CHAPTER I

INTRODUCTION

Diabetes mellitus (DM) comprises a group of common metabolic disorders that share the phenotype of hyperglycemia which can affect the metabolism of carbohydrates, lipids and proteins. Prolonged periods of hyperglycemia lead to glucose deposition within living tissues, causing accumulation of glucose within organ cells which result in complications of DM, such as coronary heart disease, nephropathy, retinopathy, and neuropathy [1-3]. In 2008, the International Diabetes Federation reported that the worldwide prevalence of DM has risen dramatically. It is estimated that by 2025 the prevalence of DM worldwide will rise from 246 million people to 380 million people. The etiology and pathophysiology of complications in DM has been a topic which has gained increased interest in recent years, especially the relationship between free radicals produced by the metabolism of proteins, DNA, and lipids in living organisms and the increased oxidative reaction which results in molecular and tissue damage in the body. The cellular toxicity caused by overproduction of free radicals is called oxidative stress. Therefore, free radical production and anti-oxidant mechanism is a popular theory used to explain the etiology and pathophysiology of the biological effects, especially in

cell damage, cellular degeneration and complications in DM. Both *in-vitro* and *in-vivo* studies have reported that hyperglycemia causes an increase of free radicals in cells, which leads to acute toxicity and molecular destruction affecting cellular mediators. These conditions lead to insulin resistance, beta cell dysfunction, and impaired insulin secretion, resulting in complications of DM. There has been evidence that anti-oxidants, which are chemicals that can decrease or inhibit oxidation, which can be found naturally or synthetically, can decrease or inhibit oxidation, implying that they could be used for reducing oxidative stress in diabetes [4-12].

The antioxidative ability and free radical scavenging ability of plant extracts have been studied by many investigators [13-20]. In 1995, the WHO stated that of the 20,000 types of plants and herbs used, only 250 had been analyzed for their components and biochemical characteristics and, furthermore at least 25% of the active compounds found in drugs produced today are extracted from plants. Even though plants and herbs have been used to treat disease and improve health for many years. However, their effectiveness in diabetes and its complications has not been completely developed. Nowadays, medicinal plants are attractive and challenging for complementary and alternative medicine. In China, 82 medicinal plants are used for reducing blood sugar in diabetes [21], whereas 130 kinds of plants are used in Thailand [22]. Bioactive ingredients rich in antioxidant properties in plants can improve health status. Recent studies have revealed the relation of ROS production and

oxidative stress to insulin resistance. Inhibitory effects of antioxidants on ROS overproduction have been also studied. Several studies showed the protective effect of antioxidants on diabetic oxidative stress. Traditional medicinal and indigenous plants are gaining popularity in obstinate incurable diseases such as diabetes mellitus, carcinoma and immune system disease. In alternative medicine, the treatment of these diseases with effective plants is alluring. Plants have radical scavenging properties that can decrease diabetic oxidative stress [23-27].

Reports on plant and vegetable research in Thailand reveal that high levels of antioxidants, particularly, polyphenolic compounds have antioxidative capacity and scavenge free radicals [28-29]. Antioxidative ability and polyphenol properties protect against protein damage induced by iron and glucose [13]. The polyphenolic compounds like phenolic acid, flavonoids and tannins have been found in plant infusions examined [30-33]. Village elders have passed down knowledge of the thousands of native Thai plants for many years from one generation to the next, but the basic scientific data about their effectiveness and mechanism of action are still lacking.

Biologically fermented plant products appear as a clear brown liquid with a sour taste due to the fermentation of plants, herbs, vegetables or fruits with sugar in a closed environment with lactic acid producing bacteria or probiotic bacteria. Current studies indicate that they are rich in anti-oxidants with anti-oxidative activity similar to butylated hydroxyanisole and green tea

[24]. Furthermore, such studies indicate that the anti-oxidative activity increased from the fermentation, which dissolves the ingredients and bacteria to release useful chemicals and phytochemicals in the fermentative process. By using the biologically fermented plant products, anti-oxidative activity can be utilized and be offered as an alternative in improving health as well as an alternative therapy for patients with such diseases as HIV and cancer patients with anti-inflammatory and anti-oxidative activity [34]. In Thailand and other countries, locally made biologically fermented plants are consumed to improve health. In 2004, a report presented in a meeting on standards and safety of biologically fermented plant products for consumption hosted by the National Science and Technology Development Agency (NSTDA) in Thailand stated that from random interviews of 235 biologically fermented plant product consumers nationwide, 10.2 percent drank the product to treat DM, although very little scientific evidence on the impact of health *in vitro* and *vivo* on diabetic patients exists.

Thai Indigenous plants and biologically fermented plant product have antioxidants which provide health benefits to consumers. Variety testing for antioxidant and oxidative stress would provide valuable information on the relative contribution of each overall activity. The hypothesis of this study is that plants and their products contain effective anti-oxidative phytochemicals which could reduce oxidative stress in diabetes. The strategy of this research aims to assess the effect of selected Thai indigenous plants carefully and

systematically. Firstly, Thirty Thai indigenous plants that are commonly used for the treatment of diabetic patients were reviewed and selected. Secondly, screening of antioxidant and antiradical activity in 30 indigenous plants was done, and active ingredients from plants with strong antioxidant activity were identified. Then, biologically fermented indigenous plant products were produced by the research and development of health products unit, Department of Pharmaceutical Science, Faculty of Pharmacy, Chiang Mai University. The antioxidative fermented effects of indigenous plants on diabetic oxidative stress were dose-dependently studied in streptozotocin-induced diabetic rats. It would be interesting to see whether the plant products could decrease oxidative stress or not. Finally, the protective effects of these screened indigenous plants on diabetic oxidative stress were evaluated and analyzed statistically.

The objectives of this study were as follows:

1. To study the antioxidant activity of 30 selected Thai indigenous plants *in vitro* measuring their oxidative stress inhibition.
2. To study the anti-oxidative effects of biologically fermented lactic acid bacterial products from Thai indigenous plants against diabetic oxidative stress in streptozotocin-induced rats.