INTRODUCTION

Type 2 diabetes mellitus is one of the most common disorders seen all over the world. It is a complex and progressive disease characterized by hyperglycemia resulting from defects in insulin sensitivity and insulin secretion. Adequate control of hyperglycemia helps in reducing the risk of microvascular (nephropathy, retinopathy, and neuropathy) and macrovascular (stroke, myocardial infarction, and cardiovascular death) complications. Diet and exercise also help in achieving glycemic control and are important aspects of Type 2 diabetes management, however, individualized pharmacotherapy is required to meet glycemic goals. Due to the progressive nature of Type 2 diabetes, failure to maintain euglycemia with oral agent monotherapy over the long term is common, and therefore patients require two or more agents to achieve their glycemic goals.

Combination therapy using agents with complementary, but different mechanisms of action that address different pathophysiologic defects of Type 2 diabetes may improve glycemic control to a greater extent than monotherapy. Combination therapy may also allow the use of lower doses of concomitant antihyperglycemic agents, which may minimize unwanted side effects. For example, weight gain and hypoglycemia are associated with some

ABSTRACT

Background: Type 2 diabetes is a fast growing epidemic affecting people globally. Good glycemic control helps in reducing the risk of macro and microvascular complications in diabetics. Alternative medicines have been used since ancient times in India to achieve good glycemic control. Tinospora cordifolia (Tc) is a well reported plant possessing anti-diabetic property. Therefore, we undertook this study to evaluate the effectiveness of Tc in reducing the blood glucose levels of Type 2 diabetic patients in the form of add-on therapy.

Methods: In the present study, we enrolled 100 Type 2 diabetic patients who met our inclusion criteria. These patients were then randomly divided into two Groups, A and B. Patients in Group A were treated as controls and they continued with their anti-diabetic medications. In Group B, Tc was added to the conventional treatment at a dose of 500 mg 3 times daily along with meals. The fasting and postprandial blood glucose levels and glycosylated hemoglobin (HbA1c) were recorded baseline and after 6 months.

Results: During the course of study, we observed a decrease in the fasting, postprandial, and HbA1c levels of the patients. However, this decrease was found to be more statistically significant (p≤0.005) in Group B.

Conclusion: The results obtained from the present study conclude that Tc, when given in the form of add-on therapy, was found to be synergistic and effective in the better management of Type 2 diabetes. The drug was well tolerated by the patients and no adverse drug event was recorded.

Keywords: Type 2 diabetes, Tinospora cordifolia, Oral hypoglycemic agents
antihyperglycemic agents, occur more frequently with higher doses, and may hinder achievement of glycemic and metabolic goals.

Over the centuries, herbs have served as a major source of medicines for prevention and treatment of diseases including diabetes mellitus. *Tinospora cordifolia* (Tc) (Guduchi) is reported to be one such herb in Ayurvedic system of medicine. It is incredibly versatile and safe herbaceous vine and is indicated to combat various diseases and is proved to be a highly potent anti-diabetic herb. Hence, we undertook this study to see the effect of Tc as an add-on therapy in controlling blood glucose levels of Type 2 diabetic patients.

**METHODS**

The present study included 100 Type 2 diabetic patients recruited from the Medicine and Diabetic OPD of King George Medical University, Lucknow (Uttar Pradesh). The study protocol was approved by the Institutional Ethics Committee and written informed consent was taken from all the participants. The procedures followed were in accordance with the Institutional Ethical Committee standards responsible for human experimentation and with the Helsinki Declaration. The subjects who were included in this study met the following inclusion criteria:

- A known case of Type 2 diabetes mellitus on oral hypoglycemic drugs
- Patients of age between 30 and 60 years, of either sex.

Subjects with the following conditions were excluded from the study:

- Type 2 patients on insulin.
- Type 1 diabetic and gestational diabetic patients.
- Patients above 60 years of age.
- Patients with Diabetic nephropathy, neuropathy, retinopathy or any other chronic complications.

Patients fulfilling the aforementioned inclusion criteria were selected. The selected patients were divided randomly into two Groups A and B. The patients in Group A were treated as controls and they continued their oral hypoglycemic drugs, while in Group B Tc was given as an add-on therapy along with their anti-diabetic medications. Tc was given in the form of immumod tablets which contains extract of Tc. One tablet of 500 mg was given three times daily along with meals for 6 months. The baseline characteristics of the patients like age, height, weight, body mass index (BMI), blood pressure were also recorded.

**Collection of blood samples**

Total 5 ml of blood was drawn from each patient under aseptic conditions from the antecubital vein. The drawn blood was collected in fluoride vials and plasma was separated and stored at −20°C.

**Estimation of blood glucose levels**

The fasting and postprandial blood glucose levels were estimated by kit using glucose oxidase peroxidase method.

**Estimation of glycosylated hemoglobin (HbA1c)**

The HbA1c was estimated by using the high performance liquid chromatographic method.

The normal values of fasting blood glucose, postprandial blood glucose, and HbA1c were taken according to WHO guidelines. These biochemical parameters were repeated after 3 months and 6 months.

**Statistical analysis**

The statistical analysis was carried out using “paired t-test” using Graph pad statistical computer software package. Level of significance (p value) was considered <0.05.

**RESULTS**

**Baseline parameters**

Table 1 shows the baseline parameters of Groups A and B. These parameters included the age, height, weight, BMI, systolic and diastolic blood pressure, fasting and postprandial blood glucose levels, HbA1c, serum urea, serum creatinine, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase of the subjects. We did not find any significant difference (p≥0.05) in these parameters between the two groups. Hence, we can say that Groups A and B were statistically similar at the beginning of the study.

**Fasting blood glucose levels**

Figure 1 shows the decrease in the fasting blood glucose levels of the patients. In Group A, the mean values decreased from 149.42±6.87 mg/dl to 120.32±4.97 mg/dl. While in Group B it decreased from 150.21±7.32 mg/dl at baseline to 115.93±3.42 mg/dl after 6 months. This reduction in the fasting blood glucose level was statistically significant in Group A (p≤0.05) and highly significant (p≤0.005) in Group B.

**Post prandial blood glucose levels**

As shown in Figure 2, the mean baseline postprandial blood glucose levels recorded were 255.53±17.38 mg/dl and 248.71±15.42 mg/dl in Groups A and B, respectively. After 6 months, the values decreased to 184.94±6.97 mg/dl in Group A and 176.89±5.37 mg/dl in Group B. The reduction in the postprandial blood glucose level was found to be statistically significant in both the groups (p≤0.05).
Glycosylated hemoglobin

The mean HbA1c recorded at baseline in Group A was 8.17±0.254% while in Group B was 8.24±0.256%. With the decrease in the fasting and postprandial blood glucose levels, the HbA1c also decreased to 7.52±0.181% in Group A and 6.98±0.130% in Group B Figure 3. This reduction in HbA1c was found to be more statistically significant in Group B as the p<0.005 as compared to Group A.

DISCUSSION

In this study, both the groups displayed similar clinical and biochemical characteristics, which enabled us to compare metabolic variables, as well as the possible influence of Tc as an add-on intervention in these patients. The results obtained from the present study showed a decrease in the fasting and postprandial blood glucose levels as well as HbA1c levels within the groups. This reduction was found
to be more significant in Group B. Earlier studies conducted by Rout in 2006 and Sudha et al. in 2011 have reported its anti-diabetic potential through a large number of biologically active phytoconstituents derived from different parts of the plant including alkaloids, tannins, cardiac glycosides, flavonoids, saponins, steroids, etc.\textsuperscript{37,38} Similar studies conducted on Tc suggest that the hypoglycemic activity is possibly due to inhibition of salivary and pancreatic amylase and glucosidase.\textsuperscript{29}

Due to its blood glucose lowering activity Tc is also reported to be used as an important constituent in many polyherbal formulations prepared for the treatment of diabetes. One Ayurvedic polyherbal formulation “Ilogen-Excel,” which contains \textit{T. cordifolia} as one of the constituents, when administered at the dose of 50 and 100 mg/kg for 60 days has shown significant decrease in blood glucose levels and increase in plasma insulin, hepatic glycogen, and total hemoglobin. The root extract of plant lowered the levels of HbA1c, plasma thiobarbituric acid reactive substances, hydroperoxides, and ceruloplasmin in diabetic rats.\textsuperscript{30} Similarly, another herbomineral formulation “Hyponidd” is reported due to the superoxide dismutase (SOD) activity of pancreatic islet cells in the rats. The formulation induces a dose-related decrease in hyperglycemia and augments islet SOD activity.\textsuperscript{32} Another polyherbal Ayurvedic formulation of the plant, “Dihar,” showed significant antihyperglycemic, antihyperlipidemic and antioxidant effects in rats. There was a significant decrease in reduced glutathione, SOD, catalase levels and increase in thiobarbituric acid reactive species levels in the liver.\textsuperscript{33} Therefore, from the results obtained from this study we can conclude that Tc can play a beneficial role in the form of alternative therapy in the treatment of Type 2 diabetes.

**CONCLUSION**

The findings of the present study suggested that Tc demonstrated a significant reduction in the blood glucose as well as HbA1c levels of the patients. In conclusion, we can say that Tc helps in maintaining good glycemic control in the form of adjunctive therapy. The drug was well tolerated and was found safe on hepatic and renal markers.

**Funding:** Indian Council of Medical Research

**Conflict of interest:** None declared

**Ethical approval:** The present study was approved by the Institutional Ethical Committee (Ref No-291/R- Cell-12)

**REFERENCES**

1. Defronzo RA. Banting lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes. 2009;58(4):773-95.
2. National Kidney Foundation. KDOQI clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease. Am J Kidney Dis. 2007;49:S12-154.
3. Fong DS, Aiello L, Gordon TW, King GL, Blankenship G, Cavallerano JD, et al. Retinopathy in diabetes. Diabetes Care. 2004;27 Suppl 1:S84-7.
4. Boulton AJ, Vinik AI, Arezzo JC, Bril V, Feldman EL, Freeman R, et al. Diabetic neuropathies: a statement by the American Diabetes Association. Diabetes Care. 2005;28(4):956-62.
5. Almdal T, Scharling H, Jensen JS, Vestergaard H. The independent effect of type 2 diabetes mellitus on ischemic heart disease, stroke, and death: a population-based study of 13,000 men and women with 20 years of follow-up. Arch Intern Med. 2004;164(13):1422-6.
6. Junttilainen A, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Type 2 diabetes as a “coronary heart disease equivalent”: an 18-year prospective population-based study in Finnish subjects. Diabetes Care. 2005;28(12):2901-7.
7. Schramm TK, Gislason GH, Kober L, Rasmussen S, Rasmussen JN, Abildstrom SZ, et al. Diabetes patients requiring glucose-lowering therapy and nondiabetics with a prior myocardial infarction carry the same cardiovascular risk: a population study of 3.3 million people. Circulation. 2008;117:1945-54.
8. Look AHEAD Research Group, Pi-Sunyer X, Blackburn G, Brancati FL, Bray GA, Bright R, et al. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the look AHEAD trial. Diabetes Care. 2007;30(6):1374-83.
9. Anderson JW, Kendall CW, Jenkins DJ. Importance of weight management in type 2 diabetes: review with meta-analysis of clinical studies. J Am Coll Nutr. 2003;22(5):331-9.
10. Klein S, Sheard NF, Pi-Sunyer X, Daly A, Wylie-Rosett J, Kulkarni K, et al. Weight management through lifestyle modification for the prevention and management of type 2 diabetes: rationale and strategies: a statement of the American Diabetes Association, the North American Association for the Study of Obesity, and the American Society for Clinical Nutrition. Diabetes Care. 2004;27(8):2067-73.
11. Brown JB, Nichols GA, Perry A. The burden of treatment failure in type 2 diabetes. Diabetes Care. 2004;27(7):1535-40.
12. Fonseca VA. Defining and characterizing the progression of type 2 diabetes. Diabetes Care. 2009;32 Suppl 2:S151-6.
13. Turner RC, Cull CA, Fught V, Holman RR. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. JAMA. 1999;281(21):2005-12.
14. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med. 2006;355(23):2427-43.
15. Bennett WL, Maruthur NM, Singh S, Segal JB, Wilson LM, Chatterjee R, et al. Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations. Ann Intern Med. 2011;154(9):602-13.
16. Riddle MC. Combined therapy with insulin plus oral agents: is there any advantage? An argument in favor. Diabetes Care. 2008;31 Suppl 2:S125-30.
17. Phung OJ, Scholle JM, Talwar M, Coleman CI. Effect of noninsulin antidiabetic drugs added to metformin therapy on
glycemic control, weight gain, and hypoglycemia in type 2 diabetes. JAMA. 2010;303(14):1410-8.

18. Barnett AH, Cradock S, Fisher M, Hall G, Hughes E, Middleton A. Key considerations around the risks and consequences of hypoglycaemia in people with type 2 diabetes. Int J Clin Pract. 2010;64(8):1121-9.

19. Peyrot M, Skovlund SE, Landgraf R. Epidemiology and correlates of weight worry in the multinational diabetes attitudes, wishes and needs study. Curr Med Res Opin. 2009;25(8):1985-93.

20. Anonymous. Quality Standards of Indian Medicinal Plants. Vol. 1. New Delhi: Indian Council of Medical Research; 2003: 212.

21. Dhar ML, Dhar MM, Dhanwan BN, Mehrotra BN, Ray C. Screening of Indian plants for biological activity: I. Indian J Exp Biol. 1968;6(4):232-47.

22. Singh KP, Gupta AS, Pendse VK, Mahatma CP, Bhandari DS, Mahawar MM. Experimental and clinical studies on Tinospora cordifolia. J Res Indian Med. 1975:10:9-14.

23. Kundnani KM, Mahajan VR, Jolly CI. A new hypoglycaemic agent from Tinospora cordifolia: Miers. Indian Drugs. 1985;23:119-20.

24. Goel HC, Prem Kumar I, Rana SV. Free radical scavenging and metal chelation by Tinospora cordifolia, a possible role in radioprotection. Indian J Exp Biol. 2002;40(6):727-34.

25. Subramanian M, Chintalwar GJ, Chattopadhyay S. Antioxidant properties of a Tinospora cordifolia polysaccharide against iron-mediated lipid damage and gamma-ray induced protein damage. Redox Rep. 2002;7(3):137-43.

26. Gupta SS, Verma SC, Garg VP, Rai M. Anti-diabetic effects of Tinospora cordifolia. I. Effect on fasting blood sugar level, glucose tolerance and adrenaline induced hyperglycaemia. Indian J Med Res. 1967;55(7):733-45.

27. Rout GR. Identification of Tinospora cordifolia (Wild.) Miers ex Hook F & Thomas using RAPD markers. Z Naturforsch C. 2006;61(1-2):118-22.

28. Sudha P, Zinjarde SS, Bhargava SY, Kumar AR. Potent a-amylase inhibitory activity of indian ayurvedic medicinal plants. BMC Complement Altern Med. 2011;11:5.

29. Chougale AD, Ghadyale VA, Panaskar SN, Avindekar AU. Alpha glucosidase inhibition by stem extract of Tinospora cordifolia. J Enzyme Inhib Med Chem. 2009;24(4):998-1001.

30. Umamaheswari S, Mainzen Prince PS. Antihyperglycaemic effect of ‘Ilogen-Excel’, an ayurvedic herbal formulation in streptozotocin-induced diabetes mellitus. Acta Pol Pharm. 2007;64(1):53-61.

31. Babu PS, Stanely Mainzen Prince P. Antihyperglycaemic and antioxidant effect of hyponidd, an ayurvedic herbomineral formulation in streptozotocin-induced diabetic rats. J Pharm Pharmacol. 2004;56(11):1435-42.

32. Bhattacharya SK, Satyan KS, Chakrabarti A. Effect of trasina, an ayurvedic herbal formulation, on pancreatic islet superoxide dismutase activity in hyperglycaemic rats. Indian J Exp Biol. 1997;35(3):297-9.

33. Patel SS, Shah RS, Goyal RK. Antihyperglycemic, antihyperlipidemic and antioxidant effects of dihar, a polyherbal ayurvedic formulation in streptozotocin induced diabetic rats. Indian J Exp Biol. 2009;47(7):564-70.

doi: 10.18203/2319-2003.ijbcp20150035
Cite this article as: Mishra S, Verma N, Bhattacharya S, Usman K, Himanshu D, Singh P, Anjum B, Verma N. Effect of Tinospora cordifolia as an add - on therapy on the blood glucose levels of patients with Type 2 diabetes. Int J Basic Clin Pharmacol 2015;4:537-41.