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RESEARCH ARTICLE

WILEY

Curalin supplement for patients with type 2 diabetes mellitus

Roni Weinberg Sibony[1] | Julio Wainstein[2,3] | Maya Ish Shalom[3] | Tali Ganz[2] | Aliza Rozenberg[4,5] | Ilan Yanuv[4,5] | Uri Eliyahu[6] | Itamar Raz[5]

[1]Faculty of Medicine, Ben-Gurion University of the Negev, Beer Sheva, Israel

[2]Diabetes Unit, Edith Wolfson Medical Center, Holon, Israel

[3]Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

[4]Department of Endocrinology and Metabolism, Diabetes Unit, Hadassah Medical Center, Jerusalem, Israel

[5]Faculty of Medicine, Hebrew University of Jerusalem, Jerusalem, Israel

[6]Department of Nutrition, Ariel University, Ariel, Israel

Correspondence
Roni Weinberg Sibony, Faculty of Medicine, Ben-Gurion University of the Negev, Beer Sheva, Israel.
Email: Roniweinb@gmail.com

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Abstract

Objective: To examine the efficacy and safety of Curalin supplement in patients with type 2 diabetes.

Research design and methods: Adult patients with type 2 diabetes were randomized 1:1 to receive Curalin supplement or placebo. The primary endpoint was HbA1c decrease at 1 month. The secondary endpoint was a decrease in HbA1c by more than 0.5% and 1% and a change in 7 daily blood glucose measurements. A satisfaction questionnaire was used as an exploratory endpoint. Safety variables and adverse events were assessed.

Results: After 1 month of intervention, HbA1c was reduced by 0.94% in the Curalin arm versus 0.4% in the placebo arm ($P = 0.008$). 72% of Curalin patients had decreased HbA1c levels >0.5% versus 35% in the placebo arm ($P < 0.05$). The Treatment Satisfaction Questionnaire indicated that Curalin arm patients reported higher overall satisfaction.

Conclusions: Curalin treatment significantly reduced HbA1c over a 1-month period and was well-tolerated.

KEYWORDS
add-on therapy, natural herbal plants, supplement, type 2 diabetes

1 | INTRODUCTION

In Western countries, the estimated prevalence of type 2 diabetes is over 10% of the adult population.[1] Patients with uncontrolled diabetes on antidiabetic drugs or who have significant side-effects might be able to improve their glycaemic indices by supplementing with complementary and alternative medicine (CAM) therapy.[2,3]

Curalin, a combination of natural herbal plants with hypoglycemic traits that are used in traditional medicine, achieves a synergistic effect through several mechanisms of action (details in supplement).[4–15]

This pilot, double-blind placebo, randomized control trial was designed to evaluate the efficacy of Curalin versus placebo as an add-on therapy among 36 adults with uncontrolled, type 2 diabetes. Safety and treatment satisfaction were also evaluated.

2 | MATERIALS AND METHODS

2.1 | Study design

The study was powered at 80% to detect any statistical difference between groups under the assumptions of a mean difference in HbA1c of 0.8% between groups, with a standard deviation of 0.75%.

Eligible patients received two capsules of either Curalin or placebo thrice daily for 30 days (Figure S1). Patients were asked to take 7 glucose measurements once-a-week on the same day using a Freestyle glucometer that was supplied to them. Information on concomitant medications was collected by study site personnel from medical record reviews and patient interviews. Visits and their timing are summarised in Table S1.

2.2 | Ethics information

The study was registered at clinicalTrials.gov (Number NCT0543 9473). Ethical approval was obtained from the Edith Wolfson Medical Center Ethics Committee (0160-20-WOMC). Patients provided written informed consent to participate.

2.3 | Outcomes

The primary efficacy endpoint was change in HbA1c after 1 month of Curalin treatment. The secondary endpoint was defined as the number of patients with significant improvement in HbA1c (>0.5% and >1%) and in the mean of the 7 blood glucose measurements taken on the same day, once-a-week. The Diabetes Treatment Satisfaction Questionnaire (DTSQ) was used as an exploratory endpoint. In addition to adverse events (Aes) and serious adverse events (SAEs), safety variables included fasting blood count, biochemical tests, and vital signs.

2.4 | Blinding and randomisation

Within 1–2 weeks after screening, the participants were randomized 1:1 into the supplement and placebo groups, using stratification based on HbA1c levels at screening (7.5%–9% and >9%–11%), according to a computer-generated randomisation scheme. Of the 36 patients in the study, 24 with HbA1c ≤ 9% and 12 with HbA1c > 9% were equally allocated between treatment arms.

2.5 | Statistical methods

Continuous baseline variables are presented as mean, standard deviation (SD), median, interquartile range (IQR), and range. 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 the Wald test or Fisher's exact score for dichotomous variables, each as appropriate. For the primary outcome of change in HbA1c, comparisons between treatment arms for the overall study sample as well as for a subgroup of predefined HbA1c levels at baseline were calculated and evaluated using a *t*-test. Linear regression was built to analyse the association between the decrease in HbA1c and the treatment group adjusted for baseline HbA1c. In addition, improvement in HbA1c was defined based on the thresholds of decrease in HbA1c during the study of at least 0.5% or at least 1%. A comparison between treatment arms was tested on the basis of Fisher's exact score. The changes in clinical measurements between treatment arms were compared using a *t*-test. Treatment satisfaction was calculated based on the DTSQ questionnaire responses at the beginning and end of the study. The total and individual scores at baseline and their change during the study are presented as mean, SD, median, interquartile range, and range. Changes in scores between treatment arms were compared using the Wilcoxon rank sum test. Means and 95% confidence intervals (CI) of the 7 daily blood glucose measurements are presented and compared using *t*-test.

Statistical significance was set at a *p*-value<0.05. All analyses were performed using R software v3.4.1.

3 | RESULTS

From 3 August 2021 to 1 May 2022, 51 patients with type 2 diabetes were enroled in the study (Figure S1). Among them, 36 eligible patients were randomized. Each treatment arm consisted of 18 patients. One patient randomized to the placebo group reported an AE and discontinued the study on day 10 due to abdominal pain. A total of 35 patients completed the study per protocol.

3.1 | Demographics and preprocedural baseline characteristics

There were no significant differences in baseline characteristics between the Curalin and placebo groups, indicating overall balanced randomisation ($P > 0.05$) (Table 1).

3.2 | HbA1c change

The primary efficacy endpoint was the mean decrease in HbA1c after 1 month of intervention was 0.94% in the Curalin arm and 0.4% in the placebo arm. The mean (SD) difference between Curalin versus placebo was 0.54% (0.57), ($P = 0.008$). The comparison of Curalin and placebo treatment arms regarding HbA1c ≤ 9% resulted in mean decreases of 0.83% (0.52) and 0.13% (0.45) in the Curalin and placebo arms, respectively ($P = 0.001$). The mean HbA1c >9% decreased by 1.16 in the Curalin group and 0.88 in the placebo group ($P = 0.458$, Table 2).

Linear regression revealed a significant decrease in HbA1c in the Curalin versus placebo arms ($P < 0.01$; Table 2). Multivariate analysis showed similar results (mean difference in decrease: 0.58 (SE = 0.18, $P < 0.01$; Table 2). The results of this analysis are based on the intention to treat 36 patients with imputation for the patient who discontinued the study due to an AE. The secondary endpoint demonstrated a significant decrease in HbA1c of >0.5% in 72% of patients treated with Curalin versus 35% of patients treated with placebo ($P < 0.05$). Among patients who received Curalin, 44.4% experienced a >1% decrease in HbA1c, compared to 11.8% of patients in the placebo group ($P = 0.06$, Figure 1).

3.3 | Glucose measurements

The mean glucose levels for all patients in both treatment arms during the 30-day trial are presented in Figure 2. There was a

TABLE 1 Patient demographics and clinical characteristics at baseline.

Variable		Total ($N = 36$)	Curalin ($N = 18$)	Placebo ($N = 18$)	p-value*	p-value**
HbA1c (%)	Mean (SD)	8.86 (0.94)	8.82 (0.87)	8.9 (1.03)	0.808	0.937
	Median (IQR)	8.62 (8.2, 9.46)	8.73 (8.08, 9.43)	8.44 (8.35, 9.49)		
	Range	(7.62, 11.3)	(7.74, 10.32)	(7.62, 11.3)		
Sex, % (n)	F	38.9 (14)	33.3 (6)	44.4 (8)	0.496	
	M	61.1 (22)	66.7 (12)	55.6 (10)		
Age, years	Mean (SD)	63.08 (8.68)	63.28 (8.17)	62.89 (9.41)	0.895	0.949
	Median (IQR)	64 (55, 69.5)	64 (55, 69)	63.5 (55, 70)		
	Range	(45, 78)	(50, 77)	(45, 78)		
Age, years (n, %)	≤65	63.9 (23)	66.7 (12)	61.1 (11)	0.730	
	>65	36.1 (13)	33.3 (6)	38.9 (7)		
Diabetes duration, years	Mean (SD)	14.2 (8.8)	13.39 (6.9)	15.06 (10.6)	0.581	0.830
	Median (IQR)	13 (7, 2)	12.5 (8, 20)	13 (7, 22)		
	Range	(2, 36)	(2, 25)	(2, 36)		
Diabetes duration, years, % (n)	≤10	44.4 (16)	44.4 (8)	44.4 (8)	>0.999	
	>10	52.8 (19)	55.6 (10)	50 (9)		
BMI (kg/m^2)	Mean (SD)	30.44 (4.49)	30.78 (4.37)	30.09 (4.71)	0.649	0.602
	Median (IQR)	30.65 (26.95, 34.25)	30.7 (27.3, 34.7)	29.95 (26.3, 33.9)		
	Range	(22.5, 41)	(23.2, 37.7)	(22.5, 41)		
BMI, % (n)	≤30	47.2 (17)	44.4 (8)	50 (9)	0.740	
	>30	52.8 (19)	55.6 (10)	50 (9)		
Waist circumference, cm	Mean (SD)	105.05 (13.71)	107.61 (11.25)	102.48 (15.7)	0.268	0.580
	Median (IQR)	106.5 (99.5, 114)	107 (101, 113)	106 (92, 114)		
	Range	(66.7, 130)	(88, 130)	(66.7, 120)		
Systolic BP, mmHg	Mean (SD)	133.3 (14.07)	133.7 (12.72)	132.8 (15.66)	0.862	0.962
	Median (IQR)	131 (122.5, 144.5)	134 (124, 144)	130.5 (120, 147)		
	Range	(106, 159)	(114, 159)	(106, 158)		
Diastolic BP, mmHg	Mean (SD)	81.11 (9.77)	81.89 (10.59)	80.33 (9.11)	0.640	0.635
	Median (IQR)	81.5 (73.5, 88)	81.5 (79, 91)	81 (73, 85)		
	Range	(61, 102)	(61, 100)	(67, 102)		
Creatinine	Mean (SD)	0.85 (0.24)	0.81 (0.23)	0.88 (0.24)	0.379	0.326
	Median (IQR)	0.84 (0.65, 0.97)	0.75 (0.65, 0.91)	0.88 (0.65, 1.02)		
	Range	(0.48, 1.34)	(0.48, 1.3)	(0.57, 1.34)		
ALT	Mean (SD)	24.11 (13.38)	22.61 (14.12)	25.61 (12.83)	0.509	0.296
	Median (IQR)	20.5 (15, 27)	20 (13, 24)	23 (16, 31)		
	Range	(8, 68)	(8, 68)	(12, 63)		
AST	Mean (SD)	19.43 (7.98)	19.88 (9.03)	19 (7.09)	0.749	0.921
	Median (IQR)	17 (14, 22)	17 (16, 22)	17.5 (13, 22)		
	Range	(9, 47)	(9, 47)	(10, 36)		
Insulin use, % (n)	No	86.1 (31)	88.9 (16)	83.3 (15)		0.632
	Yes	13.9 (5)	11.1 (2)	16.7 (3)		

Note: Continuous variables are presented as mean, SD, median, interquartile range (IQR), and range. Dichotomous variables are presented as count and proportion. Treatment arms were compared using the t-test (*) or Wilcoxon rank sum test (**). Comparison between treatment arms for dichotomous variables was performed using the Wald test (*) or Fisher's exact test (**), each as appropriate.

Abbreviations: ALT, alanine transaminase; AS, aspartate transaminase; BP, blood pressure.

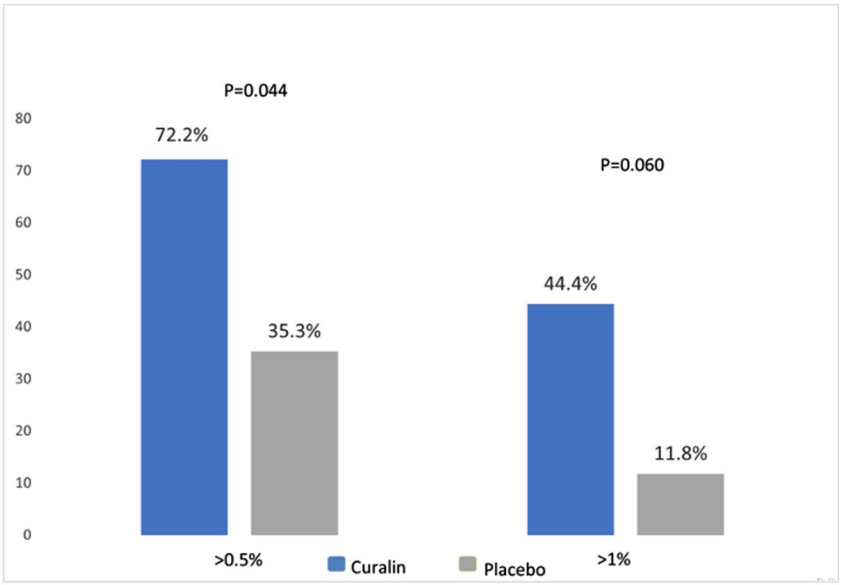
TABLE 2 Change in HbA1c from baseline to the end of the study.

Treatment		N	Mean (SD)	Median (IQR)	Range of change	p value (t-test)
Curalin		18	−0.94 (0.62)	−0.92 (−1.30, −0.34)	(−2.03, +0.03)	
Placebo		18	−0.40 (0.52)	−0.36 (−0.60, −0.05)	(−1.50, +0.54)	
Difference Curalin versus Placebo			−0.54 (0.57)			0.008
HbA1c ≤ 9%	Curalin	12	−0.83 (0.52)	−0.91 (−1.28, −0.44)	(−1.55, +0.03)	
	Placebo	12	−0.13 (0.35)	−0.09 (−0.36, 0.13)	(−0.60, +0.54)	
	Difference Curalin versus Placebo		−0.70 (0.45)			0.001
HbA1c >9%	Curalin	6	−1.16 (0.78)	−1.16 (−2.03, −0.34)	(−2.03, −0.26)	
	Placebo	6	−0.88 (0.43)	−0.88 (−1.21, −0.45)	(−1.50, −0.39)	
	Difference Curalin versus placebo		−0.28 (0.63)			0.458

Linear regression

Variable	Label	Parameter estimate (CI 95%)	Standard error	p-value
Treatment	Curalin versus placebo	−0.58 (−0.93, −0.23)	0.18	0.003
HbA1c at baseline		−0.27 (−0.43, −0.08)	0.09	0.008

Note: Change in HbA1c is presented as mean, SD, median, interquartile range, and range. A comparison between treatment arms was performed using a *t*-test. Linear regression analysed the association between a decrease in HbA1c and treatment group, adjusted for baseline HbA1c.



Improvement in HbA1c during the study was defined as a decrease in HbA1c of at least 0.5% or at least 1%. A comparison between treatment arms was tested based on the Fisher's Exact score.

FIGURE 1 Percentage of participants with a clinically significant improvement in HbA1c.

statistically significant decrease in the 7 daily blood glucose measurements of the Curalin arm versus the placebo arm during weeks 1 ($P = 0.04$), 3 ($P = 0.02$) and 4 ($P = 0.01$). Curalin treatment resulted in an overall decrease in mean blood glucose levels at all time points of the day compared with placebo (Figure S2A-G).

3.4 | Anti-diabetes drugs

Differences in drug use between treatment arms were not significant (Table S2).

3.5 | Clinical measurements

Overall, the differences between treatment arms in clinical and laboratory measurements before and at the end of the study were not significant (Table 1, Table S3).

3.6 | Treatment satisfaction questionnaire

The DTSQ was used to measure patients' treatment satisfaction at baseline and at the end of the study. DTSQ scores at baseline were

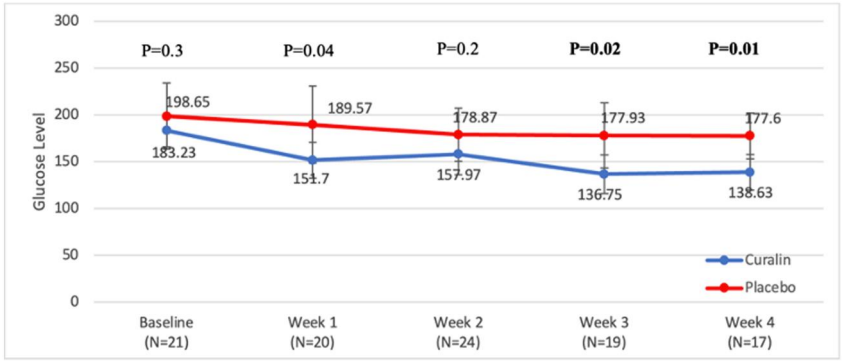


FIGURE 2 Averaged values of glucose monitoring at baseline during week 1, week 2, week 3, and week 4 of the 7-daily glucose measurements.

Presented are average of all measurements throughout the day values of glucose monitoring at baseline, during week 1, week 2, week 3, week 4, at 7-daily glucose measurements.

not significantly different between treatment arms (Table S4A). At the end of the study, the Curalin group had significantly higher scores for improvement in treatment satisfaction (Q1) ($P = 0.01$), recommendation of treatment (Q7) ($P = 0.038$), continuing treatment (Q8) ($P = 0.008$), and perceived hyper- and hypoglycemia levels (Q2 and Q3) ($P = 0.002$ and $P = 0.005$, respectively) (Table S4B).[16]

3.7 | Adverse events

Patients experiencing AEs reported them as mild. No deaths or SAEs occurred during the study (Table S5).

4 | DISCUSSION

This study evaluated the effect of Curalin as an add-on therapy for patients with type 2 diabetes mellitus. The results showed that participants in the Curalin arm experienced a significant reduction in HbA1c levels after 1 month of therapy. The study also demonstrated 2-fold and 4-fold decreases in HbA1c of >0.5% and >1% in patients treated with Curalin versus placebo. The effect was on fasting, pre-, and post-prandial blood glucose levels.

This effect was observed in 35/36 patients with long-term diabetes who had previously received anti-diabetes drugs but failed to attain the desired HbA1c target values.

In a meta-analysis of different food supplements for weight loss, subjects who took nutritional supplements were found to have reduced appetite, increased energy expenditure, and a 2 kg decrease in body weight.[17]

In the current study, the short exposure to Curalin supplement failed to result in reduced body weight. Longer studies using Curalin supplement may show a reduction in body weight as a benefit in addition to significant decreases in haemoglobin HbA1c.

Based on the DTSQ, patients in the Curalin treatment arm perceived overall higher satisfaction than placebo-treated patients. Curalin, which was added to the patients' treatment regimen that included hypoglycemic drugs, was shown to be well-tolerated.

The use of CAM for the treatment of type 2 diabetes mellitus has been previously researched; however, inter-study comparisons are challenging. Most studies that demonstrated the superiority of CAM over placebo included mostly naïve patients or patients taking one anti-diabetes drug.[18] The efficacy and minimal side-effects of Curalin therapy reported here support the need for larger and longer studies to approve the findings of this pilot study.

4.1 | Limitations

The study included a relatively small sample and was too short in duration to demonstrate the effect of the supplement on HbA1c over a long exposure. The participants were not on dietary control; consequently, we cannot draw conclusions based on their dietary behaviour. The effect of the supplement is more difficult to evaluate compared to pharmacological drugs due to possible differences in efficacy between batches.

5 | CONCLUSION

Curalin intake had a significantly positive effect on reducing HbA1c levels, demonstrated a positive safety profile, and therapeutic relevance for type 2 diabetes mellitus treatment. Based on these findings, further evaluation of Curalin as a potential CAM treatment option for type 2 diabetes mellitus should be conducted on a larger scale for a longer period.

AUTHOR CONTRIBUTIONS

Roni Weinberg Sibony collected data, wrote, reviewed, and edited the manuscript. Julio Wainstein, Maya Ish Shalom and Tali Ganz contributed to the writing of the study protocol and manuscript and supervised the study. A.H. and I.T. 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. Uri Eliyahu collected data and contributed to writing the Introduction. Itamar Raz contributed to writing, reviewing, and

editing the manuscript. All authors take responsibility for the accuracy of the manuscript. Julio Wainstein is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis and for the work as a whole.

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CONFLICTS OF INTEREST STATEMENT

Itamar Raz is a paid consultant for CuraLife. The rest of the authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Not Applicable.

CLINICAL TRIAL REGISTRATION

clinicalTrials.gov, Number NCT05439473.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1002/dmrr.3624.

REFERENCES

1. World Health Organization (WHO). Diabetes [Internet]. Diabetes - Fact sheets. 2020 [cited 2020 Nov 21]. https://www.who.int/news-room/fact-sheets/detail/diabetes
2. Kwak G, Gardner K, Bolaji B, Franklin S, Aung M, Jolly PE. Knowledge, attitudes and practices among healthcare professionals regarding complementary alternative medicine use by patients with hypertension and type 2 diabetes mellitus in Western Jamaica. *Complementary Ther Med*. 2021;57:102666. https://doi.org/10.1016/j.ctim.2021.102666
3. Sridharan K, Mohan R, Ramaratnam S, Panneerselvam D. Ayurvedic treatments for diabetes mellitus. *Cochrane Database Syst Rev*. 2011 (12):CD008288.
4. Rizvi SI, Matteucci E, Atukeren P. Traditional medicine in management of type 2 diabetes mellitus. *J Diabetes Res*. 2013;2013:580823. https://doi.org/10.1155/2013/580823
5. Akhtar MS, Ramzan A, Ali A, Ahmad M. Effect of Amla fruit (Emblica officinalis Gaertn.) on blood glucose and lipid profile of normal subjects and type 2 diabetic patients. *Int J Food Sci Nutr*. 2011;62(6):609-616. https://doi.org/10.3109/09637486.2011.560565
6. Kumar V, Van Staden J. A review of Swertia chirayita (Gentianaceae) as a traditional medicinal plant. *Front Pharmacol*. 2015;6:308. https://doi.org/10.3389/fphar.2015.00308
7. Porchezhian E, Dobriyal RM. An overview on the advances of Gymnema sylvestre: chemistry, pharmacology and patents. *Pharmazie*. 2003;58(1):5-12.
8. Husain GM, Singh PN, Kumar V. Antidiabetic activity of standardized extract of Picrorhiza kurroa in rat model of NIDDM. *Drug Discov Ther*. 2009;3(3):88-92.
9. Joshi P, Dhawan V, Dhawan V. In: swertia chirayita – an overview. *Curr Sci*. 2005;89:635-640.
10. Zhang DW, Fu M, Gao SH, Liu JL. Curcumin and diabetes: a systematic review. *Evidence-Based Complementary Altern Med*. 2013;2013:1-16. https://doi.org/10.1155/2013/636053
11. Chuengsamarn S, Rattanamongkolgul S, Luechapudiporn R, Phisalaphong C, Jirawatnotai S. Curcumin extract for prevention of type 2 diabetes. *Diabetes Care*. 2012;35(11):2121-2127. https://doi.org/10.2337/dc12-0116
12. Garau C, Cummings E, Phoenix D, Singh J. Review Beneficial Effect and Mechanism of Action of Momordica Charantia in the Treatment of Diabetes Mellitus: A Mini Review. undefined [Internet]. 2003 [cited 2022 Jul 31]; https://www.semanticscholar.org/paper/Review-Beneficial-effect-and-mechanism-of-action-of-Garau-Cummings/343da8a21077f7b7f7e7f44ccfa16ee7ed9a3846
13. Geberemeskel GA, Debebe YG, Nguse NA. Antidiabetic effect of fenugreek seed powder solution (trigonella foenum-graecum L.) on hyperlipidemia in diabetic patients. *J Diabetes Res*. 2019;2019:1-8. [Internet][cited 2020 Mar 11];2019. Available from:. https://doi.org/10.1155/2019/8507453
14. Kassaian N, Azadbakht L, Forghani B, Amini M. Effect of fenugreek seeds on blood glucose and lipid profiles in type 2 diabetic patients. *Int J Vitam Nutr Res*. 2009;79(1):34-39. https://doi.org/10.1024/0300-9831.79.1.34
15. Ranasinghe P, Jayawardana R, Galappaththy P, Constantine GR, de Vas Gunawardana N, Katulanda P. Efficacy and safety of "true" cinnamon (Cinnamomum zeylanicum) as a pharmaceutical agent in diabetes: a systematic review and meta-analysis. *Diabet Med*. 2012;29(12):1480-1492. https://doi.org/10.1111/j.1464-5491.2012.03718.x
16. Saisho Y. Use of diabetes treatment satisfaction questionnaire in diabetes care: importance of patient-reported outcomes. *Int J Environ Res Public Health*. 2018;15(5):947. https://doi.org/10.3390/ijerph15050947
17. Watanabe M, Risi R, Masi D, et al. Current evidence to propose different food supplements for weight loss: a comprehensive review. *Nutrients*. 2020;12(9):2873. https://doi.org/10.3390/nu12092873
18. Medagama AB, Bandara R. The use of Complementary and Alternative Medicines (CAMs) in the treatment of diabetes mellitus: is continued use safe and effective? *Nutr J*. 2014;13(1):102. https://doi.org/10.1186/1475-2891-13-102

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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