CHAPTER 1
INTRODUCTION

Gastritis is a disease that involves the inflammation of gastric mucosa, which affects approximately 10% of the world's population. A person with gastritis may experience a wide range of symptoms, including: heartburn, belching, lack of appetite, nausea, vomiting, stomach pain, and bloating (Ferri, 2013). Generally, it is divided into acute and chronic gastritis. Acute gastritis can be characterized based on the presence of inflammation in the mucosal region, hemorrhage and sloughing of superficial mucosa. This condition is mostly associated with oral administration of irritants, such as nonsteroidal anti-inflammatory drugs (NSAIDs), alcohol and bacterial infections (i.e. *Helicobacter pylori*) (Pooler, 2009). On the other hand, chronic gastritis is mainly caused by *H. pylori* infection and autoimmune disorder (Goodman & Fuller, 2011).

Chemical gastritis (also known as reactive gastropathy or acute erosive gastritis) is another type of gastritis, which occurred due to the prolonged usage of NSAIDs, bile reflux, or other forms of chemical injury (Maguilnik *et al.*, 2012). The prevalence of chemical gastritis is known to have increased with age, from about 2% in the first decade of life up to 23.6% and 17.9% in women older than 90 years and in men around 80-89 years, subsequently (Maguilnik *et al.*, 2012). There are several risk factors for the patient to develop reactive gastropathy, likewise severe gastroduodenal ulcerations, a history of ulcer complication, high dose of NSAIDs consumption, concomitant administration of aspirin with other NSAIDs, age older than 65, oral administration of anticoagulant and corticosteroid drugs, and *H. pylori* infection. It shares similar symptoms with other types of gastritis, particularly vomiting and epigastric pain (Pashankar *et al.*, 2002).

The histological characteristics of NSAIDs lesions in reactive gastrophy patients are epithelial hyperplasia, reactive (enlarged) nuclei, fibromuscular hyperplasia, edema, and mucin depletion. Endoscopy tests and histological staining also showed longitudinal stripes of edematous erythematous mucosa and dilated capillaries containing fibrin thrombi in the antral mucosa parts, subsequently (Kumar *et al.*, 2009). In short-term usage, the adverse effects of NSAIDs are asymptomatic. However, long-term usage of NSAIDs ingestion can induce upper GI bleeding and abdominal pain in 28% of the patients taking the NSAIDs (Walker, 2004).

In 2010, roughly 43 million (19.0%) of adults in the United States took aspirin (acetylsalicylic acid) for at least three times per week for more than 3 months. On the other hand, approximately 12.8% of the adults also consumed other NSAIDs besides aspirin (Zhou *et al.*, 2013). Similar with other NSAIDs, aspirin (acetylsalicylic acid) is commonly purchased in a dose of 500-1000 mg/day and utilized as over the counter medications for colds, fever and pain. However, prolonged use of aspirin is commonly associated with the risk of gastritis (i.e. gastric ulceration and gastric bleeding) and other GI complications (Lanas *et al.*, 2011). Although the other side effects (e.g. dyspepsia, abdominal pain and nausea) of aspirin may not be life-threatening, it might cause discomfort to the patient and discourage the patients to take appropriate medications due to lack of patient compliance. In short term-usage, the risk of these minor side effects is nearly 50-100%. On the other hand, chronic exposure to aspirin possibly increases the risk of perforations, bleeding and ulcers on the gastric (Baron *et al.*, 2013). That being said, the relative risk of aspirin GI toxicity (i.e. gastric bleeding) can be as high as 4 especially in higher risk populations (Drini, 2016).

In the case of aspirin-induced gastritis, it is best to replace or reduce the dosage of aspirin if possible. Moreover, co-administration of antacid or sucralfate is able to alleviate the symptoms and decrease the intensity of dyspepsia, whereas proton pump inhibitor (PPI) is mostly used for long-term therapy. Ingestion of misoprostol is also effective for the prevention of aspirin-induced gastric ulceration (Becker *et al.*, 2004).

Unfortunately, studies have shown that H_2 antagonists, PGs (Prostaglandins) analogues, PPI, and sucralfate might not work well for some patients due to poor effectiveness and patient compliance (Becker *et al.*, 2004). As a matter of fact, the patients are most likely going to suffer from the drug's side effects instead of retrieving the drug's therapeutic effects. For instance, PGs analogues and sucralfate are unable to reduce the severity of dyspepsia and prevent NSAIDs-associated ulceration, respectively (Silverstein *et al.*, 1995; Hudson *et al.*, 1997). Co-therapy with PGs analogues (e.g. misoprostol) is also limited due to its high dosage regimen (four times a day) and side effects (e.g. diarrhoea, abdominal pain, rigor, vomiting, and fever) (Becker *et al.*, 2004).

On the other hand, consumption of H_2 antagonists cannot stop the risk of gastric ulcer progression (Rostom *et al.*, 2000), whereas administration of PPI might induce acid rebound associated with dyspepsia if the therapy discontinued (Burchum & Rosenthal, 2014). In addition, drug interactions can also become a problem in long-term therapy for

gastritis patients because a combination of drugs may be required (Park *et al.*, 2019). Furthermore, the complications of NSAIDs-induced gastritis (e.g. aspirin-induced gastritis) may last for months and possibly re-occur if the patient ingest irritants or corrosive agents (Hughes, 2001). Thus, there is certainly a need for alternative treatment that has potentially acted as an effective gastroprotective agent to cure NSAIDs-induced gastritis.

For centuries, nature provides mankind with various natural products such as plant extracts and numerous phytochemical compounds. Natural products give opportunities for the drug discovery process due to their chemical diversities (Cosa *et al.*, 2006). According to WHO (World Health Organization), approximately 20,000 medicinal plants exist in 91 countries. WHO also stated nearly 80% of the total world population still use traditional medicine for their health needs (Duraipandiyan *et al.*, 2006). In Asia, herbal medicines have been widely used and utilized for years to treat chronic and infectious diseases (Sasidharan *et al.*, 2010). Various natural products have the ability to suppress inflammatory responses by interfering the signaling cascade or enzymatic function (Sen & Samantha, 2014). In addition, numerous medicinal plant extracts have been applied on humans to cure wounds, accelerate wound healing process and stop hemorrhage progression in the ancient times by native dwellers (Madhu *et al.*, 2017).

Nowadays, herbal medicine is also considered as an alternative therapy for digestive disorder and peptic ulcer disease management. Besides their gastroprotective and anti-ulcerogenic properties, there are many plant extracts showed effectiveness with lower side effects and lower cost (Sharifi-Rad *et al.*, 2018). Due to the progression of adverse effects and ineffectiveness of current therapy, natural products (i.e. plant extracts) can be possibly utilized as an alternative treatment for aspirin-induced gastritis. Until now, a systematic appraisal and comprehensive review regarding the role of plant extracts pharmacological activities against aspirin-induced gastritis is not yet studied. Therefore, the purpose of this systematic review aims to systematically evaluate the efficacy and pharmacological activities of plant extracts against aspirin-induced gastritis as an alternative treatment.