Survey on Herbal Medicine Use in Diabetic Patients: A Pilot Study

By

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A thesis submitted to the Department of Pharmacy in partial fulfillment of the
requirements for the degree of
Bachelor of Pharmacy (Hons.)

Department of Pharmacy
Brac University
October 2019

Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.

2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.

3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.

4. I have acknowledged all main sources of help.

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Approval

The thesis titled "Survey on Herbal Medicine Use in Diabetic Patients" submitted by Writparna Das (13346058) of Summer 2013, has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on 3rd October, 2019.

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Ethics Statement

This study does not involve any kind of animal and human trials.

Abstract

Diabetes patients' rate is increasing in worldwide vigorously. The rate is 7.1 million in Bangladesh. It is a matter of concern for every individual in controlling and preventing it. People are not satisfied with prescriptional anti-diabetic drugs and search for alternative treatment like herbal medicine. The aim of this study is to analyze the frequency of herbal medicine used in Dhaka city in diabetic patients and also their knowledge on adulterated herbal medicine in drug market. This is a pilot study including 100 diabetic patients. The participants were from the Birdem Hospital (Bangladesh Institute of Research and Rehabilitation), one of the largest diabetes hospitals in Dhaka city come regularly for their routine check -up and also from relatives and friends. Interview was taken face-face through questionnaire. The rate is 27% patients' who are using herbal medicine with combined therapy of conventional diabetic treatment. 60% patients have no knowledge on adulterated herbal medicine, 40% have which is very low. 44% patients have no side-effects and 36% face no hypoglycemia, 47% don't inform their health professional or any pharmacist. We can see from this study higher amount of diabetic patients are using herbal drugs without even informing their health professional which can cause adverse effects and ineffective diabetic management for them.

Keyword: Diabetes; Herbal medicine; Survey; Herbal medicine usage

Dedication

Dedicated to my Parents and Supervisor

Acknowledgement

At first, I would like to thank Almighty God, for which I am enabled to study in Pharmacy and also can submit the thesis paper for completing my degree of Bachelor of Pharmacy in the Department of Pharmacy of Brac University.

I would like to express my heartiest gratitude to my respected research supervisor Dr. Hasina Yasmin, Associate Professor of Department of Pharmacy for her unconditional guidance, inspiration, caring, commitment for mentoring me in my research work. She has always encouraged me whenever I face problems, related to my study and provides her effective feedback or comments on my research study. My research work cannot be completed appropriately and smoothly without my supervisor's contribution. She is highly experienced and knowledgeable and I had a great experience with madam while working on this project, feel myself fortunate to work under her supervision.

I would like to put forward my sincere regards and profound gratitude to Professor Dr. Eva Rahman Kabir, Chairperson, Department of Pharmacy, Brac University for her guidance and assistance in every steps of my completing this degree. She has been always help me whenever I face problems in throughout my all the semesters in University. I feel proud to know and meet her in this university,

I must thank to all my faculties of Pharmacy department of Brac University who has been taught me all the courses of this degree and helped me to complete my undergraduate degree smoothly

I must thank to my parents who have always support me mentally while doing this thesis.

Lastly, I would like to thanks all the participants who take part in my survey and help me in completing my research study appropriately.

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List of Acronyms

DM   Diabetes Mellitus

T2DM   Type 2 Diabetes Mellitus

IDDM   Insulin-Dependent Diabetes Mellitus

NIDDM   Non-Insulin Dependent Diabetes Mellitus

LADA   Latent Autoimmune Diabetes of Adulthood

GDM   Gestational Diabetes Mellitus

ADA   American Diabetes Association

WHO   World Health Organization

Chapter 1

Introduction

1.1 Diabetes

Diabetes is a serious, chronic disease that occurs either when the pancreas does not produce enough insulin (a hormone that regulates blood sugar or glucose) or when the body cannot effectively use the insulin it produces. It is a worldwide health related issue of the present times (Monica, Cr, & Panchaksharimath, 2016). Both the number of cases and the prevalence of diabetes have been steadily increased over the past few decades (Yatoo, Saxena, Gopalakrishnan, Alagawany, & Dhama, 2017). As indicated by the World Health Organization, 347 million individuals worldwide are experiencing diabetes, with the expectation that it will be the seventh driving reason for death in 2030. Basically, diabetes is initiated by the unstable homeostasis of sugars and lipids bringing about a high amount of glucose which is above the normal level in the blood. This genuine metabolic sickness significantly affects wellbeing, personal satisfaction, and future of diabetic patients (Damnjanovic, Kitic, Stefanovic, & Zlatkovic-guberinic, 2015). It is connected with creating of different genuine sicknesses for example micro vascular (nephropathy, retinopathy, nephropathy) and macro vascular (fringe vascular infection and coronary heart illnesses). Diabetes mellitus otherwise called diabetes which was seen as ailments related with "sweet urine" and muscle loss (Verma, Gupta, Popli, & Aggarwal, 2018). Glucose blood levels are kept controlled by insulin which is a hormone secreted from the pancreas. It is a disease that influences the body's capacity to make or utilize insulin. Insulin which produces in pancreas helps transfer of (glucose) from the circulatory system into the cells so they can separate it and use it for fuel. People cannot stay alive without insulin. Diabetes causes irregular amount of glucose in the circulatory system as a result, causes severe acute and chronic consequences

from brain damage to amputations and heart disease (Preethi, 2013). Several proof recommends that way of life changes, for example, exercise, diet and other nonpharmacological intervention can postpone and even avoid the advancement of diabetes. In any case, consistence to these mediations is low; with just about half of those with long time illness have been appeared to maintain the suggested way of life intercessions. Numerous anti-diabetic pharmaceutical medications are accessible, however the expansion in the frequency of diabetes, particularly in developing nations, together with unfavorable or unexpected events related with these medications, has stated the requirement for progressively compelling, more secure and less expensive administration ways (Gupta et al., 2017).

1.1.1 Pathophysiology of Type 1 Diabetes
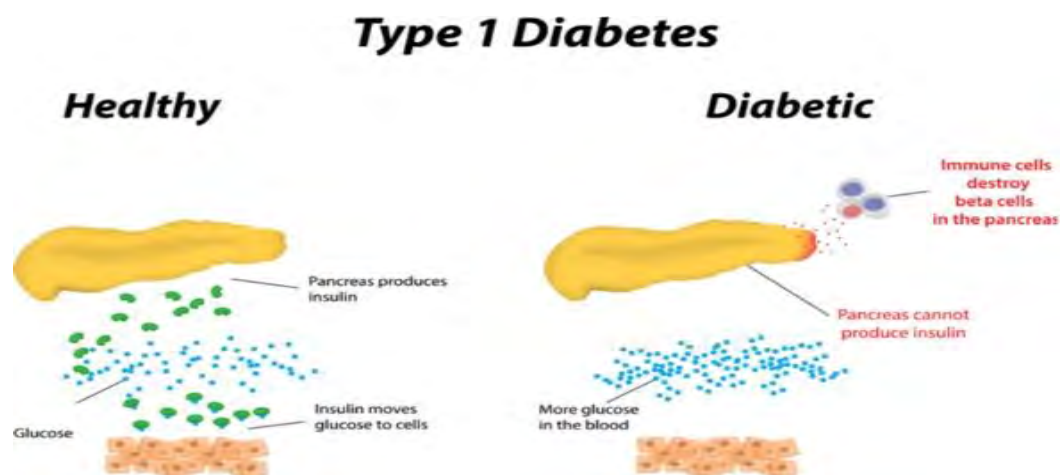
Figure 1: Pathophysiology of Type 1 Diabetes ("Diabetes Mellitus Type 1: Symptoms, Complications, and Treatment," n.d)

Type 1 diabetes is a life-long autoimmune disorder which occurs in individuals who are genetically susceptible and are also precipitated by environmental factors. The individual who are susceptible, their immune system will activate an autoimmune response opposed to the antigens which is present in changed beta cells or the compounds or molecules which are present on beta cells similar to viral proteins. It was found from the study that almost 85

percent patients with type 1 diabetes have islet cell antibodies which are circulating and they also have antibodies which are basically against insulin. This antibodies of islets cell are basically activated opposite to glutamic acid decarboxylase in between beta cells. This kind of autoimmune damage of beta cells causes lacking of insulin secretion. As the insulin secretion is disturbed this will cause metabolic disturbance in the patients' body. Moreover, as there is deficiency in insulin, the alpha cells of pancreas become abnormal which causes glucagon secretion more than normal level. Usually, hyperglycemia lowers the glucagon concentration or secretion but patients who are insulin dependent in them hyperglycemia do not blocked the secretion of glucagon (Raju and Raju, 2010). Finally, the unusual raised of glucagon level cause all the metabolic disarrangements in the presence of lower amount of insulin. We can give a known example like insulin dependent patients very quickly in them ketoacidosis occurred when they do not administer or take insulin in their body. There are disorder or defects take place not only for insulin deficiency but also for insulin administration. Several biochemical disturbance occurs when the tissue's response for insulin get impaired. Production of excess amount of amino acid in plasma and out of controlled lipolysis caused for lacking of insulin in body. This opposed for metabolising glucose in peripheral tissues for example skeletal muscle (Raju and Raju, 2010). This procedure will hamper glucose usage and it also reduces the expression of several genes which are required for targeted tissues. The targeted tissues need the genes for acting normally with insulin for example glucokinase genes in liver and glucose transporters situated in fat tissues. The main and significant metabolic disturbance or defects occurred for insulin lacking in type 1 diabetes patients are glucose metabolism, the metabolism of lipid and protein (Ozougwu, 2017).

1.1.2 Pathophysiology of Type 2 Diabetes
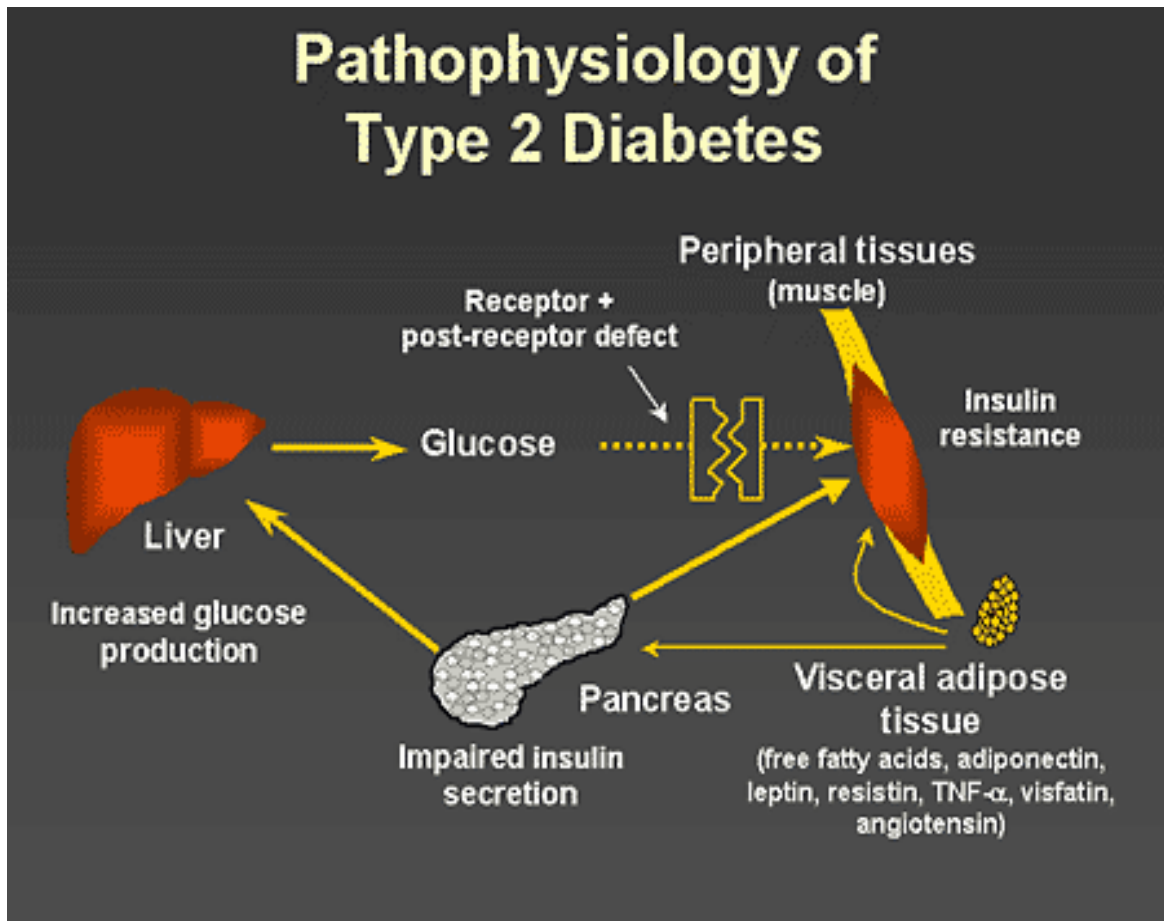
Figure 2: Pathophysiology of Type 2 Diabetes "Diabetes and Intestinal Incretin Hormones: A New Therapeutic Paradigm," n.d.)

To the development of pathophysiological condition of type 2 diabetes mainly 2 things, impaired secretion of insulin and insulin resistance contribute more or less. Impaired insulin secretion is the reduction in glucose responsiveness which is mainly started before clinical onset of disease. Beta cell dysfunction mainly starts with the impairment of insulin secretion during glucose stimulation and may create glucose intolerance in type 2 diabetes patients. Impaired glucose tolerance is observed by reduction in glucose response in first phase of insulin secretion and reduction in additional insulin secretion after meals which causes hyperglycemia. The starting of insulin response fully depends on tansmembranous transport

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of glucose and also coupling of glucose with the glucose sensor. The complex of glucose and glucose sensor then starts to increase glucokinase by stabilizing the protein and stopping its damage. This starting action of glucokinase is first step of connecting both the intermediary metabolism and apparatus of insulin secretory (Shane-McWhorter, 2009) In patients with type 2 diabetes their glucose transport in beta cells is reduced huge so the insulin secretion's control point is transfer to glucose transport system from glucokinase. Later in the disease condition, the insulin which is newly synthesized is impaired which is called beta cell glucotoxicity. This glucotoxicity is caused by paradoxical inhibitory effect on insulin of glucose and storage of glycogen in beta cell of pancreas or glycation of beta proteins (Article, 2012) In summary, the delay in impaired early phase insulin does not only act in pathogenesis of type 2 diabetes. In some patients' autoimmune destruction of beta cell does not cause late in immediate insulin response or for lack of glucokinase genes (Zaccardi, Webb, Yates, & Davies, 2015). In majority of patients, the insulin secretion is impaired because of secondary hypersecretory phase of insulin which can be caused for inheritance or of acquired defects in beta cells. This continuous destruction of beta cell function in future high glucose level in blood permanently (Hackett & Jacques, 2009). Insulin resistance is the condition where the insulin does not give sufficient action as proportionally to glucose concentration in blood. The impairment of insulin in main organs like muscles and liver is one of the common pathophysiology characteristics in Type 2 diabetes (Kaku, 2010). This action started to expand and develop before the onset of type 2 diabetes. Patients who have type 2 diabetes obviously undergone obesity, abdominal obesity is particular, this fat does not react or resistant to antilipolytic effects of insulin as a result large amount of amino acid releases which causes insulin resistance in liver and muscle cells. This causes liver gluconeogenesis and restrain muscle cells to take insulin mediated glucose. Therefore, circulating insulin are huge in number in patients' blood. When adipocytes become larger they cannot accumulate

fat anymore in them so the fats store in muscles cells, liver and pancreas for which the condition on insulin resistance get severe. This insulin resistance and huge amount of circulating glucose causes hyperinsulinemia means more amount of insulin and ultimately beta cell cannot have maintained this and their function get worsen. Finally, insulin output decrease, causes hyperglycemia and type 2 diabetes symptoms started to appear in patients' body. Hepatic glucose production is also increased due to hepatic insulin resistance in type 2 diabetes (Adler, 1999; Baynest, 2015; Nilanj, 2017; Russo et al., 2013)

1.1.3 Types of Diabetes

There are different types of diabetes. Scientists are still defining and categorizing some of these variations and establishing their prevalence in the population. Although classification of diabetes is important and has implications for the treatment strategies, this is not an easy task and many patients do not easily fit into a single class especially younger adults and 10% of those initially classified may require revision. The classical classification of diabetes as proposed by the American Diabetes Association (ADA) in 1997 as type 1, type 2, other types, and gestational diabetes mellitus (GDM) is still the most accepted classification and adopted by ADA (Kharroubi & Darwish, 2015), (Punthakee, Goldenberg, & Katz, 2018).

Type 1 Diabetes

An immune system ailment where the invulnerable framework erroneously demolishes the insulin-production beta cells of the pancreas and that's why called autoimmune disease (Zaccardi et al., 2015). It normally grows more rapidly than different types of diabetes. It is generally analyzed in kids and youths, and in some cases in youthful grown-ups. To endure, patients must control insulin medicine routinely (Dimeglio, Evans-molina, & Oram, 2018). Type 1diabetes used to be called juvenile diabetes and insulin-dependent diabetes mellitus (IDDM) (Punthakee et al., 2018). Be that as it may, those terms are not exact in light of the

fact that youngsters can create different types of diabetes, grown-ups in some cases create type 1, and different types of diabetes can require insulin treatment. A variety of type 1 that grows sometime later in life, for the most part after age 30, is called latent autoimmune diabetes of adulthood (LADA). Now and then patients with autoimmune system diabetes create insulin opposition in view of weight addition or hereditary elements which is known as double diabetes (Preethi, 2013).

Type 2 Diabetes:

It is mainly disorder of metabolism which as a rule includes obesity and insulin resistance. In these patients, the pancreas makes insulin at first, yet the body experiences difficulty utilizing this glucose-controlling hormone. It is a chronically progressive disease (Matthaei et al., 2009). Inevitably the pancreas can't deliver enough insulin to react to the body's requirement for it. Type 2 diabetes is by a wide margin the most well-known type of diabetes, representing 85 to 95% of cases in created countries and a significantly higher rate in developing countries, as indicated by the International Diabetes Federation *(Diabetes mellitus : The disease itself*, 2017).This illness may take years or decades to create (Kooti et al., 2016)It is typically forwarded by pre diabetes, in which levels of (glucose) are on the level higher than average yet not sufficiently high yet for a finding of diabetes diagnosis. Individuals with pre-diabetes can frequently avert the acceleration to type 2 diabetes by losing their weight through upgrades in exercise and diet, as the Diabetes Prevention Program and other research undertakings have illustrated. Type 2 diabetes used to be called adult-onset diabetes and non-insulin-subordinate diabetes mellitus (NIDDM). Those terms are not exact on the grounds that youngsters can likewise build up this illness, and a few patients require insulin (Preethi, 2013).
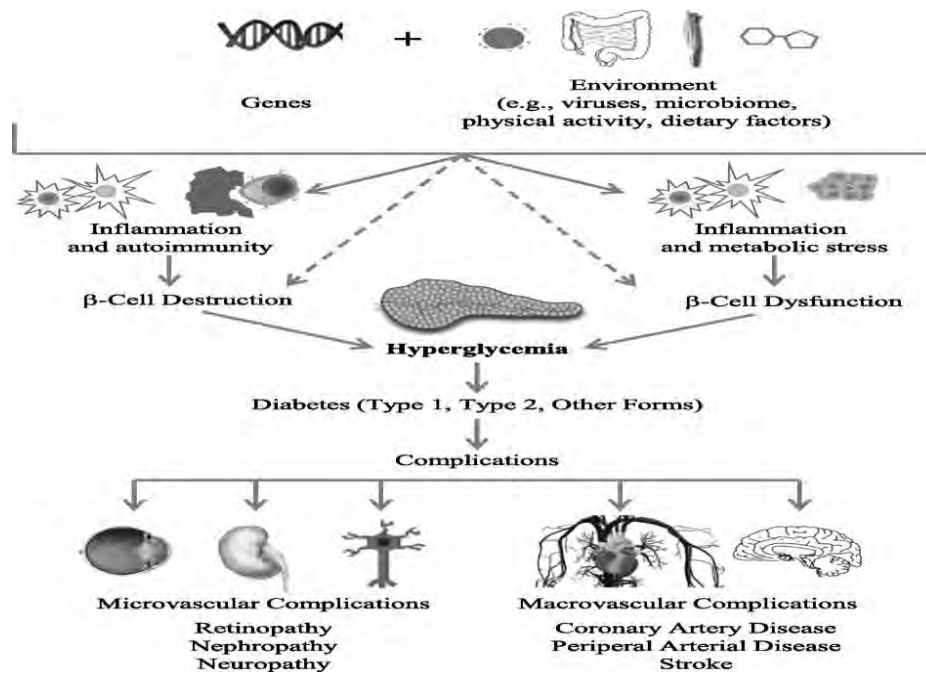
Figure 3: Causes of Diabetes (Skyler et al., 2017)

Genetic and environmental risk factors impact inflammation, autoimmunity, and metabolic stress. These states affect beta cells function such that insulin levels are eventually unable to respond sufficiently to insulin demands, causing hyperglycemia levels sufficient to diagnose diabetes. In some cases, genetic and environmental risk factors and gene-environment interactions can directly impact beta cell function. Regardless of the pathophysiology of diabetes, chronic high blood glucose levels are associated with microvascular and macrovascular complications that increase morbidity and mortality for people with diabetes. This model shows beta cells destruction and/or dysfunction as the necessary common factor to all forms of diabetes (Skyler et al., 2017).

Gestational Diabetes:

It is temporary metabolic disease which can be created during pregnancy period in woman who have no diabetes before, typically in the third trimester. The alteration of hormone alongside weight gain and also family history of diabetes can be also the causes of it. About

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4% of pregnant ladies create gestational diabetes, as indicated by the American Diabetes Association (Preethi, 2013)

Secondary Diabetes:

Diabetes which are created by other conditions. There are numerous potential causes of secondary diabetes run from illnesses, for example, pancreatitis, cystic fibrosis, down disorder and hemochromatosis to therapeutic medications including corticosteroids, other immunosuppressive, diuretics and pancreatectomy (Preethi, 2013).

1.1.4 Diagnosis of Diabetes Mellitus

The diabetes can be diagnosed through the process of determining glucose levels in patients' blood. The sugar concentration in normal man on fasting are 80 mg/dl and in postprandial state is up to the level of 160 mg/dl (Craig, & Hattersley, 2009).Other tests for examining diabetes are finger prick glucose test, then fasting glucose along with glucose resistance demonstrative test and also glycohemoglobin (Bailey, Clifford J. Day, 1989).

1.1.5 Anti-diabetic Drug

Diabetes ailments can be controlled by dealing with the glucose level in blood circulation by using various kinds of medications, securing to various kinds of exercise or yoga treatment and along with diet plan. In present time type 1 diabetes can be managed by insulin treatment and oral anti-diabetic drugs for type 2 diabetes are available. Combined therapy with insulin and oral drugs are also used in managing diabetes (Tabatabaei-malazy, Larijani, & Abdollahi, 2015; Verma et al., 2018). There are different types of insulin like long-acting, rapid, intermediate, and short acting insulin. Each has their own mechanism of action to treat type 1 diabetes.There are various group of pharmaceutical agents in treating diabetes with various mechanism of actions such as some drugs for example, enhance the body's insulin secretion (e.g., sulfonylureas), reducing the body's hepatic glucose amount and also rising the glucose

peripheral uptake (e.g., biguanides).Some portion of generally used antidiabetic drugs incorporate biguanides for example drug name metformin (through enacting for influencing insulin obstruction), the receptor named peroxisome proliferator initiated receptor (PPAR) activators, e.g., thiazolidindiones (through improving insulin restriction), vidagliptin and other related "gliptins" (through blocking DPP-4, it is a enzyme that can reduce incretion GLP-1) and α-glucosidase named inhibitors, such as, acarbose and the miglitol (through reducing the carbohydrate absorption).On the other hand, some other diabetic medicines work by targetingpp pancreatic beta-cell receptor by the process of binding to sulfonylurea receptor subunit, and by obscuring the K+-ATP channel for enhancing insulin release, mix treatments (for example sulfonylureas with biguanides, thiazolidinedione with glucosidase inhibitors) are generally used to broaden therapeutic targets for improving efficiency and for limiting both the side-effects and adverse effects (Gupta et al., 2017; Meneses et al., 2015).

Classification and structures of oral antidiabetic drugs are given below:

a.Biguanide:

Metformin is a biguanide. It is basically primary first-line treatment for treating type 2 diabetes for all the age people. This drug mainly stimulated the protein kinase in liver which is adenosine activated protein. This mechanism mainly increases hepatic glucose collection or uptake. It also prevents gluconeogenesis by working on the mitochondrial enzymes by the complex effects. This drug is particularly accepted by patients as it has very low side-effects, lesser possibility of hypoglycemia and also gaining of weight in patients, possibility is very lower (Chaudhury & Mirza, 2017)
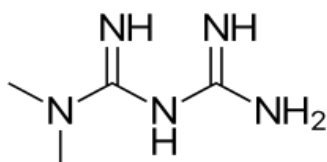
Figure 4: Metformin

b. Sulfonylureas:

Sulphonylureas is known as second-line or add one drug of choice in management of type 2 diabetes. Their mechanism of action is they completely blocked the channel named KATP in the aim of rising the amount of insulin secretion. Furthermore, they suppressed the liver gluconeogenesis and with that prevent the breaking down of lipids in to fatty acids. This way they decrease the amount of fatty acids and lower the insulin removal from liver. There are 3 division of generation of sulphonylureas. First generation of sulphonylurea are such as tolbutamide, chlorpropamide, 2nd generation are such as glibenclamide, gliclazide and the 3rd generation are such as glimepiride etc. (Chaudhury & Mirza, 2017)
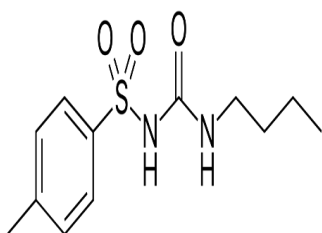
Figure 5: Tolbutamide
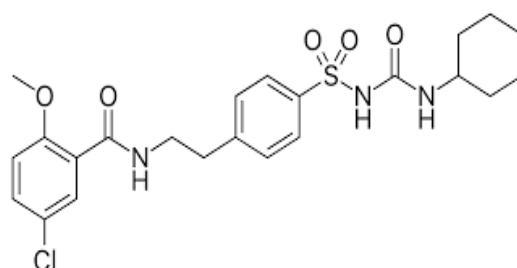
Figure 6: Glibenclamide

c. Thiazolidinedione:

They mainly increase the activity of insulin similarly as bigunides. They are basically agonists of peroxisome proliferated activated receptors and stimulate the glucose taken up by several adipose, muscle and also liver tissue. This class of drugs work my using various processes like they weaken the free fatty acid storage, decreases the inflammatory cytokines

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and conserved the beta cells function and their good condition. This all mechanism of activity must improve both the insulin resistance and beta cell weakness or dysfunction. The two drug below shown are the example of this class of drugs (Chaudhury & Mirza, 2017).
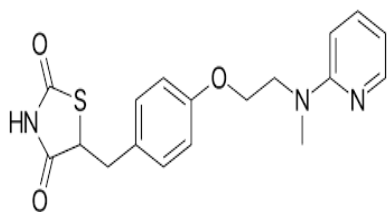
Figure 7: Rosiglitazon
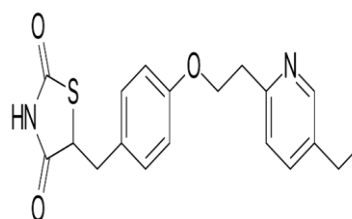
Figure 8 :Pioglitazone

d. DPP-4 Inhibitors:

The representatives of this class of drug are sitagliptin, saxagliptin, vidagliptin, linagliptin, etc. They can be used as only single treatment or in combined therapy with metformin, sulphonylurea etc. There treatments procedure is similar like other drugs and they do not cause hypoglycemic condition on the contrast with the controls (Chaudhury & Mirza, 2017)
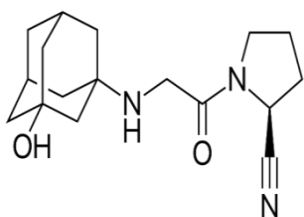
Figure 9: Vidagliptin
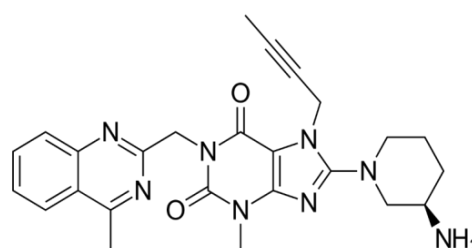
Figure 10: Linagliptin

e. GLP-receptor agonist:

In present time, exenatide and lirglutide drugs are available which are basically agonist of GLP receptor. This class of drugs mainly rises the level of obstruction of enzymatic destruction done by DPP4. The patients who have been identified with type 2 diabetes currently, who have obesity, unusual metabolic functions should take this class of drugs which will provide positive effects on lowering weight and preventing metabolic disorders (Chaudhury & Mirza, 2017)

f. SGLT-2 inhibitors:

The class of drugs are actually new groups of glucosuric agents such as: canagliflozin, dapagliflozin, etc. They mainly function by preventing glucose again absorption back in proximal renal tubule of kidney. And this is done by opposing SGLT-2. They are also effective in treating very advanced stages of patients with type 2 diabetes because of this mechanism when beta cells function is lost forever. They lower the weight and high blood pressure.
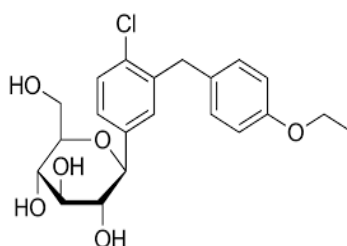
Figure 11: Dapagliflozin

1.2 Herbal Medicine

According to WHO "Traditional medicine is the sum total of the knowledge, skill, and practices based on theory beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness" (Qazi Majaz & Molvi Khurshid,

2016). According to World Health Organization herbal medicines are naturally occurring, substances derived from plant with lesser side-effects, and required no modern or industrial processing and are utilized in treatment of diseases within regional and local healing practices. Because of its natural source and minimum side-effects herbal medicines and their formulation have been used in huge ratio from past thousands of years in both developing and developed countries. Firstly, herbal medicines have been appeared in the crude drug form for example tinctures, powders, teas, poultices, and other herbal formulation (Qazi Majaz & Molvi Khurshid, 2016). Utilizing plants in regenerating or curing purposes indicates the human history and it also creates the sources of modern drugs. Traditional medicines which are mainly plant-derived have gone through several pharmacological and clinical studies and these studies are the mainstay of sources of most early medicines for examples aspirin (willow bark), digitoxin (from foxglove), morphine (from the opium poppy),quinine (from cinchona bark), and pilocarpine (Jaborandi) (Qazi Majaz & Molvi Khurshid, 2016). For 75-80 percent of population's primary health care in world particularly of developing country still now the backbone is herbal medicine (Pal & Shukla, 2014).The reason behind this are, herbal medicines are available locally, in low cost which is affordable to majority of people and the most common usual belief that herbal drugs have fewer side-effects. The utilization of herbal medicines in comparing other prescriptional drugs has crossed by two or three times in whole world and it is stated by World Health Organization (WHO) (Qazi Majaz & Molvi Khurshid, 2016).

1.2.1 Different Classes of Herbal Medicines

According to WHO, herbal medicines has been categorized in to four different groups in accordance with their source, evolution and present use (Qazi Majaz & Molvi Khurshid, 2016).The group are described below:

 A. Indigenous herbal medicines

B. Herbal medicines in systems

C. Modified herbal medicines

D. Imported products with herbal medicine base

a. Indigenous herbal medicines:

This type of herbal medicine is actually used in local community by local population and are renowned for their long time utilization in the perspective of their contents or composition, dose or dosage and curing method or treatment. Regional or local community people can use it anytime without any objection or hindrance (Qazi Majaz & Molvi Khurshid, 2016).

b. Herbal medicines in system:

However, when the herbal medicines which are used locally move from local community to drug market, they have to obviously fulfill the prerequisites or validation of safety and efficacy or potency according to the national regulations. Herbal medicines in systems which are used for longer period of time have certificated or validated theories and the concepts and are approved by the countries. For instance, Ayurveda, Unani and Siddha (Qazi Majaz & Molvi Khurshid, 2016).

c. Modified herbal medicines:

We can understand by their name that they have gone through modification in their shape, their dosage form, their route of administration, dose, their active ingredients, methodologies of their preparation, and obviously their medical indication. It is mandatory for them to fulfilled the national drug regulatory demands of safety, toxicity, and also efficacy of herbal medicines (Qazi Majaz & Molvi Khurshid, 2016).

d. Imported herbal medicines:

Imported herbal medicines are those which are get imported from foreign countries for entering in to the drug market of the country who import them which includes raw materials and products of herbal medicines. They, at first need to be registered and must be marketed in

their original country from where they have been produced and their safety and efficacy related data required to be hand over to the importing country national drug authority and must fulfilled the demand of safety and efficacy of importing country's national regulations of herbal medicine (Qazi Majaz & Molvi Khurshid, 2016).

1.2.2 Herbal Plants with Anti-Diabetic Activities

Herbs that are most frequently promoted to help manage blood glucose levels include bitter melon (*Momordica charantia*), fenugreek (*Trigonella foenum graecum*), nopal (*Opuntia* spp.),Russian tarragon (*Artemisia dracunculus*), cinnamon (*Cinnamomum cassia*), psyllium (*Plantago ovata*), and garlic (*Allium sativum*) , Aloe (*Aloe vera L*), Neem (*Azadirachta indica), Ginger (Zingiber officinale Roscoe),*Bengal Quince, Bel or Bilva (*Aegle marmelos*) etc.(Choudhury et al., 2018).These plants are described below:

a. **Aloe** (*Aloe vera L):*

Aloe is a plant from Liliaceae family and it best grows in the warm climates. The gel of Aloe is clear component and mainly get harvested from the core of leaf when primary stalk has been cut down. The gel of is used in the treatment of diabetes and also hyperlipidemia (Shane-McWhorter, 2009).

b. **Bitter Melon** *(Momordica charantia):*

 Bitter melon is a kind of plant additionally referred to by different names, for example, severe gourd, karela, resin pear, or Ampalaya tea. Bitter melon is mainly connected to honeydew melon and cantaloupe and is consumed by people in India and Asia as vegetables. Primary phytochemical constituents of bitter melon that have been stated hypoglycemic functions are named charantin mainly cucurbitane-type triterpenoids (a steroidal glycoside that is an equivalent blend of both stigmasterol glucoside and the β-sitosterol glucoside) mainly cucurbitane-type triterpenoids, karaviloside IX, momordicoside S and its aglycones

momordicosides A, B, Q, R, and T, and further also polypeptide-p, vicine, and the protein named momordin which inactivates ribosomes. The seed and fruit of bitter melon plants have hypoglycemic functions (Shane-McWhorter, 2009).There are various mechanism of action of extracts of bitter melon and from several study it was stated that bitter melon can block the glucose absorption in intestine (Grover and Yadav, 2004; Chaturvedi, 2012), it also can suppress main glucogenic enzymes (Shibib et al., 1993), reduce also hepatic gluconeogenesis (Tsai et al., 2012), (Farzaei, Rahimi, Farzaei, & Abdollahi, 2015).

c. Cinnamon (*Cinnamomum cassia*):

Cinnamomum (cinnamon) is a class of the Lauraceae family. Until this point, around 250 types of cinnamon have been recognized. There are two noteworthy kinds of cinnamon, including Cinnamomum verum, or genuine cinnamon, and Cinnamomum cassia, otherwise called Cinnamomum aromaticum. The cassia structure is utilized for diabetes. Cinnamon originates from an evergreen tree that develops in tropical atmospheres; the bark is evacuated in short lengths and dried (Shane-McWhorter, 2009). Several preclinical and clinical examinations have shown that concentrates of cinnamon species can have antidiabetic exercises, and have researched their mechanism of activity (Ukamaka, Roseline, Aderemi, Modupeola, & Ayo, 2018).The procyanidin oligomers are believed to be in charge of the antidiabetic functions of cinnamon. The system behind the antidiabetic activities of cinnamon species isnot completely been understand till now. Diverse hypoglycemic impacts have been accounted for various cinnamon species (Ota and Ulrih, 2017).

d. Fenugreek (*Trigonella foenum-graecum*):

Fenugreek is an individual from the Leguminosae or Fabaceae family and develops well in India, Egypt, and different pieces of the Middle East. Their leaves are taken by people as a vegetable. It is utilized mainly as a cooking spice and also seasoning specialist. In diabetes,

the part utilized therapeutically is the seed (Shane-McWhorter, 2009). The bioactive compounds with stated hypoglycemic functions that have been gone through several studies are diosgenin (3b-hydroxy-5-spirostene), 4-hydroxyisoleucine, along with dietary fiber division of seeds which is soluble (Fuller and Stephens, 2015). Diosgenin in fenugreek is a noteworthy aglycone of saponin, and the detailed hypoglycemic systems of its activity incorporate reestablishment of pancreatic β-cells and enhanced secretion of insulin (Ota and Ulrih, 2017).

e. Neem (*Azadirachta indica)*:

This plants hydroalcoholic extracts represented anti-diabetic effects in the rats which is streptozotocin treated and the reason it increase the uptake of glucose and storage of glycogen isolated rat hemidiaphragm (Modak et al., 2007).

f. Bengal Quince, Bel or Bilva (Aegle marmelos):

This plant aqueous leaves extract administration has improved digestion besides it reduces in alloxanized rats their level of blood glucose and urea, level of serum cholesterol as compared to control. Moreover this extract restrained the high rise in glucose level at 1 hour in the test oral glucose tolerance (Modak et al., 2007).

h. Ginger (*Zingiber officinale Roscoe) :*

It is mainly member of Zingiberaceae family. Their rhizome part is mostly use as rhizome throughout the world. It is used as herbal medicine for treating disease like cancer, rheumatism, toothache, digestive health, along with diabetes (Park and Pezzuto, 2002; Ali et al., 2008). Component of ginger like gingerols, shogaols, paradols, and zingiberene has anti-oxadative functions, along with glucose and lipid reducing functions as well as also has immunomodulatory, anti-inflammatory, antiapoptosis functions (Ota & Ulrih, 2017).

i. Nopal (Opuntia spp.):

This is also called prickly pear cactus. They mainly produce fruits which are nutritious and also formed young edible stem pad called cladodes which is mainly used in the medicine for decades. The blended shake of cladodes is utilized in treatment of diabetes.(Ota & Ulrih, 2017).

j. Black Seed *(Nigella sativa)*:

Black seed perform in regulating insulin like cumin seed and black seed is another variation of cumin. It is a member of Ranunculaceae family. They have bitter taste, and contain various chemicals than cumin seed in it such as flavonoids, unsaturated fatty acids, nigellone, thymoquinone, p-cymene and carvone etc. (Choudhury et al., 2018)

1.3 Literature review

Many other plants have anti-diabetic activity and they have been experimented in laboratory for evidence of their anti-diabetic activity by different groups (Choudhury et al., 2018; Modak et al., 2007; Ota & Ulrih, 2017).

Table 1: Medicinal plants with anti-diabetic activity

Botanical plants	Part used	Type of extract	Cases	Animal model	Result
1.Afzelia Africa	Stem bark	Aqueous extract	STZ-induced diabetes	Wistar rats	After taking this blood glucose concentration was decreased in a dose-dependent manner with the dose 200mg per kg

					body weight had given the best effect or result
2.*Urtica dioica*	Leaf	Hydroalcoholic extract	Fructose-induced insulin resistance	Wistar rats	The amount of glucose level in blood FIRI in hyperglycemic rats was decreased in dose dependent manner and the best result had been found at the dose 200 mg per kg body weight per day. With this plasma insulin amount was decreased in treatment group.
3.*Chloroxylon swietenia*	Bark	Methanolic and aqueous extract	STZ-induced diabetes	Male albino Wistar rats	Diabetic rats in treatment group showed moderate reduction in blood glucose and glycosylated hemoglobin levels, in addition, plasma insulin were elevated. The outcomes of methanolic extract were comparable to glibenclamide.

4.*Forsythia suspensa*	Fruit	Ethyl acetate fraction of methanol extract	STZ-induced diabetes	Male Kunming mice	Blood glucose was significantly decreased; insulin secretion and glucose tolerance were significantly increased.
5.*Anacardium occidentale*	Leaf	Ethanol extract	STZ-induced diabetes	Female albino Wistar mice	Blood glucose was decreased 147.67 ± 6.09 mg dL^{-1} to 123.83 ± 2.87 mg dL^{-1} after 30 days treatment with plant extract.
6.*Symplocos cochinchinesis*	Bark	Ethanol extract	High fructose and saturated fat induced insulin resistance	Male albino Sprague Dawley rats	Blood glucose was significantly reduced at 20 days
7. *Pleurotus ostreatus*	Bark	Aqueous extract	High fat diet and STZ-induced	Male Wistar rats	Treatment group showed significant reduction in fasting blood glucose level,

			diabetes		FINS and HOM-IR and increase in ISI and HOM- b in a dose-dependent manner.
8.Helicterus angustifolia	Root	Ethanol extract	STZ-induced diabetes	Sprague Dawley rats	The blood glucose, plasma insulin level and HOMA-IR were significantly reduced in treatment group
9.Uvaria chamae	Root	Hydroethanolic extract	STZ-induced diabetes	Albino rats	The treatment group showed significant blood glucose reduction with formation of regenerated islet of Langerhans shown in photomicrograph of pancreas.
10.Coccinia grandis	Leaf	Ethanolic extract	STZ-induced diabetes	Wistar rats	Significant reduction in plasma glucose level and increase in serum insulin level in a dose-dependent manner.

1.4 Advantages of Herbal Medicine in Diabetes

We cannot expect treatment of diabetes without any untoward or adverse effects and there are obvious side-effects of conventional diabetes treatments. Medical practioners still continuing on research of decreasing the adverse effects of anti-diabetic treatment. People from their consciousness are drives towards using herbal medicines. Herbal medicines are the mixture of various herbal products supplied by doctor to patients and other are the herbal remedies which are frequently used by the patients by self-medication. Herbal medicines are plant-derived substances. We get to know 800 medicinal plants are mainly used for preventing diabetes mellitus in according to world ethnobotanical. In addition, there are 450 medicinal plants which have anti-diabetic property and from there only 109 medicinal plants have showed their complete mechanism of action. From various study we got to know doctor or older people had been used herbal products in ancient time for controlling different disease for examples heart diseases, cancer and also diabetes. Herbal products contain various active constituents which have multiple targets in our body with various mechanism of action and can cure or control multiple diseases with diabetes. Normally, herbal medicines have various benefits in the treatment of diabetes.

a. They can be bought without prescription, are can be used for treating disease which are life-threating. The formulation of herbal drugs contained natural herbs, extracts of vegetable sand fruits which have been used for controlling or preventing various disorders with less side- effects while conventional or synthetic drugs are prepared synthetically in laboratories with more adverse effects. The anti-diabetic synthetic drugs cause many adverse effects like sickness, vomiting, dysentery, alcohol flush, migraine, swelling, malignant anaemia and faintness. Herbal formulation are choose over conventional drugs for less side-effects in diabetes treatment (Verma et al., 2018).

b. Herbal medicines are also used when the synthetic drugs of diabetes become resistant or ineffective in controlling it.

c. In comparison to synthetic drugs herbal drugs cost is lower. Patients who cannot afford of buying chemical drugs depends on herbal medicines and remedies, which are basically abundant in nature, eco-friendly. In addition, they are all made with natural products (Verma et al., 2018).

d. Many diabetic patients cannot comply with treatment of oral anti-diabetic drugs and insulin which are mainly most preferred in controlling diabetes and this non- adherence is the reason which has been demonstrated from several studies for the ineffective diabetes management.

e. The positive interactions in between drugs and herbs can increase the efficiency or potency of anti-diabetic agents by synergistic or additive mechanism of actions (Verma et al., 2018).

1.5 Reasons of Using Herbal Medicines by Diabetes Patients

Diabetes is a life-long disease which lowers the quality of life, increases both the mortality and morbidity and is not curable. In a aim of controlling this disease mostly preferred way are bringing changes in life-style, using oral anti-hyperglycaemic agents and insulin treatment (Bailey, Clifford J. Day, 1989).However, many diabetic individuals have substantial difficulty complying with these treatments. Many studies have demonstrated that diabetic individuals are unable to adequately comply with the medical treatments prescribed by physicians (Kasole, Martin, & Kimiywe, 2019). This problem with treatment noncompliance may be the result of factors such as the lack of a definitive treatment for diabetes, the need for lifelong treatment, the occurrence of acute/chronic complications, and the individual's inability to make behavioural changes based on the healthcare education they receive. Although insulin therapy is considered to be the corner stone in managing diabetes treating diabetes remained as a challenge requiring considerable commitment to a life-long regimen

imposed by the disease. Patients with diabetes may prefer to use herbal remedies over modern medicine for a number of reasons including; dissatisfaction with the conventional treatment, treatment related adverse effects and the perceived suitability of herbal remedies with patients' values and spiritual beliefs (Mekuria et al., 2018).The side effects of drugs used in current conventional treatment methods and the belief that natural products are always harmless and effective have led to the popularity of herbal medicine (Gupta et al., 2017).

1.6 Challenges of Herbal Medicines

Herbal remedies have various limitations though they have high medicinal value.

1. Patients taking herbal medicine don't have consistency to this treatment, they are not taking it proper way, maintaining the time schedule which is required for them. Even they don't know the specific amount required for particular disease like diabetes or others. There is a specific therapeutic amount which is necessary for fighting any disease in our body but majority of people taking herbal medicine isn't conscious of it (Verma et al., 2018).

2. The major hindrance of combining herbal medicine in modern medical practice is it has not sufficient clinical data for proving its potency and efficacy and also finding out their toxicities (Kaur, Kaur, & Mahajan, n.d.). Herbal drugs is a mixture of various active ingredients in it, and taking them with other conventional medicine can cause overdosing of the particular drug, or adulterated herbal drugs are there containing conventional drugs in it for increasing efficacy to patient, which may cause various adverse effects on body, may also progress the disease state in our body, for overcoming this proper research should be done on herbal medicines, their quality should be checked before entering markets, or those taking directly the herbal drugs in self-medication should be aware of which ingredients it contains. Clinical research should be increased for herbal medicine in order to do bioassays for

developing biological standardization. Moreover, sufficient clinical trial should be done in animal model following human volunteer for evaluating the toxicities and safety (Modak et al., 2007).

3. Herbal medicine contain various active ingredients so to it is significant to find out the active ingredients individually. Also, there is no standard producing methods of herbal drugs and separation of various active ingredients should be done so the main challenge is how to prepare these herbal drugs for achieving the acceptance and market like other conventional drugs. The solution of this is conducting more research on herbal medicine and classifying them according to their active ingredients. Further study should be increased on herbal medicine for evidence of their potentials and also study on herbal remedies (Verma et al., 2018)

1.7 Purpose of this study

The purpose of this study is to analyse the use of herbal medicine by diabetic patients. Diabetes is a disease which is matter of great concern in present days and the number of patients from children to adult is rapidly increasing in huge ratio globally. Furthermore, it is a life-long and multifactorial disease so people are chasing after controlling this disease as consequence, they are using herbal medicine along with conventional anti-diabetic drugs. From several studies, there is evidence of adulterated herbal products. Herbal products which are taken by diabetic patients may contain synthetic anti-diabetic drugs in their formulation for increasing efficacy, as a result, patients may get affected by overdosing of that particular active ingredients, may face severe hypoglycaemic effect and also others adverse effect. This study will help to know about the percentage of diabetic patients actually are aware of adulterated herbal products or not. Through this study we can examine about what percentage people are using herbal medicine. It will help to know about the effectiveness of herbal

medicines from patient's experiences and provide as evidence to health professional, research scientist for manufacturing herbal medicine. Moreover, it will assist to develop standardized method of manufacturing herbal medicine and evaluating their toxicities and safety ratio.

Chapter 2

Methodologies

The participants or sample size was 100 for this study. The participants of this survey were selected randomly from different location of Dhaka city of Bangladesh. They were taken randomly from friends, families and one of the largest Diabetes specialized hospital in Bangladesh named BIRDEM Hospital (Bangladesh Institute of Research and Rehabilitation in Diabetes). The majority of the participants had been taken from this hospital and the other rest are from relatives, friends. This survey took 2 months (June 2019 to July 2019) to complete for collecting data from patients. At first, a group of 10 participants were selected for pre-testing. Interview was taken from the participants through the questionnaire after they had filled the consent form. These participants are informed about the aim of this study properly so that they might give the answers appropriately. These 10 participant's answers are cross checked by the supervisor of this project. During evaluating, unnecessary questions had been deleted and relevant questions were added for making the survey effective. After that, questionnaire was finalized and it was decided to continue this study for research project further. This study involved 100 participants who are diabetic patients. Data had been collected from 100 patients and were categorized in Microsoft Excel 2016. Result was calculated by using Microsoft Excel 2016.

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Chapter 3

Result

The demographic detailed of the participants in this study is represented in figures 12, 13, 14, 15. This survey has been conducted for 2 months and by the end of it 100 diabetic patients have been responded to this survey from different locations of Dhaka city. In this survey 63% were male and 27% were female participant. Among them 78% patients were between the age (41-70), 15% were between (71-90) years and the rest were between (1-40) years. The survey was conducted on different classes of people among whom majority of participants 35% are service holder 25% are housewives, 28% are retired, 5% are student and 17% are businessman. The survey participants' educational level was 30 % of them had educational level below under graduation, 43% were under graduated and 27% are doing higher study.
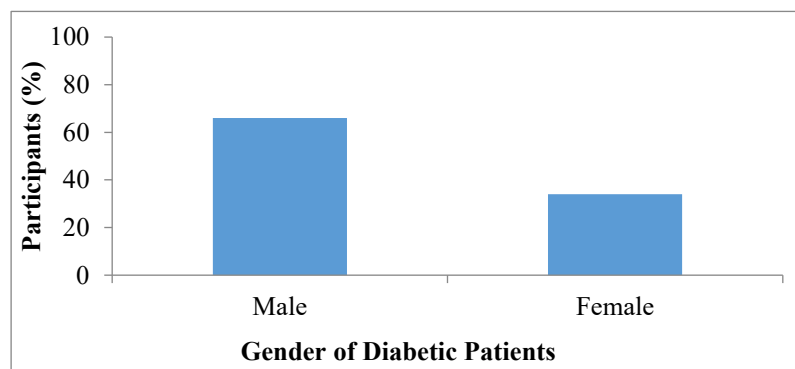

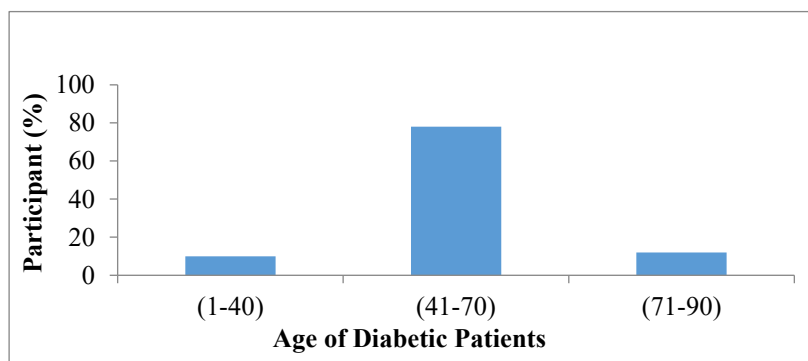*Figure 12: Gender of Diabetic Patients*
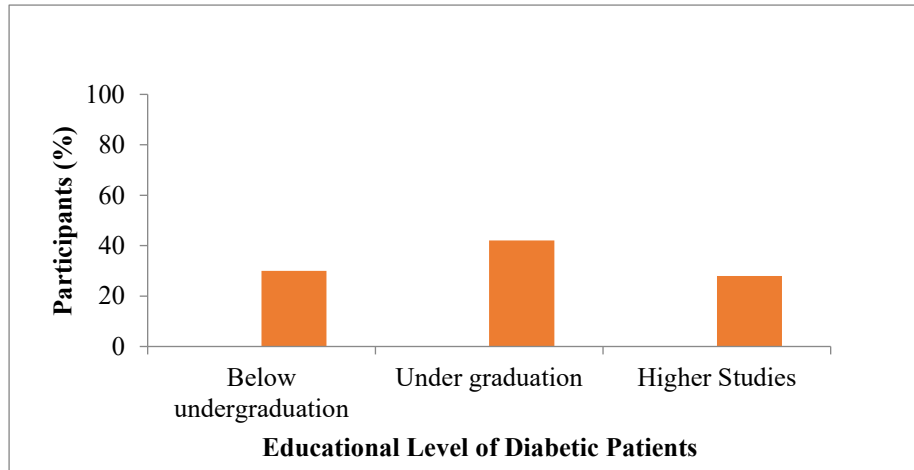

Figure 13: Age of Diabetic Patients

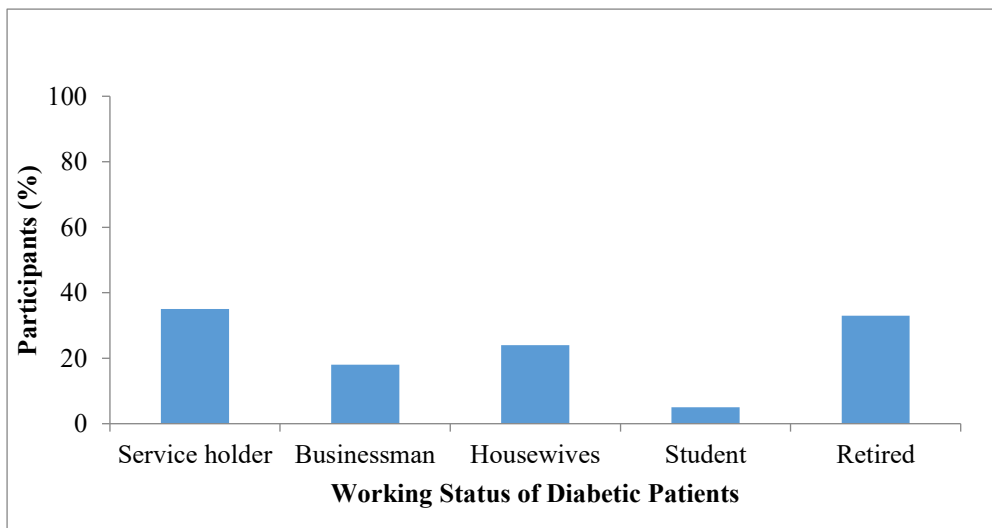*Figure 14: Educational Level of Patients*

Figure 15: Working Status of Diabetic Patients

In the figures 16, 17, 18, 19, patients' diabetes types, duration, type of anti-diabetic therapy and family history are represented. The graph in figure 16 shows, 85% of patients has type 2 diabetes which is the majority and only 15% patients have type 1 diabetes. The graph in figure 17, is illustrating duration of diabetes patients are having 45% patients are having diabetes for (1-5) years, 31% are having for (11years and above) and 24% are having diabetes for (6-10) years. Graph in figure 19, is showing 72% patient are using oral anti-diabetic drugs for controlling diabetes, and 28% patients are using both insulin and oral anti-diabetics drugs together. Figure 18, is representing 56% patients have family history of diabetes. Their

parents, grandparents and siblings etc. have diabetes. On the other hand, 25% of them have no family history of diabetes.
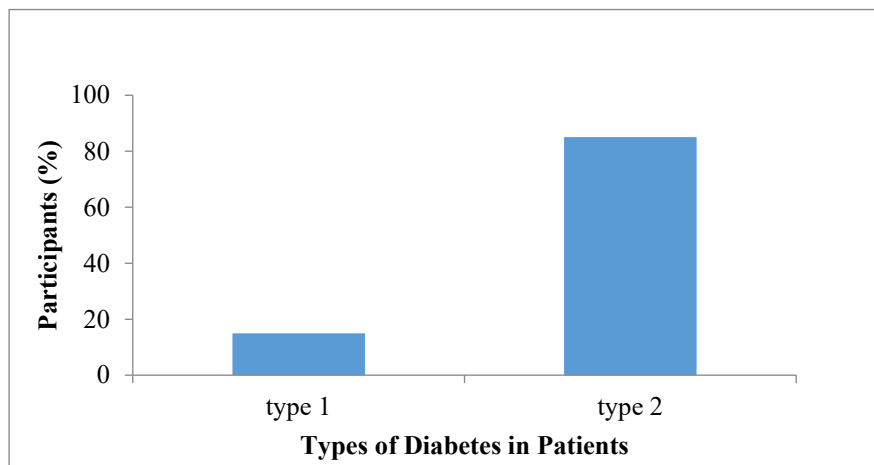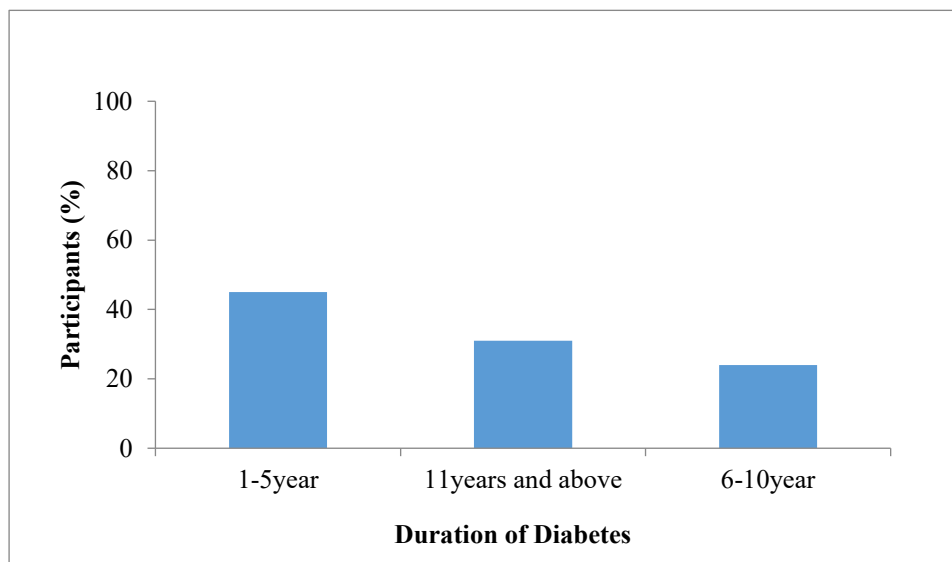

Figure 16: Types of Diabetes in Patients
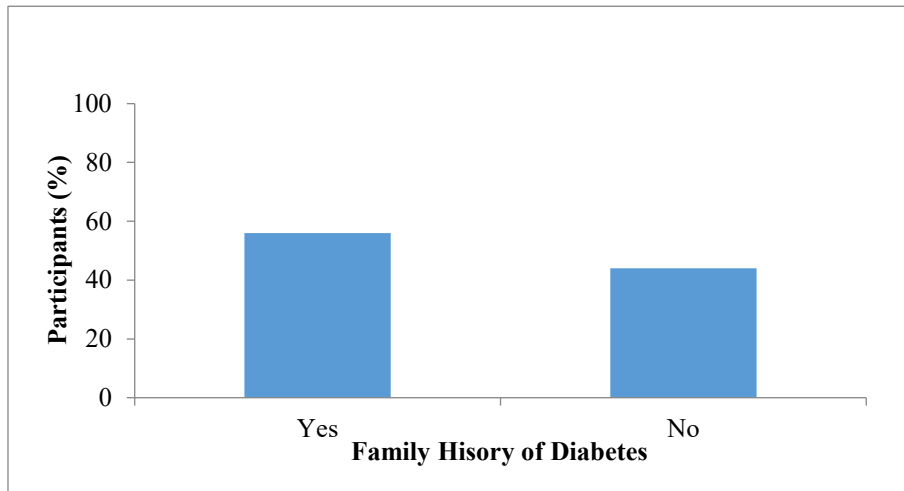

Figure 17: Duration of Diabetes
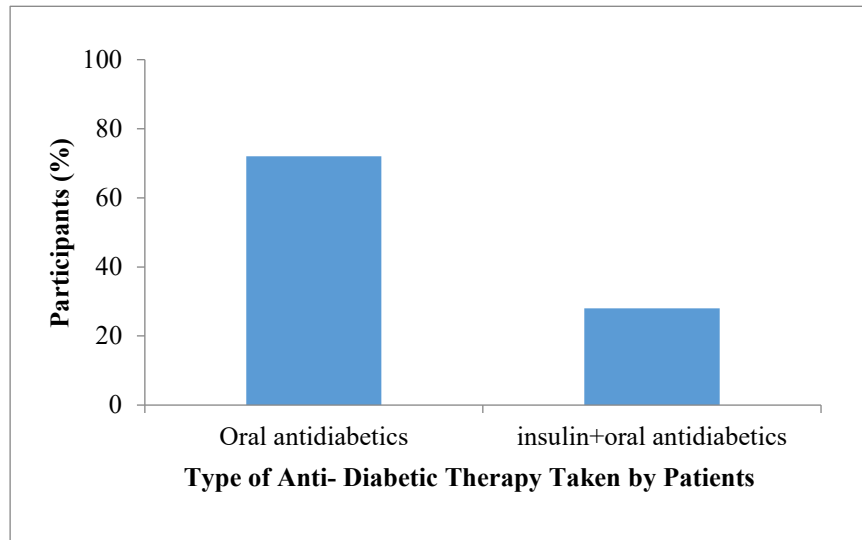
Figure 18: Family History of Diabetes

Figure 19: Type of Anti-Diabetic Therapy Taken by Patients

Graph in the 20, 21,22, 23 are representing the percentage of user of herbal medicine, primary reason of using this, the time of starting to use herbal medicine and whether patients inform to their doctors and pharmacist or not. Figure 20 shows, among 100 patients 27% patients use herbal medicine for controlling diabetes and 73% of them don't use any kind of herbal medicines. In figure 21, we can see it is showing 22% of diabetic patients are mainly using herbal medicines after the diagnosis of their disease where only 5% of them use it before diagnosis for preventing diabetes so that it may not occur in future. In figure 22, 20% are using herbal medicine for lowering their blood sugar level, 7% are using for controlling

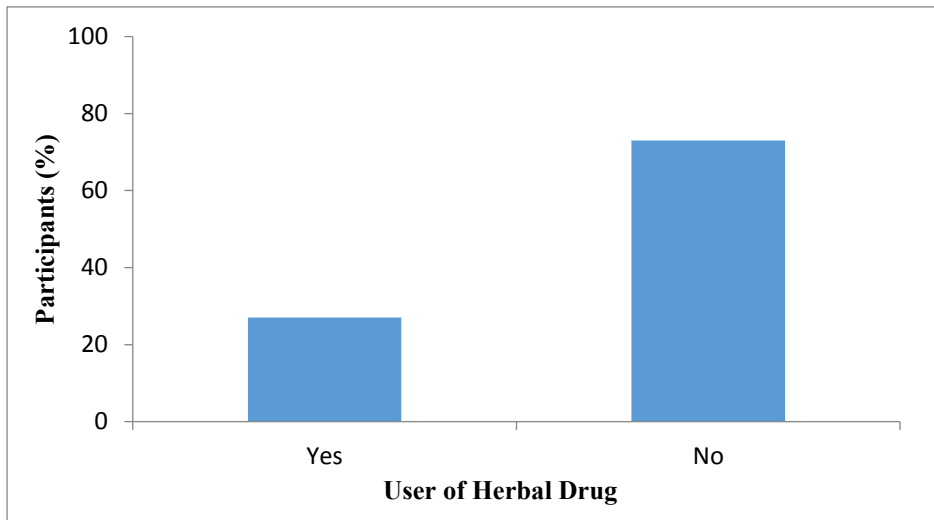diabetic other complications. In figure 23, graph shows 10% patients inform to doctor and 17% do not inform.
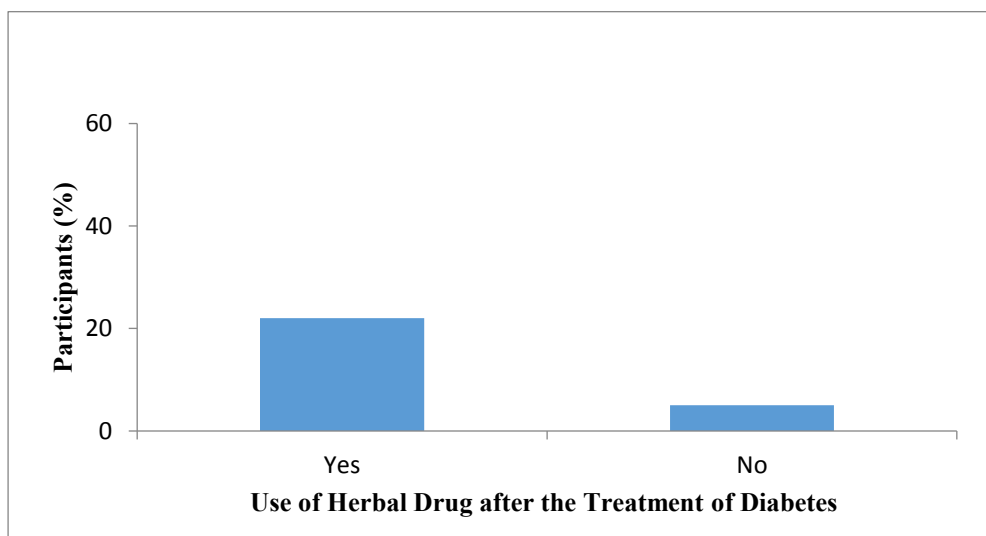

Figure 20: User of Herbal Drug

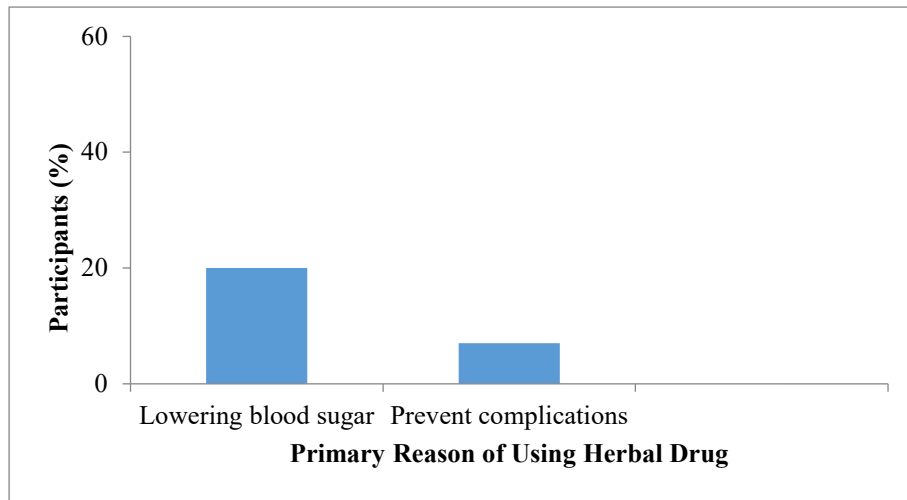*Figure 21: Use of Herbal Drug after the Treatment of Diabetes*

Figure 22: Primary Reason of Using Herbal Drug
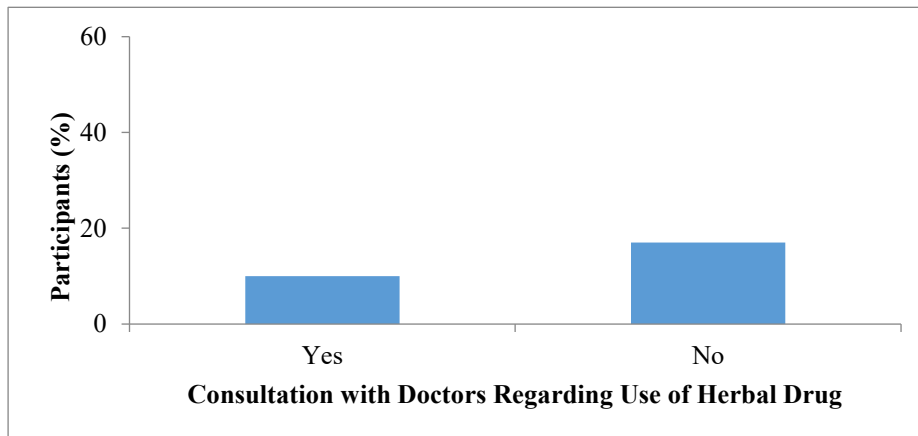
Figure 23: Consultation with Doctors Regarding Use of Herbal Drug

Figurers 24, 25, 26, 27, 28 illustrates the information sources, buying source, types of herbal medicine, cost, and time schedule of taking herbal medicines by patients. Figure 24 shows, 15% relatives, 4% internet, 6% media, 2% health professional etc. are information sources of herbal medicine to patients. Graph in figure 25, 12% of patient buy herbal medicine from herbal and spice seller, then 8% is plant collecting, 3% patients order from internet and 4% buy from other sources. 10% patient take plants and grass, 5% take food, 5% tablets, 2% take herbal teas as type of herbal medicine which is shown in figure 26. Towards, 15% patients cost of herbal medicine is average, 7% is low and 5% told high which is shown in figure 27. Among the patients 22 % take herbal medicine once or twice a day, 21% take once in 2-3

day,10% take once in a week,4% take once in 15 days and no one take in once in a month shown in figure 28.
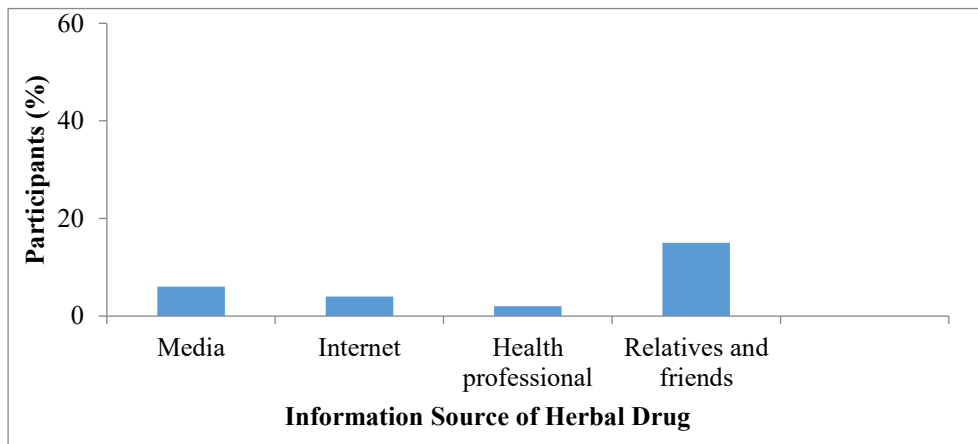
Figure 24: Information Source of Herbal drug
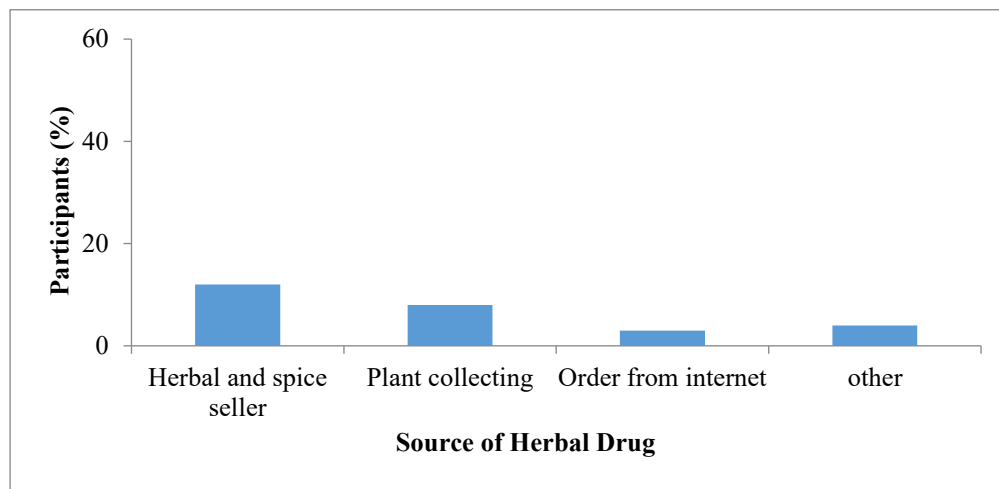
Figure 25: Source of Herbal Drug
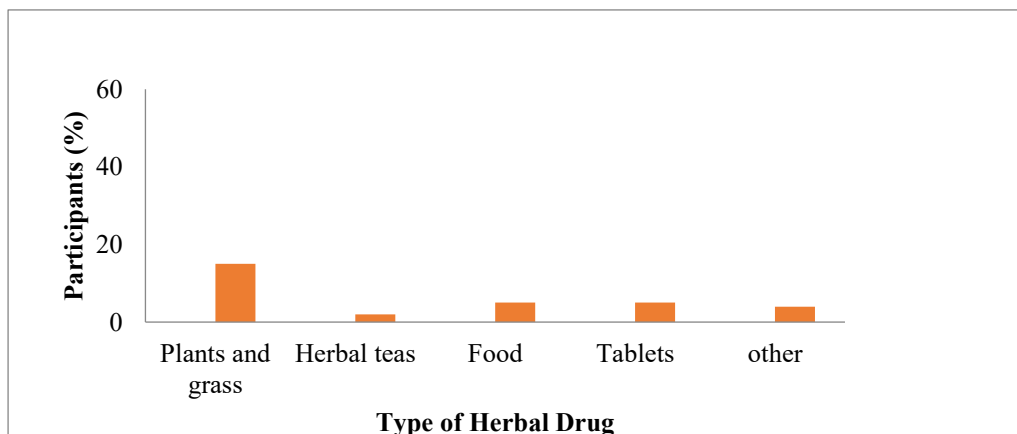
Figure 26: Type of Herbal Drug
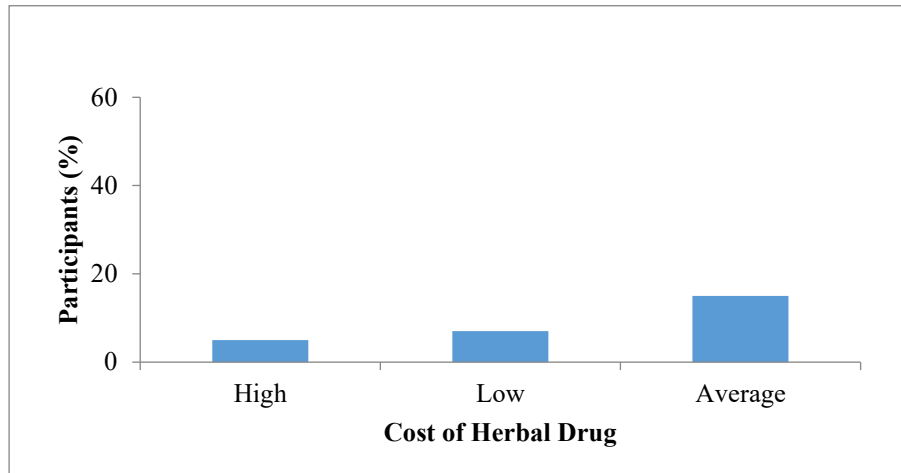
Figure 27: Cost of Herbal Drug
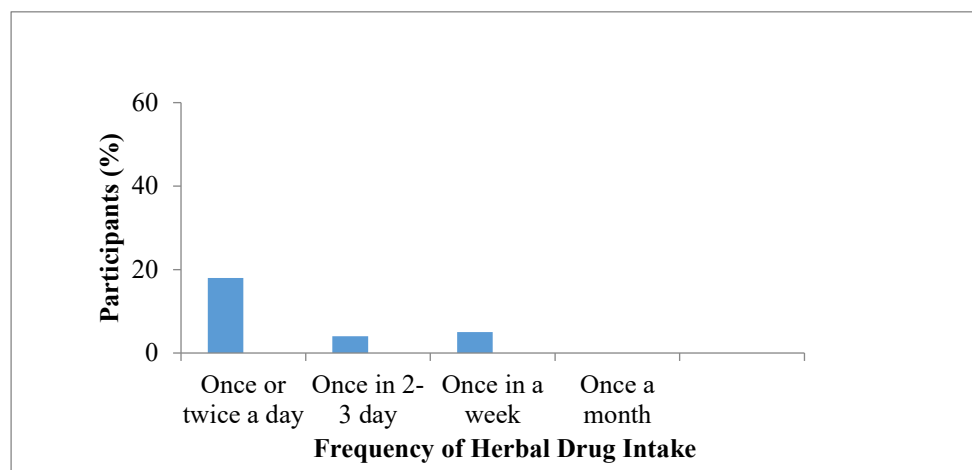
Figure 28: Frequency of Herbal Drug Intake

In the figures, 29, 30, 31, 32 satisfaction levels of patients with herbal medicine, side effects regarding herbal medicine are illustrated. In figure 29, the graph shows 19% patients are satisfied, 5% are dissatisfied, 7% told average and 14% are not sure. In figure 30, the graph shows, 10% have side-effects and 17% do not shows any side-effects. 20% face hypoglycemia and 7% do not face hypoglycemia which is shown in figure 31. Graph in figure 32 shows, 25% patients have no knowledge on adulterated herbal medicine and 2% of them have   knowledge on it which can cause severe adverse effects on them.
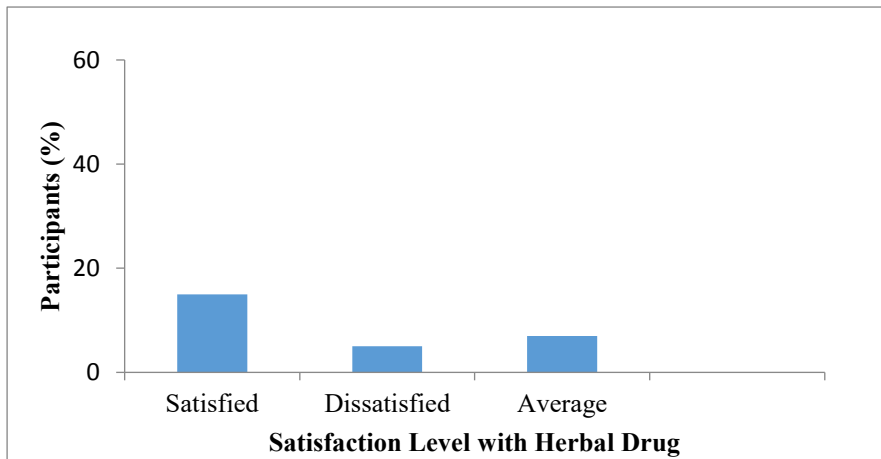
Figure 29: Satisfaction Level with Herbal Drug
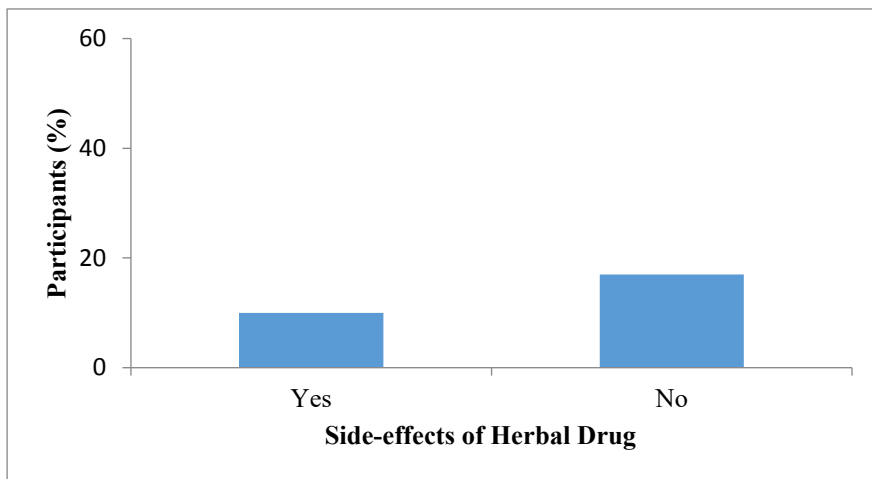
Figure 30: Side-effects of Herbal drug
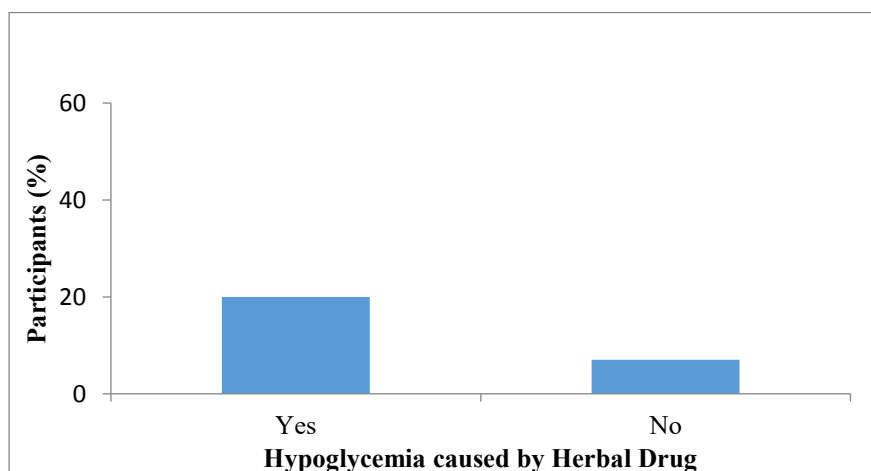
Figure 31: Hypoglycemia caused by Herbal Drug
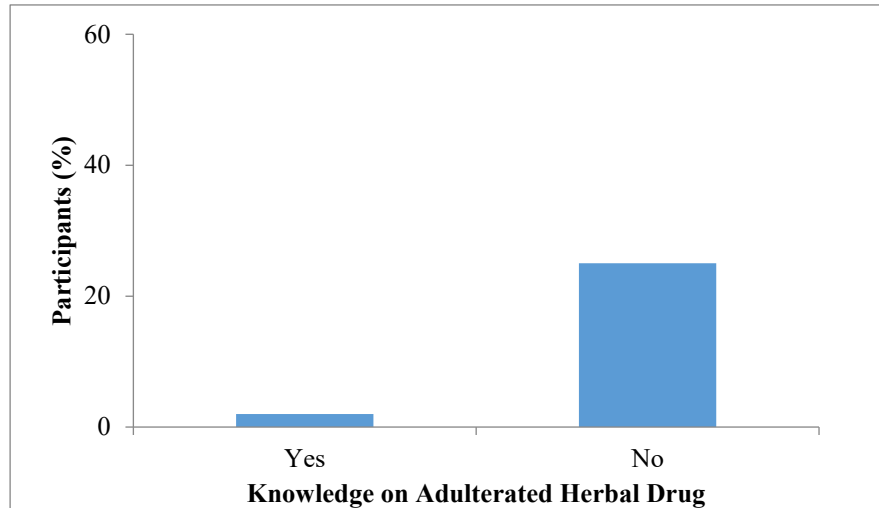
Figure 32: Knowledge on Adulterated Herbal Drug

Figures 33 and 34 represents patients with diabetic complications and other diseases. In figure 33, the graph shows 16% have retinopathy, 8% have nephropathy, 4% have cerebrovascular disease, 19% coronary heart disease, 59% have no complications. From figure 34, we can see 64% have other disease and 36% have no other diseases with diabetes.
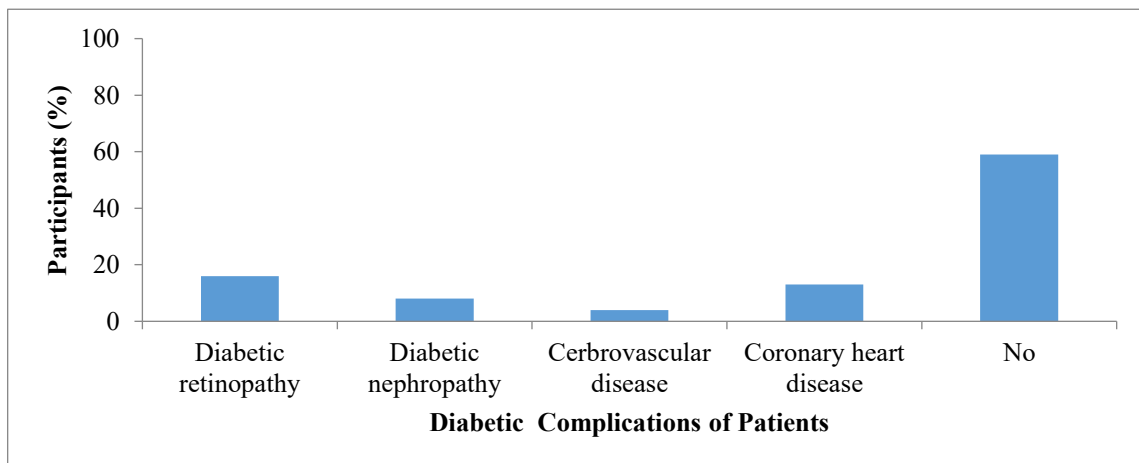
Figure 33: Diabetic Complications of Patients
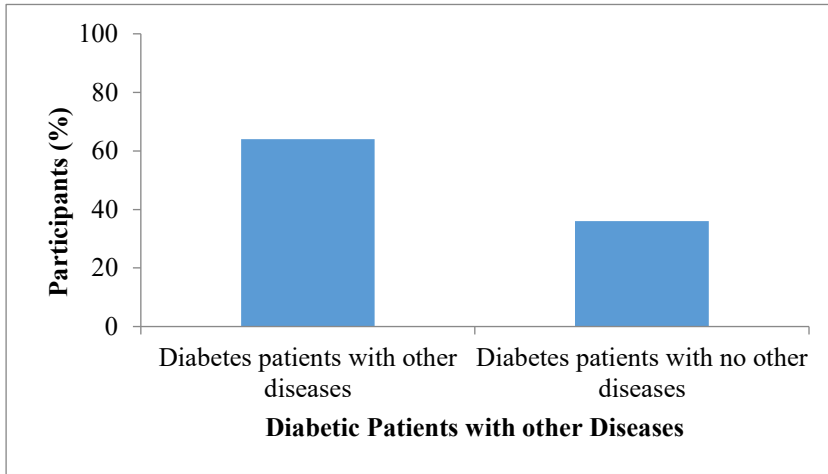
Figure 34: Diabetic Patients with other Diseases

Chapter 4

Discussion

This present study was conducted in Dhaka city of Bangladesh. The prevalence of diabetes is increasing in Bangladesh in both urban and rural areas in recent years. A recent study reported that majority of adults with type 2 diabetes in Bangladesh have uncontrolled diabetes with a high prevalence of risk factors attributing to early development of complications. Diabetes increases morbidity and mortality, impairs quality of life and thereby contributes to increased healthcare costs and burden in Bangladesh (Siddique, Islam, Banik, & Rawal, 2017). As it is a multifactorial and life-long disease people search for alternative way of controlling it and drive toward using herbal medicine. Herbal medicine usage is increasing in both developing and developed countries (Mekuria et al., 2018).

The current study was performed to gather information about herbal medicine usage in diabetic patients in Dhaka city. The sample size was 100. It is a pilot scale study. A questionnaire of 31 questions was developed and pretested. For pretesting, questionnaire was filled initially by 10 participants. These 10 participants' answers are cross checked by the Supervisor of this project. During evaluating, unnecessary questions had been deleted and relevant questions were added for making the survey effective. After that, it was decided to continue this study for research project further.

The rate of user of herbal medicine by diabetic patients is lower. But The rate is higher in other research study (Damnjanovic et al., 2015), (Lunyera et al., 2016), (Mekuria et al., 2018) which was 90% and 56.5%. The ratio is higher in other study because of resistant to conventional therapy, higher cost, cultural beliefs that herbal medicine has lesser side-effects. Herbal medicine is getting more attention in present decades of time because of its multiple targets like it can increase insulin secretion pancreas, inhibiting glucose absorption from

intestines, increasing glucose uptake by muscle and adipose tissues, inhibiting glucose production from hepatocytes etc. (Damnjanovic et al., 2015). Herbal medicine or herbal dietary supplements contain mixture of various active ingredients which can work for various targets or aim. But in this study it is low and the reason can be in our study herbal medicines still now do not get famous in our country like other country in India, Ethiopia, Palestine, people have more belief on conventional therapy rather than herbal and like to stick on that rather trying on other therapy. They are not still confident on using it.

From current study, we got to know higher rate of patients use combination type of anti-diabetic therapy, insulin with other oral anti-diabetic drugs. We found patients are using herbal medicines with conventional medicines concurrently. The similar result was found in previous study that from India 71% and Ethiopia half of the population uses herbal and prescription medicine concurrently (Damnjanovic et al., 2015).The reason can be they wanted to increase the anti-diabetic effect of their conventional medicine as because conventional medicines required more disciplined lifestyle, behavior, diet and that's why it drives them for herbal medicine. Moreover, patients used herbal medicine after the diagnosis of diabetes and very less amount uses it before diagnosis. The rate is consistent with the other study which is found 55% (Ali-Shtayeh, Jamous, & Jamous, 2012).

The primary reason of using herbal medicine is lowering blood glucose level in this study. Some of them used for preventing complication. Diabetes patient taking allopathic have a very poor control blood glucose level, patients are eager to anyhow not degrading the health condition more which is the reason, they are more prone to herbal for having good control over blood glucose. But in the study (Ali-Shtayeh et al., 2012) ,there 90% used herbal medicine for preventing complications of herbal plants. In current study, the rate of diabetes patients with family history is higher than with no family history. From the study,(Ali-Shtayeh et al., 2012), (Mekuria et al., 2018) where majority of patients had family history, we

can say family history is the largest cause of herbal medicine usage in diabetic patients. People stay aware before they had diabetes and for preventing and controlling it they started to take herbal medicine.

From the current study, the male participant's rate was higher than female but the use of herbal medicine was comparatively more in female. The rate was higher in other study,58.5% female and 45.5 % male (Alami, Aynaou, Alami, Hdidou, & Latrech, 2015). This might be because women are more attached in using herbal medicine and stay more at home than male, more conscious on self- medication by herbal product.

Among the patients, in current study higher educational level, working status have no influence over using herbal medicines. The rate of under graduation in using herbal medicine is higher than higher studies or below graduation. But the rate is higher 50% in the study (Mekuria et al., 2018), (Alami et al., 2015). The reason of educational levels do not influence patients may be higher educational status choose to explore more therapies after being confirmed with the effects and safety of therapy, they do not want to take the risk and starts any further therapy with conventional drugs. Patients with lower education may use it without even knowing the mechanisms or efficacy of it.

In the current study, relatives, friends were the main source of information to the patients and after that internet. The least used information sources were media and health professional. The rate is similar with the study conducted in Oriental Morocco (Alami et al., 2015). This proved patient's dependency on their closed ones about decision-making in health issues. This should create awareness to doctor to take care about their patients' belief and must include patient's family member in management of diabetes. The study in Ethiopia and India also represented very low percentage, 5% for media instead their patients were influenced by pharmacist and doctor (Damnjanovic et al., 2015). But in the study (Damnjanovic et al.,

2015), media provides significant role as information source which can cause adverse effects to patients as they are taking herbal medicine without confirming their efficiency.

The current study represented a higher rate of patients not informing their doctor or any pharmacist about herbal medicine and the ratio is higher in the other study (Ali-Shtayeh et al., 2012; Mekuria et al., 2018), (Prod, Msanda, & Boubaker, 2017) which was 86% and 68%.The reason can be negative responses from doctor as doctor does not give importance on herbal treatment than conventional therapy. Patients and doctor poor communication may create untoward effect in glycaemic control, many herbal medicine may contain toxic substances which can react with conventional diabetic drugs or other drugs and foods in body or may not be suitable for particular patients, this create risks for patient heath and can progress other complications. Patients should consult with doctor and pharmacist both for better advice.

In the present study, we can see the rate of patients taking herbal medicine is low but more amount of patients are taking directly herbal plant for controlling diabetes, traditional herbs which were listed contain various pharmacologically active compounds which give therapeutic effects in body. The most used herbs which are taken by higher amounts of patients regularly includes, bitter melon (*Momordica charantia*), fenugreek (*Trigonella foenum graecum*), nopal (*Opuntia* spp.), Russian tarragon (*Artemisia dracunculus*), cinnamon (*Cinnamomum cassia*), and garlic (*Allium sativum*), Aloe (*Aloe vera L*), Neem (*Azadirachta indica),* Ginger *(Zingiber officinale Roscoe),* Bengal Quince, Bel or Bilva (*Aegle marmelos*), Garlic (Allium sativum), *Black Seed (Nigella sativa*).The use of these kinds of herbs was also higher in other studies (Mekuria et al., 2018), (Alami et al., 2015). They have well defined hypoglycemic effects directly or indirectly effecting glucose breakdown in body. From other study, we got to know bitter melon when taken with metformin will decrease the serum glucose level. Ginger when taken with glibenclamide combinely will decrease more

glucose level than glibenclamide alone (Gupta et al., 2017). Fenugreek when given with metformin will have significant lower plasma level. Tulsi *(Ocimum sanctum)* when the extract of their leaves are taken glucose level goes down in normal and alloxan induced diabetic rats both. Mango (Mangifera indica) leaves extract have decrease the blood glucose level when administered with glucose or administered 60 minutes before to the streptozotocin induced diabetic rats etc. (Modak et al., 2007). These all had been experimented in other studies. The higher rate of patients used herbal plants and grass, following foods and spices comparing with herbal teas and tablets. The higher rate of patients had taken them once or twice a day or once in a week.

The rate of patients responded for side-effects of herbal medicine was lower. Side-effects like tinnitus, dizziness, vomiting, nausea, malaise, allergy, gastrointestinal problem like diarrhea, constipation etc. can appeared in patient's body as herbs and spices contain various active ingredients in it which can exposes various adverse effects after entering in body but maybe patients are not actually aware these side-effects are because of taking herbal medicine. Many of identified herbs have adverse effects found in other study (Mekuria et al., 2018). Aloe vera which lowers the blood glucose level, aloe juice if it is taken with glibenclamide anti-diabetic drug decrease blood glucose level significantly within 2 weeks (Bunyapraphatsara, Yongchaiyudha, & Chokechaijaroenporn, 1996) but can cause acute hepato-renal toxicity if it is taken in higher amounts. This study has a lower side-effects but it had reported of having side-effects like hypoglycemia and similarly higher in the study (Ali-Shtayeh et al., 2012).The current study also reported for higher rate of hypoglycemia .The reason may be patients taking herbal supplements with conventional drugs can have pharmacokinetic interaction, overdosing which causes hypoglycemia. Patients must disclose their use of herbs to doctor for avoiding multiple side-effects regarding this.

From the current study we got to know that very low amount of patients had knowledge on adulterated herbal drugs. Several herbal medicine are in drug market which contained active ingredients of conventional drug in it, or some unknown ingredients which are not approved to be used in formulation but still using by several companies for increasing their efficacy, which create overdosing and create several adverse effects, create more complications, deteriorate the disease condition more. This case was found in other study (Steyn et al., 2018), where a patient was having adulterated herbal drugs from market and her renal disease and other turned severe because of this fake medicine. This mainly occurs of having no knowledge about it, and patients not sharing appropriate information of medication they are taking to their health professional. Awareness must be created among patients about adulterated herbal medicine from doctor and whole medical system.

In the current study, patients had higher rate of diabetic complications like diabetic retinopathy, diabetic nephropathy, coronary heart disease etc. and also they had other diseases like hypertension, hypercholesteremic, gastrointestinal disease, skin disease, psychiatric disease, etc. These diseases and complications are also strong influencer of using herbal medicine along with prescription drugs. The similar result was found in other study (Lunyera et al., 2016), (Damnjanovic et al., 2015).

From this study we got to know higher rate of patients were satisfied with the effects following the rate of being not sure actually about the herbal medicine. The consistent of rate 42% was found in other study (Mekuria et al., 2018). The cost of herbal supplements were average to higher rate of patients'.

Limitation of the study:

There is some limitation of this study. As this is a pilot study, we take fewer participants to see the effect and will work for larger project on this topic. This study reveals the 100 participants result not representing whole population scenario of diabetes patients using herbal medicine. Furthermore, the beneficial and adverse effects of herbal medicine are not scientifically assessed.

Chapter 5

Conclusion

Diabetes is a life-long disease and causes of various diseases in body as a result people are conscious of controlling diabetes and are chasing for using herbal medicines. As diabetes is increasing the uses of herbal medicines are also increasing in developed and developing countries. Herbal medicines are mostly available in the nature, they are cost-effective substances with lesser side-effects comparing with the synthetic drugs and have obviously effective controlling ability of diabetes which are the reasons for attracting patients towards use of herbal medicine in diabetes disease. The usage of herbal medicine by patients taking insulin and anti-diabetic drugs is lower in this current study is lower and those patients who are taking are disclosing their usage of herbal medicine in a very lower percentage to Doctor. Herbal medicines contain various active ingredients and can have multiple targets through which pharmacokinetic interaction can occurs and create several adverse effects. Moreover, several adulterations are present in herbal medicine which will definitely have severe impacts on patients' health. Health professional must give more attention of getting information about patient' beliefs about herbal medicine, their healthcare behaviors for alternative medicine. They should ask patients about which herbal preparation they are taking with their conventional drugs, and discuss with them with the toxicities and efficiency. Furthermore, doctor should also consult with patients' family members regarding herbal medicine use as the main influencer of using herbal medicine is relatives as a result they may help them in management of diabetes disease using herbal medicine appropriately. There are many herbs or herbal medicine identified in various studies used in diabetic disorder which do not have enough medical information, scientific proves or have not gone through sufficient clinical trials for ensuring their efficacies and toxicities. Patients are not aware of this scenario,

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although they are satisfied with effects of herbal medicine but in the long run it may initiate ineffective diabetes management and adverse effects in their body. The knowledge in this field is still limited, more research in their clinical uses should be done for validating their uses in diabetic disorder. In addition, knowledge and awareness should also be increased among patients related to the use of herbal medicine in diabetes.

Chapter 6

Future Direction

Herbal medicine has been always preferred treatment option for controlling diabetes by the patients combinely with conventional treatment because of cultural belief, affordability, lesser side-effects. This present study was a pilot study, which will be considered for the further study and this study can be used as an evidence to other researchers, health professionals, drug manufacturers to do more research, clinical study on herbal medicine and for manufacturing herbal medicine with anti-diabetic activity in standardized way, particularly confirming their efficacy and toxicities before recommending to diabetic patients.

Reference

Adler, M. L. (1999). *CLINICAL REVIEW 102 Type 2 Diabetes Mellitus : Update on Diagnosis ,. 84*(4), 1165–1171.

Alami, Z., Aynaou, H., Alami, B., Hdidou, Y., & Latrech, H. (2015). Herbal medicines use among diabetic patients in Oriental Morocco. *Journal of Pharmacognosy and Phytotherapy*, *7*(2), 9–17. https://doi.org/10.5897/JPP2014.0338

Ali-Shtayeh, M. S., Jamous, R. M., & Jamous, R. M. (2012). Complementary and alternative medicine use amongst Palestinian diabetic patients. *Complementary Therapies in Clinical Practice*, *18*(1), 16–21. https://doi.org/10.1016/j.ctcp.2011.09.001

Article, R. (2012). *Type 2 Diabetes Mellitus: A Review of Current Trends*. *27*(4), 269–273.

Bailey, Clifford J. Day, C. (1989). Traditional Plant Medicines as.pdf. *Diabetes Care*, *12*(September), 553–564. https://doi.org/10.2337/diacare.12.8.553

Baynest, H. W. (2015). Classification, Pathophysiology, Diagnosis and Management of Diabetes Mellitus. *Journal of Diabetes & Metabolism*, *6*(5). https://doi.org/10.4172/2155-6156.1000541

Bunyapraphatsara, N., Yongchaiyudha, S., & Chokechaijaroenporn, O. (1996). *Antidiabetic activity of Aloe vera L . juice II . Clinical trial in diabetes mellitus patients in combination with glibenclamide*. *3*(3), 245–248. https://doi.org/10.1016/S0944-7113(96)80061-4

Chaudhury, A., & Mirza, W. (2017). *Clinical Review of Antidiabetic Drugs : Implications for Type 2 Diabetes Mellitus Management*. *8*(January). https://doi.org/10.3389/fendo.2017.00006

Choudhury, H., Pandey, M., Hua, C. K., Mun, C. S., Jing, J. K., Kong, L., … Kesharwani, P.

(2018). An update on natural compounds in the remedy of diabetes mellitus: A systematic review. *Journal of Traditional and Complementary Medicine*, *8*(3), 361–376. https://doi.org/10.1016/j.jtcme.2017.08.012

Damnjanovic, I., Kitic, D., Stefanovic, N., & Zlatkovic-guberinic, S. (2015). *Herbal self-medication use in patients with diabetes mellitus type 2*. 964–971. https://doi.org/10.3906/sag-1410-60

Diabetes and Intestinal Incretin Hormones: A New Therapeutic Paradigm. (n.d.). Retrieved October 9, 2019, from https://www.medscape.org/viewarticle/489180

Diabetes mellitus : The disease itself. (2017).

Dimeglio, L. A., Evans-molina, C., & Oram, R. A. (2018). Seminar Type 1 diabetes. *The Lancet*, *391*(10138), 2449–2462. https://doi.org/10.1016/S0140-6736(18)31320-5

Farzaei, M. H., Rahimi, R., Farzaei, F., & Abdollahi, M. (2015). ans net. *International Journal of Pharmacology*, *11*(7), 874–887. https://doi.org/10.3923/ijp.2015.874.887

Gupta, R. C., Chang, D., Nammi, S., Bensoussan, A., Bilinski, K., & Roufogalis, B. D. (2017). Interactions between antidiabetic drugs and herbs: An overview of mechanisms of action and clinical implications. *Diabetology and Metabolic Syndrome*, *9*(1), 1–12. https://doi.org/10.1186/s13098-017-0254-9

Hackett, B. E., & Jacques, N. (2009). *Type 2 diabetes pathophysiology and clinical features*. *1*(December), 475–478.

Kaku, K. (2010). *Pathophysiology of Type 2 Diabetes and*. *138*(1), 41–46.

Kasole, R., Martin, H. D., & Kimiywe, J. (2019). *Traditional Medicine and Its Role in the Management of Diabetes Mellitus : (Patients ' and Herbalists ' Perspectives)*. *2019*.

Kaur, J., Kaur, S., & Mahajan, A. (n.d.). *Herbal Medicines : Possible Risks and Benefits*. *141104*.

Kharroubi, A. T., & Darwish, H. M. (2015). *Diabetes mellitus : The epidemic of the century*. *6*(6), 850–867. https://doi.org/10.4239/wjd.v6.i6.850

Kooti, W., Farokhipour, M., Asadzadeh, Z., Ashtary-larky, D., Asadi-samani, M., Branch, A., & Plant, M. (2016). *Electronic Physician (ISSN : 2008-5842)*. (January), 1832–1842.

Lunyera, J., Wang, D., Maro, V., Karia, F., Boyd, D., Omolo, J., & Patel, U. D. (2016). Traditional medicine practices among community members with diabetes mellitus in Northern Tanzania : an ethnomedical survey. *BMC Complementary and Alternative Medicine*. https://doi.org/10.1186/s12906-016-1262-2

Matthaei, S., Bierwirth, R., Fritsche, A., Gallwitz, B., Kellerer, M., Kunt, T., … Committee, G. (2009). *Medical Antihyperglycaemic Treatment of Type 2 Diabetes Mellitus * Update of the evidence-based guideline of the German Diabetes Association*. 522–557. https://doi.org/10.1055/s-0029-1239559

Me, C., Hattersley, A., Definition, D. K. C., Craig, M. E., & Hattersley, A. (2009). *ISPAD Clinical Practice Consensus Guidelines 2009 Compendium Definition , epidemiology and classification of diabetes in children and adolescents*. *10*, 3–12. https://doi.org/10.1111/j.1399-5448.2009.00568.x

Mekuria, A. B., Belachew, S. A., Tegegn, H. G., Ali, D. S., Netere, A. K., Lemlemu, E., & Erku, D. A. (2018). *Prevalence and correlates of herbal medicine use among type 2 diabetic patients in Teaching Hospital in Ethiopia : a cross-sectional study*. 1–8.

Meneses, M. J., Silva, B. M., Sousa, M., Sá, R., Oliveira, P. F., & Alves, M. G. (2015). *Antidiabetic Drugs : Mechanisms of Action and Potential Outcomes on Cellular*

Metabolism Antidiabetic Drugs : Mechanisms of Action and Potential Outcomes on Cellular Metabolism. (July). https://doi.org/10.2174/1381612821666150710145753

Modak, M., Dixit, P., Londhe, J., Ghaskadbi, S., Paul, T., & Devasagayam, A. (2007). Serial Review Indian Herbs and Herbal Drugs Used for the Treatment of Diabetes. *J. Clin. Biochem. Nutr*, *40*(May), 163–173. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2275761/pdf/jcbn-40-163.pdf

Monica, N., Cr, J., & Panchaksharimath, P. (2016). *IJBCP International Journal of Basic and Clinical Pharmacology Original Research Article Use and satisfaction of complementary and alternative medicine among diabetic patients in a tertiary care hospital.* *5*(6), 2521–2527.

Nilanj, D. S. (2017). *Therapy Compliance in Hypertension: Indian Clinicians' Viewpoint.* *9*(3), 12–17. Retrieved from http://www.ijddr.in/drug-development/a-review-on-herbs-which-are-used-in-diabetes-mellitus.pdf

Ota, A., & Ulrih, N. P. (2017). An overview of herbal products and secondary metabolites used for management of type two diabetes. *Frontiers in Pharmacology*, *8*(JUL), 1–14. https://doi.org/10.3389/fphar.2017.00436

Ozougwu, J. (2017). *The pathogenesis and pathophysiology of type 1 and type 2 diabetes mellitus.* (October). https://doi.org/10.5897/JPAP2013.0001

Pal, S. K., & Shukla, Y. (2014). *MINI-REVIEW Herbal Medicine : Current Status and the Future.* (November 2002).

Preethi, P. J. (2013). *Review Article Herbal medicine for diabetes mellitus : A Review.* *3*(1), 1–22. https://doi.org/10.7439/ijpp

Prod, J. P. N., Katiri, A., Barkaoui, M., Msanda, F., & Boubaker, H. (2017). *Pharmacognosy*

& *Natural Products Ethnobotanical Survey of Medicinal Plants Used for the Treatment of Diabetes in the Tizi n ' Test Region (Taroudant Province , Morocco)*. *3*(1), 1–10. https://doi.org/10.4172/2472-0992.1000130

Punthakee, Z., Goldenberg, R., & Katz, P. (2018). Definition , Classification and Diagnosis of Diabetes , Prediabetes and Metabolic Syndrome Diabetes Canada Clinical Practice Guidelines Expert Committee. *Canadian Journal of Diabetes*, *42*, S10–S15. https://doi.org/10.1016/j.jcjd.2017.10.003

Qazi Majaz, A., & Molvi Khurshid, I. (2016). Herbal medicine: A comprehensive review. *International Journal of Pharmaceutical Research*, *8*(2), 1–5.

Russo, E., Scicchitano, F., Whalley, B. J., Mazzitello, C., Ciriaco, M., Esposito, S., … Sarro, G. De. (2013). *Hypericum perforatum : Pharmacokinetic , Mechanism of Action , Tolerability , and Clinical Drug – Drug Interactions*. (July).

Shane-McWhorter, L. (2009). Dietary supplements for diabetes: An evaluation of commonly used products. *Diabetes Spectrum*, *22*(4), 206–213. https://doi.org/10.2337/diaspect.22.4.206

Siddique, M. K. Bin, Islam, S. M. S., Banik, P. C., & Rawal, L. B. (2017). Diabetes knowledge and utilization of healthcare services among patients with type 2 diabetes mellitus in Dhaka, Bangladesh. *BMC Health Services Research*, *17*(1), 1–9. https://doi.org/10.1186/s12913-017-2542-3

Skyler, J. S., Bakris, G. L., Bonifacio, E., Darsow, T., Eckel, R. H., Groop, L., … Ratner, R. E. (2017). *Differentiation of Diabetes by Pathophysiology , Natural History , and Prognosis*. *66*(November 2016), 241–255. https://doi.org/10.2337/db16-0806

Steyn, M., Couchman, L., Coombes, G., Earle, K. A., Johnston, A., & Holt, D. W. (2018). A

herbal treatment for type 2 diabetes adulterated with undisclosed drugs. *The Lancet*, *391*(10138), 2411. https://doi.org/10.1016/S0140-6736(18)31134-6

Tabatabaei-malazy, O., Larijani, B., & Abdollahi, M. (2015). Targeting metabolic disorders by natural products. *Journal of Diabetes & Metabolic Disorders*, 1–21. https://doi.org/10.1186/s40200-015-0184-8

Ukamaka, O., Roseline, A., Aderemi, I., Modupeola, W., & Ayo, A. (2018). Herbal medicine use among Type 2 diabetes mellitus patients in Nigeria : understanding the magnitude and predictors of use. *International Journal of Clinical Pharmacy*. https://doi.org/10.1007/s11096-018-0648-2

Verma, S., Gupta, M., Popli, H., & Aggarwal, G. (2018). *Diabetes Mellitus Treatment Using Herbal Drugs*. *10*(1), 1–10. https://doi.org/10.5138/09750185.2181

Yatoo, M. I., Saxena, A., Gopalakrishnan, A., Alagawany, M., & Dhama, K. (2017). Promising antidiabetic drugs, medicinal plants and herbs: An update. *International Journal of Pharmacology*, *13*(7), 732–745. https://doi.org/10.3923/ijp.2017.732.745

Zaccardi, F., Webb, D. R., Yates, T., & Davies, M. J. (2015). *Pathophysiology of type 1 and type 2 diabetes mellitus : a 90-year perspective*. (1776), 1–7. https://doi.org/10.1136/postgradmedj-2015-133281

Appendix A.

Survey Questionnaire Consent form

I _____ , understand that I am being asked to participate in a survey activity that is required for the thesis work of Writuparna Das, (student of Department of Pharmacy, BRAC University) in her under graduation program. It is my understanding that this survey questionnaire has been designed to gather information about my disease condition, medication and treatment related issues.

I have been given some general information about this project and types of questions. I may withdraw to participate in it if I want. I understand that the survey is based on face to face interview and the answers will be kept confidential. I have been informed that it will take approximately thirty minutes to complete.

_____

Signature of the Participant

Date:

Questionnaire for survey on herbal medicine usage to diabetes patients

Personal information of Patient:

1.Name

2.Gender:

3.Age:

4.Marital Status:

5.Relegion:

6. Address:

7.Educational Level:

8. Working status of patient:

9.**What type of diabetes do you have?**

a) Type-1   b) Type -2

10) What is the duration of having diabetes disease?

a) (1-5) year   b) (11 years and above) c) (6-10) year

11) **Which type of antidiabetic therapy you take?**

a) Oral antidiabetics   b) Insulin + oral antidiabetics

12) **What are the names of the oral medicines you take?**

Ans:

13) **Family history of DM**

 a) Yes   b) No

If yes, Which family member have DM?

a) Parents b) Grand Parents c) Siblings

14) **Do you use herbal medicines?**

a) User   b) Non-user

15) **Do you use herbal medicine along with conventional medicines concurrently**?

a) Yes   b) No

16) **Do you use herbal product after the start of your treatment?**

a) Yes   b) No

17) **What is the primary reason of using herbal drug?**

a) Lowering blood sugar

b) Prevent complications

18) **What is the resource on herbal medicine?**

a) Media(Television)

b) Internet

c) Health professionals

d) Relatives-friend

If the answer is other than c then,

19) **Do you inform to your health professional?**

a) Yes   b) No

20) **Are you satisfied with herbal medicine?**

a) Satisfied   b) Dissatisfied   c) Average   d) Not sure

21) **Where do you obtain the herbal drug?**

a) Herbs and spice seller

b) Plant collecting

c) Order form internet or by phone

d) Other

22) **Do you face any health problem (side effects) related to the herbal medicine**?

a) Yes   b) No

23) **Did you face hypoglycemia after using herbal medicine?**

a) Yes   b) No

24) **Which type of herbal medicine do you use?**

a) Plants and grass   b.) Herbal teas   c). Foods   d) Tablets   e). Other

26) **How long do you use these products? (months)**

Ans:

25**) How frequently do you use the product**?

a) Once or twice a day

b) Once in (2-3) day

c) Once in a week

d) Once in 15 days

e) Once a month

26**) What is the cost of the herbal product**?

a) High   b) Low   c) Average

27) **Do you face diabetic complications?**

-Diabetic nephropathy.

 a) Yes b) No

-Diabetic retinopathy

 a) Yes   b) No

Coronary heart disease

 a)   Yes b) No.

Cerebrovascular disease

a) Yes b) No

28) Do you have other comorbidities?

a) Chronic liver disease

b) Peptic ulcer

c) Psychiatric diseases (anxiety, depression, psychosis, etc.)

d) Any surgical intervention

e) Other