CHAPTER I. INTRODUCTION

1.1 Background

Colorectal cancer is one of the most common malignant tumors in the world, and in recent years the morbidity and mortality rates have continued to increase due to unbalanced diets such as consuming foods that are high in fat and low in fiber (Cai & Gao, 2021). Consuming high-fat foods will lead to increased levels of cholesterol, triglycerides, unsaturated fatty acids, and bile acids. These cholesterol and bile acids will be converted into secondary bile acids, cholesterol metabolites, and toxic substances by bacteria in the colon that can damage the colon mucosa, triggering inflammation (Harahap, 2019). Cyclooxygenase (COX) is a major inflammatory factor that induces cancer development (Samadarsi et al., 2022). Colorectal cancer cases show an increase in the expression of COX-2 by 77.97% significantly against normal colorectal tissue. Overexpression of COX-2 is related to increased prostaglandin synthesis which causes increased cell proliferation, inhibition of apoptosis, changes in cell adhesion, and increased metastases (Laksmiani et al., 2018; Wu & Sun, 2015). Caspase-3 is a protein that plays a role in the process of apoptosis stimulators (pro-apoptosis). Caspase-3 functions to execute cells and cleave proteins that induce apoptosis, caspase-3 is crucial in initiating the process of cell apoptosis (Sihite & Endang, 2013). Therefore, induction of caspase-3 to increase apoptosis is an important target in the treatment of colorectal cancer.

Secondary metabolite compounds in plants are anticancer agents with minimal side effects and safe, so they can play a role in cancer treatment. Low-level plants such as liverwort can have potential as chemopreventive agents, liverwort Genus Marchantia has been widely used as herbal medicine such as blisters, snake bites, pneumonia, and liver disorders (Wang et al., 2016). The potential of liverwort as herbal medicine is supported by previous research stating that liverwort is rich in phenolic compounds, triterpenoids, flavonoids (Hardi et al., 2019; Novakovic et al., 2021). The compounds contained in liverwort reveal potential as anticancer, antifungal, antibacterial, antioxidant, anti-inflammatory and antitumor (Dziwak et al., 2022; Gokbulut et al., 2012; Jantwal et al., 2019; Mewari & Kumar, 2008). Flavonoids, a type of secondary metabolite found in liverwort, have been shown to inhibit a number of different enzymes, including nitric oxide synthase, xanthine oxidase, aldose reductase, LOX, and COX, to produce anti-inflammatory effects throughout the proliferative and exudative phases of inflammation (Idris et al., 2022). Inhibition of COx-2 action will lead to increased anticancer activity (Li et al., 2020).

Computational approaches to analyze active compounds in plants through molecular docking, pharmacophore analysis, and various other approaches have been used to design and develop new therapeutic agents that can prevent or inhibit the development of colorectal cancer (Samadarsi et al., 2022). Previous research reported metabolite compounds such as flavonoids and also their derivatives through molecular docking simulations were able to inhibit COx-2 (Idris et al., 2022). This study aims to analyze how the binding and interactions that may occur between bioactive compounds

of the non-polar fraction of liverwort (*Marchantia paleacea* Bertol.) in suppressing COX-2 through molecular docking simulation and analyzing cytotoxic activity of bioactive compounds in the non-polar fraction of liverwort (*Marchantia paleacea* Bertol.) against colorectal cancer cell line HCT-116 in vitro.

1.2 Formulation of Problem

The formulation of the problem in this study is:

1. How effective are the bioactive compounds in the non-polar fraction of liverwort (*Marchantia paleacea* Bertol.) as an anticancer agent in colorectal cancer cell line HCT-116?
2. Which of bioactive compounds in the non-polar fraction of liverwort (*Marchantia paleacea* Bertol.) are effective as an anticancer agent?
3. Molecular docking of bioactive compounds in the non-polar fraction of liverwort (*Marchantia paleacea* Bertol.) against target proteins COX-2 in silico in colorectal cancer?

1.3 Research Purposes

The purpose of this research is:

1. Analyzing the cytotoxic activity of bioactive compounds in the non-polar fraction of liverwort (*Marchantia paleacea* Bertol.) against colorectal cancer cell line HCT-116 in vitro.
2. Identify bioactive compounds in the non-polar fraction of liverwort (*Marchantia paleacea* Bertol.) that act as colorectal anticancer.

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3. Analyzing the binding affinity and potential of bioactive compounds in the non-polar fraction of liverwort (*Marchantia paleacea* Bertol.) against COX-2 target protein by molecular docking in silico in colorectal cancer.

1.4 Benefit of Research

This research is useful to increase the use value of liverwort because it is abundant and easy to find as a drug candidate in cancer cure, due to the high mortality rate due to colorectal cancer in Indonesia, besides liverwort is also reported to be rich in antioxidants that can be used as an alternative treatment for colorectal cancer.

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