Original
Hypoglycemic effect of *Lupinus mutabilis* in healthy volunteers and subjects with dysglycemia

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**Abstract**

Metabolic syndrome and type-2 diabetes are increasing health problems that negatively affect health care systems worldwide. There is a constant urge to develop new therapies with better effects, lower side effects at lower prices to treat these diseases. *Lupinus* species and their derivates are good candidates to be used as hypoglycaemic agents. A phase II clinical trial was conducted to assess the role of raw *Lupinus mutabilis* on blood glucose and insulin in normoglycemic and dysglycemic subjects. Results show that consumption of *L. mutabilis* by normal weight healthy young individuals did not change importantly blood glucose and insulin levels. On the other hand, consumption of similar doses of *lupinus* by dysglycemic individuals (fasting glucose > 100 mg/dL) decreased significantly blood glucose. *Lupinus* effects were greater in those subjects with higher basal glucose levels. Glucose lowering effects of *lupinus* were not observed after soy intake that was used as control. A statistically significant reduction in insulin levels was also observed in the *lupinus* group compared with the soy group after 60 minutes of treatment. Furthermore, only treatment with *lupinus* improved insulin resistance in dysglycemic subjects. These data demonstrate that *lupinus* consumption could be a feasible and low cost alternative to treat chronic hyperglycemic diseases.


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Key words: Lupinus mutabilis. Hypoglycemia. Diabetes. Ecuador. Alkaloids.
Introduction

Type-2 diabetes is a highly prevalent disease around the world. It was reported that 135 million people were affected in 2005 and it has been estimated that approximately 217 million will be affected with the disease by 2030.1 Unfortunately, most of the new cases are expected to come from developing countries.2 For instance, diabetes was the first cause of death in Ecuador in 2009.3 Treatment of diabetes is expensive, for the year 2000 the total cost to treat the disease was $132 billion. Considering the limited resources dedicated for heath care in developing countries most people will not be able to afford current treatments. It is estimated that approximately 30% of hospital bed-days in Latin America are used for diabetes related conditions whose cost are an important burden for health care.4 Although there are several drugs that improve the hyperglycaemic state characteristic of the disease, there is a constant urge to develop new therapies with higher efficacy, lower side effects at lower prices to treat diabetes.5

Lupinus mutabilis a sweet fabaceae is an endemic legume species of South America. In the Andean region L. mutabilis beans are known as “chochos”, “tarwi” or Andean lupin; in Spain the beans are called “altramuz”. The beans are a traditional food in Ecuador, Perú and Bolivia. Lupinus mutabilis is rich in quinolizidine alkaloids and require cooking and removal of these alkaloids before consumption. The alkaloid fraction from L. mutabilis has more than 20 different quinolizidine alkaloids and lupanine, 13-hydroxylupanine, 4-hydroxylupanine, sparteine and tetrahydrorhombifoline are the most abundant.6

Proteins and alkaloids from lupin are good candidates to be used as hypoglycaemic agents.6,7 Administration of conglutin-γ, a lupin seed protein, to rats subjected to glucose overload produces a significant reduction of plasma glucose with respect to control.6 In vitro studies demonstrate that quinolizidine alkaloids from lupinus have secretagogue effects in pancreatic isolated rat islets. Also, studies in vivo in streptozotocin-induced diabetic rats demonstrated that 2-thionospartine a quinolizidine alkaloid from lupinus lowered plasma glucose concentrations.8 Furthermore, the intravenous administration of the alkaloid sparteine to non-insulin dependent diabetic subjects decreased plasma glucose concentrations and increased insulin concentrations.8 Taken together these data demonstrate that alkaloids from lupinus could be used as hypoglycaemic agents to treat type-2 diabetes.

One of the main problems with the use of alkaloids from lupinus spp is their toxicity. The main side effects after a toxic dose of alkaloid consumptions are neurologic such as loss of motor coordination and muscle control. The lethal dose of lupinus spp alkaloids in humans is approximately 30 mg/kg of body weight.10 There are limited data regarding the toxic dose of these alkaloids in humans. However, in the study by Paolisso et al., described above the authors used a dose of 240 mg of sparteine sulphate in moderately overweight individuals without apparent acute toxicity.10 The therapeutic dose for sparteine sulfate ranges from 75 to 600 mg/day.11 Secondary data indicate that toxic doses of quinolizidinic alkaloids for human adults start at 25 mg/kg of body weight.12 Considering the hypoglycaemic effects of lupinus from alkaloids as well as their potential toxicity shown in previous work, the objective of the present study was to evaluate the effect of raw Lupinus mutabilis consumption on plasma glucose and insulin concentrations in healthy volunteers as well as in dysglycemic individuals.

Subjects and methods

The Human Subjects Protection Committee at the Universidad San Francisco de Quito, Quito Ecuador, approved this study. Each participant signed an Informed Consent form after receiving explanation of the study and its possible consequences.

Subjects and study design

A phase II clinical trial was conducted in two different populations. Young healthy normal weight individuals constituted the first group (group-one). Most participants in group-one were third year medical students. The second group was formed by volunteers with a glucose level at initial screening greater than 100 mg/dL (group-two). Most of the volunteers in group-two were either first-degree relatives of patients with type-2 diabetes or overweight/obese subjects. Most participants in group-two were recruited at the Endocrinology Unit in a health care center (Unidad Municipal de Salud del Norte). Within each of the indicated populations a control group that received raw soy was conformed for comparison. Eligible subjects were randomly assigned to the groups in a proportion of three (lupinus) to one (soy).

Source of Lupinus mutabilis and Soy

Lupinus mutabilis is the most abundant variety of lupinus and a popular legume consumed in Ecuador. Lupinus mutabilis line 450 was harvested between September and October of 2007 from Cotopaxi, which is an Andean province of Ecuador.13 The L. mutabilis was hand harvested when the beans had approximately 17% of humidity. Beans were then dried over a cement platform for approximately 48 hours until the beans were 13% water. The dried beans were then placed in sacs and stored in dry environment at room temperature 17-20º C. After milling to a 300 micron powder
L. mutabilis was encapsulated in gelatin capsules by CC-laboratories. No fillers or binders were added to the lupinus powder. Dry soybeans were purchased in a local supermarket and were processed in a similar fashion than L. mutabilis beans.

**Dose of Lupinus mutabilis**

Raw L. mutabilis or soy was administered in gelatin capsules containing 400 mg of lupine powder seeds or milled soy. Capsules were identical in appearance and were kindly prepared by (CC-Laboratorios, Quito-Ecuador). Similar amounts of L. mutabilis or soy per kilogram of body weight were administered to volunteers. To estimate the dose of L. mutabilis, the therapeutic (75 to 600 mg/day) and the toxic (25 mg/kg) doses of alkaloids present in L. mutabilis were considered.\(^{11,10}\) Thus, it was estimated that 3.1 mg/kg of body weight was safe to carry out the trial. The amount of grain containing 3.125 mg of alkaloid was 98.4 mg.

The amount of alkaloid present in raw L. mutabilis was measured as previously described and is indicated in table I.\(^{13}\)

**Anthropometric measurements**

A standardized clinic weight scale was used to determine both height and weight of each participant. Weight and height were taken with light clothing on, but shoes off.\(^{14}\)

**Glucose, insulin and homeostasis model assessment-estimated insulin resistance (HOMA) determinations**

Serum glucose was measured using a glucose oxidase method (Roche-Diagnostics) using a Hitachi Roche-917 full-automated analyzer system. Serum insulin was determined using an electrochemiluminescent immunoassay (ECLIA) following the manufacturer’s instructions (Roche/Hitachi, Quito-Ecuador) and chemiluminescent emission was measured using a fully automated analyzer system ELECSYS 2010 (Roche Diagnostics, Quito-Ecuador).

Both glucose and insulin determinations were carried out in NetLab Laboratory. NetLab maintains an internal and external quality control system (College of American Pathologists, Brazilian Society of Clinical Pathologists, SBOC).

The HOMA 2 values were calculated using a modified formula of Wallace et al, fasting plasma glucose (mg/dL) multiplied by fasting serum insulin (mU/ml) and divided by 405.\(^{15}\) The same calculation was done using serum glucose and insulin at 60 and 90 minutes after lupinus or soy intake.

**Blood samples**

Qualified personnel took blood samples in the morning between 8 am and 10 am after 12 hours of fasting. Samples were centrifuged within 2 hours and processed immediately. Two additional samples were collected at 60 and 90 minutes after treatments. Hypoglycemic effects of lupine alkaloids have been observed within two hours of alkaloid administration.\(^9\)

**Treatments**

Based on the reported toxic doses of L mutabilis alkaloids (25 mg/kg) a dose of 3.1 mg/kg of body weight was considered safe and consequently was used in this study. Control group received soy in an amount that matched L mutabilis intake.

**Statistics**

Descriptive statistics such as means and standard deviation and percentages were calculated. Due to the nature of the data non-parametric statistics were used. Kruskal Wallis was used to test statistical significance for difference between groups. Paired Wilcoxon Signed Ranks Test was used to test for differences within treatment groups.

**Results**

**Demographics and general characteristics of volunteers**

Data indicate that there were not statistically significant differences within normoglycemic and dysglycemic groups in the demographic/anthropometric variables. However, there were statistically significant

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**Table I  Alkaloid content of Lupinus mutabilis**

<table>
<thead>
<tr>
<th>Type of sample</th>
<th>Alkaloid content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raw grain with skin</td>
<td>3.26 ± 0.135</td>
</tr>
<tr>
<td>Cooked grain with skin</td>
<td>0.75 ± 0.02</td>
</tr>
<tr>
<td>Cooked grain without skin</td>
<td>0.3034 ± 0.008</td>
</tr>
<tr>
<td>Water used to cook raw grain</td>
<td>2.09 (% V/V**)</td>
</tr>
</tbody>
</table>

*W/W: Weight/weight.
** V/V: Volume/volume.
differences between normoglycemic and dysglycemic individuals in all the variables indicated in table II.

**Effect of lupinus mutabilis on blood glucose and insulin in healthy volunteers**

Twenty-one healthy volunteers were randomly assigned to consume lupinus (N = 16) or soy (N = 5). Subjects were admitted at Hospital de los Valles after an overnight fasting. After a short interview and anthropometric measurements, a blood sample was drawn from volunteers. Subsequently, a calculated dose (refer to subjects and methods) of *L mutabilis* or soy was administered to each participant. After treatments two blood samples at 60 and 90 minutes were obtained. Blood was processed as indicated before and serum glucose and insulin were measured. Table III shows the mean concentrations of these parameters before and after treatment with *L mutabilis* or soy. Data in table III indicates that consumption of *L mutabilis* or soy did not induced statistical significant changes in blood glucose and insulin after 60 and 90 minutes neither within nor between treatment groups of healthy volunteers.

Subsequently, the potential hypoglycemic effects of *L mutabilis* were evaluated in volunteers with increased concentrations of fasting glucose that were not receiving any hypoglycemic treatment.

**Effect of Lupinus mutabilis on blood glucose and insulin in dysglycemic volunteers**

Volunteers for this phase of the study were first-degree relatives of patients with type-2 diabetes or overweight/obese subjects without a previous diagnosis of diabetes. Most participants in this group were recruited in an outpatient endocrinology unit. Twenty-four volunteers were randomly allocated to consume *L mutabilis* (N = 17) or soy (N = 7) and were treated similarly than the healthy volunteer group that was normoglycemic described above.

Comparisons within groups indicate that consumption of *L mutabilis* decreased blood glucose concentrations after 60 minutes of ingestion but the decrease was not statistically significant table IV. However, *L mutabilis* ingestion produced a statistical significant decrease of serum insulin after 90 minutes of treatment. No other statistical significant changes were observed after *L mutabilis* treatment. On the other hand soy intake did not cause statistical significant changes in either glucose or insulin during the study table IV.

A close analysis of the data indicated that the greatest variability in glucose and insulin concentrations was observed in individuals that consumed *L mutabilis* and whose basal glucose concentration was greater than 100 mg/dL. The statistical analysis of the variations in blood glucose and insulin in subjects with basal glucose greater than 100 mg/dL is shown in table V.

### Table II

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Demographics compared by group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age (years)</td>
</tr>
<tr>
<td>Normoglycemic</td>
<td></td>
</tr>
<tr>
<td><em>L mutabilis</em></td>
<td>21.8 ± 2.6</td>
</tr>
<tr>
<td>Soy</td>
<td>23.8 ± 0.8</td>
</tr>
<tr>
<td>Dysglycemic</td>
<td></td>
</tr>
<tr>
<td><em>L mutabilis</em></td>
<td>55.8 ± 12.0</td>
</tr>
<tr>
<td>Soy</td>
<td>58.4 ± 4.9</td>
</tr>
</tbody>
</table>

### Table III

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Glucose</th>
<th>Glucose</th>
<th>Glucose</th>
<th>P-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 min</td>
<td>60 min</td>
<td>90 min</td>
<td>0 vs. 60 min</td>
<td>0 vs. 90 min</td>
</tr>
<tr>
<td></td>
<td>μ ± SD (mg/dL)</td>
<td>μ ± SD (mg/dL)</td>
<td>μ ± SD (mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Lupinus (N = 16)</em></td>
<td>82.8 ± 6.2</td>
<td>81.3 ± 6.6</td>
<td>80.3 ± 5.2</td>
<td>0.36</td>
<td>0.08</td>
</tr>
<tr>
<td>Soy (N = 5)</td>
<td>83.4 ± 5.8</td>
<td>80.0 ± 9.3</td>
<td>81.4 ± 9.7</td>
<td>0.35</td>
<td>0.89</td>
</tr>
<tr>
<td><em>Insulin</em></td>
<td>0 min</td>
<td>60 min</td>
<td>90 min</td>
<td>P-value</td>
<td>P-value</td>
</tr>
<tr>
<td></td>
<td>μU ± SD (mg/dL)</td>
<td>μU ± SD (mg/dL)</td>
<td>μU ± SD (mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Lupinus (N = 16)</em></td>
<td>7.3 ± 3.7</td>
<td>7.8 ± 3.6</td>
<td>6.5 ± 4</td>
<td>0.44</td>
<td>0.37</td>
</tr>
<tr>
<td>Soy (N = 5)</td>
<td>10.4 ± 9.7</td>
<td>10.5 ± 9.6</td>
<td>6.8 ± 6.8</td>
<td>1.00</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Volunteers for this phase of the study were first-degree relatives of patients with type-2 diabetes or overweight/obese subjects without a previous diagnosis of diabetes. Most participants in this group were recruited in an outpatient endocrinology unit. Twenty-four volunteers were randomly allocated to consume *L mutabilis* (N = 17) or soy (N = 7) and were treated similarly than the healthy volunteer group that was normoglycemic described above.

Comparisons within groups indicate that consumption of *L mutabilis* decreased blood glucose concentrations after 60 minutes of ingestion but the decrease was not statistically significant table IV. However, *L mutabilis* ingestion produced a statistical significant decrease of serum insulin after 90 minutes of treatment. No other statistical significant changes were observed after *L mutabilis* treatment. On the other hand soy intake did not cause statistical significant changes in either glucose or insulin during the study table IV.

A close analysis of the data indicated that the greatest variability in glucose and insulin concentrations was observed in individuals that consumed *L mutabilis* and whose basal glucose concentration was greater than 100 mg/dL. The statistical analysis of the variations in blood glucose and insulin in subjects with basal glucose greater than 100 mg/dL is shown in table V.
Table IV
Comparison of blood glucose and insulin concentrations in dysglycemic volunteers treated with lupinus mutabilis or soy

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Glucose 0 min μ ± DE (mg/dL)</th>
<th>Glucose 60 min μ ± DE (mg/dL)</th>
<th>Glucose 90 min μ ± DE (mg/dL)</th>
<th>P-value 0 vs. 60 min</th>
<th>P-value 0 vs. 90 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lupinus (N = 17)</td>
<td>107.5 ± 14.4</td>
<td>103.4 ± 7.2</td>
<td>105.3 ± 6.8</td>
<td>0.08</td>
<td>0.51</td>
</tr>
<tr>
<td>Soy (N = 7)</td>
<td>102.3 ± 6.4</td>
<td>100.6 ± 4.8</td>
<td>102.9 ± 7.0</td>
<td>0.35</td>
<td>0.92</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Insulin 0 min μU ± DE (mg/dL)</th>
<th>Insulin 60 min μU ± DE (mg/dL)</th>
<th>Insulin 90 min μU ± DE (mg/dL)</th>
<th>P-value 0 vs. 60 min</th>
<th>P-value 0 vs. 90 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lupinus (N = 17)</td>
<td>13.3 ± 16.0</td>
<td>9.9 ± 8.4</td>
<td>9.3 ± 7.7</td>
<td>0.12</td>
<td>0.00</td>
</tr>
<tr>
<td>Soy (N = 7)</td>
<td>15.7 ± 8.9</td>
<td>18.4 ± 9.2</td>
<td>11.7 ± 7.0</td>
<td>0.06</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Table V shows that in subjects with basal glucose ≥ 100 mg/dL that consumed L mutabilis had statistically significant lower concentrations of glucose after 60 and 90 minutes after treatment. In addition, insulin concentrations were also significantly lower than basal levels after 90 minutes of L mutabilis intake. On the other hand, consumption of soy did not result in significant changes in either, glucose or insulin levels over the study time figure 1 panels C and D.

Differences between treatment groups

Comparison between treatment groups that consumed L mutabilis with those that consumed soy showed that there were not statistically significant differences in the levels of blood glucose before and after treatments. However, it is notorious that in severe dysglycemic individuals that consumed L mutabilis there were statistically significant decreases in glucose levels which lasted up to 90 minutes figure 1 panel A whereas in the group that consumed soy there were not statistically significant decreases in blood glucose figure 1 panel C.

Regarding insulin concentrations, data show that after 60 minutes of treatments there was a statistically significant decrease in insulin concentration in the L mutabilis compared with the soy group (p = 0.039), figure 1 panels B vs. D. Panels B and D also show that in volunteers with dysglycemia, insulin concentrations decreased with L mutabilis consumption whereas insulin concentration in the soy group increased. Furthermore, there was a progressive inhibitory effect of L mutabilis in serum insulin that was dependent on basal glucose concentrations. The higher the basal blood glucose the greater the L mutabilis inhibitory effect on insulin level at 60 and 90 minutes post treatment figure 1 panels B vs. D.

In order to assess changes in insulin resistance in treatment groups the Homeostatic model assessment (HOMA) was calculated. HOMA indicates the degree of insulin resistance (IR) based on the levels of fasting glucose and insulin. It is well known that only fasting glucose and insulin concentrations are used to estimate HOMA. However, in order to evaluate the potential effect of L mutabilis consumption on insulin resistance the HOMA-IR was also calculated at 60 and 90 minutes.
minutes after treatments. Values of HOMA-IR greater than 2.5 are abnormal and indicate glucose intolerance or type-2 diabetes. Data indicate that in subjects with normoglycemia the HOMA values were main-
tained in the normal range after *L mutabilis* or soy consumption, figure 2 panels A and C. On the other hand, in individuals with dysglycemia that consumed *L mutabilis* there was a decrease in HOMA-IR 60 and 90 min after its intake figure 2 panel B. In the group with dysglycemia that consume *L mutabilis* the mean value of HOMA-IR went from a frank abnormal basal value to normal values at 60 and 90 minutes of treatment figure 2 panel D. Furthermore, subjects with dysglycemia that consumed soy showed initially an increase after 60 minutes and subsequently a decrease after 90 minutes in HOMA-IR values figure 2 panel D. In this last group, HOMA-IR was always maintained in the abnormal range. Some patients that received *L mutabilis* experienced dizziness, hypotension and blurred vision. Ten out of 33 subjects that consumed *L mutabilis* reported transitory dizziness, 2 were part of group with normoglycemia and 8 were subjects from the group with dysglycemia. None of the volunteers that consumed soy reported any side effects. Two of the individuals with dysglycemia that reported dizziness also had hypotension and one of them had also blurred vision.

### Discussion

Present data show that consumption of *L mutabilis* by normal weight healthy young individuals did not significantly change blood glucose and insulin levels. However, consumption of similar doses of *L mutabilis* by individuals with dysglycemia (fasting glucose > 100 mg/dL) decreased significantly blood glucose and insulin levels. *L mutabilis* effect was greater in those subjects with higher basal glucose levels. Glucose lowering effects of *L mutabilis* were not observed in a control group receiving soy. In addition, a statistically significant reduction in insulin levels was observed in the *L mutabilis* group compared with the soy group after 60 minutes of treatment. Furthermore, only treatment with *L mutabilis* improved insulin resistance in subjects with dysglycemia whereas soy treatment did not. These data demonstrate that *L mutabilis* consumption has important metabolic effects. Previous *in vitro* and *in vivo* work indicates that conglutin-γ and alkaloids from *lupinus spp* cause important metabolic effects, which are in agreement...
with the present report. Conglutin-γ, a protein from lupinus has shown specific binding to insulin and hypoglycaemic effects in rats subjected to glucose overload. The mechanisms of action of this protein for its hypoglycaemic effects have not been determined. Garcia Lopez et al., reported that quinolizidinic alkaloids from lupinus spp induced insulin release from cultured pancreatic islets from normal rats. This secretagogue effect was greater in islets cultured with high glucose concentrations than in islets cultured with low glucose. However, some alkaloids, like 2-thionosparteine, induced insulin secretion even in those islets cultured in medium with low glucose. On the other hand, alkaloids such as lupanine, the most abundant alkaloid in L mutabilis, only induced insulin release by the islets that were cultured in high glucose concentrations. In the present study, raw L mutabilis, with its entire alkaloid content decreased blood glucose levels only in individuals with high levels of glucose. This observation was evident in a volunteer with fasting glucose of 143 mg/dL whose glucose dropped to 112 mg/dL after 90 min of lupinus consumption. This represents a decrease of 22% in blood glucose.

In an in vivo model of diabetes induced by streptozotocin the intra-peritoneal injection of quinolizidine alkaloids provoked a decrease in blood glucose concentrations. In that study not all alkaloids showed the same hypoglycemic effects. Thus, in diabetic animals treated only with lupanine there was not a decrease in blood glucose while in those animals treated with 2-thionosparteine there was a significant decrease in blood glucose at 90 and 120 min after alka-loid administration. This decrease in blood glucose was similar to the observed after treatment with gliben- clamide, a commonly drug used to decrease blood glucose. However, administration of quinolizidine alkaloids to non-diabetic rats did not change blood glucose concentrations. Regarding insulin, only administration 2-thinosparteine significantly increased plasma insulin levels in non-diabetic animals. In that study alkaloid treatment increased blood insulin levels although the increase was not statistically significant.

Clinical studies in healthy volunteers or with individu-als with type-2 diabetes have shown that intravenous administration of lupinus spp alkaloids decrease blood glucose and increase insulin. Thus, administration of sparteine sulphate (240 mg i.v.) decreased blood glucose after 20 minutes of infusion to normal subjects. Glucose decrease was accompanied with an increment of serum insulin that also occurred 20 minutes after infusion. These results do not agree with the animal model of diabetes discussed previously where after alkaloid administration there were no changes in either glucose or insulin levels in animals that did not develop diabetes. Present results also indicate that oral administra- tion of raw L mutabilis did not affect significantly glucose or insulin levels in normal healthy volunteers. The limited changes observed in blood glucose and insulin could be due to the fact that participating volunteers were young healthy individuals. In normal
subjects blood glucose concentrations are finely regulated. Close regulation of blood glucose maintains a physiologic constant range of glucose between 70 and 100 mg/dL.

On the other hand, Paolisso G. et al, have reported that intravenous administration of sparteine sulphate (240 mg i.v.) to subjects with type-2 diabetes decreased blood glucose and increased insulin. In that study, changes in glucose and insulin were evident after 40 minutes of intravenous alkaloid infusion. In the present study, there was also a decrease in blood glucose in volunteers with dysglycemia after 60 minutes of lupinus consumption. Regarding insulin, in contrast to the observations of Paolisso G. et al, in the present study there was not an increase in insulin levels; on the contrary there was a statistical significant decrease of the hormone after 90 minutes of treatment. A potential explanation of these differences could be the fact that in the present study insulin was measured only at two time points 60 and 90 minutes after Lupinus mutabilis intake while Paolisso et al measured insulin every 10 minutes during one hour. This allowed them to measure the putative peak of insulin after the release from the pancreatic β-cell. In addition, the type of treatments used in the present and the indicated studies could explain the different results on the levels of insulin. In the indicated studies with normal individuals as well as with patients with type-2 diabetes, purified Lupinus spp alkaloids were used intravenously while in the present study raw Lupinus mutabilis beans were orally administered. Purified alkaloids and raw Lupinus could have a distinct pharmacokinetics. Raw Lupinus beans contain several alkaloids and micro and macronutrients that could modulate: a. the secretagogue activity of alkaloids; b. the potential effect on insulin receptor; and c. insulin half-life. Insulin is metabolized in the liver after its release from the pancreas in a relative short time, approximately 3.5 minutes. Insulin that reaches the periphery, muscle and adipose tissue, after engaging its receptor is internalized by the cells and subsequently degraded. During this process target cells are stimulated to allow glucose uptake through glucose transporter GLUT-4. Both events insulin uptake and glucose transport inside the cells could explain present observations of glucose and insulin decrease after Lupinus mutabilis consumption. In addition, the improvement in HOMA-IR observed in subjects with dysglycemia that consumed Lupinus could also be the result of a decrease in blood glucose and insulin levels. Future pharmacokinetics studies on Lupinus mutabilis and its components such as proteins and alkaloids, could clarify their effect on pancreatic β-cells as well as insulin target cells.

There were no severe side effects after raw Lupinus mutabilis consumption both in normal or volunteers with dysglycemia. However, some individuals with dysglycemia that consumed Lupinus showed transient dizziness, hypotension and blurred vision. These side effects have been reported in individuals with polymorphism for the enzyme “debrisoquin hydroxylase” that is responsible of the alkaloid sparteine metabolism. Regardless the capacities to metabolize lupinus alkaloids, 75% of these are excreted unchanged in the urine within hours of consumption. Raw Lupinus consumption without medical supervision must be discouraged to avoid potential toxicity and undesirable side effects.

Further studies are needed to determine if lower doses of raw Lupinus mutabilis decrease blood glucose and insulin. At the moment, there is evidence that the effect lasts at least 90 minutes which was the longest time measured in the present study. In addition studies that compare the effect of raw Lupinus with the putative effect of isolated proteins and alkaloids are also needed.

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