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Stevia and *Uncaria* extract (GlucoMedix®) reduces glucose levels and the need for medications in type 2 diabetes: an open label case series of six patients

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Abstract

Background: GlucoMedix® is an all-natural phytotherapy consisting of a hydro-alcoholic extract of *Stevia rebaudiana* (Bertoni) Bertoni and pentacyclic chemotype *Uncaria tomentosa* (Willd. Ex Schult.) DC. The nutraceutical product has potential for the treatment of hyperglycemia in type 2 diabetes and Metabolic Syndrome.

Methods: Six adult Hispanic type 2 diabetic patients were included in an outpatient retrospective open label physician-sponsored case series study. GlucoMedix® extract of *Stevia* plus pentacyclic chemotype *Uncaria* was administered orally at doses of 2 ml, diluted in water, two or three times daily. The patients' blood glucose levels were recorded historically, at baseline, and thereafter while taking GlucoMedix® orally.

Results: When treated with GlucoMedix®, with or without coincident advice to modify diet, all six patients manifested reductions in blood glucose levels. At baseline four of the six patients were administering one or more prescription treatments for hyperglycemia, e.g., Glibenclamide, Metformin, Vildagliptin, or Insulin. Two patients displayed substantial reductions in glucose of 50 and 70 mg/dl, and in conjunction with the removal of their prior drug treatments of Glibenclamide plus Metformin or of Vildagliptin. An Insulin-treated patient experienced a 50 mg/dl reduction while ceasing Metformin and was subsequently able to reduce the dose of Insulin by half. Thus, in three patients GlucoMedix® abrogated in whole or in part the requirement for pharmaceutical or biologic therapies to achieve substantial beneficial reductions in glycemic levels.

Conclusions: In this proof-of-principle study oral GlucoMedix® was an effective treatment for hyperglycemia in type 2 diabetic individuals. This all-natural phytotherapy can be used beneficially in conjunction with existing pharmaceutical or biological therapy regimens, and in some cases can replace in whole or in part the requirement for pharmaceutical or biologic therapies. These in-life results suggest that this natural product approach can serve as an alternative to prescription monotherapies or multimodal therapies for the regulation of hyperglycemia.

Keywords: Diabetes, Glucose, *Stevia*, *Uncaria*, cat's claw, Insulin, Alternative medicine, Natural product

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Background

Type 2 diabetes is a complex metabolic disorder of chronic hyperglycemia involving peripheral insulin resistance, insulin deficiency from pancreatic beta cells, and elevated glycosylation of proteins (e.g., Hb A1C). Glucose control in this disease progressively deteriorates over time. After the failure of diet and exercise to reverse hyperglycemia or to maintain overall health, it is necessary to add oral pharmaceutical therapies, to achieve adequate glucose control. When pharmaceutical options fail, the treatment of choice by default is Insulin. If the patient is not fully compliant with the proper use of Insulin, then the disease can worsen, causing greater weight gain, increase in adipose tissue, fatty liver, and thereby entering a harmful cycle for the patient. This can result in diabetic ulcers, impaired vision, and Metabolic Syndrome, thus, extending beyond the primary issue of hyperglycemia.

Obesity, dyslipidemia, and hypertension are often associated with type 2 diabetes in Metabolic Syndrome, which can lead to an increased risk of cardiovascular and cerebrovascular diseases [1]. Metabolic Syndrome is common and affects 34% of adults in the USA [2] and 27% in Peru [3]. Pharmacological interventions, as well as diet and exercise, can treat type 2 diabetes in some individuals. However, given that some drugs can exhibit side effects, many individuals are more interested in the use of traditional medicinal plants or herbal extracts as phytotherapies.

Stevia rebaudiana, a sweet herb native to South and Central America, has long been used by the indigenous peoples for a variety of medical conditions, including diabetes. Steviol glycosides present in dried *Stevia* leaves are responsible for their intensely sweet taste. In addition, various pharmacological effects of *Stevia* and steviol glycosides have been identified in animal models and humans, including antihypertensive [4–10] and antihyperlipidemia [11, 12] effects. Of high relevance to the current study, *Stevia* and steviol glycosides have demonstrated anti-hyperglycemic effects [6, 11, 13–18]. In view of its anti-hyperglycemic and antihypertensive effects, *Stevia* has been suggested as a possible treatment for Metabolic Syndrome [19, 20].

Uncaria tomentosa (cat's claw) is commonly used to treat various diseases by South American indigenous people groups [21–28]. Of high relevance to the current study, *Uncaria* has demonstrated anti-hyperglycemic activity [29–33], perhaps due to alpha-glucosidase and alpha-amylase inhibitory activities [34, 35]. *Uncaria* contains various pharmacologically active agents, such as oxindole alkaloids with two major chemotypes: tetracyclic oxindole alkaloids (TOA) and pentacyclic oxindole alkaloids (POA). TOAs act primarily on the central nervous system, while the POAs affect the cellular immune system [36–38]. The interaction of tetra- and pentacyclic alkaloids can be antagonistic. Thus, TOA-free *Uncaria* is preferable. Also, oxindole alkaloids in wild populations of *Uncaria tomentosa* in South America are variable [39]. Therefore, in the present study we utilized a commercial extract that contained pentacyclic chemotype *Uncaria tomentosa*.

In view of the complementary biochemical mechanisms of action of phytochemicals within *Stevia rebaudiana* and pentacyclic chemotype *Uncaria tomentosa*, a hydro-alcoholic extract admixture, GlucoMedix®, has been developed as a commercial product. This study aimed to evaluate this phytotherapy product in a retrospective open label physician-sponsored case series of type 2 diabetic patients as a proof-of-principle.

Methods

This is a retrospective physician-sponsored study of glucose levels in six Hispanic diabetic patients conducted in Peru. The outpatients were under the routine care of the physicians and were assessed and treated orally as outpatients with commercial GlucoMedix® hydro-alcoholic extract (23% ethanol) of pentacyclic chemotype *Uncaria tomentosa* (Willd.) DC (Samento® brand) and *Stevia rebaudiana*. The product was obtained from NutraMedix Inc. (Jupiter, FL, USA). The patients provided consent to the physicians for use of their anonymized results in publications. The patients were advised to administer orally 2 ml (40 drops) per dose, diluted in water, two or three times daily, for a total daily dose of 4 or 6 ml of the extract. Blood glucose levels were recorded historically, at baseline prior to the phytotherapy, and periodically subsequent to commencing the phytotherapy at intervals convenient to the patients at home and the physicians in their offices. At the professional judgment and discretion of the physicians the pharmaceutical and/or biologic treatments for glycemic control were modified in some patients while being administered GlucoMedix®.

Results

Individual case reports

Patient S1 is a 53-year-old female (Pucallpa, Peru), 67 kg weight, 163 cm height, and blood pressure of 100/70 mmHg. She was diagnosed with diabetes mellitus 12 years previously, and current diagnoses include diabetes and obesity. S1 was treated with Glibenclamide 5 mg every 12 h for 3 months, then 5 mg every 24 h for five years. Because her blood sugar levels remained high, treatment was modified to add a Metformin 850 mg tablet during breakfast and dinner, in addition to Glibenclamide 5 mg in the afternoon for four years. Despite the modifications of the pharmaceutical treatments, S1 maintained high blood sugar levels (175–200 mg/dl).

GlucoMedix® 2 ml (40 drops) was added to the dual pharmacological treatment, 30 min before breakfast and dinner, in addition to 2 ml (40 drops) before sleep, for a daily total dose of 6 ml. A decrease in blood sugar levels to 62 mg/dl was recorded 7 days after the start of the use of GlucoMedix®, so Glibenclamide was withdrawn from the pharmacological treatment.

After the second week of starting the GlucoMedix® blood sugar levels were maintained between 62 and 65 mg/dl. This change prompted a reduction in the dose of Metformin to ½ tablet (425 mg) during breakfast and dinner, which resulted in regularized blood sugar levels between 80 and 110 mg/dl.

During the third week of GlucoMedix® treatment, it was possible to completely withdraw the pharmacological portion of the treatment, leaving only the use of GlucoMedix® and a low carb diet, which resulted in the maintained blood sugar levels of < 130 mg/dl. With the use of GlucoMedix® and the removal of the low carb diet, blood sugar levels remained between 130 and 145 mg/dl.

Patient S2 is a 50-year-old female (Pucallpa, Peru), 59 kg weight, 153 cm height, and blood pressure of 110/70 mmHg. She was diagnosed with diabetes mellitus 3 years ago, and current diagnoses include diabetes and obesity. S2 was on a Vildagliptin treatment (Galvus®) 50 mg daily for 6 months and maintained high blood sugar levels of 180–200 mg/dl.

The high blood sugar levels prompted the removal of the pharmacological treatment and start of treatment with GlucoMedix® 2 ml (40 drops) 30 min before breakfast and dinner, in addition to 2 ml (40 drops) before sleeping, for a total daily dose of 6 ml, alongside a low carb diet. Blood sugar levels were recorded being between 110 and 130 mg/dl, 7 days after the start of the use of GlucoMedix®.

Patient R1 is a 53-year-old male (Pucallpa, Peru), 112 kg weight, 180 cm height, and blood pressure of 110/80 mmHg. His current diagnosis is type 1 obesity and diabetes. He reported blood sugar levels of 127 mg/dl in monthly control examinations 2 years ago, as well as being overweight.

To improve blood sugar levels, R1 began treatment with GlucoMedix® 2 ml (40 drops) 30 min before breakfast and dinner, plus 2 ml (40 drops) before sleeping, for a total daily dose of 6 ml, together with a low carb diet, which resulted in a decrease in blood sugar levels between 85 and 105 mg/dl 8 days after starting the use of GlucoMedix®. Furthermore, the patient continued to maintain blood sugar values between 100 and 120 mg/dl with the use of GlucoMedix® and without incorporating a low carb diet.

Patient O1 is a 59-year-old male (Pucallpa, Peru), 84 kg weight, 170 cm height, and blood pressure of 130/82 mmHg. He was diagnosed with type 2 diabetes 24 years ago, and current diagnoses include diabetes and obesity. He was treated with Glibenclamide 5 mg every twelve hours and Metformin 850 mg during breakfast and dinner. During the prior 15 years, despite the treatment, O4 had maintained high blood sugar levels (200–270 mg/dl).

The patient added GlucoMedix® 2 ml (40 drops) 30 min before breakfast and dinner, also 2 ml (40 drops) before sleeping, for a total daily dose of 6 ml. Together with the dual drug treatments and a low carb diet, after 4 weeks the blood sugar levels were reduced to 121 mg/dl. Treatment continued thereafter, with the patient expressing satisfaction with the addition of the phytotherapy.

Patient R2 is a 54-year-old male (Pucallpa, Peru), 72 kg weight, 171 cm height, and blood pressure of 100/70 mmHg. He was diagnosed with diabetes mellitus 17 years ago, and current diagnoses include diabetes and chronic kidney disease, as evidenced by clinical chemistry (i.e., urea 40 and creatinine 2.1). From 2004 until 2010 he was treated with Metformin 850 mg at breakfast and dinner, in addition to Glibenclamide 5 mg during breakfast and dinner. This medical approach resulted in blood sugar levels of 145–205 mg/dl.

The patient was diagnosed with chronic kidney disease in 2010, for which he was treated by a nephrologist, plus an endocrinologist exchanged the Metformin and Glibenclamide for Insulin 15 IU at breakfast and dinner. However, the patient rejected Insulin therapy in 2011, and proceeded to change his lifestyle (i.e., no alcohol, no tobacco, low carbohydrate diet, and no sugar). With these medical and lifestyle changes he managed to reduce blood sugar levels to 130 - 165 mg/dl.

The patient administered GlucoMedix® 2 ml (40 drops) 30 minutes before breakfast and dinner, plus 2 ml (40 drops) before sleeping, for a total daily dose of 6 ml. This treatment decreased glucose to 110 - 120 mg/dl at 12 days after the start of the use of GlucoMedix®. At 20 days the glucose level reached 78 - 116 mg/dl, and he continued to maintain those values thereafter for more than one year.

Patient R3 is a 65-year-old female (Tarapoto, Dept. San Martin, Peru), 64 kg weight, 154 cm height, and medicated blood pressure of 135/75 mmHg. She has had a diagnosis of type 2 diabetes for 20 years and a history of mismanagement of her disease, as evidenced by Hb A1C greater than 10%. Before the start of the use of GlucoMedix®, the patient was managed with combined therapy of Metformin 850 mg in conjunction with Insulin six years earlier. As an Insulin-dependent diabetic she has been maintained on Glargine Insulin (Lantus) 28 IU/day. She exhibited other comorbidities consistent with Metabolic Syndrome, such as hypertension grade I (Irbesartan 150 mg once daily), mixed dyslipidemia, and

obesity grade I, and chronic collateral damage as a poorly controlled diabetic patient, such as stage 2 to 3 kidney failure (mild to medium kidney damage) and mild to moderate proliferative diabetic retinopathy.

Between December 2019 and July 2021, the patient replaced Metformin 850 mg with oral GlucoMedix®. At the time of the start of the all-natural treatment, the patient was poorly managed, having high glycosylated hemoglobin values (A1C > 10%) and fluctuating glycemic levels (> 150 mg/dL). The last baseline control of Hb A1C was 11.2%, and the lipid profile showed mild mixed dyslipidemia. The initial dose of GlucoMedix® was 2 ml (40 drops) twice daily, 20 to 30 min before meals, diluted in water, for a total daily dose of 4 ml. At the same time, the patient was instructed to change her style of eating, gradually decreasing the intake of complex carbohydrates and saturated fats, and ceasing sugar from the diet. Frequently used medicines were not initially modified with the exception of discontinuing Metformin.

The first month the patient reported daily glycemic controls with a tendency to decrease, which prompted a decrease in the daily insulin dose, at a rate of 2 IU, each time the patient achieved glycemia less than 100 mg/dL. Within approximately 1 month the level managed to drop from 28 to 18 IU/day, a decrease that continued until January 2020, stabilizing at 14 IU - Insulin doses that maintained a daily glycemic level below 140 mg/dL, and remaining at this level for more than a year. The A1C levels reduced to values between 5.7% to 6.5% to the present.

A decrease in the level of glycemia was found, the effect was greater if it was accompanied by a change in the eating style in a sustained manner. In the initial adaptation phase, the patient reported symptoms similar to that of hypoglycemia (feeling of weakness, early fatigue, and nausea), so the dose of 2 ml (40 drops) twice daily was temporarily decreased to 2 ml (40 drops) once daily before breakfast, resuming it after 5 days. Improvements were observed in the results of quarterly control laboratory examinations.

During 2020, auxiliary glycemic control tests were performed on a daily and quarterly basis, as well as other complementary tests (A1C and lipid profile). It was observed that the main beneficial effect of the GlucoMedix® extract was that of being anti-hyperglycemic, and as an adjunct to her main treatment (insulin). A lipid-lowering effect was observed. However, more controls are required to determine if it was the result of the consumption of the phytotherapy, or due to other factors. The anti-hyperglycemic effect of the product substantially improves Hb A1C levels, making them acceptable compared to previously recorded baseline level of 11.2%.

Furthermore, the levels of total cholesterol, triglycerides, and LDL were regularized, achieving normal or low-risk levels (assessments in March 2020, September 2020, and January 2021). But more controls are needed to determine whether the beneficial effects are due to the *Stevia - Uncaria* extract and/or to any substantial change in nutrition.

The patient's compliance/adherence on GlucoMedix® was better than when using pharmaceutical medications (e.g., Glibenclamide, Metformin), thus favoring better long-term results and non-abandonment of adjuvant treatment(s). The gradual decrease in the dose of insulin helped to avoid greater long-term weight gain in the patient, which would have been more detrimental to her Metabolic Syndrome. Furthermore, the patient noted another benefit - the loss of the sensation of bitterness in the mouth that she had reported when using oral Metformin or Glibenclamide.

Group results

The treatment effects of GlucoMedix® in all six diabetic patients are summarized in Table 1. All patients manifested reductions in blood glucose levels within 1 week to 1 month while treated with GlucoMedix® at daily doses of 4 or 6 ml. Four of the six patients were receiving prescription drug and/or biologic treatments for hyperglycemia, such as Glibenclamide, Metformin, Vildagliptin, Insulin, or a combination thereof, prior to this study. The results from four of the patients indicate that Glucomedix® may be used beneficially in conjunction with existing pharmaceutical or biological therapy regimens for glycemic control, including tapering doses or ceasing medications.

Remarkably patients S1 and S2 displayed substantial average reductions in glucose (50 and 70 mg/dl, respectively), while replacing the pharmaceutical treatments of Glibenclamide plus Metformin or of Vildagliptin, respectively. Patient R3, who was being treated at baseline with Insulin and Metformin, experienced 50 mg/dl reductions while continuing Insulin and ceasing Metformin. She was subsequently able to reduce the dose of her Insulin by half, and experienced improvement in A1C levels. Thus, in three patients GlucoMedix treatment abrogated in part or in whole the requirement for prescription pharmaceutical or biologic therapies to achieve substantial reductions in glycemic levels [S1, S2, and R3].

Two unmedicated patients [R1 and R2] manifested reductions in glucose of 17–50 mg/dl. One medicated patient [O1] experienced a substantial reduction of 114 mg/dl from a high level of hyperglycemia, yet without modifying the pharmaceutical treatments. Thus, reductions in glucose were observed in both unmedicated and medicated patients, and in the latter category some

Table 1 Glucose Levels and Concomitant Prescription (Rx) Treatments of Type 2 Diabetic Patients at Baseline and Following Daily Oral Administration of GlucoMedix®

Patient	Age	Sex	Glucose (mg/dl) at Baseline	Rx Treatments at Baseline	Glucose (mg/dl) on GlucoMedix	Rx Treatments on GlucoMedix	Glucose (mg/dl) Reduction (Ave.)
S1	53	F	175–200	Glibenclamide, Met.	130–145	none	50
S2	50	F	180–200	Vildagliptin	110–130	none	70
R1	53	M	127	none	85–105	none + diet	32
					100–120	none	17
O1	59	M	200–270	Glibenclamide, Met.	121	Glibenclamide, Met.	114
R2	54	M	130–165	none	78–116	none	50
R3	65	F	> 150	Insulin, Metformin	< 100	Insulin	> 50
					< 140	Insulin (half dose)	> 10

Abbreviations: *Rx* prescription drugs or biologics; *Met.* Metformin

individuals were able to reduce the dose and/or cease the use of prescription medications.

Discussion & conclusions

The type 2 diabetes patients' results on oral GlucoMedix® provide initial proof-of-concept evidence of the phytotherapy's ability to regulate the level of blood glucose in humans. Can we speculate on the possible mechanisms of action? Perhaps it increases uptake of blood glucose into tissues and/or increases insulin secretion from the pancreas in diabetic patients. Beyond these possibilities, based upon previous studies on the phytochemicals from *Uncaria* and *Stevia*, this commercial extract might (also) inhibit the enzymatic catalysis of complex carbohydrates, regulate cortisol and the HPA axis, and/or exert pharmacologic effects via other mechanisms of action.

Stevia extract has long been used for the treatment of diabetes in South America [40]. *Stevia* or steviol glycosides were known in humans to affect type 2 diabetes [4, 11, 15]. *Stevia*-derived ingredients were also effective in rat models of hyperglycemia [13, 14, 17, 18, 41] and hyperlipidemia [12]. Furthermore, stevioside is a potent sweetener with no calories. Thus, *Stevia*-derived products can achieve reductions in blood glucose by at least two means: (a) as a substitute for dietary sugars, thus reducing ingested sugars; and (b) as pharmacologic active ingredients affecting glucose homeostasis.

Uncaria extracts have alpha-glucosidase and alpha-amylase inhibitory activities [34, 35]. These enzymes catalyze the hydrolysis of complex polysaccharides, such as dietary starch and endogenous glycogen. This enzymatic antagonism might reduce blood glucose derived from dietary and/or endogenous precursors. Furthermore, extracts of *Uncaria* showed a reduction in glycemic levels in mice and rat models [32, 33]. Also, *Uncaria* POAs can affect the immune system [33, 38, 42, 43], but whether this effect on immunity might possibly impact upon glucose regulation is unknown.

Yet another mechanism of action is that steviol glycosides and/or phytochemicals from *Uncaria* might be affecting the endocrine and/or neuro-endocrine system, and in particular the hypothalamic-pituitary-adrenal (HPA) axis. Cortisol levels might be a possible mediator under the influence of these bioactive phytochemicals. Cortisol is known to play a key role in glucose utilization. Patients with Metabolic Syndrome exhibit elevated HPA axis properties leading to hypercortisolism [44, 45].

In multiple rat animal models daily oral administration of GlucoMedix® has been found to reduce hyperglycemia, in addition to hyperlipidemia and hypertension, and without toxicity (Drs. Villegas Vilchez, Hidalgo Ascencios, and Dooley, manuscript submitted). Likewise other toxicologic studies in rodents have demonstrated the safety of extracts and isolated compounds of *Uncaria tomentosa* and *Stevia rebaudiana* [13, 25, 46].

Limitations of this work should be noted: (a) Open label physician-sponsored studies commonly lack randomization, blinding, a placebo control, inclusion and exclusion criteria, and statistical power analysis; (b) The pharmacologic effect(s) on glucose levels might be due to *Uncaria* alone, *Stevia* alone, or the combination thereof; (c) Was the dose of GlucoMedix® optimal? One can speculate that doses lower than 4 or 6 ml per day and/or alternative dosing schedules might also be effective; and (d) There are multiple confounding variables in an "in life" open label study, including the possible effects of dietary and/or behavioral changes coincident with this treatment.

Although the results of this pilot study are indicative of a beneficial restoration of glycemic levels in type 2 diabetic patients, additional clinical trials are merited to confirm this proof-of-principle from six patients. Regardless, a safe and effective natural product, such as

GlucoMedix®, that can address type 2 diabetes would be a welcome alternative or adjunctive therapy to pharmaceutical or biologic monotherapies (e.g., Glibenclamide, Metformin, or Insulin) or multimodal therapies (e.g., Insulin plus one or more pharmaceuticals). However, it is recommended that any changes to a patient's prescription drug and/or biologic treatments (i.e., medications, doses, and schedules) be undertaken in consultation with a licensed physician.

Acknowledgements
A physician-sponsored study (e.g., a case report or a case series) of a commercial natural product may be conducted at the discretion of the physician(s) using his/her professional judgment concerning patient care and treatment options. The patients provided consent for use of their anonymized results in publications.

Authors' contributions
JMPP and CRR conducted the physician-sponsored study, including patient assessments, treatments, and drafted the initial case report summaries. TPD was the principal author responsible for preparing the manuscript. The authors read and approved the final manuscript.

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Declarations

Competing interests
JMPP and CRR have no financial interests to declare. TPD (www.TomDooley.org) is an employee and shareholder in LivFul Inc. (www.LivFul.com), a potential distributor of the product.

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