CHAPTER I

INTRODUCTION

Rationale of the Study

Erectile dysfunction, the consistent or recurrent inability to achieve an erection adequate for sexual performance, is a common complication of diabetes mellitus [1]. There is a much higher incidence and prevalence of erectile dysfunction in men with diabetes than normal men. As many as 75% of diabetic men will be confronted with erectile dysfunction at sometime in their lives, and according to one estimate, more than 50% of diabetic men will develop erectile dysfunction with in 10 years of the onset of diabetes [2]. Erectile dysfunction can cause a profound negative impact on the quality of the patient life, resulting in loss of self confidence and depression. This disorder is a common problem affecting the well-being of men. It has been estimated that one third of adult males will develop sexual dysfunction at some point during their sexual potency period [3]. In Thailand, erectile dysfunction prevalence in men age between 40-70 years is 37.5% [4]. Similar erectile dysfunction rates are also found in North America [5], the Massachusetts Male Aging Study (MMAS) was a regional survey of 1,709 men aged 40–69 years. Of the 1,290 men who completed a paper questionnaire, 52% reported erectile dysfunction, with 10% having complete, 25% moderate and 17% minimal erectile dysfunction. The probability of complete erectile dysfunction at age 70 was threefold that at age 40, the probability of moderate erectile dysfunction was two-fold, while that of minimal erectile dysfunction remained constant across all age groups. The disorder is a common problem and the prevalence increases with age [6]. In a relatively small-scale study representative for South Australia [7], there was a significant correlation with age, 7% of the 40 to 49-year–old group, 36% of the 60 to 69-year-old group and 92% of the 80-year-old group and over reported erection difficulties. There is a much higher incidence and prevalence of erectile dysfunction in men with diabetes than normal men [2].

The causes of the disorder are organic, psychological, psychiatric, interpersonal and pharmacological factors. Erectile dysfunction is not life-threatening, however, it should not be regarded as a benign disorder as it can have a strong

negative effect on interpersonal relationships, well-being and quality of life. Although a number of treatments became available in the last two decades, problems with costs, efficacy, safety and ease to administer were experienced. The treatments of erectile dysfunction include vacuum constriction devices, intracavernosal injections of vasoactive agents and venous or arterial surgery as well as oral medication. Currently, sildenafil [8-10], tadalafil [11-13] and vardenafil [14] are the three oral agents available for the treatment of male patients with erectile dysfunction.

Sildenafil (Viagra®) is the drug approved by the FDA in 1997 for clinical used in male erectile dysfunction, launched in America in March 1998 and has become one of the most popular prescription drug [15]. It was discovered as the first orally active, potent and competitive inhibitor of type 5 cGMP-specific phosphodiesterase enzyme, the predominant isozyme in the human corpus cavernosum. It enhances cGMP activity and thereby nitric oxide function in smooth muscle relaxation causing penile erection [9, 16-19]. Moreover, sildenafil can preserves intracorporal smooth muscle content, abrogates the development of intracorporal fibrosis in human [20] and significantly increases the intracorporal endothelial cell and smooth muscle content when administered in combination with free radical scavengers [21]. Leungwattanakij et al demonstrate an increase in transforming growth factor (TGF)-β1, hypoxia inducible factor (HIF)-1α and collagen III synthesis in rat cavernosal musculature after cavernous neurotomy and suggested that cavernous fibrosis may be reduced by using various vasoactive agents or interventions that increase the oxygenation to the corporal tissue [22]. These new oral agents are effective in the treatment of erectile dysfunction, but adverse events such as facial flushing, headache, dizziness, blue vision, dyspepsia, myalgia, and back pain have also been reported [8-14]. In a recent report, US-FDA has warned about the deaths due to sildenafil and mentioned the possibility of dangerous drug interaction with other drugs as older patients may be taking drugs for treatment of other ailments as well [15]. These treatments ranged from herbal remedies used by native healers, mostly in the Eastern countries, to the more sophisticated designer drugs, which are based on a better understanding of the physiological mechanism of erection [23].

Butea superba (Roxb.), known as "Kwaao Khruea Daeng" in Thai, is a plant in the *Papilionaceae* family [24, 25]. It is almost found in the northern region of

Thailand. *B. superba* has been used as a natural product for physical and mental strength and for prevention of age-related health problems. In Thai traditional medicine, *B. superba* is a rejuvenating herb for men [26]. Compounds extracted from *B. superba* are effective in inhibiting cAMP phosphodiesterase *in vitro*, the mechanism of which has been shown to play an important role in penile erection [27] and cytotoxic [28]. Previous studied, it was shown that *B. superba* induces a penile erection by increasing ICP with the maximum effective dose at 1 mg/kg BW and relaxed the corpus cavernosal smooth muscle in rat models [29]. Thai clinical trial of *B. superba* powder treatment in the Thai male volunteers showed effective treatment of ED [30]. The plant crude extract exhibited antiproliferation effect to MCF-7 [31].

Although *B. superba* has been reported that it can induce a penile erection, its efficacy for treatment of erectile dysfunction in diabetes is still no explored. Therefore, the hypothesis of this experiment were *B. superba* alcoholic extract can prevent or reverse cavernosal dysfunction by increasing intracavernous pressure (ICP), relaxing intracorporal smooth muscle and preserving intracorporal smooth muscle and endothelial cell content and also attenuate the development of intracorporal fibrosis in streptozotocin-induced diabetic rats, which eventually results in improvement of erectile function.

Proposes of the Study

General experiment objective

This experiment is designed to evaluate the effect of the *B. superba* alcoholic extract on erectile dysfunction in STZ-induced diabetic rats.

Specific objectives

1. To study the effect of the *B. superba* alcoholic extract on intracavernous pressure (ICP) using an *in vivo* model of the STZ-induced diabetic rats.

2. To examine the effect of the *B. superba* alcoholic extract on relaxation of intracorporal smooth muscle in *in vitro* of the STZ-induced diabetic rats.

3. To investigate the effect of the *B. superba* alcoholic extract on the contents of smooth muscle, endothelial cells and connective tissue elements in the corpora cavernosa of the STZ-induced diabetic rats.

Scope of this study

1. All animals used in this experiment will be only male and weight approximately 200-250 g.

2. All stresses should be avoided to prevent the influence of stress.

3. All injections should be done at the same period to avoid influence of circadian rhythm.

4. In all experiments, control and experimental groups should be performed in parallel at the same period to avoid effect of seasonal changes.

Hypotheses

1. If *B. superba* alcoholic extract induces penile erection in animals, the diabetic animals which received *B. superba* alcoholic extract should prevent the development of erectile dysfunction secondary to diabetes mellitus.

2. If *B. superba* alcoholic extract induces penile erection in diabetic animals, the diabetic groups which received *B. superba* alcoholic extract should have higher intracavernous pressure (ICP), relaxation of intracorporal smooth muscle in *in vitro*, contents of smooth muscle cells and endothelial cells and have lower contents of connective tissue elements in the corpora cavernosa than diabetic control group.

Anticipated Outcomes

1. To provide the information about the effect of the *B. superba* alcoholic extract on intracavernous pressure (ICP) in diabetic rats.

2. To provide the information about the effect of the *B. superba* alcoholic extract on relaxation of intracorporal smooth muscle in diabetic rats.

3. To provide the information about the effect of the *B. superba* alcoholic extract on the contents of smooth muscle, endothelial cells and connective tissue elements in the corpora cavernosa in diabetic rats.

4. To provide the information for the potential use of *B. superba* extracts in human.

5. To provide the rationale for the potential use of *B. superba* extracts for treating the erectile dysfunction secondary to diabetes mellitus.