CHAPTER 1: INTRODUCTION

1.1. Background

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder that contributes up to 70% of dementia cases and characterized by impairment of cognitive domain(s), memory loss, and accompanied by occupational or social function disturbance (Castellani *et al.*, 2010). Commonly, the early stage of the disease is neglected as the signs, such as being forgetful and less active, are perceived to be normal signs of aging. While at the same time, the disease starts gradually progressing. Later, the signs become more apparent and worsen the patients' quality of life. Generally, in late stage, patients will be unable to recognize their surroundings (e.g., family, things), exhibit behavior changes, need assistance for doing activities, and unaware of place and time. The disease not only brings the impact for the patients, but also their families and caregivers, in terms of emotional, economic and physical condition (Duthey, 2013). Based on the study conducted by Brookmeyer *et al*., AD was estimated to affect globally around 26.6 million people in 2006, and predicted to quadruplicate by 2050. According to World Alzheimer Report in 2015, Asia has the highest portion (49%) of new cases, which escalate from 2012 estimates, followed by Europe and America. In addition, AD also results in financial burden for the patients' families with its high lifetime cost, which is predicted at up to $174,000 per person (dos Santos Picanco *et al.,* 2016). Generally, the expenses were spent on medical supplies, medications, groceries, in-home health care, and non-medical in-home care (Grabher, 2018).

Two hallmarks to distinguish AD from other dementias, are the presence of senile plaques or known as beta-amyloid (Aβ) plaque, and neurofibrillary tangles (NFTs). Senile plaques are the result from abnormal amyloid precursor protein (APP) cleavage by β-secretase, creating insoluble peptides instead of soluble peptides. This condition will induce inflammation for clearing the plaque. However, in the same time, the inflammation is also destructive for adjacent neurons. The presence of intracellular NFTs is due to inordinately

hyperphosphorylated and aggregated protein tau, which is hypothesized to disrupt the axonal transport component that works for neuronal survival and function. Oxidative stress (OS) is classified as one of the major underlying AD mechanisms affected by other basic OS mechanisms, like Aβ accumulation, mitochondrial dysfunction, and hyperphosphorylated tau protein (Nunomura & Perry, 2020; Uttara *et al*., 2009). The reduction of brain copper and iron due to Aβ accumulation trigger the OS, which further can lead to DNA damage (dos Santos Picanco *et al.,* 2016).

AD is also influenced by risk factors of the individuals that are classified into two, controllable and uncontrollable. The uncontrollable risk factors are associated with family history, genetics, gender, and age. Meanwhile, the controllable risk factors can be lower by workouts routine, doing activities that involves intellectual stimulation, or improving diets to lower the cholesterol level and blood pressure (Grabher, 2018). Changes in brain-derived neurotrophic factor (BDNF) and CAMP responsive element binding protein 1 (CREB1) have also been associated with AD. BDNF is a widely distributed neurotrophin within the central nervous system (CNS), essential for the survival of neurons and synaptic plasticity. AD patients likely to have lower BDNF level in the brain and serum compared to healthy elderly (Jiao *et al.*, 2016). CREB is a transcription factor for some genes, including BDNF. CREB1 is known to play roles in re-modelling synaptic plasticity and cognitive. Downregulation of CREB transcription owing to Aβ peptide, also promotes downregulation of BDNF (Avgan *et al.,* 2017; Rosa & Fahnestock, 2015). These genes will be used to assess the changes in neurogenesis expression in this study.

There are two available classes of drug used to treat AD, acetylcholinesterase inhibitor and N-methyl-D-aspartate (NMDA) receptor antagonist. The acetylcholinesterase inhibitors, such as donepezil, are applicable in all stages of AD. This class acts by inhibiting the acetylcholine breakdown which effectively increase the acetylcholine level (Korolev, 2014). Meanwhile, the NMDA receptor antagonist, like memantine, act by lowering the abnormal

glutamate neurotransmission activation (Ruparelia & Mobley, 2014). Up to this point, there is no available drugs treatment for AD that can cure or prevent the disease. The available drug treatments only aid in controlling the symptoms, but unable to reverse the development or slow the disease's progression. Besides, several potential drugs that reached clinical trial phase 3 failed to show clinical efficacy (Korolev, 2014). As the available treatments are lacking of specificity and unable to stop or prevent the disease, along with other aspects (the economic, physical and emotional burden facing by the families and caregivers), the research for finding new potential therapy for AD is essential. Especially, finding those capable to halt the disease progression or to prevent the disease.

Indonesia is a country with rich biodiversity, which suitable to support the utilization for herbal medicine, including for AD. *Coriandrum sativum L*. or coriander is one of the widely used plants due to its medicinal and nutrients properties and can be grown worldwide, including in Indonesia (Laribi *et al.,* 2015). *C. sativum* is known to have a great antioxidant activity, with an IC_{50} value of 147 µg/mL in DPPH assay. Linalool, a monoterpenoid compound presence in coriander, was found to be the key compound responsible for the neuroprotective effect, indicated by the reduction of hippocampal lactate dehydrogenase (LDH) activity that are generally release during tissue damage. Terpenes also found to be responsible for protection against oxidative damages and mitochondrial dysfunction. Earlier studies also showed that coriander possesses other biological activities, like anti-inflammatory and hypolipidemic activities making it a potential plant to be used for treating AD (Prachayasittikul *et al.*, 2018). The present study involved behavioral and gene expression assessment to evaluate the effect of coriander leaves' extract which have not been done previously.

1.2. Aim of the Study

This study aims to evaluate the anti-Alzheimer's activity of *Coriandrum sativum L*. extract in Alzheimer's mouse model through: 1.) Evaluating behavior of the mice AD model using

novel object recognition (NOR) test method, 2.) Assessing gene expression using qRT-PCR targeting BDNF and CREB1 gene.

1.3. Hypothesis

If the leaves extract of *Coriandrum sativum L*. exhibit biological activities that can interfere with the pathogenesis of Alzheimer's disease, then mice models who were treated with the extract should have improved their memory and gene expression. The extract groups were expected to have a higher preference index in NOR and absence of CREB1 and BDNF gene expression reduction, compared to the scopolamine group.