Evaluation of the efficacy of an antidiabetic herbal product (Ziabit) formulated in Bangladesh

(This report presented in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy)

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APPROVAL

This Project, **Evaluation of the efficacy of an antidiabetic herbal product (Ziabit) formulated in Bangladesh** submitted by Farzana sultana to the Department of Pharmacy, Daffodil International University, has been accepted as satisfactory for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy and approved as to it style and contents.

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DECLARATION

I hereby declare that, this project report is done by me under the supervision of Dr. Mohammad Obayed Ullah, Assistant Professor, Department of Pharmacy, Daffodil International University, impartial fulfillment of the requirements for the degree of Bachelor of Pharmacy. I am declaring that this Project is my original work. I also declare that neither this project nor any part thereof has been submitted elsewhere for the award of Bachelor or any degree.

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Its very pleasure for me to getting fund of my project from Ban-05, International science Program (ISP) of Uppsal University, Sweden. I want to give them my heartiest thanks & humble respect for this support.

Dedication

Dedicated

To

My Beloved ***Parents***

Contents

Abstracts

The usage of medicinal plants is traditionally rooted in Bangladesh and still an essential part of public healthcare. Recently, a dramatically increasing prevalence brought diabetes mellitus and its therapy to the focus of public health interests in Bangladesh. In this study, we analysis the efficacy test of Herbal Ziabits on the streptozotocin induced type 2 diabetic rats by measuring blood glucose level and body weight at different time interval. This study aims to evaluate the efficacy of the Herbal Ziabit. Group-I (Sample) diabetic rats was received only sample Herbal Ziabit according to 1.25mg/kg body weight. Group-II diabetic rats: received Metformin 5mg/kg body weight; Group –III (Water Control): Given only water. The result of the study indicates Herbal Ziabit significantly reduced blood glucose level, but decreased the body weight of rats. The study clearly supports the traditional use of Herbal Ziabit for treatment of type-2 diabetes.

Chapter One

Introduction

1.1 Diabetes mellitus

Diabetes mellitus is a principal cause of morbidity and mortality in human populations (Stephan et al., 2001). It is a syndrome characterized by hyperglycemia, polydipsia and polyuria and causes complications to the eyes, kidneys, and nerves. It is also associated with an increased incidence of cardiovascular disease (Pickup and Williams, 1991). The clinical manifestations and development of diabetes often differ significantly between countries and also between racial groups within a country. For example, diabetes currently affects an estimated 15.1 million people in North America, 18.5 million in Europe, 51.4 million in Asia, and just under 1 million in Oceania (Kuhlmann, 1996). It is estimated that globally, the number of people will rise from 151 million in the year 2000 (Amos et al., 1997), to 221 million by the year 2010, and to 300 million by 2025 (King et al., 1998.Diabetes mellitus is becoming increasingly common in Singapore population. The prevalence of type 2 diabetes doubled between 1984 and 1992 in Singaporean Chinese (Chen et al., 1999). This increase can be attributed to many factors, including a stressful lifestyle as well as improper dietary habits. This is of economic concern as the disease requires life-long treatment and is also associated with high morbidity from the resulting complications

1.2. Diagnosis of Diabetes:

The ethnobotanical information reports plants that may possess anti-diabetic potential [44] The clinical diagnosis of diabetes is often suggested by the presence of hyperglycemic symptoms and glycosuria, sometimes with drowsiness or coma. The World Health Organization (WHO) criteria define diabetes by fasting plasma glucose (FPG) level of 140mg/dL (7 mmol/L) or greater, or post-prandial 2-h plasma glucose (PG) level of 200mg/dL (11.1 mmol/L) or greater during an oral glucose tolerance test (WHO, 1985).

The National Diabetes Data Group of the National Institutes of Health recommends the following criteria for diagnosing diabetes:

a. Fasting (overnight) venous plasma glucose concentration greater than or equal to 140 mg/dL on at least two separate occasions.

b. Venous plasma glucose concentration greater than or equal to 200 mg/dL at 2-h post-ingestion of 75 g of glucose and at least one other sample during the 2-h test.

1.3. Classification of Diabetic Mellitus

The most widely accepted classification of diabetes is the etiological classification of disorders of glycemia [11]

A. Type 1 Diabetes Mellitus.

B. Type 2 Diabetes Mellitus.

C. Gestational diabetes.

D. Secondary Diabetes Mellitus.

E. Other Specific Types of Diabetes.

1.4.1 Type 1 Diabetes Mellitus (β-cell destruction, usually leading to absolutinsulin deficiency)

This form of diabetes, which accounts for only 5–10% of those with diabetes, previously encompassed by the terms insulin-dependent diabetes, type I diabetes, or juvenile-onset diabetes, results from a cellular-mediated autoimmune destruction of the β-cells of the pancreas. Markers of the immune destruction of the β-cell include islet cell autoantibodies, autoantibodies to insulin, autoantibodies to glutamic acid decarboxylase (GAD_{65}), and autoantibodies to the tyrosine phosphates IA-2 and IA-2β

1.4.2 Type 2 Diabetes Mellitus

This form of diabetes, which accounts for ~90–95% of those with diabetes, previously referred to as non-insulin-dependent diabetes, type II diabetes, or adult-onset diabetes, encompasses individuals who have insulin resistance and usually have relative (rather than absolute) insulin deficiency. At least initially, and often throughout their lifetime, these individuals do not need insulin treatment to survive. There are probably many different causes of this form of diabetes. Although the specific etiologies are not known, autoimmune destruction of β-cells does not occur, and patients do not have any of the other causes of diabetes listed above or below. Most patients with this form of diabetes are obese, and obesity itself causes some degree of insulin resistance. Patients who are not z bees by traditional weight criteria may have an increased percentage of body fat distributed predominantly in the abdominal region..

1.4.2.1 Lifestyle in type 2 diabetic

Most patients with this form of diabetes are obese, and obesity itself causes some degree of insulin resistance. Patients who are not zbese ytraditional weight criteria may have an increased percentage of body fat distributed predominantly in the abdominal region A number of lifestyle factors are known to be important to the development of T2DM. People who had high levels of physical activity, a healthy diet, did not smoke, and consumed alcohol in moderation had an 82% lower rate of diabetes [12]. Obesity has been found to contribute to approximately 55% T2DM and decreasing consumption of saturated fats and trans fatty acids while replacing them with unsaturated fats may decrease the risk [13].

1.4.2.2 Medical Conditions

There are many medical conditions which can potentially give rise to or exacerbate T2DM. These include obesity, hypertension, elevated cholesterol (combined hyperlipidemia), and with the condition often termed metabolic syndrome (it is also known as Syndrome X, Reavan's syndrome). Other causes include acromegaly, Cushing's syndrome, thyrotoxicosis, pheochromocytoma, chronic pancreatitis, cancer and drugs, additional factor founds to increase the risk of T2DM includes aging individuals do not need insulin treatment to survive. There are probably many different causes of this form of diabetes. Although the specific etiologies are not known, autoimmune destruction of β-cells does not occur, and patients do not have any of the other causes of diabetes listed above or below.

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1.4.2.3 Genetics

There is a strong inheritable genetic connection in T2DM: having relatives (especially first degree) with type 2 increases risks of developing T2DM very substantially. In addition, there is also a mutation to the Islet Amyloid Polypeptide gene at results in an earlier onset, more severe form of diabetes [15] Genes significantly associated with developing T2 DM: include TCF7L2, PPARG, FTO, NOTCH2, WFS1, CDKAL1, IGF2BP2, SLC30A8, JAZF1, and HHEX [16].

1.4.2.4 Medications

Drugs used for any of several conditions, can interfere with the insulin regulation system, possibly producing drug induced hyperglycemia. Some examples follow, giving the biochemical mechanism in each case:

a) Atypical Antipsychotics - Alter receptor binding characteristics, leading to increased insulin resistance.

b) Beta-blockers –Inhibit insulin secretion

c) Calcium Channel Blockers - Inhibits secretion of insulin by interfering with cytosolic calcium release.

d) Corticosteroids - Cause peripheral insulin resistance and gluconeogensis.

e) Fluoroquinolones- Inhibits insulin secretion by blocking ATP sensitive potassium channels.

f) Niacin - Causes increased insulin resistance due to increased free fatty acid mobilization.

g) Phenothiazines - Inhibit insulin secretion.

h) Protease Inhibitors -Inhibit the conversion of pro insulin to insulin.

i) Somatropin - May decrease sensitivity to insulin, especially in those susceptible.

j) Thiazide Diuretics - Inhibit insulin secretion due to hypokalernia. They also cause increased insulin resistance due to increased free fatty acid mobilization [18].

1.4.3 Gestational Diabetes

Gestational diabetes is a condition in which women without previously diagnosed diabetes exhibit high blood glucose levels during pregnancy. The precise mechanisms underlying gestational diabetes remain unknown. Pregnancy hormones and other factors are thought interface with the action of insulin as it binds to the insulin receptor. The interference probably occurs at the level of the cell signaling pathway behind the insulin receptor. Since insulin promotes the entry of glucose into most cells, insulin resistance prevents glucose from entering the cells properly. As a result, glucose remains in th bloodstream, where glucose levels rise. More insulin is needed to overcome this resistance [19]. Placental hormones and to a lesser extent increased fat deposits during pregnancy, seem to mediate insulin resistance during pregnancy. Early in pregnancy, maternal estrogen and progesterone increase and promote pancreatic cell hyperplasia and increase insulin release [20]. Increase in peripheral glucose utilization and glycogen storage with a concomitant reduction in hepatic glucose production, result in lower maternal fasting glucose levels [21].

1.4.4 Other specific types of diabetes

1.4.4.1 Genetic defects of the β-cell

Several forms of diabetes are associated with monogenetic defects in β-cell function. These forms of diabetes are frequently characterized by onset of hyperglycemia at an early age (generally before age 25 years). They are referred to as maturity-onset diabetes of the young and are characterized by impaired insulin secretion with minimal or no defects in insulin action. They are inherited in an autosomal dominant pattern.

1.4.4.2 Genetic defects in insulin action]

There are unusual causes of diabetes that result from genetically determined abnormalities of insulin action. The metabolic abnormalities associated with mutations of the insulin receptor may range from hyperinsulinemia and modest hyperglycemia to severe diabetes.

1.4.4.3 Diseases of the exocrine pancreas

Any process that diffusely injures the pancreas can cause diabetes. Acquired processes include pancreatitis, trauma, infection, pancreatectomy, and pancreatic carcinoma. With the exception of that caused by cancer, damage to the pancreas must be extensive for diabetes to occur; adrenocarcinomas that involve only a small portion of the pancreas have been associated with diabetes. This implies a mechanism other than simple reduction in β-cell mass. Fibrocalculouspancreatopathy may be accompanied by abdominal pain radiating to the back and pancreatic calcifications identified on X-ray examination. Pancreatic fibrosis and calcium stones in the exocrine ducts have been found at autopsy.

1.4.4.4 Endocrinopathics

Several hormones (e.g., growth hormone, cortisol, glucagon, and epinephrine) antagonize insulin action. Excess amounts of these hormones (e.g., acromegaly, Cushing's syndrome, glucagonoma, pheochromocytoma, respectively) can cause diabetes. This generally occurs in individuals with preexisting defects in insulin secretion, and hyperglycemia typically resolves when the hormone excess is resolved.

1.4.4.5 Drug- or chemical-induced diabetes

Many drugs can impair insulin secretion. These drugs may not cause diabetes by themselves, but they may precipitate diabetes in individuals with insulin resistance. In such cases, the classification is unclear because the sequence or relative importance of β-cell dysfunction and insulin resistance is unknown. Certain toxins such as Vacor (a rat poison) and intravenous pentamidine can permanently destroy pancreatic β-cells. Such drug reactions fortunately are rare. There are also many drugs and hormones that can impair insulin action. Examples include nicotinic acid and glucocorticoids. Patients receiving α-interferon have been reported to develop diabetes associated with islet cell antibodies and, in certain instances, severe insulin deficiency.

1.4.4.6 Infections

Certain viruses have been associated with β-cell destruction. Diabetes occurs in patients with congenital rubella, although most of these patients have HLA and immune markers characteristic of type 1 diabetes. In addition, coxsackievirus B, cytomegalovirus, adenovirus, and mumps have been implicated in inducing certain cases of the disease.

1.4.4.7 Uncommon forms of immune mediated diabetes

In this category, there are two known conditions, and others are likely to occur. The stiff-man syndrome is an autoimmune disorder of the central nervous system characterized by stiffness of the axial muscles with painful spasms. Patients usually have high titers of the GAD autoantibodies, and approximately one-third will develop diabetes.

Anti–insulin receptor antibodies can cause diabetes by binding to the insulin receptor, thereby blocking the binding of insulin to its receptor in target tissues.

1.4.4.8 Other genetic syndromes sometimes associated with diabetes

Many genetic syndromes are accompanied by an increased incidence of diabetes mellitus. These include the chromosomal abnormalities of Down's syndrome, Klinefelter's syndrome, and Turner's syndrome. Wolfram's syndrome is an autosomal recessive disorder characterized by insulin-deficient diabetes and the absence of β-cells at autopsy. Additional manifestations include diabetes insipidus, hypogonadism, optic atrophy, and neural deafness. Clinical aspect of diabetes mellitus generally includes, sign and symptom, complication and diagnosis [22].

1.5.1 Symptoms of Diabetes Mellitus

The classical symptoms of diabetes are polyuria (frequent urination), polydipsia (increased polyphagia (increased hunger), emaciation (unusual weight loss), extreme fatigue or lack of energy, blurred vision, frequent or recurring infections, cuts and braises (Figure 1.1) that are slow to heal, tingling or numbness in hands and/or feet. Symptoms may develop rapidly (weeks or months) in type 1 diabetes while in type 2 diabetes they usually develop much more slowly and may be subtle or absent [22]

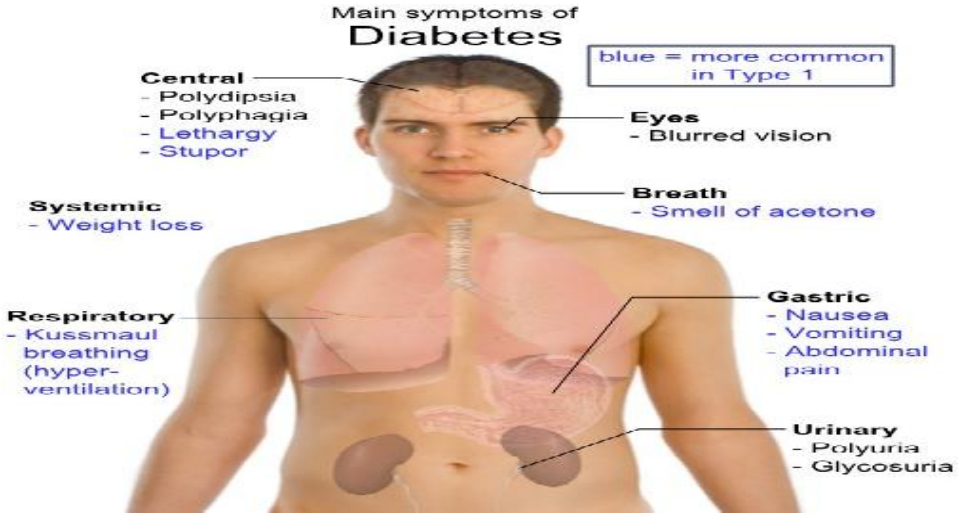

Figure 1.1 Overview of most significant symptoms of diabetes

1.5.2 Complications of Diabetes Mellitus

Diabetic complications can be classified broadly as acute glycemic (short-term) and chronic (long-term) complications. Other complications of diabetes include infections, metabolic difficulties, impotence, autonomic neuropathy and pregnancy problems [23].

1.5.2.1 Acute Glycemic Complications

Acute complication mainly include: Diabetic Ketoacidosis, Hyperglycemic Hyperosmolar Nonketotic Coma, and Hypoglycemia [23].

1.5.2.1.1 Diabetic Ketoacidosis (DKA)

Insulin deficiency causes the body to metabolize triglycerides and muscle instead of glucose for energy. Serum levels of glycerol and free fatty acids (FFAs) rise because of unstrained lipolysis, as does alanine from muscle catabolism. Glycerol and alanine provide substrate for hepatic gluconeogenesis, which is stimulated by the excess of glucagon that accompanies insulin deficiency. Glucagon also stimulates mitochondrial conversion of FFAs into ketones (Figure 1.4). Insulin normally blocks ketogenesis by inhibiting the transport of FFA derivatives into the mitochondrial matrix, but ketogenesis proceeds in the absence of insulin. The major ketoacids produced: acetoacetic acid and f3- hydroxybutyric acid are strong organic acids that create metabolic acidosis. Acetone derived from the metabolism of acetoacetic acid accumulates in serum and is slowly disposed of by respiration [24].

Vomiting, dehydration, deep gasping breathing, confusion and occasionally coma are typical symptoms of DKA **[25].**

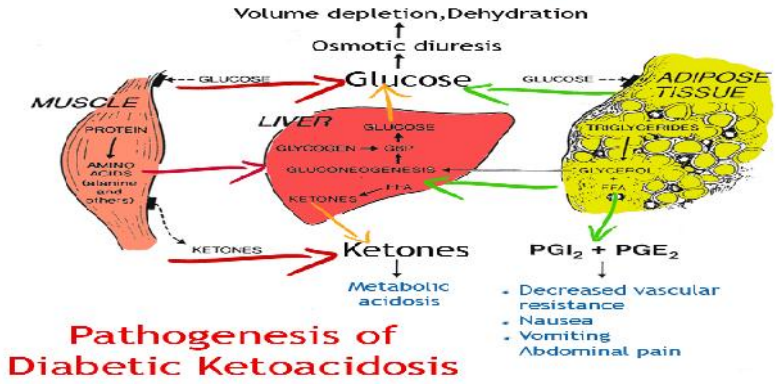

Figure 1.2 Pathogenesis of Diabetic Keratocidosis

1.5.2.1.2 Hyperglycemic hyperosmolar nonketotic coma

Hyperglycemic hyperosmolar nonketotic coma (HHNKC) is characterized by severe kyperglycemia (glucose level typically greater than 600 to 800 mg/dL), dehydration, and altered mental status due to the absence of ketosis. It usually develops after a period of symptomatic hyperglycemia in which fluid intake is inadequate to prevent extreme dehydration from the hyperglycemia-induced osmotic diuresis. In this case, focal central system deficits may occur [26].

1.5..2..1.3 Hypoglycemia

Any person with diabetes who takes an oral hypoglycemic agent or insulin may experience low blood glucose. The mechanism is depicted in figure 1.3. Severe hypoglycemia occurs when the patient inappropriately treats, ignores or does not recognize the early warning signs or when glucose counter regulation fails to return at the normal blood glucose level

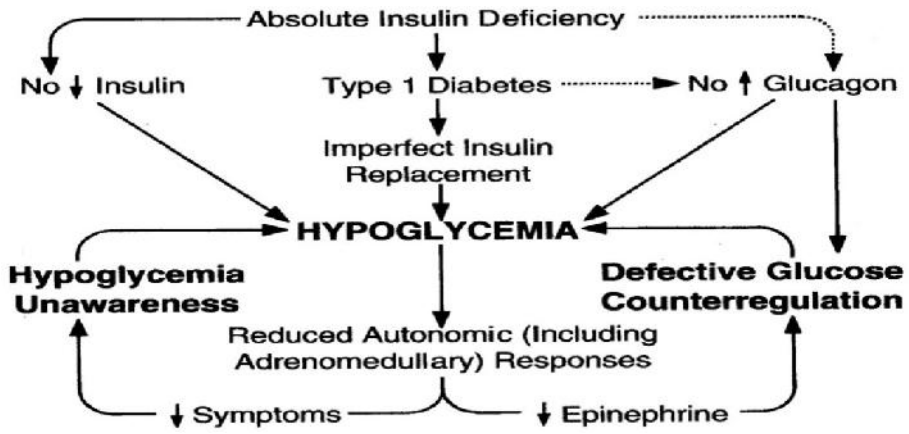

Figure 1.3 Hypoglycemia-Associated Autonomic Failures

1.5.2.2 Chronic Complications

Chronic complications generally develop after 12-15 years of diabetes. These complications may lead to organ dysfunction through micro vascular and macro vascular damage. Micro vascular complications include neuropathy (nerve damage), nephropathy (kidney disease) and vision disorders (e.g.; retinopathy, glaucoma, cataract and cornea! disease). Macro vascular complications include heart disease, stroke and peripheral vascular disease (which can lead to ulcers, gangrene and amputation)[28

1.5.2.2.1 Diabetic Neuropathy

Increased levels of glucose cause an increase in intracellular diacylglycerol, which activates PKC. Moreover, excessive activation of the polyol pathway leads to increased levels of sorbitol and reactive oxygen molecules and decreased levels of nitric oxide and glutathione, as well as increased osmotic stresses on the cell membrane. Any one of these elements alone can promote neuronal cell damage [29

1.5.2.2. 2. Diabetic Nephropathy

In kidney, thickening of basement membrane interferes with the normal filtration properties of the capillaries hi the glomerulus, resulting in increased renal failure characterized by adecreased glomerular filtration rate. As the severity increases, the filtration become so poor

that toxic end products accumulate hi the blood. Finally, total kidney failure occurs, which is known as nephropathy [30].

1.5.2.2.3 Macrovascular Disease

Macrovascular disease accounts for more than 70% of deaths hi people with diabetes, mostly from atherosclerosis (myocardial infarction), angina pectoris, congestive cardiac failure, stroke and peripheral arterial disease [31].

1.5.2.2.4 Psychological Complication

Diabetes itself does not cause changes hi personality or psychiatric illness, but particular subgroups of the diabetic population appear to be at risk for developing psychosocial problems. Young people with insulin- dependent diabetes mellitus (IDDM) may have a higher prevalence of eating disorders, such as anorexia nervosa and bulimia. Adults with longstanding diabetes may have a higher prevalence of symptoms of depression and anxiety [32].

1.6 Therapy for Diabetes Mellitus

The goal of diabetes management is to keep blood glucose levels as close to normal as safely possible. People with diabetes must take responsibility for their day-to-day care. This includes monitoring blood glucose levels, dietary management, maintaining physical activity, keeping weight and stress under control,monitoring oral medications and if required, insulin use via injections or pump [33].

1.6.1 Dietary Management and Physical Activity

In people with diabetes, food is an important part of treatment and diet has long been considered as the cornerstone in the management of diabetes. The word diet control which is generally used in this treatment does not mean eating less or sacrificing favorite foods in life, it means a planned regulated diet that will meet the nutritional needs of the body. The nutritional needs of a diabetic patient will remain same as before the diabetic was detected.

1.6.2 Antidiabetic Drugs

For treating T2DM subjects, when patients fail to maintain normoglycemia by maintaining diet and exercise alone, the first line drugs are the oral hypoglycemic agents (OHAs).

The table below shows the sites of actions of drugs used for blood glucose control in T2DM, other than insulin [34].

Table 1.3 Oral agents used in the treatment of type 2 diabetes mellitus

Class	Action	Mechanism of action	Example
Sulphonylureas	Increase insulin secretion	Binds to sulphonylurea receptor on p-cell, leading to closure of ATP-sensitive	*Glibendamid, Gliclazide*
Meglitinide Analogue			*Repaglinide Nateglinide*
Thiazolidinediones	Reduce insulin resistance	PPARϒ agonist	*Pioglitazone Rosiglitazone*
Biguanides	Reduce insulin resistance, reduce hepatic glucose output	Not known	*Metformin*
a-Glucosidase	Delay absorption of	Inhibits a- glucosidase	*Acarbose Guar gum*
Agents that reduce fat absorption		Inhibits pancreatic lipase	Orlistat
Centrally -acting		Serotonin and norepinephrine reuptake	Sibutramine

1.7.3 Insulin Therapy

Insulin therapy is often an important part of diabetes treatment. People with type 1 diabetes require supplemental insulin because their bodies can no longer produce insulin themselves. However, T2DM is different. Less than one-third of patients with T2DM take insulin [35].

There are a number of different types of insulin available to fit everyone's lifestyle. Although there are several variations, the main types of insulin are:

i. **Rapid-acting**: Starts to work in about 5 minutes, reaches the peak of effectiveness in about one hour and continues working for up to four hours [36].

ii. **Regular or Short-acting**: This type of insulin begins to work in about 30 minutes, reaches the peak of effectiveness anywhere between two and three hours and continues working up to six hours [36].

iii. **Intermediate-acting**: Usually begins to work in two to four hours, reaches the peak of effectiveness anywhere between two and three hours and continues working up to six hours [36]

iv. **Long-acting**: Usually begins to work in six to ten hours and continues working up to 24 hours [36].

1.8. Ziabit :

Ziabit is one of the most recommended Unani Medicine for better health , Diabetes or diabetes is a condition in which the body when the body can not use glucose for energy demand, and thus increases the amount of blood. Insulin helps the body cells to produce glucose. If no insulin, or the insulin producing capacity does not work properly, can increase the amount of glucose in the blood. Ziabit contains guramara the diaper, kustamaraoyarida, sour spinach and herbs and seeds prabhitira chemical elements are increase the production and performance of insulin to control blood glucose levels.

Composition :

Each capsules contains:

01. Acacia-gum - 171 mg

02. Bansalocana - 118 mg

03. Amaranth seeds sour spinach - 079 mg

04. Guramara diaper - 055 mg

05. Refined bitumen - 035 mg

06. Kusata khubachula Hadid - 022 mg

07. Kusata bayaja - 014 mg

08. Kusata maraoyarida - 008 mg

Other components - parimanamata

Dosage :

1-capsules twice daily after meal or as directed by a registered physician**.**

1.9. Objective of The study:

The study objective was to compare the efficacy and safety of herbal product on Type -2 diabetic rat model. Now- a- days traditional medicine used are most common in Bangladesh. Herbal products have been used to control diabetes and dyslipidemia in the traditional medicinal systems. Unfortunately the rationale behind the use of these medicines is not so available and most of the cases there is no scientific evidence in support of claimed efficacy of these herbal formulation. Our goal is to determine whether the drug use in the treatment of diabetes is have any efficacy or not.

Chapter Two
Method & Preparation

2.1. Preparation of Sample :

Herbal solution was made for fed the rats from tablet form. So first crush the tablet makes it powder.

Dose : Dose is given according to the body weight of the rat and that was 1.25gm/kg body weight .

Herbal Ziabit was taken in a conical flask then dissolve it with distil water and added distil water up to 10ml . Thus the concentration of dose was 1.25gm/10ml .

2.2. Preparation of standard :

Metformin used as standard. Dose reference used from the Beximco Pharmceuticals.

10ml is standard for oral dose. We dissolve 5mg/kg Metformin body weight per 10ml distilled water .

2.3.Animals :

Adult male –Long Evans'' rats weighting about 200-300gm and obtained from the Bangladesh Institute of Research & Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM) General hospital ,were used in this study . All the animal were fed the pellet diet , and water was allowed according with under strict hygienic conditions . Pellet diet was given 15gm per day for each rat into divide , one half given in the moring , another half afternoon . Before initiation of experiment, the rats were adjusted for a period of 7 days standard environmental conditions such as

temperature (26±2^{o}C relative humidity (45-55%) and 12h dark/light cycle were maintained . Animal handling and all experimental procedures were performed according to the Guidelines for Animal Experiments.

2.3.1 Induction of diabetes in experimental animals :

After fasting for 18-h, the rats were intraperitoneally injected with a single dose of 60 mg/kg STZ, freshly dissolved in citrate buffer (0.01 M, pH 4.5). Diabetes in the rats was identified by polydipsia, polyuria and by measuring non-fasting serum glucose concentration 48-h after injection of STZ. Rats with a serum glucose level above 300 mg/dL were selected for experiments.

2.4. Experimental design :

All the diabetic animals were randomly divided into three group with three animals each and treated once a day for 28 days as follows:

Group-I diabetic rats : received Ziabit 1.25mg/kg body weight . Group-II diabetic rats : received metformin 5mg/kg body weight;

Group –III (Water Control): Given only water.

Blood samples were collected on 1^{st} day , 14^{th} day and 28^{th} day and centrifuged Blood was collected from tail and finally from heart . Percentage decreases very small amount in the blood glucose levels compared to the standard. Rats weight measured after every seven days . Blood about 3-5 ml was collected directly from heart by syringes, centrifuged at 6000 rpm for 30 minutes and the serum was preserved to examine various biochemical parameters.

2.5. Statistical analysis :

Data are presented as mean +standard deviation (S.D.). Statistical significance was assessed by the fisher's test . $p<0.05$ was considered statistically significant .

Cahpter Three
Result & Discussion

3.1.Body weights :

Results showed significant decrease the body weight of the diabetic animals at the given dose.

Weight of normal rat was less decrease compared to the normal herbal Ziabit or standard group.

Table: Body weight of rats Group-I (herbal Ziabit), Group-II standard (Metformin), Group-III water control after 28 days of treatment.

Group	0 Day Weight gm.	7 Day Weight gm.	14 Day Weight gm.	21 Day Weight gm.	28 Day Weight gm.
Group-I Sample	235±19.46	214±6	208±0	222±0	218±0
Group-II Standard	216±24	152±9.89	184±15.53	180±49.53	163±25.50
Group-III Water control	252±21.94	254±9.45	260±8.32	252±10	250±11.05

Data represent mean±S.D. (n=3) for each group $p<0.005$, compared with receive herbal alisa $p<0.005$, compared with receive metformin $p<0.005$, compared with normal control

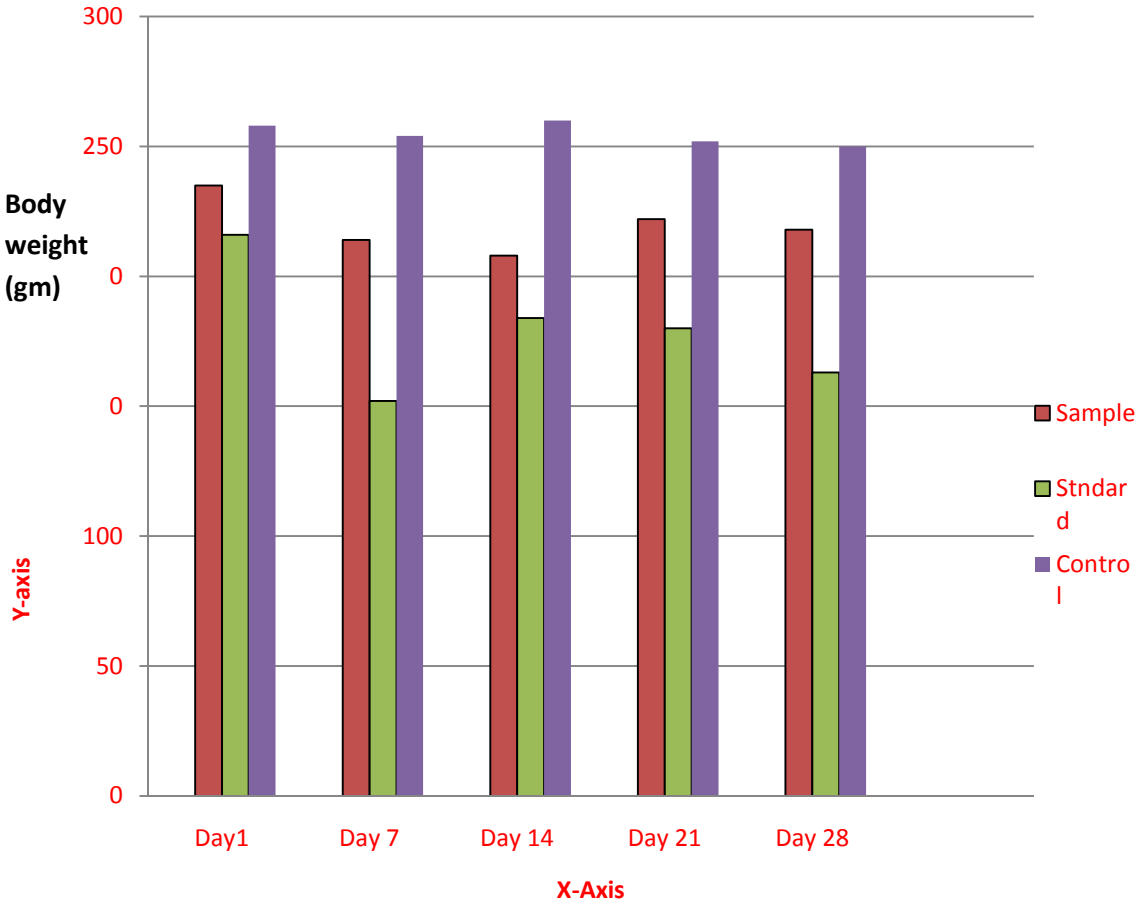

Figure1.3: Body Weight of rat at different intervals

3.2. Blood glucose level : Blood Glucose Level in rat Is significantly decrease in sample after 28th day from 9.3. to 6.2 mmol/l. In case of Standard th blood glucose level is slightly reduced into 6.9 into 5.4. But incase of water control rat no significant change of blood glucose level.

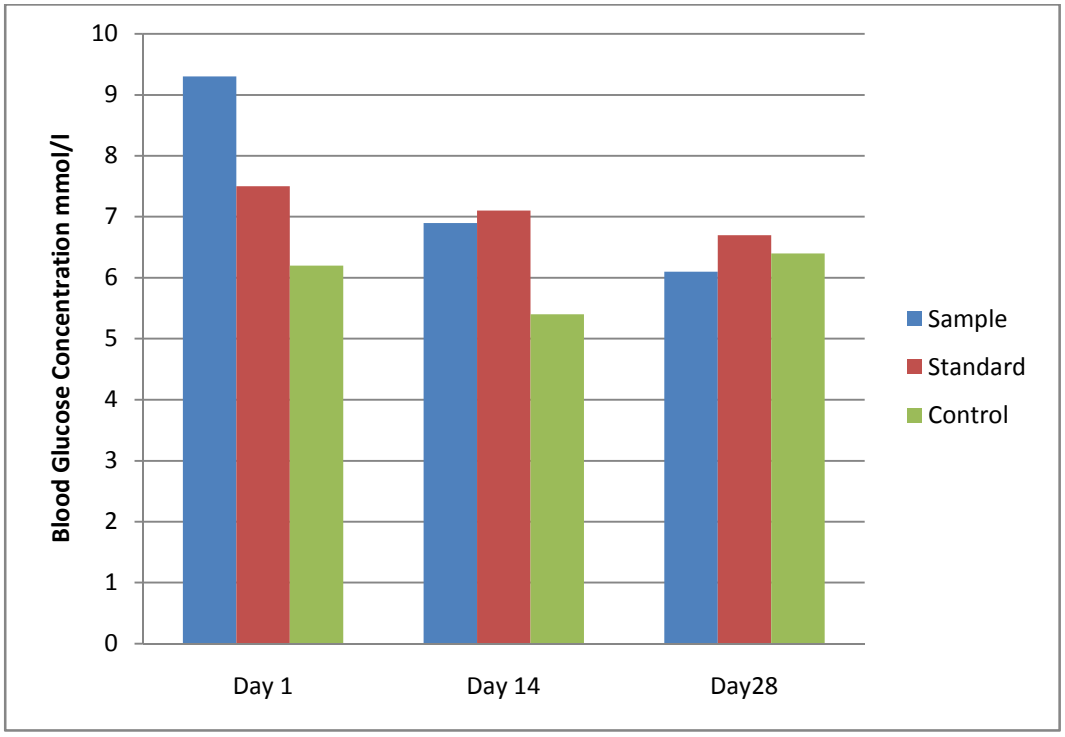

Figure 1.3: Measurement of blood glucose level at different interval

3.3.Discussion :

In Unani/herbal medicine and indigenous folk medicine system, the hypoglycemic plants have been used mostly in their natural forms, consisting of both inorganic and organic constituents of the concerned herbs. It is important to note that the inorganic part of medicinal plants containing mainly mineral, plays a contributory role in enhancing hypoglycemic activity) and their indirect role in diabetes management is increasingly recognized Therefore, the search for more effective and safer ant-diabetics/hypoglycemic agents has continued to be an important area of active research. The herbal medicine has been recommended for the treatment of diabetes and are considered less toxic with fewer side effects than the synthetic ones .

The administration of Herbal Ziabit resulted in a less significant reduction of blood glucose level of the diabetic rats when compared with diabetic rats that received no treatment and with the diabetic rats received standard ($p<0.001$)

Daily administration of herbal Ziabit , standard and water control according to body weight of the rats . The rats was identified by the mark on the tail of the rats ,water

and pellet was given two times daily . In 28 days we measured body weight of rats five times every seven days.

STZ- induced diabetes is characterized by severe loss in body weight of untreated rats. The characteristic loss of body weight is due to increase muscle wasting in diabetes . When Herbal preparation of Ziabit was administered to diabetic rats, the weight loss seems to be as a result of its less ability to reduce hyperglycemia in a short period of 28 days.

Chapter Four

Conclusion

4.1 Conclusion:

Traditional medicinal plants are commonly used in Bangladesh to treat diabetes. The available data regarding the anti-diabetic activity of the detected plants is not sufficient to adequately evaluate or recommend their use. Clinical intervention studies are required to provide evidence for a safe and effective use of the identified plants in the treatment of diabetesThere are many herbs with strong anti-diabetic properties. The natural way of healing was transferred from person to person and place to place. Parsons acting as physicians or guide were respected and were even given the status of 'a God'. As time passed, search for new herbs was intensified and numerous groups at different places were formed .In this analysis, try to find out the efficacy of Ziabit from the data of measuring body weight and blood glucose level at different time interval. In this study demonstrated efficacy of the Ziabit as an effective hypoglycemic, so Ziabit helps to regulate blood glucose level.

Chapter Five

Reference

6.1. References:

1. http://www.who.int/features/factfiles/diabetes/en/

2. "About diabetes". World Health Organization. Retrieved 4 April 2014.

3. Diabetes Fact sheet N°312". WHO. October 2013. Retrieved 25 March 2014.

4. Kitabchi, AE; Umpierrez, GE; Miles, JM; Fisher, JN (Jul 2009). "Hyperglycemic crises in adult patients with diabetes.". Diabetes Care 32

17".Greenspan'basic & clinical endocrinology (9th ed.). New York: McGraw-Hill Medical.ISBN 0-07-162243-8.

6. "Update 2014". IDF. International Diabetes Federation. Retrieved 29 November2014.

7. Williams textbook of endocrinology (12th ed.) Philadelphia: Elsevier/Saunders. pp. 1371 1435

8. Shi, Yuankai; Hu, Frank B (7 June 2014). "The global implications of diabetes and cancer". The Lancet 383 (9933)1947

9.Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, Shibuya K, Salomon JA, Abdalla S, Aboyans V et al. (Dec 15, 2012). "Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries

2010: a systematic analysis for the Global Burden of Disease Study 2010.".page 380

10. "The top 10 causes of death Fact sheet N°310". World Health Organization.Oct 2013.

11. IDF DIABETES ATLAS (PDF) (6th ed.). International Diabetes Federation.2013. p. 7.

12. American Diabetes, Association (Apr 2013). "Economic costs of diabetes in the U.S. in 2012.". Diabetes Care 36 (4): 1033–46

13. Global status report on noncommunicable diseases 2014. Geneva, World Health Organization, 2012.

14. World Health Organization. Global Health Estimates: Deaths by Cause, Age, Sex And Country, 2000-2012. Geneva, WHO, 2014.

15. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030..

16. Global status report on noncommunicable diseases 2010. Geneva, World Health

Organization, 2011.

17. Sarah Wild, Gojda Roglic, Anders Green, Richard Sicree, Hilary King, (2004). Global Prevalence of Diaberes. Estimates for the year 2000 androjections for 2030. Diabetes Care vol. 27 no. 5 1047-1053.

18. Amos, A., McCarty, D. & Zimmet, P. (1997). The rising global burden of diabetes and its complications: estimates and projections to the year 2010. Diabetic Med. 14: SI-885.

19. King H, Aubert RE, Herman WH (1998): Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. Diabetes Care 21:1414-1431.

20. Wild SH, Roglic G, Sicree R, Green A, King H (2004): Global Burden of Diabetes Mellitus in the year 2000 and projection for 2003. Diabetes Carevol 27 no. 5 1047-1053.

21. Sayeed M.A., Rumi M.A.K, Ali, L, Banu A., Hussain Z.A. and Khan A.K.Azad (2007). Effect of socioeconomic risk factors on the difference in prevalence of diabetes between rural and urban population in Bangladesh, Biological medical research council; 33(1), 1-12.

22. Shoback, edited by David G. Gardner, Dolores (2011). "Chapter17".Greenspan's basic & clinical endocrinology (9th ed.). New York: McGraw-Hill Medical. 23. Rother KI (April 2007). "Diabetes treatment—bridging the divide". The New Englan Journal oMedicine 356 (15) 1499– 501. doi:10.1056/NEJMp078030. PMID 17429082

24. "Diabetes Mellitus (DM): Diabetes Mellitus and Disorders of Carbohydrate Metabolism: Merck Manual Professional". Merck Publishing. April 2010. Retrieved 2010-07-30.

25. Dorner M, Pinget M, Brogard JM (May 1977). "Essential labile diabetes". MMW Munch Med Wochenschr (in German) 119 (19): 671–

26. Shoback, edited by David G. Gardner, Dolores (2011). "Chapter 17".Greenspan's basic & clinical endocrinology (9th ed.).

27. Risérus U, Willett WC, Hu FB (January 2009). "Dietary fats and prevention of type 2 diabetes". Progress in Lipid Research 48 (1): 44–51

28. Williams textbook of ndocrinology (12th ed. Philadelphia Elsevier/Saunders. pp. 1371–1435.

29. Malik VS, Popkin BM, Bray GA, Després JP, Hu FB (2010-03-23). "Sugar Sweetened Beverages, Obesity, Type 2 Diabetes and Cardiovascular Disease risk". Circulation 121(11):

30. Malik VS, Popkin BM, Bray GA, Després JP, Willett WC, Hu FB (November 2010)." 48 (1): 44–51.

32. Hu EA, Pan A, Malik V, Sun Q (2012-03-15). "White rice consumption and risk of type 2 diabetes: meta-analysis and systematic review". BMJ (Clinical research ed.) 344:

33. Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT (1 July 2012). "Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy". The Lancet 380 (9838): 219–29.

34. Carr DB, Gabbe S (1998). Gestational Diabetes: Detection, Management, and Implications. Clin Diabetes; 16(1): 4.

35. Kuhl C, Holst JJ (1976): Plasma glucagon and insulin: glucagon ratio in gestational diabetes. Diabetes 25:16.

36. Gabbe SG, Niebyl JR, Simpson JL, Eds. Landon MB (1996)

37. "Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications" (PDF). World Health Organisation. 1999

38. Unless otherwise specified, reference is: Table 20-5 in Mitchell, Richard Sheppard; Kumar, Vinay; Abbas, Abul K.; Fausto, Nelson. Robbins Basic Pathology (8th ed.). Philadelphia: Saunders..

39. Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJ, Seshasai SR, McMurray JJ, Freeman DJ, Jukema JW, Macfarlane PW, Packard CJ, Stott DJ, Westendorp RG, Shepherd J, Davis BR, Pressel SL, Marchioli R, Marfisi RM, Maggioni AP, Tavazzi L, Tognoni G, Kjekshus J, Pedersen TR, Cook TJ, Gotto AM, Clearfield MB, Downs JR, Nakamura H, Ohashi Y, Mizuno K, Ray KK, Ford I (February 2010). "Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials". The Lancet 375 (9716):73542.

40. Cooke DW, Plotnick L (November 2008). "Type 1 diabetes mellitus in pediatrics". Pediatr 29 (11): 374-84.

41.Sayeed M.A.,Rumi MA.K, AH. L, Banu A., Hussain Z.A.and Khan A.K.Azad (2007).

Effect of socioeconomic risk factors on the difference in prevalence of diabetes between rural and urban population in Bangladesh , Biological medical research council; 33(1), 1-12

42.Kasper DL, Braunwald E, Fauci AS (2005). "Diabetes mellitus". Harrison's Principles of Internal Medicine (16th ed.). New York, NY: McGraw-Hill. pp.2152-2180.

43.Kitabchi AE, Umpierrez GE, Murphy MB, Kreisberg RA (December 2006). "Hyperglycemic crises in adult patients with diabetes: a consensus statement from the American Diabetes Association". Diabetes Care 29 (12): 2739-48.

44. Jill P. Crandall (2007). Merck Manuals Online Medical Libraty.

45. Casparie AF, Elzing LD (1985). Severe hypoglycemia in diabetic patients. Diabetes Care. 8:141-145:

46. Marija Krzanovic, Sladana Jovanovic (2008). Chronic complications of diabetes mellitus in patients covered by home treatment and care service. Journal of Regional Section of Serbian Medical Association volume (33): 69-73.

47. Leonard DR, Farooqi MH, Myers S (January 2004). "Restoration of sensation, reduced pain, and improved balance in subjects with diabetic peripheral neuropathy: a double-blind, randomized, placebo-controlled study with monochromatic near-infrared treatment". Diabetes Care 27 (1): 168-72.

48. Rudberg S, Osterby R (1998): Diabetic glomerulopathy in young IDDM patients: preventive and diagnostic aspects. Horm Res 50 (Suppl 1): 17-22.

49. Mills GA and Horn JR (1985). Beta-blockers and glucose control Drug Intelligence & Clinical Pharmacy: Vol 19, No. 4, pp. 246-251.

50. Jacobson AM, Hauser ST (1983). Behavioral and psychological aspects of diabetes. In: Ellenberg M, Rifkin H, eds. Diabetes Mellitus: Theory and Practice. 3rd ed. Vol. 2. New Hyde Park, New York: Medical Examination.