The efficiency of Cinnamon in preventing Diabetic complications in submandibular Salivary glands of albino rats

Thesis

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LIST OF ABBREVIATIONS

ACCORD	**:**	Action to Control Cardiovascular Risk in Diabetes
ADVANCE	**:**	Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation
AGEs	**:**	Advanced Glycation End-products
ALT	**:**	Alanine aminotransferase
AMC	**:**	Age-Matched Controls
AST	**:**	Aspartate aminotransferase
BV	**:**	Blood Vessel
C.T	**:**	Connective Tissue
CCL4	**:**	Carbon Tetrachloride
CE	**:**	Cinnamon Extract
CVD	**:**	Cardiovascular Disease
CWE	**:**	Cinnamon Water Extract
DIO	**:**	high-caloric Diet-Induced Obesity
DM	**:**	Diabetes mellitus
EGF	**:**	Epidermal Growth Factors
FDA	**:**	Food and Drug Administration
Fig.	**:**	Figure
GCTs	**:**	Granular convoluted tubules
GRAS	**:**	Generally Recognized As Safe
GSK-3	**:**	Glycogen Synthase Kinase-3
H&E	**:**	Hematoxyline and Eosin
HbA1c	**:**	Glycosylated Haemoglobin
Ict	**:**	Intercalated duct
IDDM	**:**	Insulin-Dependent Diabetes Mellitus
IL-1 β	**:**	Interleukin –Beta
IPGTT	**:**	Intraperitoneal glucose tolerance test

LDL-c	**:**	Low Density Lipoprotein Cholesterol
LM	**:**	Light microscope
MTT assay	**:**	dimethyl thiazol diphenyl tetrazolium bromide
NaB	**:**	Sodium Benzoate
NIDDM	**:**	Non-Insulin Dependent Diabetes Mellitus
no.	**:**	Number
NOD	**:**	Non Obese Diabetic
RBCs	**:**	Red blood cells
RER	**:**	Rough endoplasmic reticulum
ROS	**:**	Reactive Oxygen Species
SMG	**:**	Submandibular salivary gland
STZ	**:**	Streptozotocin
TEM	**:**	Transmission Electron Microscope
TNF- α	**:**	Tumor necrosis factor- alpha
TUNEL	**:**	Terminal deoxynucleotid transferase mediated UTP biotin nick end labeled assay.
WHO	**:**	World Health Organization

INTRODUCTION

Type 2 diabetes is the most common metabolic disease worldwide, with a prevalence estimated to rise from 171 million in 2000 to 366 million in 2030 **(Wild et al., 2004).**

Although the cause of type 2 diabetes appears to be multifactorial, it has been firmly established that diet can play a major role in the incidence and progression of the disease (**Vanschoonbeek et al., 2006).**

Beside damaging the kidneys, eyes, nerves, blood vessels, and heart, long standing hyperglycemia can also be associated with buccal alterations such as periodontal disease, and many other alterations like impaired function of the salivary glands.This impaired function may lead to a reduction of salivary flow and changes in saliva's composition, taste alterations, burning mouth, greater tendency to buccal infections, delayed healing process, decays, coated tongue and halitosis **(Negrato and Tarzia, 2010).**

Although many drugs improve glycemic control, they do not necessarily provide real-world benefits. In the recent ACCORD (Action to Control Cardiovascular Risk in Diabetes) **(Gerstein et al., 2008)** and ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) **(Patel et al., 2008)** trials, intensive glycemic control had minimal effect on clinical cardiovascular outcomes.

In addition to drug treatment, dietary interventions were shown to represent an effective tool to prevent and/or treat insulin

resistance and/or type 2 diabetes **(Jenkins et al., 2002; Willett et al., 2002).**

Cinnamon, bay leaf, cloves, nutmeg, witch hazel, oregano, black and green tea have been shown to have an insulin-like biological activity. Of these substances, cinnamon has been shown to have the highest bioactivity. Cinnamon has been used for thousands of years to treat diabetes and other conditions. It is claimed to be a natural insulin sensitizer **(Khan et al., 1990; Broadhurst et al., 2000).**

The present study will investigate the efficiency of Cinnamon water extract (CE) in preventing complications of diabetes on submandibular salivary gland (SMG) of albino rats.

REVIEW OF LITERATURE

Diabetes mellitus (DM) is a chronic metabolic disorder associated with abnormalities in carbohydrate, lipid and lipoprotein metabolism, which not only lead to hyperglycemia but also cause many complications, such as hyperlipidemia, hyperinsulinemia, hypertension and atherosclerosis **(Luoa et al., 2004).**

The American Diabetes Association has recently developed a classification system based upon the aetiology and management of the disease. The classification scheme included two major forms of DM: Type I (previously insulin-dependent Diabetes Mellitus or IDDM) and type II (previously non-insulin dependent Diabetes Mellitus or NIDDM). Type I disease includes type A: immune-mediated and a type B: idiopathic DM. Type I DM is due to cell-mediated auto-immune destruction of B-cells of islets of Langerhans of the pancreas leading to complete inability of the cells to secrete insulin. It usually develops before thirty years of age, it is managed using insulin. Type II includes the most common form of DM which combines insulin resistance with an insulin secretory defect. This type is characterized by B-cells dysfunction & inability to secrete adequate amounts of insulin, particularly after meals, and/or peripheral insulin resistance. It can be managed by the control of dietary carbohydrates, control of body weight, increased physical activity, and oral hypoglycaemic agents. In addition to these two types, there are other specific forms of the disease, such as DM secondary to auto-immune

endocrinopathies, infections (e.g. congenital rubella, cytomegalo virus, coxsackie virus), genetic disease or DM induced by drugs or pregnancy **(Atkinson et al., 2001; Bingley et al., 2001; Manfredi et al., 2004).**

DM affects approximately 4% of the population worldwide and is expected to increase by 5.4% in 2025 **(Kim et al., 2006).** Several studies have linked diabetes to obesity-induced insulin resistance**.** In this regard, an estimated 41 million people in the U.S. have prediabetes, a condition of elevated fasting blood sugar that is strongly associated with hyperlipidemias and cardiovascular disease **(Borgman and McErlean, 2006).**

General Complications of Diabetes:

DM was found to have a considerable effect on lipid metabolism in both experimental animals' tissues and in the diabetic patients. They showed an increased lipolysis, fatty acid oxidation, gluconeogenesis and ketogenesis. This was accompanied by depressed fatty acid synthesis, desaturation and esterification **(Morris et al., 1992).**

The vascular changes accompanying DM lead to diabetic neuropathies; a group of nerve disorders that can be classified as peripheral, autonomic, proximal, or focal, affecting different parts of the body in various ways. Peripheral neuropathy, the most common type of diabetic neuropathy, causes pain or loss of feeling in the toes, feet, legs, hands, and arms. Autonomic neuropathy causes changes in digestion, bowel and bladder function. It can also affect the nerves supplying the heart and

controlling blood pressure, as well as nerves in the lungs and eyes. Autonomic neuropathy can also cause hypoglycaemia unawareness, a condition in which people no longer experience the warning symptoms of low blood glucose levels. Proximal neuropathy causes pain in the thighs, hips, or buttocks and leads to weakness in the legs. Focal neuropathy results in the sudden weakness of one nerve or a group of nerves, affecting eyes, ears, facial muscles, causing muscle weakness or pain. Any nerve in the body can be affected **(Bell and Hockaday, 1996).**

Recently, it has been reported that peripheral diabetic neuropathy may be a risk factor for severe tempromandibular joint dysfunction **(Collin et al., 2000).**

Hyperglycaemia, which is present in case of un-controlled DM, results in the formation of advanced glycation end-products (AGEs) and glycosylated haemoglobin (HbA1c). These AGEs result in thickening of the basement membranes of blood vessels, and capillaries. HbA1c is less effective in oxygen transport than haemoglobin, and the oxygen tension in various body tissues is thus lowered in case of DM. It is well established statistically that approximately 50% of patients with DM develop vascular chronic complications following years of DM. Blood vessels of all sizes are affected, from the Aorta to the smallest capillary and venule. The blood vessels are damaged by the accumulation of atheromatous deposits in the intimal tissues of the blood vessels lumen as well as altered endothelial cell permeability, leading to impaired leukotactic response **(Vlassara et al., 2002; Manfredi et al., 2004; Catanzaro et al., 2006).**