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A Pilot Study on the Glucose-Lowering Effects of a Nutritional Supplement in People with Prediabetes

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Abstract: Background and Objectives: Prediabetes is associated with a high risk of developing diabetes and cardiovascular disease. Early treatment with exercise and dietary interventions can reduce the progression of prediabetes to diabetes or even lead to a return of glucose levels to normal. The aim of the study was to evaluate the effect of a dietary supplement with *Portulaca oleracea* and titrated *Cistus creticus* extract on the glycemic profile of people with prediabetes. Materials and Methods: Participants were assigned to a dietary supplement with *Portulaca oleracea* and titrated *Cistus creticus* extract, along with vitamins and minerals, received once daily for 90 days. Demographics and medical history were obtained, and a complete clinical examination, measurement of somatometric characteristics, and laboratory parameters were performed at baseline. The measurement of somatometric characteristics and laboratory tests were repeated at the end of the study. Results: A total of 26 people with prediabetes participated, 11 females and 15 males. There was a tendency for a decrease in HbA1c after intervention [baseline: 5.9 (5.7–6.1)%; at the end of the study: 5.7 (5.7–6.0)%, $p = 0.062$] and a significant decrease in fasting glucose levels (from 110.8 ± 7.0 mg/dL to 103.9 ± 10.3, $p = 0.005$). Fasting insulin and homeostasis model assessment of insulin resistance (HOMA-IR) decreased significantly [baseline fasting insulin: 20.7 (9.3–34.20) μU/mL; at the end of the study: 15.1 (8.6–19.0) μU/mL, $p = 0.028$; baseline HOMA-IR: 3.6 (2.5–8.9); at the end of the study: 3.5 (2.0–4.6), $p = 0.035$]. Significant reductions were observed in alkaline phosphatase and uric acid levels. No significant change was observed in body weight, body mass index, or waist circumference after the intervention. No treatment-emergent adverse events were observed, and all participants completed the study. Conclusions: The dietary supplement from *Portulaca oleracea* and titrated *Cistus creticus* extract, along with vitamins and minerals, may improve the metabolic profile of people with prediabetes.

Keywords: purslane (*Portulaca oleracea* L.); pink rock-rose (*Cistus criticus*); polyphenols; prediabetes; glycemic control

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1. Introduction

Type 2 diabetes mellitus (T2DM) is a complex chronic systemic disease that is accompanied by metabolic disorders, including hyperglycemia, hyperinsulinemia, and hypertriglyceridemia. The incidence of T2DM has greatly increased in recent years, reaching epidemic proportions; the number of patients being diagnosed with T2DM has risen to more than 422 million to date, and they are expected to reach 592 million by 2035. Currently,

the global prevalence has been reported to be 8.5% among adults, and it is rising more rapidly in middle- and low-income countries [1]. Prediabetes is a condition associated with a high risk of progression to T2DM and cardiovascular disease. Early treatment with lifestyle changes that include physical exercise and healthy dietary interventions can slow or prevent the progression of prediabetes to T2DM and lead to the return of glucose values to normal levels.

Purslane (*Portulaca oleracea* L.), a member of the *Portulacaceae* family, possesses a wide spectrum of pharmacological properties, including neuroprotective, antimicrobial, antidiabetic, antioxidant, anti-inflammatory, antiulcerogenic, and anticancer activity [2]. Several compounds have been isolated from *Portulaca oleracea*, such as flavonoids, alkaloids, polysaccharides, fatty acids, terpenoids, sterols, proteins, vitamins, and minerals. The extract of purslane was found to induce glucose transporter type 4 (GLUT4) translocation, accompanied by an increase in intracellular glucose concentrations. In vitro studies showed that the phosphoinositide 3-kinase (PI3K) pathway is mainly responsible for the respective translocation process in an insulin-like manner [3]. A systematic review and meta-analysis of randomized controlled trials assessing the impact of purslane on blood glucose and lipid levels indicated that purslane significantly reduced fasting blood glucose (FBG) [4].

Therapeutic dietary approaches to reduce T2DM risk routinely recommend diets high in plant foods. In addition to essential micronutrients and fiber, plant-based diets contain a wide variety of polyphenols, specifically flavonoid compounds. Evidence suggests that flavonoids may confer specific benefits for T2DM risk reduction through pathways influencing glucose absorption, insulin sensitivity, and/or secretion [5]. Among the polyphenol-rich plants are *Cistaceae*. The *Cistus* genus (*Cistaceae*) comprises several medicinal plants used in traditional medicines to treat several pathological conditions [6]. The antioxidant activity of *Cistus* extract was studied using in vitro models. The extracts exhibited potent antioxidant activity and possessed a strong inhibitory effect toward α-glucosidase and significant inhibitory potential against α-amylase [7]. Similarly, in another in vitro study, *Cistus* extract was also found to be a potent inhibitor of α-glucosidase and α-amylase, possibly due to several polyphenolic compounds present in the extract. In the same study, *Cistus* extract administered to diabetic rats decreased blood glucose levels [8]. Furthermore, purified constituents of *Cistus* extract tested in vitro yielded peroxisome proliferator-activated receptor gamma agonist (PPAR-γ)-stimulating metabolites [9]. Taken together, these data suggest that phenolic-rich extracts of *Cistus* may have therapeutic potential against diseases associated with oxidative stress, and they may be useful in the management of hyperglycemia in people with T2DM.

Individuals with hyperglycemia often have altered levels of essential minerals and vitamins [10]. Chromium is an essential mineral for carbohydrate and lipid metabolism. Chromium given alone or as combined supplementation significantly improved HbA1c and FBG in patients with inadequate glycemic control at baseline, while the risk of adverse events did not differ between the chromium-receiving and placebo groups [11]. It has also been reported that zinc (Zn) dyshomeostasis is related to metabolic syndrome, T2DM, and diabetic complications [12]. Zn as part of the treatment for patients with T2DM has been shown to have positive responses in terms of glucose control outcomes [13]. Moreover, various vitamins and their derivatives have great therapeutic potential in the prevention and treatment of T2DM. The inclusion of vitamins and their derivatives as an adjunct to a composite treatment regimen potentially improves the efficiency of the prevention and treatment of T2DM [14]. Reported data from a considerable number of studies indicate that a combination of high-quality ingredients may ensure the high efficiency and safety of the proposed natural product as an adjunct treatment for the improvement of glucose metabolism and glucose normalization in hyperglycemic individuals.

The aim of this pilot study was to assess the effects of a dietary supplement containing a combination of these ingredients on the glycemic profile of subjects with prediabetes. The main ingredients of the supplement used in this proof-of-concept study comprised a

combination of *Portulaca oleracea* extract, together with a *Cistus creticus* extract standardized in polyphenols along with chromium, zinc, and vitamins B3 and B6.

2. Materials and Methods

2.1. Study Nutritional Supplement

The nutritional supplement was produced by Votaniche S.A. (Athens, Greece) as a vegetarian capsule in boxes of 30 capsules in blisters. Each capsule (468.8 mg) contained *Cistus* criticus extract titrated 20% in polyphenols, *Portulaca oleracea* extract 180 mg (as it was described in Wainstein J. et al.) [15], vitamins B3 10 mg, B6 1 mg, zinc 10 mg, and chromium 0.04 mg. The extracts of the supplement were provided to Votaniche by certified European producers.

2.2. Study Design

This was an open observational prospective study in individuals with impaired fasting glucose, according to the American Diabetes Association criteria 2022 [16]. The protocol was approved by the Ethics Committee of Laiko General Hospital (approval number 9545/11-06-2020) and was conducted according to the recommendations of the Declaration of Helsinki. Participants provided written informed consent.

2.3. Study Population

We enrolled 26 patients (15 men, 11 women) aged >18 years with prediabetes who were followed at the outpatient Diabetes Clinic, Hypertension Clinic, and Dyslipidemia Clinic of our hospital. The key exclusion criteria were as follows: diagnosed Diabetes Mellitus (DM), malignancy, estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2, Cushing's syndrome, uncontrolled hypothyroidism, or severe liver disease. We also excluded individuals on treatment with medications known to affect glucose metabolism, such as b-adrenergic receptor blockers, corticosteroids, immunosuppressants, or high doses of diuretics; individuals with alcohol abuse; and drug users. Participants underwent a thorough clinical examination at the first visit, and a detailed medical history was obtained.

2.4. Nutritional Supplement Administration

Enrolled patients received one capsule per day of the commercially available nutritional supplement for three months. They also received instructions for diet and exercise. More precisely, participants were instructed to follow a Mediterranean-type diet and to do at least 150 minutes of moderate-intensity exercise a week.

2.5. Evaluation of Somatometric Characteristics, Laboratory, and Other Parameters

The data for analysis were collected at baseline (t = 0 months) and at the end (t = 3 months) of the study.

The somatometric characteristics of the participants that were measured were body weight, height, and waist and hip circumference. Participants were weighed on a digital body weight scale, dressed in light clothing, and barefoot. Their height was measured using a floor height measuring scale, rounding the result to the nearest cm. The waist was measured at the midpoint between the lower margin of the last palpable ribs and the top of the iliac crest, using a stretch-resistant tape that provides constant 100 g tension. Hip circumference was measured around the widest portion of the buttocks, with the tape parallel to the floor. For both measurements, the individual stood with feet close together, arms at the side, and body weight evenly distributed. The subjects relaxed, and the measurements were taken at the end of normal respiration. The Body Mass Index (BMI) and waist-to-hip ratio (WHR) of each volunteer were calculated based on these measurements.

Systolic and diastolic blood pressure (SBP and DBP, respectively) and heart rate (HR) were measured using a digital cuff sphygmomanometer on each volunteer after at least

15 min of resting in a seated position. The mean value of two consecutive measurements was recorded.

A blood sample was drawn from the median antecubital vein after overnight fasting of 10–12 h. Blood was collected in vacutainers containing fluoride oxalate to avoid glycolysis, allowed to clot at room temperature for 15 min, and then centrifuged (3000 rpm for 10 min at 4 °C. Glycemic and lipid parameters were immediately assayed in an automatic analyzer (Cobas c311 clinical chemistry analyzer, Roche Diagnostics). After isolation, serum was stored at −20 °C until analysis. Biochemistry measurements [creatinine, glutamic-oxaloacetic transaminase (SGOT), glutamic pyruvic transaminase (SGPT), γ-glutamyltransferase (γ-GT), and alkaline phosphatase (ALP)] were measured with the same analyzer (Cobas c311 clinical chemistry analyzer, Roche Diagnostics). A human ELISA kit with a sensitivity range of 0.01–129 μIU/mL was used to measure serum insulin (Accubind, Los Angeles, CA, USA), and the mean intra-assay coefficient of variability was <7.0. Low-density lipoprotein cholesterol (LDL) was calculated according to the Friedewald formula [17]. Homeostatic Model Assessment for Insulin Resistance (HOMAIR) was calculated by the formula (Fasting insulin × Fasting glucose)/405 [18]. Glycated hemoglobin (HbA1c) was measured by high-performance liquid chromatography (HPLC). The glomerular filtration rate (GFR) was calculated using the CKD-EPI 2021 formula [19].

2.6. Statistical Analysis

SPSS 20.0 statistical package (SPSS, Inc., Chicago, IL, USA) was used for the statistical analysis. The Kolmogorov-Smirnov test was used to test the variables for normal distribution. Data are presented as means ± standard deviation (SD) or as median value (interquartile range). A paired *t*-test was used to compare parametric variables before and after three months of dietary supplement administration; the Wilcoxon test was used for non-parametric data; and the chi-square test was used for categorical variables. *p*-values < 0.05 (two-tailed) were considered statistically significant.

3. Results

3.1. Study Population

A total of 26 subjects with a mean age of 57.4 ± 7.8 years were selected based on the inclusion and exclusion criteria of the study. The study population consisted of 11 females (mean age 56.1 ± 9.1 years) and 15 males (mean age 58.5 ± 6.8 years). The average interval between baseline and the end of follow-up was 90.0 ± 3.3 days.

3.2. Safety Evaluation

No treatment-emergent adverse events were observed in participants who received the nutritional supplement, and all participants completed the study.

3.3. Efficacy of the Nutritional Supplement

Table 1 summarizes the main results of the study regarding the efficacy of the nutritional supplement not only on glycemic control but also on hepatic and renal functions. After three months of receiving the supplement, fasting glucose levels were reduced by about 6.2% (from 110.8 ± 7.0 mg/dL to 103.9 ± 10.3, $p = 0.005$), while fasting insulin levels were also reduced by 27.1% (from 20.7 (9.3–34.2) μU/L to 15.1 (8.6–9.0) mL μU/L, $p = 0.028$). An approximately 2.8% reduction was also noted in HOMA IR (from 3.6, 95% CI 2.5–8.9 to 3.5, 95% CI 2.0–4.6, $p = 0.035$). There was a tendency for a decrease in HbA1c in the group of people receiving the dietary supplement (decrease of 0.2%, $p = 0.062$), while ALP and uric acid also had significant reductions, by 13.2% ($p = 0.014$) and 6.8% ($p = 0.016$), respectively, over the treatment period with the dietary supplement. Meanwhile, GFR was increased by 10.2% (from 103.4 ± 24.7 to 113.9 ± 32.8 mL/min/1.73 m^2, $p < 0.001$). No other significant differences were observed in changes recorded in body weight, BMI, waist circumference, or the other measured parameters among study participants.

Table 1. Somatometric characteristics and blood test results of the participants (N = 26) at baseline and after three months of administration of the dietary supplement.

Characteristics *	At Baseline (t = 0 Months)	After Treatment (t = 3 Months)	*p*-Value
Body weight (kg)	86.1 ± 17.7	85.6 ± 18.4	0.559 *
BMI (kg/m^2)	29.1± 5.2	28.4 ± 7.2	0.308 *
Waist circumference (cm)	105.6 ± 14.2	104.4 ± 14.4	0.264 *
Hip circumference (cm)	109.8 ± 12.5	108.0 ± 11.3	0.410 *
WHR	0.96 ± 0.08	0.96 ± 0.07	0.881 *
SBP (mmHg)	135.8 ± 18.9	130.0 ± 17.4	0.143 *
DBP (mmHg)	81.1 ± 13.5	79.5 ± 11.1	0.491 *
HbA1c (%)	5.9 (5.7–6.1)	5.7 (5.7–6.0)	0.062 **
Fasting glucose (mg/dL)	110.8 ± 7.0	103.9 ± 10.3	**0.005** *
Total cholesterol (mg/dL)	209.4 ± 43.7	209.5 ± 38.7	0.744 *
HDL (mg/dL)	48.5 ± 13.0	48.2 ± 9.5	0.663 *
LDL (mg/dL)	116.3 ± 26.1	107.4 ± 22.0	0.283 *
TG (mg/dL)	138.5 (88.5–189.0)	131.0 (114.0–159.5)	0.527 **
Creatinine (mg/dL)	0.71 ± 0.18	0.71 ± 0.15	0.723 *
GFR	103.4 ± 24.7	113.9 ± 32.8	<0.001 *
SGOT (U/L)	21.7 ± 4.8	22.5 ± 8.5	0.558 *
SGPT (U/L)	26.2 ± 10.3	27.1 ± 12.5	0.456 *
γ-GT (U/L)	26.0 ± 13.2	26.1 ± 17.3	0.705 *
ALP (IU/L)	88.8 ± 36.7	77.1 ± 34.0	0.014 *
Uric acid (mg/dL)	5.7 ± 1.3	5.31 ± 1.1	0.016 *
Fasting insulin (mL U/L)	20.7 (9.3–34.2)	15.1 (8.6–19.0)	0.028 **
HOMA IR	3.6 (2.5–8.9)	3.5 (2.0–4.6)	0.035 **

BMI: Body-Mass Index, WHR: waist-to-hip ratio, SBP: systolic blood pressure, DBP: diastolic blood pressure, HbA1c: glycated hemoglobin, HDL: high-density lipoprotein cholesterol, LDL: low-density lipoprotein cholesterol, TG: triglycerides, GFR: glomerular filtration rate, SGOT: glutamic-oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase, γ-GT: γ-glutamyltransferase, ALP: alkaline phosphatase, HOMA IR: Homeostatic Model Assessment for Insulin Resistance. Data are means ± standard deviation (SD) or median value (interquartile range). * *p* values for the comparison with baseline by paired *t*-test. ** *p* values for the comparison with baseline by Wilcoxon test.

4. Discussion

In this pilot study, we investigated the effect of a dietary supplement with *Portulaca oleracea* and titrated *Cistus creticus* extract on the glycemic and metabolic profiles of people with prediabetes. We observed that the administration of the supplement for 3 months in people with prediabetes resulted in statistically significant decreases in fasting glucose levels and marginally not significant decreases in HbA1c levels, which encourages further longer-term studies. In addition, a significant reduction in fasting insulin was recorded, which indicates the value of the formulation in improving insulin resistance in individuals with prediabetes. The levels of uric acid and ALP were also significantly decreased, while no side effects were observed. Although our results are preliminary, the supplement with *Portulaca oleracea* and titrated *Cistus creticus* extract seems to have a place in the management of prediabetes and could potentially prevent the development of T2DM in this group of people.

Nutraceuticals are claimed to prevent chronic diseases, improve health, delay the aging process, increase life expectancy, and support the structure and function of the body [20]. Despite the therapeutic benefits for the treatment of T2DM, most drugs can

produce undesirable side effects. Natural products have become important resources for bioactive agents for T2DM prevention and treatment [21]. Plant-derived ingredients with a high content of polyphenolic compounds are considered to have great potential for regulating glucose metabolism. Such a plant with reported anti-diabetic properties is purslane [3]. Induction of GLUT4 translocation in the absence of insulin is considered a key concept to decrease elevated blood glucose levels in individuals with hyperglycemia [22]. In an in vitro study, the *Portulaca oleracea* extract was proven to induce GLUT4 translocation through the PI3K pathway, while in an in vivo study, the purslane extract statistically significantly decreased blood glucose levels [23].

A placebo-controlled clinical trial used a patented purslane extract in 63 adults with T2DM. The purslane extract appeared to be an effective adjunct treatment for adults with T2DM, significantly reducing HbA1c levels in the subgroup of responders after a three-month treatment period. The adverse event profile was similar to placebo [15]. In that study, individuals were permitted to receive only one antidiabetic medication, and most participants received metformin. The subgroup of participants treated with metformin before study enrollment presented a significantly greater change from baseline HbA1c when they received purslane compared to the placebo group, indicating a possible synergistic effect. In a randomized double-blind controlled clinical trial, individuals who received purslane seed extract had similar fasting and post-prandial blood glucose levels compared to those on metformin treatment [23]. A recent meta-analysis of the effect of purslane on glycemic control in patients with or without T2DM, including 16 randomized controlled trials, reported that purslane consumption significantly reduced FBG but had no effect on HbA1c, fasting insulin, and HOMA-IR [24]. We found that purslane administration significantly reduced fasting insulin and HOMA-IR, but we included a different study population. Only participants with prediabetes took part in our study, while the 16 studies included in the meta-analysis were conducted in patients with diabetes, fatty liver disease, metabolic syndrome, hypercholesterolemia, schizophrenia, or non-active females that all have different degrees of insulin resistance 95% confidence interval (−7.54, −1.53) mg/dL. Another meta-analysis of 6 randomized controlled trials including 352 participants, found that purslane reduced FBG by 4.5 mg/dL [4]. We found a mean decrease in FBG of 7.00 (−1.25, 11.75) mg/dL.

Polyphenols are a large and heterogeneous group of phytochemicals that contain phenol rings and are present in a wide variety of foods, including fruits, vegetables, legumes, and cereals, as well as in various medicinal plants. Polyphenols and other food sources of phenolics have demonstrated beneficial effects on insulin resistance, diabetic vascular complications, and other cardiometabolic risk factors [25]. Polyphenols may influence hyperglycemia by promoting the uptake of glucose in tissues and improving insulin sensitivity. Epidemiological studies and associated meta-analyses strongly suggest that a long-term diet rich in plant polyphenols offers protection against the development of cancers, cardiovascular diseases, T2DM, osteoporosis, and neurodegenerative diseases [26].

Growing evidence from animal studies supports the anti-diabetic properties of some dietary polyphenols, suggesting that dietary polyphenols could be one dietary therapy for the prevention and management of T2DM [27]. Dietary polyphenols may inhibit α-amylase and α-glucosidase, inhibit glucose absorption in the intestine by sodium-dependent glucose transporter 1 (SGLT1), stimulate insulin secretion, and reduce hepatic glucose output. Polyphenols may also enhance insulin-dependent glucose uptake, activate 5′ adenosine monophosphate-activated protein kinase (AMPK), modify the microbiome, and have anti-inflammatory effects [27]. Additionally, plant polyphenols have been shown to activate endothelial cells to increase the formation of potent vasoprotective factors, including nitric oxide (NO), and to delay endothelial aging. The intake of such polyphenol-rich products has been associated with the prevention and/or improvement of established endothelial dysfunction in several experimental models of cardiovascular diseases and humans with cardiovascular diseases [28].

Cistus species are considered to be a rich source of polyphenols. Numerous studies have confirmed their antioxidant, anti-inflammatory, and anti-glycation properties [29]. Moreover, in an in vitro study among 40 extracts, *C. creticus* extract proved to have the highest inhibitory activity on aldose reductase, the key enzyme of the polyol pathway [30]. Plant extracts rich in phenolics have been studied for the improvement of hyperglycemia in individuals with prediabetes, providing the opportunity for their use as alternative or complementary treatments with few or no adverse effects [31]. In the present study, we used a nutritional supplement that combines two rich polyphenol plant extracts, purslane and pink rock rose, which have an insulin-mimetic action, together with vitamins and minerals, with proven beneficial actions on the maintenance of glucose homeostasis. According to available literature, this is the first clinical study to evaluate the effect of the combination of *Portulaca oleracea* and *Cistus creticus* on hyperglycemia parameters in individuals with prediabetes.

The limitations of this pilot study are the small number of participants, the short duration of the intervention, and the lack of a control group to examine for potential differences between the placebo and the study product. However, this was an exploratory study to examine the potential effects of dietary supplements with *Portulaca oleracea* and titrated Cistus extract (*Cistus creticus*) on metabolic parameters in people with impaired fasting glucose or impaired glucose tolerance; therefore, the results of this study can be interpreted as indicative and not confirmatory on the effect of this nutritional supplement in people with prediabetes.

5. Conclusions

Dietary supplementation with plant extracts of purslane and pink rose appears to improve the glycemic and insulin resistance profiles of people with prediabetes; such supplements may help to reduce the occurrence of T2DM in the long run.

The results regarding the additional beneficial effects of the formulation on the liver and kidneys are interesting and merit further investigation.

Healthy dietary interventions and exercise are key pillars for the treatment of prediabetes. Additional studies with larger cohorts are needed to better characterize the potential beneficial effects of the plant extract supplement on the metabolic and glycemic profiles of people with prediabetes.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and was approved by the Ethics Committee of Laiko General Hospital (approval number 9545/11-06-2020).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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