View metadata, citation and similar papers at core.ac.uk

brought to you by CORE

provided by Online Publishing @ NISCAIR

Indian Journal of Traditional Knowledge
Vol 20(1), January 2021, pp

Evaluation of efficacy and safety of a polyherbal Unani formulation in diabetes mellitus type 2 (Zayābīṭus Sukkari Qism Sāni) - a randomised controlled clinical study

N Ahmad[a,*,†], M Nawab[b,c] M H Kazmi[a] & S H Fatima[a]

[a]Department of Moalajat (Medicine), National Research Institute of Unani Medicine for Skin Disorders Erragadda, Hyderabad 500 038, Telangana, India

[b]National Research Institute of Unani Medicine for Skin Disorders, Opp. ESI Hospital, A. G. Colony Road, Erragadda, Hyderabad 500 038, Telangana, India

E-mail: [†] drnadeemahmad85@gmail.com

Received 23 December 2019; revised 08 October 2020

Diabetes mellitus Type 2 (*Zayābīṭus Sukkari Qism Sāni*) is a major health concern in 21st century. Despite tremendous advances in modern sciences, there is a lack of relatively safe and effective drug for its management.

The primary objective of this study was to evaluate the efficacy and safety of a polyherbal Unani formulation containing Gurmar booti (*Gymnema sylvestre*), Gilo (*Tinospora cordifolia*) and Jamun (*Syzygium cumini*) in the management of Diabetes Mellitus Type 2 (DMT2). It was a randomised controlled clinical study conducted on 60 participants of DMT2 inadequately controlled by diet and exercise. The test drug was given to group-A participants (n=30) 6 g twice daily orally for 12 weeks and the standard drug metformin (500 mg) was given twice daily orally to group-B participants (n=30).

It was observed that the difference between the Mean (± SD) value of fasting blood glucose (FBG), postprandial blood glucose (PPBG) and glycosylated haemoglobin (HbA1c) in Test and Control groups at the end of the study in comparison to baseline was significant ($p<0.05$). This study concludes that the test drug was effective in reducing FBG and PPBG significantly in diabetic participants' at 12 weeks of treatment.

Keywords: Diabetes mellitus Type 2, *Gymnema sylvestre*, *Syzygium cumini*, *Tinospora cordifolia*, Unani

IPC Code: Int. Cl.[21]:C07D 277/72, A61K 36/185, A61K 36/00

Diabetes mellitus Type 2 (*Zayābīṭus Sukkari Qism Sāni*) is a major health concern in the 21st century[1,2]. It is defined as a chronic metabolic disorder that occurs due to increased glucose levels in the blood because the body cannot produce any or sufficient insulin hormone or use insulin effectively[3,4] As per WHO estimates diabetes mellitus Type 2 (DM Type 2) was the leading cause of death in 2016 globally. Its incidence is rapidly rising and reached an epidemic like situation worldwide. It was estimated that 425 million peoples are suffering from diabetes and it is supposed that it could reach 629 million by 2045[2]. Currently, there are 72.9 million peoples affected by diabetes in India[5]. As per an estimate of WHO, 1.6 million death were caused by diabetes in 2016. Retinopathy, renal failure, heart attack, stroke and lower limb amputation are the major complications of diabetes mellitus Type 2. Healthcare expenditures to manage diabetes mellitus and associated disorders become a burden for the country. In India, the treatment and healthcare cost 31 billion International Dollar (ID) to the exchequer[6].

Till this date, there is no cure for this healthcare problem. It can be managed by serum glucose level with the help of the therapeutics, diets and exercises. There are certain identified modifiable risk factors such as overweight, obesity, stress, alcohol and smoking. Diabetes can be prevented and managed by modification of lifestyle and these risk factors. Unani system of medicine (USM) offers treatment for diabetes mellitus Type 2 and other metabolic disorders by different treatment modalities such as pharmacotherapy, regimen therapy and dietotherapy. Many classical prescriptions comprising of single herbo-mineral drugs and pharmacopoeial formulations have been recommended for the management of diabetes mellitus Type 2. Preclinical studies conducted in the recent past have demonstrated the efficacy of Gurmar Booti (*Gymnema sylvestre*), Gilo Khushk (*Tinospora cordifolia*), Maghz-i-Tukhm Jamun (*Syzygium cumini*), Neem (*Azadirachta indica*) and

*Corresponding author

Karela (*Momordica charantia*) as hypoglycemic agents. The pharmacopoeial formulations comprising of Gurmar Booti (*Gymnema sylvestre*) Gilo Khushk (*Tinospora cordifolia*) and Maghz-i-Tukhm Jamun (*Syzygium cumini*) has been selected after thorough literature survey expecting a promising result[7]. The aim of this study was to record and document the efficacy and safety of the Unani formulation in the management of diabetes mellitus Type 2 which may become a piece of evidence that would validate the indication of the Unani formulation in the management of diabetes mellitus Type 2.

Materials and Methods

The present study was carried out with 60 participants (30 participants in each group) of diabetes mellitus Type 2 at outdoor patient department of Central Research Institute of Unani Medicine (CRIUM), Hyderabad during July 2018-July 2019. This study was designed as non-inferior, assessor-blinded, parallel group, randomized and active control. The first participant was enrolled after Institutional Ethics Committee approval (F.No.22-1/2016/CRIUM/ HYD/Tech./04/M) and registration of the study in Clinical Trials Registry-India (CTRI) on 20th December 2017 under registration no. CTRI/2017/ 12/010929.

The participants withdiabetes mellitus Type 2 aged between 18 years and 65 years of both sexes were included in this study based on Fasting Plasma Glucose level between 126 mg/dL and 150 mg/dL or/and Postprandial Plasma Glucose level between 200 mg/dL and 250 mg/dL or/and HbA1C level ≥6.5% and the participants had any symptom such as Utash Mufrit (Polydipsia), Kasrat al-Bawl (Polyuria), Kasrat al-Ishtiha (Polyphagia), Bawl Layli (Nocturia), I'ya (Fatigue), Naqs al-Wazn (Loss of Weight), Burning Sensation in palm and soles, Sadr (Giddiness), Naqs al-Shahwa (Loss of Libido)[8-10]. Participants having comorbid conditions such as blindness, ischemic heart disease, stroke any hepato-renal dysfunction were not included in the study. Participants on Insulin therapy and those suffering from diabetes mellitus Type-I, pregnant and lactating women were not part of the study.

Sample size estimation

The sample size for this study was estimated empirically to be 75 participants including 25% dropouts. The target sample size of this study was 60 participants: 30 participants in test group (Group-A) and control group (Group- B) each. In total 242 participants were screened but 159 participants did not fulfil the inclusion and exclusion criteria of the study. The remaining 83 participants were randomly allocated in test and control groups. Out of them, 8 participants from the test group and 12 participants from the control group were dropped out or discontinued from the study due to non-compliance of the therapy, lost to follow-up, concurrent illness and migration of the participants. Moreover, three participants were withdrawn from the study after four weeks of treatment due to continuous rise in serum glucose level beyond the cut-off blood sugar level described in inclusion criteria of the study due to poor efficacy of the Unani formulation. It was observed that the number of participants dropped-out in this study was comparatively higher than expectation.

Intervention

Participants of group A were treated with the classical Unani formulation constituting of Gurmar Booti (*Gymnema sylvestre*), Gilo Khushk (*Tinospora cordifolia*) and Maghz-i-Tukhm Jamun (*Syzygium cumini*) as a test drug in the dosage form of the powder in the study. The test drug was given in a dosage of 6 g twice daily before 30 min of meal for 84 days. In the control group, allopathic drugs metformin hydrochloride was given as standard drug in the dosage form of tablet in a dosage of 500 mg orally twice daily 30 min before meals. Each participant was advised to have a brisk walk of half an hour daily or 150 min / weeks and to take a diet as per the recommendation of the American Diabetes Association (ADA) guidelines[12].

Method of preparation of the drugs

All the three ingredients of the Unani formulation were procured from the market in raw form. These ingredients were identified and authenticated by the botanist at the Survey of Medicinal Plants Unit (SMPU) of the institute. The specimens of these plant drugs were archived in the museum of the institute with the Voucher Specimen Numbers; *Tinospora cordifolia* (SMPU/CRI-Hyd 13565), *Syzygium cumini* (SMPU/CRI-Hyd 13566), *Gymnema sylvestre* (SMPU/CRI-Hyd 13567). The formulation was prepared in the GMP certified pharmacy of the institute. All the ingredients in raw form were pulverized individually to make a fine powder. The powder form of all ingredients were mixed in the equal ratio (Table 1). Pouches of 168 g each were prepared for distribution to the participants.

The participants fulfilling the inclusion and exclusion criteria were enrolled in the study after

obtaining written informed consent form. Participants were given participant information sheets explaining thereby the rights of the participants before signing informed consent form. All the participants were recruited from Out Patient Department (OPD)/Indoor Patient Department (IPD) of Central Research Institute of Unani Medicine (CRIUM), Hyderabad and were randomly allocated into groups as per pre-specified block randomization scheme generated through a computer. The sequence of the block was concealed in envelopes. The data were recorded in case record form prepared for the study after a complete medical history, general, physical, systemic examination and investigation reports. Determination of temperament was done as per standardized questionnaire prepared by Central Council for Research in Unani Medicine (CCRUM), New Delhi, India[11]. The participants were followed-up for clinical evaluation at an interval of two weeks: 2,4,6,8,10,12 weeks. At each visit, participants were physically examined and fasting as well as postprandial serum glucose level was tested to monitor the blood glucose level. The compliance of the therapy was also recorded properly in case record form.

Assessment of the efficacy of the drug

The primary endpoint of the study was to maintain normoglyceamia at 12 weeks of treatment. The secondary endpoint was to measure a reduction in serum glucose at an interval of 14 days. The efficacy of the Unani formulation was assessed by measuring reduction in fasting plasma glucose (FPG) or postprandial plasma glucose (2 h PG) or decrease in HbA_1c level by ≥1% and improvement in symptoms of *Zayābīṭus Sukkari Qism Sāni* (Diabetes Mellitus Type 2) on visual Analogue Scale (VAS) at 12 weeks of treatment comparing from baseline

Table 1 — Polyherbal Unani formulations

Ingredients	Quantity
Gurmar Buti (*Gymnema sylvestre*)	4 g
Gilo Khushk (*Tinospora cordifolia*)	4 g
Maghz Tukhm-i -Jamun (*Syzygium cumini* Kernel seed)	4 g

Assessment of Safety

Safety and toxicity of the test drug was assessed on the basis of adverse effects (AEs) recorded at each follow-up visit (i.e., 2,4,6,8,10,12 weeks) and derangement of hepatic and renal function comparing at 12 weeks of treatment from baseline.

Statistical analysis of the data

The data collected were analysed as per protocolin this study. For primary outcome we performed non-parametric analysis of variance (ANOVA) test to assess the difference between the two treatment groups. We also conducted paired sample t-test to compare the means from the same group at different times. A p-value of <0.05 was considered significant. Statistical analysis was performed using Graph Pad Prism statistical software (v5).

Observations and Results

A total of 60 participants completed the study. It was observed that participants had an average age 47.7 years (both sexes), average weight 71.03 (±12.98) Kg, average BMI 28.05 (± 5.377) Kg/ square meter and average chronicity of 2.8 years ±2.3) years at baseline were randomized into test group (n=30) and control group (n=30) (Fig. 1). It was also observed that 27

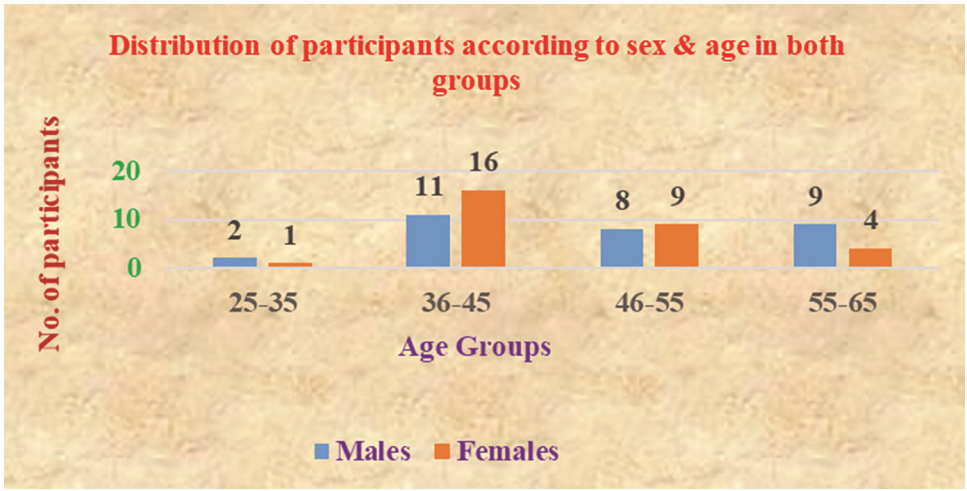

Fig. 1 —

participants (45%) belonged to the age group of 36-45 years. Out of 60 participants, 21 participants had *Balghamī* (Phlegmatic) temperaments. 60% of the participants were male among them. It was observed that the participants presented with the symptoms polyuria, polydipsia, loss of libido and burning sensation in palm and soles. In this study, the test drug showed better improvement in *Utash Mufrit* (Polydipsia), *Kasrat al-Bawl* (Polyuria), *Kasrat al-Ishtiha* (Polyphagia), *Bawl Layli* (Nocturia), *I'ya*(Fatigue), burning sensation in palm and soles and *Naqs al-Shahwa* (Loss of Libido) in comparison to control drug (Table 2 & Table 3).

In this study efficacy of the formulation was assessed in terms of reduction in fasting, postprandial serum glucose and glycosylated hemoglobin in blood at 12 weeks of treatment in comparison to base line. In the test group, mean fasting blood glucose was 147.4±5.45 mg/dL at base line whereas it was 157.5±9.03 mg/dL in the control group. At the end of the study, mean fasting blood glucose was reduced to 116.1±5.05 mg/dL and 141.7±6.9 mg/dL in test group and control group respectively (Table 4). The result showed that a reduction in mean fasting blood glucose was higher in test group at 12 weeks of treatment.

The result showed that intest group, mean postprandial blood glucose was less than that of control group at baseline. This study revealed that in the test group , mean postprandial blood glucose was reduced to 185.9±8.9 mg/dL from 225.5±7.3 mg/dL at the end of the study. But in the control group, reduction in mean postprandial blood glucose was slightly higher. The mean postprandial blood glucose came down in the control group 141.7±6.9 mg/dL from 239.64±10.9 mg/dL (Table 5). This study concluded that the study drug was non-inferior to the control drug. When mean HbA1c in both groups was compared, the difference in the mean HbA1c between test and control groups was significant ($p<0.05$). The mean HbA1c (%) in test and control groups at baseline was 8.33±0.2833 and 8.28±0.3402 whereas at the end of 12 weeks of study

Table 2 — Effect of test drug on subjective parameters, (n=30)

Parameters	Present/ Absent	Test Drug			
		BT		AT	
		No. of Pts.	% of Pts.	No. of Pts.	% of Pts.
Polyurea	Present	19	63.33	02	6.67
	Absent	11	36.67	28	93.34
Polydipsia	Present	25	83.34	07	6.67
	Absent	05	16.67	23	93.34
Polyphagia	Present	14	46.67	20	66.67
	Absent	16	53.34	10	33.34
Nocturia	Present	14	46.67	05	16.67
	Absent	16	53.67	25	83.34
Fatigue	Present	18	60	08	26.67
	Absent	12	40	22	73.34
Loss of Wt.	Present	02	6.67	00	00
	Absent	28	93.34	30	100
Giddiness	Present	04	13.34	04	13.34
	Absent	26	86.67	26	86.67
Loss of libido	Present	07	23.34	04	13.34
	Absent	23	76.67	26	86.67
Burning sensation in Palm & Sole	Present	18	60	05	16.67
	Absent	12	40	25	83.34

Table 3 — Effects of control drug on subjective parameters (n=30)

Parameters	Present/ Absent	Control Drug			
		BT		AT	
		No. of Pts.	% of Pts.	No. of Pts.	% of Pts.
Polyuria	Present	22	73.34	09	30
	Absent	08	26.67	21	70
Polydipsia	Present	26	86.67	05	16.67
	Absent	04	13.34	25	83.34
Polyphagia	Present	18	60	03	10
	Absent	12	40	27	90
Nocturia	Present	18	60	08	26.67
	Absent	12	40	22	73.34
Fatigue	Present	20	66.67	11	36.67
	Absent	10	33.34	19	63.33
Loss of Weight	Present	05	16.67	27	90
	Absent	25	83.34	03	10
Giddiness	Present	07	23.34	02	6.67
	Absent	23	76.67	28	93.34
Loss of libido	Present	08	26.67	08	26.67
	Absent	22	73.34	22	73.34
Burning sensation in Palm & Sole	Present	18	60	08	26.67
	Absent	12	40	22	73.34

Table 4 — Effect on fasting blood glucose (FBG), (Mean ±SEM)

Group	B.L.	1st F.U.	2nd F.U.	3rd F.U.	4th F.U.	5th F.U.	6th F.U.
Test	147.4± 5.45	170.7± 12.2	170.1± 11.21	158.2± 12.35	160.2± 13.74	160.4± 13.47	116.1± 5.05
Control	157.5± 9.03	167.03± 14.2	157.1± 8.88	148.8± 10.60	147.93± 9.4	142.47± 7.9	141.7± 6.9

Note: F.U.- Follow-Up

Table 5 — Effect on post prandial blood glucose (PPBG) (Mean ±SEM)

Groups	B.L.	1st F.U.	2nd F.U.	3rd F.U.	4th F.U.	5th F.U.	6th F.U.
Test	225.5±7.375	255.7±17.86	253.6±13.98	242.3±18.37	251.2±18.74	240.8±19.24	185.9±8.966
Control	239.64±10.9	222.16±16.5	231.8±13.07	220.5±15.2	228.76±14.8	209.93±12.7	141.7±6.9

the level of glycated haemoglobin in test and control groups was reduced to 7.303±0.2627 and 7.153 ±0.2553 respectively (Table 6).

Table 6 — Effect on HbA1c % (Mean ±SEM)

Group	Assessment HbA1c on base line and 6th follow-Up	
	Base Line	6th F.U.
Test	8.330±0.2833	7.303±0.2627
Control	8.28±0.3402	7.153 ±0.2553

Discussion

This prospective study compared glycemic control, clinical outcome and amelioration of subjective symptoms in participants with diabetes mellitus Type 2 treated with a Unani formulation in group-A and metformin hydrochloride in group-B participants. We observed that both treatments resulted in sustained improvement in glycemic control. During the study event of hypoglycemia was not observed in both the groups. It was also observed that primary outcome to maintain normoglyceamia at 12 weeks of treatment was found significant. The Unani formulation showed efficacy in terms of reduction in serum glucose at 12 weeks of treatment. The possible mechanism of action of the Unani formulation to act as hypoglycemic and ameliorative to the symptoms may be hypothesized. The Unani formulation constituted of three herbal medicines having anti-diabetic activities may be acted synergistically to control and maintain normoglycaemia. The Unani formulation might be responsible for the secretion of insulin in required quantity from the beta cells of the pancreas[13,14]. It might also be possible that the Unani formulation causes to lessen insulin resistance to tissue and thereby control serum glucose level. The ingredient *T. cordifolia* increases the activity of the glycogen synthase in liver and also increases the storage of glucose in hepatocytes[15]. The biologically active component of *S. cumini*, Jamboline also possesses glucose lowering effect[13]. Presence of gymnemic acid in *G. sylvestre* also produces hypoglycemia[16]. Moreover, these plants possess antioxidant, hypolipidemic and hepatoprotective properties which help in amelioration of subjective symptoms of the participants[13,14].

Metformin is a known potential oral hypoglycemic and is first-line medication to manage diabetes mellitus Type 2. Jennifer A Hirst reported that metformin monotherapy lowered HbA1C by 1.12% and this effect was sustained at 24 weeks[17].

This study had several limitations. The sample size was very small and the duration of protocol therapy was also very short. The duration of the study was limited to two years due to academic restrictions. The participants, therefore, could not be followed for a long time in the post-trial period.

The Unani formulation was found safe and showed no adverse effect. Haemoglobin per cent, RBC count, total leucocyte counts, differential leucocyte counts, platelets counts, liver function tests (S. Bilirubin, SGOT, SGPT, ALP) and kidney function tests (S. Creatinine, S.Urea) were within normal limits at 12 weeks of treatment,

Conclusion

DM Type 2 is prevalent in India and other neighbouring countries. Its rising incidence and prevalence become a burden for the nation. Oral hypoglycaemics are not capable to deal with DM Type 2. In this study, an attempt was made to test the efficacy of the Unani formulation in DM Type 2 participants with an intent to treat concept in search of an effective, cheap and comparatively better medicine. This study showed that the Unani formulation reduced 20% fasting blood glucose and 17% postprandial blood glucose level at 12 weeks of treatment in the majority of the participants. The results also showed that the Unani formulation was non-inferior to active control drug metformin hydrochloride. Althoughthe study was conducted with a single fixed dose of the Unani formulation. For a better understanding of the efficacy of the Unani formulation, multiple-dose studies may be conducted with a large sample size and longer duration of the study. The Unani formulation was tolerated well and showed no systemic toxicity. This Unani formulation was constituted of herbal drugs having hypoglycemic activities. This study was the first attempt to study the safety and efficacy of the Unani formulation on scientific parameters. It may be suggested that maximum therapeutic dosage, pharmacokinetics and pharmacodynamics of the Unani formulation may be

studied in near future. A clinical trial may be also conducted with a large sample size to establish its efficacy in reducing serum glucose.

Conflict of interest

None

Acknowledgement

We are thankful to Prof Asim Ali Khan, Director General of Central Council for Research in Unani Medicine, New Delhi for his assistance and kind support.

Contribution of the authors

N A conducted this clinical study, collected the data and drafted this manuscript. M N supervised this study and edited the manuscript. S H F conducted laboratory investigations. M H K vetted the manuscript and provided technical support during the study.

References

1 Anonymous, GBD 2015 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015, *Lancet,* (388) (2016) 1659-1724. doi: 10.1016/S0140-6736(16)31679-8

2 Anonymous, *IDF Diabetes Atlas 2017*, (International Diabetes Federation, Belgium), 2017, 42. https://www.diabetesatlas.org /upload/resources/previous/files/8/IDF_DA_8e-EN-final.pdf

3 Anonymous, *IDF Diabetes Atlas 2017*, (International Diabetes Federation,Belgium), 2017, 16.

4 De Fronzo R A, Ferrannini E, Zimmet P & George M K, Alberti M, *International Textbook of Diabetes Mellitus*, 4thed (2) (Wiley-Blackwell, USA) 2015, 03.

5 Anonymous, *IDF Diabetes Atlas 2017*, (International Diabetes Federation, Belgium), 2017, 43-47.

6 Anonymous, *IDF Diabetes Atlas 2017*, (International Diabetes Federation, Belgium), 2017, 52.

7 Kabiruddin M., *Bayaz-e-Kabir*, 5th ed. Vol 1, (Hikmat Book Depot, Hyderabad), 1935, 177-179.

8 Anonymous, Classification and diagnosis of diabetes: Standards of Medical Care in Diabetes- 2018. *Diabetes Care* 2018; 41 (Suppl. 1): S13–S27. https://doi.org/10.2337/dc18-S002

9 Jameson, Fauci AS, Kasper, Hauser, Longo et al, *Harrison's Principles of Internal Medicine*, 19th ed, Vol 2 (McGraw Hill, USA), 2015, 2399-2420.

10 Chandalia H B, Sridhar G R, Das A K, Madhu S V & Mohan V*, et al*, *RSSDI Textbook of Diabetes Mellitus*, (3rd ed), (Jaypee Brothers Medical Publishers (P) Ltd, New Delhi), 2014, 367-371**.**

11 Naaz F, Mastan A, Abid M & Khan N, Clinical Evaluation of Mizaj (Temperament) of the Subjects of Pelvic inflammatory disease, *World J Pharm Res,* 5 (8) (2016) 713-728.

12 Anonymous, Prevention or delay of Type 2 diabetes: Standards of Medical Care in Diabetes- 2018. *Diabetes Care* 2018; 41 (Suppl. 1): S51–S54. https://doi.org/10.2337/dc18-S005

13 Ahmad N, Nawab M & Kazmi MH, Medicinal Potential of Jamun (*Syzygium cumini* L), A Review, Journal of Drug Delivery and Therapeutics, 9 (5) (2019) 175-180. https://doi.org/10.22270/jddt.v9i5.3568

14 Ahmad N, Nawab M & Qamar-Uddin, Medicinal Properties of Gilo (*Tinospora cordifolia*) - A Review, *World J Phar Pharm Sci*; 8 (8) (2019) 430-440.

15 Puranic N & Devi S. Anti-diabetic activity of Tinospora cordifolia in streptozocin diabetic rats, does it act like sulfonylurea, *Turk J Med Sci*, 40 (2) (2010) 265-270.

16 Sugihara Y, Nojima H, Matsuda H, Murakami T & Yoshikawa M, et al, Antihyperglycemic effects of gymnemic acid IV, a compound derived from Gymnema sylvestre leaves in streptozotocin diabetic mice, *J Asian Nat Prod Res*, (2) (2000) 321–7. https://doi.org/10.1080/10286020008041372

17 Hirst J A, Farmer A J, Ali R, Roberts NW & Stevens RJ, Quantifying the effect of metformin treatment and dose on glycaemic control, *Diabetes Care*, (35) (2012) 446-454. https://doi.org/10.2337/dc11-1465