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An Open Label Clinical Trial to Assess the Safety and Efficacy of CV-HFD01 Tablets as Adjuvant Therapy in Patients with Type 2 DM

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ABSTRACT

Background: Test product "CV-HFD01 Tablet" was developed by Climic Health Pvt. Ltd, as adjuvant therapy in patients with Type 2 diabetes mellitus. **Objective:** The main objective of the study was to assess the safety and efficacy of "CV-HFD01 Tablet" in patients with type 2 diabetes mellitus as adjuvant therapy. **Materials and Methods:** An open-label, single-arm, and prospective, interventional clinical study was conducted. 33 subjects were randomly allocated in the study and advised to consume 1 tablet of CV-HFD01 twice daily orally before a meal with water for 3 months along with the ongoing treatment for diabetes or as a monotherapy. The assessment for change in Fasting Plasma Glucose (FPG) and change in 2-hr Post-Meal Glucose (PMG) from baseline; change in Haemoglobin A1c (HbA1c) from baseline and subjective assessment in each follow up regarding improvement of the clinical symptoms and evaluation tolerability and safety of CV-HFD01 was performed. **Results:** The significant decrease in elevated levels of Fasting Plasma Glucose, Post Meal Plasma Glucose and HbA1 were observed. Also, there was a significant reduction in doses of conventional treatment by CV-HFD01 tablets. The product also proved significantly effective in improving symptoms such as polydipsia, polyphagia and polyuria related to diabetes. **Conclusion:** CV-HFD01 ascertained to be a safe and effective alternative as a monotherapy as well as an adjuvant in Diabetes mellitus Type 2. Also, it holds promising potential in metabolic disorders.

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INTRODUCTION

Diabetes mellitus is a group of metabolic diseases characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Diabetes mellitus (DM) is probably one of the oldest diseases known to man. It was first reported in the Egyptian manuscript about 3000 years ago. In 1936, the distinction between type 1 and type 2 DM was made. Type 2 DM was first described as a component of metabolic syndrome in 1988. Type 2 DM (formerly known as non-insulin dependent DM) is the most common form of DM characterized by hyperglycemia, insulin resistance, and relative insulin deficiency. Type 2 DM results from the interaction between genetic, environmental and behavioral risk factors. People living with type 2 DM are more vulnerable to various forms of both short- and long-term complications, which often lead to their premature death. This tendency of increased morbidity and mortality is seen in patients with type 2 DM because of the commonness of this type of DM, its insidious onset and late recognition, especially in resource-poor developing countries like Africa. (1-3)

Epidemiology

It is estimated that 366 million people had DM in 2011; by 2030 this would have risen to 552 million. The number of people with type 2 DM is increasing in every country with 80% of people with DM living in low- and middle-income countries. DM caused 4.6 million deaths in 2011. It is estimated that 439 million people would have type 2 DM by the year 2030. The incidence of type 2 DM varies substantially from one geographical region to the other as a result of environmental and lifestyle risk factors. A literature search has shown that there are few data available on the prevalence of type 2 DM in Africa as a whole. The majority of the DM burden in Africa appears to be type 2 DM, with less than 10% of DM cases being type 1 DM. A 2011 Centre for Disease Control and Prevention (CDC) report estimates that DM affects about 25.8 million people in the US (7.8% of the population) in 2010 with 90% to 95% of them being type 2 DM. It is predicted that the prevalence of DM in adults of which type 2 DM is becoming prominent will increase in the next two decades and much of the increase will occur in developing countries where the majority of patients are aged between 45 and 64 years. (4-7)

In developed countries, approximately 87% to 91% of the diagnosed diabetic people are estimated to have type II diabetes, 7% to 12% present type 1 diabetes while 1% to 3% to have

other types of diabetes. In underdeveloped and developing countries the relative cases of type I and type II diabetes have not been studied in great detail. Nonetheless, it seems that type I diabetes is less frequent than type II diabetes, as well as it is increasing by almost 3% each year globally. (8-11) It has been correlated that in most developed countries, the greater part of DM cases in toddlers and juveniles is associated with type I diabetes whereas type II diabetes is reported as a more common condition. Mostly, type II diabetes presence has been elevated alongside accelerated socio-cultural alterations: aging populations, increasing people living in urban areas, low physical activity, increased sugar consumption as well as low fruit and vegetable intake. (12-13)

It is projected that the latter will equal or even exceed the former in developing nations, thus culminating in a double burden as a result of the current trend of transition from communicable to non-communicable diseases. Lifestyle, Genetics, and Medical Conditions Type 2 DM is due primarily to lifestyle factors and genetics. Several lifestyle factors are known to be important to the development of type 2 DM. These are physical inactivity, sedentary lifestyle, cigarette smoking and generous consumption of alcohol. Obesity has been found to contribute to approximately 55% of cases of type 2 DM. The increased rate of childhood obesity between the 1960s and 2000s is believed to have led to an increase in type 2 DM in children and adolescents. Environmental toxins may contribute to the recent increases in the rate of type 2 DM. A weak positive correlation has been found between the concentrations in the urine of bisphenol A, a constituent of some plastics, and the incidence of type 2 DM. There is a strong inheritable genetic connection in type 2 DM, having relatives (especially first degree) with type 2 DM increases the risks of developing type 2 DM substantially. Concordance among monozygotic twins is close to 100%, and about 25% of those with the disease have a family history of DM. Recently, genes discovered to be significantly associated with developing type 2 DM, include TCF7L2, PPARG, FTO, KCNJ11, NOTCH2, WFS1, CDKAL1, IGF2BP2, SLC30A8, JAZF1, and HHEX. KCNJ11 (potassium inwardly-rectifying channel, subfamily J, member 11), encodes the islet ATP-sensitive potassium channel Kir6.2, and TCF7L2 (transcription factor 7-like 2) regulates proglucagon gene expression and thus the production of glucagonlike peptide-1. (14-17)

Pathophysiology

Type 2 DM is characterized by insulin insensitivity as a result of insulin resistance, declining insulin production, and eventual pancreatic beta-cell failure. This leads to a decrease in

glucose transport into the liver, muscle cells, and fat cells. There is an increase in the breakdown of fat with hyperglycemia. The involvement of impaired alpha-cell function has recently been recognized in the pathophysiology of type 2 DM. As a result of this dysfunction, glucagon and hepatic glucose levels that rise during fasting are not suppressed with a meal. Given inadequate levels of insulin and increased insulin resistance, hyperglycemia results. The incretins are important to gut mediators of insulin release, and in the case of GLP-1, of glucagon suppression. Although GIP activity is impaired in those with type 2 DM, GLP1 insulinotropic effects are preserved, and thus GLP-1 represents a potentially beneficial therapeutic option. However, like GIP; GLP-1 is rapidly inactivated by DPP-IV in vivo. Two therapeutic approaches to this problem have been developed: GLP-1 analogs with increased half-lives, and DPPIV inhibitors, which prevent the breakdown of endogenous GLP1 as well as GIP. Both classes of agents have shown promise, with potential not only to normalize fasting and postprandial glucose levels but also to improve beta-cell functioning and mass. Studies are ongoing on the role of mitochondrial dysfunction in the development of insulin resistance and the etiology of type 2 DM. Also very important is adipose tissue, as endocrine organ hypothesis (secretion of various adipocytokines, i.e., leptin, TNFalpha, resistin, and adiponectin implicated in insulin resistance and possibly beta-cell dysfunction). A majority of individuals suffering from type 2 DM are obese, with central visceral adiposity. Therefore, adipose tissue plays a crucial role in the pathogenesis of type 2 DM. Although the predominant theory used to explain this link is the portal/visceral hypothesis giving a key role in elevated non-esterified fatty acid concentrations, two new emerging theories are the ectopic fat storage syndrome (deposition of triglycerides in muscle, liver and pancreatic cells). These two hypotheses constitute the framework for the study of the interplay between insulin resistance and beta-cell dysfunction in type 2 DM as well as between our obesogenic environment and DM risk in the next decade. (18-20)

Insulin resistance in type 2 diabetes patients increases the demand for insulin in insulin-target tissues. In addition to insulin resistance, the increased demand for insulin could not be met by the pancreatic β cells due to defects in the function of these cells. On the contrary, insulin secretion decreases with the increased demand for insulin by time due to the gradual destruction of β cells that could transform some of type 2 diabetes patients from being independent to become dependent on insulin. Most type 2 diabetes patients are not dependent on insulin where insulin secretion continues and insulin depletion rarely occurs. Dependence on insulin is one of the major differences between type 1 diabetes. Other differences include

the absence of ketoacidosis in most patients of type 2 diabetes and autoimmune destruction of β cells does not occur. Both type 1 and type 2 diabetes have a genetic predisposition, however, it is stronger in type 2 but the genes are more characterized in type 1 (the TCF7L2 gene is strongly associated with type 2 diabetes). Due to the mild symptoms of type 2 diabetes, in the beginning, its diagnosis is usually delayed for years especially in countries where regular checkup without symptoms is not part of the culture. This delay in diagnosis could increase the incidence of long-term complications in type 2 diabetes patients since hyperglycemia is not treated during this undiagnosed period. In addition to diabetes, insulin resistance has many manifestations that include obesity, nephropathy, essential hypertension, dyslipidemia (hypertriglyceridemia, low HDL, decreased LDL particle diameter, enhanced postprandial lipemia, and remnant lipoprotein accumulation), ovarian hyperandrogenism and premature adrenarche, non-alcoholic fatty liver disease and systemic inflammation. The presence of type 2 diabetes in children and adolescents who are not obese, the occasional severe dehydration and the presence of ketoacidosis in some pediatric patients with type 2 diabetes had led to the misclassification of type 2 to type 1 diabetes. Some patients with many features of type 2 diabetes have some type 1 characteristics including the presence of islet cell autoantibodies or autoantibodies to GAD65 are classified as a distinct type of diabetes called latent autoimmune diabetes in adults (LADA). People diagnosed with LADA do not require insulin treatment. In a recent study, reported 7.1% of European patients with type 2 diabetes with a mean age of 62 years, tested positive for GAD autoantibodies and the prevalence of LADA was higher in patients diagnosed with diabetes at a younger age. This classification of LADA as a distinct type of diabetes is still controversial. (21-22)

Complications of diabetes mellitus

- Acute complications: Hypoglycemia, Hyperglycemic crises, Diabetes Ketoacidosis (DKA), Hyperglycemic hyperosmolar state (HHS)

- Chronic complications:

1. Microvascular complications: Diabetic retinopathy, Diabetic nephropathy, Diabetic neuropathy

2. Macrovascular disease

3. Other complications and associated conditions: Impaired growth and development; Associated autoimmune conditions such as Hypothyroidism, Hyperthyroidism, Celiac disease, Vitiligo, Primary adrenal insufficiency (Addison's disease); Lipodystrophy (lipoatrophy and lipohypertrophy); Necrobiosis lipoidica diabeticorum; Non-alcoholic fatty liver disease; Infections seen in patients with diabetes; Limited joint mobility; Edema

Goals of management

Primary prevention is the main aim of preventing diabetes from occurring in susceptible individuals or the general population. Regular physical activity is an important component of the prevention and management of type 2 diabetes mellitus. Prospective cohort studies have shown that increased physical activity, independently of other risk factors, has a protective effect against the development of type 2 diabetes. Dietary and lifestyle modifications are the main goals of treatment and management for type 2 diabetes. The majority of people with type 2 diabetes is overweight and usually has other metabolic disorders of the insulin resistance syndrome, so the major aims of dietary and lifestyle changes are to reduce weight, improve glycemic control and reduce the risk of coronary heart disease (CHD), which accounts for 70% to 80% of deaths among those with diabetes. Insulin replacement therapy is the mainstay for patients with type 1 DM while diet and lifestyle modifications are considered the cornerstone for the treatment and management of type 2 DM. Insulin is also important in type 2 DM when blood glucose levels cannot be controlled by diet, weight loss, exercise, and oral medications. Oral hypoglycemic agents are also useful in the treatment of type 2 DM. Oral hypoglycemic agents include sulphonylureas, biguanides, alpha-glucosidase inhibitors and thiazolidinediones. Their main goal is to restore normal metabolic disorders such as insulin resistance and inadequate insulin secretion from the pancreas. Diet and lifestyle strategies are to reduce weight, improve glycemic control and reduce the risk of cardiovascular complications, which account for 70% to 80% of deaths among those with diabetes. (23-27)

Herbal treatment of diabetes

In the last few decades eco-friendly, bio-friendly, cost-effective and relatively safe, plant-based medicines have moved from the fringe to the mainstream with increased research in the field of traditional medicine. There are several literature reviews by different authors about anti-diabetic herbal agents, but the most informative is the review by Atta-ar-Rahman who

has documented more than 300 plant species accepted for their hypoglycemic properties.This review has classified the plants according to their botanical name, country of origin; parts used and nature of active agents. One such plant is Momordica charantia (Family: Cucurbitaceae). WHO has listed 21,000 plants, which are used for medicinal purposes around the world. Among these 2500 species are in India, out of which 150 species are used commercially on a fairly large scale. India is the largest producer of medicinal herbs and is called the botanical garden of the world. (28-29)

MATERIAL AND METHODS

Test Product

The composition of the test product "CV-HFD01" described in table 1.

Table No. 1: Composition of Test Product

Sr. No.	Common Name of Ingredients	Botanical Name of Ingredients
1	Karela Extract	*Momordica charantia*
2	Gudmar Extract	*Gymnema sylvestre*
3	Jamun Extract	*Syzygium cumini*
5	Methi Extract	*Trigonella foenum graecum*
6	Chirayata Extract	*Swertia chirata*
7	Amla Extract	*Emblica officinalis*

Ethics

The study was initiated only after a written approval obtained from the Independent/Institutional Ethics Committee (IEC). The study was conducted as per approved protocol and as per Good Clinical Practices (GCP) guidelines given by AYUSH in March 2013. After getting approval from the ethics committee, the study was registered on the website of the Clinical Trial Registry of India (CTRI). The CTRI number of the study is CTRI/2019/04/018403, registered on 02/04/2019. Subjects were enrolled in the study only after registration of the study on the CTRI website.

Study Design

It was an open-label, single-arm, and prospective, interventional clinical study.

Study Objective

The primary objective of the study was to assess change in Fasting Plasma Glucose (FPG) and change in 2-hr Post-Meal Glucose (PMG) from baseline. The secondary objectives of the study were to evaluate change in Haemoglobin A1c (HbA1c) from baseline and subjective assessment in each follow up regarding improvement of the clinical symptoms such as Polyurea, Polyphagia, Polydypsia and Fatigue associated with type 2 DM and also to evaluate tolerability and safety of CV-HFD01 in patients with Type 2 DM.

Subject Recruitment Plan

33 subjects were recruited in the study to get 30 completers (30 in each group) at the end of the study. Subjects who were ready to provide written informed consent and ready to provide regular follow-ups till the completion of the study and met inclusion and exclusion criteria were recruited in the study. Precautions were taken not to recruit the subjects belonging to possible vulnerable groups.

Subject Inclusion Criteria

Patients between 30-60 yrs (both inclusive) age, both sex; receiving Oral Hypoglycemic Agents as ongoing treatment for Type 2 DM; Hemoglobin A1c (HbA1c) >6.5% and < 10%; fasting blood sugar between 130 mg/dL and 250 mg/dL both inclusive and willing to give informed consent were included in the study.

Subject Exclusion Criteria

Patients having Type 1 diabetes; under Insulin treatment; concurrent serious Hepatic Dysfunction (defined as AST and/or ALT >3 times of the upper normal limit) or Renal Dysfunction (defined as S. creatinine >1.4 mg/dl), uncontrolled Pulmonary Dysfunction (asthmatic and COPD patients) or other concurrent severe disease were excluded from the study. Women who are pregnant or lactating were not included in the study. Smokers/Alcoholics and/or drug abusers were also excluded from the study. Patients with poorly controlled Hypertension; evidence of malignancy and systemic illness necessitating long term drug treatment (Rheumatoid arthritis, Psycho-Neuro- Endocrinal disorders, etc.) were not included in the study.

Dosage and Treatment Duration

1 tablet of CV-HFD01 twice daily orally before a meal with water for 3 months along with the ongoing treatment for diabetes or as a monotherapy. Subjects were advised lifestyle modifications (nutritious diet, exercise, etc.) Subjects were called for follow up at Day 30, Day 60 and Day 90 after consumption of medication.

Diet /Activity/Other

All the subjects were advised to continue their diet and exercise regimen (which they were already following) during the entire study.

Study Visits/ Follow-Ups

Screening Visit (Up to Day- 5), Baseline Visit (Day 0), Visit 1 (Day 30), Visit 2 (Day 60), Visit 3 (Day 90). Subjects were allowed to come for follow up either 5 days prior or after the scheduled follow up visit time. A screening window of up to 5 days was kept, in case if there was a delay in the availability of test reports or in case a few tests needed to be repeated.

Study Assessments

Assessment of efficacy

The primary efficacy endpoints assessed were changes in biochemical evaluation and biochemical parameters such as fasting blood sugar and postprandial blood sugar. The secondary efficacy endpoints assessed were changes in mean % of HbA1C in patients; changes in symptoms associated with diabetes like- Polyuria, Polyphagia, and polydipsia; evaluation of tolerability and safety of CV-HFDT01 tablets in patients with Diabetes; evaluation of quality of life; Global evaluation for overall improvement by physician and subject; evaluation of adverse events; evaluation of vitals during period of study; assessment of adverse event and assessment of Physician's and Subject's Clinical Global evaluation for overall efficacy.

Study Procedures

Written informed consent was obtained from the interesting subjects before screening for possible inclusion in the study. During the Informed consent process, they were given enough time to read ICD (Informed Consent Document) which was printed in the languages best

understood by them. Subjects were given the freedom to ask the questions and all questions were answered by the Investigator or by other study staff. If he/she agreed to participate in the study, written informed consent for the same was obtained from him/her.

The screening phase was designed to confirm that the subject fulfilled all inclusion and exclusion criteria. The screening evaluations were completed before the initiation of study treatments. Subjects were having Type 2 Diabetes were screened for recruitment. 30 subjects completed at the end of the study.

On screening visits (up to day -5), written informed consent was obtained from the subject for his/ her participation in the study. The subject underwent physical and systemic examinations. The subject's medical and surgical history was taken. Subject's current medication if any was noted in the Subject was called next day morning on empty stomach for laboratory investigations. Subject's investigations Renal Function Tests were done. Subject's data regarding conventional treatment were recorded. Also, subjects were advised to refrain from any Nutraceutical, Ayurvedic, homeopathic, Siddha, Unani, etc. treatment for diabetes. A screening window of up to 5 days was kept, in case if there was a delay in the availability of test reports or in case a few tests needed to be repeated. Subjects were called on the baseline visit (day 0).

On baseline visit, subjects were recruited if he/she met all the inclusion criteria. Subjects underwent general and systemic examinations and symptom gradation. Subjects were instructed to consume CV-HFD01 tablets before a meal. Subjects were advised to follow the visit schedule i.e. Day 30, 60 and 90 respectively after consumption of CV-HGD01 tablets. Subjects were given medication packed in a single HDPE container each containing 60 tabs. Subjects were allowed to come for follow up either 5 prior or after the scheduled follow up visit, provided subject consumed the given treatment. Subjects were called on Day 30 for the first follow up visit.

At follow up visits (Day 30 and 60), all the subjects were closely monitored for any Adverse Events. If the subject had AE/SAE, the details of the incidents were documented in the source document and CRF. SAE, if any, was reported to the IEC in an SAE reporting form. Rescue medication used, if any, was recorded in the CRF.

At the final visit (Day 90), all the subjects were closely monitored for any Adverse Events. If the subject had AE/SAE, the details of the incidents were documented in the source

document and CRF. SAE, if any, was reported to the IEC in an SAE reporting form. Rescue medication used, if any, was recorded in the CRF. On Day 90 visit, a blood sample was collected and assessed for renal function tests and symptom gradation with quality of life assessment. On Day 90, the subject's global evaluation for overall improvement and Investigator's global evaluation for overall improvement were done. The subject's tolerability towards CV-HFD01 tablets was assessed. Subjects were advised not to consume alcohol, caffeine, and nicotine during the study period.

STATISTICS

Sample size consideration

Sample size calculation was derived based on the primary endpoint i.e. change in fasting blood sugar levels. Based on the assumptions that mean change in uric acid would be with a standard deviation of 2.08, with desired precision of 5%, a total of 30 completed cases (30 in each group) were needed to assess the study objective at 80% power and 5% level of significance. Additional subjects were recruited to complete the required number of completed subjects for analysis. The software used for calculation of sample size was SPSS version 10.0.

Efficacy Analysis

Primary endpoints taken under consideration were levels of Blood Glucose. Data describing quantitative measures are expressed as median or mean ± SD or SE or the mean with range and data analyzed by one way ANOVA followed by Bonferroni. Percentage change in subjective clinical signs and symptoms from baseline to each visit and end of therapy was analyzed and tested by the Chi-Square test. In this study, all P values were reported based on two-sided tests and these statistical tests were interpreted at a 5% level of significance. Symptom gradation was analyzed by the chi-square test. Qualitative variables are presented as counts and percentages.

RESULTS

In the present study, 33 subjects were screened. Out of 33 subjects, 3 did not meet inclusion and exclusion criteria as found to be with higher levels of HbA1C, hence were not recruited

in the study. 30 subjects were considered evaluable cases at the end of the study. There were no dropouts in the study.

Demographic Data

Out of 30 completed subjects, 17 were male subjects with the mean age of 48.12 ± 9.51 years. Out of 30 completed subjects, 13 were female subjects with the mean age of 49.25 ± 10.33 years. If compared between the sex and age between male and female groups, the difference was statistically insignificant. The details were presented in table 2.

Table No. 2: Demographic details

Parameters	Female	Male
No. of Cases	13	17
Mean	49.25	48.12
SD	10.33	9.51
Range	38 to 60 years	39 to 60 years

Efficacy Assessments

Fasting Plasma Glucose (FPG)

At the baseline visit, the mean FPG level was 241.70 ± 7.96 mg/dl, for day 30 it was reduced up-to 199.51 ± 10.12 mg/dl and was 170.80 ± 12.55 mg/dl and 155.63 ± 10.15 mg/dl at the end of the study i.e. at day 60 and 90. The mean FPG was observed to be significant with p-value <0.001 on day 30 as well as significant with p-value <0.001 on day 60 and 90 i.e. at the end of the study. The details were presented in table 3.

Table No. 3: Mean Fasting Plasma Glucose (FPG)

Duration	Mean FPG (mg/dl)
Baseline	241.70 ± 7.96
Day 30	199.51 ± 10.12 ***
Day 60	170.80 ± 12.55 ***
Day 90	155.63 ± 10.15 ***

Analyzed by One way ANOVA followed by Selective Multiple Comparison test with significance < 0.0001 ***

Post Meal Plasma Glucose (PMG)

At the baseline visit, the mean Post-meal PG level was 359.63 ± 6.88 mg/dl, for day 30 it was reduced up-to 305.81 ± 12.55 mg/dl and was 230.48 ± 10.44 mg/dl and 198.26 ± 11.61 mg/dl at the end of study i.e. at day 60 and 90. The mean Post-meal PG was observed to be significant with p-value <0.001 on day 30 as well as significant with p-value <0.0001 on day 60 and 90 i.e. at the end of the study. The details were presented in table 4.

Table No. 4: Mean Post Meal Fasting Plasma Glucose (PMG)

Duration	**Mean PMG (mg/dl)**
Baseline	359.63 ± 6.88
Day 30	305.81 ± 12.55 ***
Day 60	230.48 ± 10.44 ****
Day 90	198.26 ± 11.61 ****

*Analyzed by One way ANOVA followed by Selective Multiple Comparison test with significance <0.0001 *** and <0.00001 ****

Percent HbA1C

At the baseline visit, the mean HbA1C % level was 9.35 ± 1.46, for day 90 it was reduced up-to 7.16 ± 0.83 mg/dl. The mean HbA1C % was observed to be significant with p-value <0.001 on day 90 i.e. at the end of the study. The details were presented in table 5.

Table No. 5: Mean % HbA1C

Duration	**Mean HbA1C (%)**
Baseline	9.35 ± 1.46
Day 90	7.16± 0.83 **

*Analyzed by One way ANOVA followed by Selective Multiple Comparison test with significance <0.001***

Assessment of polyuria

The number of subjects presenting assessment category based on grades* (Represented as 4number of subjects as well as % population). The details were presented in table 6.

Assessment of Symptoms (*Grades- 0 = None, 5= Mild, 7= Moderate and 9= Severe). The value represents the No. of subjects representing the assessment score. Chi-Square test was used to assess the values between baseline, day 30, 60 and end of the study P<0.0001 Significant.

Table No. 6: Assessment of polyuria

Score	Baseline	Day 30	Day 60	Day 90
0	0	0	0	8 (26.67 %)
1	0	12 (40%)	15 (50%)	22 (73.33)
2	23 (76.67 %)	18 (60%)	15 (50%)	0
3	7 (23.33 %)	0	0	0

Assessment of polydipsia

Several subjects presenting assessment categories based on grades* (Represented as several subjects as well as % population). The details were presented in table 7. Assessment of Symptoms (*Grades- 0 = None, 5= Mild, 7= Moderate and 9= Severe). The value represents the No. of subjects representing the assessment score. Chi-Square test was used to assess the values between baseline, day 30 and end of the study P<0.0001 Significant.

Table No. 7: Assessment of polydipsia

Score	Baseline	Day 30	Day 60	Day 90
0	0	0	1 (3.33 %)	9 (30 %)
1	0	12 (40.00 %)	26 (86.66 %)	21 (70 %)
2	19 (63.33 %)	18 (60.00 %)	3 (10 %)	0
3	11 (36.66 %)	0	0	0

Assessment of polyphagia

Several subjects presenting assessment categories based on grades* (Represented as several subjects as well as % population). The details were presented in table 8. Assessment of Symptoms (*Grades- 0 = None, 5= Mild, 7= Moderate and 9= Severe). The value represents the No. of subjects representing the assessment score. Chi-Square test was used to assess the values between baseline, day 30 and end of the study P<0.0001 Significant.

Table No. 8: Assessment of polyphagia

Score	Baseline	Day 30	Day 60	Day 90
0	0	0	6 (20 %)	20 (66.66 %)
1	0	0	22 (73.33 %)	10 (33.33 %)
2	9 (30 %)	21 (70 %)	2 (6.66 %)	0
3	21 (70 %)	9 (30 %)	0	0

Assessment of global evaluation for overall improvement by the investigator

In Test Group N=30, 26 (86.7%) subjects reported very much overall improvement and 04 (13.3%) subjects reported much overall improvement at the end of the study as per investigator assessment.

Global assessment for overall improvement by subject

In Test Group N=30, 21 (70.00%) subjects reported very much overall improvement and 08 (26.66%) subjects reported much overall improvement at the end of the study as per subject assessment. 01 (3.33%) subjects reported minimally overall improvement at the end of the study as per the subject assessment.

Tolerability of study drug by physician

As per physician, In Test Group N=30, the physician reported excellent Tolerability of study drugs for 25 (83.33%) and the physician reported Good Tolerability of study drugs for 5 (16.66%) at the end of the study as per physician assessment.

Tolerability of study drug by subjects

As per subjects In Test Group N=30, 20 (66.66%) subjects reported excellent Tolerability of study drugs and 10 (33.33%) subjects reported Good Tolerability of study drugs at the end of the study as per physician assessment.

Profile of adverse events

The analysis reveals that 30% (09 subjects) had adverse events such as headache, vomiting, fever; hyperacidity and body ache with 28 adverse events out of 9 patients. These adverse events are not probably related to study drug. There was no need to discontinue the test drug.

These adverse events were mild to moderate in nature. These adverse events were resolved completely after rescue medication was given.

Reduction in the dose of conventional treatment for Diabetes

There is a significant reduction in doses of conventional treatment by CV-HFD01 tablets. Out of 30 subjects, 25 subjects were on conventional medicine alongside CV-HFD01 tablets, out of which 12 (48 %) showed a reduction in doses at day 30 and 6 (24 %) at day 90. The details presented in table 9.

Table no 9: No. of subjects with and without ongoing treatment for Diabetes

Parameters	No. of subjects
With conventional medication	25
Without conventional medication	5

DISCUSSION

Diabetes Mellitus, characterized by persistent hyperglycemia, is a heterogeneous group of disorders of multiple aetiologies. It affects the human body at multiple organ levels thus making it difficult to follow a particular line of the treatment protocol and requires a multimodal approach. The increasing medical burden on patients with diabetes-related complications results in an enormous economic burden, which could severely impair global economic growth shortly. This shows that today's healthcare system has conventionally been poorly equipped towards confronting the mounting impact of diabetes on a global scale and demands an urgent need for newer and better options. The overall challenge of this field of diabetes treatment is to identify the individualized factors that can lead to improved glycaemic control. Plants are traditionally used worldwide as remedies for diabetes healing. They synthesize a diverse array of biologically active compounds having antidiabetic properties. Different plants modulate different metabolic pathways such as glycolysis, Krebs cycle, gluconeogenesis, glycogen synthesis and degradation, cholesterol synthesis, carbohydrate metabolism as well as peroxisome proliferator-activated receptor activation, dipeptidyl peptidase inhibition, and free radical scavenging action. The aim is to provide a rich reservoir of pharmacologically established antidiabetic phytoconstituents with specific references to the novel, cost-effective interventions, which might be of relevance to other low-income and middle-income countries of the world.

Karela Extract present in formulation possesses the following activities: Karela is also known as bitter gourd and *M. charantia*, is the most widely used and popular anti-diabetic plant. The main constituents which are responsible for the antidiabetic effects are triterpene, proteid, steroid, alkaloid, inorganic, lipid, and phenolic compounds. In particular, four triterpenoids have AMP-activated protein kinase activity which is a plausible hypoglycaemic mechanism of *M. charantia*. It also contains a lectin that has a hypoglycemic effect which develops after eating bitter gourd by acting on peripheral tissues and suppressing appetite, it's similar to insulin's effects in the brain. (30,31)

Gudmar Extract present in formulation possesses the following activities: The leaves of *Gymnema* are reported to be bitter, astringent and acrid. They temporally paralyze the sensory perception of sweet and for this amazing property it is known as "GUDMAR". It is also known as 'Sugar Destroyer'. *Gymnema* leaves have a mixture of bioactive constituent's triterpenes and saponins viz. Gymnemic acids, Gymnemagenin and Gurmarin due to them this plant represents the antidiabetic property. The herb exhibits a broad range of therapeutic effects as an effective natural remedy for diabetes, besides being used for arthritis, diuretic, anemia, osteoporosis, hypercholesterolemia, cardiopathy, asthma, constipation, microbial infections, indigestion, and anti-inflammatory. *G. Sylvestre* has good prospects in the treatment of diabetes as it shows positive effects on blood sugar homeostasis, controls sugar cravings, and promotes regeneration of the pancreas. The herbal extract is used in dietary supplements since it reduces body weight, blood cholesterol, and triglyceride levels and holds great prospects in dietary as well as pharmacological applications. (32, 33)

Jamun Extract present in formulation possesses the following activities: The Jamun, *Syzygium cumini* belonging to family Myrtaceae has been used in traditional medicine for the treatment of diabetes. The hypoglycaemic and hypolipidemic activities of Jamun may be due scavenging of free radicals as diabetes is caused by excess oxidative stress, elevated activities of catalase glutathione peroxidase, glutathione-s-transferase and increased synthesis of glutathione coupled with reduced lipid peroxidation. Jamun may have activated PPARγ and PPARα genes that suppressed the transcription of NF-κB, COX, iNOS, TNF- α and other inflammatory cytokines followed by the upregulation of Nrf2. The studies had concluded that Jamun is a potential source of naturally occurring bioactive components, thus regulating the blood glucose profile and may be used as curing therapy in diabetes. Jamun seed powder should be explored as an easily available, cheap alternative to currently available drugs that

decrease complications; leading to a decrease in health care and economic burden on family, society, and nation. (34-36)

Methi Extract present in formulation possesses the following activities: Fenugreek seed also known as *Trigonella foenum-graecum* is commonly used as herbal preparation for diabetes treatment. Multiple mechanisms are suggested for their efficacy in the diabetes population. Soluble fibers in fenugreek including glucomannan fiber delay intestinal absorption of ingested sugars and alkaloids such as fenugreek and trigonelline have demonstrated to possess hypoglycemic action, and 4 hydroxy isoleucine (4-OH Ile) amino acids act on the pancreas to release insulin. Diosgenin, present in fenugreek improves glucose metabolism by promoting adipocyte differentiation and inhibiting inflammation in adipose tissue. Also, the clinical studies have proven that methi seeds significantly showed a reduction in fasting plasma glucose (FPG), postprandial plasma glucose (PPPG) and low-density lipoprotein cholesterol (LDLc) whereas serum insulin increased significantly. (37-39)

Chirayata Extract present in formulation possesses the following activities: The hypoglycemic and antidiabetic role of *S. chirata* was studied using 95% ethanolic root extract, which showed significant antidiabetic effect via decreased blood sugar level. S. chirata root extract significantly decreased the cholesterol and lipid levels. The S. chirata is also known to contain some phytochemicals such as amarogentin, mangiferin, and swertia merin so on. Mangiferin is known to have blood glucose lowering property and also decreases lipid levels. (40,41)

Amla Extract present in formulation possesses the following activities: Research concludes that amla supplement is effective in reducing the Fasting and Post Prandial blood glucose levels and HbA1c levels. The tannoids of *E. officinalis* are potent inhibitors of Aldose Reductase (AR) and suggest that exploring the therapeutic value of natural ingredients that people can incorporate into everyday life may be an effective approach in the management of diabetic complications. Emblica and its tannoids might counter the polyol pathway-induced oxidative stress as there was a reversal of changes concerning lipid peroxidation, protein carbonyl content, and activities of antioxidant enzymes. Emblica also prevented aggregation and insolubilization of lens proteins caused by hyperglycemia. Aldose reductase plays a role in the development of secondary complications of diabetes including cataract. Amla inhibits aldose reductase and has antihyperglycemic properties. The capacity of tannins to enhance glucose uptake and inhibit adipogenesis makes them potential drugs for

the treatment of non-insulin dependent diabetes mellitus. One of the therapeutic approaches for decreasing postprandial hyperglycemia is to prevent or delay the absorption of glucose by the inhibition of carbohydrate hydrolyzing enzymes, α-amylase, and αglucosidase, in the digestive organs. Literature suggests that phenolic phytochemicals are natural inhibitors of α-amylase and α–glucosidase with a strong inhibitory effect on α-glucosidase, but a mild inhibitory effect on α-amylase and thus can be effective in preventing postprandial hyperglycemia after ingestion of a mixed carbohydrate diet which could be an effective strategy in the control of type 2 diabetes. (42-43)

CONCLUSION

There was a significant reduction in doses of conventional treatment by CV-HFD01 tablets. Out of 30 subjects, 25 subjects were on conventional medicine alongside CV-HFD01 tablets, out of which 12 (48 %) showed a reduction in doses at day 30 and 6 (24 %) at day 90. Thus CV-HFD01 was found to be a safe and effective alternative as a monotherapy as well as an adjuvant in Diabetes mellitus Type 2. The product CV-HFG01 holds promising potential in metabolic disorders. The future scope of the study will be to evaluate long term study as a therapeutic intervention in diabetic complications like diabetic hypertension and nephropathy.

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