Chapter 1

INTRODUCTION

1.1. Background

As one of most common malignancies in the world, CRC ranks third on both male and female and the incidence is expected to continue to increase in the coming years (Kuipers, et al., 2016). Etiologic studies show that CRC could be developed through genetic factors but mostly it is sporadic with a strong correlation over lifestyle, specifically on dietary habit of red meat and processed meat intake (Kuipers, et al., 2016). Furthermore, other accumulated studies show that eating patterns of certain plant-based diets is also discovered to have a strong correlation with CRC treatment.

Plant-based diet utilizes plants in various forms to be consumed. Aside from vegetables, fruits, legumes, and tubers; spices also play an important role as the research models for its phytochemical and antioxidant content. In cancer research, plant-based sources have been carefully researched as the world started to give specific attention to herbal medicine instead of conventional medicine mainly because of dissatisfaction with conventional medicine (Welz, 2019). In correlation with colorectal cancer development, plant-based sources that will be discussed are chilli from the fruit group and ginger from spices group.

Plants from the genus *Capsicum*, members of the nightshade family: *Solanaceae*; produces a fruit called chilli that contains CAP as its major pungent ingredient (Bode & Dong, 2011). The plants have been cultivated as part of human diet since at least 7500 BC and have been widely consumed in the cuisine all over the world (Bode & Dong, 2011). Therefore, cancer research attempts to observe the effect of CAP in various cancer types including CRC.

It has been years that the role of capsaicin remains a controversy in its potency against risk of gallbladder and gastric cancer, with the most debated factor being the dosage and duration of CAP exposure (Bode & Dong, 2011). In the case of CRC, various anticancer effects of CAP have been reported for years through IVS and ARS. However, one of the IVS reported that CAP in low

concentration promotes migration and invasion of CRC cell lines as well as the EMT (Yang, J., et al., 2013). CAP effect on CRC remained a discussion for newer research production until a case-control study (CCS) confirmed that CAP consumption does not increase or decrease the risk of CRC (Yang, J., et al., 2019). Another review study also confirmed that the administration of CAP in combination with known carcinogenic substances, in almost all cases, reduces tumors or did not potentiate them (Bley, K., et al., 2012).

The next plant-based source that will be discussed is root-based spices called ginger from the genus *Zingiber*, members of the *Zingiberaceae* family. The root of this plant has been globally marketed for its beneficial properties as cooking spice and herbal medicine (Mao Q.Q., 2019). Ginger contains many bioactive compounds and one of them is the major pungent polyphenol called GIN. Various bioactivities of ginger are reported to have anticancer properties against various types of cancer by inhibiting proliferation and inducing apoptosis (Mao Q.Q., 2019). Therefore, CRC research also attempts to observe the effect of GIN.

The IVS and ARS for anticancer effects of GIN are agreed upon in CRC. Various anticancer effects of GIN have been reported through IVS and ARS. Author concluded from the studies that GIN mainly works through an apoptosis pathway in the CRC cell line (Lin, Lin, & Tsay, 2012; Radhakrishnan et al., 2014). There are no contraindications against CRC in dose and duration dependent manner reported so far.

Finally, although CAP and GIN came from different genus and family, the author selected these compounds as the focus for this thesis project under the reason of their similar characteristics. Both CAP and GIN are known to be agonist to TRPV1 that correlates with the work of EGFR for various anticancer pathways (Geng S., et al., 2016).

Author found a literature that observed the effect of CAP and GIN combination based on an ARS of urethane-induced lung cancer mice model, GIN was observed to reverse co-carcinogenic effect of CAP which is noted to induce pro-inflammatory and oxidative stress-promoting effect and also induce pro-proliferation and EMT-promoting effect during lung carcinogenesis (Geng S., et al., 2016).

1.2. Research Objectives

However, in contrast to the literature, both CAP and GIN alone generally have beneficial effects as natural compounds in CRC. The compounds could add to natural compound candidates for CRC treatment research. Furthermore, it is known that each CAP and GIN have the same pungent characteristics through the anticancer pharmacokinetics viewpoint. Exploring its potential anticancer effects of either additive or synergism in the combination of CAP and GIN would be an interesting value to find out. Unfortunately, there is a lack of study that discusses the combination design of natural compounds for CRC alone. The current available evidence only provides the synergistics effect of a combination of CAP with 3,3'-Diindolylmethane (Clark, Lee, & Lee, 2015). Another evidence reported synergistics effect of a combination of GIN and γ-T3 (Yusof K. M. et al., 2015; & 2019). This leads to the needs for deeper evaluation of CAP and GIN potency as a contribution to CRC treatment research.

Thus, the present thesis project aims to explore the potential anticancer effects of CAP and GIN combination in CRC.