CHAPTER 1

INTRODUCTION

1.1. Project Background

Plants are found in every habitable environment, where the majority of plants are growing on soil. Plants have been shown to have medical uses and have been utilized to treat a variety of pathological condition (Thomford et al*.,* 2018). Medicinal plants have been the source of up to 50% of the approved drugs in the past 30 years (Veeresham, 2012). The market of medicinal plants as medicine is still growing and predicted by Limited Liability Company (LLC, 2020) the market size will exceed USD 411.2 billion by 2021.

Indonesia is a Southeast Asia country, located between the Indian Ocean and Pacific Ocean. Indonesia, an archipelago country, consisting of 17,000 islands, where around 990 of them are permanently inhabited. According to Conservation International, Indonesia is one of the 17 megadiverse countries, and one of the world's 25 global biodiversity hotspots. Indonesia's biogeographic, geological, climate, and ecological factor have resulted in a megadiverse fauna and flora. In addition, Indonesia is known to have around 40,000 different plant species, and about 6,000 plants have been used for traditional healing processes (Jadid et al., 2020). Therefore, comprehensive study on the medicinal plants in Indonesia will be beneficial to discover the pharmacological activity that might improve the quality of life of Indonesian and also discover cure for incurable diseases in the world.

Alzheimer's Disease (AD) considered as the most common cause of dementia and defined as a chronic, incurable neurodegenerative disorder marked by progressive memory loss and disturbed emotional state (Kwakowsky et al*.,* 2018). In the United States (US), AD is the sixth major cause of death for people of all ages and the fifth major cause of death in those 65 and older. A study found that this disorder affects approximately 5% of people between the ages of 65 and 74, and almost 50% those older than the age of 85. The risk of getting AD increases with age, thus, more prevalent on

elderly. AD is hard to cure, making the annual cost of AD treatment expensive, with an approximate value of USD 148 billion in the US alone. In addition, the available treatments for AD are considered to be not very effective because the treatment only relieves the symptoms but not stops the progression of the disease (Casey et al*.,* 2010). Hence, there is an urgency of developing effective therapies for AD.

The build-up of amyloid-β peptides (Aβ) composed of aggregated amyloid-β (Aβ) and neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau protein are the characteristic of AD. In the central nervous system (CNS), there are two types of synapses called glutamatergic and GABAergic, which have excitatory and inhibitory effects are impaired during the AD progression, respectively (Li et al*.,* 2016). The gamma-aminobutyric acid (GABA) inhibitory effect is mediated by three distinct receptor subfamilies known as $GABA_A$, $GABA_B$, and $GABA_C$ receptors. An alteration of synaptic balance has been identified as a pathological factor in neuronal disorders including AD. The GABA receptors that are predominantly involved in maintaining the dynamic balance against the excitatory systems are the $GABA_A$ Receptors ($GABA_A$Rs) (Rissman & Mobley, 2011). The level of GABA and glutamate neurotransmitter were substantially lower in the temporal cortex of AD patients, indicating decreased synaptic function and neuronal transmission. Therefore, modulating the inhibitory effect of GABA via $GABA_A$Rs could be a possible strategy for AD (Li et al., 2016).

One of the popular plants from Indonesia that has a potential pharmacological activity on the nervous system is Coriander Leaves (*Coriandrum sativum* L.). Coriander belongs to the apiaceae family (Asgarpanah, 2012). Numerous studies have shown that coriander leaves extract is able to prevent AD, memory impairment, and improved memory in mice (Mani & Parle, 2009; Cioanca et al*.,* 2013; Jasira et al*.,* 2017). Moreover, it exerts antioxidant activity, neuromodulatory effect and induces neuroprotective activity (Casey et al*.,* 2010; Ghorbani et al*.,* 2011; Pourzaki et al*.,* 2017; Prasad & Muralidhar, 2019). Therefore, coriander leaves are potential herbs to be used as AD treatment.

Moreover, coriander leaves contain flavonoid compound which are a group of natural substances with variable phenolic structures and are ubiquitous in plants (Nambiar et al., 2009; Hwang

et al., 2014). Since flavonoids are able to cross the blood-brain barrier (BBB), they can exert an immediate effect on the brain (de Andrade Teles et al., 2018). Furthermore, flavonoids exert an anxiolytic, sedative, anticonvulsant, and analgesic effect on the CNS via interactions with a variety of receptors and signalling systems, including GABA receptors. Therefore, flavonoids are believed to prevent neurodegeneration associated with AD and improve cognitive function (Hanrahan et al., 2011; de Andrade Teles et al., 2018).

1.2. Research Objectives

The objective of this research is to evaluate the antioxidant activity of coriander leaves and investigate the possible involvement of $GABA_A$Rs in mediating the activity of coriander leaves in animal model of memory impairments

1.3. Research Hypothesis

The coriander leaves extracted in ethanol 80% exerts antioxidant activity and modulates $GABA_A$Rs, thus potentially being useful to prevent or cure AD.

1.4. Research Scope

The experiment will be conducted in Indonesia International Institute for Life Sciences (i3L) research laboratories with the details of:

- Antioxidant Assay—using DPPH method to evaluate the antioxidant activity of coriander leaves extract
- Gene Expression Study on animal model of Alzheimer's-like diseases—using reverse transcription-quantitative polymerase chain reaction (RT-qPCR) to investigate the expression of $GABA_A$Rs subunits, which are GABRAα_1, GABRAγ_1, and GABRAδ.