diabetesresearchandclinicalpractice218(2024)111912

Contents lists available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.journals.elsevier.com/diabetes-research-and-clinical-practice

Curalin supplement as add-on therapy for type 2 diabetes Mellitus

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ARTICLE INFO

Keywords:
Add-on therapy
Natural herbal plants
Supplement
Type 2 diabetes

ABSTRACT

Aims: To examine the efficacy and safety of Curalin, as a supplement to anti-diabetic drugs (ADD).
Methods: 135 patients were enrolled in the study. Among them, 109, ages 18–85 years, with HA1c 7.5–10 % under treatment with ADD were randomized 1:1 to receive Curalin supplement or placebo. The primary efficacy endpoint was the change in HbA1c after 3 months. The secondary endpoint was a decrease in HbA1c by more than 0.5 % and by more than 1 %. The exploratory endpoints included the Diabetes Treatment Satisfaction Questionnaire (DTSQ), clinical and laboratory results.
Results: After 3 months, the mean reduction in HbA1c was 1.30 % (SD = 0.79) in the Curalin group compared to 0.10 % (SD = 0.70) in the placebo group ($P < 0.0001$). A decrease in HbA1c of ≥ 0.5 % was observed in 90.0 % of Curalin patients versus 19.0 % of placebo patients ($P < 0.0001$). HbA1c reduction of ≥ 1 % occurred in 64.0 % of Curalin patients and 11.9 % of placebo patients ($P < 0.0001$). Curalin patients reported higher satisfaction (DTSQ) with no severe adverse events.
Conclusions: Curalin treatment significantly reduced HbA1c over a period of 3 months and was well-tolerated.

1. Introduction

Currently, available treatment options for patients with type 2 diabetes include lifestyle changes and pharmacological interventions [1–3]. Globally, the use of conventional medicine for the treatment of type 2 diabetes is recommended; however, the use of complementary, and alternative medicine (CAM) that consists of dietary supplementation with over-the-counter agents is increasing [4,5]. The use of CAM for type 2 diabetes has been controversial, mostly due to the lack of regulated safety and efficacy studies [6]. Nevertheless, patients consider CAM to be an acceptable, if not preferable, long-term option for the treatment of various diseases.

Curalin, a combination of natural herbal plants with hypoglycemic traits that are known to have been used in the Ayurvedic traditional holistic care, achieves a synergistic effect through several mechanisms of action [7–17]. Curalin formula consists of nine plants. The effect of some is to improve beta-cell function (Bitter melon, fenugreek, Swertia chirayita, Gymnema sylvestre, and Emblica officinalis (, increase insulin sensitivity (Curcuma longa), reduce the rate of glycogenolysis between meals in the liver (bitter melon and *S. chirayita)* and prevent carbohydrate absorption (Bitter melon, Swertia chirayita, fenugreek, and Gymnema sylvestre). Together, these actions help regulate blood glucose levels and improve overall metabolic health.

A one month randomized, double blind study involving 36 adults with uncontrolled type 2 diabetes, demonstrated great efficacy and safety with the use of Curalin [18]. Here, we present the results of a 3-month, double blinded, multi-centered, randomized control trial, immediately followed by a 3-month open label study.

2. Research design and methods

2.1. Study Design

This was a multi-centered, randomized, double-blind study. Patients ages 18–85 years with type 2 diabetes and HbA1c 7.5–10 %, who were treated with ADD for 3 months or more were recruited. Patients were

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https://doi.org/10.1016/j.diabres.2024.111912
Received 16 September 2024; Received in revised form 19 October 2024; Accepted 4 November 2024
Available online 6 November 2024

screened for eligibility (Table S1) 7–14 days before randomization. The patients were blindly randomized to receive Curalin or placebo. After randomization, patients visited the clinic at week 6 and for a final double-blind visit of the study at week 12. Clinical measurements and blood for HbA1c were taken at these visits.

Safety blood tests including blood count, liver and kidney function tests were taken at the beginning and after 12 weeks. A total satisfaction assessment was performed at these visits, based on the Diabetes Treatment Satisfaction Questionnaire (DTSQ).

Patients were required to take two capsules of either Curalin or placebo, (consists of a substance called Maltodextrin and is coated with gelatin), three times a day after meals, for three months. After three months of the double-blind study, patients were invited to participate in a three-month, open label study in which all participants received Curalin supplements. Visits and their timing are summarized in Table S1.

Information on concomitant medications was collected by study site personnel from medical record reviews and patient interviews.

2.2. Participant eligibility

2.2.1. Criteria for Inclusion

Written informed consent, age 18–85, HbA1c at screening is 7.5 % – 10 %, Body mass index (BMI) $>$ 25, Stable body weight ($\pm$10 %) within the 3 months preceding study entry, patients were steadily treated with non-insulin ADD for at least 3 months or more prior to study entry.

2.2.2. Criteria for Exclusion

Using Curalin At least once in the past 3 months, known sensitivity to any of the components of the Curalin product, eGFR $\leq$ 30 mL/min/1.73 m2, pregnant or lactating or at risk to be pregnant, patients currently treated with insulin, patients under steroids and immunosuppressive drugs. History of stroke, transient ischemic attack, or myocardial infarction within six months prior to screening, hypertension (systolic blood pressure $\geq$ 180 mmHg / diastolic blood pressure $\geq$ 100 mmHg), TSH $>$ 1.5 above the upper limit of normal, liver disease, bilirubin $>$ 2 times the upper limit of normal and aspartate aminotransferase (AST) or alanine aminotransferase levels (ALT) $>$ 3 times the upper limit of normal. Potassium $>$ 6 mEq/L, Sodium $\leq$ 130 mEq/L, Hemoglobin under 10 g/dl for women, or under 11 g/dl for men (details in the supplement).

2.2.3. Data and Resource Availability

The raw data were transferred directly to the statisticians and held by them until there was a decision made to open the study to open the study. The entire process was conducted blindly for both the researchers and the company.

2.2.4. Ethics Information

The study was registered at clinicalTrials.gov (Number NCT05631431). Ethical approval was obtained at each of the four centers in Israel that took part in this study (Soroka Hospital, Beer Sheva, Ethics Committee 0319-20SOR, Tel Aviv Sourasky Medical Center – Ichilov Hospital, Tel Aviv, Ethics Committee 0021–21-TLV; Lin Medical Center, Haifa, Ethics Committee 0110–19-COM1, and Herzliya Medical Center Ethics Committee COM1-0212–20). All patients provided written informed consent to participate in the study.

2.2.5. Outcome Measures

The primary efficacy endpoint was change in HbA1c after the 3-month, double blind, randomized controlled treatment with Curalin vs. placebo. The secondary endpoint was the number of patients with significant improvement in HbA1c, defined as $\geq$ 0.5 % or $\geq$ 1 %. Other clinical measurements, such as body weight, blood pressure and the DTSQ were used as an exploratory endpoint.

The DTSQ consists of 6 items regarding treatment satisfaction and convenience, and 2 items regarding frequency of hyper- and hypoglycemia. Total satisfaction was calculated based on the sum of responses to items regarding treatment satisfaction and convenience (1,4,5,6,7 and 8), according to the DTSQ guidelines.

Adverse events (AEs) and Serious adverse events (SAEs) were documented, as well as safety variables, including vital signs and biochemical tests.

2.3. Blinding and randomization

Within 1–2 weeks after screening, the participants were randomized 1:1 into the Curalin supplement or placebo group, using stratification based on HbA1c levels at screening (7.5 %–8.5 % and $>$ 8.5 %–10 %), within each medical center, according to a computer-generated randomization scheme.

2.3.1. Statistical Methods

Assuming a mean difference in HbA1c between 0.5—0.6 % between groups, with SD of 1 % and a 5 % rate of drop out, a sample size of 94 to 120 participants is required to enable detection of statistical superiority difference between groups with a power of 80 %. Therefore, a sample size of 120 participants was chosen, evenly allocated between treatment groups.

Continuous baseline variables are presented as mean and standard deviation (SD) or median and interquartile range (IQR), as appropriate. Dichotomous variables are presented as count and proportion. Treatment arms were compared using both the *t*-test and Wilcoxon rank sum test for continuous variables and Wald test or Fisher's exact score for dichotomous variables, each as appropriate. These data, and the following analyses, are presented for the ITT population.

For the primary outcome of continuous change in HbA1c, the treatment arms for the overall study sample were compared using *t*-test. The differences between treatment arms are presented as mean, SD and 95 % confidence intervals (CI). Imputation based on the last observation carried forward method (LOCF) was carried out when HbA1c values were missing. sensitivity analyses were performed as well, including all enrolled participants and only for those who completed the end of study visit. A multivariate analysis for the treatment effect on change in HbA1c was performed using linear regression, adjusting for age and baseline HbA1c.

The secondary endpoint of the rate of participants who achieved clinically significant improvement in HbA1c of at least 0.5 % or at least 1 %, was compared between treatment arms using Wald test or Fisher's exact score, as appropriate.

These primary and secondary endpoints were further analyzed for predefined subgroups of HbA1c levels and metformin users at baseline, using similar statistical tests.

The exploratory endpoints of change in other continuous clinical measurements between treatment arms were compared using *t*-test.

Diabetes treatment satisfaction was calculated based on DTSQ at the beginning and end of the study. The total scores, and those for each question are presented at baseline, along with their change during the study. Data are presented as mean and SD. A comparison between treatment arms was tested using *t*-test.

Statistical significance was accepted at a P-value $<$ 0.05. All analyses were performed using R software v3.4.1.

3. Results

From December 14, 2021, to June 29, 2023, 135 patients with type 2 diabetes were enrolled in the study. Among them, 109 eligible patients were randomized, 56 to the Curalin supplement group and 53 to placebo. On June 29th the study was stopped due to false suspicion of a safety issue that was later found to be negligible (Supplement), at that time, the double-blind study was opened (Table S2). Among 109 patients, 14 did not reach visit 3 and therefore had no HbA1c measurement

after baseline, another 3 patients withdraw consent after their baseline visit. Thus, 17 patients were removed from the intention to treat (ITT) analysis.

The 92 patients included in the ITT of the double-blind study. 68 of them, finished another three months of open label study, 56 had HbA1c measurements after the last open label visit (Fig. 1).

3.1. Demographic and Preprocedural baseline characteristics

No significant differences were found in baseline characteristics between the Curalin and placebo groups, except age, indicating a balanced randomization ($P > 0.05$) (Table 1). Curalin participants were younger on average (SD), compared to placebo (64.4 (9.7) vs. 68.8 (8.1) years, respectively, $P = 0.024$).

3.2. Primary and secondary endpoints

The primary efficacy endpoint, which measured the mean decrease in HbA1c after 3 months of intervention, was 1.30 % (0.79) in the Curalin arm and 0.10 % (0.69) in the placebo arm. The mean difference in decrease between Curalin and placebo was 1.20 % (95 % CI: [0.89–1.51], $P < 0.0001$), favoring Curalin (Table 2). This was calculated based on the ITT population after LOCF imputation for 5 participants, 3 in the Curalin arm and 2 in placebo (Table S2). Sensitivity analyses were performed. Once included only those with visit 4 measurements, yielding similar results, (Table 2). Second, including all participants with at least baseline values of HbA1c. I.e.,106 participants who enrolled in the study and did not withdraw their consent. The results demonstrated a statistically significant benefit for the Curalin arm with a 1.18 % (0.84) reduction in HbA1c versus 0.08 % (0.63) in the placebo arm (after LOCF imputation), $p < 0.0001$. Furthermore, the change in HbA1c was analyzed based on baseline levels. Participants with HbA1c < 8.5 % at baseline experienced a mean decrease of 1.01 % (0.63) in the Curalin arm and an increase of 0.07 % (0.46) in the placebo arm ($P < 0.001$). Participants with HbA1c ≥ 8.5 % at baseline had a 1.82 % (0.80) decrease in HbA1c in the Curalin arm and 0.37 % (0.92) in the placebo arm ($P < 0.0001$); (Table 2, Figure S1).

In a multivariate analysis, adjusted for age, the effect of Curalin versus placebo was 1.20 %, 95 % CI = [0.90, 1.51], $P < 0.0001$. The multivariate model was repeated, adjusting for age and HbA1c at baseline. The HbA1c reduction in the Curalin group versus placebo resulted in a similar significant effect, at 1.14 %, 95 % CI = [0.85, 1.42], $P < 0.0001$ (Table 2).

The secondary endpoint revealed a statistically significant decrease in the rates of improvement in HbA1c. The rate of HbA1c decrease of at least 0.5 % occurred in 90.0 % of patients treated with Curalin compared to 19.0 % of patients treated with placebo ($P < 0.001$) and a rate of at least 1 % decrease in HbA1c occurred in 64.0 % of patients treated with Curalin, in contrast to 11.9 % of placebo-treated patients ($P < 0.0001$, Figure S2). An analysis of differences between treatment arms in the rate of meaningful decreases in HbA1c conducted for other visits and at different baseline HbA1c levels, consistently demonstrated a statistically significant benefit of Curalin in all comparisons (Table 3). Most patients were treated with metformin or metformin in combination with SGLT-2 or DPP4 inhibitors. The analysis indicates a significant reduction in HbA1c among these patients (Table S3).

For the additional, open label, 3-month follow-up, in which 56 patients with HbA1c values were recorded at the end of the open label follow-up (28 who received Curalin and 28 who received placebo during the double-blind study). The average decrease in HbA1c after 6 months of the Curalin arm was 1.48 % (95 %CI: [1.14—1.82]), and in the arm that received 3 months of placebo in the double-blind study and 3 months of Curalin in the open label portion, the decrease in HbA1c from the end of double-blind period to the end of the open label follow-up was 1.02 % (95 %CI: [0.81—1.34]). (Figure S3).

3.3. Clinical measurements

Overall, for change during the study in clinical and laboratory measurements, no statistically significant differences were observed between treatment arms (Table S4).

3.4. Treatment satisfaction questionnaire

The treatment satisfaction questionnaire was completed by 64 participants (33 and 31 in the Curalin and placebo arms, respectively; approximately 75 % of those who completed the double-blind phase). Total mean (SD) DTSQ scores at baseline were 24.94 (6.89) and 26.84 (6.60) for Curalin and placebo, respectively ($P = 0.265$). Among those receiving Curalin, satisfaction scores improved during the study by an

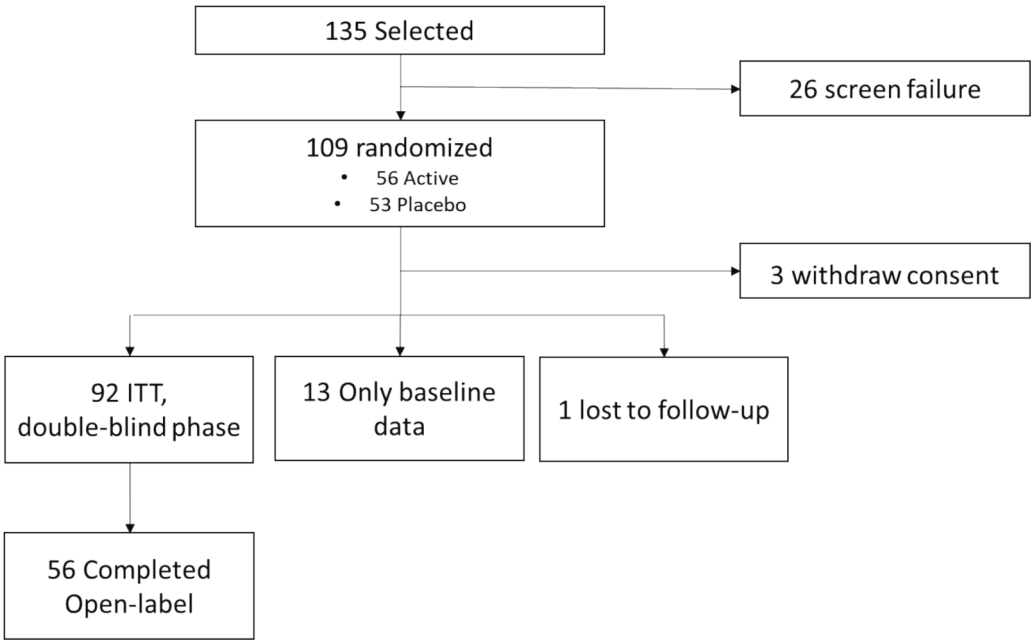

Fig. 1. Study Consort.

Table 1
Patient demographics and clinical characteristics at baseline.

Variable	Overall		Curalin (Active)		Placebo		
	N		N		N		P-value
Age, years, mean (SD)	92	66.4 (9.2)	50	64.4 (9.7)	42	68.8 (8.1)	0.024
Sex, n (%)							
Male		61 (66.3 %)		34 (68.)		27 (64.3 %)	0.878
Female		31 (33.7 %)		16 (32.0 %)		15 (35.7 %)	
Diabetes complications, n (%)							
Yes		8 (9.1 %)		5 (10.0 %)		3 (7.9 %)	>0.999
No		80 (90.9 %)		45 (90.0 %)		35 (92.1 %)	
Diabetes duration, years,mean (SD)	79	14.50 (5.73)	44	14.56 (5.92)	35	14.43 (5.57)	0.919
Height, cm, mean (SD)	89	167.07 (8.67)	49	167.00 (9.08)	40	167.15 (8.26)	0.936
Weight, kg, mean (SD)	89	81.22 (11.74)	49	81.71 (12.09)	40	80.62 (11.43)	0.666
BMI, kg/m^2, mean (SD)	89	29.08 (3.58)	49	29.30 (3.83)	40	28.81 (3.28)	0.521
Waist circumference, cm, mean (SD)	89	103.98 (9.99)	49	105.18 (9.17)	40	102.50 (10.85)	0.209
Follow up on double blind, month, median (IQR)	92	2.83 (2.8, 3.09)	50	2.92 (2.8, 3.19)	42	2.82 (2.77, 3.01)	0.204
Laboratory measurements							
HbA1c, %, mean (SD)	92	8.36 (0.69)	50	8.44 (0.75)	42	8.26 (0.61)	0.227
Urea, mg/dL, mean (SD)	66	18.47 (5.48)	37	18.24 (4.89)	29	18.76 (6.22)	0.707
Creatinine, mg/dL, mean (SD)	64	1.66 (6.14)	35	2.29 (8.31)	29	0.90 (0.19)	0.373
GGT, U/L, mean (SD)	66	28.50 (41.09)	37	32.11 (53.25)	29	23.90 (15.29)	0.425
ALT, U/L, mean (SD)	66	25.88 (11.21)	37	27.70 (11.33)	29	23.55 (10.81)	0.137
Hemoglobin, g/dL, mean (SD)	65	13.93 (3.01)	36	14.11 (3.04)	29	13.71 (3.00)	0.600
eGFR, ml/min/1.73 m^2, mean (SD)	66	84.43 (18.94)	37	84.58 (21.03)	29	84.24 (16.35)	0.943
Pulse, bpm, mean (SD)	88	75.15 (10.80)	48	75.31 (11.40)	40	74.95 (10.18)	0.876
Systolic BP, mm Hg, mean (SD)	88	133.33 (14.86)	48	132.04 (13.00)	40	134.87 (16.86)	0.377
Diastolic BP, mm Hg, mean (SD)	88	74.36 (8.66)	48	73.90 (9.04)	40	74.91 (8.27)	0.588
Diabetes related baseline medications							
Metformin, n (%)		53 (57.6 %)		29 (58 %)		24 (57.1 %)	>0.999
Metformin combination n (%)		42 (45.7 %)		21 (42 %)		21 (50 %)	0.577
Any Metformin, n (%)		81 (88 %)		44 (88 %)		37 (88.1 %)	>0.999
SGLT-2, n (%)		33 (35.9 %)		18 (36 %)		15 (35.7 %)	>0.999
DPP-4i, n (%)		7 (7.6 %)		3 (6 %)		4 (9.5 %)	0.810
Sulfonylurea, n (%)		13 (14.1 %)		6 (12 %)		7 (16.7 %)	0.734
GLP-1-RA, n (%)		40 (43.5 %)		21 (42 %)		19 (45.2 %)	0.920
Meglitinide, n (%)		7 (7.6 %)		3 (6 %)		4 (9.5 %)	0.810

Continuous variables are presented as mean, SD. Dichotomous variables are presented as count and proportion. Treatment arms were compared using the *t*-test or Wilcoxon rank sum test, for continuous variables and Wald test or Fisher's exact test for dichotomous variables, each as appropriate.
ALT = alanine transaminase; GGT = Gamma-glutamyl transpeptidase.

average of 6.91 (8.04) points, while the placebo arm scores increased 0.26 (9.07; P = 0.003). A significant difference in favor of the Curalin arm compared to placebo was found for items regarding current satisfaction, convenience, recommend to others and willingness to continue with treatment (Questions 1,4,7 and 8). No significant difference was found for the other items (Table 4).

3.5. Hypoglycemia/ hyperglycemia

The recommendation to the investigators was to avoid, if possible, addition of ADD during the double-blind part of the study. Patients were closely monitored throughout the three-month blinded study, and investigators were instructed to exclude patients in the event of a significant increase in blood glucose levels, as specified in the protocol. Episodes of hypoglycemia were managed by adjusting the doses of other hypoglycemic medications, and, when necessary, by reducing the dose of the supplement.

Overall, 19 cases of hypoglycemia were reported during the study (among 14 participants), 8 in the Curalin arm (7 participants) and 11 in the placebo arm (7 participants). Of these cases, 17 were mild and 2 were moderate (1 participant). The moderate case was in the Curalin arm and did not need third person assistance.

3.6. Adverse events

Most adverse events were classified as mild by participants. Gastrointestinal disturbances were the predominant mild side effect, affecting 23 participants in the Curalin group and 17 in the placebo group. Urinary complaints were reported by 3 individuals in each group. Notably, weakness was observed more frequently in the Curalin group, with 5 reports, as opposed to a single report from the placebo group. Hyperkalemia was reported by 2 participants receiving placebo and 1 receiving Curalin. During 6 months on the supplement, blood count, kidney and liver blood tests were unchanged and stable in both groups.

Concerning severe side effects, the Curalin group had 1 reported case of supraventricular tachycardia that required ablation. Conversely, the placebo group reported 2 SAEs: 1 instance of postmenopausal bleeding and 1 case of grade 3 endometrial carcinoma. These severe side effects were reported by the investigator as unrelated to the study drug.

4. Discussion

The aim of this study was to investigate whether patients with

Table 2
Continuous change in HbA1c from baseline to each study visit.

Variable	Visit	Overall		Curalin (Active)		Placebo		PV
		N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	
HbA1c for entire population	Screening	92	8.36 (0.69)	50	8.44 (0.75)	42	8.26 (0.61)	0.227
	Change to V3	83	0.58 (0.63)	44	0.97 (0.55)	39	0.15 (0.41)	<0.001
	Change to V4	87	0.75 (0.98)	47	1.32 (0.80)	40	0.09 (0.71)	<0.001
	Change to V4 with LOCF	92	0.75 (0.96)	50	1.30 (0.79)	42	0.10 (0.69)	<0.001
HbA1c at baseline 7-<8.5	Screening	58	7.91 (0.27)	32	7.96 (0.30)	26	7.84 (0.22)	0.110
	Change to V3	50	0.46 (0.53)	27	0.79 (0.44)	23	0.07 (0.30)	<0.001
	Change to V4	55	0.53 (0.79)	31	1.02 (0.64)	24	−0.10 (0.46)	<0.001
	Change to V4 with LOCF	58	0.52 (0.77)	32	1.01 (0.63)	26	−0.07 (0.46)	<0.001
HbA1c at baseline ≥ 8.5	Screening	34	9.14 (0.46)	18	9.30 (0.48)	16	8.95 (0.37)	0.025
	Change to V3	33	0.77 (0.74)	17	1.25 (0.59)	16	0.27 (0.51)	<0.001
	Change to V4	32	1.14 (1.15)	16	1.91 (0.78)	16	0.37 (0.92)	<0.001
	Change to V4 with LOCF	34	1.14 (1.12)	18	1.82 (0.80)	16	0.37 (0.92)	<0.001
Linear Regression								
	Variable	**Label**		**Parameter Estimate**		**(CI 95 %)**		**P-value**
Model 1. Adjusted for age	Treatment arm	**Curalin vs. placebo**		**1.20**		**[0.90, 1.51]**		**<0.0001**
	Age			0.00		[-0.02, 0.02]		0.9267
Model 2. Adjusted for age and baseline HbA1c	Treatment arm	**Curalin vs. placebo**		**1.14**		**[0.85, 1.42]**		**<0.0001**
	Age			0.01		[-0.01, 0.02]		0.4358
	Baseline HbA1c			0.51		[0.31, 0.72]		<0.0001

Change in HbA1c is presented as mean, SD. Treatment arms were compared using a *t*-test. Linear regression analyzed the association between a decrease in HbA1c and treatment group, adjusted for age and baseline HbA1c.

Table 3
Significant improvements in HbA1c from screening to each visit, by treatment arm.

Variable		Study Visit	Overall		Curalin (Active)		Placebo		P-value between treatment arms
			N	%	N	%	N	%	
HbA1c for entire population	HbA1c change ≥ 0.5 %	Change to V3	83	55.4 %	44	88.6 %	39	18.0 %	<0.0001
		Change to V4	87	56.3 %	47	89.4 %	40	17.5 %	<0.0001
		Change to V4 with LOCF	92	57.6 %	50	90.0 %	42	19.0 %	<0.0001
	HbA1c change ≥ 1 %	Change to V3	83	25.3 %	44	45.5 %	39	2.6 %	<0.0001
		Change to V4	87	41.4 %	47	66.0 %	40	12.5 %	<0.0001
		Change to V4 with LOCF	92	40.2 %	50	64.0 %	42	11.9 %	<0.0001
HbA1c at baseline 7- <8.5	HbA1c change ≥ 0.5 %	Change to V3	50	88.0 %	27	85.2 %	23	91.3 %	<0.0001
		Change to V4	55	49.1 %	31	83.9 %	24	4.2 %	<0.0001
		Change to V4 with LOCF	58	50.0 %	32	84.4 %	26	7.7 %	<0.0001
	HbA1c change ≥ 1 %	Change to V3	50	16.0 %	27	29.6 %	23	0.0 %	0.0124
		Change to V4	55	29.1 %	31	51.6 %	24	0.0 %	<0.0001
		Change to V4 with LOCF	58	27.6 %	32	50.0 %	26	0.0 %	<0.0001
HbA1c at baseline ≥ 8.5	HbA1c change ≥ 0.5 %	Change to V3	33	63.6 %	17	94.1 %	16	31.3 %	0.0002
		Change to V4	32	68.8 %	16	100.0 %	16	37.5 %	<0.0001
		Change to V4 with LOCF	34	70.6 %	18	100.0 %	16	37.5 %	<0.0001
	HbA1c change ≥ 1 %	Change to V3	33	39.4 %	17	70.6 %	16	6.3 %	0.0001
		Change to V4	32	62.5 %	16	93.8 %	16	31.3 %	0.0003
		Change to V4 with LOCF	34	61.8 %	18	88.9 %	16	31.3 %	0.0011

Treatment arms were compared using Wald test or Fisher's exact test for binary data, as appropriate. LOCF, last observation carried forward method.

uncontrolled diabetes, despite treatment with ADD except insulin, would benefit from the addition of Curalin.

The primary efficacy endpoint of the mean decrease in HbA1c after 3 months of double-blind randomization to Curalin vs. placebo, was 1.30 % (SD = 0.79) in the Curalin arm and 0.10 % (SD = 0.70) in the placebo arm, ($P < 0.001$). Participants with HbA1c < 8.5 % at baseline experienced a mean decrease in HbA1c of 1.01 % (0.63) in the Curalin arm, and those with HbA1c ≥ 8.5 % at baseline showed a decrease in HbA1c of 1.82 % (0.80). Additionally, the multivariate model was repeated, adjusting for age and HbA1c at baseline, and the HbA1c reduction in the Curalin group versus placebo remained significant with a similar effect.

The secondary endpoint revealed a significant decrease in HbA1c of at least 0.5 % and at least 1 % in the patients of the Curalin arm compared to the placebo arm.

The open-label, 3-month follow-up study conducted after 12 weeks of double-blind study, demonstrated a consistently positive effect of Curalin on decreasing HbA1c.

Although the mechanism by which Curalin reduces HbA1c was not explored in this study, it is likely related to the effect of the supplement on beta cell function, insulin resistance, and gastrointestinal absorption, as suggested in other small studies on the plants used in these supplements.

Curalin, a combination of 9 plants with hypoglycemic traits that are known to have been used in the Ayurvedic traditional holistic care or

Table 4
Diabetes Treatment Satisfaction Questionnaire (DTSQ) scores at baseline, end of double-blind phase and change from baseline to the end of the study.

Visit	Question	Overall	Active	Placebo	P-value
	n	64	33	31	
Baseline	**Total**	**25.86 (6.77)**	**24.94 (6.89)**	**26.84 (6.60)**	**0.265**
	Current satisfaction (Q1)	4.27 (1.51)	4.03 (1.49)	4.52 (1.52)	0.202
	Frequency of hyperglycemia (Q2)	3.95 (1.68)	3.94 (1.82)	3.97 (1.54)	0.947
	Frequency of hypoglycemia (Q3)	1.23 (1.73)	1.36 (1.88)	1.10 (1.58)	0.543
	Convenience (Q4)	4.53 (1.43)	4.33 (1.49)	4.74 (1.34)	0.255
	Flexibility (Q5)	4.28 (1.59)	4.09 (1.63)	4.48 (1.55)	0.327
	Understanding of diabetes (Q6)	4.67 (1.22)	4.70 (1.31)	4.65 (1.14)	0.867
	Recommend to others (Q7)	4.09 (1.77)	3.91 (1.83)	4.29 (1.72)	0.394
	Willingness to continue (Q8)	4.02 (1.62)	3.88 (1.69)	0.16 (1.55)	0.490
Visit 4	**Total**	**29.55 (7.48)**	**31.85 (4.85)**	**27.10 (8.96)**	**0.010**
	Current satisfaction (Q1)	5.00 (1.63)	5.55 (0.79)	4.42 (2.06)	0.005
	Frequency of hyperglycemia (Q2)	2.84 (2.11)	2.27 (1.82)	3.45 (2.25)	0.024
	Frequency of hypoglycemia (Q3)	2.17 (1.98)	2.73 (2.08)	1.58 (1.71)	0.019
	Convenience (Q4)	4.73 (1.44)	5.06 (1.06)	4.39 (1.71)	0.061
	Flexibility (Q5)	4.78 (1.44)	5.00 (1.44)	4.55 (1.43)	0.213
	Understanding of diabetes (Q6)	5.09 (1.12)	5.30 (0.81)	4.87 (1.36)	0.125
	Recommend to others (Q7)	4.89 (1.73)	5.48 (1.15)	4.26 (2.02)	0.004
	Willingness to continue (Q8)	5.05 (1.42)	5.45 (1.03)	4.61 (1.65)	0.016
Difference between baseline and visit 4	**Total**	**3.69 (9.12)**	**6.91 (8.04)**	**0.26 (9.07)**	**0.003**
	Current satisfaction (Q1)	0.73 (2.12)	1.52 (1.54)	−0.10 (2.34)	**0.002**
	Frequency of hyperglycemia (Q2)	−1.11 (2.67)	−1.67 (2.48)	−0.52 (2.78)	0.085
	Frequency of hypoglycemia (Q3)	0.94 (2.65)	1.36 (2.92)	0.48 (2.29)	0.187
	Convenience (Q4)	0.20 (1.75)	0.73 (1.63)	−0.35 (1.72)	**0.012**
	Flexibility (Q5)	0.50 (2.08)	0.91 (2.27)	0.06 (1.79)	0.105
	Understanding of diabetes (Q6)	0.42 (1.49)	0.61 (1.56)	0.23 (1.41)	0.311
	Recommend to others (Q7)	0.80 (2.26)	1.58 (1.90)	−0.03 (2.34)	**0.004**
	Willingness to continue (Q8)	1.03 (1.97)	1.58 (1.94)	0.45 (1.86)	**0.021**

approach, achieves a synergistic effect through several mechanisms of action. Its formula consists of the following plants: *Momordica charantia* (bitter melon), *Trigonella Foenum Graecum* (fenugreek), *Swertia chirayita*, *Emblica officinalis*, *Gymnema sylvestre*, *Curcuma longa* (turmeric), *Picrorhiza kurroa*, *Eugenia jambolana,* and *Cinnamomum zeylanicum*.

M. charantia, *P. emblica officinalis*, *S. chirayita*, *T. foenum graecum*, and *G. sylvestre* restore the ability of pancreatic cells to secrete insulin [7–10]. In addition to restoring insulin secretion, *C. longa* raises sensitivity to insulin through the enzymatic activity of PPARy in muscle and fat cells [13]. *C. longa* modulates immune activity; thus, preventing an increase in insulin resistance, [13,14]. Bitter melon, *S. chirayita*, *G. sylvestre*, and fenugreek are well known to inhibit the absorption and breakdown of sugars in the intestine [9,10,15,16,19]. Cinnamon and *Eugenia jambolana* have been shown to have beneficial effects by promoting glycemic control and reducing insulin resistance [17,20]. Finally, bitter melon and *S. chirayita* reduce the rate of glycogenolysis between meals in the liver [9,19]. Patients with poor glycemic control despite adhering to their treatment regimen, may be able to intensify their treatment by supplementing with CAM therapy.

This study highlights the potential role of supplements in improving blood glucose control in patients who struggle to achieve glycemic control with conventional anti-diabetic drugs, either due to a low response to the drug, or limited use of these drugs due to side effects. In recent years, the recommendation to use insulin therapy in patients who failed to achieve the target of HbA1c has decreased due to concerns of patients from weight gain and hypoglycemia [21]. Quite often both patients and physicians hesitate to start treatment with insulin reducing the ability to achieve the target of HbA1c. Some oral treatments have limitations due to their side effects. Pioglitazone has several deleterious side effects like weight gain, fluid retention, and fractures in women after menopause [22,23]. Sulphonylurea cause weight gain, hypoglycemia, and fail to sustain blood glucose over time [24,25]. The use of the new families of SGLT2 inhibitors and GLP1 agonists that replace some of the old drugs, also have side effects that might prevent their use due to genital infections mainly in women, and gastrointestinal side effects in both men and women [26–29]. Moreover the use of oral ADD and injectable GLP1 sometimes fails to achieve the target of HbA1c [23,25].

The results of our study suggest that in patients who are not well-controlled using conventional ADD, Curalin could be a valuable option with high efficacy over a relatively long duration. The efficacy of the supplement was similar in patients treated with Metformin (stand-alone or in combination with DPP4 inhibitors, SGLT2 inhibitors, or GLP1 agonists). The effect was significant in patients with HbA1c below or above 8.5 %. 3-month open label follow up of patients randomized to Curalin demonstrated the sustainability of the effect on HbA1c reduction.

In contrast to the side effects seen with ADD, the use of Curalin hardly caused any significant side effect that might stop its use. hypoglycemia was mild with similar events in both arms.

During the study there was no sign of safety issues clinically or laboratory. We ensured the safety of the supplement by monitoring liver enzymes and kidney function in the beginning and in the end of the study and didn't find any sign of deleterious effect. However, as this study was relatively short, larger, and longer studies are needed to fully confirm the safety of the combined supplement.

The treatment had high patient satisfaction, due to its great effect on their blood glucose levels, minimal side effects, and a low tendency for hypoglycemia.

This study had several limitations. The sample in the double-blind study was relatively small, and the study duration was relatively short. The age of the group receiving Curalin therapy was significantly younger than the placebo group. Additionally, we did not measure insulin and c-peptide that might be different between groups at baseline.

Artificial break of the study after 109 patients were randomized, of which 17 patients had only baseline HbA1c, resulted in a reduction of ITT patients to 92 only. In this study ITT is based on 92 patients that completed the double-blind study (87) or had HbA1c results in visits after randomization (5).

While no safety issues were identified, it will be important to assess this in larger and longer-term studies. The open-label study, which demonstrated the sustainability of the supplement, was also small and of short duration. Longer-term studies, mechanistic investigations, and cost-effectiveness analyses are essential for a comprehensive

understanding of the potential benefits and risks of Curalin.

5. Conclusion

Curalin supplement as add-on therapy for Type 2 diabet patients with uncontrolled diabetes under ADD was safe, with minimal side effects and resulted in significant improvement in blood glucose control and patient satisfaction.

Author Contributions and guarantor Statement

I.R. contributed to writing, reviewing, and editing the manuscript. R. W.S. collected data, wrote, reviewed, and edited the manuscript. O.S. and S.D. contributed to reviewing. A.R. and I.Y. contributed to the data collection and performed the statistical analysis. O.Y. and R.E. on behalf of CuraLife oversaw that the study was conducted according to the protocol. All authors take responsibility for the accuracy of the manuscript.

I.R. is the guarantor of this work and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Funding and assistance

This study was fully funded by CuraLife. CuraLife did not influence the conduct of the study.

CRediT authorship contribution statement

Itamar Raz: Writing – review & editing, Writing – original draft, Supervision. **Roni Weinberg Sibony:** Writing – review & editing, Writing – original draft. **Saar Dor:** Writing – review & editing. **Aliza Rozenberg:** Formal analysis, Data curation. **Ilan Yanuv:** Formal analysis, Data curation. **Ofer Yigdal:** . **Ron Elul:** . **Omri Segev:** Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Itamar Raz is a paid consultant for CuraLife. The rest of the authors have no conflicts of interest to declare.].

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2024.111912.

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