Available online at www.sciencedirect.com

Integrative Medicine Research

journal homepage: www.imr-journal.com

Original Article

Study of the effect of the herbal composition SR2004 on hemoglobin A1c, fasting blood glucose, and lipids in patients with type 2 diabetes mellitus

Sumit Chatterji[a,*], *Dov Fogel*[b]

[a] *Sheba Medical Center, Tel Hashomer, Ramat Gan, Israel*
[b] *D.S. Polyclinic, Givat Shmuel, Israel*

ARTICLE INFO

Article history:
Received 24 January 2018
Revised 23 March 2018
Accepted 5 April 2018

Keywords:
Glucose
Herbal
Lipids
Retinopathy
Type 2 diabetes mellitus

ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by raised blood glucose levels and peripheral insulin resistance. It is an increasingly prevalent global healthcare concern. Conventional treatment options are limited and in this context, there is renewed interest in evaluating the clinical and biological effects of traditional therapies. We assess the effect of a new herbal composition SR2004 on the hemoglobin A1c (HbA1c), fasting blood glucose, and lipid profiles of patients with T2DM.

Methods: This is a single center, unblinded, prospective interventional study conducted in Israel. The composition SR2004 includes *Morus alba*, *Artemisia dracunculus*, *Urtica dioica*, *Cinnamomum zeylanicum*, and *Taraxacum officinale*. One hundred and nineteen patients with diagnosed T2DM were enrolled and received SR2004 in addition to their usual medications. HbA1c, fasting blood glucose, and lipid profiles at 12 weeks were compared with baseline. In addition, the tolerability and side effects of SR2004 were recorded.

Results: One hundred and three patients completed 12 weeks of follow-up (87%) and were included in the results. At 12 weeks, HbA1c reduced from 9.0% to 7.1% (22%; $p < 0.0001$), mean blood glucose decreased from 211 mg/dL to 133 mg/dL (37% reduction; $p < 0.0001$), mean total cholesterol to 185 mg/dL (13% reduction; $p < 0.01$) and mean serum triglycerides to160 mg/dL (a reduction of 40% from baseline; $p < 0.001$). Twelve patients (12%) had no response with SR2004 supplementation. In addition, of thirteen patients who took insulin at baseline, five required only oral hypoglycemics and another five reduced their daily insulin requirements by 30% at 12 weeks. Clinical observations included improvements in vasculopathy, including reversal of established retinopathic changes in two patients.

No major adverse effects were observed, with minor abdominal symptoms reported in sixteen patients (16%).

* *Corresponding at*: Sheba Medical Center, Tel Hashomer, 52621 Ramat Gan, Israel
E-mail address: Sumitchatterji2016@gmail.com (S. Chatterji).

https://doi.org/10.1016/j.imr.2018.04.002

Conclusion: SR2004 supplementation significantly reduced HbA1c, blood glucose, and lipids with good tolerability and no observed adverse interactions with conventional medications. Some interesting findings relating to the reversal of microvascular phenomena warrant further research to elucidate the mechanisms of action of this novel composition.

1. Introduction

Currently, an estimated 382 million people live with diabetes mellitus worldwide and a further 316 million have impaired glucose tolerance making them high-risk for the disease. In 2013, diabetes caused 5.1 million deaths and cost USD 548 billion in healthcare spending – 30 percent of the total healthcare expenditure.[1] Type 2 diabetes mellitus (T2DM) accounts for 90% of all cases[2] with its incidence increasing and mirroring the worldwide increase in levels of obesity in adults and children. The causes of this epidemic are a complex interaction between genetic and epigenetic factors and societal influences that determine diet and levels of physical activity. The current strategy used for the treatment of T2DM depends on a dual combination of insulin secretagogue and an insulin sensitizer and despite reasonable glycemic control provided by these drugs initially, over time their efficacy tends to diminish. Moreover, side-effects such as severe hypoglycemia, lactic acidosis, idiosyncratic liver cell injury, digestive discomfort, dizziness, and even death are recognized and can limit their use.[3,4] Furthermore, although there is good evidence of mortality reduction with intensive lipid-control strategies in diabetes,[5] lipid control remains poor using mainstream lipid-lowering medications.[6] Together, these factors contribute to the healthcare burden associated with T2DM and make a case for new approaches to manage this complex disease.

The use of plants and recognition of their medicinal functions has been documented for millennia. In fact, the development of metformin, a biguanide, was based on the observation that the hypoglycemic effect of *Galega officinalis* (French lilac) was due to the presence of compounds related to guanidine, including an alkaloid called galegine, that were potent hypoglycemic agents.[7] Renewed interest in phytotherapy in diabetes is identifying a large number of bioactive plant constituents with wide-ranging effects on animal and human glucose and lipid metabolism[8] which may hold some promise for new therapies. Specifically, addressing the properties of the plant constituents in the composition SR2004 used in this study, *Morus* (mulberry) leaf extracts have been studied in humans and streptozotocin-induced diabetic rat models[9–11] showing reversible inhibition of small intestinal brush border α-glucosidase activity by the compound 1-deoxynojirimycin (DNJ) found in high concentrations in the leaves, as well as plant flavonoids and high levels of alkaloidal sugar-mimic glycosidase inhibitors found in the leaf *latex*, which together reduce postprandial hyperglycemia.[12–16] Additionally, leaf extracts have insulin secretagogue activity[17] and reduce peripheral insulin resistance.[18] Park et al, using diabetic db/db mice to test the antidiabetic properties of Mulberry leaf water extract, also found increased expressions of liver peroxisome proliferator-activated receptor alpha (PPARα) mRNA in liver and PPARγ in adipose tissue.[19] PPAR receptors are important nuclear hormone receptors involved in glucose and lipid homeostasis through ligand-activated transcriptional regulation whose effects include enhanced peripheral glucose uptake through increasing glucose transporter-4 (GLUT4) expression and translocation in adipocytes,[20] as well as decreasing hepatic glucose output.[21]

Artemisia (mugwort, wormwood) is a diverse genus of plants that contains up to 400 species. *In vivo* studies have shown enhanced pancreatic beta cell activity,[22] hepatic glucose metabolism,[23] reduced peripheral insulin resistance, and increased skeletal muscle glycogen storage.[24,25] Sun et al, in their study of Artemisia extract in women with gestational diabetes, found increased insulin sensitivity with an increase in circulating levels of the adipocytokine adiponectin.[26] This hormone, secreted by adipocytes (and upregulated by PPAR activation), has an important role in glucose and lipid storage in skeletal muscle and liver, with levels typically lower in patients with T2DM.[27] Additionally, an ethanol extract from *Artemisia dracunculus* called Tarralin has been demonstrated in a murine diabetic model to potentiate the effect of incretin (GLP1), a gut hormone secreted in response to a meal.[28] This hormone also has a variety of effects including glucose-dependent insulin secretion, inhibition of glucagon secretion, and a protective effect on pancreatic β-cells.

Urtica (nettle) leaf extracts also show potent PPARα/γ activation[29] and protective effects on pancreatic beta cells exposed to oxidative stress.[30–32] Several clinical studies in humans have shown glucose reduction in diabetic patients[33–35] and protective effects in diabetic nephropathy.[36]

Studies of *Cinnamomum* (cinnamon) bark in T2DM[37–40] that include a recent meta-analysis of 10 randomized controlled trials ($n = 543$ patients)[41] have shown that it reduces fasting blood glucose levels and improves blood lipid profiles. Its primary mechanisms of action may relate to enhancement of peripheral glucose uptake[42] and through insulinomimetic or secretagogue activity.[8,43]

Finally, the genus *Taraxacum* (dandelion), found in the temperate zone of the northern hemisphere, has been shown to possess antidiabetic and pancreatic beta cell protective effects due to nontoxic bioactive components found in all parts of the plant (some with high concentration in the roots) that include chicoric acid, triterpenes/phytosterols (taraxasterol), chlorogenic acid and sesquiterpene lactones.[44–47] Furthermore,

these phytochemicals demonstrate lipid-lowering effects,[48–51] as well as antioxidant, anticancer, and anti-inflammatory properties.[44,52–54]

All herbal components used in SR2004 are classified as 'generally recognized as safe' (GRAS) by the US Food and Drug Administration. To test the possibility of a synergistic effect of combining plant extracts, based on the available knowledge of the predominant mechanisms of action of the components, a smaller initial unpublished pilot/safety study was conducted by the authors on 52 patients with T2DM. This compared the effect on HbA1c of *Morus alba* latex extract, to a mixture of *Urtica dioica* with *A. dracunculus* (leaf extracts), versus SR2004 in liquid form. There was a reduction in HbA1c at 12 weeks of 10.5%, 14%, and 28%, respectively with no significant side effects reported in all groups (data available on request).

The objectives of this study were, therefore, to evaluate the effect of SR2004 on HbA1c, fasting blood glucose levels, and the blood lipid profile in patients with T2DM.

The primary endpoints were HbA1c and fasting blood glucose after 12 weeks of study, with evaluation of the safety and tolerability profile.

The secondary endpoints were total cholesterol and triglyceride levels at 12 weeks.

2. Methods

2.1. Study design

This is a single center, unblinded, prospective interventional study conducted in Israel, with a minimum follow-up period of 12 weeks (ISRCTN12562776). Adult patients with T2DM were referred by local health insurance or hospital-based physicians, or self-referred. All patients were screened with regard to trial criteria at the first visit. If screening criteria were met, baseline tests were performed as per details in Table 1 at week −2 and week −1 and thereafter were assessed weekly to week 12 and then at week 24. Written informed consent was obtained from all patients. The trial protocol was approved by the Helsinki committee of Maccabi health services Israel (Reference number 20080395) and conducted as per Good Medical Practice guidelines. The patient characteristics are described in Table 2.

Table 2 – Patient Characteristics and Medication Use at Trial Entry

No. enrolled	119
No. completing 12 weeks follow up (Male/Female)	103 (60/43)
Median age years (range)	57 (28–78)
Mean weight kilograms (range)	81 (49–135)
Mean Body Mass Index (kg/m^2)	30.3
Mean fasting glucose mg/dL (range)	211 (107–513)
Mean Hemoglobin A1c % (range)	9 (6–17)
Mean total cholesterol mg/dL (range)	212 (100–706)
Mean triglyceride mg/dL (range)	266 (151–1520)
Insulin use no. (% of total patients)	13 (12.6%)
Sulphonylurea use no. (% of total)	19 (18.4%)
Biguanide use no. (% of total)	44(42.7%)
Meglitinide uses no. (% of total)	2 (1.94%)
Combination oral hypoglycemic use no. (% of total)	25 (24.3%)
Antihypertensive medications % of total	38%
Anti-lipid medication (statins and fibrates) % of total	45%

mg/dL = milligrams per deciliter. kg/m^2 = kilograms per square meter.

2.2. Inclusion criteria

Inclusion criteria included a confirmed diagnosis of T2DM *and* any combination of oral hypoglycemics and/or insulin with a HbA1c 7.1–10% in the last 6 months, body mass index (BMI) < 45 kg/m^2, ability to provide written informed consent, and no participation in an investigational drug study (or use of herbal supplementation) within the prior 30 days. Women of childbearing age were required to have a negative pregnancy test and use contraception for the duration of the trial.

2.3. Exclusion criteria

The exclusion criteria included Type 1 diabetes mellitus, treatment with the drugs acarbose or rosiglitazone for more than 2 weeks in the last six months, a concomitant condition such as malignancy, heart failure grade 2–4 (American Heart Association), liver dysfunction (alanine aminotransferase or aspartate aminotransferase more than 3 times upper limit of normal values) or renal failure (serum creatinine more than 1.3 times upper limit normal for women and 1.4 for men), and a history of severe psychiatric illness on medication.

Table 1 – Parameters Checked at Baseline and During the Trial Follow-up Period

	Week no.															
	−2	−1	0	1	2	3	4	5	6	7	8	9	10	11	12	24
Physical examination	×		×						×						×	×
Informed consent	×															
Height/weight	×						×				×				×	×
Urinalysis	×								×						×	×
Blood pressure, pulse	×		×				×		×		×				×	×
General chemistry	×								×						×	×
Lipids (total cholesterol, triglycerides)	×								×						×	×
Complete blood count	×								×						×	×
Hemoglobin A1c	×		×												×	×
Fasting glucose	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×	×

Lipid-lowering medications such as Ezetimibe and Lomitapide were not used.

2.4. SR2004 herbal composition

The composition includes leaves of *M. alba* L., the leaves of *U. dioica* L., the bark of *Cinnamomum* (all of Unicorn Natural Products, Telangana, India), leaves of *A. dracunculus* L. (Jiaherb Phytochem, Xi'an, China), and *Taraxacum officinale* L. root extract (Stryka Botanics, New Jersey, USA). All botanicals received certificates of authenticity and purity from suppliers. The processing and extraction technique is described in detail in the European patent EP2170360B1. In summary, the leaves and flowers were cleaned and processed fresh (i.e.: while retaining their original color, shape, and turgor) with a combination of cutting, pressing, and heat extraction with brewing to maximize the extraction of plant products, including leaf latex. After this, the liquid was rapidly cooled to 20–30 degrees Celsius and then filtered. The root and bark components were cleaned and then processed using heat extraction followed by cooling. The mixed solution comprised (by weight percent of the total solution weight) 50% *Morus*, 20% *Artemisia*, 10% *Urtica*, 10% *Cinnamomum*, and 10% *Taraxacum*. This produced a liquid formulation that was used in the initial 56 patients at a dose of 300 milliliters (mL) three times a day, 30 minutes before meals. Because of the feedback of trial participants on the bitterness of the solution, a dry powder compound in the form of a capsule containing 500 milligrams (mg) with 40% herbal extracts (with the same percentage composition by dry weight) and 60% inert calcium phosphate carrier was developed (Karmat Ltd, Ramot Menashe, Israel). The dose was 2 capsules three times a day, 30 minutes before meals taken with water.

High-performance anion-exchange chromatography with pulsed amperometric detection (HPAEC-PAD) was used to initially determine the concentration of DNJ – a marker of *M. alba* – in the liquid formulation (Bar Ilan University, Ramat Gan, Israel) Using HPAEC-PAD on a CarboPac MA1 column with sodium hydroxide gradient, a clear and measurable separation of the DNJ extract from the water content could be demonstrated. Thermal stability studies confirmed that DNJ was stable. This process was later used to determine the concentrations of the other constituent herbs in the solution. Using this method, the herbal concentrations of two 500 mg capsules were calculated equivalent to 300 mL solution.

2.5. Patient management and monitoring

All patients continued their previously recommended diets, medical treatments, and exercise regimes. Alterations to the dose of hypoglycemic medications were made at the physician's discretion based on recorded glucose values. Where blood glucose control was achieved, a stepwise reduction in conventional hypoglycemic medications was initiated and closely monitored by the trial physician. Monitoring of patients during the trial period was performed according to the schedule in Table 1. Where necessary, patients were also reviewed by their usual diabetes physician.

2.6. Sample size and statistical methods

Using HbA1c at week 12 as the primary endpoint, with a reduction of 1.0% considered clinically relevant and a standard deviation of 1.2%, a required sample size of 90 was calculated.

Data analysis was conducted by the Statistical Laboratory, School of Mathematics, Tel-Aviv University.

The statistical paired sample *T*-test method was used to calculate the significance of changes in values from week 0 to week 12. If necessary, a nonparametric Wilcoxon Rank sum test was applied. Additionally, an analysis of covariance model was applied to the 12-week endpoint using the baseline value as a covariate. A p-value < 0.05 was considered statistically significant.

3. Results

One hundred and nineteen patients were enrolled. One hundred and three patients (87%) completed at least 12 weeks of follow-up. Of the sixteen patients who did not complete the trial, twelve patients dropped out of the study for reasons that included poor adherence to the study protocol, inability to follow up, problems associated with the taste of the solution, difficulties in traveling with the solution, or serious intervening illness. Four patients (3%) did not complete the study due to flatulence or loose bowel movements. These sixteen patients were excluded from the final data analysis. Fig. 1 summarizes the recruitment and retention of the test.

There were no significant baseline sex differences in blood levels of fasting glucose ($p = 0.463$), HbA1c ($p = 0.696$), triglycerides ($p = 0.780$), or total cholesterol ($p = 0.140$). No significant change in body weight was observed during the trial period.

3.1. Primary and secondary endpoints

The results are summarized in Table 3. Nine patients (9%) had no changes in the primary endpoint values and three patients (3%) showed an increase.

Improvements in biochemical parameters were typically observed from week three of the study and were maintained during supplementation with SR2004.

Of thirteen patients treated with insulin at the beginning of the study, five reduced their daily dose by an average of 30% and five other patients managed to control their disease with only oral hypoglycemic agents while taking SR2004. All of them subsequently demonstrated the deterioration of the biochemical parameters within four months after the interruption of the SR2004 supplementation and required an increase in the conventional hypoglycemic treatment.

There were no serious events reported. In 14 patients (14%) and abdominal pain in 2 patients (2%), minor symptoms of abdominal discomfort, flatulence, or increased bowel movements were reported.

3.2. Additional clinical observations

Several cases demonstrated improvement of vascular phenomena such as impotence (five men resumed sexual activity; three had been using Sildenafil concurrently), renal

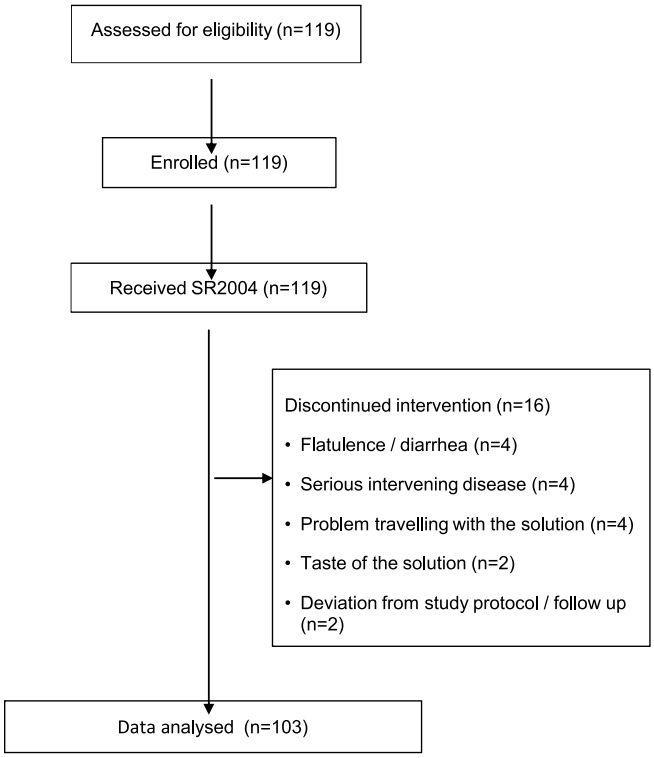

Fig. 1 – Flow diagram of trial recruitment and retention.

Table 3 – Primary and Secondary Endpoint Results

Endpoint	Baseline mean (SD)	Week 12 mean (SD)	Percentage change	*p*-value
Hemoglobin A1c	9.1% (1.9)	7.1% (1.2)	−22	<0.0001
Fasting blood glucose	211 mg/dL (65)	133 mg/dL (38)	−37	<0.0001
Total cholesterol	213 mg/dL (85)	185 mg/dL (42)	−13	<0.01
Triglycerides	266 mg/dL (244)	160 mg/dL (81)	−40	<0.0001

impairment ($n = 3$; maintained during SR2004 treatment), and limb claudication ($n = 2$). Improvement in established retinopathic changes was also seen, including two patients who had prior photocoagulation but were found to have "normalized fundoscopic findings with no diabetic retinopathy" by an independent ophthalmologist who had been monitoring them with serial clinical assessments. Although early retinopathy can revert with normalization of blood glucose values, the reversal of established severe retinopathic changes (in this case with prior photocoagulation) has only been described in the context of intraocular antivascular endothelial growth factors (anti-VEGF) treatments such as bevacizumab and pegaptabnib[55] rather than systemically active agents. The retinopathic observations are summarized in Fig. 2.

4. Discussion

This study is the first to evaluate the effect of the herbal composition used in SR2004 on blood glucose and lipid profiles in human subjects with T2DM who take conventional diabetic drugs and lipid reducers. It shows statistically significant reductions in serum levels of HbA1c, fasting blood glucose, triglycerides and total cholesterol with a good safety and tolerability profile when combined with other medications in a "real world" clinical setting. The clinical effects were typically apparent after week 3 and were maintained with continuous treatment. The results were independent of weight changes or activity levels; in fact, there was no significant weight reduction in the group as a whole.

On the basis of previous animal, human and *in vitro* studies of the effects of the constituent compounds used in SR2004, it is probable that glucose homeostasis is influenced by effects in multiple anatomic and cellular locations. These include the inhibition of intestinal disaccharidase activity, lectin-mediated binding of intestinal carbohydrate residues, upregulation of gluconeogenesis, reduction of tissue insulin resistance and glycolysis, with additional effects on insulinomimetic activity or secretory activity of pancreatic beta cells.[8–31,33–35,37–47] The resultant effects are a reduction in postprandial and basal glucose levels.

It is recognized that chronically high levels of glucose in T2DM (called glucose toxicity) *in itself* leads to a deterioration in insulin secretion and a possible defect in glycogen synthesis.[56] Garvey et al, in a study of insulin therapy in patients with T2DM, showed a partial reversal in the post-binding defect of peripheral insulin action, reversion to an almost normal basal hepatic glucose output and enhanced

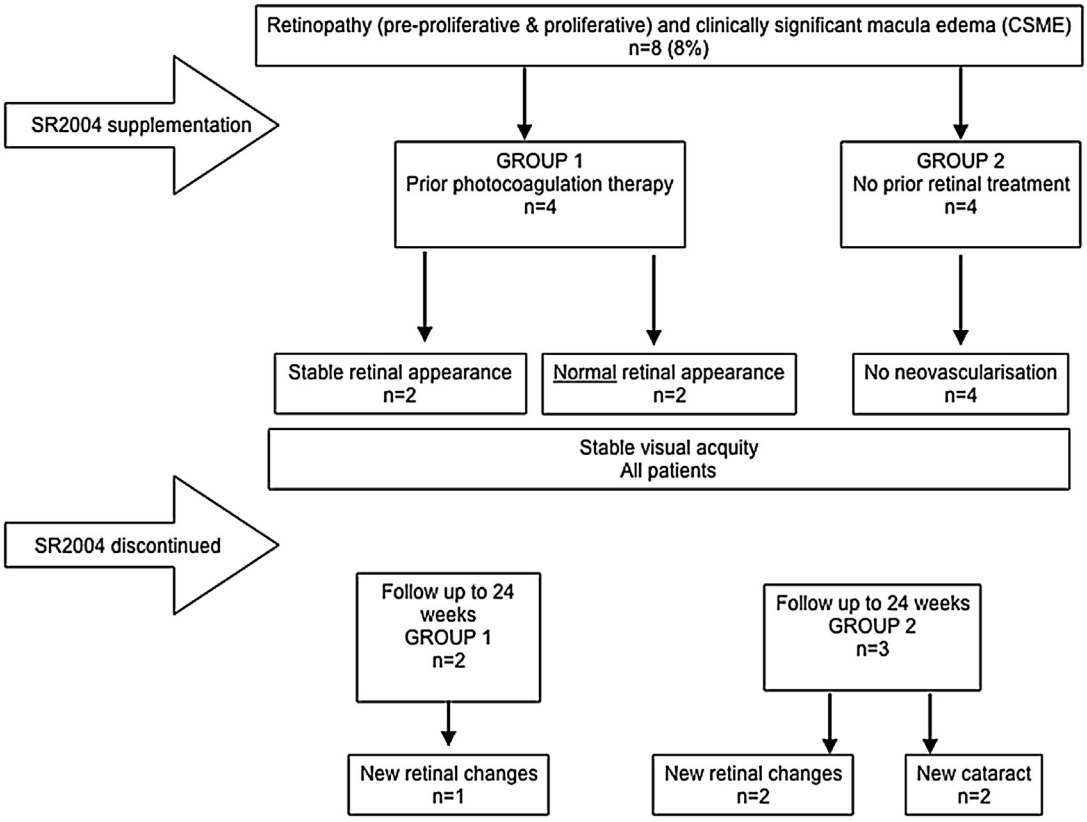

Fig. 2 – Clinical observations of patients with retinopathy and clinically significant macula edema. Effect of SR2004 supplementation and withdrawal on retinal appearances in patients with retinopathy and clinically significant macula edema. Group 1 (prior photocoagulation therapy, $n = 4$) and Group 2 (no prior photocoagulation, $n = 4$).

endogenous insulin secretion when glycemic control was improved.[57] In their study, the average daily insulin requirement decreased by approximately 23% after two weeks of therapy and stabilized thereafter. Similarly, in our cohort, 10 of 13 patients treated with insulin were able to suspend insulin or reduce their dose by one-third on average through improved blood sugar control.

Diabetic dyslipidemia is a common finding characterized by a lipoprotein pattern of a modest elevation in triglycerides, an increase in low density lipoprotein cholesterol (LDL-C) particles and reduced levels of high density lipoprotein cholesterol (HDL-C). The LDL-C, in particular, are highly atherogenic due to their greater susceptibility to oxidative modification with greater absorption by the arterial wall and promote the macrovascular problems found in T2DM. With triglyceride levels above 132 mg/dL, small LDL-C particles become common and are the most potent predictors of coronary artery disease. In its updated 2015 recommendations, despite moving away from treatment based primarily on LDL-C levels, the American Diabetes Association maintained a recommended LDL-C level of less than 100 mg/dL. With the exception of type 2 diabetics under 40 years of age without other cardiovascular risk factors, treatment with statins (moderate or high intensity) is currently recommended to achieve a reduction in LDL-C levels.[58] To date, no study has shown an incremental benefit in reducing cardiovascular risk with combination antilipid therapy, with the exception of a modest reduction in the risk of myocardial infarction in the IMPROVE-IT study comparing simvastatin and ezetimibe versus simvastatin alone (HR 0.936, 95% CI 0.89–0.99, $p = 0.016$).[59] In our cohort, the combination of SR2004 with therapy with statins or fibrates (liver PPARα activators) resulted in a significant reduction of total cholesterol and particularly triglycerides (mean reduction of 40%).

The reduction in LDL-C and triglycerides noted in this study can be explained, in part, by better glycemic control and a consequent reduction in lipolysis, but other mechanistic possibilities include a direct effect on lipid metabolism by activating PPARα/γ pathways. These ligand-activated transcription factors are found in a wide variety of body tissues and regulate the expression of several genes that play critical roles in the metabolism of lipids and lipoproteins. It has been shown that PPAR activation increases β-oxidation of fatty acids in the liver, which is associated with large reductions in serum lipids and adipose tissue mass and is considered an important part of lipid homeostasis.[21,60,61] Additional consequences of PPAR activation include transcriptional upregulation and release of adiponectin, an adipocyte protein hormone[62,63] with systemic effects that include reduced hepatic gluconeogenesis, increased triglyceride clearance, and reduction in Tissue necrosis factor alpha (TNFα) and interleukin 6 (IL-6), both important proinflammatory cytokines increased in obesity that promote lipolysis and insulin resistance. Several studies both *in vitro* and *in vivo* have demonstrated PPAR receptor activation and increased production of adiponectin after

treatment with *Artemisia, Morus* and *Urtica*,[8,26,29,42,45,64,19] which may be part of a mechanistic explanation of SR2004.

It was observed that some patients in this study had significant improvements in vascular ischemic phenomena associated with diabetes, including claudication of the limbs, impotence, renal dysfunction due to renovascular disease, and most interestingly, the reversion of proliferative retinopathy in two cases. The mechanism underlying these improvements is not elucidated and this study was not designed to investigate them further, but it raises some interesting possibilities which deserve discussion. In general, the macrovascular complications of diabetes are due to accelerated atherosclerosis due to the combined effects of elevated LDL-C levels, peripheral insulin resistance, and, commonly, hypertensive endothelial stress. As discussed, the activation of PPAR and increased adiponectin levels would be expected to have beneficial effects on atherosclerotic plaques and macrovascular disease. However, the pathological mechanisms underlying microvascular complications characterized by thickening of the basal membranes, loss of pericytes, neovascularization, and the formation of microaneurysms probably include different factors. Oxidative stress may play an important role in cellular injury in hyperglycemia with the formation of free radicals and reactive oxygen species toxic to endothelial cells.[65] Neovascularization depends on the presence of several angiogenic factors, including nitric oxide (NO), prostaglandin-E2 (PGE2), and cytokines, such as VEGF, interleukin-1β, interleukin 6 (IL-6), and TNFα. Systemic levels of VEGF are often increased in diabetic patients and high intraocular levels are typically observed in those with proliferative changes due to elevated levels of hypoxia-inducible factor (HIF), a transcription factor, which in turn stimulates the release of VEGF-A.[66] Once bound to VEGF receptors on endothelial cells, angiogenesis is promoted through a tyrosine kinase-mediated pathway. In humans, the only strategy currently demonstrated to induce regression of retinal neovascularization involves local (intraocular) blockade of this pathway.[55] Two out of four patients in this study with established chronic retinopathic changes and previous laser photocoagulation showed a complete reversal of the fundal findings during the 12 weeks of follow-up. Xhu et al evaluated *in vitro* the effect of sesquiterpene lactones, flavonoids and coumarins derived from *Artemisia annua* L. on NO production induced by lipopolysaccharides and a variety of angiogenic cytokines including VEGF, TNFα, and IL-6 in rat mesothelial and mononuclear cells from human peripheral blood.[67] Their findings indicated that several metabolites derived from *Artemisia* were antiangiogenic and that the flavonoids casticin and chrysosplenol D demonstrated potent dual-inhibition of NO and PGE. Whether these properties are beneficial *in vivo* has not been investigated in humans to our knowledge and would seem to be a suitable line of investigation.

This study has some limitations which include a potential referral bias, with either more motivated patients seeking out the trial, or those with the disease at the more severe end of the diabetic spectrum being referred. The effect of SR2004 in patients with well-controlled blood sugars, on conventional diabetic medications, is not determined. Furthermore, the study was unblinded as the initial formulation was a liquid with distinctive appearance and taste which required refrigeration. The subsequent successful development of flavorless capsules makes a blinded study feasible, along with the introduction of a control arm.

In conclusion, this study demonstrates the herbal composition SR2004 improved levels of HbA1c, blood glucose, and lipids, in a group of patients with T2DM, regardless of weight changes, activity levels or the use of conventional diabetic medications and lipid-reducing medications. Interesting vascular effects – including reversal of chronic retinopathic changes in some patients – were observed during the 12-week trial and returned during the 12-week observation period thereafter. Further research is required to determine the precise bioactive components in SR2004 and their mechanisms of action, as well as a double-blinded, crossover trial to corroborate the findings of this preliminary study.

Conflict of interest

The authors declare no conflict of interest.

Funding

Funded by a grant from Maccabi Health Services, Israel. Grant number 30246. There was no involvement in the design of the study and collection, analysis, and interpretation of data, and in writing the manuscript by the grant-awarding body.

Trial registration

Reference: ISRCTN12562776

http://www.isrctn.com/ISRCTN12562776

Date of registration: 12.6.2017. Registered retrospectively.

Acknowledgements

Prof. Alf Fischbein, Sackler School of Medicine, Tel Aviv University, Israel.

Dr. Rafael Bitzur, Lipid Center, Sheba Medical Center, Tel Hashomer, Israel.

References

1. Williams DRR. The economics of diabetes care: a global perspective. In: *International textbook of diabetes mellitus*. 4th ed. Chichester, UK: Wiley Blackwell; 2015.
2. Danaei G, Finucane MM, Lu Y, Singh GM. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. *Lancet* 2011;378:31–40.
3. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837–53.
4. Gerstein HC, Miller ME, Byington RP. Effects of intensive glucose lowering in type 2 diabetes. *New Engl J Med* 2008;358:2545–59.
5. Colhoun, Helen M. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the

Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004;364:685–96.
6. Improving health and social care through evidence-based guidance. National Institute for Health and Care Excellence. www.nice.org.uk. 12th September 2012 'Majority of people with diabetes not meeting cholesterol targets'. Accessed 9 May, 2017.
7. Bailey CJ, Day C. Metformin: it's botanical background. *Pract Diabetes Int* 2004;21:115–7.
8. El-Abhar H, Schaalan M. Phytotherapy in diabetes: review on potential mechanistic perspectives. *World J Diabetes* 2014;5:176–97.
9. Andallu B, Varadacharyulu NC. Gluconeogenic substrates and hepatic gluconeogenic enzymes in streptozotocin-diabetic rats: effect of Mulberry (*Morus indica* L.) leaves. *J Med Food* 2007;10:41–8.
10. Lown M, Fuller R, Lightowler H, Fraser A. Mulberry extract improves glucose tolerance and decreases insulin concentrations in normoglycaemic adults: results of a randomised, double-blind, placebo-controlled study. *PLoS ONE* 2017;12:e0172239.
11. Chan EW, Lye PY, Wong SK. Phytochemistry, pharmacology and clinical trials of *Morus alba*. *Chin J Nat Med* 2016;14:17–30.
12. Asano N, Tomioka E, Kizu H. Sugars with nitrogen in the ring isolated from the leaves of *Morus bombycis*. *Carbohydr Res* 1994;253:235–45.
13. Kumar S, Narwal S, Kumar V, Prakash O. α-Glucosidase inhibitors from plants: a natural approach to treat diabetes. *Pharmacogn Rev* 2011;5:19–29.
14. Oku T, Yamada M, Nakamura M, Sadamori N, Nakamura S. Inhibitory effects of extractives from leaves of *Morus alba* on human and rat small intestinal disaccharidase activity. *Br J Nutr* 2006;95:933–8.
15. Hansawasdi C, Kawabata J. Alpha-glucosidase inhibitory effect of mulberry (*Morus alba*) leaves on Caco-2. *Fitoterapia* 2006;77:568–73.
16. Konno K, Ono H, Nakamura M, Tateishi K, Hirayama C. Mulberry latex rich in antidiabetic sugar-mimic alkaloids forces dieting on caterpillars. *Proc Natl Acad Sci U S A* 2006;103:1337–41.
17. Sharma SB, Gupta S, Ac R, Singh UR. Antidiabetogenic action of *Morus rubra* L. leaf extract in streptozotocin-induced diabetic rats. *J Pharm Pharmacol* 2010;62:247–55.
18. Cai S, Sun W, Fan Y, Guo X. Effect of Mulberry leaf (Folium Mori) on insulin resistance via IRS-1/P13K/Glut-4 signaling pathway in type 2 diabetes mellitus rats. *Pharm Biol* 2016;54:2685–91.
19. Park MY, Lee KS, Sung MK. Effects of dietary mulberry, Korean red ginseng, and banaba on glucose homeostasis in relation to PPAR-alpha, PPAR-gamma, and LPL mRNA expressions. *Life Sci* 2005;77:3344–54.
20. Armoni M, Kritz N, Harel C, Bar-Yoseph F. Peroxisome proliferator-activated receptor gamma represses GLUT4 promoter activity in primary adipocytes, and rosiglitazone alleviates this effect. *J Biol Chem* 2003;278:30614–23.
21. Nagashima K, Lopez C, Donovan D, Ngai C. Effects of the PPARgamma agonist pioglitazone on lipoprotein metabolism in patients with type 2 diabetes mellitus. *J Clin Invest* 2005;115:1323–32.
22. Abderrahmane M, Mohamed E. Artemisia herba alba: a popular plant with potential medicinal properties. *Pakistan J Biol Sci* 2012;15:1152–9.
23. Kang YJ, Jung UJ, Lee MK, Kim HJ. Eupatilin, isolated from *Artemisia princeps* Pampanini, enhances hepatic glucose metabolism and pancreatic beta cell function in type 2 diabetic mice. *Diabetes Res Clin Pract* 2008;82:25–32.
24. Scherp P, Putluri N, LeBlanc GJ, Wang ZQ. Proteomic analysis reveals cellular pathways regulating carbohydrate metabolism that are modulated in primary human skeletal muscle culture due to treatment with bioactive from *Artemisia dracunculus* L. *J Proteomics* 2012;75:3199–210.
25. Wang ZQ, Ribnicky D, Zhang ZH, Raskin I. Bioactives of *Artemisia dracunculus* L enhance cellular insulin signaling in primary human skeletal muscle culture. *Metabolism* 2008;57(Suppl 1):S58–64.
26. Sun X, Sun H, Zhang J, Ji X. Artemisia extract improves insulin sensitivity in women with gestational diabetes mellitus by up-regulating adiponectin. *J Clin Pharmacol* 2016;56:1550–4.
27. Hotta K, Funahashi T, Arita Y, Takahashi M. Plasma concentrations of a novel,adipose-specific protein, adiponectin, in type 2 diabetic patients. *Arterioscler Thromb Vasc Biol* 2000;20:1595–9.
28. Ribnicky DM, Poulev A, Watford M, Cefalu WT, Raskin I. Antihyperglycemic activity of Tarralin, an ethanolic extract of *Artemisia dracunculus* L. *Phytomedicine* 2006;13:550–7.
29. Rau O, Wurglics M, Fingermann T, Abdel-Talab M, Schubert-Zsilavecz M. Screening of herbal extracts for activation of the human peroxisome proliferator-activated receptor. *Pharmazie* 2006;61:952–6.
30. Ranjbari A, Azerbaijani MA, Yusof A, Halim Mokhtar A. In vivo and in vitro evaluation of the effects of *Urtica dioica* and swimming activity on diabetic factors and pancreatic beta cells. *BMC Complement Altern Med* 2016 March 15;16:101.
31. Golalipour MJ, Khori V. The protective activity of *Urtica dioica* leaves on blood glucose concentration and beta-cells in streptozotocin-diabetic rats. *Pay J Biol Sci* 2007;10:1200–4.
32. Vengerovskii AI, Yakimova TV, Nasanova ON. Influence of medicinal plant extract on the functions and antioxidant protection of erythrocytes in rats with experimental diabetes mellitus. *Eksp Klin Farmakol* 2016;79:29–33.
33. Kianbakht S, Khalighi-Sigaroodi F, Heidari A. *Urtica dioica* L. in treatment of patients with type 2 diabetes mellitus: a randomized double-blind placebo-controlled clinical trial. *Int J Pharmaceut Res Bio-Sci* 2012;1:533–42.
34. Namazi N, Tarighat A, Bahrami A. The effect of hydro alcoholic nettle (*Urtica dioica*) extract on oxidative stress in patients with type 2 diabetes: a randomized double-blind clinical trial. *Pakistan J Biol Sci* 2012;15:98–102.
35. Namazi N, Esfanjani AT, Heshmati J, Bahrami A. The effect of hydro alcoholic nettle (*Urtica dioica*) extracts on insulin sensitivity and some inflammatory indicators in patients with type 2 diabetes: a randomized double-blind control trial. *Pakistan J Biol Sci* 2011;14:775–9.
36. Cao H, Ji Y, Li W, Liu Y. Protective effects of the total coumarin fraction of *Urtica dentata* on experimental diabetic nephropathy in vitro and in vivo. *Plants Med* 2015;81:1353–60.
37. Lu T, Sheng H, Wu J, Cheng Y. Cinnamon extract improves fasting blood glucose and glycosylated hemoglobin level in Chinese patients with type 2 diabetes. *Nutr Res* 2012;32:408–12.
38. Akilen R, Tsiami A, Devendra D, Robinson N. Glycated haemoglobin and blood pressure-lowering effect of cinnamon in multi-ethnic Type 2 diabetic patients in the UK: a randomized, placebo-controlled, double-blind clinical trial. *Diabet Med* 2010;27:1159–67.
39. Verspohl EJ, Bauer K, Neddermann E. Anti-diabetic effect of *Cinnamomum cassia* and *Cinnamomum zeylanicum* in vivo and in vitro. *Phytother Res* 2005;19:203–6.
40. Costello RB, Dwyer JT, Saldanha L, Bailey RL. Do cinnamon supplements have a role in glycemic control in type 2 diabetes? a narrative review. *J Acad Nutr Diet* 2016;116:1794–802.
41. Allen RW, Schwarzman E, Baker WL, Coleman CI. Cinnamon use in type 2 diabetes: an updated systematic review and meta-analysis. *Ann Fam Med* 2013;11:452–9.

42. Roffey B, Atwal A, Kubow S. Cinnamon water extracts increase glucose uptake but inhibit adiponectin secretion in 3T3-L1 adipose cells. *Mol Nutr Food Res* 2006;50:739–45.
43. Imparl-Radosevich J, Deas S, Polansky MM, Baedke DA. Regulation of PTP-1 and insulin receptor kinase by fractions from cinnamon: implications for cinnamon regulation of insulin signalling. *Horm Res* 1998;50:177–82.
44. Wirngo FE, Lambert MN, Jeppesen PB. The physiological effects of dandelion (*Taraxacum officinale*) in type 2 diabetes. *Rev Diabetic Stud* 2016;13:113–31.
45. Gonzalez-Castejon M, Visioli F, Rodriguez-Casado A. Diverse biological activities of dandelion. *Nutr Rev* 2012;70:534–47.
46. Schutz K, Carle R, Schieber A. Taraxacum – a review on its phytochemical and pharmacological profile. *J Ethnopharmacol* 2006;107:313–23.
47. Esatbeyoglu T, Obermair B, Dorn T, Siems K. Sesquiterpene lactone composition and cellular Nrf2 induction of *Taraxacum officinale* leaves and roots and taraxinic acid β-D-glucopyranosyl ester. *J Med Food* 2017;20:71–8.
48. Zhang J, Kang MJ, Kim MJ. Pancreatic lipase inhibitory activity of *Taraxacum officinale* in vitro and in vivo. *Nutr Res Pract* 2008;2:200–3.
49. Davaatseren M, Hur HJ, Yang HJ, Hwang JT. Taraxacum official (dandelion) leaf extract alleviates high-fat diet-induced nonalcoholic fatty liver. *Food Chem Toxicol* 2013;58:30–6.
50. Cho SY, Park JY, Park EM, Choi MS. Alternation of hepatic antioxidant enzyme activities and lipid profile in streptozotocin-induced diabetic rats by supplementation of dandelion water extract. *Clin Chim Acta* 2002;317:109–17.
51. Cho AS, Jeon SM, Kim MJ, Yeo J. Chlorogenic acid exhibits anti-obesity property and improves lipid metabolism in high-fat diet-induced obese mice. *Food Chem Toxicol* 2010;48:937–43.
52. You Y, Yoo S, Yoon HG, Park J. In vitro and in vivo hepatoprotective effects of the aqueous extract from *Taraxacum officinale* (dandelion) root against alcohol-induced oxidative stress. *Food Chem Toxicol* 2010;48:1632–7.
53. Hagymasi K, Blazovics A, Feher J, Lugasi A. The in vitro effect of dandelions antioxidants on microsomal lipid peroxidation. *Phytother Res* 2000;14:43–4.
54. Hu C, Kitts DD. Dandelion (*Taraxacum officinale*) flower extract suppresses both reactive oxygen species and nitric oxide and prevents lipid oxidation in vitro. *Phytomedicine* 2005;12:588–97.
55. Osaadon P, Fagan XJ, Lifshitz T, Levy J. A review of anti-VEGF agents for proliferative diabetic retinopathy. *Eye* 2014;28:510–20.
56. Rossetti L, Giaccari A, DeFronzo RA. Glucose toxicity. *Diabetes Care* 1990;13:610–30.
57. Garvey WT, Olefsky JM, Griffin J. The effect of insulin treatment on insulin secretion and insulin. *Diabetes* 1985;34:222–34.
58. American Diabetes Association. Standards of medical care in diabetes—2015. *Diabetes Care* 2015;38(Suppl 1):S1–93.
59. Cannon C, Blazing MA, Giugliano MD. IMPROVE-IT. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015;372:2387–97.
60. Lena Burri G, Thoresen H, Berge RK. The role of PPAR activation in liver and muscle. *PPAR Res* 2010:11. Article ID 542359.
61. Gervois P, Torra IP, Fruchart JC, Staels B. Regulation of lipid and lipoprotein metabolism by PPAR activators. *Clin Chem Lab Med* 2000;38:3–11.
62. Maeda N, Takahashi M, Funahashi T, Kihara S. PPAR gamma ligands increase expression and plasma concentrations of adiponectin, an adipose-derived protein. *Diabetes* 2001;50:2094–9.
63. Yang WS, Jeng CY, Wu TJ, Tanaka S. Synthetic peroxisome proliferator-activated receptor-gamma agonist, rosiglitazone, increases plasma level of adiponectin in type 2 diabetic patients. *Diabetes Care* 2002;25:376–80.
64. Tsuduki T, Kikuchi I, Kimura T, Nakagawa K, Miyazawa T. Intake of mulberry 1-deoxynojirimycin prevents diet-induced obesity through increases in adiponectin in mice. *Food Chem* 2013;139:16–23.
65. Giacco F, Brownlee M. Oxidative stress and diabetic complications. *Circ Res* 2010;107:1058–70.
66. Tarr JM, Kaul K, Chopra M, Kohner EM, Chibber R. Pathophysiology of diabetic retinopathy. *ISRN Ophthalmol* 2013;2013:13. Article ID 343560.
67. Xhu X, Yang L, Li Y, Zhang D. Effects of sesquiterpene, flavonoid and coumarin types of compounds from *Artemisia annua* L. on production of mediators of angiogenesis. *Pharmacol Rep* 2013;65:410–20.