

## Chapter I

### Introduction

#### 1.1. Problem Background

Cancer is the accumulation of over-proliferated mutant cells and tumor microenvironment cells which are able to sustain their life by manipulating the normal systems of the body (Hanahan & Weinberg, 2011). The over-proliferated cells could disrupt normal homeostasis and the normal function of affected organs. Consequently, cancer is the second leading cause of death in the world and is responsible for 9.6 million deaths worldwide in 2018 (Bray et al., 2018). Two of the most frequently diagnosed cancers worldwide are breast cancer and colorectal cancer. Based on gender distribution of cancer incidence, female breast cancer is more common compared to male breast cancer. Male breast cancer accounts <1% of all breast cancer incidence in the USA (Leon-Ferre et al., 2018). While, the incidence of female breast cancer in Indonesia has decreased from 61,682 cases in 2013 to 48,988 cases in 2014 (World Health Organization, 2014; Kementerian Kesehatan RI, 2015). In contrast, colorectal cancer is more common to develop in male compared to female. A data analysis of colorectal cancer between 2008 to 2012 in Indonesia showed male as higher incidence compared to female which is 54% and 46%, respectively (Khairina et al., 2018). In addition, the mortality of Indonesian colorectal cancer in 2014 reached 10.2% in 103,100 male patients and 8.2% in 92,200 in female patients (World Health Organization, 2014).

#### 1.2. Problem Formulation

The burden of cancer has brought global attention among researchers to reduce it. The treatments of cancer are limited to surgery, chemotherapy, radiotherapy, and targeted therapy (Kuipers et al., 2015; Waks & Winer, 2019). Although it could reduce the burden and prevent tumor recurrent subsequently to tumor removal surgery, some of the treatments, namely radiotherapy and chemotherapy are not target-specific and toxic to the highly

proliferated normal cells notably hair root cell and skin cell (Barnett et al., 2009; and Palumbo et al., 2013). Furthermore, long-term conventional chemotherapy usage is prone to induce tumor resistance due to DNA mutations and metabolic changes (Housman et al., 2014). Hence, a better approach to manage cancer is required to prevent healthy cell damage and cell resistance to the regimen.

Natural products have been used widely as the source of many human disease treatments. Over 60% of current cancer therapeutic agents are derived from natural products (Cragg & Pezzuto, 2016). The most common natural products that are studied for its detrimental effect on cancerous cell are spices. *Syzygium polyanthum* (Wight) Walp. or known as *Syzygium polyanthum* leaf is a common home spice in Indonesia households that is used for culinary and a traditional medication to treat ulcer, hypertension, diabetes, hyperuricemia, diarrheal, gastritis, skin diseases, and inflammation (Ramli, Radu, Shaari & Rukayadi, 2017). A phytochemical analysis detected tocopherol, terpene, aldehyde, flavonoid, and alkene compounds in three different *Syzygium polyanthum* leaf extracts; hexane, ethyl acetate, and methanol extraction (Abd Rahim, Ismail, Omar, Rahmat & Wan Ahmad, 2018). These compounds possess anti-inflammatory, antioxidant, anti-carcinogenesis, anti-tumor, and cytotoxic activity that might give negative effects to cancerous cells. A study by Sulistiyani et al. (2014) showed a cytotoxic activity of flavonoid extract from *Syzygium polyanthum* leaf towards HB4C5 hybridoma and colon 26 adenocarcinoma cell derived from BALB/c mice. However, an extensive pre-clinical study of *Syzygium polyanthum* leaf towards human colorectal cancer and human breast cancer cell has not been studied yet.

This study will provide information focusing on the cytotoxic activity of *Syzygium polyanthum* towards human colorectal cancer (WiDr) cell and human breast cancer (T47D) cell lines and its involvement in cell cycle distribution and apoptotic activity of the cells. Furthermore, it is expected to contribute as a fundamental knowledge for future studies

related to the development of natural remedies as an alternative treatment towards colorectal cancer and breast cancer.

### **1.3. Objective**

The objectives of this project are:

- To detect bioactive compounds of *Syzygium polyanthum* leaves powder by phytochemical analysis
- To detect bioactive compounds of hexane and methanolic *Syzygium polyanthum* leaves extract by thin layer chromatography technique.
- To investigate the cytotoxic effect of *Syzygium polyanthum* extract towards tumorigenic and immortalized non-tumorigenic cell lines by using MTT assay.
- To examine cell cycle distribution and apoptotic activity of WiDr and T47D cell line treated with *Syzygium polyanthum* extract.