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STUDY OF WITHANIA COAGULANS EXTRACTS FOR ANTIDIABETIC ACTIVITY IN EXPERIMENTAL RAT MODELS

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ABSTRACT

The present study defines the systematic evaluation and the role of active constituents by their glycemic potential of extracts of Withania coagulans fruits in order to develop an effective and safe alternative treatment for diabetes mellitus. Experimental diabetes was induced in 30 albino rats with intraperitoneal injection of streptozotocin (50 mg/kg). The rats were divided into five groups receiving the following treatments orally for 4 weeks: Vehicle, glipizide (2.5 mg/kg), WCDF extract (1000 mg/kg), WCDF extract (1000 mg/kg) plus glipizide (1 mg/kg) and WCDF extract (1000 mg/kg) plus glipizide (2.5 mg/kg). Fasting and postprandial blood glucose levels were measured every week for 4 weeks. The 4‐week treatment with WCDF extract significantly reversed hyperglycemia in streptozotocin‐induced diabetes that was comparable to glipizide. When combined with glipizide (2.5 mg/kg), WCDF extract produced a synergistic antihyperglycemic effect. The present study, besides confirming hypoglycemic and antidiabetic activities of W. coagulans, helps in identifying the role of trace minerals like Mg & Ca responsible for antidiabetic potential of this potent indigenous shrub.

KEYWORDS: Antidiabetic, Diabetes, Hypoglycemic, Indian Cheese maker, Withania coagulans.

INTRODUCTION

Diabetes mellitus (DM) and its attendant acute and long‐term complications are a major health hazard globally. Its prevalence has now reached pandemic proportions in India. The mention of the disease in ancient Indian texts as ‘‘madhumeha’’ suggests its presence in India even before 2500 BC.

Type 2 diabetes mellitus (T2DM) is possibly the world's fastest growing metabolic disorder that results from defects in insulin secretion (Kahn, 2001) on one side, and insulin resistance on the other side (Polonsky et al., 1996). About 90% diabetic patients are of T2DM with insulin resistance and are playing a key role in the development of disease (National Diabetes Statistics, 2011). The progression of T2DM begins with an impairment of glucose tolerance (Zimmet and Thomas, 2003) and is often associated with a state of insulin resistance (Robertson and Harmon, 2006). In recent years, there has been global upsurge in the clinical use of drugs from herbal sources. Indian medicinal plants and their derivatives have been an invaluable source of therapeutic agents to treat various disorders, including diabetes.

Many oral hypoglycemic agents are available along with insulin for the treatment of diabetes. But these synthetic agents can produce serious side effects; furthermore, they are not suitable for use during pregnancy. This leads to an increase in demand for natural products having antidiabetic activity with fewer side effects and are relatively economical as compared to oral hypoglycemic agents. It is assumed that herbal medicine can be effective alternative to oral hypogly-cemic agents in the treatment of T2DM, where pancreatic islets are not totally destroyed.

Withania coagulans Dunal (family: Solanaceae), commonly known as Indian cheese maker or Paneer dodi is widely used in Ayurvedic system of medicine for over 3,000 years in India (Indian Pharmacopoeia, 1985). The adaptogenic, hepatoprotective, anti-inflammatory, antihyperglycemic, hypolipidaemic (cardio-protective), antioxidant, antimicrobial, cardiovascular, central nervous system depressant, immunomodulating, anti-platelet (wound healing), antitumour, and cytotoxic activities of W. coagulans have been documented by Maurya et al. (2010), Ojha and Arya (2009) and Prasad et al. (2010). The aqueous extract of the fruits of W. coagulans has been shown to exert antiangiogenic (Mirjalili et al., 2009) and antidiabetic (Jaiswal et al.,

2010) activities. According to Jaleel et al. (2008) *Triadimefon* a triazole derivative plant growth regulator isolated from *Withania somnifera*) can be used to enhance the antioxidant potential like superoxide dismutase, peroxidase, polyphenol oxidase, and catalase activities. Anwar et al. (2008) found improved insulin sensitivity index, that is, reduction in elevated blood glucose levels, glycated haemoglobin (HbA1c) and insulin in T2DM rats treated with *W. somnifera* extract. Hoda et al. (2010) found that aqueous extract of *W. coagulans* showed highly significant decrease ($p < 0.01$) in the blood glucose (52%), triglyceride, total cholesterol, low density lipoprotein (LDL), and very low density lipoprotein (VLDL) level and highly significant increase ($p < 0.01$) in high density lipoprotein (HDL) level. They also observed anti hyperglycemic effect slightly superior (6%) to metformin.

MATERIALS AND METHODS

Collection of laboratory Animals (rats) and plant materials (W. coagulans)

Young healthy male 15 days old Wister rats and weighing between 100 - 180g were collected in a metal cage. The animals (rats) were acclimatized for before being subjected to experimental study. The rats were kept in plastic perforated cages and maintained under standard conditions. They were then allowed free access to rat pellets and portable water throughout the period of experimentation while fresh dried fruits of W. coagulans in powdered form was purchased from Natural Remedies, Bangalore, India.

Preparation of *W.* Coagulans Extract

The whole fruits (1 kg) were mechanically crushed (mesh size 20) and extracted with a water‑alcohol mixture (60% ethyl alcohol) through cold percolation at room temperature up to 72 hrs. The extract was filtered and concentrated in rotary evaporator under reduced pressure to obtain semisolid material, which was then lyophilized to get a powder (yield: 24.3% w/w). The lyophilized powder was dissolved in distilled water and used.

METHODS

Methods to Evaluate the Antidiabetic Potential of WCDF extract

Induction of diabetes mellitus

DM was induced by a single intraperitonial injection of freshly prepared STZ 50 mg/kg in 0.1 M citrate buffer (pH: 4.6) to all groups of overnight fasted rats. After a gap of 5 days following Streptozotocin administration, fasting blood glucose levels were measured, and rats with fasting blood glucose above 150 mg/dL were selected for the study.

Animal Grouping

A total of 30 rats with Streptozotocin induced hyperglycemia were divided randomly into five groups, each containing six animals. The rats were fed orally with the respective regimens for 4 weeks using a feeding cannula:

Group 1: Negative control receiving vehicle (2% CMC solution).
Group 2: Positive control receiving glipizide at a dose of 2.5 mg/kg as a standard drug.
Group 3: Receiving WCDF extract at a dose of 1000 mg/kg.
Group 4: Receiving WCDF extract at a dose of 1000 mg/kg plus glipizide at a dose of 2.5 mg/kg.
Group 5: Receiving WCDF extract at a dose of 1000 mg/kg plus glipizide at a dose of 1 mg/kg.

Assessment Parameters

Fasting and Postprandial Blood Glucose

Animals were deprived of food overnight and for at least 16 h but allowed free access to drinking water. Fasting blood glucose was estimated in such state. The same rats were then given an oral glucose load (2 g/kg). Postprandial blood glucose levels were estimated 2 h after such oral glucose challenge. Blood was drawn from tip of the tail with the help of disposable lancet. Blood glucose levels were estimated in each group before and after Streptozotocin administration and then weekly up to 4 weeks with the help of strip and glucometer.

RESULTS

Evaluation of the Antidiabetic Potential of WCDF

Effect on fasting blood glucose (FBG) level

The base line value in all the five groups of rats showed that the FBG levels were within normal levels. After single dose (50 mg/kg) of STZ administration in all the groups, diabetes was effectively induced, as evidenced by statistically significant increase in FBG level from the baseline value 5 days following STZ administration. The WCDF extract treatment for just a week in Group 3, resulted in statistically significant reduction in FBG level. With increase in duration of WCDF treatment, the reduction in blood glucose levels was more and more pronounced.

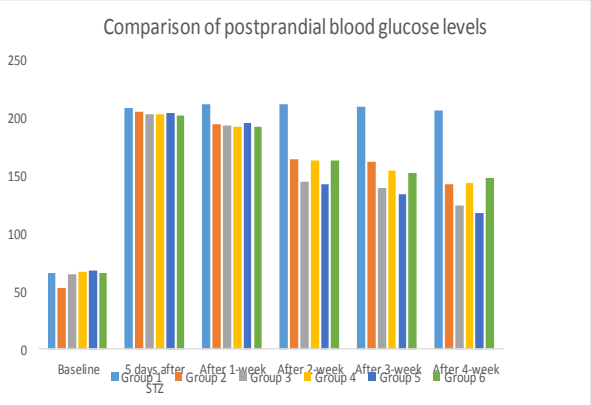
Similarly, a qualitatively equivalent trend in blood glucose lowering effect was seen with glipizide treatment in Group 2 rats. In both the Groups 4 and 5, the statistically significant impact of the combination treatments was apparent with just 1-week treatment that became more and more pronounced with increasing duration of treatment. When the data sets were compared between groups after 4 weeks of treatment, the most pronounced impact was seen with Group 4 that received the optimum standard dose of glipizide plus 1000 mg/kg/day WCDF extract. A qualitatively similar effect were also seen with Group 5 that received suboptimal dose of glipizide plus 1000 mg/kg/day WCDF extract; there were significant lowering of fasting blood glucose compared to Group 2 or Group 3, respectively.

Thus, it points to a synergistic effect exerted by the combination regimen. Effect on postprandial glucose

(PPG) level Both glipizide and WCDF extract treatment when used alone, that is, in Groups 2 and 3 respectively, significantly lowered PPG level, after 2-week treatment in the former and even with 1-week of treatment in case of latter group. However, the reduction was more significant with the increased duration in treatment in either group.

In Group 4, where glipizide and WCDF extract were combined (WCDF extract 1000 mg/kg plus glipizide 2.5 mg/kg) statistically significant synergistic impact on PPG lowering was demonstrated even with just 1-week treatment. Such impact was more pronounced with longer duration of treatment.

An analysis of observations on PPG values in Group 5 (WCDF extract 1000 mg/kg plus glipizide 1 mg/kg) demonstrated that although there was a general trend of synergism, this was much less as compared to Group 4 (WCDF extract 1000 mg/kg plus glipizide 2.5 mg/kg) findings.



CONCLUSION

The above study may be concluded that the WCDF extract can be considered as an adjuvant in the treatment of type 2 DM which can possibly lower the dose requirement of standard oral hypoglycemic agents like glipizide. Further studies with reduced dose of WCDF extract and human studies are needed to prove the safety and efficacy of long-term administration of this drug as potential antihyperlipidemic agent in routine clinical practice.

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