

CHAPTER 1 INTRODUCTION

1.1 Background

The main function of liver is to remove our body metabolic waste products and also for detoxification (Raoofi *et al.*, 2016). It is one of the largest internal organ in the body. The liver maintains homeostasis of the body with its important metabolic functions. (Aboubakr and Abdelazem, 2016). Liver tissues is considered one of the most at risk or sensitive tissue in the body against side effects and damage from medications (Najafian *et al.*, 2014). Hepatotoxicity happens when the function of the liver becomes irregular or damaged by outside factors like for example drugs (Aboubakr and Abdelazem, 2016). Tea acts as a protector to the liver from damaging effects caused by toxic substances (Khan *et al.*, 2015).

One of the most important functional beverage worldwide is tea. Tea is also the second most popular consumed beverage in among all beverages globally. For thousands of years, tea is brewed for its taste, specific aroma and positive physiological benefits (Weerawatanakorn *et al.*, 2015). China, especially South China, is the main part of the world where Oolong tea is mostly popular, produced and consumed (He *et al.*, 2009). All tea is produced from the leave of a plant called *Camellia sinensis* but with different processing results (Yuan *et al.*, 2011). Approximately the tea produced and consumed in the world is 78% black tea, 20% green tea and less than 2% of tea is Oolong tea (Mukhtar and Ahmed, 2000). Oolong tea is a type of partially fermented tea. There are around 4000 kinds of

chemicals founded in tea most with health properties (Yung *et al.*, 2008). There are many beneficial potential health and also physiological properties due to compounds which are amino acids, vitamins, carbohydrates, caffeine, purine alkaloids and also polyphenols (Koca and Bostancı 2014).

Gentamicin is one of the medications that are most frequently used as antibiotics with among which toxicity with aminoglycosides. Gentamicin is often used to cure infections like Gram-negative bacteria (Noorani *et al.*, 2011). Unfortunately, antibiotics like gentamicin has also side effects. Hepatotoxicity is one of the major side effects from using gentamicin (Aboubakr and Abdelazem, 2016). Gentamicin is one kind of aminoglycosides that causes hepatotoxicity (Aubrecht *et al.*, 1997). According to Martines *et al.*, 1988, aminoglycosides like gentamicin causes renal damage which also leads to liver injury. Gentamicin at levels which are insignificantly higher than therapeutic range is potentially toxic (Klemens *et al.*, 2003). With extended period of gentamicin exposure with concentrations of 2ml and above, hepatotoxicity usually occurs (Zimmerman, 1999). Today the use of gentamicin is limited because it has side effects to the body. According to some studies, hepatotoxicity properties of gentamicin is exerted by the creation of free radicals (Najafian *et al.*, 2014).

After the use of gentamicin, production of Reactive Oxygen Species (ROS) increases. ROS induces toxic impacts of gentamicin on the function and structure of the liver tissues (Wojciech *et al.*, 2005) (Jeffrey *et al.*, 1988). Production of hydrogen peroxide, hydroxyl radical and superoxide anion by mitochondria is elevate by the use of gentamicin (Yang *et al.*, 1995). Breakage of deoxyribonucleic

acid (DNA) strand, denaturation of protein and phospholipid membrane peroxidation is caused by free radicals. Peroxidation of unsaturated lipid by active metabolites effects the membrane fluidity enabling even larger molecules like enzymes to permeable through the membrane (Najafian *et al.*, 2014). Hydropic degeneration of hepatocytes, inflammatory cell infiltration, fatty changes, and portal vein congestion are the histopathological changes of liver when induced with gentamicin (Galaly *et al.*, 2014).

Oolong tea has antioxidant properties and one of the main properties are EGCG, thearubigins and also theaflavins. It is reported that Oolong tea leaf extract contains a high activity of lipooxygenase inhibitory and also a high amount of antioxidant properties (Xie *et al.*, 1993). Oolong tea has to second most amount of catechins which is around (23.2%) compared to green tea which is (26.7%) and black tea which is (4.3%) (Yen *et al.*, 1995). Oolong tea also contains various pharmacological activities like antioxidant activity that is able to reduce oxidative stress, anti-obesity, anti-cancer (Weerawatanakorn *et al.*, 2015). Antioxidants are able to prevent and treat many diseases (Mahmood *et al.*, 2010). The antioxidant in Oolong tea protects the liver by reducing the elevated serum alkaline phosphatase (ALP), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activities, overpowering the increase in hepatic malondialdehyde (MDA), and improving glutathione peroxidase (GPX) and superoxide dismutase SOD activities (Cui *et al.*, 2014).

Based on the background above, it is needed to carry out the research to see if Oolong tea leaf extract has the protective effect to hepatotoxicity in gentamicin-induced white rats by evaluation of liver histopathology changes.

1.2 Problem Statement

Based on the background above, the problem statement is that the protective effect of Oolong tea leaf extract on gentamicin-induced hepatotoxicity in white rats.

1.3 Research Purpose

The purpose of this research is to obtain the protective effect of Oolong tea leaf extract on gentamicin-induced hepatotoxicity in white rats.

1.4 Benefits of Research

1.4.1 Theoretical Benefits

The benefit of this research is to give the explanation about the protective effect of Oolong tea leaf extract on gentamicin-induced hepatotoxicity in white rats.

1.4.2 Practical Benefits

The result of this research is expected to give knowledge and information about the protective effect of Oolong tea leaf extract on gentamicin-induced hepatotoxicity in white rats.

1.4.3 Theoretical Base

Gentamicin is a type of aminoglycoside antibiotics that have been used in antibacterial therapy for a long time and is derived from *Micromonospora purpurea*. It is used to kill life threatening Gram negative bacterial infections (Kaloyanides *et al.*, 1991). Gentamicin produces free radical generation which causes pathological changes to the body leading to tissue injury like hepatotoxicity (Aboubakr and Abdelazem, 2016). Reactive oxygen species are free radicals in the form of oxygen

and their derivatives are very reactive. ROS has the procedure of obtaining electrons from other substances that make free radicals reactive. ROS's reactive nature can attack and modify many molecules in cells such as proteins, lipids and DNA that cause cellular stress (Yao *et al.*, 2007). It is proven gentamicin will cause hepatotoxicity (Lee, 2003). Hepatotoxicity causes lesions like hydropic degeneration, necrosis, portal inflammation and fibrosis (David *et al.*, 2010).

Dietary antioxidants are essential to strengthen the innate oxidant defense system in our body against ROS (Espin *et al.*, 2000). It is proven that flavonoids functions as antioxidants and has the ability to reduced incidence of many types of disease. Oolong tea is very rich in flavonoids and other polyphenols. Oolong tea extract has a very high amount of lipoxygenase and antioxidative properties (Qin *et al.*, 2002). Oolong tea has an antioxidant value that ranges between 233-532mol/g (Benzie *et al.*, 1999). Many clinical research have proven that Oolong tea has therapeutic and preventive effect on oxidative stress related diseases for example liver disease (Li *et al.*, 2013) (Li *et al.*, 2014). Oolong tea has inhibitory effects on erythrocyte hemolysis and DNA damage which shows there is radical scavenging activity in Oolong tea (Qin *et al.*, 2002). It is also proven that Oolong tea has the ability to reduce oxidative stress especially oxidative DNA damage (Higdon *et al.*, 2003).

Antioxidants have the ability to overcome oxidative stress (Werdhasari, 2014). Antioxidants protects macromolecules and membrane lipids against ROS damage by removing free radicals from the cellular environment. Antioxidants neutralizes and reduces the capacity damage of a rampaging free radical by donating

an electron to it. Antioxidants acts as a scavenging property by inhibiting and delaying cellular damage. (Halliwell, 1995). Before vital molecules are damaged, low-molecular-weight antioxidants can safely interact with free radicals and terminate the chain reaction (Pham-Huy *et al.*, 2008).

1.5 Hypothesis

According to problem statement and purpose of this research, hypothesis of this research is that Oolong tea leaf extract has protective effect on gentamicin-induced hepatotoxicity in white rats.