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Efficacy and safety of Trikgud as an add-on medicine in uncontrolled type 2 diabetes mellitus (T2DM) patients with metformin monotherapy: A randomized controlled trial

Abstract

Metformin is quite effective in managing Type 2 diabetes mellitus (T2DM). Studies have reported that the combined use of oral hypoglycemic medicines is prescribed in uncontrolled T2DM metformin monotherapy. So, we aim to evaluate the efficacy and safety of Ayurvedic herbo-mineral formulation (*Trikgud*) in managing uncontrolled T2DM with metformin monotherapy in Nepalese population. This study was a randomized controlled trial. A total of 56 participants with the diagnosis of T2DM were randomly assigned to the intervention group (Trikgudmet) or control (Met) group in a ratio of 1:1 for 12weeks. The primary outcome measures were the difference in the change in glycated haemoglobulin (HbA1C), fasting plasma glucose (FPG) and 2-h postprandial plasma glucose (2-h PPG) between the groups, and secondary outcome measures were the change in body mass index (BMI), waist-hip ratio (WHR), lipid profile, liver function tests and renal function tests between the baseline and at 12weeks after intervention. At week 12, there were significant differences of FPG and 2-h PPG in both Trikgudmet group and Met group when compared with week 0. There was a statistically significant decrease of 8.6% and 10.1% of HbA1C levels in Trikgudmet and Met groups, respectively. This study may provide "a new evidence for use of *Trikgud* as an add-on therapy for uncontrolled T2DM patients with metformin monotherapy in context of Nepal.

Keywords: Type 2 diabetes mellitus, trikgud, metformin

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Abbreviations: SEAR, southeast asia region; IDF, international diabetes federation; T2DM, Type 2 diabetes mellitus; FBG, fasting blood sugar; STZ, streptozotocin; PPG, post prandial blood glucose; HbA1c, glycosylated hemoglobin; NARTC, national ayurveda research and training center; FPG, fasting plasma glucose; 2-h PG, 2-h plasma glucose; OGTT, oral glucose tolerance test; RPG, random plasma glucose; API, ayurvedic pharmacopoeia of India; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BMI, body mass index; WC, waist circumference; WHR, waist-hip ratio; SPSS, statistical package for the social sciences.

Introduction

Diabetes is a chronic metabolic disease with a major impact on human being worldwide. It is estimated that 537million adults aged 20-79years are currently living with diabetes. The total number of people with diabetes is predicted to increase to 11.3% by 2030 AD and 12.2% by 2045 AD. Diabetes mellitus is also a growing public health concern in the Southeast Asia region (SEAR), where more than 90.2million people are living with diabetes. International Diabetes Federation (IDF) projects that the number of people with diabetes in the SEAR will increase 68%, reaching 152million by 2045 AD. The number of people with diabetes aged 20-79years in Nepal is 1.1million.[1]

Type 2 diabetes mellitus (T2DM) is the most common type of diabetes, accounting for over 90% of all diabetes worldwide. The first choice of managing T2DM is by improving a healthy lifestyle. If not controlled with healthy diet, proper physical activity and other healthy lifestyle measures, oral medication is usually initiated.[1] Metformin is the first-line medicine for T2DM and the most commonly prescribed drug for T2DM worldwide, either alone or in combination with other glucose-lowering therapies or insulin. Metformin is a biguanide, a drug class of herbal origin that has been widely used to treat diabetes since the 1950s.[2] It is difficult to determine the right choice of additional anti-hyperglycemic drug to manage uncontrolled T2DM with metformin monotherapy.[3] Even though previous clinical studies have shown that the combined use of oral hypoglycemic medications is more effective than antidiabetic monotherapy,[4-6] but, a systemic review and meta-analysis for add-on therapies to metformin have shown similar effect to those for monotherapies.[7]

Although modern drugs are quite effective in getting blood glucose level down, it is subject to sustaining certain side effects.[8-14] Hence, a quest of alternative approach in the management of T2DM is essential and Ayurveda treatment modality is one such approach to manage T2DM.

In Ayurveda, the term *Madhumeha* (one type of *Prameha*) is used as synonym of diabetes mellitus. Although *Prameha* is a *Tridoshaja* disease (a disease involving all three of the psycho-physiologic principles termed as *Doshas*), but *Doshas* may get involved in different proportions and produce *Kaphaja, Pittaja and Vataja Prameha*.[15] *Madhumeha* is a type of *Vataja Prameha* which occurs either due to genetic causes (*Sahaja Pramehi*) or improper management of *Prameha* (*Apathyanimittaja*).[16] *Madhumeha*, therefore, is a terminal stage of *Prameha* and is incurable or extremely difficult to cure.[17]

As regards to drugs in Ayurveda, there are so many drugs and formularies but the main drugs are either bitter (*Tikta*) or astringent (*Kashaya*) in taste. They improve the fat and carbohydrate metabolism.[18] The selected herbs {*Kutaki* (*Picrorhiza kurroa*),

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Guduchi (*Tinospora cordifolia*), *Daruharidra* (*Berberis aristata*)} and *Rasa ausadhi* (herbo-mineral formulation) i.e *Trivanga Bhasma* {Incinerated *Naga* (Lead; Plumbum), *Vanga* (Tin; Stanum) and *Yashada* (Zinc)} were based on *Pramehahara* (Anti-diabetic) property mentioned in *Bhavaprakasha Nighantu*[19] and *Rasa Kaumudi*[20], authentic textbooks of Ayurveda in 16th century, respectively.

In vivo pharmacological screening study showed that *Trivanga Bhasma* possesses anti-diabetic property, diuretic activity and has less toxicity.[21] Similarly, in animal model study, fasting blood sugar (FBG) level of *Trivanga Bhasma* dosed streptozotocin (STZ)-induced diabetic rats were significantly reduced than that of control STZ-induced diabetic rats after 30days of treatment. Histopathology of liver, kidney, heart and pancreas were also found to be normal and well formed in treated rats as compared to diabetic ones in the same study.[22] Rasheed et al. also reported *Trivanga Bhasma* possessed anti-diabetic activity.[23] Previous studies reported that hydro-alcoholic, alcoholic or aqueous extract of *Picrorhiza kurroa* displayed β-cell regeneration with enhanced insulin production, increase GLUT-4 expression and anti-hyperglycemic effects.[24-28].In one study, aqueous, alcoholic, and chloroform extracts of the leaves of *Tinospora cordifolia* have an insulin-like action and can significantly reduce the blood glucose in normal rabbits and in alloxan-induced diabetic rabbits.[29] Several studies on extracts of *Tinospora cordifolia* and isolated phytoconstituents have reported that it is a preventive and curative antidiabetic herb, which are substantiated by clinical trials.[30] Clinical study of *Tinospora cordifolia* (powdered stem; 50mg/kg body weight, p. o.) for 15days in type 2 diabetic patients resulted significant decrease in the level of fasting blood sugar.[31] Similarly, *Tinospora cordifolia* was found effective as an add-on therapy in patients with type-2 diabetes decreasing the FBG, post prandial blood glucose (PPG) levels and glycosylated hemoglobin (HbA1c) of the patients.[32,33] Another study revealed that *Berberis* fruit extract has beneficial metabolic effects in patients with type II diabetes.[34] Previous study suggested that aqueous ethanolic root extract of *Berberis aristata* was found to lower blood glucose in alloxan induced diabetic rats, reduce oxidative stress and modulate enzymes responsible for glucose metabolism.[35] Extracts and compounds obtained from *Berberis* species have shown effectiveness in the management of diabetes and other metabolic diseases in various cell, animal disease models and clinical trials.[36]

To our knowledge, no research has been done to investigate the effect of Trikgud (combination of *Trivanga Bhasma, Kutaki, Guduchi, and Daruharidra*) on T2DM patients in Nepal. So, we aimed to study a randomized controlled trial to evaluate the efficacy and safety of Trikgud as an add-on medication in uncontrolled T2DM patients with metformin monotherapy in Nepalese population.

Materials and methods

Study design

This clinical trial was a randomized controlled trial to evaluate the clinical efficacy and safety of Trikgud as an add-on drug in uncontrolled T2DM patients with metformin monotherapy. The patients were recruited at research hospital of National Ayurveda Research and Training Center (NARTC), Kirtipur, Nepal. Uncontrolled T2DM patients with only metformin monotherapy were selected for a standardized baseline evaluation which included detailed history taking, physical examination and biochemical analysis.

Diagnosis criteria

Diabetes was diagnosed based on plasma glucose criteria, either the fasting plasma glucose (FPG) ≥126mg/dL or the 2-h plasma glucose (2-h PG) ≥ 200mg/dL during a 75-g oral glucose tolerance test (OGTT) or the random plasma glucose (RPG) ≥200mg/dL or A1C ≥6.5%.[37]

Inclusion criteria

Patients that met the following criteria were eligible for the study: (1) who met the diagnostic criteria, (2) were 18 to 70 years old, (3) had been receiving metformin in a steady dose for over three months and (4) who gave written informed consent.

Exclusion criteria

Patients were excluded from the study if they met one of the following conditions: (1) who were taking insulin; (2) were pregnant or nursing women; (3) had diabetes related complications (peripheral neuropathy, retinopathy etc.); (4) had severe immune deficiency; (5) had recent participation in other clinical trials; (6) were hospitalized for hypoglycemic episodes; (7) had recent major surgical procedure; (8) had any history of malignancy and (9) diagnosed as Type I diabetes mellitus.

Study participants

The total number of the patients participated for the study was 156. After assessing the exclusion criteria, 124 patients were enrolled for the study. The enrolled study participants were randomly divided into two groups, Trikgudmet group and Met group. Participants in the Trikgudmet group took Trikgud 2 pills orally thrice a day along with usual dosage of ongoing metformin at the time of recruitment for 12 weeks, whereas participants in the Met group took dose adjusted metformin monotherapy ranging from 500 mg to 2000 mg/day after the recruitment for 12 weeks. Participants visited at every 2 weeks for the general examination, FPG and 2-h PPG investigation. However, anthropometric and other biochemical laboratory investigations for the study participants were only done at week 12. Finally, only 56 participants were analyzed for the study. The reasons for not including participants for the final analysis of the study were: had poor compliance (n=27), had taken another oral hypoglycemic drug (n=19), loss of follow up (n=15) and withdrawn from the study (n=7).

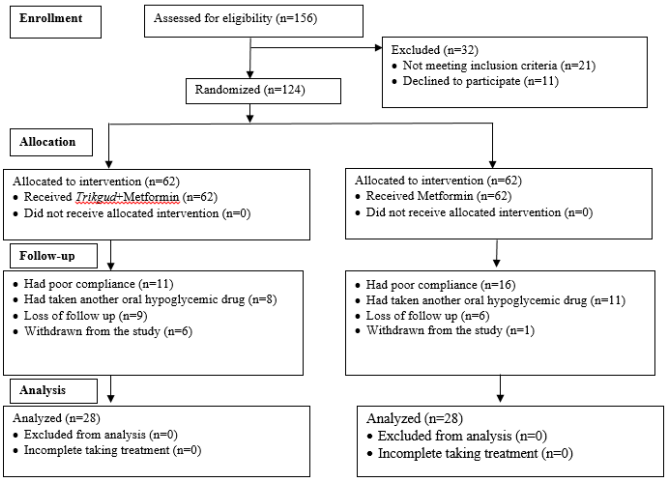

Figure 1 Flowchart of study population's enrollment, allocation, follow-up and analysis

Materials

Each pill of Trikgud consists of *Trivanga Bhasma*: 28.8 mg, powdered form of rhizome of *Kutaki (Picorrhiza kurroa)*: 115.4 mg,

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aqueous extract of stem of *Guduchi (Tinospora cordifolia)*: 115.4 mg and powdered form of stem of *Daruharidra (Berberis aristata)*: 115.4 mg. Each herb was selected based on merely free of microbial contamination examined at NARTC's laboratory whereas *Trivanga Bhasma* was selected on the basis of meeting standard Ayurvedic parameters and its non-toxic effect when taken orally. Dosage of each herb and *Trivanga Bhasma* was calculated on the basis on therapeutic dosage indicated in *Rasa Shastra* and The Ayurvedic Pharmacopoeia of India (API), respectively[23,38-40].

Outcome measures

Trained laboratory technicians and doctors performed the standard biochemical and anthropometric measurements at hospital building of NARTC.

Primary outcomes

The primary outcomes were the difference in the change in HbA1C, FPG and 2-h PPG between the groups.

Secondary outcomes

Secondary outcomes monitored were blood urea, serum creatinine, sodium, potassium, total bilirubin, direct bilirubin, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), alkaline phosphatase, total cholesterol, triglycerides, high-density lipoprotein (HDL), and low-density lipoprotein (LDL).

Physical examination

Blood pressure, weight, height, waist and hip circumference were measured by nurses. Weight and height were measured to the nearest 0.1kg and 0.1cm, respectively. Body mass index (BMI) was calculated as body weight in kilograms divided by the square of height in meters. Waist circumference (WC) was measured at the midpoint between the lower costal margin and iliac crest to the nearest 0.1cm. Hip circumference was measured around the point with the maximum circumference over the buttocks to the nearest 0.1cm. Waist-hip ratio (WHR) was the ratio of the circumference of the waist to that of the hip in centimeters.

Blood specimen collection and analysis

To assess RPG for screening, experienced lab technicians withdrew 3ml of blood specimen of the participants. After screening, the eligible participants were further contacted for second visit (baseline data) and at 12week (after intervention) from whom 5ml of fasting blood specimens were collected after an eight hour overnight fast. The blood samples were sent to the diagnostic pathology laboratory of NARTC for analysis.

Statistics

Statistical package for the social sciences (SPSS) version 17.0 (SPSS, Inc., Chicago, IL) software was used for data analysis. Comparisons of variables between the groups were evaluated using the χ^2 test for distribution of qualitative variables, unpaired *t*-test for normal distribution and Mann-Whitney U test for non-normal distribution of continuous data, whereas comparisons of variables within the group were evaluated by paired *t*-test for normal distribution and Wilcoxon signed-rank test for non-normal distribution of continuous data. All the statistical tests were 2-sided tests, and *p*-value of <0.05 was considered statistically significant.

The trial was approved by the ethics committee of NARTC and followed the ethical guidelines for research in Ayurveda.[41]

Results

Out of 56 participants, 43 (76.8%) and 13 (23.2%) participants were male and female, respectively (Table 1). According to ethnicity categorization, more participants belonged to Chhetri ethnicity (37.5%) followed by Brahman (25.0%), Indigenous (23.2%), others (8.9%) and Madhesi (3.0%) (Table 1). In context of occupation, 25.0% of the participants were retired, 21.4% were private employees, 19.6% were government employees, 19.6% were house-workers and 14.3% were business persons (Table 1). Participants with graduate and above (48.2%) were more predominant than other education category (Table 1). The frequency of participants with current physical activity is higher than frequency of participants with no physical activity (67.9% vs. 32.1%) (Table 1). In the study participants, non-alcohol consumers (76.8%), non-tobacco users (83.9%) and vegetarians (60.7%) were more frequent than alcohol consumers (23.2%), tobacco users (16.1%) and non-vegetarians (39.3%), respectively (Table 1). Among the participants, only 44.6% had a family history of diabetes (Table 1). When compared between Trikgudmet and Met groups, no significant differences were observed except for meat consumers (Table 1). In Met group, 89.3% were vegetarian while in Trikgudmet group, 67.9% were non-vegetarian (Table 1).

Table 1 Demographic and lifestyle characteristics of the patients in Trikgudmet and Met group

Demographic and lifestyle characteristics	Trikgudmet group n (%)	Met group n (%)	Total patients n
Sex			
Male	23 (82.1)	20 (71.4)	43
Female	5 (17.9)	8 (28.6)	13
Ethnicity			
Brahman	10 (35.7)	4 (14.3)	14
Chhetri	8 (28.6)	13 (46.4)	21
Indigenous	7 (25.0)	6 (21.4)	13
Madhesi	2 (7.1)	1 (3.6)	3
Others	1 (3.6)	4 (14.3)	5
Occupation			
Government employee	6 (21.4)	5 (17.9)	11
Private employee	4 (14.3)	8 (28.6)	12
Business	6 (21.4)	2 (7.1)	8
Retired	9 (32.1)	5 (17.9)	14
House-work	3 (10.7)	8 (28.6)	11
Education			
Primary	3 (10.7)	2 (7.1)	5
Lower secondary	6 (21.4)	6 (21.4)	12
Higher secondary	4 (14.3)	1 (3.6)	5
Graduate and above	13 (46.4)	14 (50.0)	27
None	2 (7.1)	5 (17.9)	7
Exercise			
Current physical activity	22 (78.6)	16 (57.1)	38
No physical activity	6 (21.4)	12 (42.9)	18
Alcohol			
Alcohol consumers	5 (17.9)	8 (28.6)	13

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Table Continued...

Demographic and lifestyle characteristics	Trikgudmet group n (%)	Met group n (%)	Total patients n
Non-alcohol consumers	23 (82.1)	20 (71.4)	43
Tobacco			
Tobacco users	2 (7.1)	7 (25.0)	9
Non tobacco users	26 (92.9)	21 (75.0)	47
Meat			
Non-vegetarian	19 (67.9)	3 (10.7)	22
Vegetarian	9 (32.1)	25 (89.3)	34
Family history of Diabetes			
Yes	11(39.3)	14 (50.0)	
No	17 (60.7)	14 (50.0)	

Table 2 shows the baseline characteristics differences between Trikgudmet group and Met group. There was no significant differences between the baseline characteristics except for WC (p=0.04) and WHR (p=0.0001). WC and WHR were more in Trikgudmet group than Met group (Table 2).

Table 2 Baseline characteristics differences between Trikgudmet group and Met group

Variables	Trikgudmet group (n = 28)[a,b]	Met group (n = 28)[a,b]	p – value[c,d]
Age (years)	52.5 (9.4)[a]	53.0 (6.8)[a]	0.81[c]
Body weight (kg)	70.4 (8.9)[a]	67.2 (9.6)[a]	0.21[c]
Body height (m)	1.64 (0.08)[a]	1.62 (0.07)[a]	0.40[c]
Body mass index (kg/m^2)	26.1 (2.1)[a]	25.5 (2.9)[a]	0.36[c]
Waist circumference (cm)	96.5 (6.3)[a]	92.8 (7.2)[a]	0.04[c]
Hip circumference (cm)	97.3 (5.6)[a]	96.8 (6.3)[a]	0.75[c]
Waist-hip ratio	0.99 (0.03)[a]	0.96 (0.03)[a]	0.0001[c]
Systolic blood pressure (mm Hg)	126.2 (11.0)[a]	125.4 (14.1)[a]	0.80[c]
Diastolic blood pressure (mm Hg)	83.7 (7.0)[a]	84.9 (9.9)[a]	0.61[c]
Diabetic duration (yr)	4.00 (2.25, 6.75)[b]	2.00 (0.00, 6.00)[b]	1.36[d]
Metformin daily dose (g)	1.00 (0.85, 1.00)[b]	1.00 (0.85, 1.00)[b]	0.78[d]
Fasting plasma glucose (mg/dl)	135.1 (26.3)[a]	145.1 (25.2)[a]	0.13[c]
2-h Postprandial glucose (mg/dl)	235.4 (62.3)[a]	221.2 (61.4)[a]	0.40[c]
Glycosylated hemoglobin (%)	7.65 (7.10, 8.85)[b]	7.40 (6.70, 8.76)[b]	0.44[d]
Blood urea nitrogen (mg/dL)	19.8 (4.5)[a]	19.9 (3.6)[a]	0.94[c]
Serum creatinine (mg/dL)	0.88 (0.19)[a]	0.96 (0.17)[a]	0.10[c]
Sodium (mEq/L)	142.3 (3.4)[a]	140.7 (2.9)[a]	0.05[c]
Potassium (mEq/L)	4.4 (0.5)[a]	4.3 (0.4)[a]	0.29[c]
Total bilirubin (mg/dL)	0.60 (0.53, 0.60)[b]	0.60 (0.50, 0.68)[b]	0.72[d]
Direct bilirubin (mg/dL)	0.10 (0.10, 0.10)[b]	0.10 (0.10, 0.18)[b]	0.48[d]
Alanine aminotransferase (IU/L)	25.0 (11.3)[a]	27.6 (10.5)[a]	0.38[c]
Aspartate aminotransferase (IU/L)	23.7 (8.2)[a]	23.8 (8.5)[a]	0.96[c]
Alkaline phosphatase (IU/L)	84.6 (21.1)[a]	83.4 (22.1)[a]	0.83[c]
Total cholesterol (mg/dL)	150.0 (36.2)[a]	145.1 (44.0)[a]	0.65[c]
Triglycerides (mg/dL)	151.8 (62.5)[a]	150.9 (34.4)[a]	0.95[c]
High density lipoprotein (mg/dL)	41.4 (4.4)[a]	44.0 (5.6)[a]	0.06[c]
Low density lipoprotein (mg/dL)	76.6 (27.2)[a]	77.9 (36.5)[a]	0.88[c]

[a]Variables are expressed as mean (standard deviation) for normal distribution.

[b]Variables are expressed as median (interquartile range) for non-normal distribution.

[c]Analyzed by unpaired *t*-test.

[d]Analyzed by Mann-Whitney U test.

The levels of FPG and 2-h PPG at week 0, week 4, week 8 and week 12 between and within Trikgudmet group and Met group are shown in Table 3. At week 12, there was significant differences of FPG and 2-h PPG in both Trikgudmet group (p=0.0002 & p=0.0001) and Met group (p=0.0002 & p=0.0001) when compared with week 0 (Table 3). Likewise, when FPG and 2-h PPG levels were compared between week 0 and week 4; week 0 and week 8, a statistically significant decrease of FPG and 2-h PPG was observed in Trikgudmet group (Table 3). However, there was a statistically significant increase at week 4 but a significant decrease at week 8 of FPG when compared with week 0 in Met group (Table 3). When 2-h PPG level were compared between week 0 and week 4; week 0 and week 8 in Met group, a statistically significant decrease of 2-h PPG was resulted. While comparing between Trikgudmet and Met group, statistically significant difference was only seen for FPG level at week 4 (p=0.0001).

There was a statistically significant decrease of 8.6% in HbA1C level (p = 0.0001) and a significant increase of 29.0% in HDL cholesterol level and 25.0% in total bilirubin level (p = 0.0003 & p = 0.00, respectively) when before (week 0) and after (week 12) intervention in Trikgudmet group was compared (Table 4).

When anthropometric and biochemical variables were compared before (week 0) and after (week 12) intervention in Met group, there was a statistically significant decrease of 10.1% in HbA1C level (p = 0.02), 16.7% in serum creatinine level (p = 0.0002) and 18.5% in triglyceride level. (p = 0.004) (Table 5). Unlikely, ALT, AST, alkaline phosphatase and HDL levels showed a statistically significant increase after week 12 intervention in Met group (Table 5).

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Table 3 Changes in Fasting plasma glucose and 2-h Postprandial glucose within and between Trikgudmet group and Met group during the 12 week period

Variables		Trikgudmet group (n = 28)[a]	Met group (n = 28)[a]	*p* – value[b]
Fasting plasma glucose (mg/dl)				
Week 0	Before	133.8 (26.1)	145.1 (25.2)	0.10
Week 4	After	126.6 (30.8)	221.2 (61.4)	0.0001
	p – value[c]	0.02	0.0001	
Week 4	Before	126.6 (30.8)	221.2 (61.4)	0.0001
Week 8	After	119.7 (20.1)	123.2 (24.6)	0.56
	p – value[c]	0.05	0.0001	
Week 8	Before	119.7 (20.1)	123.2 (24.6)	0.56
Week 12	After	118.0 (19.4)	121.1 (20.6)	0.56
	p – value[c]	0.52	0.55	
Week 0	Before	133.8 (26.1)	145.1 (25.2)	0.10
Week 12	After	118.0 (19.4)	121.1 (20.6)	0.56
	p – value[c]	0.0002	0.0001	
2-h Postprandial glucose (mg/dl)				
Week 0	Before	235.4 (62.3)	221.2 (61.4)	0.40
Week 4	After	188.5 (49.5)	185.3 (32.3)	0.77
	p – value[c]	0.0001	0.002	
Week 4	Before	188.5 (49.5)	185.3 (32.3)	0.77
Week 8	After	171.9 (40.3)	162.5 (24.4)	0.30
	p – value[c]	0.04	0.003	
Week 8	Before	171.9 (40.3)	162.5 (24.4)	0.30
Week 12	After	163.1 (30.9)	172.5 (27.5)	0.24
	p – value[c]	0.05	0.07	
Week 0	Before	235.4 (62.3)	221.2 (61.4)	0.40
Week 12	After	163.1 (30.9)	172.5 (27.5)	0.24
	p – value[c]	0.0001	0.0002	

[a]Variables are expressed as mean (standard deviation) for normal distribution.

[b]Analyzed by unpaired *t*-test.

[c]Analyzed by paired *t*-test.

Table 4 Comparison of variables before and after treatment in Trikgudmet group

Variables	Before treatment (n = 28)[a,b]	After treatment (n = 28)[a,b]	*p* – value[c,d]
Body weight (kg)	70.4 (8.9)[a]	70.1 (8.2)[a]	0.48[c]
Body mass index (kg/m^2)	26.1 (2.1)[a]	26.0 (1.8)[a]	0.50[c]
Waist circumference (cm)	96.5 (6.3)[a]	96.3 (6.0)[a]	0.21[c]
Hip circumference (cm)	97.3 (5.6)[a]	97.0 (5.3)[a]	0.14[c]
Waist-hip ratio	0.99 (0.03)[a]	0.99 (0.03)[a]	0.62[c]
Systolic blood pressure (mm Hg)	126.2 (11.0)[a]	125.9 (12.4)[a]	0.87[c]
Diastolic blood pressure (mm Hg)	83.7 (7.0)[a]	82.3 (7.4)[a]	0.35[c]
Glycosylated hemoglobin (%)*	8.0 (1.2)[a]	7.3 (0.8)[a]	0.0001[c]
Blood urea nitrogen (mg/dL)	19.8 (4.5)[a]	21.2 (4.3)[a]	0.23[c]
Serum creatinine (mg/dL)	0.88 (0.19)[a]	0.80 (0.20)[a]	0.16[c]
Sodium (mEq/L)	142.3 (3.4)[a]	142.3 (2.1)[a]	0.99[c]
Potassium (mEq/L)	4.4 (0.5)[a]	4.5 (0.5)[a]	0.76[c]
Total Bilirubin (mg/dL)	0.60 (0.53, 0.60)[b]	0.75 (0.60, 0.90)[b]	0.00[d]
Direct Bilirubin (mg/dL)	0.10 (0.10, 0.10)[b]	0.10 (0.10, 0.20)[b]	0.08[d]
Alanine aminotransferase (IU/L)	25.0 (11.3)[a]	24.8 (9.0)[a]	0.93[c]
Aspartate aminotransferase (IU/L)	23.7 (8.2)[a]	25.1 (6.6)[a]	0.39[c]
Alkaline phosphatase (IU/L)	84.6 (21.1)[a]	84.6 (20.6)[a]	1.0[c]
Total cholesterol (mg/dL)	150.0 (36.2)[a]	152.4 (37.3)[a]	0.80[c]
Triglycerides (mg/dL)	151.8 (62.5)[a]	138.4 (58.7)[a]	0.35[c]
High density lipoprotein (mg/dL)	41.4 (4.4)[a]	53.4 (14.1)[a]	0.0003[c]
Low density lipoprotein (mg/dL)	76.6 (27.2)[a]	76.5 (25.8)[a]	0.99[c]

[a]Variables are expressed as mean (standard deviation) for normal distribution.

[b]Variables are expressed as median (interquartile range) for non-normal distribution.

[c]Analyzed by paired *t*-test.

[d]Analyzed by Wilcoxon Signed-Rank test.

*Analyzed by paired *t*-test even though dataset of before treatment is non-normal distribution.

Table 5 Comparison of variables before and after treatment in Met group

Variables	Before treatment (n = 28)[a,b]	After treatment (n = 28)[a,b]	*p* – value[c,d]
Body weight (kg)	67.2 (9.6)[a]	67.5 (8.9)[a]	0.60[c]
Body mass index (kg/m^2)	25.5 (2.9)[a]	25.6 (2.8)[a]	0.55[c]
Waist circumference (cm)	92.8 (7.2)[a]	92.3 (6.8)[a]	0.17[c]

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Table Continued...

Variables	Before treatment (n = 28)[a,b]	After treatment (n = 28)[a,b]	*p* – value[c,d]
Hip circumference (cm)	96.8 (6.3)[a]	96.8 (6.0)[a]	1.00[c]
Waist-hip ratio	0.96 (0.03)[a]	0.95 (0.03)[a]	0.07[c]
Systolic blood pressure (mm Hg)	125.4 (14.1)[a]	124.0 (15.0)[a]	0.52[c]
Diastolic blood pressure (mm Hg)	84.9 (9.9)[a]	82.6 (8.7)[a]	0.18[c]
Glycosylated hemoglobin (%)	7.9 (1.9)[a]	7.1 (0.6)[a]	0.02[a]
Blood urea nitrogen (mg/dL)	19.9 (3.6)[a]	21.0 (2.4)[a]	0.21[c]
Serum creatinine (mg/dL)	0.96 (0.17)[a]	0.80 (0.20)[a]	0.0002[c]
Sodium (mEq/L)	140.7 (2.9)[a]	140.7 (2.3)[a]	0.91[c]
Potassium (mEq/L)	4.3 (0.4)[a]	4.3 (0.4)[a]	0.32[c]
Total bilirubin (mg/dL)	0.60 (0.50, 0.68)[b]	0.60 (0.50, 0.70)[b]	0.65[d]
Direct bilirubin (mg/dL)	0.10 (0.10, 0.18)[b]	0.10 (0.10, 0.20)[b]	0.22[d]
Alanine aminotransferase (IU/L)	27.6 (10.5)[a]	31.9 (10.6)[a]	0.02[c]
Aspartate aminotransferase (IU/L)	23.8 (8.5)[a]	30.4 (7.2)[a]	0.005[c]
Alkaline phosphatase (IU/L)	83.4 (22.1)[a]	101.1 (23.0)[a]	0.004[c]
Total cholesterol (mg/dL)	145.1 (44.0)[a]	154.7 (42.6)[a]	0.40[c]
Triglycerides (mg/dL)	150.9 (34.4)[a]	123.0 (42.6)[a]	0.004[c]
High density lipoprotein (mg/dL)	44.0 (5.6)[a]	62.8 (16.5)[a]	0.0001[c]
Low density lipoprotein (mg/dL)	77.9 (36.5)[a]	78.9 (28.1)[a]	0.89[c]

[a]Variables are expressed as mean (standard deviation) for normal distribution.

[b]Variables are expressed as median (interquartile range) for non-normal distribution.

[c]Analyzed by paired *t*-test.

[d]Analyzed by Wilcoxon Signed-Rank test.

[*]Analyzed by paired *t*-test even though dataset of before treatment is non-normal distribution

Table 6 shows the comparison of variables between Trikgudmet and Met groups after intervention. Statistical significance differences were only observed for WC ($p = 0.03$), WHR ($p = 0.0001$), sodium ($p = 0.009$), total bilirubin ($p = 0.001$), ALT ($p = 0.01$), AST ($p = 0.006$), alkaline phosphatase (0.006) and HDL ($p = 0.03$) between Trikgudmet and Met groups (Table 6). Nonetheless, the values were within the normal range in both groups.

Table 6 Comparison of variables between Trikgudmet group and Met group after intervention

Variables	Trikgudmet group (n = 28)[a,b]	Met group (n = 28)[a,b]	*p* – value[c,d]
Body weight (kg)	70.1 (8.2)[a]	67.5 (8.9)[a]	0.26[c]
Body mass index (kg/m^2)	26.0 (1.8)[a]	25.6 (2.8)[a]	0.50[c]
Waist circumference (cm)	96.3 (6.0)[a]	92.3 (6.8)[a]	0.03[c]
Hip circumference (cm)	97.0 (5.3)[a]	96.8 (6.0)[a]	0.85[c]
Waist-hip ratio	0.99 (0.03)[a]	0.95 (0.03)[a]	0.0001[c]
Systolic blood pressure (mm Hg)	124.0 (15.0)[a]	125.9 (12.4)[a]	0.62[c]
Diastolic blood pressure (mm Hg)	82.3 (7.4)[a]	82.6 (8.7)[a]	0.90[c]
Fasting plasma glucose (mg/dl)	118.0 (19.4)[a]	121.1 (20.6)[a]	0.56[c]
2-h Postprandial glucose (mg/dl)	163.1 (30.9)[a]	172.5 (27.5)[a]	0.24[c]
Glycosylated hemoglobin (%)	7.3 (0.8)[a]	7.1 (0.7)[a]	0.48[c]
Blood urea nitrogen (mg/dL)	21.2 (4.3)[a]	21.0 (2.4)[a]	0.79[c]
Serum creatinine (mg/dL)	0.81 (0.20)[a]	0.80 (0.20)[a]	0.84[c]
Sodium (mEq/L)	142.3 (2.1)[a]	140.7 (2.3)[a]	0.009[c]
Potassium (mEq/L)	4.5 (0.5)[a]	4.3 (0.4)[a]	0.08[c]
Total bilirubin (mg/dL)	0.75 (0.60, 0.90)[b]	0.60 (0.50, 0.70)[b]	0.001[d]
Direct bilirubin (mg/dL)	0.10 (0.10, 0.20)[b]	0.10 (0.10, 0.20)[b]	0.98[d]
Alanine aminotransferase (IU/L)	24.8 (9.0)[a]	31.9 (10.6)[a]	0.01[c]
Aspartate aminotransferase (IU/L)	25.1 (6.6)[a]	30.4 (7.2)[a]	0.006[c]
Alkaline phosphatase (IU/L)	84.6 (20.6)[a]	101.1 (23.0)[a]	0.006[c]
Total cholesterol (mg/dL)	152.4 (37.3)[a]	154.7 (42.6)[a]	0.83[c]
Triglycerides (mg/dL)	138.4 (58.7)[a]	123.0 (42.6)[a]	0.27[c]
High density lipoprotein (mg/dL)	53.4 (14.1)[a]	62.8 (16.5)[a]	0.03[c]
Low density lipoprotein (mg/dL)	76.5 (25.8)[a]	78.9 (28.1)[a]	0.74[c]

[a]Variables are expressed as mean (standard deviation) for normal distribution.

[b]Variables are expressed as median (interquartile range) for non-normal distribution.

[c]Analyzed by unpaired *t*-test.

[d]Analyzed by Mann-Whitney U test.

Discussion

The present study showed that add-on Ayurvedic medicine Trikgud can cause hypoglycemic effect in uncontrolled T2DM patients with

metformin monotherapy which was evident as a significant decrease in the FPG, 2-h PPG and HbA1C level after 12weeks intervention. Although statistical significance differences were observed for WC, WHR, sodium, total bilirubin, ALT, AST, alkaline phosphatase and HDL between Trikgudmet and Met groups, the values of biochemical parameters were within the normal range in both groups.

A significantly higher frequency of male than female in the present study was consistent with the previous studies.[42–45] The higher proportion of non-alcohol consumers, non-tobacco users and vegetarian in Nepalese population were similar with our previous studies.[46, 47] In our study, the frequency of current physical activity was also higher than no physical activity. This may have occurred as the patients diagnosed with T2DM are prone to change healthy lifestyle factors than the non-diabetic people.

The present study participants had more BMI and WHR and thus, our study also suggests the relationship between the anthropometric indices of adiposity and T2DM risk like the previous studies.[48–59] Daily dose of metformin in our study ranges from 500mg to 2000mg/day which is consistent with the previous study.[60] The median duration of diabetes was 4years like the previous study.[61]

A potential benefit of initial combination therapy on glycemic outcomes in diabetes compared to metformin monotherapy have been suggested.[62-63] In our study, there was a statistically significant decline of FPG, 2h-PPG and HbA1C levels in both Trikgudmet and Met groups and there was no significant difference of FBG, 2h-PPG and HbA1C when compared between the groups. Thus, the present findings suggest that *Trikgud* can be used as an initial combination therapy to metformin monotherapy in uncontrolled T2DM patients.

The present study did not reveal any significant changes in hepatic, renal and lipid functions tests. The *Trigud* formulation is well tolerated without any adverse effects.

To our knowledge, this is the first study to show hypoglycemic effect of *Trikgud* in uncontrolled T2DM. However, there are several studies which showed the beneficial effects of each ingredients of *Trikgud* in T2DM patients. *In vivo* studies reported anti-diabetic property of *Trivanga Bhasma*, one of the components of *Trikgud*.[21, 22] Similarly, several previous studies showed anti-hyperglycemic effects of *Picrorhiza kurroa* extract.[24-28] Likewise, several studies on extracts of *Tinospora cordifolia* and isolated phytoconstituents have reported to possess anti-diabetic property.[29-33] Extracts and compounds obtained from *Berberis* species have shown effectiveness in the management of diabetes in various cell, animal disease models and clinical trials.[34-36]

There are several limitations in our study. Although, the gold standard of clinical trial is double blinded, randomized, placebo controlled clinical trial, but we used combination of *Trikgud* and metformin in intervention group and metformin in control group. This might have not postulated the true efficacy of *Trikgud*. The reason behind this is the ethical committee did not approve the study to use placebo controlled, double blinded, randomized clinical trial. The sample size of the present study was limited and was not withdrawn through the methodology of sample size calculation. We did not categorize the study participants by gender. We could not elucidate the possible biological mechanism of our formulation as an oral anti-diabetic agent. It may be due to chance finding as the sample size is small.

Conclusion

To our knowledge, this is the first study to evaluate the efficacy and safety of *Trikgud* in management of T2DM in Nepalese population. As a novel add-on drug to metformin monotherapy, *Trikgud* (Ayurvedic herbo-mineral formulation) may have a potential clinical use in diabetes management. So, Ayurvedic medicines could be a better alternative to manage T2DM, thereby reducing complications in the long run. Nonetheless, more randomized placebo controlled trials are required to confirm the efficacy and safety of *Trikgud* intervention in managing T2DM.

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Conflicts of interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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