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Effect of *Panax notoginsenoside* Rg1 on bidirectional regulation of blood glucose level in mice

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Panax notoginseng saponin (PNS) is one of the key bioactive components of dry root and rhizome of *Panax notoginseng* (Burk.), a well known as Tianqi in Traditional Chinese Medicine (TCM). Although PNS has been shown to possess various pharmacological activities, such as being antithrombotic, neuroprotective, anti-inflammatory and hypolipidemic, etc., its effects on blood glucose levels have not been well documented but for some preliminary reports. It deserves a detailed *in vivo* investigation in animal model. Thus, to investigate the bi-directional regulation of ginsenoside Rgl (Rg1) on blood glucose in mice, Rg1 with high purity was prepared from panax notoginseng saponins by normal phase silica gel column chromatography and reverse phase C18 preparative chromatography. Normal 4-week-old mice were randomly divided into normal control group, normal control group with Rg1, glucose gavage control group, glucose gavage control group with Rg1, insulin treated control group and overnight fasting control group with or without Rg1 (n = 10). The mice in the control group were intragastrically administered with PBS solution, and the mice in the Rg1 groups were intragastrically administered with Rg1 once a day at the doses of 0.5, 1.0 and 1.5 mg/kg for consecutive 7 days. After the last drug, blood glucose (BG) levels were measured at 0.5 (30 min) and 1 h after administration using a simultaneous automatic biochemical analyzer to observe the effect of Rg1 on BG levels. Compared with the model group, Rg1 significantly decreased the BG levels of hyperglycemic mice induced by glucose gavage (P <0.05), significantly increased the BG level of overnight fasted mice (P <0.05), and had no significant effects on the normal group of mice. Panax notoginseng saponin Rgl has a significant bidirectional regulatory effect on glucose levels in mice. When the blood glucose of mice increases, intragastric administration of Rg1 can effectively reduce the blood glucose; conversely, when the blood glucose of mice is low, Rg1 can effectively increase the blood glucose value.

Keywords: Antidiabetic, Bidirectional regulation, Chinese ginseng, Diabetes management, Herbal, Hyperglycemia, Hypoglycemia, Notoginsenoside Rgl, Saponin, Tianqi, Traditional medicine

Panax notoginseng, as a member of the Araliaceae family, is a rare Chinese medicinal herb[1,2]. Its main effective component is panax notoginseng saponins (PNS), of which the contents of monomeric notoginsenoside Rgl and notoginsenoside Rbl are the highest and belong to dammarane type tetracyclic triterpenoid saponin[3-5]. According to traditional Chinese medicine, PNS and its monomers, Rgl and Rbl, are clinically used for cerebral infarction, cerebral hemorrhage, and traumatic injury due to their effects of promoting blood circulation, removing blood stasis and activating blood vessels[6,7]. With the advancements in research, many new pharmacological effects of PNS and its monomers have been discovered, such as scavenging free radicals, oxygen, and anti-oxidation[8,9].

The incidences of diabetes are increasing exponentially. According to a report published by International Diabetes Federation (IDF) on 3st December 2020, among adults (20–79 years of age), there were approximately 625 million people lived with diabetes worldwide, and by 2035, the number is expected to rise to an estimated 1.01 billion [10]. Another epidemiological report of 2018 projects that the incidence of diabetes had reached 11.6% among Chinese adults, while the prevalence of pre-diabetes was as high as 50.5%[11]. With the advance research focus on the prevention and treatment of diabetes, it has been established that blood glucose management is not limited to the target of glycated haemoglobin (%HbA1c) percentage and the overall level of blood glucose, and blood glucose variation, as an evaluation index, has been paid more and more attention by the academic community[9,10-12]. However, the existing hypoglycemic drugs could only reduce blood glucose unidirectional, and diabetics often face unstable blood glucose fluctuation or symptoms of hypoglycemia

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with the development of the disease[13,14]. Moreover, hypoglycemia has been reported to be more harmful than hyperglycemia[15]. Hyperglycemia for short durations poses no threat when compared to hypoglycemia, which is rapid and likely to cause coma or can prove fatal in severe cases, especially among elders with weak perception[16,17]. Studies have confirmed that blood glucose fluctuation is an independent risk factor for cardiovascular disease, which triggers oxygen stress and promote expression of inflammatory factors, and vascular endothelial cell apoptosis, atherosclerosis, and islet β cell function damage[18,19]. Meanwhile, increasing evidences have demonstrated that blood glucose fluctuation is also an independent risk factor for diabetic complications[20]. Therefore, sustained improvements in glycemic control, which not only control hyperglycemia, but also prevent hypoglycemia, and tries to keep the body's blood glucose in a stable state, is vital in diabetic patients.

At present, apart from antidiabetic drugs, diet regulation, exercise and frequent blood glucose monitoring are used to prevent and treat unstable blood glucose and hypoglycemia in diabetic patients[21]. However, patients' non-adherence to recommended treatment regimes is influenced by various barriers. Diabetes related distress has been identified as a major factor responsible for poor adherence to available treatment[22] Diabetic patients have adapted to traditional Chinese medicine (TCM) due to promising results in the ailment of diabetes and its associated complications.[23] Nevertheless, TCM cannot be promoted to cure diabetes due to its poor universality and inadequate knowledge about its active pharmaceutical ingredient[24,25]. In this study, we tried to evaluate whether or not Panax notoginseng saponin Rgl holds the potential to bilaterally regulate the blood glucose in mice.

Materials and Methods

Chemicals and animals

Panax notoginseng saponins were purchased from Shanghai yuanye Bio-Technology Co., Ltd (Shanghai, China). Chromatogram grade methanol and acetonitrile and the other reagents of AR grade were obtained from ANPEL Laboratory Technologies Inc. (Shanghai, China). Common reagents were purchased from Sigma Aldrich (Merck, Germany). Kunming mice, half male and half female, weighing 17 to 23 g were provided by the Experimental Animal Center of Guangxi University of Traditional Chinese Medicine.

Separation and purification of Rg1 from panax notoginseng

The separation and purification of Rg1 from *Panax notoginseng* was completed in following steps[5]: (i) Pretreatment of packing: Thin-layer chromatography silica gel was dried at 100 to 120°C for 24 h, followed by 150°C for 6 h. After cooling, the gel was ready for purification; (ii) Qualitative analysis by thin layer chromatography: The colour was developed with 10% thioacid using n-butanol: ethyl acetate: water in ratio of 4:1:5 as the developing solvent. Each group of fractions was subjected to thin-layer detection, and according to the Rf value, the fraction solutions were pooled; (iii) Quantitative analysis by liquid chromatography: Reference solution: Weigh accurately 1.00 mg of Rg1 reference substance, place them in a 10 mL volumetric flask, dissolve them with methanol, and then accurately pipette 1.0 mL into a 10 mL volumetric flask, add methanol to volume, and then prepare a solution with mass concentration of 10 μg/mL, and Test solution: Accurately weigh an appropriate amount of panax notoginseng saponins powder, place it in a 25 mL volumetric flask, use mobile phase to dissolve ultrasonic solubilization, fully dissolve it, and filter the microporous filter membrane for later use; and (iv) Preparation of standard curve: Accurately pipette 0.5, 1.0, 1.5, 2.0, and 2.5 mL of Rg1 reference solution (10 μg/mL) into 10 mL volumetric flasks, respectively, then dilute to volume with methanol, and shake well. According to the above chromatographic conditions, accurately inject 20 μL into the liquid chromatograph, determine the peak area and draw the standard curve with the mass concentration (μg/mL) of the reference substance as the abscissa and the peak area as the ordinate.

Effects of Rg1 on the blood glucose levels in normal mice

Forty normal mice were randomly divided into normal control group and high, medium and low doses of Rg1 treated groups with 10 mice in each group[12]. Three Rg1 groups and normal control group were daily administered 0.5, 1.0, 1.5 mg/kg, and equal volume of distilled water with a dose volume of 20 mL/kg for 7 days, respectively. Blood samples were collected from the orbital venous plexus of mice at 0.5, 1.0 and 2 h after medication. The blood samples were centrifuged at 3500 rpm/min for 15 min after blood coagulation, followed by serum separation, and blood glucose levels were further measured using a Beckman Kurt automatic biochemical analyzer (Beckman, USA).

Effects of Rg1 on blood glucose levels in hyperglycemic mice

Fifty normal mice were randomly divided into normal control group, high glucose control group and high glucose groups administered with high, medium and low doses of Rg1 (0.5, 1.0 and 1.5 mg/kg), respectively, with 10 mice in each group[8]. Three Rg1 groups were intragastrically administered once a day, and the high glucose control group and the normal control group were given an equal volume of distilled water with a dose volume of 20 mL/kg for 7 days. Blood glucose levels of mice in each group were measured in a manner as described above.

Effects of Rg1 on blood glucose levels in hypoglycemic mice

Fifty normal mice were randomly divided into normal control group, insulin control group and hypoglycemia group administered with high, medium and low doses of Rg1 (n = 10)[8]. Among them, three doses of Rg1 (0.5, 1.0 and 1.5 mg/kg) were intragastrically administered once a day, and the hypoglycemia group and the normal control group were given an equal volume of distilled water with a dose volume of 20 mL/kg for 7 days. After administration, except for the normal control group, the other groups of mice were intramuscularly injected with 0.5 U dose of insulin, and then the sample collection time-points of mice in each group, sampling and determination method were as described above.

Statistical analysis

All measured variables are presented as mean ± SD. Differences in all parameters were tested using one-way ANOVA. *P* values lower than 0.05 were considered significant.

Results

Purification and characterization of Rg1 from *P. notoginseng*

The normal phase silica gel column was used for the separation of Rg1 and a total of 115 bottles of volume 500 mL were collected. According to TLC detection, the fraction solutions with the same Rf value were combined to obtain four fractions. Fraction Zd1 is mainly a saponin with low polarity; fraction Zd2 mainly contains Rg1 with a retention time of 11.3 min and an area percentage ratio of 52%. The fraction Zd3 is mainly a highly polar saponin, and the fraction Zd2 were separated on silica gel column (6 × 60 cm) with 200 ~ 300 mesh, mobile phase dichloromethane:methanol in different ratios [100:3, 100:5, 100:8, 100:10], and 10 L solvent per gradient. As the elution curve shown in Fig. 1A, eluent of Rg1 was dichloromethane 2 methanol solution with a volume ratio of 10:1. The HPLC detection result showed in Fig. 1B revealed that the purity of Rg1 can be increased to 99.3%.

Effect of notoginsenoside Rg1 on blood glucose levels in normal mice

As shown in Table 1, the normal C57BL/6J mice intragastrically received PBS exhibited not significant changes in blood glucose level (BGL), and glucose level of the mice at 0.5 h also showed no obvious difference with the BGL of 1.0 and 2.0 h (P >0.05).

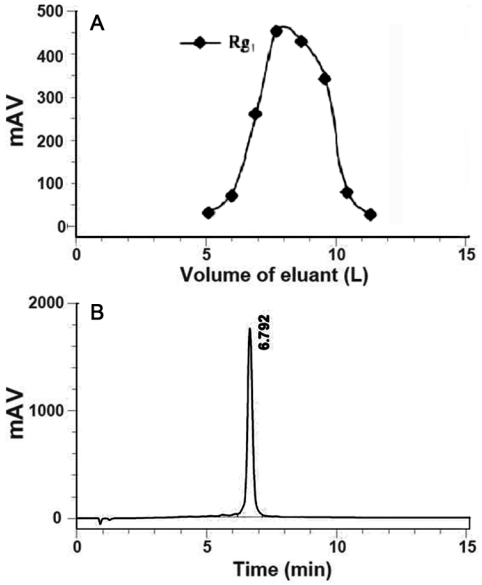

Fig. 1 —Elution curve (A) and HPLC analysis (B) of Rg1 from *Panax notoginseng*

Table 1— Effect of notoginsenoside Rg1 on blood glucose level in normal, hyperglycemic and hypoglycemic mice

Groups	Dose (mg/kg)	Glucose level (mmol/L) 0.5 h	1 h	2 h
		Normal mice		
Control	PBS	6.9±0.5	6.4±0.8	6.5±0.9
Rg1	0.5	6.8±1.1	6.1±1.0	6.7±1.3
	1.0	6.5±0.8	6.4±0.9	6.5±1.1
	1.5	6.3±0.6	6.5±1.2	6.6±0.8
		Hyperglycemic mice		
Normal	PBS	6.4±0.9	6.6±0.8	6.5±1.2
Control	PBS	16.3±2.2	19.4±3.6	12.2±2.2
Rg1	0.5	10.1±3.2*	11.2±1.4***	6.8±1.7**
	1.0	9.5±1.9*	10.4±1.5***	5.9±1.5**
	1.5	7.4±1.2***	6.5±1.1***	7.1±1.0***
		Hypoglycemic mice		
Normal	PBS	6.8±0.5	6.7±0.3	6.6±0.8
Control	PBS	2.9±0.1	3.4±0.1	3.9±0.2
Rg1	0.5	4.2±0.5*	4.5±0.7	4.4±0.7*
	1.0	5.8±0.8**	6.4±0.5**	5.9±0.6**
	1.5	6.3±1.5***	7.1±1.2***	7.4±0.5***

[*, **, *** P <0.05, 0.02, 0.001 using one-way ANOVA *vs.* control, respectively. All data are expressed as mean ± SD (n = 10)]

Compared with the PBS control group, intragastric administration of Rg1 did not significantly change the BGLs of mice at three time points (0.5, 1.0 and 2.0 h) (P >0.05) indicating that gavage administration of Rg1 did not cause significant fluctuations in blood glucose in normal mice.

Effect of notoginsenoside Rg1 on blood glucose levels in hyperglycemic mice

Except the mice in normal group, all the other groups intragastrically received 2g/kg glucose at the late of medication. As is showed in Table 1, the BGLs of control mice remained stable during the entire experimental period, while those of the mice received Rg1 were all higher than 16 mmoL/L at 0.5 h, and peaked at 1.0 h, then decreased to 12.2 mmoL/L at 2.0 h. Compared with the control group, intragastric administration of three doses of Rg1 significantly reduced the BGLs of mice at three time points (0.5, 1.0 and 2.0 h) in a dose-dependent manner (P <0.05). Above results indicated that gavage administration of Rg1 could effectively ameliorate the hyperglycemia in the hyperglycemic mice.

Effect of notoginsenoside Rg1 on blood glucose levels in hypoglycemic mice

The five groups of mice, except the normal group, were intramuscularly injected with 0.5 U of insulin, followed by intragastric administration of PBS, 0.5, 1.0 and 1.5 mg/kg of Rg1, respectively. Immediately 0.5 h, 1.0 h and 2.0 h after drug administration, blood samples were obtained by orbital blood sampling to measure the BGLs of the mice in each group. As showed in Table 1, the blood glucose of mice in the control group after insulin injection were significantly lower than those of the mice in normal group with a minimum BGL of 2.9 mmol/L. However, the blood glucose changes of mice in the medium and high dose of Rg1 treated groups were not significant compared with the normal group, and the low dose group was still extremely significantly higher than the control group. The above results revealed that intragastric administration of Rg1 effectively improved the state of hypoglycemia in mice.

Discussion

Panax notoginseng has varying effects on the central nervous system, cardiovascular system, digestive system, immune system, endocrine system and genitourinary system, which can also improve the physical and intellectual activity and enhance the non-specific resistance of the body to harmful stimuli[2, 27]. The pharmacological activity of Panax notoginseng often acts bi-directionally due to different functional states of the body, so it is a typical representative drug with "adaptogenic"-like effects[2].

According to different studies, notoginsenoside hold pharmacological activities and positive effects on many diseases, such as atherosclerosis, liver dysfunction, cerebrovascular disease, hypertension, menopausal syndrome, cancer and wound healing[28-30]. Additionally, it can exert therapeutic effects through different mechanisms, for example, notoginsenoside hypoglycemic could regulate the insulin secretion and transcription factors, control blood glucose level, improve insulin sensitivity and glucose transport[31]. Moreover, it can regulate immune function by controlling the production of cytokine, increasing the viability of T cells and restoring the function of T lymphocytes[32,33]. Furthermore, notoginseng can also exert anticancer effects through enhancing cytotoxicity, anti-tumor metastasis, inhibiting angiogenesis and acting in combination with other chemotherapeutic agents to reduce drug resistance[29].

Recently, it has been seen that both postprandial hyperglycemia and hypoglycemia induced by hypoglycemic drugs are the main causes of blood glucose fluctuation in patients with type 2 diabete[34]. Fluctuating hyperglycemia can promote endothelial cell apoptosis, and accelerate the damage of cell morphology and function via improving protein kinase C activity and simultaneously activating oxidative stress response[19]. At the same time, it significantly increases the risk of microangiopathy and cardiovascular death in patients with type 2 diabetes[35]. Impaired blood glucose regulation mechanism in diabetic patients, combining with poor diet control, poor treatment compliance, improper medication and other factors, lead to significant blood glucose fluctuations especially the increase in blood glucose levels[13].

Current study showed that Panax notoginseng Rg1 could effectively improve hyperglycemia induced by intragastric administration of glucose in mice and antagonized the glucose-increasing effect caused by glucose absorption in the body. Therefore, it was considered that Panax notoginseng Rg1 could reduce the level of hyperglycemia, reduce the fluctuations in blood glucose, and slow down the damage effect of blood glucose fluctuation on body cells in diabetic mice. Its mechanism of action may be related to hindering the absorption of glucose, promoting the

utilization of glucose by peripheral tissues, and increasing the synthesis of glycogen. Although western medicine has hypoglycemic effects, however, it leads to hypoglycemia, lactic acidosis and other adverse reactions[14]. Panax ginseng based ginsenosides Rb2 regulates hepatic gluconeogenesis through AMP-activated protein kinase (AMPK) and the orphan nuclear receptor small heterodimer partner (SHP) in hyperlipidemic conditions among *in vitro* model of type 2 diabetes[36]. On the other hand, hypoglycemia often indicates excessive glycemic excursions. The current clinical application confirm that the hypoglycemic effect of Chinese herbal medicine is stable and causes less adverse reactions[37]. Furthermore, current study investigated the effect of IHAE on blood glucose levels in normal mice, and the results showed that three doses of Panax notoginseng Rg1 had no significant effect on blood glucose levels in normal mice (P >0.05). Therefore, notoginseng Rg1 less often leads to too low blood glucose levels.

Conclusion

Current study showed that *Panax notoginseng* Rg1 holds bidirectional regulatory effects on blood glucose in mice, which could reduce the level of hyperglycemia and increase the level of hypoglycemia, however, intragastric administration of Rg1 did not cause significantly significant fluctuations in blood glucose in normal mice. Thus, our findings further validated the bidirectional regulatory effects of Chinese herbal notoginseng Rg1 saponin on blood glucose levels. However, further investigation of the effects of other components in *Panax notoginseng* saponins on blood glucose levels in mice might provide necessary significant support for the role of *Panax notoginseng* saponins in bidirectional glycemic control, and hence its use in diabetic conditions.

Conflict of interest

The authors declare no conflicts of interest.

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