CHAPTER 1

INTRODUCTION

1.1   Introduction

Cancer is a major health problem and one of the leading causes of mortality worldwide. The World Health Organization (WHO) reported in 2012, approximately 14 million new cancer cases occur worldwide and the number is predicted to increase by around 70% in the next two decades. In Indonesia, the prevalence of cancer cases across the country was 347,792 in 2013 and it is continuously rising each year (Indonesia Ministry of Health, 2013). Meanwhile, the latest data in 2019 shows that 1,762,450 new cancer cases and 606,880 cancer deaths are projected to occur in the United States (American Cancer Society, 2019). Among the gynecological cancers, cervical cancer is the most common type of cancer, followed by ovarium cancer, uterus, vulva, vagina, and fallopian tube cancer (Aziz MF, 2009). In 2012, WHO reported about 20,928 new cervical cancer cases are diagnosed annually in Indonesia (HPV Centre, 2015). Furthermore, cervical cancer mortality rate in Indonesia is around 2.5% lower compared to the average of deaths in South-East Asia (HPV Centre, 2015).

Cancer patients are mostly treated with chemotherapy, radiotherapy, and surgery. Despite the progress in cancer diagnosis and treatment, there are many side effects of the cancer treatment that might cause different health problem in cancer patients. Chemotherapy treatment that acts throughout the patient body not only suppresses the fast-growing cancerous cell, but also the normal healthy cells. These side effects appear due to the damage of various healthy cells, such as blood-forming cells in the bone marrow, cells in the digestive tract and reproductive system, as well as hair follicle cell (Chakraborty *et al*., 2012). Targeted delivery of cytotoxic drugs should be achieved in order to eliminate nonspecific toxicities, therefore it is important to perceive and minimize nonspecific interactions with non-tumorigenic cells (McNerny *et al*, 2010).

Further, the cancer cells that are exposed to chemotherapy often become resistant to the treatment. Cancer drug resistance arises due to various factors, most likely due to cancer cell's ability to mutate and modify itself, which lead to drug inactivation. (Housman, *et al*., 2014). Due to the inherent complications and side effect of chemotherapeutic drug, lack of target specificity of the treatment, along with cancer drug resistance, highlights the need to discover potential new chemotherapeutic agents; including those agents derived from bacteria and their associated bioactive compounds (Ragus *et al*, 2008).

Current research has shown the intriguing result of bacteria utilization for cancer treatment, suggesting that bacteria has great potential as a new source of cancer therapy (Huang, 2010). In recent decades, the therapeutic potency of bioactive compounds from bacteria has gained attention in pharmaceutical research. Researchers have established various strategies in the utilization of bacterial products such as proteins, enzymes, immunotoxins, and secondary metabolites, which able to specifically target cancer cells and induce tumor regression through growth inhibition, cell cycle arrest, or apoptosis induction (Bernardes *et al*, 2009). These specific biomolecules derived from bacteria are being evaluated for their ability to act as new anticancer agents with minimum side effect compared to radiotherapy and/or chemotherapy.

Indonesia is a country rich in biodiversity with many species organisms yet to be discovered. Multiple studies estimate that the total number of extant species of macroorganisms covers a range between 5 to over 30 million. With only 1.75 million species described; we are a long way from being able to circumscribe the planet's biota (Webb *et al*., 2010). In addition, microbiological biodiversity puts Indonesia as a promising source of new molecules with potential health beneficial effects. In 1940, the first actinomycin D was discovered. Most of the reported cases of actinomycin D have been in patients with right-sided Wilms liver tumors, where the successful rates as high as 90 % have been achieved for rhabdomyosarcoma and Ewings sarcoma (DeLeve, 2013). Since that, many molecules with

anticancer properties have been isolated from natural sources and more than 1,000 species of actinomyces were isolated from diverse ecosystems in Indonesia (Demain and Sanchez, 2009).

During the period 2014-2017, i3L conducted a research project funded by the USAID agency in order to identify novel microorganisms and microbial enzymes from Indonesian peatland and herbivores manures to improve bioconversion processes. Various samples were taken from different sources, starting from rotten foods, rain forest plants, herbivores manures and to peat soil. These samples were analyzed and more than 500 isolates were identified and classified as bacteria, yeast, and fungi. Among the genus discovered, some of them have been described, or have members among the group, as antibiotic, anti-fungal, and cytotoxic compounds producers. This project aims to further analyze bacteria samples that may lead to new chemical scaffolds among their secondary metabolites with cytotoxic activity. The final aim of the project would be to identify a specific bacterium strain that able to produce metabolites with cytotoxic activity.

1.2   Research Objectives

The objectives of this research are:

1.2.1   To analyze the database of bacteria isolated from Indonesia peatland and identify candidates with potential production of new bioactive molecules.

1.2.2   To evaluate the ability of extract from selected bacteria strain on HeLa cell and the non-tumorigenic cell NIH-3T3 Fibroblast cell lines.