Pilot study on Anti diabetic potential of Churu-5

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Abstract

Churu-5 is used for the treatment of diabetes in traditional medicine. It is composed of *Phyllunthus emblica*Linn.*Curcuma Longa* Linn., *Berberies aristata* Berberidaceae, Thlaspi arvense L. and Tribulus terristries L. We conducted a pilot study to investigate the efficacy of herbal formula, Churu-5, in treating patients with type 2 diabetes mellitus.Thirty patients with type 2 diabetes mellitus received 3 tablets of Churu-5 three times daily for 28 days. The primary outcome was change in glycaemic control as evidenced by fasting blood glucose (FBG) and 2 hours postprandial blood glucose (PPBG). Other measures included body mass index, waist circumference, body weight and diabetic symptoms such as polyuria, polyphagia, polydipsia and fatigue. In the result some significant difference were observed.Therefore the present pilot-study shows that the traditional medicine Churu-5 tablet has improved PPBG level and it can be used for reducing diabetic symptoms in adults with type 2 diabetes mellitus. More over people with wind dominant and phlegm dominant constitution are more likely to be susceptible to diabetes.

Introduction

The number of patients with type 2 diabetes is increasing rapidly in both developed and developing countries around the world. The emerging pandemic is driven by the combined effects of population ageing, rising levels of obesity and inactivity.[1] Alternative systems of medicine based on traditional wisdom have thrived through ages and are still practiced by a large population for the management of diabetes. A large number of plants have proved their efficacy in management of diabetes especially hyperglycemia. In many cases, scientific studies have validated the anti-diabetic nature of plant-based medicines[2].Over the past few decades, herbal medicines have attracted much attention as potential therapeutic agents in the prevention and treatment of diabetic complications due to their multiple targets and less toxic side effects. Number of patients seeking alternative treatment in traditional medicine is seen to be increasing as per the records maintained by some traditional physicians. According to the JDWNRH diabetes clinic record, number of new patients in 2012 was 340 and 484 in 2011. Likewise more than 215 diabetes patients turned up to seek traditional treatment in Thimphu alone.Nearly 400 herbs and plant preparations are reported to have beneficial effects in the treatment of diabetes mellitus.[3]Churu-5, also known as U-nga-5 is used for the treatment of all kinds of diabetes in Tibetan traditional medicine.[4] It is composed of *Phyllanthus emblica* Linn.*, Curcuma longa* Linn.*, Berberies aristata* Berberidaceae*, Thlaspi arvense* L.and *Tribulus terristris* L.[5] Recent studies have shown the antidiabetic effects of almost all ingredients of Churu-5 although there is no study done on churu 5 as a drug.Therefore the aim of this pilot study was to determine antidiabetegenic potential of Churu-5, which is currently in use for treatment of diabetes in Bhutan. This is the first study to evaluate the efficacy of Churu-5 on Bhutanese adults with diabetes mellitus not in the insulin requiring stage. This study got the approval from Research Ethical Board of Health, Ministry of Health, Bhutan.

Materials and Methods

Materials
Churu 5 is manufactured by Menjong Sorig Pharmaceuticles in Bhutan, using traditional sorig formulas. It is consisted of 5 herbal medicines. They are *Phyllanthus emblica* Linn. Family Euphorbiaceae (0.3333kg) *Curcuma longa* Linn. Family Zingiberaceae (0.1667kg) *Berberies aristata* DC. Family Berberidaceae (0.1667kg) *Thlaspi arvense* Linn. Family Brassicaceae (0.1667kg)and *Tribulus terristris* L. Family Zygophllaceae (0.1667kg). Each tablet weighs 500 mg. Each dosage consists of 3 tablets. Patients were given 3 doses per day, morning, mid-day and before bed.Churu-5 tablet was administered with warm boiled water. All the doses were given 1 to 2 hours before meal.

Methods: Setting of the study
This study work was implemented at Jigmi Dorji Wangchuck National Referral Hospital for the period of 28 days, starting from 10th October to 7th November 2013.

Diabetic patients and recruitment
Total of 30 subjects who were interested to get the treatment from National Traditional medicine Hospital after being diabetes mellitus patients for 2-5years were enrolled to the study. We used diabetes self care hand book for patient's demographic information and duration of diabetes they suffered. Diabetes self care hand book and follow up record is a book given to all the diabetes patients from the diabetes clinic the day they join the clinic for treatment or advices.The subjects included in this study are those who are between the ages of 18 to 69years. They are the confirmed diabetes patients who have their baseline FBG ≥126 mg/dl and PPBS ≥200 mg/dl. They are the patients who control their blood sugar with regular exercise and required diet pattern as advised by the dietitians but no extra workouts. Their participation was voluntary and all the subjects signed informed consent form before the study.

Inclusion criteria
1. Both gender between the ages of 18-69 years
2. Participants who are able and willing to perform the study protocol and participate throughout the entire trial period.
3. The patients who understand the risks and benefits of the study and signed a written informed consent.
4. Patients whose FBG concentration is 100-190mg/dl
5. Patients whose 2-hour postprandial concentration range 140-250mg/dl (after meal).

Exclusion criteria
1. Presently on other blood glucose level controlling agents.
2. History of allergy to the herbal products.
3. Daily intake of alcoholic beverages.
4. Smokers consuming more than 1 pack/day.
5. Presently having acute diseases or other untreated illness requiring treatment.
6. Impaired hepatic or renal functions.
7. Pregnant, breastfeeding status or female of reproductive age, not using proper contraception.
8. Participant in other clinical trials or a blood donor, within the past 1 month.
9. History of severe disease or any condition, in the investigators opinion, that would endanger the individual's safety or affect the study result.
10. Patients diagnosed as type 1 and type 2 diabetes mellitus in insulin requiring stage.

Study design

As this was a pilot study and there was no prior human data on the effects of the Churu-5 from which to perform a power calculation, the sample size was set at 30, in take all basis. This pilot study is designed as case series of 4 weeks (before and after) study after following the instruction of Ethical committee of Bhutan. A case series is a descriptive study that follows a group of patients who have a similar diagnosis or who are undergoing the same procedure over a certain period of time. It is a particularly common way of delineating the clinical picture of a disease.

Outcome measures of the study

Primary outcomes were the changes in FBG and PPBG in patients treated with Churu-5 from baseline to the conclusion of the study. None of the pre-diabetic patients were involved so that the results of this study remain specific for diabetic patients only. The secondary outcomes selected to explain the primary outcome results were body mass index (BMI), waist circumference, and hip circumference and diabetes symptoms like polyuria, polydipsia, polyphagia, and fatigue.We examined the effects of Churu-5 tableton FBG, 2 hrs after PPBS in patients with type 2 diabetes mellitus. Thirty well-controlled patients with type 2 diabetes mellitus from the diabetes outpatient clinic of our hospital were recruited to a pilot study of 4 weeks before and after case series study. Participants in the intervention were instructed not to consume any other antidiabetic medicine besides Churu-5 tablet.FBG and PPBG, diabetes symptoms observation, and anthropometric measurements were conducted at baseline and weekly visits for 28 days. Also body constituents and its susceptibilityto diabetes were determined by using the traditional medicine constitution table.

Blood glucose level of diabetic patients

Blood glucose levels were measured using Auto analyser CS-600 (made in China) as a part of daily routine work by the lab personnel in JDWNRH laboratory.Blood was collected every visit from a vein from all 30 participants and kept in a bottle containing sodium fluoride (NaF) and potassium oxalate mixed at proportion of 1 : 3 usually 4 mg of the mixture is required. Both the substances act as anticoagulant and NaF prevents glycolysis in RBC's by inhibiting the enzyme 'enolase'.

a) FBS: The blood samples were collected after the patient fasts for 12 hours or overnight.

b) PPBS: After the patient fasts for 12 hours, blood was collected 2 hours after the ingestion of the meal.The blood test reports were then collected by the investigator 4 hours later from the laborator

Observation of diabetic symptoms

Visual analogue scale (VAS) was used to measure the secondary symptoms; polyuria, polyphagia, polydipsia and fatigue. Polyuria is a condition where there is excessive urination. Polyphagia is a condition of excessive hunger. Polydipsia is a condition of excessive thirst. Fatigue is a tiredness which is distinct from weakness. VAS is a straight horizontal line of fixed length, usually 100 mm. The ends were defined as the extreme limits of the parameter to be measured orientated from the left (no symptom) to the right (worst symptom). The score was obtained by measuring the line from "No symptom" to the point indicated by the subject that represents their symptom level, the higher the VAS score, the higher the symptom. The patient is requested to draw a line at the point that best describes his or her symptom level. The point where the line is drawn is taken as the reading and noted in the case report form.It is the most widely used scale for assessment of pain

and symptoms in clinical setting and has been reported to be sensitive and reliable. VAS was selected because it has been widely used and validated in a number of studies and has been found to correlate well with pain measuring method (Agnes Paul-dauphin et al, 1999).

Anthropometric measurement of the diabetic patients
All participants were measured in light garments (estimated approximately 0.5 kg) and bare feet. The waist circumference (WC: recorded to the nearest 0.1 cm) were taken 2.5 cm above the umbilicus at the upright position. The hip circumference (HC: to the nearest 0.1 cm) were measured at the horizontal level of the widest part of the hip. The participants were asked to stand with his/her back to the height rule. The back of the head, back, buttock, calves and heels touching the upright, feet together. The top of the external auditory meatus (ear canal) leveled with the inferior margin of the bony orbit (cheek bone). The participants were asked to look straight to get the correct height measurement. All the measurements were noted in the case report form (annexed).We calculated BMI by dividing weight in kg by height in m^2. The BMI is used in a wide variety of contexts as a simple method to assess how much an individual's body weight departs from what is normal or desirable for a person of his or her height.It was taken as the second parameter to see the relation between body mass index and diabetes in our study. We also tried to determine if Churu-5 tablet has any effect on body mass index.

Determination of traditional body constitution
The body constitutions of the patients were determined using a table (annexed) in which characteristics of patients are categorized into wind, bile and phlegm. The characteristic consists of pulse reading, physical body features, behaviors, nature, and memory, location of discomfort, and place where they feel uncomfortable. Patients were checked, observed, questioned and put tick mark on the appropriate boxes one by one. At last ticked boxes were counted down. The highest number indicated the dominating constitution. When there was double equal numbers or results which are very close it meant that the patient has combined constitution. When the numbers are equal it means that patient have balanced constitution and a good equilibrium between constitutions. We applied this table to evaluate the association between the diabetes susceptibility and the patient's constitution.

Compliance calculation
The researchers provided the investigational drug to the participants in time and explained medication to them. Compliance of subjects were evaluated by the below formula. Subjects are asked to return remaining drugs. Compliance (%) = [(distributed drugs-remained drugs)/distributed drugs] ×100
Adverse event reporting.We kept our adverse events reporting form ready if incase any patients experienced some adverse effects and report to us.

Data collection
Laboratory results were collected from the lab weekly, beginning from the baseline to day 28. The case report form (annexed) was filled up at the baseline and every visit. The case report form was used to get the information of patient's demography, vital signs, anthropometric measurements, and diabetic symptom measurements. Data for diabetic symptoms like polyuria, polydipsia, polyphagia and fatigue were obtained from the marking done by patient themselves on the visual analogue scale on every visit. The scale reading on which they draw the line was taken as their

symptom reading. Data for the determination of traditional body constitution was done by reading the pulse and using the questionnaire at the baseline.

Statistical analysis
The participants who have completed the 4 weeks without major protocol violations and kept compliance rate over 80% was analyzed by the per protocol method. The anti-diabetic potential of Churu-5 tablet was assessed by using the paired t-test. With values of $p<0.05$ considered statistically significant, SPSS for windows version 17.0 was used for analyses.

Results
Patients for this study consisted of 47% male and 53% female. None of the patients consumed alcohol and coffee. None of the patients smoked. There were no patients who fall under age group of 18 to 30 years. 43% of patients fall under the age group of 31 to 50years. Majority of patients in this study were of age between 51 to 69 years with 57%. None of the diabetes patients were under weight. 13% of participants were with normal body mass index. 12% were who fall under overweight. 5% of patients were obese class I.

Effect of Churu-5 on FBG levels
Levels of FBG slightly decreased after Churu-5 treatment but it was not significantly different between the baseline and the follow up days of the treatment.

Effect of Churu-5 on PPBG
2 hrs PPBG levels were not significantly different between the baseline and days of 7 and 14. However, 2 hrs PPBG levels significantly decreased at day 21(211 ± 29.2 mg/dl) and day 28 ($208+36.5$mg/dl) after Churu-5 treatment comparing to the baseline (221 ± 21.7mg/dl). Data are shown in Table 1.

Effect of Churu-5 on Anthropometric measurements
BMI significantly decreased at 14 (25.4 ± 4.4kg/m^2:p=0.04), 21(25.4 ± 4.4kg/m^2:p=0.01) and 28 (25.4 ± 4.44kg/m^2:p=0.008) days after Churu-5 treatment comparing to baseline (25.6 ± 4.5kg/m^2). Data are shown in Table 1.
There was no significant difference between the baseline and follow up 7, 14, 21 and 28 days on waist circumference (Table1)

Effects of Churu-5 on diabetes symptoms
Polyuria and fatigue were significantly decreased by Churu-5 at every visits comparing to the baseline (Table 2). Polydipsia and polyphagia were significantly decreased at 14, 21 and 28 days by Churu-5 treatment compared to the baseline (Table 2).

Table 1 Clinical measures

Parameter	Day 0	Day 7	Day 14	Day 21	Day 28
Fasting blood glucose (mmol/L)	153 ± 22.1	149 ± 20.4	146 ± 24.4	147 ± 26.4	148 ± 31.2
Postprandial blood glucose (mmol/L)	221 ± 21.7	218 ± 23.5	215 ± 26.0	211 ± 29.2*	208 ± 36.5*
Weight (kg)	69.7 ± 13.8	69.8 ± 13.6	69 ± 13.3	69.2 ± 13.2*	69.2 ± 13.3*

± is mean standard deviation unless stated otherwise.
*p<0.05,
**p<0.02,
***p<0.01

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BMI (kg/m2)	25.6 ± 4.5	25.6 ± 4.5	25.4 ± 4.4	25.4 ± 4.4	25.4 ± 4.4
Waist (cm)	81.6 ± 9.7	81.6 ± 9.7	82 ± 9.6	81.4 ± 9.5	81.3 ± 9.5
Systolic blood pressure (mmhg)	161 ± 36.1	166± 31.1	169 ± 32.2	169 ± 32.3	169 ± 32.2
Diastolic blood pressure (mmhg)	86.8 ± 5.9	85.7 ± 4.0	86.1 ± 3.7	85.8 ± 3.7	85.7 ± 3.6

Table 2 Diabetes symptoms

Symptoms	Day 0	Day 7	Day 14	Day 21	Day 28
Polyuria	6.3±1.3	6.0±1.4	5.5±1.2	5.0±1.4	4.8±1.4
Polydipsia	6.2±1.6	6.2±1.5	5.6±1.3	4.8±1.3	4.9±1.7
Polyphagia	4.4±1.4	4.3±1.3	4.1±1.4	3.7±1.4	3.7±1.4
Fatigue	5.0±1.6	4.9±1.6	4.6±1.4	4.2±1.2	3.9±1.2

± is mean standard deviation unless stated otherwise. $*p<0.05$, $**p<0.02$, $***p<0.01$

Body constitutions of the diabetes patients.

Body constitutions of the patients with diabetes mellitus were determined before the treatment with Churu-5 tablet or at baseline by reading the pulse and using the table which categorizes a person into 7 constitutions, in traditional medicine**.**All 30 patients were having combined constitution of wind, bile and phlegm out of which 33.3% wasphlegm dominant and 33.3%of wind dominant. 13.3% of bile dominant, 10% were of wind and phlegm combined constitution dominant, 6.75% of bile and phlegm combined constitution dominant and 3.3% were of wind and bile combined constitution dominant as shown in Figure 1.

Figure1. Traditional Body Constitution. Number of patients=30
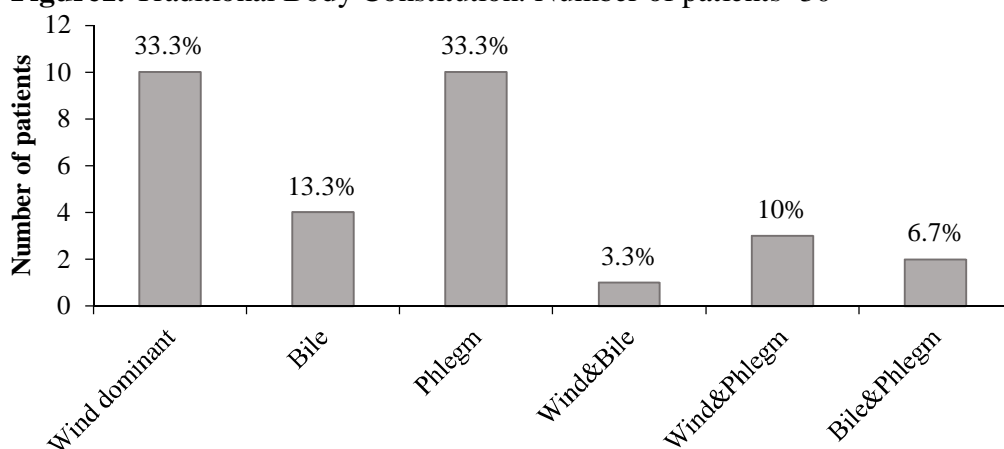
Discussion

The purpose of this pilot study was to evaluate the effect of traditional herbal medicine Churu-5 tablet in the treatment of type 2 diabetes mellitus, since traditional medicines have been increasingly used as a co-adjuvant treatment of chronic diseases, including diabetes mellitus. Documentation about its effects in the treatment of type 2 diabetes mellitus however is very little.

Participants in our study consisted of 30 diabetes patients. Out of 30 patients 47% were male and 53% were female. There were no patients who fall under age group of 18 to 30 years. 43% of

patients fall under the age group of 31 to 50 years. Majority of patients in this study were of age between 51 to 69 years with 57%.

The results of our study show that Churu-5 is effective for diabetes mellitus. It lowered the blood sugar levels. It significantly improved the secondary measures (diabetic symptoms and anthropometric measurements).

Power of Churu-5 ingredients against *gChin-nyi* or diabetes

gChin-nyi is a name for diabetes in traditional Tibetan medicine. It is classified into *rLung* (wind) type, *mKhrispa* (bile) and *Badkan* (phlegm) type, which are further classified into 10 types of *Badkan zakhu*(Za means to consume and Khu means fluid), 6 types of *mKhrispa zakhu* and 4 types of *rLung zakhu*. ZaKhu is nothing but body fluid mixed with the body nutrients. It is named after the types of fluid excreted in the urine. It is not necessary to be the single type because g*chin-nyi* always occurs with mixed type. One of the *zakhu* of wind is sweet like honey. This type of *zakhu* confirms g*chin-nyi* of traditional medicine as diabetes in modern medicine.[12]All the ingredients of Churu-5 tablet have the property of repelling *phlegm* or *wind* or *bile* whereby together curing *gchin-nyi* as a whole.

Glucose lowering property of Churu-5

Since all the ingredients of Churu-5tablet dispel *phlegm* which isaccumulated as excessive fat and sugar in the body, Churu-5tablet must have decreasedblood glucose and improved diabetic symptoms. Churu-5 tabletsignificantly reduced PPBG levels beginning from the day 21 ($p<0.05$). At the day 28, it improved further showing the statistical significant difference ($p<0.05$). It slightly decreased FBG levels but didn't show any significant improvement. The possible explanation may include the size of the sample which was not sufficiently large to detect an effect. The short duration of the study must be the second reason of failing to prove the effect. The reason could be also because of the possible variation in patient's diet since none of them are inpatients.The improvement in the blood glucose must have been the effect of curcumin, the active component of *Curcuma longa,* comprising about 2-8% of the spice. The study showed that the ingestion of 6g *Curcuma longa* increased postprandial serum insulin concentration without affecting plasma glucose in healthy subjects.

Guitsed et al. showed that Yuna-4 significantly reduced (26 %)alloxan monohydrate-induced increases in blood levels of glucose compared to control ($p<0.05$).[6] Another study by L.Batgerel et al. showed that the Antidiabet-3 compound exhibited antihyperglycemic, antihyperlipidemic, hepatoprotective, renoprotective, membranomodulator, immunemodulatory, and antioxidant activities. Churu-5tablet and Antidiabet-3 has one same ingredient *Tribulus terrestris*.[2]

Diabetes symptom improvements by Churu-5

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycaemia and other symptoms like polyuria (frequent urination), polydipsia (increased thrist) and polyphagia (increased hunger) which ultimately causes various other complications like retinophathy, neurophathy, nephropathy and microangiopathy (Kumar S. et al.2013).

In this study diabetic symptoms polyuria improved showing the significant difference comparing to the baseline. It began to show its effect from day7 with a significant difference ($p<0.02$) comparing to the baseline. It improved further at day 21 and day 28. The standard deviations in

the figures showing diabetic symptoms look same because consistency of data differed least throughout the visits. This improvement from the day7 shows that effect of Churu-5 tablet doesn't take much time to give its effect. It also shows that prolonged treatment of diabetes with Churu-5 tabletcan at least help reduce the symptom. It may help to eliminate diabetic complications due to polyuria in a long run. Polyuria has been defined as urine output exceeding 3 L/day in adults and 2 L/m2/day in children. The most common causes are: psychogenic polydipsia, diabetes insipidus (central and nephrogenic), chronic kidney diseases, and uncontrolled diabetes mellitus (Wieliczko M. et al. 2013).

Polydipsia of diabetic subjects participating in this study showed significant improvement beginning from the day 14 ($p<0.01$). It kept on improving at day 21 and day 28 significantly. Based on the traditional medical concepts it could be the effect of *Phyllantus emblica*, because thirst in traditional medicine is caused by disturbance of *wind* and *bile*. Some traditional medicine for *wind* (for example Agar-35) and *bile* (for example Norbu-7 decoction) contains *Phyllantus emblica*. Usually these medicines are advised for the treatment of thirst in traditional medicine. Thirst is also said to be caused by the accumulation of *bad-mkhris* (combination of *phlegm* and *bile*). *Berberis aristata* syrub with honey is advised for the thirst caused due to *phlegm* as per the traditional Tibetan medicine.

Polyphagia improved beginning from the day 14, showing the significant difference ($p<0.05$) comparing to the baseline. It kept on improving at day 21 and day 28 significantly ($p<0.01$).

Fatigue improved beginning from the day 7, showing the significant difference ($p<0.04$) comparing to the baseline. It kept on improving at day 14 and day 21 and day 28 showing the significant difference ($p<0.01$). The fatigue can be discussed traditionally as disruption of *wind* humor. The Churu-5 tabletmust have shown the positive effect because of its effect on *wind*. The main medicine for *wind* is Agar-35, which contains *Phyllanthus emblica* in huge ratio as its ingredient.[5]

Body weight and BMI reducing potential of Churu-5
None of the diabetes patients in this study fall in underweight group. 13% of participants were with normal body mass index. 12% were overweight. 5% of patients were obese class I.
Churu-5 tabletsignificantlyreduced body mass index after 14 days of treatment ($p<0.05$) compared to the baseline. The mean level remained the same on day21 and even after day28. It can mean that Churu-5 tablet can control the weight loss and BMI of diabetes patients in long run although it seems to show the reduction in first week.Likewise the body weight at the baseline had the mean level of 69.7 ± 13.8kg and it decreased at the day28 showing the significant difference of ($p<0.05$).Interestingly body weight was more prominently reduced in over weight and obese patients.These patients are found to be people with phlegm dominant constitution and wind dominant constitution.Guitsed et al showed that prolonged treatment of normal animals with Yuna-4 had no significant effects on body weight.Yuna-4 significantly increased body weight of rats given alloxan monohydrate ($p<0.05$). Gentamicin-induced body weight loss of rats significantly improved by Yuna-4.

Body constitution and diabetes
Traditionally people with wind dominant constitution and phlegm dominant constitution are likely to be susceptible to suffer from diabetes. This study confirmed this concept when 33.3% of patients

participating in this study were found to havewind dominant constitution and another 33% of subjects participating in this study had phlegm dominant constitution. It may be because 57% of patients enrolled in this study are those who fall in age group of 51-69 years. Traditional medicine describes people with higher age as wind constituents in nature. The main cause of diabetes in traditional medicine is due to indigestion caused by excess phlegm. Therefore more patients are seen as phlegm constituents in this study. Among the combined constitution also patients with wind-phlegm dominant constitution were more than the other combined constitutions.The majority of diabetes patients in this study showed wind dominant constitution. It may be because this study has 57% of participants between 51 years to 69 years old who are likely to have more wind constitution character due to their age. Moreover diabetes patients develop stress adding to show the wind constitution nature. The more participants have phlegm dominant constitution in this study may be because the nature and the cause of diabetes in traditional medicine are due to increase in phlegm and there by showing the characteristic of phlegm constitution.

Safety concerns of Churu-5

In this study no side effects were observed during the Churu-5tablet treatment and one week waiting time of adverse effect reports. By Guitsed et al. study, no morbidity was occurred in mice given Yuna-4 at doses of 50-5000 mg/kg.Prolonged treatment of Yuna-4(50-500mg/kg) had no significant effects on body weight, weight of internal organs, amount of hemoglobin, coagulation time, numbers of leukocytes and erythrocytes, serum levels of aspartate aminotransferase, alanine aminotransferase cholesterol, gamma glutamyltransferase, alcaline phosphatase, glucose, and uric acid.[6]

Conclusion

1. The present pilot-study shows that the traditional medicine Churu-5 tablet has improved PPBG level in adults with diabetes mellitus type 2.
2. Churu-5 tablet can be used for reducing diabetic symptoms in adults with diabetes mellitus type 2.
3. People with wind dominant and phlegm dominant constitution are more susceptible to diabetes.

Therefore, Churu-5 tablet may be potential to complement the modern treatment for type2 diabetes mellitus. Churu-5 tabletwas administered safely, without adverse events. The results of this study suggest that conducting a larger placebo-controlled trial to determine the effects of Churu-5tableton diabetes mellitus type 2 is warranted.

References

1. vanDieren S,Beulens JW, van der Schouw YT, Grobbee DE&Neal B.(2010) *The global burden of diabetes and its complications: an emerging pandemic.Europe.*
2. *Throru Tshering Namgyal (2000) Sorig rgud-zhie drelchen drang song zhel lung (Words of Hermit: Great commentaries on four tantra of medicine).*
3. *Shefali Dham, Viral Shah, Sondra Hirsch RN, Mary Ann Banerji. (2006)The role of complementary and alternative medicine in diabetes. Current diabetes Reports.*
4. *Chophel Karma (1993) Duetsi smengi thrungpay. (Elixir of medicinal plants origin) Tibetan Public publication. Dharamsala.*
5. *Traditional medicine formulary of Bhutan (2007) Menjong Sorig Pharmaceutical.*

6. *Guitsed A (2013) Effect of traditional drug Yuna-4 on animal model of diabetes and kidney injury. Ph.D. Dissertation. Ulaanbaatar. Health Sciences University of Mongolia.*

7. *Kalekar SA, Munshi RP, Bhalerao SS, Thatte UM (2013) Insulin sensitizing effect of 3 Indian medicinal plants: an in vitro study. Indian J Pharmacol.*

8. *Yiu WF, Kwan PL, Wong CY, Kam TS, Chiu SM, Chan SW, Chan R. (2011) Attenuation of fatty liver and prevention of hypercholesterolemia by extract of Curcuma longa through regulating the expression of CYP7A1, LDL-receptor, HO-1, and HMG-CoA reductase. J Food Sci.*

9. *Nampoothiri SV, Praseetha EK, Venugopalan VV, Nirmala Menon A.(2012) Process development for the enrichment of curcuminoids in turmeric spent oleoresin and its inhibitory potential against LDL oxidation and angiotensin-converting enzyme. Int J Food Sci Nutr.*

10. *Nwozo SO, Osunmadewa DA, Oyinloye BE. (2014) Anti-fatty liver effects of oils from Zingiber officinale and Curcuma longa on ethanol-induced fatty liver in rats. J Integr Med.*

11. *Zhou Y, Cao S, Wang Y, Xu P, Yan J, Bin W, Qiu F, Kang N.(2013) Berberine metabolites could induce low density lipoprotein receptor up-regulation to exert lipid-lowering effects in human hepatoma cells.*

12. *Di Pierro F, Putignano P, Villanova N, Montesi L, Moscatiello S, Marchesini. (2013)Preliminary study about the possible glycemic clinical advantage in using a fixed combination of Berberis aristataand Silybum marianum standardized extracts versus only Berberis aristata in patients with type 2 diabetes. Fitoterapia.*

13. *Derosa G, Bonaventura A, Bianchi L, Romano D, D'Angelo A, Fogari E, Maffioli P. (2013) Berberis aristata/Silybum marianum fixed combination on lipid profile and insulin secretion in dyslipidemic patients.*

14. *Nain P, Saini V, Sharma S, Nain J. (2012) Antidiabetic and antioxidant potential of Emblica officinalis Gaertn. Leaves extract in streptozotocin-induced type-2 diabetes mellitus (T2DM) rats. J Ethnopharmacol.*

15. *Trujillo J, Chirino YI, Molina-Jijón E, Andérica-Romero AC, Tapia E, Pedraza-Chaverrí J. (2013) Renoprotective effect of the antioxidant curcumin: Recent findings.Redox Biol.*

16. *Koshy SM, Bobby Z, Hariharan AP, Gopalakrishna SM. (2012) Amla (Emblica officinalis) extract is effective in preventing high fructose diet-induced insulin resistance and atherogenic dyslipidemic profile in ovariectomized female albino rats. Menopause.*

17. *Akhtar MS, Ramzan A, Ali A, Ahmad M.(2011) Effect of Amla fruit (Emblica officinalis Gaertn.) on blood glucose and lipid profile of normal subjects and type 2 diabetic patients. Int J Food Sci Nutr.*