

# Study of the Effect of *Panax Ginseng* versus Gliclazide on Hyperglycaemia Induced by Dexamethasone in Experimental Animals

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## دراسة تأثير نبات باناكس جنسنج ومقارنته بدواء الجليكلازيد في تخفيف مستوى سكر الدم المحفز بواسطة الديكساميثازون في حيوانات التجارب

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**الملخص:** الهدف: دراسة تخفيف مستوى سكر الدم العالي الناجم عن الديكساميثازون باستعمال نبات باناكس جنسنج ومقارنتها بدواء الجليكلازيد في حيوانات التجارب. الطريقة: تم هذه الدراسة في قسم علم الأدوية بجامعة العلوم والتكنولوجيا في صنعاء (اليمن). تم تقسيم 24 أرنبًا إلى أربع مجموعات. أعطى دواء الديكساميثازون بجرعة فموية مقدارها 10 ملجم/كجم لمدة 14 يوماً لتحفيز ارتفاع السكر في ثلاث مجموعات بينما بقيت المجموعة الرابعة كمجموعة ضابطة. تم معالجة مجموعتين منها بنبات الجنسنج بجرعة 200 ملجم/كجم. ودواء الجليكلازيد بجرعة 80 ملجم/كجم لمدة أسبوعين. النتائج: أظهرت الدراسة أن نبات باناكس جنسنج أعطى نتائج ذات دلالة إحصائية معندة في تخفيف مستوى سكر الدم بعد إعطاء ديكساميثازون بجرعة 10 ملجم / كجم (من  $215.33 \pm 27.67$  ملجم / 100 مل ) إلى ( $21.18 \pm 154.17$  ملجم / 100 مل) . كذلك عمل نبات جنسنج على تخفيف الوزن بشكل معندي إحصائيا. الخلاصة: هناك فرق ذو دلالة إحصائية معندة بين نبات باناكس جنسنج ودواء الجليكلازيد في تخفيف سكر الدم والوزن . من هذه النتائج يمكن استخلاص أن نبات الجنسنج يمكن أن يستخدم من قبل مرضى السكري الذين يعانون من السمنة أو الذين يعانون من مقاومة الأنسولين . حيث يقل الوزن ويتحسن العمل في مستلمات الأنسولين .

**مفتاح الكلمات:** نبات باناكس جنسنج . جليكلازيد . زيادة سكر الدم . ديكساميثازون.

**ABSTRACT Objectives:** To study the effect of panax ginseng versus gliclazide on hyperglycaemia induced by dexamethasone in experimental animals. **Methods:** The current study was conducted in the Department of Pharmacology, University of Science & Technology, Sana'a, Yemen. Twenty-four rabbits were divided to 4 groups. Three of them were administered oral doses of dexamethasone (10 mg/kg) for 14 days, one group was kept as a control. Ginseng at dose (200 mg/kg) and gliclazide (80 mg/kg) were administered to rabbits with dexamethasone-induced hyperglycaemia. **Results:** The effects of ginseng and gliclazide on fasting blood sugar (FBS) and body weight after continuous administration of dexamethasone (10 mg/kg) were measured. Oral administration of ginseng (200mg/kg) for 2 weeks produced significant ( $p < 0.05$ ) reduction in FBS from  $215.33 \pm 27.67$  mg/dl in the dexamethasone group to  $154.17 \pm 21.18$  mg/dl in the ginseng treated group. In addition, ginseng produced significant ( $p < 0.05$ ) reduction in body weight. **Conclusion:** There was a significant difference between ginseng and gliclazide in reduction of FBS and body weight. From these results, it is suggested that ginseng could be used in obese diabetic patients or those suffering from insulin resistance as it reduces body weight.

**Key words:** Panax ginseng; Gliclazide; Hyperglycaemia; Dexamethasone.

### Advances in Knowledge

- Unlike other studies, this study focused on the comparison between herbal and chemical medicines in regard to their efficacy and safety for treatment of chronic diseases like diabetes.
- This study supports the efficacy of panax ginseng as a potent antidiabetic agent, which also produces reduction in body weight, in experimental animal subjects.

- Panax ginseng may be used as a supportive therapy, but should not replace current diabetes medications like sulfonylurea.

#### ***Application to Patient care***

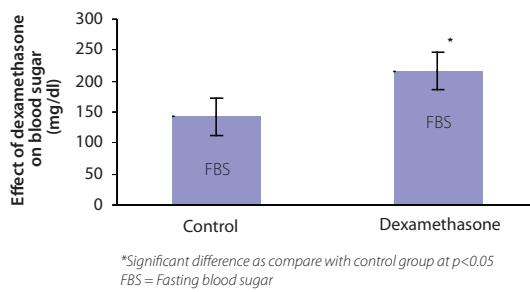
- Diabetes is a serious chronic metabolic disease and has significant impact on patient's lives as well as making demands of health care systems.
- Panax ginseng possessed a significant antidiabetic effect as compared with well known sulfonylurea member gliclazide in experimental animals.
- Our data, suggest that panax ginseng as a dietary supplement or as medicine may have functional efficacy in obese diabetic patients or those suffering from insulin resistance as it is considered a potent antioxidant agent.

**P**LASMA GLUCOSE IS DERIVED FROM THREE sources: intestinal absorption following digestion of dietary carbohydrates, glycogenolysis or the breakdown of glycogen (polymerised storage form of glucose) and gluconeogenesis.<sup>1</sup> Insulin is a hormone produced by the pancreas that helps unlock the body's cells so that sugar (glucose) from the food can be used by the cells for energy.<sup>2</sup> An increase in plasma glucose concentration is the most important physiologic regulator of insulin secretion. Glucose metabolism, initiated by the enzyme glucokinase, which converts glucose to glucose-6-phosphate, is closely linked to insulin secretion. However, an increase of the adenosine triphosphate/adenosine diphosphate (ATP/ADP) ratio results in inhibition of ATP-sensitive K<sub>ATP</sub> efflux channels. This causes depolarisation of beta cells and activation of voltage-sensitive Ca channels. The Ca influx results in insulin secretion.<sup>3</sup> Insulin binds to a receptor on the cell membrane, allowing the entry into muscle and fat cells of glucose to form glycogen, fatty acids to generate triglycerides, and amino acids for protein synthesis. It is a potent stimulator of growth factors, including insulin-growth factor 1 (IGF-1). It also inhibits catabolic processes such as the breakdown of glycogen and fat, and decreases gluconeogenesis (the production of glucose from lactate and amino acids);<sup>4</sup> however, if there are any disturbances to the binding of insulin to the receptors, or of the receptor response to insulin, there will be reduced insulin activity, or insulin resistance. If insulin is not functioning, there is reduced glucose entry into the cells, which is detected by the pancreas as raised blood sugar (hyperglycaemia). The pancreatic response is then to produce more insulin, (hyperinsulinaemia) to compensate for the lack of cellular response to the hyperglycaemia.<sup>5</sup>

The most common species of ginseng is *Panax quinquefolius*, commonly known as American or Western ginseng. The most commonly sought part of the plant is its root. Other characteristics of the wild or cultivated plant and different shapes of the root make it more valuable. Traditionally, the best plants are at least 6 years old. Panax ginseng is known as the Asian, Korean or Japanese ginseng.<sup>6</sup>

Ginseng is composed primarily of ginsenosides, also known as panaxosides. Other components of the plant, isolated for pharmacologic effects, include a volatile oil, beta-elemene, sterols, flavonoids, peptides, vitamins (B1, B2, B12, pantothenic acid, nicotinic acid, and biotin), fats, polyacetylenes, enzymes and choline. The elements phosphorus, potassium, calcium, thallium, manganese, iron, copper, zinc and strontium were detected by screening the components of ginseng.<sup>7</sup> Several pharmacologic effects have been noted that vary with dose and duration of treatment. The panaxosides found in the root, are thought to be the pharmacologically active agents. They have anticonvulsant, analgesic, antipsychotic effects and stress-ulcer preventing action. In addition, they show antiarrhythmic activity similar to verapamil and amiodarone. Oral ginseng was found to reduce cholesterol and triglycerides, decrease platelet adhesiveness, impair coagulation, and increase fibrinolysis in cholesterol-fed rats.<sup>8</sup>

Moreover, ginseng decreased fasting blood glucose and haemoglobin A1C in both diabetic and nondiabetic patients such that some diabetics were free of insulin therapy for the duration of the study.<sup>9</sup> Some studies in animals have documented ginseng's anti-inflammatory and antiviral activities,<sup>10</sup> hepatoprotective



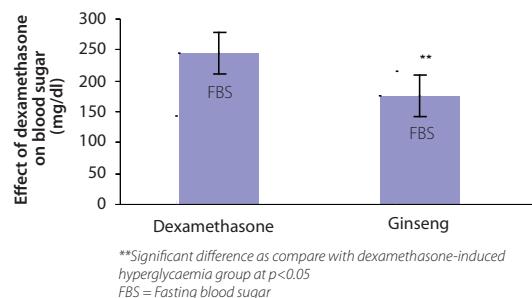
**Figure 1:** Effect of oral administration of dexamethasone (10 mg/kg) on the mean (mean  $\pm$  SE) fasting blood sugar in adult male rabbits ( $n = 6$ )

and tumors suppressant effects<sup>11</sup> and its beneficial use in colon cancer.<sup>12,13</sup>

Gliclazide is a hypoglycaemic agent of the sulfonylurea group. Its hypoglycaemic action is related to an improvement in insulin secretion from the functioning beta-cells of the pancreas.<sup>14</sup> Gliclazide is rapidly absorbed from the gastrointestinal tract and the plasma peak of gliclazide occurs between 4 and 6 hours. It is highly bound to plasma proteins, about 94%. The mean elimination half-life approximates 10.4 hours.<sup>15</sup> However, gliclazide controls diabetes mellitus of stable, mild, non-ketosis prone, maturity onset or adult types which can not be controlled by proper dietary management and exercise, or when insulin therapy is not appropriate.<sup>16</sup> Recently, it was found that gliclazide inhibits ischaemia-induced retinal neovascularisation.<sup>17</sup> The side effects of this drug include hypoglycaemic reactions and, as with other sulfonylurea drugs, manifestations of hypoglycaemia including dizziness, lack of energy, drowsiness, headache and sweating as well as weakness, nervousness, shakiness and paresthesia. Sulfonylurea unfortunately has a tendency to promote weight gain. This effect is aggravated by insulin resistance.<sup>18</sup>

#### METHODS

This study was conducted in Department of Pharmacology, University of Science and Technology, Sana'a, Yemen between May and June 2008. The following criteria were used to include subjects in the study: adult male rabbits weighing 1-1.5 kg. The following subjects were excluded from this study: adult female rabbits in order to eliminate the influence of the oestrous cycle and pregnancy on our parameters.



**Figure 2:** Effect of oral administration of ginseng (200mg/kg) on the average mean (Mean  $\pm$  SE) fasting blood sugar in dexamethasone induced hyperglycaemia in adult male rabbits ( $n=6$ )

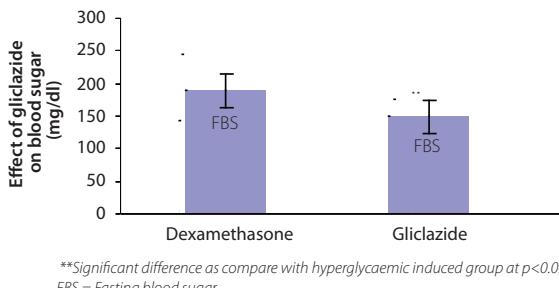
The rabbits were purchased from Yemeni markets, habituated to the new environment at constant temperature, and fed with a standard chow diet ad libitum for 1 week for acclimatisation. A total of 24 rabbits were used in the experiment. After one week's habituation period, the animals were divided into 4 groups (6 animals in each group), one group being kept as control. Both control and experimental groups were maintained under the similar experimental conditions. The control group was given only normal saline, while the other three groups were given continuous oral administration of dexamethasone (10mg/kg) for two weeks for induction of hyperglycaemia (above the human dose). Daily oral doses of Panax ginseng (200 mg/kg) or gliclazide (80 mg/kg) were used to treat dexamethasone-induced hyperglycaemia in the third and fourth groups of animals respectively for two weeks.

Blood samples were collected after the end of the experiment early in the morning when the animals had been kept fasting over the night. The fasting blood sugar measurement was done according to the method of Trinder.<sup>19</sup> The body weight was measured regularly for 14 days.

Data were collected and analysed using the SPSS (Statistical Package for the Social Sciences) programme for data analysis, Version 13. They are shown as mean  $\pm$  standard error; 'n' indicates the number of animals used. Statistical analysis was performed with Student's t test for unpaired observations. Differences were considered to be statistically significant when  $p$  was less than 0.05.

#### RESULTS

Administration of dexamethasone (10mg/kg) for 2 weeks produced significant ( $p < 0.05$ ) increase in FBS:



**Figure 3:** Effect of oral administration of gliclazide (80mg/kg) on the average mean (Mean  $\pm$  SE) fasting blood sugar in dexamethasone induced hyperglycaemia in adult male rabbits ( $n = 6$ )

$142.83 \pm 15.77$  mg/dl in the control group compared to  $215.33 \pm 27.67$  mg/dl in the dexamethasone group as shown in Figure 1.

Oral administration of *Panax ginseng* (200mg/kg) for 2 weeks produced a significant ( $p < 0.05$ ) decrease in FBS: from  $215.33 \pm 27.67$  mg/dl, in the dexamethasone group to  $154.17 \pm 21.18$  mg/dl, in the *Panax ginseng* treated group as shown in Figure 2.

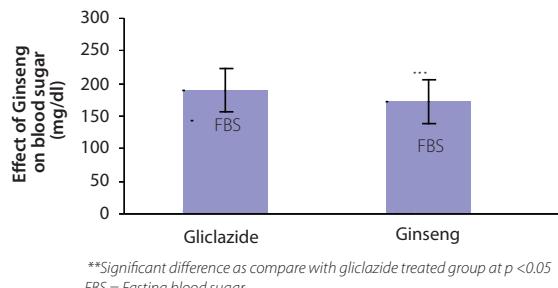
Oral administration of gliclazide (80mg/kg) for 2 weeks produced significant ( $p < 0.05$ ) decrease in FBS: from  $215.33 \pm 27.67$  mg/dl in the dexamethasone group to  $169.33 \pm 16.51$  mg/dl in the gliclazide treated group as shown in Figure 3.

Oral administration of *Panax ginseng* (200mg/kg) produced significant ( $p < 0.05$ ) reduction in FBS ( $154.17 \pm 21.18$  mg/dl) in the *Panax ginseng* treated group compared with the gliclazide treated group ( $169.33 \pm 16.51$  mg/dl) as shown in Figure 4.

## DISCUSSION

The present study showed that continuous oral administration of ginseng in doses of (200mg/kg) for 2 weeks produced significant reduction in FBS as compared with dexamethasone-induced hyperglycaemia in rabbits.

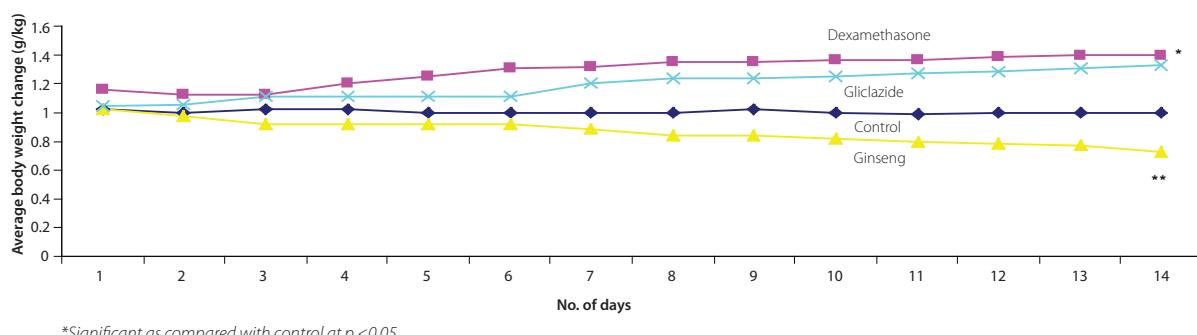
Our result was in agreement with Luo and Luo who found that ginseng attenuates hyperglycaemia in two ways: first, through enhancing pancreatic beta cell function and second, by reducing insulin resistance. This would make ginseng effective in both Type I and Type II diabetes.<sup>20</sup> Other studies showed that ginseng affects pancreatic beta cells through altering cell metabolism, increasing insulin production and reducing apoptosis in a dosage dependent manner.<sup>21</sup> In addition, ginseng extracts were able to enhance ATP produc-



**Figure 4:** Effect of oral administration of *Panax ginseng* (200mg/kg) or gliclazide (80 mg/kg) on the average mean (mean  $\pm$  SE) fasting blood sugar in dexamethasone induced hyperglycaemia in adult male rabbits ( $n = 6$ )

tion and in turn increase insulin production, as insulin deficiency is often linked to a lack of ATP.<sup>22, 23</sup> Along with an increase in ATP production, ginseng reduced mitochondrial protein uncoupling protein 2 (UCP-2), which negatively regulates insulin secretion.<sup>22</sup> However, another study showed that the insulin secretion-stimulating activity of ginseng was presumably associated with the ATP sensitive K channel. This effect, however, was almost completely abolished in the presence of diazoxide (K channel opener) or nifedipine (Ca channel blocker).<sup>24</sup> In addition, compound K (CK), which is a final metabolite of ginsenosides, shifted glucose metabolism from hepatic glucose production to hepatic glucose utilisation in the liver and improved insulin sensitivity through enhancing plasma adiponectin levels, resulting in over expression of genes for adipogenesis and glucose transporters in adipose tissue. All these effects may suggest that ginseng could be developed as therapeutic tool in Type 2 diabetic patients with insulin secretion disability and/or insulin resistance.<sup>25</sup> Another study suggests that ginseng may inhibit cytokine-induced apoptosis in beta cells and, thus, may contribute via this action to the antidiabetic influence in Type 1 diabetes.<sup>26</sup>

Continuous administration of gliclazide in an oral dose (80mg/kg) for 2 weeks produced significant reduction in FBS. Our result is supported by Wangnoo who found that gliclazide is one of the most frequently used sulfonylurea for the treatment of Type 2 diabetes.<sup>27</sup> Its hypoglycaemic action is related to an improvement in insulin secretion from the functioning beta cells of the pancreas. It potentiates the insulin release and improves the dynamics of insulin. In addition, antidiabetic sulfonylureas are thought to stimulate insulin secretion solely by inhibiting their high-



\*Significant as compared with control at  $p < 0.05$

\*\*Significant as compared with dexamethasone induced hyperglycaemia at  $p < 0.05$

**Figure 5: Effect of continuous oral administration of Panax ginseng (200mg/kg) or gliclazide (80mg/kg) on average total body weight in adult male rabbits (n = 6)**

affinity ATP-sensitive potassium ( $K_ATP$ ) channel receptors at the plasma membrane of beta-cells. This normally occurs during glucose stimulation, where ATP inhibition of plasmalemmal  $K_ATP$  channels leads to voltage activation of L-type calcium channels for rapidly switching on and off calcium influx, governing the duration of insulin secretion.<sup>28</sup> In contrast, another study showed that chronic sulfonylurea treatment *in vivo* causes loss of insulin secretory capacity due to beta-cell hyperexcitability, but also revealed rapid reversibility of this secretory failure, arguing against beta-cell apoptosis or other cell death induced by sulfonylureas. These *in vivo* studies may help to explain why patients with Type 2 diabetes can show long term secondary failure to secrete insulin in response to sulfonylureas, but experience restoration of insulin secretion after a drug resting period, without permanent damage to beta-cells.<sup>29</sup>

In addition, ginseng showed significant ( $p < 0.05$ ) reduction in total body weight compared with the dexamethasone and gliclazide groups [Figure 5]. This effect is controversial owing to its mechanism of action. However, this effect may be due to the inhibition of pancreatic lipase activity.<sup>30</sup> However, some studies showed that sulfonylurea may increase body weight due to an increase in leptin (an obesity gene product)<sup>31</sup> or due to an insulin secretion effect.<sup>27</sup>

This is a single study with a small number of animals so these limitations have to be kept in mind when interpreting the results. Further experimental and clinical investigations should be done to support the results of this work.

## CONCLUSION

It seems that ginseng is effective as an antidiabetic agent in experimental animal models. It is more than

likely that ginseng affects not only the pancreas to increase insulin production, but also other tissue to utilise insulin as well as decrease insulin resistance through its various components. There was a significant difference between ginseng and gliclazide in reducing fasting blood sugar and body weight. From these results, it is suggested that ginseng might be used in obese diabetic patients or those patients suffering from insulin resistance as it reduces body weight so improving insulin receptors.

## RECOMMENDATIONS

This study showed that *Panax ginseng* may help to reduce blood glucose level and improve insulin sensitivity and hence may have potential use in management of diabetes mellitus patients with obesity.

It was found that both agents are working by the same mechanism as they stimulate secretion of insulin from beta cell of pancreas. Expected synergistic hypoglycaemic effect may be resulted if they are combined together. *Panax ginseng* should be used cautiously in patients taking any hypoglycaemic medications. Drug-drug interactions with digoxin and warfarin have also been reported.

**SOURCE OF FUNDING:** University of Science & Technology, Sana'a, Yemen

**CONFLICT OF INTEREST:** None declared

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