Hypoglycaemic Evaluation of Panax Ginseng (Radix rubra) in Normal and Alloxan Diabetic Rabbits

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ABSTRACT

Background: The present study was planned to observe the hypoglycaemic effect of Panax ginseng C.A. Meyer (Radix rubra) a traditional Far Eastern medicinal plant. This research was performed to study the possible role of medicinal plants in the treatment of Diabetes mellitus type

Study Design: It is a comparative and non interventional study.


Setting: Department of Pharmacology FPGMI.

Subjects & Methods: 96 rabbits were divided into two main groups. Group 1 of normal rabbits was further subdivided into 6 subgroups (A-F) of 8 animals each. Subgroup A served as control and received 5 ml of water only.

Subgroups B, C and D were administered ginseng root powder in aqueous solution, in doses of 25, 50, 100 mg/kg body weight per 5 ml of distilled water. Subgroup E and F were administered 5 mg of glibenclamide and 250 mg of metformin each dissolved in 5 ml of distilled water respectively. The alloxan diabetic rabbits (Group 2) were also subdivided into 6 subgroups (G-L) on the same pattern. The blood glucose levels were estimated before and 2, 4, 8, 10, 12, 14 and 16 hours after administration of the aqueous solutions of ginseng, glibenclamide and metformin.

Results: The aqueous solution of Panax ginseng exerted a significant hypoglycaemic action (P value <0.5) at 2 hours with the 50 mg/kg dose continuing till 4 hours with the 100 mg/kg body weight dose in the normal rabbits. In the alloxan diabetic rabbits there was statistically significant hypoglycemic action (P value <0.5) with the 50 mg/kg dose at the 12th hour proceeding till the 14th hour with the 100 mg/kg body weight dose. The doses used did not show acute toxicity or result in behavioral changes.

Conclusion: From this study, it maybe concluded that the powdered Panax ginseng (Radix rubra) root has a significant, mild & short lived hypoglycemic action in both normal and in alloxan induced diabetic rabbits.

Key Words: Panax ginseng, hypoglycemia, rabbits.

INTRODUCTION

The Ginseng Plant has a history of more than 2000 years of use by the Chinese, Koreans and Japanese. It is a smooth herbaceous plant 45-60 cm tall belonging to the Ivy family Araliaceae. It is indigenous to Far East Asia including Korean Peninsula, Manchuria, China, Japan, Cambodia and other areas of eastern Asia including Russia as well as North America. The botanical name of Korean Ginseng is Panax ginseng C.A. Meyer. Panax comes from the greek word panacea or Cure all. Whereas Ginseng is due to the man like appearance of the root1. All parts of the plant are used as herbal medication i.e. root, stem, leaves, berries. The different pharmacological activities of the above are due to distinct ginsenosides (steroidal saponins) profiles2. The leaves have immunological, anti-ulcer and anti-complement activities3. Berries have proven hypoglycemic action4. The roots have many important pharmacologically active constituents5. Ginseng has been used in traditional system of medicine in the treatment of impotence6. GIT disorders such as gastritis and ulcers7-9. Some uses described in folk medicine not supported by experimental or clinical data are treatment of liver
disease, coughs, fevers, TB, Rheumatism, Vomiting of pregnancy, Hypothermia, dyspnea and nervous disorders.

AIMS AND OBJECTIVES

The present work was undertaken with the aim to study the hypoglycemic effect of, orally administered aqueous solution of Panax ginseng powdered root of different strengths on blood sugar of normal and alloxan diabetic rabbits. A comparison of its anti-diabetic action to that of standard oral hypoglycemic drugs glibenclamide and metformin was also done.

MATERIALS & METHODS

Animals

Experiments were performed on 96 male adult rabbits of a local strain weighing 1000-1800 g. The animals were kept at the animal house of the Shaikh Zayed Federal Post Graduate Medical Institute. They were fed green fodder, wheat grains and grams ad libitum. Fresh and wholesome water was also provided ad libitum.

Chemicals

1. Ginseng 100 gms of good quality and well dried, crushed Panax ginseng C. A. Meyer root (Korean Ginseng Radix rubra) was obtained from Prof. Koh, a research scholar at the Korea Ginseng Institute at ChungAng University, Seoul, South Korea. It has been stored in the refrigerator in a well closed glass bottle at 4 degree centigrade.
2. Alloxan monohydrate – Acros Organics, New Jersey, USA. (NH-CO-NH-CO-CO.H2O)
3. Glibenclamide (Daonil) – Aventis Pharma Deutschland GmbH, Germany
4. Metformin (Glucophage) – Merck Pharmaceuticals Limited.

Grouping of rabbits:

96 rabbits were randomly divided into 2 major groups (Normal group & Alloxan treated group). Each group was further divided into six sub groups of 8 rabbits each. Group 1: 48 animals of group-1 (normal rabbits) were further sub-divided into the following 6 subgroups of 8 rabbits each:

- Subgroup-A were given orally 5 ml of distilled water each.
- Subgroup-B were given orally 25 mg of ginseng/kg body weight.
- Subgroup-C were given orally 50 mg of ginseng/kg body weight.
- Subgroup-D were given orally 100 mg of ginseng/kg body weight.
- Subgroup-E were orally given 5 mg/kg of Glibenclamide each.
- Subgroup-F were given orally 250 mg/kg of Metformin each.

Forty eight animals of group 2 Diabetic (Alloxan treated group) were further sub-divided into the following 6 subgroups of 8 rabbits each:

Likewise each dose was prepared in 5 ml of distilled water

- Subgroup-G were given orally 5 ml of water each.
- Subgroup-H were given orally 25 mg of ginseng/kg body weight.
- Subgroup-I were given orally 50 mg of ginseng/kg body weight.
- Subgroup-J were given orally 100 mg of ginseng/kg body weight.
- Subgroup-K were given orally 5 mg/kg of Glibenclamide each.
- Subgroup-L were given orally 250 mg/kg of Metformin each.

Preparation of panax ginseng aqueous solution:

The crushed steam extracted Panax Ginseng C.A. Meyer (Radix rubra) is fully soluble in distilled water. It was reconstituted in a dilution/strength of 25 mg / 50 mg / 100 mg per kg body weight in 5 ml of distilled water each, as per dose requirement.

Preparation of diabetic rabbits

A group of rabbits was made diabetic by
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injecting alloxan monohydrate in doses of 75-110 mg/kg body weight intravenously into the marginal ear veins. 8 days after injection the blood glucose levels of the surviving rabbits were estimated. Rabbits with blood glucose levels above 200mg/dl were considered as diabetic.

Administration of ginseng aqueous solution
The solution was administered to each rabbit using a stomach tube attached to a standard syringe containing it. The tube was inserted into the stomach through the oesophagus and the plunger was depressed slowly and steadily. Immediate sneezing and coughing indicated injection into the lungs and in such a condition the tube was withdrawn and another animal was taken instead. The Glibenclamide and Metformin solutions were administered in a similar manner.

Collection of blood
Blood was collected from the marginal ear veins of the rabbits at 0 hours (pre-drug) and at 2, 4, 8, 10, 12, 14 and 16 hours post administration.

Blood glucose estimations
Blood glucose estimations was done using the GOD-PAP method as described in the Cenix diagnostic kit literature

Statistical analysis
Statistical analysis was done using SPSS version 10. The independent, paired T test & one way ANOVA were applied. All numerical variables were represented as Mean±SEM as a basis in all the tests.

A p-value <0.5 was considered significant for all analysis.

DISCUSSION

Concluding all the data in normal rabbits reveals that ginseng root powder at 25 mg/kg is ineffective. 50 and 100 mg/kg doses of ginseng exhibit an early and identical time of onset of milder hypoglycaemic action, but shorter duration of action than glibenclamide. This could be due to release of preformed insulin from the Beta cells of the islets of Langerhans in normal rabbits, similar to, but less potent than glibenclamide(sulphonyl urea), whose duration of action is longer on account of a stronger insulin secretagogue effect. Some of the ginsenosides, a glycan-panaxan B12, polypeptides and peptidoglycan DPG 3-2 on parenteral administration have demonstrated hypoglycaemic activity by insulin secretagogue activity from cultured islets and in different animal models. The activity of ginsenosides or polypeptides in the powdered ginseng root extract can therefore not be refuted and could lay the basis for the roots’ oral hypoglycaemic action in normal rabbits.

In an effort to explore its hypoglycaemic mechanisms further, P ginseng powdered root extract was also administered to alloxan diabetic rabbits. No insulin was given to these rabbits to prevent interference with research results.

Blood sugar random values for diabetic rabbits reveal that all the ginseng doses at 25 mg/kg, 50 mg/kg and 100 mg/kg show delayed onset of significant, yet mild hypoglycemic action (p<0.05) at 12 hrs post drug administration. The duration of action of both the 25 and 50 mg doses was 2 hrs while for the 100 mg/kg dose was 4 hrs as the lowering of blood sugar levels gradually became insignificant (p>0.05) at the 16th hr. Glibenclamide 5 mg/kg and metformin 250 mg/kg as reflected by tables 9 and 10 had similar times of onset of hypoglycaemic activity i.e. 8 hrs post drug administration which was considerably earlier than the ginseng doses (12 hrs). These drugs however showed different patterns of hypoglycaemic action. The duration and efficacy of anti hyperglycemic effect in the case of glibenclamide was less than metformin, as it showed significant lowering of BSR (p<0.05) for 6 hrs ending at the 14th hr. Metformin in doses of 250 mg/kgbody wt proved the moved efficacious and longest acting (8 hrs) of the three drugs in diabetic rabbits. It had alternating highly significant (p>0.001) and significant BSR lowering (p<0.05) commencing at the 8th hr and continuing till the end of observations at the 16th hr.

The afore mentioned results in diabetic rabbits reveal that the delayed onset of ginseng root hypoglycaemic activity in all the dose strengths could be due to slow digestion of food and decreased rate of the carbohydrate absorption from the gut. In addition, in vitro tests on ginseng...
protopanaxatriol saponins have shown them to inhibit spontaneous motility of the rabbits' jejunum\(^{16}\) which could be another reason for the delayed onset of hypoglycaemic behaviour of ginseng. Others have reported that gastric secretion in vitro was inhibited by ginseng\(^{17}\). It was also reported that American ginseng root extract inhibited brain stem neuronal activity via gastric vagal afferents\(^{18}\). All these reports would concur with the current finding of delayed onset of action.

The panaxan components of the ginseng root have demonstrated an insulin sensitizing effect\(^{19}\) and an increased basal glucose utilization in the skeletal muscle\(^{20}\) after parenteral administration in rats. However the panaxans are inactive following oral administration\(^{21}\). As ginseng was administered via oral route to normal and diabetic rabbits the panaxan component of the ginseng root would thus have been ineffective in producing hypoglycaemic action by both of the stated mechanisms.

As rabbits having severe hyperglycemia >500 mg/dl upto 800 mg/dl also survived without insulin, an insulin like substance such as pyrolglutamic acid\(^{22}\) or effect could be hypothesized. A similar in vitro effect was noted by\(^{23}\). For confirming this hypothesis further measurements of serum insulin levels is required.

In vivo, enzyme pathways may also be responsible for the hypoglycemia of ginseng powdered root in both normal and diabetic rabbits, as in vitro purified ginseng saponins\(^{24}\) and ginsenoside RB2\(^{25}\) have been shown to regulate the activity of enzymes like glucose 6 phosphate dehydrogenase, glucokinase and glucose 6 phosphatase\(^{26}\).

A drug interaction with the rabbits endogenous corticosteroids could be involved in ginsengs' hypoglycaemic action. Ginseng is known to have a steroid nucleus\(^{27}\) by which it could possibly interact with corticosteroids through an antagonism at the corticosteroid receptor level. Further testing is required to determine this.

A hormonal effect through control on intrinsic glucagon release cannot be ruled out. Glucagon plasma release is inhibited by both glibenclamide and metformin\(^{28}\). Ginseng could also have this glucagon inhibitory effect, causing indirect inhibition of glucagon secretion from A cells of pancreas by enhanced release of somatostatin, linked to its insulin secretagogue effect.

No acute or chronic toxicity of ginseng was recorded in normal or diabetic rabbits during the 16 hour intervals for the entire research duration.

Due to its hypoglycemic potential ginseng holds promise. Therefore upon completion of this animal study, further confirmation of its mechanism of action is planned. A double blind placebo controlled clinical trial for affirmation of the same activity in humans, can be envisaged. The benefits of such a trial could be significant for the indigenous Type-2 diabetic population.

**CONCLUSION**

In final conclusion, hypoglycaemic evaluation of Panax ginseng (Radix rubra) reveals a mild and short lived blood sugar lowering action in comparison to both glibenclamide 5 mg/kg and metformin 250 mg/kg in normal as well as alloxan diabetic rabbits. In normal rabbits, ginseng's root powder (Radix rubra) is ineffective in a dose of 25 mg/kg. However, its doses of 50 mg/kg and 100 mg/kg show significant and early onset of hypoglycaemic action (2 hours post administration). Surprisingly in alloxan diabetic rabbits, all 3 doses of ginseng 25 mg/kg, 50 mg/kg and 100 mg/kg are effective and have delayed onset of hypoglycaemic action (12th hour). The 100 mg/kg ginseng dose is the most efficacious of the 3 doses, in both normal and alloxan diabetic rabbits, giving a longer duration of blood sugar lowering action (4 hours) as compared to a 2-hour effective hypoglycaemic period for 25 mg/kg and 50 mg/kg doses of ginseng.

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