CHAPTER I
INTRODUCTION

1. Background and Rationale of the study

Diabetes mellitus, a complex metabolic disorder resulting from lack of insulin production or insulin resistance, is a leading cause of morbidity and mortality in the developed world. It has been recognized as a global problem which induces a devastative social and economic impact. At present, around 250 million people worldwide are living with Diabetes and this number is expected to increase to over 380 and 439 million within 2025 and 2030, respectively (Mohan *et al.*, 2004; Shaw *et al.*, 2010). Substantial evidence has shown that diabetic patients are more likely to develop long term complications which reduce the quality of life of patients, incur heavy burdens to the health care system, and increase diabetic mortality (Solli *et al.*, 2010).

It has been reported that diabetic peripheral neuropathy is one of the most common complications of diabetes, occurring in 28–55% of diabetic patients (Boulton *et al.*, 2004). Diabetic neuropathy is now the most common neuropathy in industrialized countries and may be the most common in the world. It is characterized by a progressive loss of nerve fiber function in diabetic patient and can manifest with a wide variety of sensory, motor, and autonomic symptoms. However, the commonly forms of diabetic neuropathy are distal polyneuropathy and mononeuropathy (Dyck *et al.*, 1991). Diabetic neuropathy can severely disturb quality of life of the suffering cases but the therapeutic efficacy remains a challenge for this decade.

In addition to diabetic neuropathy, cataract and retinopathy are also regarded as the important diabetic complications which show a hyperglycemia-related sight-threatening disorder (Engerman and Kern, 1986; Pollreisz and Schmidt-Erfurth, 2010). The epidemiological study has shown that the prevalence of both cataract and retinopathy in diabetic patients are increased (Ding and Wong, 2012; Obrosova *et al.*, 2010) in accompany with the increased diabetic patients worldwide. The effective treatment of diabetic cataract and diabetic retinopathy requires the skillful physician. Therefore, these conditions still induce the important heath problems in the developing countries especially in a rural area so the prevention strategy is very much important.

It is accepted that oxidative stress results from an imbalance between the generation of oxygen derived radicals and the organism's antioxidant potential (Abdollahi *et al.*, 2004). Various studies have shown that diabetes mellitus is associated with an increased formation of free radicals and a decrease in antioxidant potential. Due to these events, the balance between the free radicals formation and the free radicals protection is disturbed. This leads to oxidative damage of cell components such as proteins, lipids, and nucleic acids. It has been reported that hyperglycemia induced by diabetes mellitus enhances oxidative stress through multiple pathways such as an elevation of aldose reductase and sorbitol dehydrogenase activities in polyol pathway which in turn enhances the excess reactive oxygen species (Yagihashi *et al.*, 2001). Hyperglycemia also increases the advanced glycation end product (Brownlee *et al.*, 1998) and the change of hypoxanthine to uric acid via xanthine oxidase (Desco MC. *et al.*, 2002). Moreover, it can enhance auto-oxidation of glucose and nitric oxide syntase activity which in turn gives rise to the enhanced nitric oxide and excess free radicals. The excess free radicals will attack various cell organelles leading to cell damage in various tissues including nerve and lens and resulting in diabetic neuropathy, cataract and retinopathy.

Numerous vegetables and fruits have been long-term implemented in the management and treatment of diabetic complications. They can be used either as a single or by polyherbal formulation. However, in traditional folklore especially in Oriental Medicine such as Ayurveda and Traditional Chinese Medicine (TCM), polyherbal formulations are more commonly used than single herb application based on the belief that polyherbalism can approach multi-targets and provide better benefit due to the synergistic effect of the ingredients (Nadeem *et al.*, 1996).

Based on the role of oxidative stress and aldose reductase on the pathophysiology of diabetic neuropathy, cataract and retinopathy mentioned earlier and the synergistic effect of polyherbal formulation, it has been hypothesized that novel heath recipe which targets at oxidative stress balance and the suppression of aldose reductase activity may provide beneficial effects to protect against both peripheral nerve damage and lens resulting in the attenuation of diabetic neuropathy, cataract and retinopathy. It has been found that numerous fruits and vegetables possessing medicinal properties such as purple waxy corn (*Zea mays* L. var. *ceratina*

Kulesh), ginger (*Zingiber officinale* Roscoe), mulberry (*Morus alba* L.), red onion (*Allium cepa* L.) and papaya (*Carica papaya* L.) are widely consumed in the Northeast Thailand and some plants also show the potential to suppress aldose reductase activity. Moreover, these plants are widely available in the Northeast regions of Thailand with cheap cost. Therefore, the development of novel health product from these plants has gained much attention in order to provide the alternative choice to strengthen the health status via dietary therapy which is cheap and easy to approach. In addition, the agricultural products can be increased their values in the market.

2. Objectives of the Study

2.1 General experimental objective

This experiment was designed to develop and to evaluate the effects of the novel health product from the selected plants in the Northeast of Thailand, on peripheral neuropathy, cataract and retinopathy induced by diabetes mellitus.

2.2 Specific objectives

2.2.1 To screen the biological activities of the selected plants which were widely consumed in Northeast of Thailand.

2.2.2 To develop a health recipe targeting at the protective effect against diabetic neuropathy, diabetic cataract and diabetic retinopathy from the combination extract from selected plants.

2.2.3 To determine an acute toxicity and the biological activities of the developed health recipe.

2.2.4 To determine the protective effect of the developed health recipe against diabetic neuropathy

2.2.5 To determine the effect of the developed health recipe against diabetic cataract and retinopathy

2.2.6 To determine the possible underlying mechanisms of the developed health recipe by focusing on the alteration of aldose reductase, oxidative stress damage markers including the level of malondialdehyde (MDA) product and the alteration of scavenging enzymes activities including superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) in lesion nerve and lens.

3. Hypothesis

3.1 If the selected plants widely consumed in Northeast Thailand have the potential to serve as natural resource for the development of the novel health recipe against diabetic complications such as diabetic neuropathy, diabetic cataract and diabetic retinopathy, they should show the optimal benefits on the alteration of biological activities associated with the pathophysiology of the as diabetic neuropathy, diabetic cataract and diabetic retinopathy such as antioxidant and aldose suppression activities.

3.2 If the developed health recipe has the potential be served as food supplement against diabetic complications such as diabetic neuropathy, diabetic cataract and diabetic retinopathy, it should show the optimal benefits on the alteration of biological activities associated with the pathophysiology of the diabetic neuropathy, diabetic cataract and diabetic retinopathy such as antioxidant and aldose suppression activities.

3.3 If the developed heath recipe has the potential to be served as the food supplement and adjuvant therapy for diabetic patients, it should have the high lethal dose 50 (LD50)

3.4 If the developed heath recipe has the potential to be served as the food supplement and adjuvant therapy to improve diabetic neuropathy, it should show the beneficial effects in animal model of diabetic neuropathy.

3.5 If the developed heath recipe exerts the beneficial effect to improve diabetic neuropathy via the decreased oxidative stress or via the suppression of polyol pathway, it should show the improved oxidative stress status or the decreased aldose reductase activity in the lesion nerve.

3.6 If the has the potential to be served as the food supplement to protect against diabetic cataract and diabetic retinopathy, it should show the beneficial effects in the model of the mentioned conditions.

3.7 If the developed heath recipe exerts the beneficial effect to protect against diabetic cataract and diabetic retinopathy via the decreased oxidative stress or via the suppression of polyol pathway, it should show the improved oxidative stress status or the decreased aldose reductase activity in the lens of diabetic cataract and in the lesion nerve of diabetic retinopathy models.

4. Anticipated Outcome

4.1 The information about the potential health benefit of the selected plants.

4.2 The recipe of the prototype of health product to improve diabetic neuropathy, diabetic cataract and diabetic retinopathy.

4.3 To provide the alternative choice to decrease the burden from diabetic complications such as diabetic neuropathy, diabetic cataract and diabetic retinopathy via the dietary therapy.

4.4 To provide the potential strategy to produce additive value for the agricultural products.