



Effect of single oral dose of proanthocyanidin on postprandial hyperglycemia in healthy rats: A comparative study with sitagliptin

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ABSTRACT

Background: Many of flavonoid rich natural products found to have a significant influence on postprandial hyperglycemia, a major risk factor for diabetic complications. Enhancement of insulinotropic gut hormones by inhibition of dipeptidyl peptidase-IV (DPP-IV) are among the newest strategies for treatments of Type 2 diabetes which thought to be the underlying action through which flavonoid can reduce postprandial hyperglycemia. **Aim:** This study aim was designed to investigate the potential role of standardized grape seed proanthocyanidin in controlling postprandial hyperglycemia by enhancing the regulatory incretin effect of gut hormones in response to oral and intraperitoneal (I.P) glucose load in healthy rats. **Materials and Methods:** Five groups of animals each of six rats were used in this study, which was conducted in March 2013. Groups (II and V) treated with single oral dose of proanthocyanidin (50 mg/kg), Group III received single oral dose of sitagliptin (40 mg/kg) and Groups (I and IV) treated with vehicle serve as control groups. All treatments were given 30 min before oral or I.P glucose load. Blood glucose was estimated over 2 h duration at (0, 30, 60, 90, and 120) min from glucose load. **Result:** Both proanthocyanidin and sitagliptin significantly improve hyperglycemia induced by oral glucose load relative to control. While non-significant changes were achieved by proanthocyanidin after I.P glucose challenge compared to untreated control group. **Conclusion:** The result of this study indicated that proanthocyanidin may possess an enhancement of incretin effect of gut peptides, which could be responsible for some of its action on glucose homeostasis. This finding may provide an opportunity for further pharmacological studies using more specific models to clarify the possible action of proanthocyanidin as a natural DPP-IV inhibitor.

KEY WORDS: Postprandial hyperglycemia, proanthocyanidin, sitagliptin

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Received: February 05, 2014

Accepted: April 09, 2014

Published: May 23, 2014

INTRODUCTION

Diabetes mellitus (DM), is a heterogeneous metabolic disorder in which there is a defect in insulin action and secretion and/or insulin resistance where there is improper insulin response of the body to manage dietary glucose result in hyperglycemia [1,2]. Postprandial hyperglycemia found to be a major risk factor for micro- and macro-vascular complications such as retinopathy, nephropathy and neuropathy associated with diabetes [3,4], since the acute glucose fluctuations during the postprandial period have a considerable effect in the progression of oxidative damage that implicated in the development diabetic vascular complications. Therefore, effective controlling of blood glucose is one of the major goals for DM treatment to reduce the incidence of chronic vascular complications [5,6], accordingly, the recommended therapy in Type 2 diabetes should be directed to control the acute glucose oscillation in addition to mean blood glucose and hemoglobin A_{1c} [7,8]. Although, vast advances have been made in the development

and clinical application of oral hypoglycemic agents, but still the most current hypoglycemic agents have undesirable side-effects and reduced efficacy over time [9]. This highlights the needs for the development of bioactive natural components with antidiabetic activities and fewer side effects to be a leading potential candidate for treatment of DM [10,11]. The theory of meal-induced insulin secretion (the incretin effect) states that glucose is more effective on the pancreatic cells when administered orally than given through intravenous or subcutaneous injections due to the glucose regulatory effect of many gut derived peptides including glucagon like peptide-1 (GLP-1) and glucose dependent insulinotropic peptide (GIP) that produced from the L-cells and K-cells of the intestinal mucosa under normal metabolic conditions to improve glucose homeostasis [12,13]. In Type 2 DM, there is a decrease in the incretin effect and rapid degradation of short lived GLP-I and GIP by dipeptidyl peptidase-IV (DPP-IV) present at the site of their production [14,15]. Therefore, preventing the degradation of endogenous incretins by inhibiting

DPP-IV has been emerged as a new strategy for the control of glucose homeostasis and treatment of Type 2 diabetes [16]. Historical records together with later scientific evidence clearly indicates that the consumption of herbal medicine enriched in polyphenolic compounds has been associated with a reduced risk of developing Type 2 diabetes, where pancreatic islet are not totally destroyed [17]. Many studies have shown that grape seed extract (GSE) have anti-platelet aggregation, antioxidant, cardioprotective activity, improvement of endothelial function, reduction of postprandial hypertriglyceridemia and hypercholesterolemia in insulin resistant animals [18-21]. Moreover, growing evidence indicates that various dietary polyphenols may influence carbohydrate metabolism and regulate glucose homeostasis. There are also indications for the function of blueberry *Vaccinium angustifolium* polyphenols on β -cells by mechanisms affecting insulin secretion and proliferation of β -cells [22,23]. In addition, different polyphenols and GSE also work as anti-diabetic food factors through inhibition of α -glucosidases, pancreatic α -amylase activities in the small intestinal endothelium [24,25]. Procyanidin, abundant bioactive compound in grape, have shown to modulate glucose hemostasis and possess hypolipidemic and anti-hyperglycemic effect in diabetic animals [26-29]. Given the emerging role of DPP-IV as a target for glucose homeostasis regulation, the glucose lowering effect of proanthocyanidins might also mediated by the inhibition or modulation of DPP-IV; however, there are only few studies on the effects of phenolic compounds on DPP-IV activity, and there is lack of evidences about the role of proanthocyanidin in this respect. Therefore, the present study was designed to evaluate the effect of single oral dose of standardized GSE on blood glucose levels after oral and intra peritoneal glucose challenge in normoglycemic animals compared with the standard DPP-IV inhibitor sitagliptin.

MATERIALS AND METHODS

Chemicals

Chemicals and drugs used in this study were of good quality. The glucose powder was purchased from SDI, Iraq, Sitagliptin phosphate (Januvia® 100 mg) tablet (MERK Co., Italy) and standardized GSE proanthocyanidin (Antoxid® 50 mg) tablet obtained from (Balsam Pharma Co, Syria).

Animals and Study Design

Thirty adult male Wister albino rats weighing (100-150 g) were used in this study. They were brought from the animal house of the College of Pharmacy, University of Baghdad after full acclimatization in polyethylene cages under controlled humidity and temperature ($22^{\circ}\text{C} \pm 5^{\circ}\text{C}$) with 12 h light/dark cycle. They were maintained on standard pellet diet and tap water provided *ad libitum* until the day of treatment, where the animals deprived from food 12 h before the experiment. In the first part of the study, three groups of overnight fasted normoglycemic rats (each of six animals) were treated as follows: Group I (control group) received vehicle alone (distilled water)

30 min before oral glucose load (2 g/kg); Group II (test group), received single oral dose of proanthocyanidin (50 mg/kg) 30 min before an oral glucose load (2 g/kg); Group III (standard group), received single oral dose of sitagliptin (40 mg/kg) [30] followed by oral glucose load (2 g/kg) 30 min later. In the second part, two groups of rats were treated as follow: Group IV (control group), challenged with intraperitoneal (I.P) glucose (1 g/kg) after oral administration of vehicle (distilled water); while in Group V (test group), the rats were treated with single oral dose of proanthocyanidin (50 mg/kg) before I.P glucose load (1 g/kg). Blood samples were collected from all animals by tail snipping at different time intervals from administration of glucose (0, 30, 90, and 120 min) for analysis of glucose levels using glucose oxidase-peroxidase reactive strips and a glucometer (ACCU-check, Germany). The present study was conducted at 2013.

Statistical Analysis

Data were expressed as mean \pm standard deviation. The statistical differences between groups were performed using Student's *t*-test and one-way analysis of variance, followed by *post-hoc* analysis using GraphPad Prism 5.0 software for windows. $P < 0.05$ were considered to be statistically significant.

RESULTS

Administration of oral glucose (2 g/kg) increases the blood glucose concentrations with the maximum increase achieved after 30 min (58.37 mg/dl), while comparable decrease in blood glucose was produced by both sitagliptin and proanthocyanidin over the 2 h period of observation which is significantly different with control, and the increase in blood glucose after 30 min was (40.76 and 38.2 mg/dl, respectively) [Table 1 and Figure 1]. When the values of blood glucose after oral glucose challenge are plotted against time, significant decrease of area under the curve ($\text{AUC}_{0-120 \text{ min}}$) was obtained in proanthocyanidin treated group relative to control, but comparable to that produced by sitagliptin at all tested intervals [Figure 2] and the maximum percent of decrement in blood glucose was calculated to be (29.8%) and (28.5%) respectively after 30 min from glucose load. In the second part of the study, the possible contribution of incretin effect in the hypoglycemic action of proanthocyanidin was evaluated through monitoring changes in blood glucose after I.P glucose load. The results showed that blood glucose levels and $\text{AUC}_{0-120 \text{ min}}$ were not significantly changed after single oral dose of proanthocyanidin when compared with control animals challenged with I.P glucose dose [Table 2, Figures 3 and 4].

DISCUSSION

The control of postprandial hyperglycemia is important in achieving tight control of blood glucose level, which is a major target in diabetic therapy [31,32]. Emerging of incretin-based therapy reveals several potential sites of action for the treatment of Type 2 diabetes ranging from increasing insulin secretion, reducing glucagon secretion, and regulating glucose control [33]. However, the major limiting factor of GLP-1 is its susceptibility to degradation by DPP-IV reducing its plasma half-life. This

Table 1: Blood glucose level (mg/dL) in different groups over 2 h period after oral glucose load

Treatment group (n=6)	Zero time	30 min	60 min	90 min	120 min
Control glucose	77±5.4	185.2±2.1	166.6±15.8	146±15.1	124.16±10.6
Sitagliptin + glucose	71.2±5.8	130±27.5*	133.3±11.4*	120±7.2*	108.2±13.6*
Proanthocyanidin + glucose	81.5±10.4	132.3±10.6*	132±9.5*	117.2±7.2*	104±8.4*

Data are expressed as mean±SD. n=6 animals for each group. *Significantly different compared to control group (P<0.05). SD: Standard deviation

Table 2: Blood glucose level mg/dL in proanthocyanidin-treated animals over 2 h period after I.P. glucose load

Treatment group	Zero time	30 min	60 min	120 min	180 min
Control-glucose	75.8±5.89	151±21	153.2±7.4	137.2±4.4	129±2
Proantho-glucose	74.4±4.82	174.4±28.2	143±23	131.4±19.1	116.6±15.7

Data are expressed as mean±SD. n=6 animals in each group. SD: Standard deviation, I.P.: Intraperitoneal

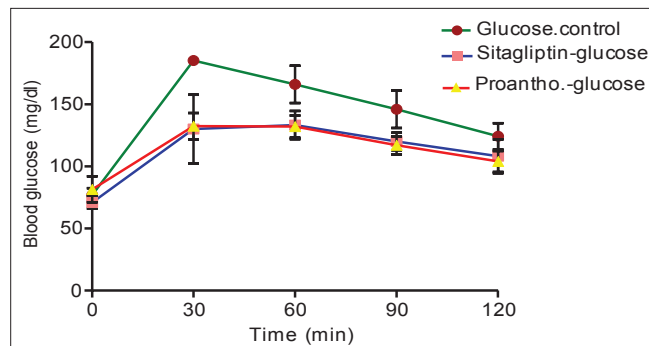


Figure 1: Effects of single oral dose of proanthocyanidin (50 mg/kg) and sitagliptin (40 mg/kg) on postprandial glucose excursion after oral glucose load in normal rats

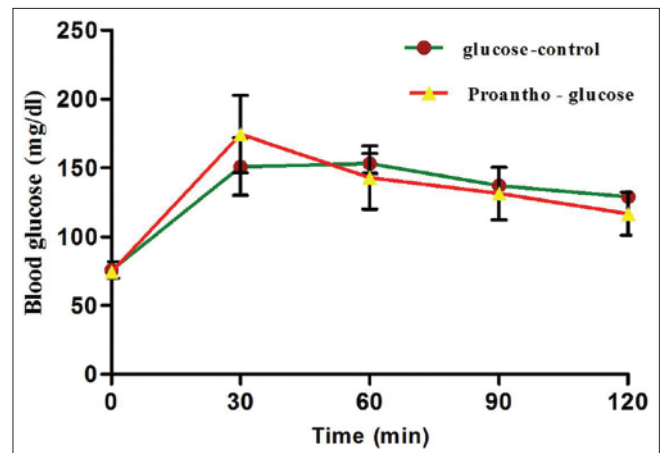


Figure 3: Effect of single oral dose of proanthocyanidin on glucose tolerance test in animals loaded with intraperitoneal glucose in comparison with control

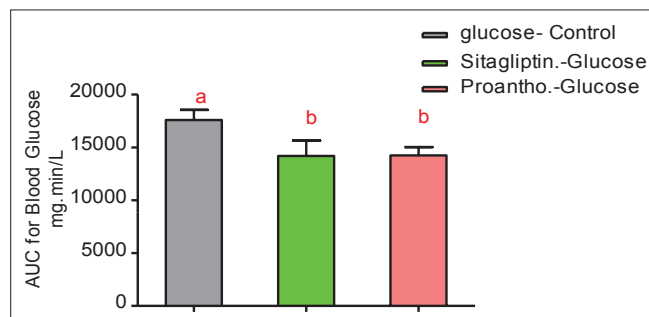


Figure 2: Effects of single oral dose of proanthocyanidin (50 mg/kg) and sitagliptin (40 mg/kg) on changes of area under the curve_{0-120 min} in normal rats after glucose load in comparison to control. Values with non-identical superscript (a and b) are significantly different P < 0.05

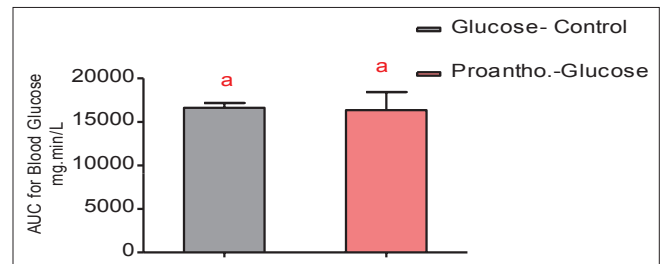


Figure 4: Effect of proanthocyanidin on area under the curve_{0-120 min} after intraperitoneal glucose load in comparison with control. Values with identical superscript (a) are not significantly different P > 0.05

rise need for new anti-diabetic treatments having potential to regress the activity of DPP-IV [34]. Phenolic compounds, as flavonoids that widely abundant in fruits and vegetables, have been suggested as important compounds for diabetes reduction [35,36]. Previous studies on wine compounds and biological activity indicated that such activity is attributed to the presence of several phenolic compounds as a mixture containing trans resveratrol, cinnamic and hydroxycinnamic acids, procyanidins, and some phenolic acids; the inhibitory action of long-term administration of anthocyanin enriched mixture from fermented blackberry and orange peel extract on DPP-IV activity was reported. Moreover, recent study was shown that the administration of resveratrol for 5 weeks increased

glucose-induced GLP-1 secretion in mice through modulation of enteroendocrine system *in vivo* [37]. However, at least to our knowledge, there is lack of evidence about the role of single ingestion of individual components in this respect. Accordingly, it is necessary to elucidate the effect of other natural products on DPP-IV using standardized compound like proanthocyanidin. In previously published work, we demonstrated the potential hypoglycemic effect of proanthocyanidin after maltose load in normal young adults [38]. Based on finding and that reported in other studies indicating that grape seed proanthocyanidin (GSP) extract can inhibit digestive enzymes and possess anti-postprandial hyperglycemic effect in an animal model of experimentally induced diabetes by acting on different sites.

In addition, chronic use of GSP extract produced a marked increase of insulin/glucose ratio in healthy rats, suggesting the valuable benefit of such bioactive product in the management of impaired glucose tolerance in Type 2 diabetes [25,39]. Accordingly, in this preliminary study, we try to shed a light on the possible role of acute administration of proanthocyanidins in augmenting the action of gut hormones through a possible effect on DPP-IV activity. The present data showed that proanthocyanidin significantly decreases postprandial hyperglycemia relative to untreated control; such decrease was found comparable to that produced by sitagliptin at all tested intervals. This result reflects the potency of proanthocyanidin in attenuating postprandial hyperglycemic spikes and alleviating oral glucose tolerance test, which may rise the possibility of GSP to enhance the action of gut hormones, as an inhibitor of DPP-IV enzyme since proanthocyanidin treatment produces statistically significant results through alteration of glucose handling over 2 h period, as indicated by the results of AUC₀₋₁₂₀ and percent decrement of blood glucose, which is comparable to the pretreatment with single oral dose of sitagliptin. This result was in tune with that reported by others, where pretreatment with GSP in both healthy rats and those with acute renal failure showed modulatory effect on DPP-IV activity in the kidney [40], and anthocyanins of berries extract provided the potential for inhibition of DPP-IV [41]. Moreover, many extracts rich in flavonoids can inhibit plasma DPP-IV [42]. Therefore, the hypoglycemic effect of acute treatment with standardized GSP might be partly mediated through increasing the intestinal incretin activity as a consequence of direct effect on of intestinal DPP-IV activity; this assumption was based on the fact that no significant changes observed in term of both glucose tolerance and AUC_{0-120 min} when glucose load was given by I.P route to bypass the role of gut peptide in controlling postprandial hyperglycemia. Although in the current preliminary study we did not measure any inhibitory effect on DPP-IV, there remains a possibility that proanthocyanidin has such activity, and this finding aids in directing our future search toward more specific experimental conditions and models to explore the possible effects of proanthocyanidin on intestinal DPP-IV activity. In conclusion, acute administration of standardized proanthocyanidin improves tolerance to orally administered glucose, but not to the intraperitoneally injected one, suggesting its role in prevention of hyperglycemia and DM by possible attenuation of DPP-IV activity and involvement of incretin like effect.

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Source of Support: Nil, Conflict of Interest: None declared.