been transmitted to 200 countries worldwide. This disease is transmitted by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Li et al., 2020). Furthermore, the World Health Organization (WHO) announced more than 196 million confirmed cases of COVID-19 on July 30, 2021, with more than 4 million deaths.

Coronavirus polyproteins encode two proteases that work together to digest and release translated non-structural proteins (NSPs), the papain-like protease (Plpro) and the main protease known as 3-C-like protease (Mpro). Both Mpro and Plpro are critical targets for drug discovery against ongoing COVID pestilences, such as MERS and SARS CoV. Mpro, the most recent crystal structure of the COVID-19 protein, was reported in February 2020 (Kandeel & Al-Nazawi, 2020). Mpro is responsible for cleavage and transformation of two large polyproteins (pp1a and pp1b) into mature NSPs. The main protease is a crucial enzyme of SARS-CoV-2 that mediates viral replication and transcription, making it an appealing therapeutic target (Naqvi et al., 2020).

Coronavirus Mpro is phylogenetically similar to SARS CoV, but not to Middle East Respiratory Syndrome (MERS) CoV. When the COVID-19/MERS and CoV COVID-19/SARS sequences were compared, the percentages of identicalness were 51.61 and 96,061 respectively. The top 20 medications in the simulated screening sample featured a wide variety of antivirals such as ribavirin and telbivudine, supplements, and multiple systemic drugs. Interestingly, ribavirin has been used to treat SARS CoV cases. Kandeel and Al-Nazawi (2020) conducted detailed research on the key completed COVID-19 Mpro structure and discovered suitable stored drugs to use

against the Mpro virus. Several drugs on Kandeel and Al-Nazawi (2020) list can be combined and used to treat COVID-19.

People in Indonesia choose to consume conventional herbal remedies due to religious practices, and some of the findings are deemed satisfactory. Indonesians are often accustomed to consuming traditional concoctions as a practice passed down through generations, especially among people who live or come from Java (Rohaeti et al., 2015). Jamu is an example of a popular herbal dish in Indonesia. People use herbs to improve strength and endurance, increase energy, and avoid a number of diseases (Widyowati & Agil, 2018).

Ginger (*Zingiber officinale*) is one of the ingredients used in the manufacture of herbal medicine. Ginger is a well-known and widely used spice. It contains a variety of chemical elements such as polysaccharides, amino acids, raw fiber, phenolic compounds, terpenes, and lipids. Ginger's medicinal qualities are largely due to its phenolic compounds, such as gingerols and shogaols. Ginger has a variety of biological functions, including antimicrobial, cardiovascular defense, antidiabetic, antioxidant, anti-inflammatory, anticancer, neuroprotective, and respiratory protection, according to studies (Mao *et al*., 2019).

Turmeric (*Curcuma longa*) has long been used in Ayurvedic medicine to treat inflammatory disease. Turmeric contains three curcuminoids: curcumin, demethoxycurcumin, and bisdemethoxycurcumin, as well as proteins, sugars, volatile oils, and resins. Although curcumin has been linked to a variety of pharmacological activities, including antioxidant and antimicrobial effects, this article focuses on curcumin's anti-inflammatory properties and its use in the treatment of inflammatory conditions (Jurenka, 2009).

The chemical components in ginger and turmeric drinks are expected to bind to and inhibit the action of a specific protease in the SARS-CoV-2 virus. Proteases are essential for cell and viral

health and viability. Cells cannot execute several critical activities if proteases are blocked, such as replication. Therefore, the authors were curious about the bioactive compounds found in ginger and turmeric that could be used as antiviral agents against SARS-CoV-2. There is no research that has been conducted a molecular simulation approach that targets Mpro by using compounds from ginger and turmeric, hence this research is considered novel. Although vaccinations were being carried out at the time of this research, it was still required to find another antiviral against SARS-CoV-2 and herbal beverage is needed as another option of possible medication to prevent COVID-19.

1.2 Objective

The objective of this research is to determine which bioactive compounds in *Zingiber officinale* and *Curcuma longa* are potential drug design candidates to target SARS-CoV-2 by performing molecular docking to screen the most potential bio compound to target Mpro and performing molecular dynamics simulation to see the dynamical structural and energetic information about the ligand and protein interactions. This research also applied quantitative structure–activity relationship (QSAR) to get specific bioactive compounds in *Zingiber officinale* and *Curcuma longa* and move on to the next step, which are molecular screening and molecular dynamics simulation.

The objectives of this project are:

- To implement QSAR prediction to the bioactive compounds of *Zingiber officinale* and *Curcuma longa.*
- To implement molecular screening to all of the bioactive compounds in *Zingiber officinale* and *Curcuma longa* as the ligands and SARS-CoV-2 Mpro as the target protein.

- To implement molecular dynamics simulation to the most potential bioactive compound in *Zingiber officinale* and *Curcuma longa* targeting SARS-CoV-2 Mpro.

1.3 Significance, Scope and Definitions

The SARS-CoV-2 protease structure was obtained from Protein Data Bank (PDB) and the ligands were obtained from PubChem database. Computer simulations such as molecular docking and molecular dynamics simulations were used in this work to illustrate how the Mpro in the SARS-CoV-2 virus behaved when exposed to a variety of different chemical compounds known for their 3C-like protease inhibitor action and antiviral activity. This research will improve the scientific aspects of jamu, especially for turmeric and ginger in Indonesia.