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Smallanthus sonchifolius (Yacon) leaves: an emerging source of compounds for diabetes management

Authors:
Stella Maris Honoré ,
Susana Beatriz Genta,
Sara Serafina Sánchez,

Institution:
Dpto. Biología del Desarrollo, INSIBIO (Consejo Nacional de Investigaciones Científicas y Técnicas-Universidad Nacional de Tucumán (CONICET-UNT).
Chacabuco 461, T4000ILI San Miguel de Tucumán, Argentina

Corresponding author:
Sara Sánchez

Email Id:

ssanchez@fbqf.unt.edu.ar

Web Address:
http://jresearchbiology.com/documents/RA0502.pdf

ABSTRACT:

Diabetes mellitus is a chronic metabolic disease that develops mainly due to insulin deficiency or resistance to insulin action. All forms of diabetes are characterized by chronic hyperglycemia, which has an important role in the pathogenesis of diabetic complications. Leaves of Smallanthus sonchifolius (Poepp.&Endl.) H. Robinson (yacon) have been used since ancient times to prepare medicinal herbal tea with beneficial health properties. This review aims to discuss some key aspects related to the potential use of *S. sonchifolius* leaves and their natural biomolecules for the prophylaxis and treatment of diabetes as well as the potential mechanisms of action.

Keywords:

Smallanthus sonchifolius; yacón; diabetes; hypoglucemic effect; phenolic compounds; sesquiterpenic lactones.

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INTRODUCTION

Diabetes mellitus is a group of metabolic disorders resulting from a defect in insulin secretion, insulin action or both which causes disturbances of carbohydrates, fat and protein metabolism (ADA 2009; Patel *et al.,*2012). There are three main types of diabetes, namely type 1 diabetes (juvenile diabetes), type 2 diabetes and gestational diabetes. In type 1 diabetes, the β-cells of the pancreas do not make sufficient insulin. Type 2 diabetes is the major form of diabetes, accounting for approximately 90–95% of all diabetic cases. This form of diabetes usually begins with insulin insensitivity, a condition in which muscle, liver and fat cells do not respond to insulin properly. The pancreas eventually loses the ability to produce and secrete enough insulin in response to food intake. Gestational diabetes is caused by hormonal changes during pregnancy or by insulin insufficiency. Glucose in the blood fails to enter cells, thereby increasing the glucose level in the blood (Hui *et al*.,2009).

The long-term diabetes is associated with the occurrence of complications that reduced quality of life and increased risk factors for mortality and morbidity (Strojek 2003). Hyperglycemia is a common effect of uncontrolled diabetes and long-term is an important step in the development and progression of serious damage in different body systems, especially the nerves and blood vessels. These alterations are divided into two types.”. Micro vascular complications include eye disease, kidney disease and neural damage which are commonly named as retinopathy, nephropathy and neuropathy respectively (Forbes and Cooper, 2013). Macro vascular complications include accelerated cardiovascular disease resulting in myocardial infarction and cerebrovascular disease manifesting as strokes (Luscher and Steffel 2008; Beckman *et al.,* 2013; Paneni *et al.,* 2013). Diabetic retinopathy and cardiovascular disease are one among the leading causes of blindness and deaths, respectively. The disease is associated with reduced quality of life and increased risk factors for mortality and morbidity.

Diabetes mellitus is a common condition that affects people on both developed and developing countries. The World Health Organization estimates that almost 3 million deaths occurring annually are as a result of diabetes (WHO 2002) and is a major and growing public health problem throughout the world. Globally, 382 million people were detected with diabetes in 2013, and the number is expected to project to 592 million by 2035 (Diabetes Atlas 2014). This worldwide epidemic of diabetes has been stimulating the search for new concepts and targets for the treatment of this incurable but controllable disease.

Conventional drugs used in diabetes treatment attempt to improve insulin sensitivity, increase insulin production and / or decrease the amount of glucose in the blood. However, in addition to the possible adverse effects, the existing synthetic drugs have several limitations (Arumugam *et al*.,2013). Pharmacological treatments do not always succeed in maintaining normal blood glucose levels and avoid long-term consequences of diabetes (Prabhakar and Doble 2011). It became imperative to discover and develop newer, safer and effective antidiabetic therapeutics which will not only control diabetes but also its associated complications (Sridhar *et al.,* 2014). Therefore, it is prudent to look for options in herbal medicines for diabetes as well.

This review aims to discuss some key aspects related to the potential use one of the species of the genus *Smallanthus*, S. *sonchifolius*, and their natural biomolecules for the prophylaxis and treatment of diabetes as well as the potential mechanisms of action.

Medicinal plants with potential antidiabetic activity

Natural products are the major mine for discovering promising lead candidates, which play an important role in future drug development programs.

Medicinal plants have been an integral part of human healthcare systems for centuries. They have been used either in the form of pure phytochemicals (e.g.

taxol, artemisinin etc.) or crude extracts (single or combinations) for the treatment of various diseases. The easy availability, few side effects and low cost make herbal preparations key players from all available therapies, especially in rural areas (Arya *et al.,* 2011; Medagama and Bandara, 2014).

Through the years, several plants has been considered as a natural source of potent anti-diabetic drugs playing a key role in the management of diabetes mellitus. It is suggested that they have a promising future in diabetic prevention and treatment due to integrated effects (Singh *et al.,* 2011). Several species of herbs drugs have been described in the scientific and popular literature as having antidiabetic activity. Ethnobotanical information indicates that more than 1000 plant species are used as traditional remedies for the treatment of diabetes and these traditional medicines when verified scientifically provided a number of promising drugs for new antidiabetic agents (Alarcon-Aguilar *et al.,* 2008; Upendra Rao *et al*., 2010; Pandhare *et al*., 2012). But, further studies about efficacy, precise mechanisms of action and safety of herbal extract use need to be developed.

Several plant-derived products are used in alternative medicine for the diabetes management being their biological action related to their chemical composition. The main compounds responsible for these effects are phenolic compounds, terpenoids, flavonoids and coumarins (Upendra Rao and others 2010; Singh and others 2011). At times the observed clinical activity has also been ascribed to group of phytochemicals displaying synergy. Thus, a single antidiabetic herb with thousands of phytochemicals may have multiple benefits by targeting several metabolic pathways (Chang *et al*., 2013).

Smallanthus sonchifolius

Yacon (*Smallanthus sonchifolius* [Poepp. & Endl.] H. Robinson) is an Andean crop which belongs to the family Compositae (*Asteraceae*) (Grau and Rea 1997). Yacon and related plants were originally classified under the genus Polymnia (Asteraceae, Heliantheae, Melampodinae) (Wells 1965; Ohyama *et al*., 1990; Asami *et al.,* 1989). However Robinson in 1978 determined that many species of Polymnia genus, including the yacón, actually belongs to the genus *Smallanthus.* The new classification, *S. sonchifolius* (Poepp. & Endl.), is currently preferred while the old name *Polymnia sonchifolia* Poepp. & Endl. is considered as synonymous (Grau and Rea 1997; Valentová and Ulrichová 2003). Common names used in different parts of the Andes are yacon, llacón, aricoma, jicama and some derivatives as llaqon, llacum, llacuma, yacumpi, aricuma, chicama, jíquima and jiquimilla (Grau and Rea 1997; Seminario *et al.,* 2003).

There are records of the use of yacón centuries before the Incas (NRC, 1989). The oldest yacon representation has been found in archaeological reserve Nazca (500–1200 A.C.) (Grau and Rea, 1997).

Smallanthus sensu Robinson includes at least 21 species, all American, ranging mostly through southern Mexico, Central America to northwestern Argentina. From the Andes, yacon was transferred in the 20th century through the New Zealand to Japan (Tsukihashi *et al.,*1989). Its cultivation was successfully introduced into Italy, Germany, France and USA though yacon is still not remarkably diffused there. In 1993, it was introduced into the Czech Republic in the form of caudices originating from New Zealand (Valentová *et al.,* 2001). More recently, it has also been introduced into Russia (Tyukavin 2002). Among the South American species, some have been grouped into what is known as "yacon group" comprising 7 species with similar morphological characteristics: *S. sonchifolius; S. macroscyphus, S. connatus, S. riparius, S. suffruticosus, S. meridensis* and *S. siegesbeckius* (Grau and Rea 1997).

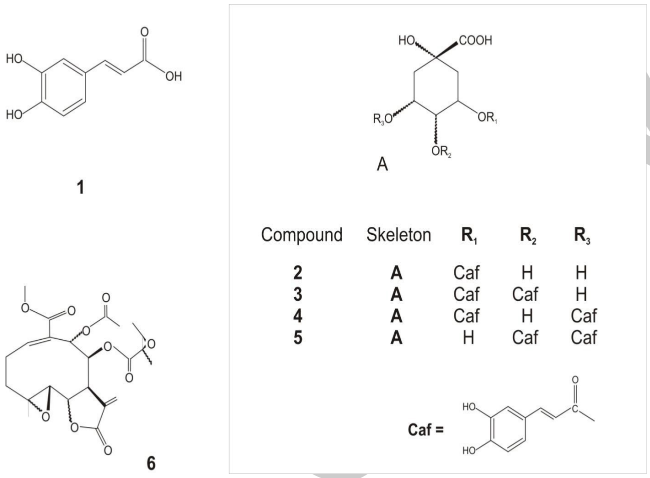
The species *S. sonchifolius;* are perennial herbs, less frequently shrubs or small trees and only rarely annuals. Yacon grows up to 1.5-3 m tall (Figure 1A, B).

Figure 1. *Smallanthus sonchifolius* [Poepp. & Endl.] H. Robinson (yacon). **A:** Plant height. **B:** Aerial parts of the yacon plant **C:** Storage roots and rhizome **D:** Leaves. E: Glandular trichomes. **F:** yacon Inflorescence. From Grau and Rea, 1997; Cabrera WM, 2013. Doctoral Thesis.

The plant is extremely hard and grows in warm, temperate Andean valleys, but can be found at the altitudes of 880 to 3500 m. In most cases, just a few plants are cultivated for family consumption (Zardini 1991; Hermann *et al.,* 1999).The plant produces large tuberous roots similar to sweet potatoes in appearance, but they have a much sweeter taste and crunchy fresh and have cylindrical and fistulous stems at maturity (Figure 1C). Yacon has large crossed opposite leaves, simple, ovate to ovate-lanceolate, apex acuminate, base truncated sagital and jagged-serrated margin (Figure 1D). Winged petiole presents overlapping stipules, often connate at the leaf base. The average size is 17 cm long x 13.7 cm lat in the middle part of the blade and 17.2 cm in the basal region.

Trichomes and glands are present in the lower and upper epidermis with a spherical morphology as a result of accumulation of secretory products when they reach the stage of maturity (Figure 1E). The trichomes are involved in the synthesis of various chemical compounds that are very important in the interactions of the plant and in adaptation to biotic and abiotic factors (Valkama *et al*., 2003; Wagner *et al.,* 2004).

Like the sunflower, the yacon presents distributed big leaves of to even along very little ramified shafts. It represents the typical inflorescence –grouping of yellow-orange flowers, 3 cm in size– in a called structure chapter (Figure 1F).



Compound	Skeleton	R_1	R_2	R_3
2	A	Caf	H	H
3	A	Caf	Caf	H
4	A	Caf	H	Caf
5	A	H	Caf	Caf

Figure 2. Major chemical constituents present in yacon leaves decoction. Caffeic acid (**1**), chlorogenic acid (**2**) and three dicaffeoylquinic acids: 3,4-dicaffeoylquinic (**3**); 3,5-dicaffeoylquinic (**4**)¸ 4,5-dicaffeoylquinic (**5**) and the sesquiterpene lactone enhydrin (**6**). *Original.*

Chemical constituents

S. sonchifolius, leaves consists of a variety of chemical compounds. The first report of yacon composition includes the isolation of four kaurenoids and four sesquiterpene lactones from the leaves (Kakuta *et al*., 1992). Other majority constituents present in yacon leaves were catechol, terpenes and flavonoids (Valentová *et al*., 2001).

Valentova *et al.,*(2003) extracted dried leaves in several ways determining two fractions (ethyl acetate and OF9 fraction) with high content of phenolic compounds. The compounds were identified as protocatechuic, chlorogenic, caffeic and ferulic (traces) acids by RP-HPLC. The presence of large amounts of phenolic compounds such as protocatechuic, rosmarinic, gallic, vanillico and gentisic, caffeic acids and their derivatives were also confirmed by HPLC coupled with electrochemical detection (HPLC-ECD) (Jirovsky *et al.,* 2003, Jandera *et al.,* 2005, Valentova *et al.,* 2005; Terada *et al.,* 2009). Ferulic acid, three isomers of dicaffeoylquinic acids (Mr = 516), an unknown derivative of chlorogenic acid (Mr = 562) and an equally unknown flavonoid were reported for the first time by Simonovska *et al.,* (2003) as constituents of yacon leaves. Recently, Genta and others (2010) have identifyed by IR spectrum, TLC and HPLC three isomeric dicaffeoylquinic acids such as 3,4-dicaffeoylquinic, 3,5-dicaffeoylquinic and 4,5-dicaffeoylquinic as the major constituents of differents yacon leaves extracts Genta *et al.,* (2010) (Figure 2).

Interestingly, ethanol extracts and decoction extracts of five landraces of *S. sonchifolius* revealed the presence of higher amount of flavonoids, as luteolin 3′,7-O-diglucoside and luteolin 7-O-glucoside together with apigenin and luteolin (Russo *et al.,* 2014).

Kakuta and others (1992) determined in the methanol extract of yacon leaves the presence of *ent*kaurenoic acid and related diterpenoid substances (*ent* -kaur-16-en-19-oic acid 15-angeloyloxy ester, 18-angeloyloxy-*ent*-kaur-16-en-19-oic acid and 15-angeloyloxy-*ent*-kauren-19-oic acid 16-epoxide. The authors suggested that these compounds probably play a certain physiological role in the defense mechanisms of this plant and it is highly pest-resistant. In the damaged leaves of yacon, Hashidoko *et al*., (1993, 1994) found 4-hydroxystyrene and 3,4-dihydroxystyrene that were probably formed by oxidative decarboxylation of *p*-coumaric and caffeic acids by enzymatic systems of epiphytic bacteria. Twelve novel diterpenoids: were found by Dou *et al.,*2008; 2010; Ragasa *et al.,*2008; Qiu *et al.,*2008; Raga *et al.,*2010; Zheng *et al.,* 2010).

Dou *et al*., (2008) determined the presence of Smallanthaditerpenic acids A, B, C and D in yacon leaves together with the presence of chlorogenic and caffeic acid. Recently, two new acyclic diterpenes derived from geranylnerol smallanthaditerpenic acids E and F were isolated by Mercado *et al.,* (2010). Significant variations in leaf phenolics content could be determined in plants cultivated in different places and collected in different times of the year (Valentová *et al.,* 2006, Xiang *et al.,* 2010).

Phytochemical studies of yacon leaves also showed the presence of several melampolide-type sesquiterpene lactones such as sonchifolin, uvedalin, enhydrin, fluctuanin (Inoue *et al*., 1995, Lin *et al.,* 2003, Schorr *et al*., 2007, Hong *et al*., 2008). These substances are also contained in other *Smallanthus* species, e.g. *S. uvedalia*, *S. fruticosus* and *S. maculatus*, as well as species from the genus *Melampodium* (Asteraceae), which has given the name to these compounds (Bohlmann *et al.,* 1980; 1984; Castro *et al.,* 1989). Six new lactones were identified recently propionate and butirate analogs of sonchifolin, tiglate analog on C8 of polymatin B, fluctuadin, polymatin C and the aldheyde derivative on C14 of uvedalin (Mercado *et al.,* 2010).

Among these lactones, enhydrin is the most abundant one isolated from yacon leaves (Schorr and Da Costa 2005). It was suggested that this compound comes presumably from intact glandular trichomes of yacon leaves, given that the sesquiterpene lactones are produced and stored in these numerous Asteraceae epidermal structures (Mercado *et al.,* 2006; Lopes *et al.,* 2013). While most of the methods concerning the quantification of sesquiterpene lactones are focused on the preparation of extracts from powdered plant material, Schorr and Da Costa (2005) evaluated the enhydrin content in diverse leaf rinse extracts as well as in foliar glandular trichomes of intact leaves. Such an approach can be used as a procedure in chemical quality control of *S. sonchifolius* or its derived preparations. GC–MS analysis of similar preparations showed 94.1% enhydrin and 5.9% uvedalin (Genta *et al.,* 2010). A wide range of essential oils such as beta-pinene, caryophylene, y-cadinene, β-phellandrene, β-cubebene, β-caryophyllene and β-bourbonene has been reported from leaves and its relative content was important for specification of yacon varieties (Adam *et al*., 2005; Li *et al*., 2009).

Antidiabetic activity

Yacon leaves have been used for centuries by the original inhabitants from the Andes valley as tradicional folk medicine to treat cronic diseases (Kakihara *et al.,* 1997). In Japan, yacon leaves are used alone or in combination with common tea leaves to prepare medicinal infusion. In a first attempt to scientifically validate its use, Volpato *et al*., (1997) suggest that yacon leaves can reduce blood glucose levels. In the past decade scientific evidence for the antidiabetic activity of the water extract of yacon leaves leaves in an experimental model of diabetes induced by STZ in rats was done (Aybar *et al*., 2001). Streptozotocin (STZ) injection in rats has been described as a good experimental model to study the effects of drugs on diabetes and some changes occurring in this state. In this model there is destruction of the β-cells of the islet of Langerhans of the pancreas (Lenzen *et al*., 2008). The results showed that the intraperitoneal administration of STZ effectively induced diabetes in normal non-fasted rats in a dose depended manner. This was reflected by glycosuria, high glycemia, polyphagia, polydypsia and body weight loss compared with normal control rats. The administration of 2% yacon tea and 10% yacón decoction for a 30 day period significantly inhibited the hyperglycemic action of STZ. Diabetic manifestations in yacon- treated rats were reduced as revealed by clinical parameters. Interestingly, lipid profile of diabetic animals was improved and the altered creatinine and albumin concentrations were normalized (Aybar *et al*., 2001; Honoré *et al*., 2012). Moreover, yacon decoction proved to have a hypoglycemic effect on healthy, transiently hyperglycemic and diabetic rats, a fact that led to suppose that a certain pancreatic activity was necessary for such an effect to occur. Yacon decoction also caused a significant decrease in the hyperglycemic peak during the glucose tolerance test which was fairly comparable to that of glymepiride.

Thereafter, similar results were reported by Baroni *et al.,* (2008) using crude extracts of yacon leaves obtained by hot or cold aqueous extraction or hydro-ethanolic preparation. Yacon leaf extracts have also shown hypoglycemic activity on KK-Ay mice, which suffer from genetically induced diabetes and in alloxan diabetic mice (Miura *et al*., 2004, Miura 2007; Raga *et al*., 2010). Furthermore, a clinical study has shown that ingestion of yacon leaf and stem powder was effective to reduce post-prandial peak of glucose in humans (Ogose *et al.,* 2006).

The bioactivity screening of five organic extracts of yacon leaves provided an effective guide for the identification of the most active hypoglycaemic compounds. The methanol, butanol and chloroform extracts were found to have an effective hypoglycemic activity at minimum doses of 50, 10 and 20 mg/kg body weight, respectively. Oral administration of a single-dose of each extract produced a slight lowering effect in the fasting blood glucose level of normal healthy rats, whereas each extract tempered significantly the hyperglycemic peak after food ingestion. Moreover, Genta and others 2010 observed that daily administration of different extracts of yacón leaves during 8 weeks produced an effective glycemic control in diabetic animals with an increase in the plasma insulin level. These results were in concordance with previous *in vitro* studies where organic fractions and aqueous extracts from *S. sonchifolius leaves* reduced glucose production via gluconeogenesis and glycogenolysis pathways in rat hepatocytes (Valentová *et al.,* 2004). The phytochemical analysis of the most active fraction the butanol extract, revealed that caffeic, chlorogenic and three dicaffeoilquinic acids were significant components (Genta *et al.,* 2010) (Figure 2). These chemical compounds have been involved as active principles in glucose metabolism regulation (Nicasio *et al.,*2005; Jung *et al.,* 2006). Thus, caffeic acid produced a marked plasma glucose-lowering effect in diabetic rats (Hsu *et al.,* 2000) while chlorogenic acid improved glucose tolerance and insulin resistance in obese (fa/fa) Zucker rats (Rodríguez de Sotillo *et al.,* 2002, Ong *et al.,* 2013).

Additionally, enhydrin, the major sesquiterpene lactone of yacon leaves (Figure 2), was found effective to reduce post-prandial glucose and useful in the treatment of diabetic animals (minimum dose: 0.8 mg/kg body weight). These results validated for the first time the antidiabetic effect of this sesquiterpene constituent (Genta *et al.,* 2010). However the hypoglycemic effect had previously been suggested together with a number of biological activities (Hwang *et al.,* 1996; Kawashima *et al.,* 2001). During the last few years, some new compounds isolated from yacon leaves were proved to be also responsible of the anti-diabetic properties in alloxan-induced diabetic mice (Raga *et al.,* 2010).

Recently Ogose *et al*., (2009) examined the inhibitory effect of a single ingestion of a test food which consisted in leaves and stem extract on postprandial blood glucose in subjects with normal blood glucose or borderline diabetes suggesting that a diet containing yacon would be useful for diabetes prevention.

Hipoglycemic and *anti-hiper glycaemic* activities

The most important goal in the management of diabetic patients is to maintain blood glucose level as close to normal as possible (Mooradian and Thurman 1999). In addition, postprandial hyperglycemia or hyperinsulinemia are independent risk factors for the development of macrovascular complications of diabetes mellitus (Kim *et al.,* 2000). There are several possibility for the mechanisms by which the plant reduces blood glucose concentration: reduction of the intestinal absorption of glucose, increase in glucose uptake by tissues and organs, increased release of insulin through stimulation of the β-pancreatic cells, resistance to the hormones that increase the rate of glucose release, increase of the number and sensitivity of the insulin receptors and decreased release glycogen degradation, among others (Negri 2005).

Aquous extracts of *S. sonchifollius* leaves administered by 30 days were found to significantly increase circulating insulin levels and decreased blood glucose level in STZ-diabetic rats (Aybar *et al*., 2001, Honoré *et al*., 2012). So, leaf phytochemical leaves compounds, responsible for its hypoglycemic activity may have the ability to increase the number of β-cells, stimulate insulin synthesis/release from pancreatic β-cells, inhibit insulin degradation or of both. Inmunohistochemical procedure showed that the amount of insulin secreting β-cells of the islets of Langerhans is greater in yacon treated-diabetic rats in comparison to control group suggesting that yacon also have the potential to protect it from STZ-induced damage in experimental animals (Honoré *et al.,* 2012) (Figure 3). Enhidryn were also found to increase the number of β-cells and insulin mRNA levels in pancreatic islets of STZ -diabetic rats (Serra Barcellona *et al.,* 2014).

In addition, an insulin-like effect of yacón leaves extracts has been reported in FAO cells, a hepatoma cell line, which not requires specific insulin supplementation of the culture medium (de Waziers and others 1995; Valentova *et al.,*2004). Using this model, Valentova *et al*., (2005) showed that differtent organic

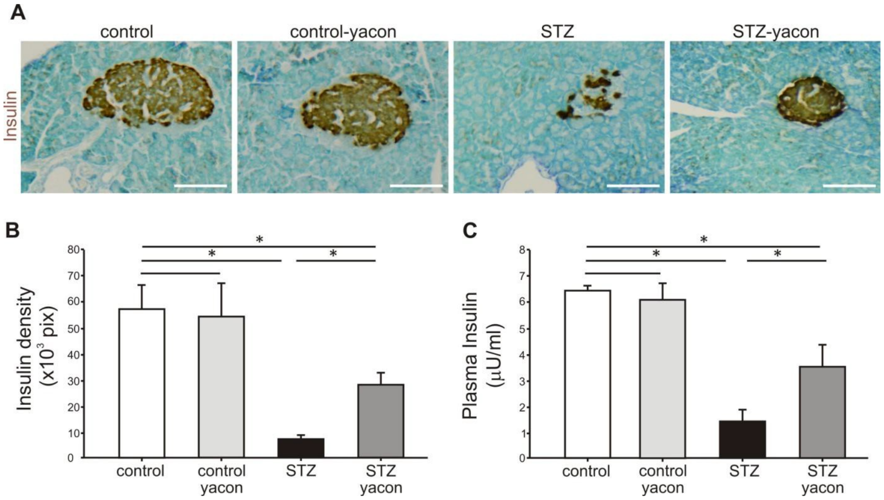


Figure 3. Effects of 10% yacon decoction on insulin. **A:** Immunofluorescence staining of insulin in the pancreas. Representative histological sections of pancreatic islets of control, yacon-control, STZ and STZ-yacon rats incubated with anti-insulin antibody. Bars: 50µm. **B:** Quantitative analysis of insulin positive area. Data expressed as means ± DE, (p<0.05, n=10). **C:** Fasting plasma insulin levels. Data expressed as means ± DE, (p<0.05, n=10). *From Honoré and others 2012. Food and Chemical Toxicology 50:1704-1715.*

extracts of *S. Sonchifollius* were able to down-regulated CYP2E and cytochrome CYP2B mRNA expression similarly to insulin.

In that sense, it has been proposed that antidiabetic effect of *S. sonchifollius* observed *in vivo* is probably due not only due to its effects on plasma insulin concentration, but also, to a specific action on hepatic metabolism. Valentova *et al*., (2005), have demonstrated that organic yacon leaf extracts were able to reduce glucose production in hepatocyte primary cultures by inhibition of gluconeogenesis and glycogenolysis pathways.

Also, Baroni *et al*., (2014) demonstrated that diabetic rats treated with yacon extracts presented a significant improvement in the glucose-6-phosphate dehydrogenase (G-6-PDH) activity. Furthermore, it was observed that yacon treatment increased the hepatic and muscle glycogen content and caused a reduction in hepatic Aspartate Aminotransferase (AST) activity in diabetic rats.

Probably these effects could be due to the presence of polyphenolics compounds as chlorogenic acid and its derivatives in yacon leaves, which, has been shown to be competitive inhibitors of glucose-6-phosphatase reducing glucose production in isolated perfused rat liver (Arion *et al*., 1997; Hemmerle *et al*., 1997).

Several reports have mentioned that many phytochemical compounds may also act as hypoglycemic by delaying the transfer of glucose from the stomach to the small intestine, the main site of glucose absorption and by inhibiting the glucose transport at the site of intestinal brush border membranes (Tiwari and Rao 2002).

In this context, Matsuura *et al.,* (2004) analyzed the inhibitory effects on the intestinal digestion and absortion of sugar of Japanese commercial health teas, including yacon. However, the authors observed no significant changes in portal plasma glucose concentration after administration of health teas during continuous intragastric infusion of sucrose.

Polyphenolics derived from aqueous extracts have been reported to inhibit *a*-amylase and sucrase, and have been shown to be the principle substance for suppressing postprandial hyperglycemia. Furthermore, these polyphenolics also inhibit glucose transport across the intestine by inhibiting sodium glucose co-transporter (S-GLUT-1) (Kobayashi *et al*., 2000). Oboh and others (2015) provided evidence that both caffeic and chlorogenic acid derivatives identified in extracts from yacon leaves inhibited *α*-amylase and *α*-glucosidase activities in a dose-dependent manner. Moreover, the esterification of caffeic acid with quinic acid, producing chlorogenic acid, reduces their ability to inhibit *α*-amylase and *a*-glucosidase activities. In a previous study another phenolic component from yacon leaves, the tricaffeoylaldaric acid, has been demonstrated to have strong antioxidant and *α*-glucosidase activity (Terada *et al*., 2009).

In vivo and *in vitro* studies in normal and diabetic rats showed that the sesquiterpenic lactone enhydrin has an inhibitory effect on *α*-glucosidase activity in a dose-dependent manner (Serra Barcellona *et al*., 2010). Also, Xiang *et al.,* (2010) observed the same inhibitory effect of smallanthaditerpenic acids A, B, C and D isolated from yacon leaves, all of which may account for the effective capacity of the leaves to attenuate intestinal glucose absorption.

Antioxidant activity

Oxidative stress has been linked to the development of most chronic diseases (Valko *et al.,* 2007; Chang and Chuang 2010). Specifically, in diabetes, it is thought to play a role in both pathogenesis and course of the disease (Baynes 1991; Chang and Chuang 2010). Diabetes creates a condition conducive for the promotion of oxidative stress, and in turn free radicals produced in excess from glucose auto-oxidation and protein glycation with a simultaneous decline of the antioxidant defense system that mediate some of the harmful effects of hyperglycemia, which manifest as complications of the disease (King and Loeken 2004, Giacco and Brownlee 2010). Much scientific evidence revealed that antioxidant defense system represents a complex network with interactions, synergy and specific tasks for a given antioxidant. So, effort to find suitable antidiabetic and antioxidant therapy are necessary.

The leaves of yacon have high content of phenolic compounds, recognized for their ability to capture free radicals. Thus, the presence of protocatechuic, chlorogenic, caffeic and ferulic acids in the two fractions extracted from *S. sonchifolius* leaves showed potent antioxidant activity in 1,1-diphenyl-2-picrylhydrazyl and xanthine/XOD superoxide radical scavenging tests, they inhibited the lipoperoxidation of rat liver subcellular membranes and they protected rat hepatocytes against oxidative injury (Valentovà *et al.,* 2003; 2004; 2005). Hot water extract of the aerial part of yacon also showed potent free radical-scavenging activity and inhibitory effects on lipid peroxidation in rat brain homogenate, being 2,3,5-tricaffeoylaltraric acid the major component in the fraction (Terada *et al*., 2006).

As was mentioned above, Baroni *et al.,* (2014) demonstrated *in vivo* that hydroethanolic extracts of *S. sonchifolius* improved the activity of G-6-PDH. Increased expression of this enzyme has been associated with increased glutathione levels and resistance to oxidative stress (Oberley 1988). Previous reports have indicated that the NADPH produced by G-6-PDH participates in the elimination of reactive oxygen species via glutathione peroxidase and catalase in both hepatic and extrahepatic tissues (Salvemini *et al*., 1999).

Preliminary studies confirmed the strong antioxidant potential of yacón leaves and the isolated compound enhydrin of in normal and diabetic rats (Serra Barcellona *et al*., 2012a).

Renal protective effect

Diabetic nephropathy is considered as the most common cause of renal damage and is the major microvascular complication in long-standing patients of both type 1 and type 2 diabetes mellitus, leading to end-stage renal disease (Schrijvers *et al*., 2004; Kanwar *et al*., 2008). Pathological changes such as expansion of mesangial cells, accumulation of extracellular matrix proteins, thickening of glomerular and tubular basement

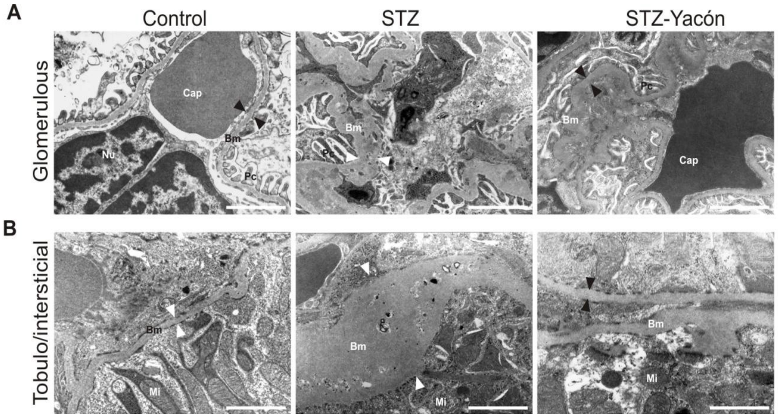


Figure 4. Effects of 10% yacon decoction on ultrastructural changes in diabetic kidney. Glomerular ultrastructure and tubulointerstitial ultrastructure of control, STZ and STZ-yacon rats. Segmental thickness of glomerular basement membrane and excessively deposited tubulointerstitial matrix were observed. Yacon decoction treatment improved STZ -induced renal ultrastructural abnormalities. Bm: Basement membrane; Pc: podocyte; Mi: mitochondria; Cap: capillary. Bars: (A) 0.8µm; (B-C) 50µm. *From Honoré and others 2012. Food and Chemical Toxicology 50:1704-1715.*

membranes, tubulointerstitial fibrosis, glomerulosclerosis and renal endothelial dysfunction occur in the diabetic kidney (Kanwar *et al*., 2008). For this reason, in the last years has intensified the search for new therapeutic agents that can prevent the onset of nephropathy or delay the progression of glomerulosclerosis.

A number of studies have now definitely proved that improved metabolic control that achieves near-normoglycemia can significantly decrease the development and progression of diabetic nephropathy and the early identification of microalbuminuria is considered to be clinically relevant (Gomes *et al*., 1997). Aybar *et al*., (2001) showed that yacon tea treatment improves the general condition of diabetic rats and tends to restore certain normal renal parameters. Honoré *et al.,* (2012) demonstrated an effective renoprotective action of 10% yacon decoction. Indeed, the treatment for 4 weeks of attenuated diabetes induced renal dysfunction by reducing mesangial matrix expansion, tubulointerstitial fibrosis and tubular atrophia in diabetic rat (Figure 4). These findings were correlated with down-regulated expression of TGF-β 1/Smad signaling, a cytokines involved in kidney fibroblast activation and proliferation (Balakumar *et al*., 2009; Liu 2011). In fact, in this study, yacon treatment down-regulated Smad2/3 phosphorylation blocking TGF-β signaling, particularly in areas where severe tubulointerstitial fibrosis had been observed. Moreover, Serra Barcelona *et al.,* (2012) showed that yacon leaves decoction had an important *in vivo* antioxidant activity in the kidney of diabetic rats, protecting cells from lipid peroxidation slowing down the progression of early diabetic nephropathy.

Other pharmacological activities

Anti microbial activity

The newly identifed compound, 8b-tigloyloxymelampolid-14-oic acid methyl ester isolated from yacon leaves, exhibited a potent antimicrobial activity against *Bacillus subtilis* and antifungal activity against *Pyricularia oryzae.* Also, fluctuanin exhibited the strongest antibacterial activity against *B. subtilis* among six identified sesquiterpene lactones present in the yacón leaves extract (Lin *et al* 2003). In addition, different aquous and organic extracts of yacon leaves have demonstrated antimicrobial activity against Methicillin-resistant *Staphylococcus aureus* (Joung *et al*., 2010). Furthermore, Choi *et al*., (2010) showed that enhydrin can be considered as an antibacterial compound against against 2 strains of Methicillin-resistant *Staphylococcus aureus* ATCC 33591, ATCC 25923.

Anti parasitary activity

In a recent work, the trypanocidal activity of the species *S. sonchifolius* has been evaluated by in vitro assays (Frank *et al*., 2013). Dichloromethane extract of the leaves induced a significant growth inhibition when tested against *Trypanosoma cruzi* epimastigotes. Through chromatographic separations of the more active fractions, the authors have isolated three structurally related germacranolide melampolide-type sesquiterpene lactones, which were identified as enhydrin, uvedalin, and polymatin B. According to the results, enhydrin and uvedalin might have potential as agents against Chagas disease and could serve as lead molecules to develop new drugs (Fabian *et al*., 2013).

Anti inflammatory activity

Two new melampolide-type sesquiterpene lactones, 8b -epoxyangeloyloxy-9a-ethoxy-14-oxo-acanthospermolide and 8b -angeloyloxy-9a-ethoxy-14-oxo-acanthospermolide, together with eleven known lactones isolated from yacon leaves shown to inhibit nitric oxide (NO) production in LPS-stimulated murine macrophage RAW 264.7 cells (Hong *et al.,* 2008). This action is interesting since, NO is involved in physiological and pathological process, such as vasodilation and chronic or acute inflammation (Hobbs *et al*., 1999).

On the other hand, yacon leaf rinse extract exhibited topical antiedematous activity *in vivo*. This activity may be a consequence of an anti-inflammatory action, as evidenced by neutrophil migration inhibition, and NO, TNF-α and PGE2 inhibition.The authors also showed that both sesquiterpene lactones and chlorogenic acid derivatives contribute to the anti-inflammatory action, suggesting that yacon leaves could have a potential use as topical anti-inflammatory agent (Oliveira *et al*., 2013)

Anti cancer activity

The sesquiterpenic lactones isolated from yacon leaves enhydrin, uvedalin and sonchifolin caused cytotoxicity to HeLa cells through induction of apoptosis (Siriwan *et al*., 2011). These authors have been demonstrated for the first time, that yacon sesquiterpenic lactones can induce apoptosis via increased activation of caspase-3/7. These finding were supported with the evidence of morphological analysis, lactate dehydrogenase release and DNA synthesis inhibition. Furthermore, sesquiterpenic lactones can inhibit the activation of NF-κB binding protein. Interestingly, enhydrin may possibly have another mechanism of high anti-cervical cancer activity because caspase-3/7 activity was lower than uvedalin and sonchifolin even though its cytotoxicity showed the greatest values. These new findings may offer information for further development of new chemotherapeutic agents or its analogs for cervical cancer therapy.

Other biological effects

Mycotoxins are probably the best known and most intensively researched in the world. Particularly, aflatoxins are toxic metabolites produced by certain fungi in/on foods and feeds and have been associated with various diseases in human beings and domestic animals (Eaton and Groopman 1994). Aqueous extract and isolated compounds from *Polymnia sonchifolia* leaves have found to inhibit *Aspergillus flavus* growth and production of aflatoxin B1 (Pinto and others 2001; Gonçalez *et al*., 2003, Fernandes *et al*., 2005; Pak *et al*., 2006). Whereby, yacon can be used as an alternative method in the chemical control of mycotoxin production.

Safety

Despite the traditional use of decoction yacon leaves, in the literature there are few studies that evaluate the toxic potential of both yacon leaves extract and pure compounds (de Oliveira *et al.,* 2011; Fernandes *et al*., 2005; Genta *et al*., 2010; Ogose *et al.,* 2009; Siriwan et al., 2011).

The degree of side effects or toxicity presented by extracts or compounds of medicinal plants depends on many complex factors. The effects of a single large dose of a toxic substance may not necessarily reflect the risks associated with the long- term low-level consumption commonly used in folk medicine. In addition, long-term studies are essential to determine a range of bioactivities to a no-observed-adverse-effect level (NOAEL) (Serra Barcellona and others, 2012b; Alexeeff *et al.,*2002).

The safety of yacón consumption was evaluated at first time in an acute toxicity test. Normal healthy rats treated with 2, 5, 10 times greater than the effective dose of different organic extract of yacón leaves or isolated compund enhydrin, evidenced no deaths or noticeable signs of acute toxicity. (Genta *et al.,* 2010; 2012). Moreover, Ogose *et al.,* (2009) judged that the administration of yacon extracts to rats for two generations had no effects on either the reproductive functions or the development of the liveborn pups.

A recent acute toxicity experiment tested a specific range of doses of the 10% yacon leaves decoction (25, 50 and 100 times) and enhydrin (100, 200 and 400 times) for the effective hypoglycaemic dose. Up to 14 days of administration no signs of toxicity or deaths were recorded suggesting that the LD50 of the 10% decoction and of enhydrin would be above 14.0 and 0.32 g/kg bw, respectively (Serra Barcellona *et al*., 2012b). These values were significantly higher than the effective hypoglycaemic doses (Aybar *et al.,* 2001; Honoré *et al.,* 2012). Also 10% decoction orally administered were found non toxic, at least up to the maximum level assayed (0.28 g/kg bw/day). Similarly, isolated enhydrin had no toxic effects at a dose range of 0.4 to 8.0 mg/kg bw/day (Serra Barcellona and others 2012b).

The beneficial effects associated with the consumption of organic or aqueous extracts of yacon leaves for long periods might suggest that they have a high safety margin (Valentova *et al,* 2003, 2005; Genta *et al*., 2010; Honoré *et al.,* 2012; Serra Barcellona *et al.,* 2012b). However, de Oliveira *et al.,* (2011) showed that prolonged oral administration (90 days) of 2% of yacon leaves infusion and a leaf rinse extract was associated with kidney damage and attributed it to the presence of sesquiterpene lactones and flavonoids as 3-*O*-methylquercetyn in the extract. Such differences could be related to the the differences in the phytochemical preparations analyzed by both groups. Moreover, it is well known that chemical composition of yacon leaves could present significant differences among the studied landraces and different times of the year collection (Russo *et al*., 2010; Xiang *et al*., 2010).

In vitro cytotoxicity assays were performed with a selection of different cell lines based in the main target organs. Cytotoxicity study based in metabolic competence assay, showed a concentration-dependent decrease in mitochondrial function and consequently in cell viability. COS1 cells were the most resistant to the treatment with both 10% yacon decoction or enhydrin and the normal epithelial Vero cells showed intermediate values of IC50, very similar to epithelial-like CHO-K1 cell line, evidencing the different response to potential adverse or toxic effects of the extracts or pure compound under investigation (Serra Barcellona *et al.,* 2012b). However it is interesting to mention that *in vivo* toxicity studies unlike the *in vitro* assays, the effects of an oral dose are subject to systemic bioavailability and hepatic metabolism, pharmacokinetic processes that are absent in a cell culture model (Singh, 2006).

Conclusion

S. sonchifollius, popularly known as *yacón,* is the species among all Andean food plants which is that is the most likely to attract worldwide attention in the near future because of its wide range of uses.

Different aqueous and organic extracts or even isolated biomolecules from yacon leaves have been tested for their antidiabetic properties using both *in vivo* and *in vitro* approaches and were reviewed here. Some of these compounds show promising effects, indicating that dietary intake of phytochemicals present in yacon leaves could be a promising strategy for the management of diabetes.

The combination of radical scavenging, cytoprotective and antihyperglycemic activity makes *S. sonchifollius* leaves a good candidate for preventing or treating chronic disease involving oxidative stress. Additionally, toxicity studies of *S. sonchifollius* extract and isolated compounds have demonstrated their safety when taken in recommended doses.

Therapies based on yacon phytochemicals could constitute a novel pharmacological approach that would reinforce existing treatments.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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