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A proposal to examine anti-diabetic effects of *Withania coagulans*

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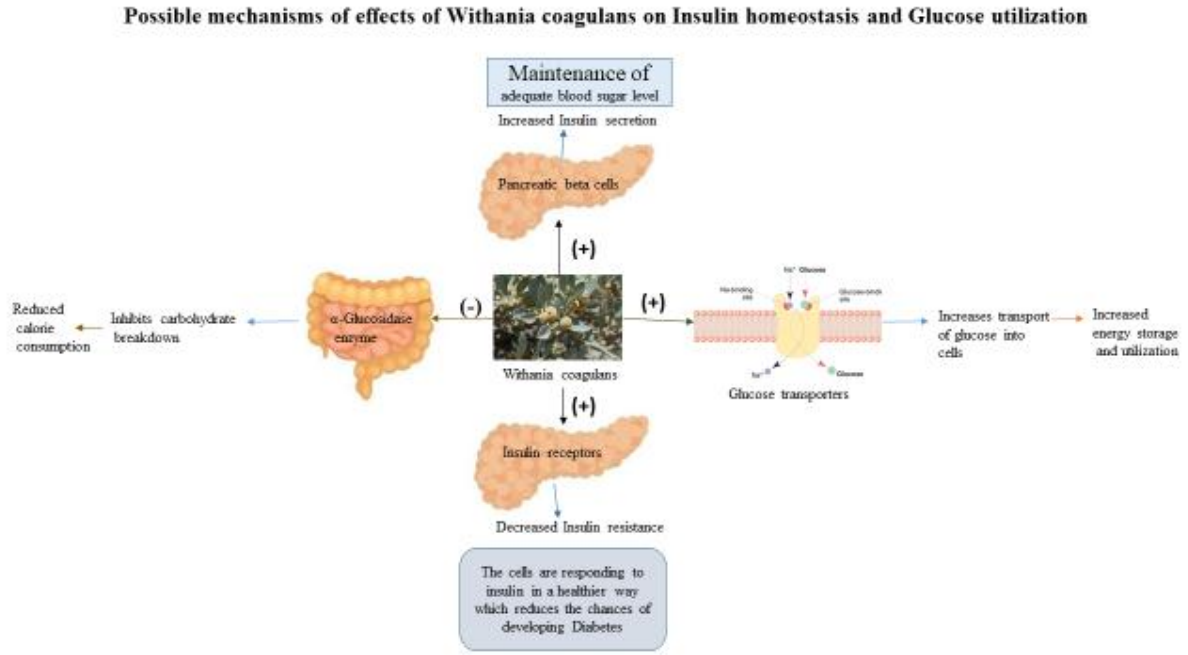
ABSTRACT
Diabetes is characterized by defects in metabolism of carbohydrate, lipid and lipoprotein, which leads to hyperglycaemia, besides there are complications like hyperlipidemia, hyperinsulinemia, hypertension and atherosclerosis. The complications of diabetes are the major cause of morbidity and mortality and the management of diabetes warding off the complications still pose a major challenge to the medical practice.
Medicinal plants have played an important role in preventing and treating variety of diseases throughout the world. This serves as a scope to develop novel treatment strategies which serves as a long term solution to the problem of diabetes control. The use of naturally derived products to delay or cure the disease will assist in disease management and reduce burden on the health care system.
Key words: Diabetes, metabolism, medicinal plants, treatment, health care



Graphical description of the proposed mechanisms of Withania coagulans(also known as Paneer doddi/Ashutosh booti)on Insulin homeostasis and Glucose utilization

I. Introduction

Diabetic disease accounts for more than 62 million diagnosed individuals in India, thereby giving a potential epidemic status to the country (1,2,3).In 2000, India (31.7 million) topped the world with highest number of people with diabetes mellitus followed by China (20.8 million) and United States (17.7 million)in second and third place respectively. Wild et al.(4) has predicted that the prevalence of diabetes is to double globally from 171

million in 2000 to 366 million in 2030 with a maximum increase in India. It is estimated that by 2030 diabetes mellitus may affect upto 79.4 million individuals in India, while China(42.3 million) and United States (30.3 million) will also show a significant increase in those affected by the disease(4,5).

The incidence of diabetes in India is multifactorial and includes genetic factors along with environmental predispositions such as obesity, rise in living standards , and steady lifestyle changes(1).

Withania coagulans has been known for its anti-diabetic, anti-inflammatory, cardioprotective and hepatoprotective potential. The extract from its fruits has been tested in a few in vitro and in vivo studies. Different parts of Withania coagulans such as root and fruit has shown health benefits (6).

National status of research about Withania coagulans

Multiple studies have examined anti-diabetic and anti-lipidogenic activity of Withania coagulans extracts (7,8). Aqueous, alcoholic or chloroform extracts of WC have been used so far. Apart from these two, anti-oxidative and anti-inflammatory potential of these extracts has been tested. Hyperlipidemic or hyperglycemic rodent models have been used to demonstrate the anti-oxidative potential of these extracts (9,10). The ability of the extracts to reduce oxidative stress resulted in neuroprotective effect of administration of these extracts in an Ischemia model (11). Further, another study tested the wound healing activity of WC extracts in diabetic rats (12). These extracts have also been used in Benign Prostatic Hyperplasia due to their ability to cause cell apoptosis (13).

Withania coagulans is an important medicinal plant. In view of its varied therapeutic potential, it has also been the subject of numerous pharmacological investigations. .*Jaiswal et al*.in 2009 (14) has systematically evaluated the role of minerals in glycaemic potential of aqueous extracts of Withania coagulans fruits in order to develop an effective and safe alternative treatment for diabetes mellitus. Laser Induced Breakdown Spectroscopy was used for glycemic element detection. The study is based on the results of lowering in blood glucose levels of normal, sub, mild and severely diabetic rats assessed during fasting blood glucose, glucose tolerance test and post prandial glucose studies.*Saxena et al* in 2010 (15) presented a study aimed to investigate the anti-atherosclerotic activity of an aqueous extract of Withaniacoagulans (AWC) in terms of atherogenic index (AI) in normal and streptozotocin (STZ)-induced diabetes.

The effect of aqueous extract of W. coagulans on insulin sensitivity in Poloxamer-407 (PX-407) induced type 2 diabetes mellitus (T2DM) rats was evaluated in a study by *Bharti et al. 2012* (16). Treatment with W. coagulans extract reduced the elevated levels of blood glucose, HbA1c, and insulin in T2DM rats.*Datta et al* in 2013 (17) evaluated the antidiabetic potential of the hydroalcoholic extract of Withania coagulans Dunal dried fruit (WCDF) alone and in combination with glipizide, in streptozotocin-induced diabetes, and evaluation of possible antihyperlipidemic activity of the same extract in high-cholesterol diet-induced hyperlipidemia, in albino rats.

Scientific rationale of the proposal

Diabetes Mellitus is a metabolic disorder associated with either inability of cells to produce insulin or dysregulation of insulin usage by the body. This disorder is associated with other chronic illnesses such as cardiovascular disease, kidney dysfunction, and retinopathy.The complications involve various organs causing nephropathy,neuropathy,retinopathy, several microvascular and macrovascular diseases and decreased immunity(18).

The vast majority of DM cases fall into two broad aetiopathogenetic categories.

In the first category (type 1), the cause is the destruction of the islet cells of the pancreas due to the development of autoimmunity to these cells. Individuals at increased risk of developing this type of diabetes can often be identified by serological tests and genetic markers. In the second category (type 2), the cause is a combination of resistance to insulin action and an inadequately compensated insulin secretory response. In type 1 DM, affected persons are dependent on insulin for prevention of ketosis, coma and death (hence the other name, insulin dependent diabetes mellitus). On the other hand, people with type 2 DM may require insulin at a later stage for controlling hyperglycaemia, but they are not dependent on insulin for survival.That is why the condition was previously known as non-insulin dependent diabetes mellitus. The acute metabolic decompensation in type 1 DM is diabetic ketoacidosis as opposed to the non-ketotic hyperosmolar state in type 2 DM. Exceptions to this observation have been well-documented. It is important to recognise which type of diabetes the patient is suffering from because management is so different (19).

Impaired glucose tolerance (IGT) is defined as a blood glucose level higher than normal but less than that required for diagnosis of DM. This was previously called borderline diabetes, latent diabetes, chemical diabetes or pre-diabetes. It is likely that all patients with DM progress through the stage of IGT. As expected, it is of short duration in type 1 DM (as the pathogenetic process is acute) while it is of longer duration in type 2 DM. Patients are asymptomatic at this stage, so IGT is only diagnosed from blood tests(20).

Glucose intolerance that develops during pregnancy or is detected for the first time during pregnancy is defined as gestational diabetes mellitus (GDM)(21).

Understandably, any pancreatic disease can give rise to secondary diabetes. However, unless and until 90 per cent of the islet cells are affected, hyperglycaemia does not ensue. Diabetes can be due to various endocrine diseases such as acromegaly or Cushing's syndrome. Hyperglycaemia can be associated with rare genetic syndromes, such as Down's syndrome, Turner's syndrome and Klinefelter's syndrome (22).

Diabetes mellitus, a global health problem is now emerging as an epidemic worldwide. Around two thirds of the world population affected by diabetes live in the developing countries of the world, the highest prevalence of the disease being in India and China. According to the World Health Organization (WHO) report 65-80% of the world population in developing countries depends on plants for their primary health care due to poverty and lack of access to modern medicine(23).Therefore to decrease the economic burden of the health care due to diabetic causes and increase the quality of life it is necessary to investigate potential means to develop a novel disease treatment.

Proposal

In the proposed work, we will use a combination of aqueous extract of Withania coagulans fruits with herbal tea to understand its anti-diabetic effect on a mouse model of diabetes, with a potential to commercialize the product. Additionally, the antioxidant property of Withania will also be determined. Doses and treatment regimens relevant to human consumption will be tested as well.

We propose to further improve and expand on existing methodologies to

(a) To test the healing effects of the compounds present in Withania coagulans in mouse model of diabetic disease.

(b) To effectively develop a safe and alternative treatment of diabetes mellitus utilising the antidiabetic, antihyperlipidemic potential and antioxidant property of the indigenous herb, Withania and extrapolate the effects in human subjects.

(c) To minimize the side effects of diabetes which is still a challenge to the medical system.

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