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

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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.

Abbreviations: anti-VEGF, antivascular endothelial growth factor; BMI, body mass index; DNJ, 1-deoxynojirimycin; GLP1, incretin; GLUT4, glucose transporter 4; GRAS, generally recognized as safe; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HIF, hypoxia-inducible factor; HPAEC-PAD, high-performance anion-exchange chromatography with pulsed amperometric detection; IL-1β, interleukin 1β; IL-6, interleukin 6; IL-10, interleukin 10; LDL-C, low-density lipoprotein cholesterol; mRNA, messenger ribonucleic acid; NO, nitric oxide; PGE2, prostaglandin E2; PPAR, peroxisome proliferator-activated receptors; T2DM, type 2 diabetes mellitus; TG, triglycerides; TNFα, tissue necrosis factor α; VEGF, vascular endothelial growth factor.

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

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. Background

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,

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