PHARMACOLOGICAL INTEGRATION: ADJUNCT EFFECT OF DB14201, A NEW HERBAL FORMULATION DEVELOPED BASED ON AYURVEDIC PRINCIPLES, WHEN CO-ADMINISTERED WITH GLIBENCLAMIDE: RESULTS OF A PLACEBO CONTROLLED TRIAL

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Abstract:

There exist many therapeutic windows in the clinical area of Type 2 Diabetes. Traditional Medicines, including Ayurveda should be explored to identify safe and effective medicines for diabetes. DB14201 is an herbal formulation from Ayurvedic traditional knowledge and has been safely used by diabetics as a supplement drink for several years. Diabetics on hypoglycemic agents soon outgrow the effectiveness of an oral hypoglycemic agent and needs to add more of the same medicine or medicines with different mechanisms of action or insulin. A safe herbal add-on to oral hypoglycemics which can improve the efficacy of glycemic control and offer longer window of time for a specific dosage would greatly improve the current management of diabetes. The current study proves that DB14201 when used with glibenclamide as an add-on improves its efficacy in glycemic control as evidenced by comparatively lower fasting and post prandial blood sugar level in the study group as against the placebo group. The addition of DB14201 also helps in reduction of HbA1c levels by nearly 1% points over a period of 90 days.

Introduction

Integrative Medicine (IM) is broadly defined as the process of bringing different systems of medicine together to offer best modalities of prevention, cure, care, and management in healthcare.[1] Pharmacological Integration is one of the first steps in its pathway, bringing pharmaceutical entities of different medical systems judiciously together, for better clinical management of the patient.

Type 2 Diabetes Mellitus (T2DM) is a clinical condition which presents with tremendous opportunity for Pharmacological Integration, owing to the huge body of unmet clinical needs. The sheer number of T2DM patients and the humongous human, social, and economic costs it incur could be the primary reason. World Diabetic population will increase to 592 million by 2035. Considering the diabetic population of 382 million in 2013 this is a 55% increase in nearly 20 years. [2]. Among adults (aged 20-79) the prevalence was 6.4%, in 2010, affecting 285 million people. This will increase to 7.7% and 439 million adults by 2030. Between 2010 and 2030, there will be a 69% increase in numbers of adults with diabetes in developing countries and a 20% increase in developed countries. These predictions, based on a larger number of studies than previous estimates, indicate a growing burden of diabetes, particularly in developing countries[3]. "By the end of 2013, diabetes will have caused 5.1 million deaths and cost USD 548 billion in healthcare spending. Without concerted action to prevent diabetes, in less than 25 years' time there will be 592 million people living with the disease."[2].

Pharmacologic agents currently available to treat T2DM patients, do not prevent the progressive decline of pancreatic β-cell function and insulin secretion. Single agents and combination therapies are able to achieve target glycemic goals only for limited periods of time and that too in a subset of patients. Current therapies also fail to address the complications of diabetes. Several patient safety issues have been flagged as caused by prevalent medical interventions for diabetes. Thus diabetes offers a therapeutic space for several new drugs and therapeutics.[4]

"Ayurvedic knowledge and experiential database can provide new functional leads to reduce time, money and toxicity – the three main hurdles in drug development. These records are particularly valuable, since effectively these medicines have been tested for thousands of years on people" (Patwardhan et al) [5].There are several hundreds of Ayurvedic medicines in the market, making claims of effective management in diabetes mellitus. It is considered worthwhile an effort to explore the efficacy of few of these drugs with intend to improve current therapeutic capabilities. This paper describes in brief, the clinical observations obtained as part of an evaluation done on such an Ayurvedic formulation, DB14201, when used as an add-on to standard of care drug, glibenclamide.

DB14201, is a 100% herbal formulation, protected with IP, and developed based on Ayurvedic principles, as a *Pramehaghna* medicine. Word '*Pramehaghna'* is a combination of two words, "*Prameha*", the clinical condition described in Ayurveda which encompasses the syndrome complex of diabetes mellitus, and "*ghna*" which means destroying or eliminating. Thus "*Pramehaghna*" implies management of *Prameha* / DM the disease, as the therapeutic end-point, thanthe management of

blood glucose levels alone. DB14201 has been marketed since 2002 under Ayurvedic license issued by Drug Controller of the State of Kerala, under the trade name Diabedrink[[6], [7], [8]].

Review of customer responses and feed-back from physicians prescribing Diabedrink, suggested excellent safety profile, and possible synergistic benefits with oral hypoglycemic for the formulation. Therefore a study was conducted to assess the benefit of using Diabedrinkon T2DM patients, who were using Glibenclamide as the oral hypoglycemic agent, but with inadequate blood glucose control.

Aim of the study:

To study the effects of the herbal formulation DB14201, on Fasting and Post Prandial Blood Glucose levels, and Glycosylated Hemoglobin levels, when introduced as an add-ontherapy, in Type 2 Diabetic patients who are on oral hypoglycemic drug-Glibenclamide, since more than 90 days, but showing insufficient glycemic control.

Materials and Methods:

A placebo controlled clinical evaluation to assess the effectiveness of supplementation with DB14201(Diabedrink), on patients using Glibenclamide (a Sulfonylurea) was conducted in the year 2003-2004.The study protocol was approved by the ethics committee headed by Dr Raveendranathan Nair, Director, College of Pharmaceutical Sciences, Medical College, Thiruvananthapuram, Kerala. Patients were recruited from the out-patient department of Sanjeevani Ayurveda hospital, Thiruvananthapuram, Kerala during the monthly diabetic specialty clinics run by ROOTS, Bangalore. Following the prescribed inclusion and exclusion criteria, and the due consenting process, 30 patients each, were recruited into each of the group. This prospective, subject blinded, placebo controlled, outpatient based study recruited consenting subjects fulfilling the requirements of the inclusion and exclusion criteria, on alternate basis into each group. The study period for each subject was 90 days with a follow-up of 15 days thereafter. The entire evaluation was completed in 11 months.

The Study drug constituted of the formulation DB14201, a combination of 16 herbs used in Ayurveda. It contains Zizyphus jujube, Terminalia chebula, Mangiferaindica, Emblicao-fficinalis, Embeliaribes, Curcuma longa, Aervalanata, Syzygiumcumini, Cosciniumfenestratum, Salacia Oblonga, CycleaPeltata, Biophytum Sensitivum, Strychnos Potatorum, Cyperus Rotundus, Vetiveria Zizanioides, and Centella Asiatica as ingredients. The herbs were mixed together in the specific ratio and crushed and ground to a coarse powder-30 mesh.

The Placebo constituted of a combinationof corn-sheaths (Zea mays) and castor oil plant– roots (Ricinuscommunis); mixed together in equal quantity and crushed and ground to a coarse powder-30 mesh.

Advise on preparation of supplement drink given to subjects of both the groups:

Both the study drug as well as the placebo was provided to the subjects in wide mouthed plastic jars with air-tight lids, containing 33 unmarked, plain-white, sealed paper packets. Each of the paper packet contained 2.5 grams of the drug or the placebo, in coarse powder form. The subjects were advised to use contents of one packet for the preparation of medicines per day. They were advised to put the contents of one packet, in 1 liter of water, then apply heat and once the water starts boiling, allow boiling for 2 minutes. Thereafter they had to sieve the decoction off the herbal ingredients and store the clear decoction in a hygienic container. They were informed that the prepared drink was good to be consumed within 24 hours and they had to make the drink every day. The subjects were requested to come to the OPD for review and sample collection any day between the 28th and 32nd day, from the date of every visit.

Method of Administration

The subjects were advised to use the drink as an alternative to drinking water and to spread its use across the day, drinking it in divided doses, as and when they felt thirsty. They were informed that they were allowed to consume other fluids, including normal water, in case they felt the need to, during the course of the day, while participating in the study. Glibenclamide was maintained at the same dose that the patients were taking, throughout the study period.

Subjects, Randomization and recruitment methods followed:

Subjects were Type 2 Diabetes patients on single oral hypoglycemic agent Glibenclamide, since more than three months but with inadequately controlled blood sugar levels (FBS level >120 mg/dl and/ or PPBS levels >200 mg/dl) on the day of recruitment. Subjects were recruited from the out-patient department of Sanjeevani Ayurveda hospital, Thiruvananthapuram, Kerala during the monthly diabetic specialty clinics run by ROOTS, Bangalore. After a thorough history taking and following the prescribed inclusion and exclusion criteria, and the due consenting process, 30 subjects each, were recruited into each of the group. This prospective, subject blinded, placebo controlled, outpatient based study recruited consenting subjects fulfilling the requirements of the inclusion and exclusion criteria, on alternate basis into each group.

Trial and Follow-up Period:

The Trail period was 105 days. During the first 90 days (from screening) the add-on therapy was introduced to the subjects' daily routine. Day 91 to 105 was the period of add-o free follow-up, during which the add-on drugs related to the study were completely withdrawn and the subjects continued to take glibenclamide in the same dose.

Life style advice:

All patients were asked to continue the diet that they were following while they were being recruited for the study. They were requested to keep a daily, diet and physical activity diary, which they were required to bring with them when they came for review visits.

Inclusion criteria

Subjects of both genders, who are diagnosed as Type 2 Diabetes and on single drug therapy of oral hypoglycemic agentglibenclamide, since more than three months, with inadequately controlled blood sugar levels (FBS level >120 mg/dl and/ or PPBS levels >200 mg/dl on the day of recruitment)and between the agesof29-71 years were included in the study. Other requisites for Inclusion were, Informed consent, no known cardiovascular disease (history), ready to follow life style advised, not pregnant (history), not breast feeding (history), agreeing to use reliable contraceptives during the study period of three months (informed consent), readiness to continue medications for 12 weeks subject to his / her rights as a study subject, normal BU/ Creatinine, LFT: OT /PT < 2 times ULN.

Exclusion Criteria

Subjects beyond the age group of 30 and 70 years, Subjects with Type 1 Diabetes, subjects on oral hypoglycemics other than Glibenclamide, or taking other classes of oral hypoglycemics along with glibenclamide, or on Insulin, subjects who had recently (<30 days) added lipid /blood pressure/ diabetes lowering medicine to their medication regimen (history), subjects who are smokers, subjects with systemic diseases as diabetic complication, subjects with poorly controlled HTN (Systolic >160 mm of Hg; Diastolic > 100 mm of Hg) during recruitment, subjects with known and diagnosed acute or chronic liver / renal disorders, and subjects with known allergies to ingredients (history).

Investigations:

Forming part of assessment:

1. Fasting blood sugar – Every 15 days for 105 days.
2. Post-prandial blood sugar – Every 15 days for 105 days.
3. Glycosylated hemoglobin- before and after 90 days of add-on therapy

For compliance with inclusion and exclusion criteria, and safety (before recruitment and at 90 days):

- Blood Pressure
- Liver Function Test
- Lipid profile
- Renal Function Test
- Complete Blood Count
- ESR , and Hemoglobin percentage

Data and analysis methods:

Data collected were entered into a master sheet and statistical tables constructed. All the values are expressed as in terms of means and standard deviation. Comparison between Study and Placebo groups were performed using Independent Student t test. Paired Student t – test was used to compare the mean difference of individual quantitative parameters between base line and various follow-up reference points. Diagrams and charts are given wherever necessary to substantiate the important findings. All statistical test were 2 - tailed, and a p – value of < 0.05 was considered statistically significant. Statistical analysis was performed in SPSS, version 18.0.

Data analysis and Statistical results:

Table 1: Comparison of Mean Fasting Glucose levels -between base lineandvarious follow-up reference points in Study group

Follow-Up At	Paired Differences for Fasting Glucose in Study Group					t - value	p – value
	Screening (Mean ± SD)	Follow-Up (Mean ± SD)	Mean Difference	95% Confidence Interval of the Difference			
				Lower	Upper		
Day 15	152.07±26.9	130.97±19.3	21.100	11.281	30.919	4.395	.000*
Day 30	152.07±26.9	118.80±13.6	33.267	24.443	42.090	7.711	.000*
Day 45	152.07±26.9	113.90±14.7	38.167	27.182	49.152	7.106	.000*
Day 60	152.07±26.9	108.59±12.6	43.690	32.147	55.232	7.753	.000*
Day 75	152.07±26.9	108.83±12.5	43.448	33.231	53.666	8.710	.000*
Day 90	152.07±26.9	106.24±12.9	46.034	34.785	57.284	8.383	.000*
Day 105	152.07±26.9	118.14±11.4	34.138	24.372	43.904	7.160	.000*

* p –value < 0.05, statistically significant

Table 2: Comparison of Mean Fasting Glucose levels -between base line andvarious follow-up reference pointsin Placebo group

Follow-Up At	Paired Differences for Fasting Glucose in Placebo Group					t - value	p – value
	Screening (Mean ± SD)	Follow-Up (Mean ± SD)	Mean Difference	95% Confidence Interval of the Difference			
				Lower	Upper		
Day 15	155.57±24.5	150.77±23.2	4.800	-.563	10.163	1.830	.077
Day 30	155.57±24.5	146.77±24.7	8.800	1.147	16.453	2.352	.026*
Day 45	155.57±24.5	146.07±23.4	9.500	3.212	15.788	3.090	.004*
Day 60	155.57±24.5	148.24±14.3	7.966	2.122	13.809	2.792	.009*
Day 75	155.57±24.5	144.57±24.2	12.214	5.446	18.983	3.703	.001*
Day 90	155.57±24.5	145.59±26.0	11.741	4.433	19.049	3.302	.003*
Day 105	155.57±24.5	146.1±25.4	11.222	4.192	18.252	3.281	.003*

* p –value < 0.05, statistically significant

Table 3: Comparison of Mean Fasting Glucose levels - between Study and Placebo group –during corresponding follow-up reference pointsacross the study

Follow-Up At	Study Groups	Placebo group	Mean Difference	t – value	95% Confidence Interval of the Difference		p – value
					Lower	Upper	
Screening	152.07±26.9	155.57±24.5	-3.500	-.527	-16.790	9.790	.600
Day 15	130.97±19.3	150.77±23.2	-19.800	-3.592	-30.833	-8.767	.001*
Day 30	118.80±13.6	146.77±24.7	-27.967	-5.429	-38.278	-17.656	.000*
Day 45	113.90±14.7	146.07±23.4	-32.167	-6.372	-42.271	-22.062	.000*
Day 60	108.59±12.6	148.24±24.3	-39.655	-7.802	-49.837	-29.473	.000*
Day 75	108.83±12.5	144.57±24.2	-35.744	-7.035	-45.926	-25.561	.000*
Day 90	106.24±12.9	145.6±26.0	-39.351	-7.262	-50.215	-28.487	.000*
Day 105	118.14±11.4	146.11±25.4	-27.973	-5.379	-38.399	-17.547	.000*

* p –value < 0.05, statistically significant

Table 4: Comparison of Mean Post Prandial Glucose levels -between base line and various follow-up reference points in Study group

Follow-Up At	Paired Differences for Post Prandial in Study Group					t - value	p – value
	Screening (Mean ± SD)	Follow-Up (Mean ± SD)	Mean Difference	95% Confidence Interval of the Difference			
				Lower	Upper		
Day 15	241.13±25.6	218.70±32.4	22.433	14.334	30.533	5.665	.000*
Day 30	241.13±25.6	197.8±21.1	43.300	33.229	53.371	8.794	.000*
Day 45	241.13±25.6	188.23±22.1	52.900	38.686	67.114	7.612	.000*
Day 60	241.13±25.6	184.0±18.4	59.759	46.870	72.647	9.498	.000*
Day 75	241.13±25.6	182.38±16.4	61.379	48.820	73.939	10.011	.000*
Day 90	241.13±25.6	179.93±18.4	63.828	49.237	78.418	8.961	.000*
Day 105	241.13±25.6	203.62±19.6	40.138	28.188	52.088	6.880	.000*

* p –value < 0.05, statistically significant

Table 5: Comparison of Mean Post Prandial Glucose levels -between base line and various follow-up reference points in Placebo group

Follow-Up At	Paired Differences for Post Prandial in Placebo Group					t - value	p – value
	Screening (Mean ± SD)	Follow-Up (Mean ± SD)	Mean Difference	95% Confidence Interval of the Difference			
				Lower	Upper		
Day 15	226.70±32.5	223.17±34.1	3.533	-.770	7.837	1.679	.104*
Day 30	226.70±32.5	219.83±38.6	6.867	-.127	13.861	2.008	.054
Day 45	226.70±32.5	218.97±43.7	7.733	-2.468	17.935	1.550	.132
Day 60	226.70±32.5	217.00±41.6	8.586	-.575	17.747	1.920	.065
Day 75	226.70±32.5	208.93±43.9	14.071	1.895	26.248	2.371	.025*
Day 90	226.70±32.5	205.30±39.7	16.000	4.823	27.177	2.943	.007*
Day 105	226.70±32.5	210.48±39.7	10.815	-.802	22.431	1.914	.067

* p –value < 0.05, statistically significant

Table 6: Comparison of Mean Post Prandial Glucose levels - between Study and Placebo group – during corresponding follow-up reference pointsacross the study

Follow-Up At	Study Groups	Placebo group	Mean Difference	t – value	95% Confidence Interval of the Difference		p – value
					Lower	Upper	
Screening	241.13±35.6	226.70±32.5	14.433	1.638	-3.210	32.077	.107
Day 15	218.70±32.4	223.17±34.1	-4.467	-.520	-21.650	12.717	.605
Day 30	197.83±21.1	219.8±38.6	-22.000	-2.739	-38.078	-5.922	.008*
Day 45	188.23±22.1	218.97±43.7	-30.733	-3.434	-48.649	-12.818	.001*
Day 60	184.00±18.4	217.00±41.6	-33.000	-3.907	-49.922	-16.078	.000*
Day 75	182.38±16.4	208.93±43.9	-26.549	-3.046	-44.018	-9.080	.004*
Day 90	179.93±18.4	205.30±39.7	-25.365	-3.102	-41.761	-8.970	.003*
Day 105	203.62±19.6	210.48±39.7	-6.861	-.829	-23.452	9.731	.411

* p –value < 0.05, statistically significant

Table 7: Comparison of Mean HbA1c level values within Groups - at base line and 90 days

Groups	Paired Differences for HbA1c levels between the groups					t – value	p – value
	Screening (Mean ± SD)	Follow-Up at 90 days (Mean ± SD)	Mean Difference	95% Confidence Interval of the Difference			
				Lower	Upper		
Study Group	7.53±0.6	6.65±0.4	0.8793	.6591	1.0996	8.178	0.000*
Placebo Group	7.23±0.5	7.07±0.5	0.1556	-.0066	.3177	1.972	0.059

* p –value < 0.05, statistically significant

Table 8: Comparison of Mean HbA1c level values between Groups - at base line and 90 days

Data collected at	Study Groups	Placebo group	Mean Difference	t – value	95% Confidence Interval of the Difference		p – value
					Lower	Upper	
Screening	7.54±0.6	7.3.±0.5	.2400	1.666	-.0483	.5283	.101
Day 90	6.65±0.4	7.07±0.5	-.4223	-3.366	-.6739	-.1708	.001*****

* p –value < 0.05, statistically significant

Adverse events

Throughout the study, no serious or otherwise adverse events were reported in either group. DB14201 was very well tolerated by the subjects and none of the lab parameters concerning safety were compromised during the 90 days of study. There were no signs or symptoms which could be classified as adverse events reported during the study period in either group.

Discussion

Results of statistical analysis of the data generated during the clinical study, shows that the herbal formulation DB14201 is safe in T2DM patients when administered along with glibenclamide and improves the effectiveness of glibenclamide in offering better glycemic control. The addition of the formulation provides significant improvement in fasting and post prandial blood sugar levels in comparison to addition of placebo and also significantly reduces HbA1c levels.

Addition of the DB14201, to glibenclamide improves Fasting blood glucose control in T2DM patients with highly significant reduction ($p < .000$) right from the 15th day of administration. (Table 1) It is also noted that the FBS levels remain reduced with high significance in comparison to data available at screening, even 15 days after withdrawal of the formulation.

In comparison to this, addition of placebo, showed reduction in FBS levels but varied considerably in significance with the study group (Table 2). A statistically significant reduction in FBS was observed after 30 days ($p< 0.026$) after adding the placebo to glibenclamide therapy. The most significant reduction ($p <0.001$) was observed during the 75th day, but the values of FBS went up in the subsequent tests in 90 days to a statically significant but comparatively (to Study drug) less significant value of $p <0.03$. This value of p was seen retained in the data of day 105 (even after 15 days of withdrawal of the placebo from the regimen).

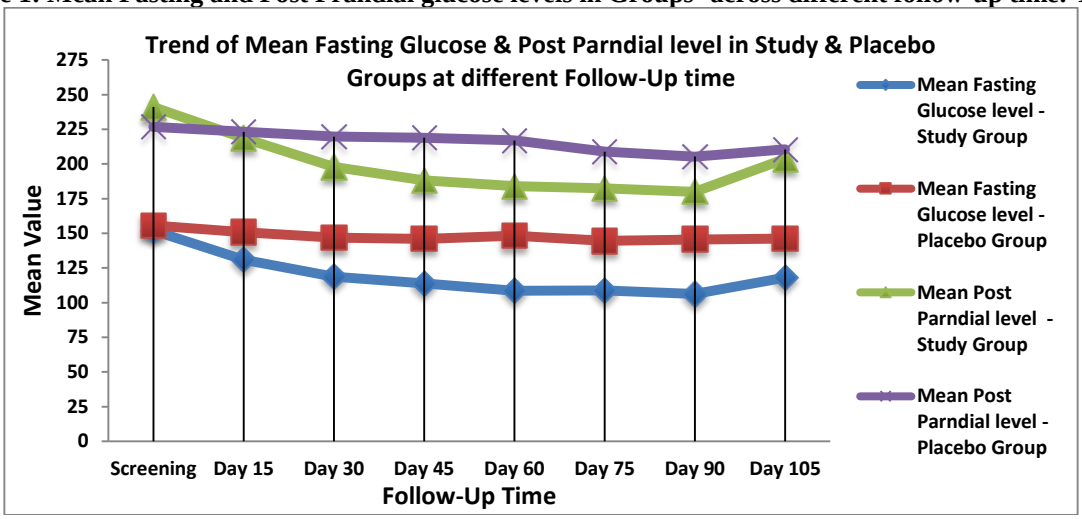
Considering that both the placebo and study drug showed reduction in FBS to significant levels while comparing the intragroup changes of FBS values, a comparative analysis of reduction of FBS between the groups was done to assess the significance of this finding. It has been noted that right from the 15th day the Study group showed statistically significant benefit in FBS reduction ($p < 0.001$) than the placebo group during the same period (Table 3). From the 30th day the difference of FBS reduction between the groups become highly significant ($p < 0.000$) and remained so throughout the study until day 105, even after 15 days of withdrawal of the add-on therapeutic agents from the study.

Similar to the finding in the case of FBS, the Post Prandial Blood Sugar levels of subjects in the DB14201 group showed highly significant statistical results right from the 15th day of the study (Table 4). This highly significant difference ($p < 0.000$) in comparison to the values obtained at screening, continued throughout the different reference points across the study, till the 105th day, even when the subject was off the adjuvant medication for 15 consecutive days.

The PPBS values of the Placebo group, unlike the FBS values, showed inconsistent reduction (Table 5), with statistical significance only on three occasions.

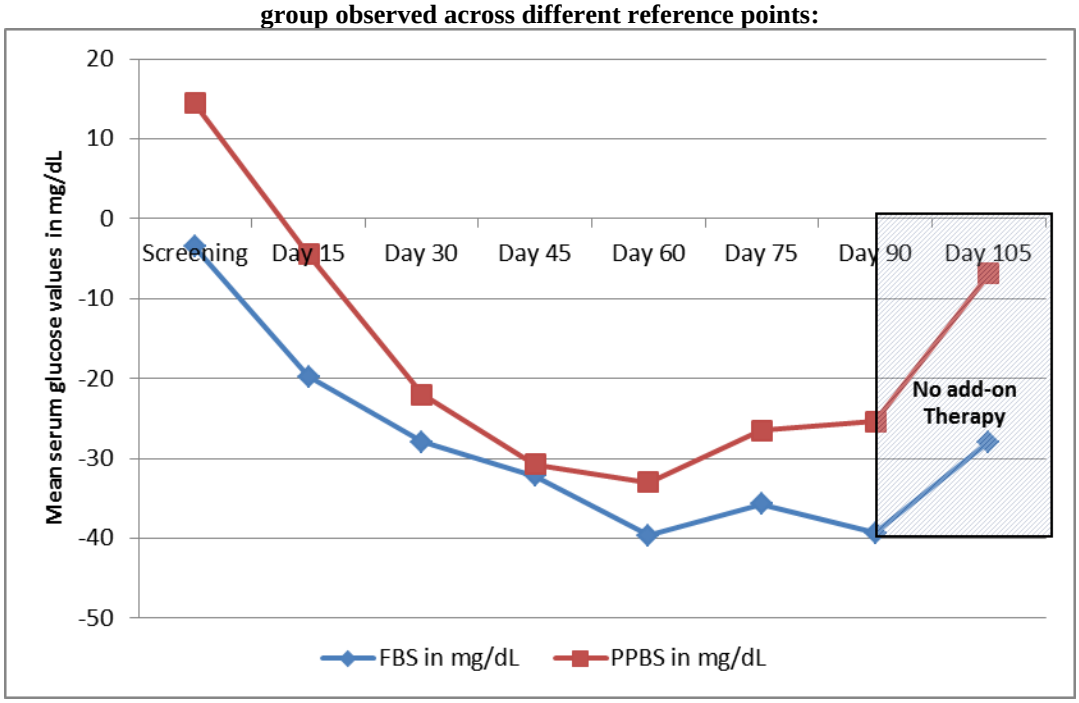
Comparison of intra-group data from Study and Placebo group suggests that PPBS levels are better managed by addition of DB14201 than Placebo. However comparison of mean PPBS values of both groups across the entire study at similar reference intervals (Table 6) shows clearly that the difference in blood sugar reduction is much more and strongly significant in DB14201 group than the Placebo group during the same interval. The highly significant inter-group difference favoring a stronger PPBS reduction capability of DB14201 continues till the 90th day. After 15 days of stopping the adjuvant, the difference between the groups is found to be insignificant; suggesting that the reduction in PPBS levels seen by the addition of DB14201 is reversible.

Figure 1: Mean Fasting and Post Prandial glucose levels in Groups- across different follow-up time: Trend



Re-examining the effect of DB14201 on FBS and PPBS we can assume that addition of the formulation offers better overall glycemic control (Figure 1). All the currently used (~11) classes of drugs for the treatment of T2DM, primarilyfocus on improvement of overall glycemic control. While some of these agents achieve this by predominantly lowering the fasting plasma glucose level (sulfonylureas, metformin and basal insulins); some others lower postprandial plasma glucose deviations (α-glucosidase inhibitors, meglitinides, pramlintide, exenatide and prandial insulins); and few others reduce both (thiazolidinediones, dipeptidyl peptidase 4 [DPP4] inhibitors, liraglutide and mixed insulins).[9]. From results of the current study, it is evident that adding DB14201 to the sulfonylureas, may expand the activity of sulfonylureas to include effective lowering of post prandial sugar levels (Figure 3).

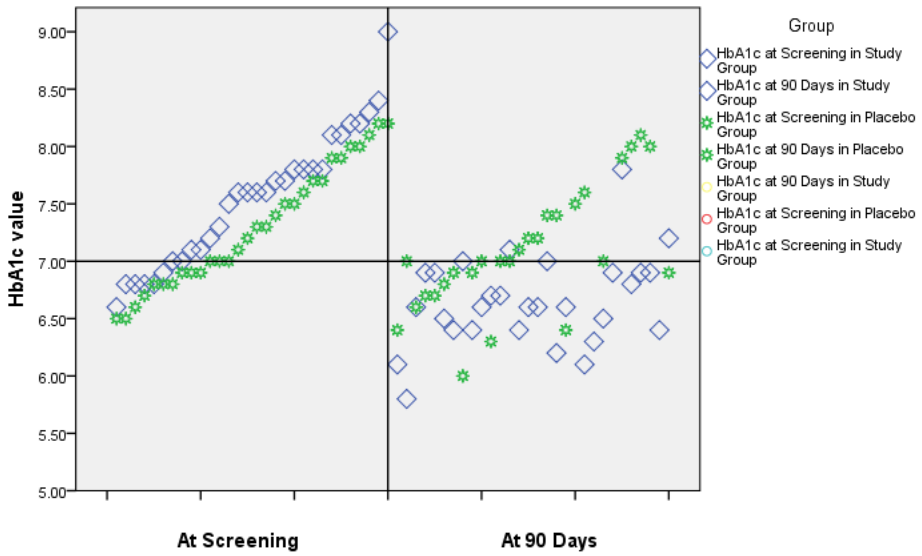
Figure 2: Mean difference of FBS and PPBS reduction in Study group (DB14201) in comparison to Placebo group observed across different reference points:



Addition of DB14201 reduced HbA1c levels significantly ($p < 0.000$) and by nearly 1% as compared to less than 0.2 % in the placebo group (which gave an insignificant statistical result). Comparing the HbA1c values observed at the beginning and at 90 days, the study group shows highly significant benefit reduction in HbA1c. (Tables 7 & 8). The graphical representation of the HbA1c values of the two groups across the two time points

clearly suggests a shift of the Study group HbA1cvalues from predominantly above 7% at screening to below 7% at 90 days. The HbA1c values of the placebo group remains without much change during this duration, i.e. predominantly above 7% (Figure 3).

Figure 3: Comparison of Mean HbA1c level values between Groups - at base line and 90 days



Many studies show that lifestyle modification can improve glycemic control in patients with T2DM; however, lifestyle modification alone is rarely sufficient to achieve target glycemic goals. In most patients, lifestyle modification must be combined with pharmacologic agents. However, the addition of a single pharmacologic agent to lifestyle modification is unlikely to result in long-term glycemic control. During the progressive decline in β-cell function that occurs with increasing duration of T2DM, patients will probably require multiple agents with different mechanisms of action and eventually combinations of drugs that include insulin preparations.[9]

Even though insulin preparations should theoretically be able to lower HbA1c to any desired level, its non-physiologic route of administration, prolonged duration of action, and the large doses needed to overcome insulin resistance, prevents mimicking natural insulin production. The incidence of moderate and severe hypoglycemia and progressive weight gain, exceeding 10 kg associated with intensive insulin treatment, often outweighs the benefits in T2DM patients.[9]Also vascular complications of T2DM are not addressed well by the current therapeutics.[10]. Over and above the inadequacy in blood sugar management, the current therapies also present with several patient safety issues. [9].Thus opportunities for new drugs and therapeutics in the field of diabetes are several [11]

The results of the current study suggest that among known traditional herbal medicinal products, there could be many formulations which could be safe to humans and effective in specific clinical conditions. In the case of type 2 diabetes these formulations may prove to be effective add-ons to current therapeutics, improving their efficacy and offering safe alternatives rather than increase dosage of the currently used oral hypoglycemic or adding a different class of oral hypoglycemic or insulin.

Summary

DB14201 improves glycemic control when co-administered with glibenclamide. It reduces Fasting and Post Prandial blood sugar levels by an average mean value of 30 mg/dL more than the Placebo. It also reduces the HbA1c values by nearly 1% in a period of 90 days. It may be used as a safe herbal add-on to glibenclamide to improve therapeutic action and increase effective dose duration. A larger study needs to be undertaken to understand the add-on effect of DB14201 with glibenclamide and other classes of hypoglycemic agents. Such a study should also concentrate on other mechanisms of action of the supplement sincethe data from the current study points to an equally significant reduction in PPBS levels, as noticed in FBS levels, suggesting such possibilities.

Acknowledgement:

I would like to acknowledge the unstinted support of Mr. Manish Kumar Singh, Bio-Statistician, in organizing and statistically analyzing the raw data available from the study. He has also lend is expertise in interpreting the statistical results. I would also like to thank Dr Sunil Kumar and the entire staff of Sanjeevani Ayurveda Hospital, Thiruvananthapuram, and Kerala who had cooperated

and supported in the conduct of the clinical evaluation.

Disclosure:

Geetha Krishna Pillai Gopalakrishnan has been granted a US and EU patent for the formulation during this period. He is currently pursuing further research activities on the formulation with collaborative partners. He is a minority share-holder in Innoveda Biological Solutions (P) ltd, which owns the commercial rights of the formulation.

References:

1. Pillai GKG, Sharma P. Finding a sustainable prototype for integrative medicine. *J Ayurveda Integr Med* 2014;5:134–8. doi:10.4103/0975-9476.140466
2. IDF Diabetes Atlas Committee 6th Edition. IDF Diabetes Atlas : Executive Summary. Brussels, Belgium: 2013. doi:10.1037/e530172011-002
3. Shaw JE, Sicree R a, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res Clin Pract* 2010;87:4–14. doi: 10.1016/ j.diabres.2009.10.007
4. Krishnan GG. A Herbal Formulation For Prevention And Treatment Of Diabetes And Associated Complications. 2010;:66.
5. Patwardhan B, Vaidya ADB, Chorghade M. Ayurveda and natural products drug discovery. *Curr Sci* 2004;86:789–99.
6. Tushar K V., George S, Remashree AB, *et al.* Coscinium fenestratum (Gaertn.) Colebr.-A Review on this Rare, Critically Endangered and Highly-Traded Medicinal Species. *J Plant Sci* 2008;3:133–45.
7. Pillai R, Gray AI, Uma VS. Targeted isolation of alkaloid from Cyclea Peltata and determination of structural formula of Tetrandrine alkaloid based on NMR studies. *Int J Phytomedicine* 2010;2:392–401. doi:10.5138/ijpm.2010.0975.0185.02055
8. Shivanna MB, Vasanthakumari MM, Mangala MC. Regeneration of Biophytum sensitivum (Linn .) DC . through organogenesis and somatic embryogenesis. *Indian J Biotechnol* 2009;8:127–31.
9. Lebovitz HE. Type 2 diabetes mellitus--current therapies and the emergence of surgical options. *Nat Rev Endocrinol* 2011;7:408–19. doi: 10.1038/ nrendo.2011.10
10. Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. *Diabetes* 2005; 54: 1615–25.http://www.ncbi.nlm.nih.gov/pubmed/ 15919781
11. Geetha Krishnan Gopalakrishna Pillai. Developing Novel Anti- Diabetic Drugs for Geriatric Population : Prospecting for Lead compounds among Botanical Formulations of Traditional Medicine. *OPEN E-JOURNAL Geriatr CARE* 2013;December:30–5.http://oejgc.open-journal.com/index.php/OeJGC/ article /view/12/10

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