# Ph.D. SYNOPSIS (2017-18)

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“Pre-clinical evaluation of Ameliorative potential for some nutraceutical induced diabetic complications.”

A SYNOPSIS SUBMITTED FOR THE REGISTRATION OF DEGREE OF

DOCTOR OF PHILOSOPHY

In the Faculty of Pharmaceutical Sciences & Technology

Submitted

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1. **Abstract of proposed work plan/ problem:**

Diabetes mellitus is a metabolic disorder with grievous pathophysiological complications which affects various parts of the body and manifesting in different ways which include acute and chronic neuropathy, nephropathy, retinopathy, micro and macro cardiovascular disorders and erectile dysfunction. Incidence and prevalence of diabetes mellitus is fast becoming high in middle and low income countries where about 80% of people living in those countries depend on orthodox medicine. Numerous and varied reports abound in literature on studies conducted to investigate the ameliorative effects of nutraceuticals on various pathophysiological complications of diabetes mellitus.

**Keywords**- Diabetes mellitus, nutraceuticals, diabetes complications, neuropathy, nephropathy, retinopathy, erectile dysfunction, cardiovascular diseases.
2. Introduction:
Diabetes mellitus (DM), commonly referred to as diabetes, is a group of metabolic disorders in which there are high blood sugar levels over a prolonged period. Symptoms of high blood sugar include frequent urination, increased thirst, and increased hunger. If left untreated, diabetes can cause many complications. Acute complications can include diabetic ketoacidosis, hyperosmolar hyperglycemic state, or death. Serious long-term complications include cardiovascular disease, stroke, chronic kidney disease, foot ulcers, and damage to the eyes.

Diabetic condition arises due to either the pancreas not produce enough insulin or the cells of the body not respond properly to the insulin produced. There are three main types of diabetes mellitus:

- Type 1 DM results from the pancreas's failure to produce enough insulin. This form was previously referred to as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes". The cause is unknown.
- Type 2 DM begins with insulin resistance, a condition in which cells fail to respond to insulin properly. As the disease progresses a lack of insulin may also develop. This form was previously referred to as "non insulin-dependent diabetes mellitus" (NIDDM) or "adult-onset diabetes". The most common cause is excessive body weight and insufficient exercise.
- Gestational diabetes is the third main form, and occurs when pregnant women without a previous history of diabetes develop high blood sugar levels.

Prevention and treatment involve maintaining a healthy diet, regular physical exercise, a normal body weight, and avoiding use of tobacco. Control of blood pressure and maintaining proper foot care are important for people with the disease. Type 1 DM must be managed with insulin injections. Type 2 DM may be treated with medications with or without insulin. Insulin and some oral medications can cause low blood sugar. Weight loss surgery in those with obesity is sometimes an effective measure in those with type 2 DM. Gestational diabetes usually resolves after the birth of the baby.


Metabolic Complications:

Acute-

Hyperglycemia hyperosmolar state-
Nonketotic hyperosmolar coma (HNS) is an acute complication sharing many symptoms with DKA, but an entirely different origin and different treatment. A person with very high (usually considered to be above 300 mg/dl (16 mmol/L)) blood glucose levels, water is osmotically drawn out of cells into the blood and the kidneys eventually begin to dump glucose into the urine. This results in loss of water and an increase in blood osmolarity.

Hypoglycemia-
Hypoglycemia, or abnormally low blood glucose, is an acute complication of several diabetes treatments. It is rare otherwise, either in diabetic or non-diabetic patients. The patient may become agitated, sweaty, weak, and have many symptoms of sympathetic activation of the autonomic nervous system resulting in feelings akin to dread and immobilized panic. Consciousness can be altered or even lost in extreme cases, leading to coma, seizures, or even brain damage and death. It is more accurate to note that iatrogenic hypoglycemia is typically the result of the interplay of absolute (or relative) insulin excess and compromised glucose counter regulation in type 1 and advanced type 2 diabetes.

Chronic-

Microangiopathy-
The damage to small blood vessels leads to a microangiopathy, which can cause one or more of the following:

- Diabetic nephropathy, damage to the kidney which can lead to chronic renal failure, eventually requiring renal dialysis. It is the most common cause of adult kidney failure in the developed world.
- Diabetic neuropathy, abnormal and decreased sensation, usually in a 'glove and stocking' distribution starting with the feet but potentially in other nerves, later often fingers and hands. When combined with damaged blood vessels this can lead to diabetic foot (see below). Other forms of diabetic neuropathy may present as
mononeuritis or autonomic neuropathy. Diabetic amyotrophy is muscle weakness due to neuropathy.

- **Diabetic retinopathy**, growth of friable and poor-quality new blood vessels in the retina as well as macular edema (swelling of the macula), which can lead to severe vision loss or blindness. Retinopathy is the most common cause of blindness among non-elderly adults in the developed world.

- **Diabetic encephalopathy**, is the increased cognitive decline and risk of dementia, including (but not limited to) the Alzheimer's type, observed in diabetes. Various mechanisms are proposed, like alterations to the vascular supply of the brain and the interaction of insulin with the brain itself.

- **Diabetic cardiomyopathy**, damage to the heart muscle, leading to impaired relaxation and filling of the heart with blood (diastolic dysfunction) and eventually heart failure; this condition can occur independent of damage done to the blood vessels over time from high levels of blood glucose.

- **Erectile Dysfunction**: Estimates of the prevalence of erectile dysfunction in men with diabetes range from 20 to 85 percent when defined as consistent inability to have an erection firm enough for sexual intercourse. Among men with erectile dysfunction, those with diabetes are likely to have experienced the problem as much as 10 to 15 years earlier than men without diabetes.

- **Periodontal disease** (gum disease) is associated with diabetes. Which may make diabetes more difficult to treat? A number of trials have found improved blood sugar levels in type 2 diabetics who have undergone periodontal treatment.

**Macrovascular disease**- Macrovascular disease leads to cardiovascular disease, to which accelerated atherosclerosis is a contributor:

- Coronary artery disease, leading to angina or myocardial infarction ("heart attack")
- Diabetic myonecrosis ('muscle wasting')
- Peripheral vascular disease, which contributes to intermittent claudication (exertion-related leg and foot pain) as well as diabetic foot.
- Stroke (mainly the ischemic type)
• Carotid artery stenosis does not occur more often in diabetes, and there appears to be a lower prevalence of abdominal aortic aneurysm. However, diabetes does cause higher morbidity, mortality and operative risks with these conditions.

• Diabetic foot, often due to a combination of sensory neuropathy (numbness or insensitivity) and vascular damage, increases rates of skin ulcers (diabetic foot ulcers) and infection and, in serious cases, necrosis and gangrene. It is why it takes longer for diabetics to heal from leg and foot wounds and why diabetics are prone to leg and foot infections. In the developed world is the most common cause of non-traumatic adult amputation, usually of toes and or feet.

• Female infertility is more common in women with diabetes type 1, despite modern treatment, also delayed puberty and menarche, menstrual irregularities (especially oligomenorrhea), mild hyperandrogenism, polycystic ovarian syndrome, fewer live born children and possibly earlier menopause. Animal models indicate that on the molecular level diabetes causes defective leptin, insulin and kiss peptin signaling.

**Abnormal immune responses**

The immune response is impaired in individuals with diabetes mellitus. Cellular studies have shown that hyperglycemia both reduces the function of immune cells and increases inflammation.

• Respiratory infections such as pneumonia and influenza are more common among individuals with diabetes. Lung function is altered by vascular disease and inflammation, which leads to an increase in susceptibility to respiratory agents. Several studies also show diabetes associated with a worse disease course and slower recovery from respiratory infections.

• Restrictive lung disease is known to be associated with diabetes. Lung restriction in diabetes could result from chronic low-grade tissue inflammation, microangiopathy, and/or accumulation of advanced glycation end products. In fact the presence restrictive lung defect in association with diabetes has been shown even in presence of obstructive lung diseases like asthma and COPD in diabetic patients.
• Lipohypertrophy may be caused by insulin therapy. Repeated insulin injections at the same site, or near to, causes an accumulation of extra subcutaneous fat and may present as a large lump under the skin. It may be unsightly, mildly painful, and may change the timing or completeness of insulin action.

• Depression was associated with diabetes in a 2010 longitudinal study of 4,263 individuals with type 2 diabetes, followed from 2005–2007. They were found to have a statistically significant association with depression and a high risk of micro and macro-vascular events.  

Sulfonylureas and weight gain-

Sulfonylureas lower blood glucose level by increasing insulin secretion in the pancreas by blocking the KATP channels. They also limit gluconeogenesis in the liver. Sulfonylureas decrease breakdown of lipids to fatty acids and reduce clearance of insulin in the liver. Sulfonylureas are currently prescribed as second line or add-on treatment options for management of T2DM. They are divided into two groups: first-generation agents, which includes chlorpropamide, tolazamide, and tolbutamide, and second-generation agents, which includes glipizide, glimepiride, and glyburide. Currently, in clinical practice, second-generation sulfonylureas are prescribed and more preferred over first-generation agents because they are proven to be more potent (given to patients at lower doses with less frequency), with the safest profile being that of glimepiride. Hypoglycemia is the major side effect of all sulfonylureas, while minor side effects such as headache, dizziness, nausea, hypersensitivity reactions, and weight gain are also common.

Metformin and Lactic Acidosis-

Lactic acidosis is an anion-gap metabolic acidosis defined by plasma lactate level greater than 5 mmol/L and pH less than 7.35. When severe, it is associated with multisystem organ dysfunction— particularly neurologic (stupor, coma, seizures) and cardiovascular (hypotension, ventricular fibrillation)—and carries a high mortality risk. Small series involving patients hospitalized with lactic acidosis have explored associations with metformin exposure.
**Erectile Dysfunction- in Diabetic-**

Prevalence of ED among patients with type-1 and type-2 DM It is unclear whether erectile disorder is more common among men with non-insulin dependent diabetes (type-2, T2DM, late onset) or those with insulin-dependent diabetes (type-1, T1DM, early onset). Only a few studies include a prevalence of erectile disorder by diabetic type. In this regarding, one study reported that men with elevated body mass index (BMI) and T1DM showed a significantly higher risk of ED than men with elevated BMI and T2DM. The same study also showed that the age-adjusted prevalence of ED was higher in men with T1DM (51%) than with T2DM (37%). But Miccoli et al., found that 40% and 52% of insulin-dependent and non-insulin dependent DM participants respectively had impotence. Fedele et al., in 2001 also reported that the incidence of ED in Italian men with diabetes was higher in T2DM than in T1DM (74 versus 45 cases per 1,000 person-years).

**Neutraceuticals – drug interaction and its mechanisms of action-**

**Categorizing nutraceuticals-**

Nutraceuticals can be organized in several ways depending upon its easier understanding and application, i.e. for academic instruction, clinical trial design, functional food development or dietary recommendations. Some of the most common ways of classifying nutraceuticals can be based on food sources, mechanism of action, chemical nature etc. The food sources used as nutraceuticals are all natural and can be categorized as: 1. Dietary Fibre, 2. Probiotics, 3. Prebiotics, 4. Polyunsaturated fatty acids, 5. Antioxidant vitamins, 6. Polyphenols, 7. Spices. More broadly, nutraceuticals can be classified in two groups i) Potential nutraceuticals, ii) Established nutraceuticals (8)

Two (or more) drugs when administered together have the potential to cause chemical or pharmacological interactions. Such interactions may alter the effect of either agent, leading to decreased or increased effectiveness or severity of adverse effects. The outcomes are dependent on many chemical and pharmacological factors, such as the physicochemical nature of the drugs in use and how they affect each other pharmacokinetically and pharmacodynamically (Fig. 1). although, the mechanisms of interactions between herbs and drugs are similar, they are more complex in nature when several compounds are involved. Herb–drug interactions (HDI) may affect clinical safety and efficacy via additive/synergistic
or antagonistic interactions among the neutraceuticals and drug molecules. Whilst negative or harmful interactions tend to receive more attention due to safety considerations, additive/synergistic effects induced by HDIs may result in an enhancement of desired pharmacological effects. For example, the blood glucose lowering effect of antidiabetic drugs has been shown to be increased by agrimony.

Fig. 1: Mechanism of Neutraceuticals-Drug Interactions

**Common Neutraceuticals –drug interactions in diabetes:**

**Ginseng-Panax ginseng and Panax quinquefolium**

Both *Panax ginseng* and *Panax quinquefolium*, two important members of the ginseng family, have been shown to possess antidiabetic properties affecting insulin dependent and insulin independent pathways. The bioactive constituents responsible for ginseng’s antidiabetic actions are likely to be attributed to its ginsenosides. Although the precise active components responsible for this anti-diabetic action are unknown, studies with compound K (CK), a final metabolite of protopanaxadiolginsenosides demonstrate that CK exhibits anti-hyperglycaemic effects through an insulin secreting action similar to metformin. The combined treatment of CK and metformin has been shown to elicit additive effects compared to individual components being used alone. Significant improvements were observed in plasma glucose and insulin levels, homeostasis model assessment-insulin resistance (HOMA-IR) and in haematoxylin and eosin-stained liver tissues.\(^9\)

**Aloe Vera**

In diabetic patients, treatment with A. Vera has been shown to cause significant reduction in blood glucose and blood pressure, as well as to improve the lipid profile. Due to its hypoglycemic nature, A. Vera interacts with anti-diabetics.
Evidence of herb–drug interaction

In obese individuals with pre diabetes or early untreated diabetes mellitus, treatment with an A. Vera gel complex reduced the body weight, body fat mass, and insulin resistance. Diabetic patients treated with A. Vera juice with or without glibenclamide showed reduced blood-glucose levels. Yagi showed a possible effect of long-term ingestion of A. Vera gel metabolites on insulin sensitivity. In high-fat diet-induced mice, 3 weeks of treatment with aloesin and aloesinol decreased plasma insulin levels by 37.9 and 46.7 %, respectively. In diabetes (db/db) mice, a chromone-standardized aloe-based composition decreased fasting triglyceride and plasma glucose levels by 33.7 and 46.0 %, respectively, after 10 weeks of oral treatment. Similarly, enhanced improvement in plasma insulin levels and a statistically significant reduction in triglyceride levels were observed in animals treated with the same chromone-standardized aloe-based composition.

Mechanism-

The metabolites of aloe polymannose, such as a mannoooligosaccharide and short chain fatty acids, synergistically modulate insulin sensitivity in tissues with a combination of phenolics, such as aloesin, aloe emodin, and salicylate. Nutrigenomic studies were conducted to elucidate the mechanism of the hypoglycemic and insulin-sensitizing effects of A. Vera, and the results showed that A. Vera reduced hepatic fat accumulation and enhanced insulin signaling in adipose tissue. This study provided a mechanistic explanation for the in vivo effects of enhanced insulin sensitivity and decreased blood glucose in mouse diabetes and prediabetes models. Moreover, A. Vera was found to exert inhibitory effects on CYP3A4 and CYP2D6. Antidiabetic drugs pioglitazone and repaglinide are substrates of CYP3A4.(10)

Fenugreek—Trigonellafoenum-graecum

Fenugreek is commonly used as a spice in south Asia and is known for its hyperglycaemic and hypocholesterolemic properties. The proximate composition of fenugreek (seeds, husk and cotyledons) contains saponin, protein and polyphenols. Interactions of fenugreek with known antidiabetics have been evaluated in several chemically induced diabetic animal models. The combination of fenugreek (150 mg/kg) and metformin (100 mg/kg) produced a significant reduction in plasma glucose level (20.7%) in type 2 diabetes. In a similar study,
lipid peroxidation (LPO) induced by ferrous sulphate, hydrogen peroxide and carbon tetrachloride in liver were performed. The combination treatment with fenugreek seed extract and glibenclamide exhibited a greater inhibition of the hepatic LPO activities and a greater antioxidant activity compared to the individual components alone, highlighting a potential benefit of the combination treatment.\(^{(11)}\)

**Green tea-Camellia sinensis-**

Originated from and mainly produced in China and is made from the leaves of the plant Camellia sinensis, an inherent herb from southern China. The leaves are thermogenic, appetizer, digestive, carminative, diuretic, and useful in cardiology, haemorrhoids, inflammation and abdominal disorders. Apart from the use of green tea in acute liver injury and oxidative stress injury, green tea is proved to be useful in preventing Hepatic C Virus (HCV) entry into the liver cells. Green tea is composed of active compounds such as catechin, gallocatechin, epicatechin, epigallocatechin, epicatechingallate, and epigallocatechingallate (EGCG) in which EGCG is considered the most therapeutically significant compound. Studies also show that EGCG is believed to cause liver toxicity if taken in excess of the recommendation. Green tea is also documented as having stimulant effects which are believed to be due to the effect of some alkaloids, such as caffeine, theobromine, and theophylline. L-theanine, an amino acid compound found in green tea, has been studied for its calming effects on the nervous system.\(^{(12)}\)

**Zinger- Zingiber officinale-**

Aqueous extract of ginger decreased the signs of both acute and chronic inflammation and was comparable to standard anti-inflammatory drug diclofenac sodium. As currently available anti-inflammatory drugs are associated with number of side-effects, ginger can be potentially explored as an anti-inflammatory agent with minimal or no side-effects.\(^{(13)}\)

**Garlic- Allium sativum L.-**

Many investigations that were carried out in experimental models have demonstrated the ability of garlic intake to protect against a variety of free-radical-induced renal toxicities, such as gentamicin-induced renal damage, renal ischaemia/reperfusion injury, cyclosporine-
induced nephrotoxicity and potassium dichromate-induced nephrotoxicity. Different garlic preparations were reported previously to have in vivo and/or in vitro antioxidant properties through their scavenging ability against different reactive oxygen and nitrogen species, including O2− [46], H2O2, OH, peroxynitrite anion (ONOO−) and hypochlorous acid (HOCl) and also reported that only aged garlic extract has a potent free-radical-scavenging activity, while other types of garlic preparations have an oxidant effect\(^{(14)}\).

**Curcumin- Curcuma Longa**

A phytochemical found in the spice turmeric, has been used in India for centuries, and it has no known side effects. It has been shown to have some beneficial effects against various chronic illnesses. Many of these therapeutic actions can be attributed to its potent anti-oxidant and anti-inflammatory activities. In view of the oxidative stress and inflammatory mechanisms of DM, curcumin can be considered suitable for the prevention and amelioration of diabetes\(^{(15)}\).
3. Review of Literature and Development in the subject (Previous work done in the relevant area):

Potential side effects of common diabetes drugs:

- **Sulfonylureas**: Low blood sugar, upset stomach, skin rash or itching, weight gain
- **Biguanides/Metformin**: Sickness with alcohol, kidney complications, upset stomach, tiredness or dizziness, metal taste
- **Alpha-glucosidase inhibitors**: Gas, bloating and diarrhoea
- **Thiazolidinediones**: Weight gain, risk of liver disease, anaemia risk, swelling of legs or ankles,
- **Meglitinides**: Weight gain, low blood sugar.

1. Yimam M, Zhao J, Corneliusen B, Pantier M, Brownell LA, Jia Q. UP780, a chromone-enriched aloe composition improves insulin sensitivity. *Metabolic Syndrome Related Disorders*. 2013; 11(4):267–7: In this study of diabetes, aloe vera has been shown to significantly reduce blood glucose levels. Also several studies report shows potential interactions between aloe vera and antidiabetic drugs. Note is its interaction with glibenclamide, a sulphonylurea which exerts its antidiabetic potential by inhibiting ATP sensitive potassium channels in pancreatic β cells, so resulting in cell membrane depolarization and subsequent insulin release. Thus the combination of aloe vera and antidiabetics has generally been shown to have an additive effect. For this instance, aloe has been shown to produce a greater anti-hyperglycaemic effect, when compared to the sole therapy with glibenclamide, pioglitazone or repaglinide.

2. Xiong Y, Shen L, Liu KJ, Tso P, Xiong Y, Wang G, Woods SC, Liu M. Antiobesity and antihyperglycemic effects of ginsenoside Rb1 in rats. *Diabetes*. 2010;59(10):2505–12: They found that the both Panax ginseng and Panaxquinquefolium, two important members of the ginseng family, have been shown to possess antidiabetic properties affecting insulin dependent and insulin independent pathways and the bioactive constituents responsible for ginseng’s antidiabetic actions are likely to be attributed to its ginsenosides.
3. Tongia A, Tongia SK, Dave M. Phytochemical determination and extraction of Momordicacharantia fruit and its hypoglycemic potentiation of oral hypoglycemic drugs in diabetes mellitus (NIDDM). Indian J PhysiolPharmacol. 2004; 48(2):241–4: 

Karela: According to their search their results showed that the combined interventions elicited a greater hypoglycemic effect when compared to that of full doses of metformin or glibenclamide alone, indicating a possible additive effect. Also these results have also been obtained in animal studies whereby the combined treatments of karela fruit juice/extracts and metformin have been shown to produce greater hypoglycemic effects than either treatment alone in rat models of diabetes.

4. Roufogalis BD. Zingiber officinale (Ginger): a future outlook on it’s potential in prevention and treatment of diabetes and prediabetes states. New J Sci. 2014; 2014:1–15: They found that the pungent principles, accounting for 25% of the oleoresins, consist mainly of gingerols and related phenolic compounds. Also, in a study done by Al-Omaria in a rat model of streptozotocin (STZ)-induced diabetes, a concurrent treatment of ginger extract in a dose of 25 or 50 mg/kg and glibenclamide of 5 mg/kg dose significantly reduced non-fasting blood glucose level by 26 and 25%, respectively, compared to 7.9% reduction when glibenclamide was used alone. In another study, a combination of ginger extract and a sub-optimal dose of glibenclamide (0.5 mg/kg) was found to exert effects similar to a full therapeutic dose of glibenclamide (1 mg/kg) in the STZ-induced diabetic model, highlighting the possibility of reduced side-effects of antidiabetics (due to the lower dose required) when used in combination with ginger extract and in addition, ginger has been shown to have renal protective effects when used with metformin.

5. Sankar D, Ali A, Sambandam G, Rao R. Sesame oil exhibits synergistic effect with anti-diabetic medication in patients with type 2 diabetes mellitus. ClinNutr. 2011;30(3):351–8: Use of the combination group showed a greater anti-hyperglycaemic effect with a 43% reduction of glycosylated hemoglobin and 36% reduction of blood glucose level when compared to those receiving sesame oil and glibenclamide monotherapy. Improvements were also observed in enzymatic and non-enzymatic antioxidant levels in
patients treated with sesame oil alone or in combination with glibenclamide, suggesting that sesame oil has an additive/synergistic effect when co-administered with glibenclamide.

6. Neha S, Anand K, Sunanda P. Administration of fenugreek seed extract produces better effects in the glibenclamide-induced inhibition in hepatic lipid peroxidation: an in vitro study. Chin J Integr Med. 2015;21:1: Use of the combination of fenugreek (150 mg/kg) and metformin (100 mg/kg) produced a significant reduction in plasma glucose level (20.7%) in type 2 diabetes.

7. Poonam T, Prakash GP, Kumar LV. Effect of co-administration of Allium sativum extract and Metformin on Blood glucose of Streptozotocin induced diabetic rats. J Intercult Ethno pharmacology. 2013;2:81–4: In this study combination therapy of garlic extract (50 or 100 mg/kg) and metformin over 28 days was tested in a rat model of streptozocin-induced diabetes. Later they found that garlic alone, as well as in combination with metformin, improved body weight, whilst the combination therapy was more effective in reducing blood glucose levels, highlighting that garlic extract potentiates the hypoglycemic effect of metformin.

From the review of literature, its well documented fact that the antidiabetics drugs produced several side effects and adverse reactions. The diabetic population is always prone for metabolic complications. The metabolic complications can be effectively managed using concurrent nutraceuticals.
4. Objectives of Research/ Proposed Hypothesis:

Need of Study:
1. Antidiabetic drugs show many side effects, and develop complications.
2. Nutraceuticals easily available.
3. Combine study of these interactions is necessary for effective management of diabetic complications.
4. Dosage regimen of diabetes can be minimized/reduced or optimized for better outcome.

Aim and objectives of Research Topics:
1. To decrease the severity of the side effects of antidiabetic drugs.
2. To decrease the severity of the metabolic complications of antidiabetic drugs.
4. Modification of dosages regimen to manage erectile dysfunction.
5. Modification of dosages regimen to manage retinopathy.
6. Modification of dosages regimen to manage obesity.
7. Modification of dosages regimen to manage wound healing.
8. Modification of dosages regimen to manage inflammation.
5. Methodology to be adopted:

Following are the few models for Drug-herbal medicine interactions-

i) Evaluation of effects of drug and herb in diabetic rat.

ii) Evaluation of effects of drug and herb on obesity in Streptozocin induced diabetic rat.

iii) Evaluation of effects of drug and herb on erectile dysfunction in Streptozocin induced diabetic rat.

iv) Evaluation of combined effects of drug and herb on nephritic dysfunction in Streptozocin induced diabetic rat.

Screening models:

Based on different mechanisms, following models were used in the present study.

1. Streptozocin (STZ) induced diabetes:

Streptozocin (STZ) is a naturally occurring chemical. It particularly produces toxic to the beta cells of pancreas. It is used in medical research as an animal model to produce hyperglycemia. STZ alters the blood insulin and glucose concentrations. Two hours after injection, it produces the hyperglycemia and it is due to the decreased in blood insulin levels. Six hours later, hypoglycemia occurs due to the high levels of blood insulin. At last hyperglycemia develops and blood insulin level drops. STZ impairs glucose oxidation and decrease insulin synthesis and release. It was observed that STZ at first abolished the beta cell response to glucose (20-21).

2. Obesity- High-fat diet-induced obesity

Even though the contribution of diets with a high-fat content to human adiposity is disputed , it is clear that the exposure of animals to high-fat (HF) diets often results in the development of obesity (16).

3. Erectile dysfunction: Reflective erection tests

To perform this test, male rats are restrained on their back and the prepuce is retract ed with a metal loop. Lengthening of the penile body, glans engorgement, cups (intense glans erection with flaring of glans extremity) and flips (dorsiflexions of penile body) are the
reflex responses which are observed and counted. The observational period is of 15 min, starting from the first reflex response. One can also monitor the ICP simultaneously. Generally the peaks of ICP are seen during reflex erection, which cease to occur after the pelvic nerve is cut bilaterally. This model gives an insight in the physiology of erections that the spinal autonomic nuclei (parasympathetic activity), are originators of reflexive erections (17).

4. Ratinopathy-

Decreased total retinal thickness, as well as decreased number of cells in the RGC layer, the ONL, and the INL was also reported. Regarding the vascular changes, blood-retinal-barrier (BRB) break down was evident at 2 weeks of hyperglycemia. Increased adherent leukocytes and arterial or venous capillaries basement membrane thickening were observed at 8 weeks and 12 months after hyperglycemia, respectively. Retinal function was affected from 2 weeks after the onset of hyperglycemia as reflected by the ERG. Reduced b-wave, and a-wave amplitudes were progressively found at 2 weeks, 8 weeks, and 10 weeks of hyperglycemia (18).

5. Inflammation-

Carrageenan-Induced Paw Edema in Rats. This model is based on the principle of release of various inflammatory mediators by carrageenan. Edema formation due to carrageenan in the rat paw is biphasic, where in the initial phase the release of histamine and serotonin takes place. The second phase is due to the release of prostaglandins, protease and lysosome. Subcutaneous injection of carrageenan into the rat paw produces inflammation resulting from plasma extravasations, increased tissue water and plasma protein exudation, along with neutrophil extravasations, due to the metabolism of arachidonic acid (19).
**Animals requirement:**
Wistar rats either male or females of weight 150-250 grams. The animals will be kept under control conditions of temperature (23± 2ºC) and 12 hrs. light-dark cycles. The animals will be randomized into control and test groups each groups having 6 animals. They will be housed into polypropylene cages with free access to food and water *ad-libitum*.

**Data & Statistical analysis:**
Data obtained will be evaluated as mean± Standard Error Mean (SEM). Significance between the groups will determine using the unpaired Student’s t-test. Statistical comparison between all groups will be performs by using two way ANOVA followed by the Dunnett test.
6. Importance of study/ Society application:

► International status:

Worldwide, the number of people with diabetes has substantially increased between 1980 and 2014, rising from 108 million to current numbers that are around four times higher. Forty percent of this increase is estimated to result from population growth and ageing, 28% from a rise in age-specific prevalence, and 32% from the interaction of the two. Diabetic retinopathy caused 1.9% of moderate or severe visual impairment globally and 2.6% of blindness in 2010. Studies suggest that prevalence of any retinopathy in persons with diabetes is 35% while proliferative (vision-threatening) retinopathy is 7%. Pooled data from 54 countries show that at least 80% of cases of end-stage renal disease (ESRD) is caused by diabetes, hypertension or a combination of the two.\(^{(22)}\)

NMDAR antagonists represent a new class of anti-diabetic agents that may hold the potential to slow down or even prevent diabetes progression and to reduce diabetic long-term complications, such as CV disease, nephropathy and retinopathy. Accumulating evidence indicates that NMDAR antagonists possess angio-, nephro- and retinoprotective properties. Furthermore, the NMDAR antagonist DXM has already been proven effective to some extent in the treatment of painful diabetic neuropathy in humans with T2DM\(^{(23)}\).

► National Status:

As per survey done by WHO in 2016 every year around, 5.8 million Indian die from noncommunicable diseases like lung diseases, heart diseases, stroke, diabetes and others causes in 30-69 of age group.
## Targets and Indicators - National Monitoring Framework for Prevention and Control of Non-Communicable Diseases (NCDs) as per W.H.O for India.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Framework element</th>
<th>Outcome</th>
<th>Targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Premature mortality from NCDs</td>
<td>Relative reduction in overall mortality from diabetes, cancer, CVS diseases, respiratory diseases.</td>
<td>10%</td>
</tr>
<tr>
<td>2.</td>
<td>Alcohol use</td>
<td>Relative reduction in alcohol use</td>
<td>5%</td>
</tr>
<tr>
<td>3.</td>
<td>Obesity and diabetes</td>
<td>Halt the rise in obesity and diabetes prevalence</td>
<td>No mid-term target set</td>
</tr>
<tr>
<td>4.</td>
<td>Physical inactivity</td>
<td>Relative reduction in prevalence of insufficient physical activity</td>
<td>5%</td>
</tr>
<tr>
<td>5.</td>
<td>Raised blood pressure</td>
<td>Relative reduction in prevalence of raised blood pressure.</td>
<td>10%</td>
</tr>
<tr>
<td>6.</td>
<td>Tobacco use</td>
<td>Relative reduction in prevalence of current tobacco use.</td>
<td>15%</td>
</tr>
<tr>
<td>7.</td>
<td>Drug therapy to prevent heart attacks and strokes</td>
<td>Eligible people receiving drug therapy and counseling to prevent heart attacks and strokes (including glycemic control)</td>
<td>30%</td>
</tr>
<tr>
<td>8.</td>
<td>Essential NCD medicines and basic technologies to treat major NCDs</td>
<td>Availability and affordability of quality, safe and efficacious essential NCD medicines including generics, and basic technologies in both public and private facilities.</td>
<td>60%</td>
</tr>
</tbody>
</table>
Significance of the study:

Research Outcomes:
Scientific evidence demonstrates the important role of inflammation in the pathogenesis of diabetic complications, which may be explained by several molecular mechanisms, particularly the NF-B signaling pathways. Phytochemicals occurring in many nutraceuticals act through these mechanisms and provide safe and effective candidates for drug design and development of treatment for diabetic complications. At the same time, the study of the mechanisms of action and active components in nutraceuticals have greatly enhanced our understanding on the rationale underpinning popular usage of some nutraceuticals for the prevention and treatment of diabetic complications. Further studies are required to generate a matrix of scientific evidence at the clinical and pre-clinical levels, including chemical, cellular and animal studies, in order to develop effective medicines for the prevention and treatment of diabetic complications.
7. Proposed work Plan/ Formulation and Structure of Study:
Year-wise Plan of work and targets to be achieved:

<table>
<thead>
<tr>
<th>Sr. no.</th>
<th>Name of Activity</th>
<th>Tentative duration (in Months)</th>
<th>Tentative duration (in Year)</th>
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</thead>
<tbody>
<tr>
<td>1.</td>
<td>Literature survey</td>
<td>06</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Collection and authentication of nutraceuticals.</td>
<td>03</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Analysis and characterization of nutraceuticals.</td>
<td>03</td>
<td></td>
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<tr>
<td>4.</td>
<td>Designing of Screening models</td>
<td>03</td>
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<tr>
<td>5.</td>
<td>Evaluation of nutraceuticals -drugs interactions.</td>
<td>14</td>
<td></td>
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<tr>
<td>6.</td>
<td>Compilation, interpretation of data.</td>
<td>03</td>
<td></td>
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<tr>
<td>7.</td>
<td>Writing of thesis</td>
<td>04</td>
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<td>8.</td>
<td>Total</td>
<td>36</td>
<td>03</td>
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9. **Key References:**


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<tbody>
<tr>
<td>2.</td>
<td>Remarks of the research Supervisor</td>
</tr>
<tr>
<td>3.</td>
<td>Name &amp; Designation of Guide</td>
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<tr>
<td></td>
<td>Signature of research Supervisor</td>
</tr>
<tr>
<td>4.</td>
<td>Signature of Director / Principal</td>
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</table>