CHAPTER 1

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1.1 Historical background of diabetes mellitus

Diabetes mellitus (DM) has affected human beings as early as prehistoric times. It was first identified by Hesy Ra an Egyptian physician about 3,500 years ago (CDA, 1999). The term siphon was first used to describe the disease as "diabetes" which means excessive loss of body fluid through excess urination from diabetic patients. The ethiopathogenesis of the disease was discovered in the 20^{th} century by ancient Chinese, who observed the attraction of ants to the urine of people suffering from diabetes. In 1672, Thomas Willis added the term "mellitus" to distinguish diabetes from other causes of excessive urination. This disease was further divided into "diabetes gras" (fat) or "diabetes maigre" (thin) by Bouchardat and Lancereaux (1880). They are now recognized as obese and non obese forms of diabetes mellitus. Before the discovery of insulin there was an invariable death sentence due to lack of clinical diagnosis of the disease. In 1922, Banting and Best discovered the use of insulin extracted from the islet tissues of animals for the treatment of diabetes mellitus. This discovery confirmed that some diabetic individuals are not insulin dependent (Berson and Yalow, 1954). Presently, the term diabetes mellitus is now defined as chronic metabolic disorder caused by insulin deficiency or inability of the body to use insulin properly or both (Lanza et al., 1999). It is characterized with hyperglycaemia that plays a key role in the progression of the disease and its complications (Rang et al., 1991).

1.2 Rationale and justification for this study

The current prevalence of DM worldwide constitutes a global public health burden (Boyle et al., 2001). Despite the development of new drugs to prevent the incidence of diabetes, it was still predicted to hit 220 million by 2010 (Erasmus et al., 1999). The prevalence of DM has impeded many developing nations through increased morbidity and mortality (Rang et al., 1991). This is because, there is no satisfactory effective therapy such as insulin or oral hypoglycaemic drugs that could normalize blood glucose homeostasis (Sumana and Suryawanshi, 2001). Moreover, they are not devoid of significant adverse side effects such as hypoglycemia, weight gain, edema, abnormal liver function and diarrhea (ADA, 2006). In addition, they are very expensive and as a result beyond the reach of diabetic patients especially those living in the rural areas. Owing to this fact, diabetic individuals have resorted to the use of herbal medicines with antidiabetic potential and probable fewer side effects (Addy and Nyarko, 1988; Nyarko et al., 1999). Majority of these herbal antidiabetic drugs have long been published but a large number of them remain unexplored. Further studies on pharmacognostic, mechanisms of actions and toxicological properties of these plants are necessitated to justify their folkloric usage (Hansotia and Drucker, 2005).

1.3 The choice of *Strychnos henningsii* for this study

The use of *S. henningsii* (Loganiaceae) by traditional healers for the management of diabetes was discovered in Nkonkobe Municipality, Eastern Cape, South Africa during our ethnobotanical survey (Oyedemi et al., 2009). The plant was frequently mentioned by the traditional healers and herbalists for the treatment of DM. It is a small evergreen tree with leathery leaves. The bark is crown compact with dark green, glossy foliage and the fruit is

oblong which turns brown when ripe. The leaves of the plant have a characteristic aromatic-pungent odour with rough texture (Leeuwenberg, 1969). It is commonly used in south and east Africa traditional medicine for the treatment of rheumatism, gynaecological complaints, abdominal pain, snake bite, gastrointestinal pain, DM as well as malaria (Hutchings, 1989; Bisset, 1970). Despite the acclaimed folkloric use of *Strychnos henningsii* as an antidiabetic agent, there is dearth of scientific evidence to substantiate the claim. Therefore, this study aimed at providing information on the antidiabetic, probable mechanisms of action and toxicity effect of this plant with a view to validating its acclaimed use by the traditional medicine practitioners of Eastern Cape. At the beginning of this study, there was no information in scientific literature on the antidiabetic properties of *S. henningsii*.

Figure 1: *Strychnos henningsii* Gilg (SH). A: SH in its natural habitat in Pirie mission garden (King William's Town). B: Bark of SH.

1.4 The aims and objectives of this study

The primary aim of this study was to validate the folkloric uses of aqueous stem bark extract of *Strychnos henningsii* for the management of DM.

Specific objectives

1.4.1 Ethnobotanical survey of plants

Ethnobotanical study is a process used to search for locally important plant species with low side effects especially for drug development which entails ethnomedical and ethnobotanical field work. The search for anti-diabetic plants has been focused on plants because of leads provided by natural products with better treatment than currently used drugs. Previous studies have revealed antidiabetic plants used for the management of DM in the Eastern Cape Province of South Africa. However, the medicinal plants used traditionally for the management of DM in some areas of the Province had not been explored or documented. In traditional medicine, the number of plants used in the treatment of diseases associated with physiological disorder such as diabetes is limited. Therefore, there is need to document plants and their indigenous knowledge considering the rate at which vegetation is getting depleted in this part of the world.

1.4.2 *In vivo* and *in vitro* antioxidant activities of plant extract

Oxidative stress, the consequence of the imbalance between prooxidants and antioxidants in an organism, is considered to play a very important role in the pathogenesis of several degenerative diseases. These include diabetes, aging, cancer, cardiovascular diseases,

metabolic syndrome, and atherosclerosis. High levels of oxidative stress with excessive generation of free radicals and depleted levels of antioxidant defense system have been demonstrated in animal models and human diabetic subjects (Turk et al., 2002). Free radicals have been reported to induce β – cell dysfunction in type 1 DM by auto-immune reactions and inflammatory cytokines (Cnop et al., 2005). Similarly, these radicals have also been indicated in type 2 diabetes to activate β –apoptotic pathways, impair insulin synthesis and thus contribute to insulin resistance (Evans et al., 2003; Ravi et al., 2004). Recently, an array of medicinal plants has been investigated as new potential sources of antioxidant with lesser or no toxicity effect. The presence of phytochemicals with strong antioxidant activity in these plants may enhance their ability to protect cells against the oxidative damage caused by these radicals. Research into antioxidant properties and phytochemicals of herbs may provide information on their mechanisms of action to support their ethnotherapeutic usage. A vast majority of these plants are used in traditional medicine in South Africa but have not been currently evaluated for their antioxidant potential. One of such plants is *Strychnos henningsii*.

1.4.3 Toxicological effects of *S. henningsii* in rats.

Plants consist of biologically active compounds such as cyanogenic glycosides, glycoalkaloid, salts of oxalic acid and alkaloids. These compounds have been reported to be toxic in animals when ingested at certain concentrations (Joseph and Eloy, 1982). Several reports in both developed and developing countries have indicated adverse side effects allegedly arising from the use of medicinal plants. (Elvin -Lewis, 2001). These effects could be attributed to the presence of phytotoxic compounds in the plant extracts and lack of knowledge of actual dosage necessary for the treatment of diseases (Azaizeh et al., 2003). Assessment of haematological parameters could be used to determine the extent of

deleterious effect of plant extract on the blood constituents of animals. These adverse effects may manifest significant alterations in the levels of biomolecules such as enzymes and metabolic products, normal functioning and histomorphology of the organs. The alterations may be used to predict toxicity in humans when the data are translated from animal studies (Olson et al., 2000). Although, the folkloric usage of these plants was mentioned by the traditional healers, there was no scientific attempt to evaluate their toxicity effects. Therefore, an attempt was made in this present study for scientific investigation on the toxicological profiles of *S. henningsii* extract using different doses in rats.

1.4.4 Antidiabetic and clinical significance of *S. henningsii* extract

The intra-peritoneal induction of DM by streptozotocin has been reported by several authors to damage some vital tissues in diabetic animals model (Kirsch and Groot, 2001; Muhammad et al., 2007). Some of these damages manifested by increased level of alanine (ALT) and aspartate transferases (AST), urea, albumin and creatinine in the liver and kidney of experimental diabetic animals (Sokeng et al., 2005). The findings of Pushparaj et al. (2000) also confirmed coronary heart disease in diabetic animals owing to the elevated level of cholesterol and triacylglycerol. The decreased level of red blood cells and its related indices was also evidenced in diabetic subject that leads to hypochromic microcytic anaemia (Baskar et al., 2006). Therefore, the present study was undertaken to provide scientific credence on the antidiabetic and beneficial effect of *S. henningsii* extract on some clinical parameters in diabetic rats.

1.4.5 In vitro antidiabetic properties of *Strychnos henningsii* stem bark extract used in South African herbal medicine

The impairment of insulin in glucose utilization is known as the main disturbance of nutrient metabolism (Bailey and Day, 2004). This occurs mostly in target tissues such as skeletal muscle, adipose tissue and liver cells of type 2 diabetic patients (Baynes and Dominiczak, 2004; Guyton and Hall, 2005). Similarly, the ability of *S. henningsii* extracts to inhibit α - glucosidase and amylase were explored to establish its usefulness as herbal medicine. An inhibitor of these enzymes is useful to prevent diabetes and obesity by retarding carbohydrate digestion and absorption. It has been recognized that oxidative stress is another factor apart from hyperglycemia that enhances protein glycation that further resulted to diabetic complications (Miyata et al., 1999). To delay or prevent diabetic complications botanical consumption that can inhibit protein glycation as well as lipid accumulation during diabetes is highly needed (Edwin et al., 2008; Hu et al., 2003). The present study was an attempt to understand the mechanisms of action underlying the antidiabetic activities observed in animal model. The inhibitory effect of *S. henningsii* extract against protein glycation, lipid accumulation as well as glucose utilization in 3T3-L1 and Chang liver cell lines including cell viability were tested.

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