CHAPTER 1 INTRODUCTION

1.1. Background

Every day, around 2,000 people under 18 smoke their first cigarette and more than 300 people under 18 become daily smokers. Globally, around 9.7% of school students currently smoke cigarettes. Smoking becomes a global health problem in the world (FDA, 2019). Cigarette smoke consists of more than 7000 chemical substances. However, around 250 chemical substances have been identified poisonous and 70 others are carcinogenic (Martin, 2018).

Knowing that harmful fact, a lot of people still smoke even it will risk their own life. The reason of why smokers still smoke because nicotine can release dopamine in our body and that makes the body want it more and more. In severe condition, nicotine can also affect several organs. Especially in the liver, one of the detoxification organs. If liver hampered, it will be a massive problem to other system organs and all over the body (Mollazadeh and Hosseinzadeh, 2014).

Nicotine in the body, will produce Reactive Oxygen Species (ROS). ROS, including O_2^-, H_2O_2, ONOO, OH^- and $HOCl^-$ are excess products of normal metabolic in the cells (Muriel, 2009). In the liver, ROS primarily produced in mitochondria and endoplasmic reticulum (ER) of hepatocytes through cytochrome P450 enzymes (Cichoz-Lach and Michalak, 2014). In normal condition, the number of oxidative compounds and antioxidant compounds have to be balanced. If there is an imbalance of oxidative compounds in the body, it will trigger pro-inflammatory cytokines such as IL-1β, IL-6, IL 10, TNF-α, IFN-γ and PGE2. Which promoting an inflammatory response and the body will induce IL-10 and IL-

3 to reduce that inflammatory response. And if it keeps pilling up, the body cannot excrete it normally it becomes to oxidative stress (El-Zayadi, 2006). There are three kinds of inducement oxidative stress, by ROS, lipid peroxidase, and DNA damage (Cichoz-Lach and Michalak, 2014). That oxidative compound and oxidative stress are known as the leading causes of many diseases such as liver injury and many substances can induce oxidative damage by generation of ROS the body (Mollazadeh and Hosseinzadeh, 2014). Over time will inflict to liver function and in a long time of period, the organ will run into lipid degeneration, organ necrotic, and genetic mutation (El-Zayadi, 2006).

Reported that heavy smokers will accumulate excess iron in hepatocytes which induces fibrosis and development of hepatocellular carcinoma. In some condition, suppressed mood, a common feature among heavy smokers, develop the risk of liver cancer (El-Zayadi, 2006). In many research found, an antioxidant is substances that can heal cancer slowly with non-chemical treatment.

Antioxidant from outside the body is really needed to help the body to reduce oxidative compounds. There are two kinds of antioxidants, man-made and natural substances that may prevent or delay some types of cell damage. A man-made antioxidant such as vitamin A, vitamin C, and vitamin E, commonly consumed as a supplement. But if too many of vitamin that consumed, and cannot be clearly metabolized and it becomes hypervitaminosis and can caused some diseases. For example, high doses of vitamin E may increase risks of prostate cancer and one type of stroke (NCBI, 2019). And now, antioxidant which found in foods, including fruits and vegetables now are really popular for alternative medicine of

antioxidant agent. One of plant that has high antioxidant is *Nigella sativa. Nigella sativa* is commonly known as black seed or black cumin. Among the whole medicinal plants, *Nigella sativa* is known as a miracle herb with historical and religious background since many kinds of research reveal its potential from a lot of aspects (Ahmad *et al.*, 2013).

Based on the studies, this research was done by intraperitoneal injection of nicotine with *Nigella sativa* extract peroral as a hepato-protector in the liver tissue of male mice. In this research did intraperitoneal injection because it conditioned as heavy smokers also studies using passive delivery of nicotine absorption through subcutaneous or intraperitoneal injection is much slower than through inhalation, and the speed of administration has been shown to critically intensify effects of drugs of abuse (Cohen and George, 2013).

1.2. Formulation of the Problem

Is *Nigella sativa (N. sativa)* extract able to protect liver tissue of mice induced with nicotine?

1.3. Theoretical Basis

One of the most popular antioxidants is thymoquinone. *Nigella sativa* is known contain a lot of thymoquinone and other antioxidants. Thymoquinone mechanism is to protect the liver from injury via inhibition of iron-dependent lipid peroxidation, elevation of thiol content and glutathione level, radical agent, increasing activity of quinone reductase, catalase, superoxide dismutase, and glutathione transferase, inhibition of NF-κB activity and inhibition of cyclooxygenase and lipoxygenase (Behesti *et al.,* 2018). Thymoquinone also

increased in the ratio of helper to suppressor T cells, increase activity of a natural killer cell, increase production of IL-10, IL-3 and stimulate macrophages effect (Mollazadeh and Hosseinzadeh, 2014).

From those studies, can conclude that *Nigella sativa* administration protects hepatic tissue from some oxidative agent. Hopefully *Nigella sativa* can work as hepato-protective agent from hazardous effect of nicotine.

Nicotine is alkaloid in *Nicotiana tabacum* leaves which the major active molecule in cigarette (Taghavi *et al.*, 2012). In the body, nicotine will produce free radicals, waste substances produced by cells from processes food and reacts to the environment. If the body cannot process and remove free radicals efficiently, ROS can result (Ware, 2018). ROS is a natural part of aerobic life, responsible for the manifestation of cellular functions ranging from signal transduction pathways, it can defense invading microorganisms and gene expression the promotion of growth or death (Lee *et al.*, 2012). For example, if nicotine metabolized in the body, nitrosation of nicotine *in vivo* could lead to the formation of N-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK). Which are known highly carcinogenic. Nicotine adducts form liver DNA which increases its mutagenic potential (Mishra, 2015). Which caused by oxidative stress from immune response (Ware, 2018). Oxidative stress is one of the main causes of liver injury that depletes the antioxidant enzymes sources and decreases the ability of cells in functioning against injury. Beneficial effects of ROS disrupt when the balance between the amount of ROS and antioxidants is diminished. This imbalance state defines as oxidative stress (Muriel, 2009). Liver is a very important

metabolism organ in the body. It is very sensitive to oxidative stress and damages caused by free radicals. Before it tends to be a hazardous agent, it has to be prevented with antioxidant, that defense and minimize the adverse effects of them (Tsukamoto and Lu, 2001).

1.4. Research Purpose

Purpose of this research is:

To find out *Nigella sativa (N. sativa)* extract ability to protect liver tissue of mice induced with nicotine.

1.5. Benefits of Research

1.5.1. Theoretical Benefits

To find out if *Nigella sativa* extract can protect from liver damage which induced with nicotine.

1.5.2. Practical Benefits

Can be an alternative medicine to protect smokers from liver damage and hope this research can be a knowledge for the next research and smokers.

1.6. Hypothesis

Nigella sativa (N. sativa) is able to protect mice from liver damage induced with nicotine.