CHAPTER 1

INTRODUCTION

1.1. Introduction

Colorectal cancer (CRC), is a heterogeneous disease of the colon and/or rectum, and can also be termed as either colon cancer or rectal cancer based on its origin (Chu, 2007; Rawla, Sunkara, & Barsouk, 2019). CRC most often arises from the glandular, epithelial cells of the large intestine, and it usually develops from dysplastic adenomatous polyp. It commonly progresses through a multistep process consisting of the sequential inactivation of various tumor suppressor genes in parallel with the activation of proto-oncogenes (Chu, 2007; Marley & Nan, 2016; Rawla, Sunkara, & Barsouk, 2019).

CRC is currently the third leading cause of cancer-related death and the fourth most commonly diagnosed cancer with about two million new cases and approximately one million deaths each year across the world (International Agency for Research on Cancer, 2018; Rawla, Sunkara, & Barsouk, 2019). In Indonesia, CRC has the fourth highest incidence rate for cancer, constituting about 8.6% of all cases, with about thirty thousand new cases and causing around sixteen thousand deaths every year (International Agency for Research on Cancer, 2018). In addition, most CRC cases in Indonesia were detected at either stage three or four, approximately 76.7% and 13.1% cases respectively (Widjaja & Yo, 2016). At these late stages, metastasis would have occurred and patients' survival would be significantly low. Thus, it is clear that CRC is considered as one of the major public health issues in Indonesia (Abdullah et al., 2012).

Current treatments for metastatic CRC include a number of chemotherapy drugs possessing significant antitumor activity including 5-fluorouracil (5-FU), irinotecan, oxaliplatin, capecitabine, raltitrexed, trifluridine and tipiracil (El-Shami et al., 2015). However, chemotherapy and

radiotherapy, especially in long-term treatments, have various side effects, such as nausea, vomiting, dehydration, dry skin, rashes, easy bruising or bleeding, acne, loss of appetite, sleep difficulty, urinary incontinence, sexual dysfunction, hair loss and fatigue, or even more serious adverse effects, such as mucositis, allergic reactions, severe diarrhea, hand and foot syndrome, peripheral neuropathy, gastrointestinal problems, anxiety and depression (Denlinger & Barsevick, 2009; El-Shami et al., 2015).

Despite all the breakthroughs and advancements in current clinical research studies, it remains a significant challenge to construct a comprehensive molecular therapy for CRC treatment. The reason for this problem are due to the presence of various different types of mutations and mutagens that could lead to the development of CRC and also due to the rapid progression of drug resistant cancer cells and cancer recurrence that suppress the efficacy of cytotoxic therapies (Colussi et al., 2013; Sideris & Papagrigoriadis, 2014; Rawla, Sunkara, & Barsouk, 2019). Not to mention, treatments for CRC are incredibly expensive and there is still very limited and unequal accessibility for the treatments of CRC in Indonesia, possibly due to geographical and economic reasons. Hence, there needs to be more research aimed at developing more accessible and affordable alternative treatments for CRC.

Since drug development requires a lot of time and production cost, investigating the effect of existing drugs and/or natural products in cancer cells, presents an appealing and convenient opportunity that might lead to discovering new therapies for cancer treatment (Beckwitt, Shiraha, & Wells, 2018). Thus, the combination of natural products and drugs with favorable safety profiles, could be considered as a visible cancer treatment. (Wahab et al., 2018). Combination therapy for cancer treatment has several advantages, such as being able to achieve more potent effects because it can combat cancer cells through targeting multiple pathways and generate efficacy using lower doses of drugs. In addition, combination therapy also minimizes the possibility of cells to develop drug resistance since it is more difficult for the cancer cells to adapt to simultaneous toxic effects

produced by two or more therapeutic agents (Karjalainen & Repasky, 2016; Mokhtari et al., 2017). These reasons support the investigation and development of novel alternative treatments and regimens using combination therapy.

Simvastatin (Zocor), is one of the most common lipid lowering drugs for the treatment of hypercholesterolemia (Moghadasian, 1999; Beckwitt, Shiraha, & Wells, 2018; Wang et al., 2018). Simvastatin works by competitively inhibiting the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, which is responsible for the conversion of HMG-CoA into mevalonic acid, therefore inhibiting hepatic synthesis of very-low-density lipoprotein (VLDL) and decreases plasma low-density lipoprotein (LDL) and VLDL levels (Moghadasian, 1999; Talreja & Cassagnol, 2019) (Wang et al., 2018). The mechanism in which simvastatin inhibits HMG-CoA reductase was found to also inhibit the proliferation and induced apoptosis in several cancer cell lines, including CRC (Pisanti et al., 2014). Currently, there are several epidemiological studies suggesting correlation between the use of simvastatin use and lower CRC risk (Dobrzycka et al., 2018; Hassanabad, 2019). Therefore, simvastatin might be a great anticancer agent alternative.

A. muricata , mostly known as soursop, is a tree producing soft, edible, green, heart-shaped, spiny skinned fruits that could be found in Southeast Asia, including Indonesia (Cassé, 2018; Rady et al., 2018; Wahab et al., 2018). According to numerous phytochemical studies, *A. muricata* leaves extracts have been reported to have anticancer properties, such as antioxidants, alkaloids, sterols, phenolic compounds, acetogenins and megastigmanes (Leboeuf et al., 1980; Yang et al., 2015; Coria-Téllez et al., 2018; Rady et al., 2018). Previous studies have assessed the cytotoxicity of *A. muricata* leaves extracts on several cancer cell lines, the results showed the extracts were highly toxic to cancerous cells but not to normal healthy cells (Gavamukulya et al., 2017; Rady et al., 2018; Wahab et al., 2018). According to several studies, extract of A. muricata leaves proved to be toxic in cancer cells, while not affecting the viability of healthy cells and the most effective in decreasing the

viability of cancer cells (Cassé, 2018). Thus, studies have proven that *A. muricata* leaves extract has the potential as an anticancer agent candidate.

The aim of this review was to evaluate whether simvastatin and *A. muricata* leaf extract, compared to other treatments, effective in inducing anticancer effects against CRC cells. Therefore, the author synthesized published studies on the effect of simvastatin and *A. muricata* leaf extract in cell lines, animals, and CRC patients. In addition, the author also highlighted the potential of simvastatin and *A. muricata* leaf extract to be used in combination with other anticancer treatments.

1.2. Objectives

The aims of this review were:

- To synthesise published studies on the individual effects of simvastatin and *A. muricata* leaf extract on CRC cells.
- To highlight the potential of using simvastatin and *A. muricata* leaf extract in combination treatments.