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Original Article

Evaluating the Efficacy of Cresvin beta on Type 2 Diabetes Mellitus Management: A Randomized Comparative Clinical Trial

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ABSTRACT

Background: In this current state, Type 2 Diabetes Mellitus (T2DM) is more prevalent in the population, and metformin is used as a first-line medication for treating it, but gradually prevalence and incident rate of T2DM is increased. There was an upsurge in the utilization of alternative therapies in managing of diabetes. Especially in diabetes, Herbal medicines are considered safe and reliable by the majority of the population. This research aims to estimate the safety and efficacy of poly herbal metabolite compounds of Cresvin beta capsules in adults with T2DM. **Methods:** In this study, 60 T2DM patients aged 18-60 years were randomly assigned to Groups A (30), receiving Metformin 500 mg twice a day after food, and Group B (30), receiving Cresvin beta capsule 500 mg twice a day, after food in a prospective, randomized and open-label clinical study. The *in-silico* simulation study was performed on selected plants major compounds on target protein Insulin-like Growth Factor-1 (1K3A). **Results:** The Cresvin beta is found to be safe and effective in the management of T2DM. The FBS, PPBS and HbA1c were significantly lowered ($p<0.001$) in post-treatment in both the Metformin and Cresvin beta capsules. Similarly, the levels of IGF1, adiponectin, EL-1, IL-6, and TNF-α showed significant alteration ($p<0.001$) after the treatment. The alterations found in the post-treatment results of Cresvin beta, including the reduced levels of creatinine and triglycerides, express the efficacy. **Conclusion:** The research results conclude, that the Cresvin beta capsule would be one of the suitable choices for increasing the efficacy in the management of diabetes mellitus.

Keywords: Diabetes; Cresvin beta; Cardiovascular complications; Insulin resistance; Metformin.

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INTRODUCTION

Diabetes is a multifactorial complication that leads to major cardiovascular complications. Diabetes mellitus is brought on by high blood sugar levels that interfere with insulin metabolism and homeostasis[1]. The metabolic condition with the clinical presentation of long-lasting hyperglycemia is diabetes mellitus. When there is impairment in a person's capacity to control the amount of glucose in their blood, it leads to diabetes, which can lead to both microvascular and macrovascular complications[2,3]. Globally, 1 in 11 adults suffer from diabetes mellitus. Among these, 90% suffer from type 2 diabetes mellitus[4]. People nowadays lead unhealthy, sedentary lifestyles, eat unhealthy foods and beverages, consume inadequate amounts of fibre, have irregular sleep patterns, and engage in less physical activity. This contributes to the manifestation of a variety of pathologies, including diabetes mellitus[5]. Diabetes is a multifaceted illness with intricate organ-to-organ and target-to-target interaction. The current and conventional treatment options available to treat diabetes are focused on reducing hyperglycemia using targeted approaches[6]. They are insufficient to treat the complex etiopathology, chronicity, and systemic consequences of diabetes, even while they effectively lower hyperglycemia. A multiple approach is needed to manage the complications of diabetes. Herbal medicines are thought to be the lead molecules in the current developments and the contribution of oxidative stress to the difficulties of diabetes mellitus. Utilizing medicinal plants, vitamins, and critical elements is a low-cost diabetic preventative and treatment technique[7]. A comprehensive and systemic approach is therefore necessary for its effective management. Herbal therapy, the Indian system of medicine, can be an important and effective option to fill this gap[8].

The usage of herbal formulation has steadily increasing in the last few years and is receiving increased global attention. Single or multiple herbs polyherbal formulation (PHF) are utilized for treatment in various disease manifestations[9]. PHFs are considered more beneficial as they provide better therapeutic efficacy and less toxicity when compared to single herbal formulations[10]. Through animal studies and human trials, a variety of polyherbal formulations have been demonstrated to have positive effects on the control of diabetes[11]. Cresvin beta Capsules are one such PHF which was found to possess antidiabetic and antioxidant properties. Cresvin beta` capsules consist of the following herbal extracts of Pterocarpus marsupium, Withania somnifera, Salacia reticulata, Gymnema sylvestre extract, Curcuma longa, Vitis vinifera, and Piper nigrum. It possesses antidiabetic and antioxidant properties. Pterocarpus marsupium and Gymnema sylvestre lower fasting glucose and postprandial blood glucose; additionally, the latter reduces glycosylated haemoglobin and serum lipid levels as well. Salacia reticulata is also known to lower blood glucose levels[12]. Curcuma longa contains curcumin, which is the main ingredient and is known to lower

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blood glucose levels and serum lipid levels. Piper nigrum possesses hypolipidemic and hypoglycemic properties[13]. Withania somnifera is well known herbal medicine which is known for its anti-diabetic and anti-inflammatory properties[14]. Vitis vinifera contents like resveratrol is known to possess hypoglycemic and antioxidant properties[15]. We have performed a Preclinical study conducted to ensure the impact of Cresvin beta tablet[16]. However, the safety and efficacy of Cresvin beta capsules have not been established in humans. Thereby this study is aimed to evaluate the safety and efficacy of Cresvin beta capsules in patients with T2DM.

MATERIALS AND METHODS

Study design

In this prospective, clinical study conducted at the Interdisciplinary Institute of Indian System of Medicine (IIISM), SRM IST, Kattankulathur, all the participants were recruited at the general medicine outpatient clinic and the ayurvedic outpatient clinic at SRM Medical College Hospital and Research Centre, Tamil Nadu, India (conducted from April 2022–June 2022). All the laboratory investigations were collected at the Metabolic Ward, the Interdisciplinary Institute of Indian System of Medicine (IIISM), and SRM IST and sent for examination. The study protocol was approved by the Institutional Ethics Committee (2914/IEC/2021), followed by the study was registered in CTRI (CTRI/2022/05/042422) and participants (aged 18–60 years) who voluntarily signed the informed consent were included in the study.

Randomization and blinding

Randomization was done based on computer random allocation software version 2.0. The concealment of the randomization code was done by a third party who was not involved in the trial. This was done to avoid selection bias. Each allocation was written on paper and concealed in a serially numbered, opaque envelope. There was no blinding involved.

Inclusion criteria

Participants of both genders were included if they were in the age range of 18 to 60 years with T2DM being newly diagnosed or diagnosed within the last 10 years having fasting blood glucose (FBS) ≥ 126 mg/dl, post-prandial blood glucose (PPBS) ≥ 200 mg/dl, and glycated hemoglobin (HbA1C) between 7-9.5%, patients who is on treatment with metformin 500mg two times a day.

Exclusion criteria

lactating women diabetes, body mass index (BMI) >35 kg/m2 or less than 20 kg/m2,severe hyperglycemia (FBS > 234 mg/dl or PPBS > 360 mg/dl), abnormal lipid parameters such as cholesterol > 260 mg/dl, serum triglycerides > 300 mg/dl, HbA1C greater than 9.5%, aspartate amino transferase (AST) and alanine amino transferase (ALT) levels greater than 2.5 times the upper normal limit, psychiatric disorder, a history of smoking and alcohol use, severe renal, hepatic, cardiac, gastrointestinal, neurological, hematological or respiratory disorders, history of intake of any ayurvedic/herbal/homeopathic/dietary supplements in the last two months, patients who have participated in any investigational study in the last 12 weeks, known hypersensitivity to the study drugs, women in childbearing age refusing to use contraceptive, pregnant and lactating women were excluded.

Intervention

In this clinical study, which was conducted on 60 patients suffering from T2DM, the patients were assigned to two groups: Group A (n = 30) with Metformin 500 mg twice a day after food and Group B (n = 30) with Cresvin beta, which was given 500 mg twice a day before food. Laboratory investigations were collected at the time of screening and at the end of 90 days in both groups.

Molecular docking

Molecular docking enables researchers to predict the binding modes of major bioactive compounds (Table 1) with target proteins at the atomic level. This precision aids in understanding the specific interactions that contribute to the pharmacological activity. By simulating the docking process, researchers can identify critical amino acid residues and structural features crucial for ligand binding, offering a detailed map of the molecular landscape. Molecular docking is a computational technique used in drug discovery and structural biology to predict the binding mode and strength of a ligand (in this case, the listed compounds) to a target protein (in this case, the 1K3A target)[17].

Clinical parameters analysis

Fasting blood sample was collected for analyzing FBS and one and half hour later blood sample collected after breakfast for analyzing PPBS. Serum and whole blood samples were collected for analyzing biochemical and hematological parameters. The biochemical parameters such as FBS, PPBS, Creatinine, Triglycerides, LDL, SGOT, SGPT, and CRP were measured by fully automated biochemistry equipment (Beckman AU480). Hematology parameters such as WBC, Platelets, Heamoglobulin and ESR were measured by Sysmex XN 1000 Hematology Analyzer. HbA1C was done by Biorad D10 analyser.

ELISA analysis

Accourding to manufacture instruction, we estimated the following parameters such as IGF-1 (cat log no: EHIGF1, Invitrogen), IL-6 (cat log no: EH2IL6, Invitrogen), Adiponectin (cat log no: KHP0041, Invitrogen), Endothelin (cat log no: EIAET1, Invitrogen), and TNF-α (cat log no: KHC3011, Invitrogen) using ELISA.

Statistical analysis

Statistical analysis of all the participants who took part from the starting till the end of the study were analyzed. Mean, Standard deviation and paired T-test were employed in statistical analysis of both Group A and Group B. The significance level was set to be 0.05 to compare the difference in efficacy between Group A and Group B. The statistical analysis was performed in GraphPad Prism version 8 by one-way ANOVA method. The consort flow chart of the study is illustrated in figure 1.

RESULTS

In this clinical study 80 patients were assessed for eligibility and 60 were randomized and enrolled in Group A (n=30) and Group B (n=30) respectively. All the participants took part till the end of the study and no participants withdrew from the study. The majority of patients 53.4%, were reported in the age group of 41–50 years, followed by 30% in the age group of 51–60 years, 13.3% in the age group of 31–40 years, and 3.3% in the age group of 18–30 year were found in the study. Among these 65% were male and 35% were female. Additionally, 10% of the patients were newly diagnosed with T2DM, while 20% of the recruited subjects had a previous history of T2DM. All the biochemical parameters of metformin treated group and investigational treated group were expressed in terms of Mean ±SD and the significance (p value) of all biological parameters are depicted in Table 2.

Effect on blood glucose

In group A, the glycaemic parameters (FBS, PPBS, and HbA1c) were significantly lower after the treatment of metformin. In pre-treatment, the concentrations (mean ± SD) of FBS (183.34 ± 29.21),

Table 1: Composition of Cresvin beta capsules preparation and their major chemical compounds.

S. No.	Name of the Plant	Parts used	Capsule contains extracts	Major compounds	Reference
1	*Pterocarpus marsupium*	Heartwood	150mg	Epicatechin, propterol, marsupin, liquiritigenin, isoliquiritigenin, isoliquiritin, pterosupin, pterostlbene.	Badkhane et al.[18], Tiwari et al.[19], Katiyar et al.[20] , Rahman et al.[21].
2	*Withania somnifera*	Root	100mg	β-sitosterol, stigmasterol, β-sitosterol glucoside, stigmasterol glucoside, α + β glucose, 8, Propoxycedrane, cedrane 8,13diol	Misra et al.[22], Rautela et al.[23].
3	*Salacia reticulate*	Root	100mg	Xanthone, kotalanol, salacinol, 1,3diketones, dulcitol and leucopelargonidin, iguesterin, epicatechin, lambertic acid, and maytenfolic acid	Yuhao et al.[24], Yoshikawa et al.[25], Arunakumara and Subasinghe[26].
4	*Gymnema sylvestre*	Leaves	50mg	Gymnemic acid, Gymnemanol	Saneja et al.[27], Ibrahim[28].
5	*Curcuma longa*	Rhizome	25mg	Curcumin (**1**), demethoxycurcumin (**2**), and bisdemethoxycurcumin (**5**)	Li et al.[29].
6	*Vitis vinifera*	Fruit skin	10mg	Flavonols, anthocyanins, quercetin, vanillic acid, kaempferol, syringic acid, and gallic acid	Colombo et al.[30], Tkacz et al.[31], Cotoras et al.[32].
7	*Piper nigrum*	Seed	5mg	3-carene,D-limonene,caryophyllene,and β-pinene	Tran et al.[33].

Table 2: The biological parameters of metformin treated group and Investigational drug treated group.

Parameters	Group A (n=30)			Group B (n=30)		
	Mean ± SD			Mean ± SD		
	Pre-Treatment	Post Treatment	p value	Pre-Treatment	Post Treatment	p value
FBS	183.34 ± 29.21	151.44±27.09	0.0001***	171.86±34.09	121.17±18.68	0.0001***
PPBS	236.51±44.28	198.96±26.99	0.0003**	239.03±48.62	190.37±23.33	0.0001***
HbA1C	9.09±0.682	8.37±0.683	0.0002**	9.15±0.67	7.73±0.66	0.0001***
WBC	9448.3±1443.36	7679.3±1541.89	0.0001***	9431.03±1350.16	7675.86±161	0.0001***
Heamoglobulin	11.96±1.17	13.19±1.25	0.0003***	11.86±1.08	12.99±1.21	0.0004***
ESR	4.79±2.43	4.07±1.93	0.2132	5.52±2.50	3.14±1.60	0.0001***
Platelets	3.46±0.87	3.34±1.71	0.7366	2.98±0.51	3.08±0.53	0.4671
SGOT	26.42±5.81	23.97±6.72	0.1425	24.03±6.12	21.86±7.71	0.2409
SGPT	28.72±4.12	28.48±4.64	0.8349	28.96±3.43	28.51±5.24	0.7019
Creatinine	1.26±0.28	0.87±0.19	0.0001***	1.39±0.27	0.9±17	0.001***
CRP	8.10±0.97	7.26±1.67	0.023	8.14±0.97	5.52±1.11	0.001***
TGL	166.66±107.53	163.62±94.73	0.9096	169.25±54.25	136.41±37.46	0.0096**
LDL	141.93±54.95	136.48±41.43	0.6715	123.51±36.90	111.55±25.56	0.1568
IGF-1	93.41 ± 2.23	98.21 ± 3.21	0.0001**	84.59 ± 2.12	89.93 ± 4.71	0.0001**
Adiponectin	12.18±2.23	15.84±2.17	0.0001**	11.43±5.05	18.83±3.84	0.001***
Endothelin	4.27±0.56	3.84±0.55	0.0048**	5.10±0.86	4.06±0.83	0.001***
IL-6	3.16±0.45	2.48±2.16	0.1037	3.10±0.69	2.33±0.95	0.008***
TNF-α	11.99±1.74	10.54±2.10	0.0073**	12.38±1.95	10.27±1.90	0.0016**

All the variables were depicted in Mean ±SD
**Statistically significant at p<0.01
***Statistically significant at p<0.001

PPBS (236.51±44.28), and HbA1c (9.09±0.682) were observed at higher levels. After metformin treatment, FBS (151.44±27.09), PPBS (198.96±26.99), and HbA1c (8.37±0.683) concentrations were observed to be lower in group A patients. The extreme statistical significance (p<0.0001) was observed between the pre- and post-treatment of FBS, PPBS, and HbA1c in metformin-treated group patients. Similarly, the glycaemic parameters (FBS, PPBS, and HbA1c) were significantly lower after the Cresvin beta treated patients in group B. In pre-treatment, the concentrations (mean ± SD) of FBS (183.34 ± 29.21), PPBS (236.51±44.28), and HbA1c (9.09±0.682) were observed at higher levels. After Cresvin beta treatment, FBS (151.44±27.09), PPBS (198.96±26.99), and HbA1c (8.37±0.683) concentrations were observed to be lower in group B patients. The extreme statistical significance (p<0.0001) was observed between the pre- and post-treatment of FBS, PPBS, and HbA1c in Cresvin beta-treated group patients. Glycaemic parameters were significantly reduced after the treatment of both Cresvin beta and Metformin in the study groups.

Effect on Liver function Tests

The mean difference of SGOT in Cresvin beta group from pre-treatment to post-treatment was 2.17 (p=0.1425), whereas in Metformin it was 2.45 (p=0.1425). Both Metformin and Cresvin beta do not show significant differences nor have much beneficial activity in the management of SGOT. The mean difference of SGPT in Cresvin beta from pre-treatment to post-treatment was 0.45(p=0.7019), whereas Metformin was 0.24 (p-value - 0.8349). The p-value of both Metformin and Cresvin beta do not have much beneficial activity in the management of SGPT.

Effect on Haematological Parameters

The mean difference in total WBC in Cresvin beta group from pre-treatment to post-treatment was 1755.17, whereas in Metformin group it was 1769. Both depict high statistical significance with p-value less than 0.001. Both Cresvin beta and Metformin confer the same effect.

Table 3: Docking score and amino acid residues of major bioactive compounds towards 1K3A target.

S. No.	Compound name	Docking score against 1K3A target (kcal/mol.)
1.	Epicatechin	-6.9
2.	Propterol	**-7.8**
3.	Marsupin	-5.2
4.	Liquiritigenin	-6.4
5.	Isoliquiritigenin	-6.6
6.	Soliquiritin	-6.6
7.	Pterosupin	-5.4
8.	β-sitosterol	**-7.8**
9.	Stigmasterol	**-7.2**
10.	β-sitosterol glucoside,	**-9.5**
11.	Stigmasterol glucoside	-7.4
12.	Cedrane-8,13-diol	-5.8
13.	Xanthone	**-6.5**
14.	Kotalanol,	-5.4
15.	Salacinol	-5.1
16.	Dulcitol	-5.0
17.	Leucopelargonidin	**-6.9**
18.	Iguesterin	**-8.0**
19.	Lambertic acid,	**-6.3**
20.	Maytenfolic acid	**-8.1**
21.	Gymnemic acid	**-7.6**
22.	Curcumin	**-6.8**
23.	Demethoxycurcumin	**-7.0**
24.	Bisdemethoxycurcumin	**-7.1**
25.	Quercetin	-6.2
26.	Kaempferol	**-7.1**
27.	Vanillic acid	-5.5
28.	Syringic acid	-4.9
29.	Gallic acid	-5.8
30.	3-carene	-5.3
31.	D-limonene	-4.9
32.	Caryophyllene	-6.2
33.	β-pinene	-4.7

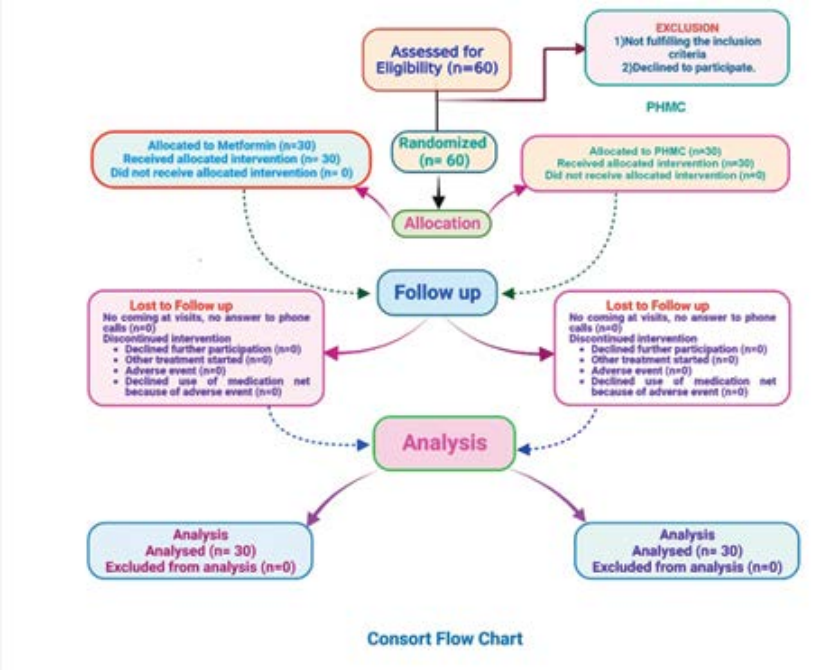

Figure 1. Consort flow chart.

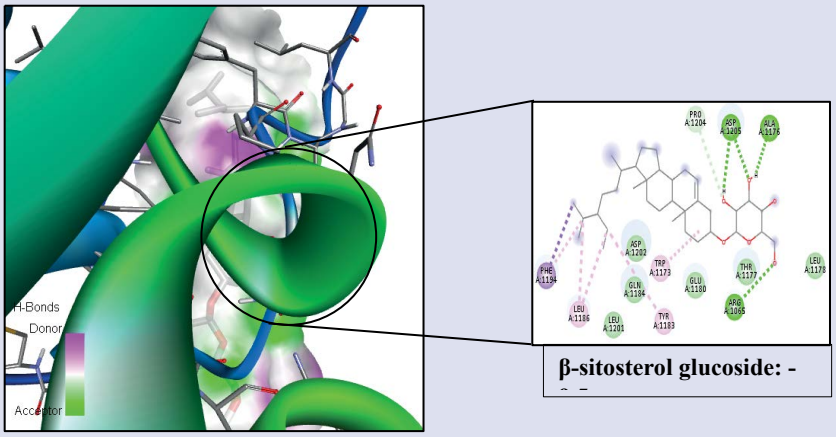

Figure 2: The figure represents the H-bond docking interaction and amino acid residue of β-sitosterol glucoside against 1K3A target.

The mean difference of haemoglobin in Cresvin beta group from pre-treatment to post-treatment was -1.13(p=0.0004), whereas it was -1.23 (p=0.0003) in the Metformin group. Cresvin beta shows fair statistical significance, whereas Metformin showed better improvement for Hb. However, Cresvin beta doesn't fall too far behind.

The mean difference of ESR in the Cresvin beta group from pre-treatment to post-treatment was 2.38 (P<0.0001), whereas in Metformin it was 0.73(p=0.2132). Cresvin beta shows high statistical significance and showed a beneficial effect in the improvement of ESR. The mean difference in platelet count in Cresvin beta group from pre-treatment to post-treatment was -0.1(p=0.4671,), whereas Metformin group it was 0.12 (p=0.7366). Both Cresvin beta and Metformin showed less beneficial activity in the management of platelets.

The mean difference of CRP in Cresvin beta group from pretreatment to post treatment was 2.62 (p=0.0001), whereas Metformin group it was 0.84 (p=0.0230). Though Metformin has a beneficial activity in the management of CRP, Cresvin beta has more acceptable results similar to that of Metformin by showing better statistical significance.

Effect on Renal Function

The mean difference of creatinine in the Cresvin beta group from pre-treatment to post-treatment was 0.47(p<0.0001), whereas for Metformin it was 0.39 (p<0.0001). Both Cresvin beta and Metformin show beneficial effects in the improvement of creatinine level.

Effect on lipid parameters

The mean difference of triglycerides in Cresvin beta group from pre-treatment to post-treatment was 32.84 (p=0.0096), whereas in the Metformin group it was 3.03 (p=0.9077). In terms of triglyceride management, Cresvin beta outperforms Metformin. The mean difference of LDL in Cresvin beta from pretreatment to posttreatment was 11.96 (p=0.1568), whereas for Metformin it was 5.45 (p=0.6715). Both Cresvin beta and Metformin showed no significant value and have little effect on LDL levels.

Effect on insulin resistance

The mean difference of IGF1 in Cresvin beta group from pre-treatment to post-treatment was -5.34 (p<0.0001); whereas in Metformin group it was -4.8 (p<0.0001). Both Cresvin beta and metformin produce acceptable results in regulating IGF1 levels.

The mean difference of adiponectin in Cresvin beta group from pre-treatment to post-treatment was -7.4 (p<0.0001); whereas in Metformin group it was -3.67 (p<0.0001). Both Cresvin beta and metformin produce acceptable results in regulating adiponectin levels.

The mean difference of endothelin in Cresvin beta group from pre-treatment to post-treatment was 1.04 (p<0.0001), whereas in Metformin group it was 0.43 (p<0.0048). When it comes to managing endothelin levels, Cresvin beta is beneficial as metformin by exhibiting fair statistical difference.

Effect on inflammatory mediator

The mean difference of IL6 in Cresvin beta from pre-treatment to post-treatment was 0.8 (p=0.0008), whereas in the Metformin group it was 0.68 (p=0.1037). Cresvin beta shows better results when compared to the metformin group at lowering IL-6 levels.

The mean difference of TNF-alpha in Cresvin beta group from pre-treatment to post-treatment was 2.11 (p<0.0011), whereas Metformin was 1.45 (p<0.0073). Although the difference is less statistical significance, Cresvin beta has acceptable results similar to Metformin for the management of TNF-alpha.

Molecular docking analysis

The docking scores provided in the table 3 represent the calculated binding affinities of each main compounds to the target protein, measured in kilocalories per mole (kcal/mol). The docking efficacy was represented in the figure 2.

A lower docking score generally indicates a stronger binding affinity. Maytenfolic acid is a natural compound that can be found in certain plant species. It belongs to the class of phytochemicals, which bioactive compounds are derived from seven plants. The present research such as Propterol (-7.8), β-sitosterol (-7.8), Stigmasterol (-7.2), β-sitosterol glucoside (-9.5), Xanthone (-6.5), Leucopelargonidin (-6.9), Iguesterin (-8.0), Maytenfolic acid (-8.1), Curcumin (-6.8), Gymnemic acid (-7.6), and Kaempferol (-7.1) showed high binding affinity on 1K3A target. These compounds are often investigated for their potential health benefits, including their impact on various diseases, such as diabetes. Maytenfolic acid has been studied for its potential anti-diabetic properties. Some research suggests that it may exhibit effects that could be beneficial in managing diabetes. These effects may include improving insulin sensitivity, reducing blood glucose levels, and modulating key pathways involved in glucose metabolism. Anti-Inflammatory Effects: Chronic inflammation is closely linked to the development of diabetes and its complications. Maytenfolic acid, like many other phytochemicals, possesses anti-inflammatory properties.

By reducing inflammation, it may contribute to better glycemic control and overall metabolic health. Antioxidant Activity: Oxidative stress is another factor implicated in the progression of diabetes. Maytenfolic acid, with its antioxidant properties, may help neutralize free

radicals and reduce oxidative stress, potentially providing protective effects against diabetes-related complications. Insulin Sensitization: Improving insulin sensitivity is a key aspect of diabetes management. Substances that enhance insulin sensitivity can contribute to better control of blood sugar levels. Maytenfolic acid may influence insulin signaling pathways, leading to improved insulin sensitivity.

DISCUSSION

In this randomized study, we evaluated the safety and efficacy of Cresvin beta capsule, a polyherbal metabolite formulation. The Cresvin beta capsule was administered to the test group (Group B) at a dose of 500 mg twice daily before food. The control group (Group A) received Metformin 500 mg twice daily after food over a period of 3 months. We found that Cresvin beta showed better effects like Metformin in the management of Diabetes Mellitus. This is the first randomized controlled trial conducted on human subjects to discern the safety and efficacy of Cresvin beta capsules. The three main tests that are used to monitor chronic glycemia around the world are FBS, PPBS, and HbA1c, which particularly is considered as the gold standard test for assessing glycemic control during follow-up. FBS, PPBS, HbA1C were found to be improved with extreme statistical significance by Cresvin beta. Metformin did not show any improvement in FBS but Cresvin beta was found to effectively improve it besides outperforming Metformin in the improvement of last two parameters. Numerous factors, such as an increase in the production of reactive oxygen species (ROS) and the development of advanced glycation end products (AGEs) as a result of chronic hyperglycemia, might contribute to alterations in haematological parameters in diabetic patients. These haematological abnormalities may cause complications such as anaemia and a hypercoagulable state, and they may also be a factor in the precipitation of CVD [34, 35].

Cresvin beta was found to improve WBC levels extremely and similar effect was also observed in metformin group. Cresvin beta shows superiority in managing CRP levels even though metformin also showed same improvement. However, when it comes to ESR, Cresvin beta showed improvement. One of the main causes of kidney failure and chronic kidney disease is T2DM. Serum creatinine is a reliable biomarker which indicates impaired kidney function[36].

Both Cresvin beta and metformin was found to improve creatinine in this study. Dyslipidemia frequently coexists with Diabetes Mellitus (T2DM). High total cholesterol, high triglycerides (TGL), and increased levels of Low density lipoprotein (LDL) are frequently found in diabetic patients with lipid abnormalities which increases the risk of developing CVD[37]. I n this study, it was observed that treatment with Metformin and Cresvin beta resulted in significant alterations in LDL and triglyceride (TGL) levels in the individuals treated. However, Cresvin beta have similar effect like metformin in the management of TGL. Similar results were seen when it comes to Interleukin-6 (IL-6) levels, which is a type of proinflammatory cytokine which is normally present in tissues, but its irregular production and prolonged exposure causes inflammation, which in turn can cause over insulin resistance resulting in T2DM[38]. Reduced adiponectin and increased IGF-1 and endothelin (ET)-1 expression leads to dysregulated production of adipocytokine TNF- α has been linked to a number of human disorders, including T2DM[39]. These factors play a role in influencing the glucose metabolism by inhibiting the action of insulin[40-43]. Both Cresvin beta and Metformin shows good effect in managing adiponectin and IGF1[44, 45]. However, Cresvin beta additionally outshines metformin in managing ET-1 and TNF- α. On the other hand, when it comes to liver function tests such as SGOT and SGPT, both Cresvin beta as well as Metformin was found to have little influence in their management. No adverse drug reactions or events were reported in both the groups along with no participants withdrawing during the course of this study. One of the limitations of the study is the number of participants included. No Adverse drug reaction was reported during the study period. The primary and secondary outcomes were assessed with the given number of participants.

The plant compound maytenfolic acid is derived from natural sources, and its potential as a therapeutic agent for diabetes aligns with the growing interest in using plant-based compounds as complementary or alternative treatments[46]. β-sitosterol glucoside is a plant-derived compound belonging to the group of phytosterols, which are structurally similar to cholesterol. It is often found in various plant sources, including fruits, vegetables, nuts, and seeds. Insulin Sensitivity: β-sitosterol glucoside may contribute to improved insulin sensitivity, allowing cells to respond more effectively to insulin and facilitating the uptake of glucose from the bloodstream. The compound may modulate multiple pathways related to glucose metabolism, potentially aiding in the regulation of blood sugar levels. Chronic inflammation, a key contributor to insulin resistance and diabetes, may be mitigated by β-sitosterol glucoside, a phytosterol that exhibits anti-inflammatory properties, which could be advantageous in managing diabetes[47]. However future studies should be done with more participants over a long period of time with incorporation of additional parameters like Homeostatic Model Assessment for Insulin Resistance, High-density lipoprotein cholesterol, Very-low-density lipoprotein cholesterol, Total Cholesterol and Urine albumin-to-creatinine ratio.

CONCLUSION

Clinical improvement of Type 2 Diabetes mellitus was observed over the course of a 3-month period following the administration of Cresvin beta. Our research results express that the test drug Cresvin beta shows good effects similar to metformin in the management of type 2 diabetes mellitus while pertaining excellent safety. Cresvin beta can be considered as a safe and effective treatment option in the management of type 2 diabetes mellitus apart from the standard treatment. With this clinical evidence, we have concluded that the investigational product has a significant role in the management of diabetes mellitus. However, multi-centric trials are required to cover the impact of selection bias, race, ethnicity modification, and drug-food interaction.

AUTHOR CONTRIBUTIONS

Conceptualization: V.P., V.S.S., and S.R.C; Methodology: N.K.N and B.M; Software: P.S and M.N.; Validation: N.K.N., P.S., and M.N; Formal Analysis: N.K.N and B.M; Investigation: N.K.N and B.M; Resources: S.R.C and B.M; Data Curation: N.K.N., M.N and P.S; Writing – Original Draft Preparation: N.K.N., M.N., and P.S; Writing – Review & Editing: All authors; Visualization: N.K.N., M.N and P.S; Supervision: V.P and S.R.C; Project Administration: N.K.N., V.S.S., M.N., B.M and P.S.

INSTITUTIONAL REVIEW BOARD STATEMENT

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Ethics Committee of SRM Medical College Hospital and Research Centre (Approval Number: 2914/IEC/2021). Additionally, the trial was registered with the Clinical Trials Registry - India (CTRI/2022/05/042422).

INFORMED CONSENT STATEMENT

Informed consent was obtained from all subjects involved in the study. Prior to their participation, all participants were provided with comprehensive information about the study's purpose, procedures, potential risks, and benefits. This information was delivered both verbally and in writing.

DATA AVAILABILITY STATEMENT

No additional data beyond what is presented in this manuscript are available. All relevant data are included within the article.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Yedjou, C G, Grigsby J; Mbemi, A; Nelson, D; Mildort B; Latinwo, L; Tchounwou, P B. The Management of Diabetes Mellitus Using Medicinal Plants and Vitamins. Int. J. Mol. Sci. 2023, 24. https://doi.org/10.3390/ijms24109085
2. Kaul, K; Tarr, J M; Ahmad, S I; Kohner, E M; Chibber R. Introduction to diabetes mellitus. Adv. Exp. Med. Biol. 2012, 771: 1-11. https://doi.org/10.1007/978-1-4614-5441-0_1
3. Garg, P; Duggal, N. Type 2 diabetes mellitus, its impact on quality of life and how the disease can be managed-a review. Obes. Med. 2022, 35: 100459. https://doi.org/10.1016/j.obmed.2022.100459
4. Zheng, Y; Ley, S H; Hu, F B. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat. Rev. Endocrinol. 2018, 14: 88-98. https://doi.org/10.1038/nrendo.2017.151
5. Kolb, H; Martin, S. Environmental/lifestyle factors in the pathogenesis and prevention of type 2 diabetes. BMC Med. 2017, 15: 131. https://doi.org/10.1186/s12916-017-0901-x.
6. Singh, A., Dhanasekaran, D; Ganamurali, N; Preethi, L; Sabarathinam, S. Junk food-induced obesity-a growing threat to youngsters during the pandemic. Obes. Med. 2021, 26:100364. https://doi.org/10.1016/j.obmed.2021.100364
7. Modak, M; P. Dixit, P; Londhe, J; Ghaskadbi, S; Devasagayam, T P. Indian herbs and herbal drugs used for the treatment of diabetes. J. Clin. Biochem. Nutr. 2007, 40:163-173. https://doi.org/10.3164/jcbn.40.163
8. Thottapillil, A; Kouser, S; Kukkupuni, S K; Vishnuprasad C N. An Ayurveda-Biology platform for integrative diabetes management. J. Ethnopharmacol. 2021, 268:113575. https://doi.org/10.1016/j.jep.2020.113575
9. Sabarathinam S; Satheesh, S; Raja, A. Plant-based medicines in the treatment of cardiometabolic disorders: A special view on sarcopenic obesity. Obes. Med. 2023, 41:100497. https://doi.org/10.1016/j.obmed.2023.100497
10. Parasuraman, S., Thing, G S; & Dhanaraj, S A. Polyherbal formulation: Concept of ayurveda. Pharmacogn. Rev. 2014, 8:73-80. https://doi.org/10.4103/0973-7847.134229
11. Zarvandi, M; Rakhshandeh, H;Abazari, M; Shafiee-Nick, R; A.Ghorbani, A. Safety and efficacy of a polyherbal formulation for the management of dyslipidemia and hyperglycemia in patients with advanced-stage of type-2 diabetes. Biomed. Pharmacother. 2017, 89:69-75. https://doi.org/10.1016/j.biopha.2017.02.016
12. Grover, J K; Yadav, S; Vats, V. Medicinal plants of India with anti-diabetic potential. J. Ethnopharmacolog. 2022, 81:81-100. https://doi.org/10.1016/s0378-8741(02)00059-4
13. Khaliq, T; Sarfraz, M; Ashraf, M A. Recent Progress for the Utilization of Curcuma longa, Piper nigrum and Phoenix dactylifera Seeds against Type 2 Diabetes. West Indian Med. J. 2015, 64:527-532, https://doi.org/10.7727/wimj.2016.176
14. Mandlik Ingawale, D S; Namdeo, A G. Pharmacological evaluation of Ashwagandha highlighting its healthcare claims, safety, and toxicity aspects. J. Diet. Suppl. 2021, 18:183-226, https://doi.org/10.1080/19390211.2020.1741484
15. Orhan, N; Aslan, M; Orhan, D D; Ergun, F; Yeşilada, E. In-vivo assessment of antidiabetic and antioxidant activities of grapevine leaves (Vitis vinifera) in diabetic rats. J. Ethnopharmacol. 2006, 108: 280-286. https://doi.org/10.1016/j.jep.2006.05.010
16. Kn, K; Chandra R C S; Balasubramanian, D; Balasundar, S; D.Mothiswaran, J.Narayanan, S.Vishakan, V.Chitra, P.Venkataraman. Acute and subacute toxicity assessment of polyherbal metabolites of PHMC tablets. J Hunan University (Natural Science Edition). 2022, 49:1779.
17. Favelyukis, S., Till, J H; Hubbard, S R; Miller, W T. Structure and autoregulation of the insulin-like growth factor 1 receptor kinase. Nature structural Biol. 2001, 8:1058-1063. https://doi.org/10.1038/nsb721
18. Badkhane, Y; Yadav, A S; Sharma, A K; Raghuwanshi, D K; Uikey, S K; Mir, F A. Pterocarpus marsupium Roxb-Biological activities and medicinal properties. Inter J Advances in Pharma Sci. 2010, 1:350-357. https://doi.org/10.5138/ijaps.2010.0976.1055.01050
19. Tiwari, M A; Sharma, M A; Khare H N. Chemical constituents and medicinal uses of Pterocarpus marsupium Roxb. Flora and Fauna. 2015, 21:55-59.
20. Katiyar, D; Singh, V; Ali, M. Phytochemical and pharmacological profile of Pterocarpus marsupium: A review. The Pharma Innovation. 2016, 5:31.
21. Rahman, M S; Mujahid, M D; Siddiqui, M D; Rahman, M A; Arif, M; Eram, S; Khan, A; Azeemuddin, M D. Ethnobotanical uses, phytochemistry and pharmacological activities of Pterocarpus marsupium: a review. Pharmacog J. 2018, 10:1-8.
22. Misra, L; Mishra, P; Pandey, A; Sangwan, R S; Sangwan, N S; Tuli, R. Withanolides from Withania somnifera roots. Phytochem. 2008, 69:1000-1004.
23. Rautela, I., M.D.Sharma, Sharma, N; Kishor, K; Singh, K; Sharma, N. Comparative GC-MS analysis of leaf and root extract of medicinal plant Withania somnifera. World J Pharm Res. 2008, 7:956-972.
24. Yuhao, L; Huang, T H; Yamahara J. Salacia root, a unique Ayurvedic medicine, meets multiple targets in diabetes and obesity. Life Sci. 2008, 82:1045–1049.
25. Yoshikawa, M; Nishida, N; Shimoda, H; Takada, M. Polyphenol constituents from Salacia species: quantitative analysis of mangiferin with alpha-glucosidase and aldose reductase inhibitory activities. Yakugaku Zasshi. 2001, 121:371-378.
26. Arunakumara, K K I U; Subasinghe, S. Salacia reticulata Wight: A review of botany, phytochemistry and pharmacology. Tropical Agri Res Exten. 2010, 13:41-47.
27. Saneja, A; Sharma, C; Aneja, K R; Pahwa, R. Gymnema sylvestre (Gurmar): A review Der Pharmacia Lettre. 2010, 2:275-284.
28. Ibrahim, D S. Role of Gymnema sylvestre leaf extract on hepatotoxicity induced by cisplatin in rats. Egyptian J Exp Biol (Zoology). 2022, 18:163-170.
29. Li, S; Yuan, W; Deng, G; Wang, P; Yang, P; Aggarwal, B. Chemical composition and product quality control of turmeric (Curcuma longa L.). Pharmaceutical Crops. 2011, 2:28-54.
30. Colombo, F; Di Lorenzo, C; Regazzoni, L; Fumagalli, M; Sangiovanni, E; Peres de Sousa, L; Bavaresco, L; Tomasi, D; Bosso, A; Aldini, G; Restani, P; DellAgli, M. Phenolic profiles and anti-inflammatory activities of sixteen table grape (Vitis vinifera L.) varieties. Food Funct. 2019, 10:1797-1807.
31. Tkacz, K; A.Wojdyło, P.Nowicka, I.Turkiewicz, T.Golis, T. Characterization in vitro potency of biological active fractions of seeds, skins and flesh from selected Vitis vinifera L. cultivars and interspecific hybrids. J Func Foods. 2019, 56:353-363.
32. Cotoras, M; Vivanco, H; Melo, R; Aguirre, M; Silva, E; Mendoza, L. In Vitro and in Vivo Evaluation of the Antioxidant and Prooxidant Activity of Phenolic Compounds Obtained from Grape (Vitis vinifera) Pomace. Molecules. 2014, 19:21154-21167.
33. Tran, T H; Ke Ha, L; Nguyen, D C; Dao, T P; Thi Hong Nhan, L;Nguyen, D H; Nguyen, T D N; Vo, D V; Tran, Q T; Bach, L G. The study on extraction process and analysis of components in essential oils of black pepper (Piper nigrum L.) seeds harvested in Gia Lai Province, Vietnam. Processes. 2019, 7:56.

34. Arkew, M; Yemane, T; Mengistu, Y; Gemechu, K; Tesfaye G. Hematological parameters of type 2 diabetic adult patients at Debre Berhan Referral Hospital, Northeast Ethiopia: A comparative cross-sectional study. PloS one. 2021, 16:0253286. https://doi.org/10.1371/journal.pone.0253286

35. Tiwari Pandey, A; Pandey, I; Kanase, A; Verma, A; Garcia-Canibano, B; Dakua, S P; Balakrishnan, S; Singh, M P. Validating Anti-Infective Activity of Pleurotus Opuntiae via Standardization of Its Bioactive Mycoconstituents through Multimodal Biochemical Approach. 2021, 11:484.

36. Kene, K; Wondimnew, T; Welde, M; Mateos, T; Adugna, T; Gerema, U; Abdisa, D; Abera, D. Prevalence and determinants of Impaired Serum Creatinine and Urea among type 2 diabetic patients of Jimma Medical Center, Jimma, Southwestern Ethiopia. Endocrine and Metabolic Science. 2021, 3:100096, https://doi.org/10.1016/j.endmts.2021.100096

37. Athyros, V G; Doumas, M; Imprialos, K P; Stavropoulos, K; Georgianou, E; Katsimardou, A; Karagiannis, A. Diabetes and lipid metabolism. Hormones (Athens, Greece). 2018, 17:61-67, https://doi.org/10.1007/s42000-018-0014-8

38. Rehman, K; Akash, M S H; Liaqat, A; Kamal, S; Qadir, M I; Rasul, A. Role of Interleukin-6 in Development of Insulin Resistance and Type 2 Diabetes Mellitus. Critical reviews in eukaryotic gene expression. 2017, 27:229-236, https://doi.org/10.1615/CritRevEukaryotGeneExpr.2017019712

39. Mohanraj, N., Prasanth, S., Rajapriya, P., Vinothkumar, G., Vinodhini, V.M., Janardhanan, R. and Venkataraman, P., 2023. Bisphenol A accelerates the vascular complications in patients with Type 2 diabetes mellitus through vascular calcification—a molecular approach. International Archives of Occupational and Environmental Health, 96(9), pp.1291-1299. https://doi.org/10.1007/s00420-023-02007-1.

40. Achari, A E; Jain, S K. Adiponectin, a Therapeutic Target for Obesity, Diabetes, and Endothelial Dysfunction. International journal of molecular sciences. 2017, 18:1321. https://doi.org/10.3390/ijms18061321

41. Idris-Khodja, N; Ouerd, S; Mian, M O R; Gornitsky, J; Barhoumi, T; Paradis, P; Schiffrin E L. Endothelin-1 Overexpression Exaggerates Diabetes-Induced Endothelial Dysfunction by Altering Oxidative Stress. American journal of hypertension. 2016, 29:1245-1251, https://doi.org/10.1093/ajh/hpw078

42. Swaroop, J J; Rajarajeswari, D; Naidu J N; Association of TNF-α with insulin resistance in type 2 diabetes mellitus. The Indian journal of medical research. 2012, 135:127-130. https://doi.org10.4103/0971-5916.93435

43. TaheriChadorneshin, H; Cheragh-Birjandi, S; Goodarzy, S; Ahmadabadi, F. The impact of high intensity interval training on serum chemerin, tumor necrosis factor-alpha and insulin resistance in overweight women. Obesity Medicine. 2019, 14:100101. https://doi.org/10.1016/j.obmed.2019.100101

44. Pandey, A T; Pandey, I; Kerkar, P; Singh, M P. Antimicrobial activity and mycochemical profile of methanol extract from Pleurotus flabellatus. Vegetos. 2021, 34:619-629. https://doi.org/10.1007/s42535-021-00242-w

45. AbdelMassih, A F; Ye, J; Kamel, A; Mishriky, F; Ismail, H A; Ragab, H A; El Qadi, L; Malak, L; Abdu, M; El-Husseiny, M. A multicenter consensus: A role of furin in the endothelial tropism in obese patients with COVID-19 infection. Obesity Medicine 2020, 19:100281, https://doi.org/10.1016/j.obmed.2020.100281

46. Oboh, M; Govender, L; Siwela, M; Mkhwanazi B N. Anti-diabetic potential of plant-based pentacyclic triterpene derivatives: Progress made to improve efficacy and bioavailability. Molecule. 2021, 26:7243.

47. Ramalingam, S; Packirisamy, M; Karuppiah, M; Vasu, G; Gopalakrishnan, R; Gothandam, K; Thiruppathi, M. Effect of β-sitosterol on glucose homeostasis by sensitization of insulin resistance via enhanced protein expression of PPRγ and glucose transporter 4 in high fat diet and streptozotocin-induced diabetic rats. Cytotechnology. 2020, 72:357-366.

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