Effect of Ginseng (Panax Ginseng) on Experimentally Induced Diabetes Mellitus in Male Rabbits

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Abstract

This study was conducted to investigate the effect of orally administered panax ginseng on some biochemical parameters in diabetic male rabbits. The rabbits were divided into 5 equal groups; a 1st normal control, a 2nd diabetic non-herb treated, and a 3rd normal rabbit treated with the herb, panax ginseng at 150mg/kg . While, each of the 4th and 5th groups were diabetic rabbits treated with the herb, panax ginseng at 300mg/kg and 600mg/kg, respectively. The results in the diabetic rabbits in group 2 showed an increase in serum glucose, cholesterol, triglyceride and increase the normal rang of main parameters in the body like SC, BUN, ALP and ALT, AST. While, oral administration of panax ginseng at 300, and 600 mg/kg showed a significant reduction in total lipids in diabetic rabbits and have no any adverse effect on the main parameters of the body which taken to be as indicator for health state of liver, kidney, heart and muscle tissues in the body.

تأثير عشب البناكس جينسينك على السكري المحدث تجريبياً في ذكور الأرانب

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الخلاصة

كان الهدف من أجراء هذه الدراسة هي لمعرفة تأثير عشب البناكس جينسينك على بعض المقاييس الكيميائية الحياتية في ذكور الأرانب المصابة بداء السكر المستحدث تجريبا بالالوكسان. وتم تقسيم الأرانب إلى خمسة مجاميع؛ الأولى سيطرة سليمة، والثانية المصابة تجريبيا بداء السكر، والثالثة سليمة لكن معالجة بعشب البناكس جينسينك (150 ملغ/ كغم). أما أرانب المجموعتين الرابعة والخامسة، المصابة بداء السكري تجريبيا، فقد عولجت بعشب البناكس جينسينك بتركيز 300 ملغم/ كغم و600 مليغرام/ كغم من وزن الحيوان على التوالي. وأظهرت نتائج التجربة إن أرانب المجموعة الثانية المصابة بالسكري المستحدث تجريبيا بالالوكسان قد عانت من الزيادة في مستويات الكلوكوز, الكوليستيرول والشحوم الكليسريدية في الدم، بالمقارنة مع الأرانب السليمة في المجموعة الأولى. كما لوحظ وجود زيادة معنوية في أهم المقاييس الحيوية في الجسم والتي أخذت كدليل على المستوى الصحي للجسم والأعضاء الحيوية فيه مثل القلب, والكلية, والكبد، والعضلات. أما المجموعة الثالثة التي عولجت بعشب البناكس جينسينك، فلم يبين العلاج بالعشب أحداث تغييرات سلبية على القياسات الكيميائية الحياتية للدم فيها. في حين أعطى العلاج بالعشب وبكلى التركيزين، حماية ضد أي زيادة في مستويات الكلوكوز, الكوليستيرول والشحوم الكليسريدية واهم المقاييس الحيوية في جسم الأرانب المصابة بالسكري في المجموعتين الرابعة والخامسة.

Introduction

Ginseng often described as the king herb, because it holds an important position in traditional oriental medicine in many countries (1). The herb, red Asian panax ginseng, is the most commonly used ginseng, having five leaflets on each leaf, scarlet berries, and an aromatic root. The highly valued plant is currently cultivated in China, and many other global countries (1). Ginsenosides from panax ginseng have been shown to have a variety of beneficial effects including anti-inflammatory, antioxidant, anticancer, improve psychological function, immune function and promotes the function of the endocrine glands and the

reproductive organs in the body and condition associated with diabetes. Ginsenosides compounds have a chemical structure similar to human hormones and it is believed that they may work similarly (2). The aim of the present study was to clarify the antidiabetic role of grinded Panax ginseng root given orally in rabbits.

Materials and Methods

- **Animals:** Twenty five male domestic rabbits from local breed were used in this experiment. Their age and body weight were from 6 -to- 8 months and 1.6 -1.8 kg respectively. The rabbits were physically healthy and were adapted pre-experimentally for two weeks, by allocating two per housing cage and were given food (barely and vegetables) and tap water during the experimental period. They were reared at an optimal room temperature ranged between 22-25°C and were exposed to artificial light for 12 hrs/day.
- **Experimental design:** the rabbits were divided randomly and equally in to 5 groups:

Group 1 (control group); the rabbits were treated by one ml of distilled water (D.W.), once orally for 30 consecutive days.

Group 2 (diabetic group); diabetic mellitus was induced experimentally by treatment with a single dose of alloxan monohydrate (150 mg/kg), administered intraperitoneally.

Group 3; these were normal rabbits, but fed orally with the herb, ginseng panax, at dose 150 mg/kg by gavagesô needle, for 30 consecutive days.

Group 4 and 5 (GD1 & GD2). The rabbits in both these groups were suffering from diabetic mellitus, were treated for 30 consecutive days with a daily single oral dose of ginseng panax 300 mg/kg, and 600 mg/day, subsequently, by gavage syringe.

- **Induction diabetic mellitus**: after the animals were fasted for 12 h they allowed access to the water before induction of diabetes. Alloxan monohydrate administered intraperitoneally at single dose of 150mg/kg of body weight after estimation of blood glucose level those animals that have over 200 mg/dl serum glucose they were considered diabetic and used for the further experiment, Since alloxan is capable of producing fatal hypoglycemia, animals were treated with 20% glucose solution intraperitoneally after 6 h (3).
- **Preparation of the herb ginseng panax:** The shade dried plant was obtained from Raz Hasti Zamin Co. ltd (Iran). It was choped into small pieces and then grinded by an electric grinder into powder. Sixty grams from the grinded crude powder was mixed with 100 ml distilled water (600 mg/ml). Finally, two further subsequent dilutions (i.e., 300 mg/ml and 150 mg/ml) were also prepared from the same stock solution. The 300 mg/ml solution was reconstituted from the 1st stock solution by taking 50 ml from the stock to which D.W. was added and completed to 100 ml. While, the 2nd dilution was by taking 50 ml from the previous stock and its volume was completed to 100 ml by D.W. (4).

Fig. (1) Samples from the crude Ginseng Panax plant, that supplied by Raz Hasti Zamin Co. ltd (Iran)

- **Blood Sampling:** Blood samples were collected from the rabbitôs marginal ear vein which was made clearly obvious by xylene. Then centrifuged at 3000 round per minutes for ten minutes. Then, by using of micropipette, the serum were collected in clean test tube with covers (5). Different tests (serum glucose, cholesterol, triglyceride, SC, BUN, ALP and ALT, AST were analyzed at the same day by using LISA 200 (Pejohesh- co., France). All kits that are specifically work on LISA 200 were purchased from (Pars company-Iran). LISA 200 is an auto analyzer which enables handling of a wide range of analyses of biochemical assays of substrates, enzymes and electrolytes.
- **Statistical Analysis:** Data are shown as the mean ± SE (Stander Error) when a significant interaction between major factors was identified by ANOVA SPSS version 10.0., the data were split on the basis of the interacting factor and reanalyzed. Duncanôs new multiple range tests was used post- ANOVA to identify significant differences between mean values at probability level of ($p < 0.05$) was taken as significant.

Results

The results of oral administration of ginseng panax to the experimental rabbits on different serum parameters in C, D, G, GD1, and GD2 groups are presented as Mean ± SD values, for each group(n = 5 rabbits),and are showed in tables number; 1, 2, 3, 4, 5, 6, 7 and 8.

Table (1) Effects on serum blood urea nitrogen levels (mg/dl) in different experimental groups and periods

Rabbits Groups	Treatment	Pretreatment	2 Weeks post-treatment	4 Weeks Post-treatment
C	Control (D.W)	11.81 ± 0.3 a	11.75 ± 0.132 a	11.80 ± 0.47 a
D	Alloxan 150 mg/kg	11.84 ±0.971 a	20.54 ±0.113 c	29.44 ± 0.398 d
G	Ginseng 150 mg/kg	11.85 ± 0.268 a	11.78± 0.564 a	11.84± 0.632 a
GD1	Ginseng 300 mg/kg Alloxan 150 mg/kg	11.79 ± 0.200 a	14.39± 0.138 b	15.50 ± 0.139 b
GD2	Ginseng 600mg/kg Alloxan 150 mg/kg	11.80 ± 0.09 a	11.72 ± 0.186 a	11.50 ± 0.116 a

Values are expressed as mean ± SE; No. of rabbits /groups = 5; a and b Values within columns with no common superscripts differ significantly (p≤0.05)

Table (2) Effects on serum alkaline phosphates levels (mg/dl) in different experimental groups and periods

Group	Treatment	Pretreatment	2nd Week	4 week
C	Control (water)	220.20 ± 0.46 a	219.22 ± 0.132 a	220.71 ± 0.426 a
D	Alloxan 150mg/kg	219.20 ±0.921 a	229.54 ±0.156 b	240.44 ± 0.356 c
G	Ginseng (150mg/kg)	220.22± 0.267 a	218.78± 0.991 a	217.44± 0.932 a
GD1	Ginseng 300mg/kg+ alloxan	220.53 ± 0.661 a	228.39± 0.999 b	231.90 ± 0.139 b
GD2	Ginseng(600mg/kg) alloxan 150mg/kg	221.67 ± 0.999 a	220.52 ± 1.32 a	219.50 ± 0.987 a

Values are expressed as mean ± SE; No. of rabbits /groups = 5; a-d Values within columns with no common superscripts differ significantly (p≤0.05)

Table (3) Affects on serum Creatinine levels (mg/dl) in different experimental groups and periods

Group	Treatment	Pretreatment	2nd Week	4 week
C	Control (water)	1.58 ± 0.532 a	1.60 ± 0.132 a	1.59 ± 1.96 a
D	Alloxan 150mg/kg in single dose	1.58 ± 0.911 a	3.54 ±1.13 c	5.44 ± 2.98 d
G	Ginseng (150mg/kg)	1.59 ± 0.012 a	1.62 ± 0.016 a	1.59± 0.174 a
GD1	Ginseng 300mg/kg+ 150 mg/kg alloxan	1.63 ± 0.200 a	2 ± 0.138 b	2.50 ± 0.199 b
GD2	Ginseng 600mg/kg alloxan 150mg/kg in single dose	1.57 ± 0.99 a	1.59 ± 0.186 a	1.57 ± 0.116 a

Values are expressed as mean ± SE; No. of rabbits /groups= 5; a-d Values within columns with no common superscripts differ significantly (p≤0.05)

Table (4) Effects on serum glucose levels (mg/dl) in different experimental groups and periods

Group	Treatment	Pretreatment	2nd Week	4 week
C	Control (water)	91.26± 1.210 a	90.11 ± 1.324 a	91.59 ± 0.968 a
D	Alloxan 150mg/kg	92.1 ± 0.911 a	272.31±1.132 b	383 ± 1.988 c
G	Ginseng 150mg/kg	91.21 ± 0.012 a	94.2 ± 0.016 a	92.4± 0.174 a
GD1	Ginseng 300mg/kg+ alloxan	90± 0.459 a	99 ± 0.138 a	106 ± 2.154 a
GD2	Ginseng 600mg/kg alloxan 150 mg/kg	91.7 ± 0.991 a	93 ± 0.186 a	94 ± 1.267 a

Values are expressed as mean ± SE; No. of rabbits /groups = 5; a-c Values within columns with no common superscripts differ significantly (p≤0.05)

Table (5) Effects on serum cholesterol levels (mg/100ml) in different experimental groups and periods

Group	Treatment	Pretreatment	2nd Week	4 week
C	Control (water)	90.65± 1.21 a	90.11 ± 1.324 a	91.59 ± 0.968 a
D	Alloxan hydrate 150mg/kg	91.13 ± 0.343 a	220.31±1.132 b	330 ± 3.1 c
G	Ginseng 150mg/kg	93.13 ± 1.1 a	93.2 ± 0.016 a	92.4± 0.174 a
GD1	Ginseng 300mg/kg+ alloxan	92.2± 1.9 a	94 ± 0.138 a	94 ± 1.54 a
GD2	Ginseng 600mg/kg alloxan 150mg/kg	91.7 ± 0.976 a	93 ± 0.986 a	92.9 ± 1.756 a

Values are expressed as mean ± SE; No. of rabbits /groups = 5; a-d Values within columns with no common superscripts differ significantly (p≤0.05)

Table (6) Effect of the treatment on the serum aspartate amino transferase levels (mg/dl) in different experimental groups and periods

Group	Treatment	Pre-treatment	2nd Week Post-treatment	4 Week Post-treatment
C	Control (water)	254.20 ± 1.1 a	251.22 ± 0.982 a	253.7 ± 1.1 a
D	Alloxan hydrate 150mg/kg	252.20 ± 0.921 a	259.54 ±0.666 b	260.44 ± 0.356 b
G	Ginseng (150mg/kg)	255 ± 0.91 a	255.78 ± 0.991 a	254.44 ± 0.998 a
GD1	Ginseng 300 mg/kg + alloxan	254.53 ± 1.43 a	254.39 ± 0.999 a	248.90 ± 0.139 a
GD2	Ginseng (600 mg/kg) and alloxan 150 mg/kg	255.67 ± 2.11 a	252.52 ± 1.32 a	253.50 ± 1.987 a

Values are expressed as mean ± SE; No. of rabbits\ groups = 5; a-b Values within columns with no common superscripts differ significantly (p≤0.05).

Table (7) Effect of the treatment on the serum alanine aminotransferase levels (mg/dl) in different experimental groups and periods

Group	Treatment	Pretreatment	2nd Week	4 week
C	Control (water)	146.20 ± 1.1 a	145 ± 1.5 a	147.71 ± 1.9 a
D	Alloxan hydrate 150mg/kg	150.20 ±0.921 a	159.54 ±1.156 b	163.44 ± 0.356 b
G	Ginseng (150mg/kg)	150.22± 0.267 a	149.78± 1.1 a	150.113± 0.932 a
GD1	Ginseng 300mg/kg+ alloxan	145.33 ± 0.669 a	148.39± 0.999 a	150..90 ± 0.139 a
GD2	Ginseng 600mg/kg) alloxan 150 mg/kg	147.67 ± 0.999 a	148.52 ± 1.32 a	150 ± 1.987 a

Table (8) Effect of the treatment on the serum triglyceride levels (mg/100 ml) in different experimental groups and periods

Group	Treatment	Pretreatment	2nd Week	4 week
C	Control (water)	86.67± 1.8 a	87.13 ± 0.122 a	88.31 ± 0.727 a
D	Alloxan hydrate 150 mg/kg	89.31±1.1 a	135 ± 0.156 b	155.44 ± 1.9 c
G	Ginseng 150 mg/kg	88.21± 0.444 a	86.10± 0.991 a	85.443± 0.932 a
GD1	Ginseng 300mg/kg + alloxan	89.53 ± 0.661 a	95.39± 0.999 a	99.90 ± 0.111 a
GD2	Ginseng 600mg/kg alloxan 150 mg/kg	90.67 ± 1.999 a	91.52 ± 1.39 a	91.50 ± 0.987 a

Values are expressed as mean ± SE; No. of rabbits\ groups = 5

Discussion

Diabetes mellitus is a complex disease associated with peripheral and central complications. These complications include retinopathy, nephropathy and neuropathy. Several investigations have confirmed the role of oxidative stress in developmental diabetic mediated disorders, possibly via the formation of free radicals (6). In a study by El-Khayat, *et. al*., (7) considering the potential effects of ginseng in decreasing hyperglucoseaemia, investigated whether administration of ginseng root extract had any protective effect against oxidative stress and whether it could ameliorate serum glucose, total cholesterol and triglycerides levels in rats with streptozotocin (STZ)- induced diabetes. Their results were in compatible with the results is in this study in reducing the level of serum glucose cholesterol and triglyceride. In

the present investigation the experimentally induced diabetes by alloxan whish is a toxic glucose analogue, selectively destroys insulin-producing cells in the pancreas (beta cells) when administered to the rabbits. This caused an insulin-dependent diabetes mellitus, known as "Alloxan Diabetes" in rabbits and other laboratory animals (7). On the other hand, Liu *et al*. (8) found that ginseng extracts scavenge oxidative species. Also, Surh *et al*. (9) indicated that ginseng extracts attenuate lipid peroxidation. That is, it may be related to saponins which play a major role in antioxidant activities. In addition, ginsenoides, an active ingredient, heavily present in ginseng and have a powerful antioxidant activities and radical scavenging activities by stimulating gene expression of antioxidant enzymes and enhancing their activities (10). Studies in rats have indicated that the increase in dopaminergic receptors in the brain observed under conditions of stress and was prevented by pretreatment with ginseng (2). Chung *et al.* (11) showed that the antidiabetic effect of ginseng root could be attributed to blocking intestinal glucose absorption and inhibiting hepatic glucose-6-phosphatase activity. In the present study, no significant changes in serum lipid profile levels in the normal rabbits treated with the ginseng compared to the normal rabbits in the 1st control group. While, the mean values of serum cholesterol, triglycerides were significantly increased in the alloxan treated group 2 rabbitôs, compared to the normal control (group 1), and the group 3, GD1, and GD2, groups. Interestingly, all these values were significantly decreased after treatment with ginseng. The reduction in the serum glucose levels especially at dose of 600 mg/kg, in this study was due to the effects of ginseng. A study done by Wang *et al*., (12) on mice treated with ginseng glycoprotein. They revealed that ginseng can decrease blood glucose level in normal and experimentally induced hyperglycemic patient. Lee *et al.,* (13) suggest that ginsenoside has the ability to increase insulin secretion as a result of the release of ACh from nerve terminals that then stimulates muscarinic receptors in pancreatic cells. Ginseng might mediate its anti diabetic effect through a variety of mechanisms including; actions on the insulin-secreting pancreatic B cells stimulation and the target tissues that take up glucose, ginseng treatment increased insulin release from pancreatic B cells stimulation and increased insulin synthesis. It is also believed that ginseng lead to increase the activity of glucose transporter, reduce the rate of glucose absorption and reduce glycogenolysis thus reducing hyperglycemia (11). Further reputable studies in Japan and united state have shown that ginseng stimulate every conceivable aspects of protein and nucleic acid metabolism and may help to maintain or facilitate the capacity of cells to tolerate anaerobic oxidation. Better put, ginseng may help reduce cell damage, thus helping to counteract age related changes. Other properties such as anti oxidant activity of the ginseng may help protect pancreas and other tissue from the oxidant stress during hyperglycemia (14). In vitro studies using isolated rat pancreatic islets have shown that ginsenosides promote an insulin release which is independent of extracellular calcium and which utilises a different mechanism to that of glucose. In addition, *in vivo* studies in rats reported that a ginseng extract increases the number of insulin receptors in bone marrow and reduces die number of glucocorticoid receptors in rat brain homogenate. Both of these actions are thought to contribute to the antidiabetic action of ginseng (2, 15). The statistical reduction in the values of SG, SC, BUN, ALP and ALT, AST one month after treatment with ginseng was thought to be due to its effect on body cells particularly these sensitive to absence or reduction of insulin levels such as heart, liver, kidneys, and bones which have considerable levels of these biochemical parameters. The reduction in above values confirmed both toxic effect of alloxan and the possible protective effect of ginseng on the most important body tissues and organs in the ginseng treated groups. Ginseng is the most efficacious for immune stimulation and the prevention of diabetes (12). The Creatinine is a waste product which must be excreted

by the kidney mainly through glomerular filtration. Any increase in the value of this product indicates decreased excretion or impaired renal function. Therefore, creatinine clearance enables a quite estimation of the glomerular filtration rate. Alloxan treated animals (group A), showed a significant increase in creatinine level ($P< 0.05$**)** along the treatment period. The level of serum creatinine increased 2 or 3 folds following alloxan treatment alone, in comparison to the normal values in control group C, while treatment with ginseng along the rabbits in all the three groups completely protected them from alloxan toxicity as indicated by the stability of serum creatinine level that was nearly like that of their normal level in control group. Blood urea nitrogen test is a dependable test which indicates impairment of renal function Levinson (16), states associated with elevated levels of urea in blood are referred to as hyper uremia. The values of BUN were significantly increased during the second week of treatment. Oral administration of ginseng protected the rabbits in groups G, GD1, and GD2 from the experimentally induced damage to the renal tissues, as seen from the absence of changes in BUN parameters in comparison to the alloxan treated D group. Alkaline phosphatase is another parameter which is a hydrolytic enzyme associated with microvili of secretory and absorptive cells. It can be taken as indicator of the state of liver, kidney and muscle stress (17). The results for treatment with different doses of ginseng showed that all the biochemical parameters remained normal during the periods of treatment. Also, a reduction in serum triglycerides level was observed after treatment. These results were in agreement with the results of Dixit *et al.* (18) who mentioned that ginseng markedly reduced serum triglycerides and cholesterol in hyper lipidemic monkeys. Oral administration of ginseng to rats fed a high cholesterol diet reduced serum cholesterol and triglycerides, decreased platelet adhesiveness, and decreased fatty changes to the liver. Ginseng has also been reported to reduce blood coagulation and enhance fibrinolysis (2). Alloxan treatment showed positively time related toxic effects represented by the results of clinical chemistry tests (increase in serum Creatinine and blood urea nitrogen, serum glucose and serum cholesterol and serum triglyceride), as well as an increase in serum enzymes level (alanine aminotransferase, aspartate amino transferase and alkaline phosphatase). Yet a combination treatment of alloxan and ginseng in dose 600mg/kg results in complete ameliorating toxic effect of alloxan induced diabetes, and a dose 300mg/kg result in complete to partial protection from toxic effect of alloxan. In conclusion, this study showed that panax ginseng posses antidiabetic activity through decreasing levels of serum glucose, cholesterol, serum triglyceride and protective mechanism against any diabetic and oxidant effect that happened by alloxan so it give protection to the most important organs and systems in the body. From the acquired results it is recommend that ginseng could be given as combination treatment either alone or as new formulating drug to reduce the chance of patient with the most chronic dangerous disease or decrease their toxic side effects.

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