



Evaluating Hypoglycaemic Activity of Pomegranate Peel Powder and Defatted Soybean Flour Formulated Cookies in STZ Induced Diabetic Rats

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Authors' contributions

This work was carried out in collaboration among all authors. Author HT did the biochemical studies, data curation, data analysis and statistical analysis and wrote the original draft of the manuscript.

Author Bhuvaneshwari did the conceptualization, investigation, performed methodology and data curation. Authors SLJ and DT supervised the work. Author VMC performed the methodology and did literature searches. Authors PP and SVRR wrote the original draft, reviewed and edited the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Pomegranate fruit peel is an inedible part obtained during the processing of pomegranate juice. Compared to the pulp fraction, it contains more total polyphenols and has a better antioxidant potential. Even though they are good sources of protein, dietary fiber, a variety of minerals, and phytochemicals, soybeans often have a nutritional function. When soybeans are utilized to partially replace wheat in bread items, the nutritional quality will be improved. In the present investigation, defatted soybean flour (DSF) and pomegranate peel powder (PPP) based cookies were made, and their effectiveness on the glycemic activity at the serum level was investigated using two concentrations—5 g and 10 g/rat/day in diabetic and non-diabetic induced rats for up to 21 days. Serum glucose, cholesterol, and haemoglobin levels were favourably affected (-56.92%, -56.33%,

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and +22.34% correspondingly) by the laboratory diet plus 10g of cookies per rat per day in the G6 group of rats after the trial (21 days). In diabetic and non-diabetic rats, PPP and DSF included cookies that lowered blood glucose and cholesterol levels and raised haemoglobin content, but it kept their levels at the required range regardless of the dosage of cookies.

Keywords: Pomegranate peel powder; cookies; type 2 diabetes; hypoglycemic activity.

1. INTRODUCTION

The pomegranate (*Punica granatum* L.) is one of the world's most renowned and enduringly popular fruits, especially in tropical and subtropical areas. It is a member of the Lythraceae family, which is known as the "fruit of paradise." It is a metaphor for "ampleness" and is also known as the "seed apple. Pomegranate production is predicted to be 3186 MT with an estimated 328 million hectares of pomegranate cultivation worldwide. The edible part of a pomegranate is the sweet and juicy arils with seeds. Pomegranate fruit peel is an inedible part obtained during the processing of pomegranate juice. Pomegranate peel (PP), which makes up around 50% of the fresh fruit's weight and is often thrown but is also sold as a dietary supplement. Pomegranate peel is thought to be a great source of ellagitannins (ETs) and ellagic acids (EA), which are both thought to have health advantages. Recent in vitro investigations revealed that the anti-inflammatory, antioxidant, and digestive enzyme inhibitory effects of pomegranate peel's ETs and EA were what made them beneficial for human health. A very recent in vitro study showed that PP flour could release tannic acid and ellagic acid during an in vitro sequential enzyme digestion, which might modify antioxidant status and lead to the production of short-chain fatty acids inside the GIT [1]. The potential utility of PP as a functional component in baked food items, however, is still not well understood in the literature.

Pomegranate peel is currently highly valued by the scientific community as a functional component and bio-preservative in a variety of culinary preparations. To make cookies that are both palatable and nutritionally fortified, pomegranate peel can be added to wheat flour as a source of dietary fiber, minerals, and biological antioxidants. Pomegranate peel recycling and subsequent use in bakery goods as a natural preservative and potential fortifier may help avoid the health concerns associated with synthetic additives, which frequently result in a greater financial burden on the individual and the community. Similarly, soybean (*Glycine max*)

is an annual leguminous crop with a pod as an edible product that is high in free fats and protein [2]. Soybean flour is mainly used in the bakery industry as a replacement for wheat flour since it is a rich source of protein. It is commercially available in 2 forms, i.e., defatted and full-fat form. Defatted soybean flour is a concentrated form of flour wherein oil is removed during the production process [3]. Cookies are baked or prepared foods that are typically classified as desserts. Cookies are often loved by a wide range of individuals, regardless of age. It is typically offered as a refreshment snack with tea or coffee. However, because carbohydrate-rich wheat was a prominent component, diabetics did not enjoy the cookies.

Diabetes mellitus is a metabolic condition that results in an elevated blood glucose level. This type of diabetes disease is linked to both heredity and lifestyle. Maintaining a healthy diet and exercising regularly will aid in the management of type 2 diabetes mellitus. Although there are already various hypoglycemic drugs on the market, including insulin, individuals are increasingly drawn to natural therapies that are less expensive to combat this ailment [4]. Furthermore, plant-based products have no negative effects when compared to synthetic drugs. To bridge this gap, an experiment was designed to make cookies out of pomegranate peel powder and defatted soybean flour, and the efficacy on glycemic activity was investigated at the pre-clinical stage using a varied dose.

2. MATERIALS AND METHODS

2.1 Biological Materials

Fresh pomegranate fruits cv. Bhagwa were harvested from the Pomegranate Orchard, Fruit Research Station, Sector 70, University of Horticultural Sciences, Bagalkot (longitude: 75°42' East; latitude: 16°10'). The peels are exposed to a 2% salt solution for 10 minutes after they have been separated from the arils. The peels are once more rinsed with clean tap water, drained, and let dry in the air to eliminate any remaining moisture. To get the dried peel,

these peels were dehydrated in a tray dryer at 65°C for 24 hours. In a mixer grinder, the dried peels were ground into a powder. To get uniform-sized particles, the resultant peel powder was run through a sieve with a mesh size of 0.5 mm.

Other components used to make cookies, such as sugar, baking powder, defatted soybean flour powder, hydrogenated fat, and wheat flour, were procured from the local market. Following clearance from the Animal Ethical Committee (Ref. No: IAEC/HSKCOP/April 2019/UHS 2), 36 male Wistar weanling rats weighing 150–250 g were provided by the animal house of the Department of Pharmacology, College of Pharmacy, BVVS, Bagalkot, Karnataka.

2.2 Preparation of Cookies

The recipe recommended by [5] was followed, with a minor adjustment that involved substituting a portion of the refined wheat flour with 5% pomegranate peel powder and 30% defatted soybean flour (Fig. 1). These cookies were then employed for additional pre-clinical tests.

2.3 Preparation of Wistar Rats and Treatment Details for Pre-clinical Studies

Thirty-six weaning male Wistar rats weighing 150-250 g were obtained from the animal house and were transferred to the laboratory of the Department of Pharmacology, College of

Pharmacy, BVVS, Bagalkot, Karnataka. The rats were maintained in the study environment (room temperature: 25 °C with a 12 h light/dark cycle) for an initial 5 days as an acclimatization period. The rats were fed with water ad libitum as a laboratory diet during the acclimatization period (5 days) and experimental period (21 days).

The rats were divided into six major groups, consisting of six rats in each group. In the first three groups, the rats were not treated with alloxan streptozotocin (non-diabetic rats), in which the first group was given only the laboratory diet (G1), the second was given 5g cookies per kg body weight along with the laboratory diet (G2), and the third group was given 10g cookies per kg body weight along with the laboratory diet (G3) (Table 1).

The same treatments were replicated in the other three groups, where the rats were treated with STZ for the induction of diabetic (diabetic) rats [6]. Diabetes was induced by a single injection of 140 mg/kg body weight of alloxan streptozotocin (STZ) at 0.9% (w/v) saline solution to overnight fasted rats. The treatments in this group will be rats given only the laboratory diet, which can also be considered as diabetic control (G4), rats given 5 g of cookies per kg of body weight along with the laboratory diet (G5), and rats given 10 g of cookies per kg of body weight along with the laboratory diet (G6). The cookies were given for up to 21 days on a daily basis along with a regular laboratory diet (Table 1).

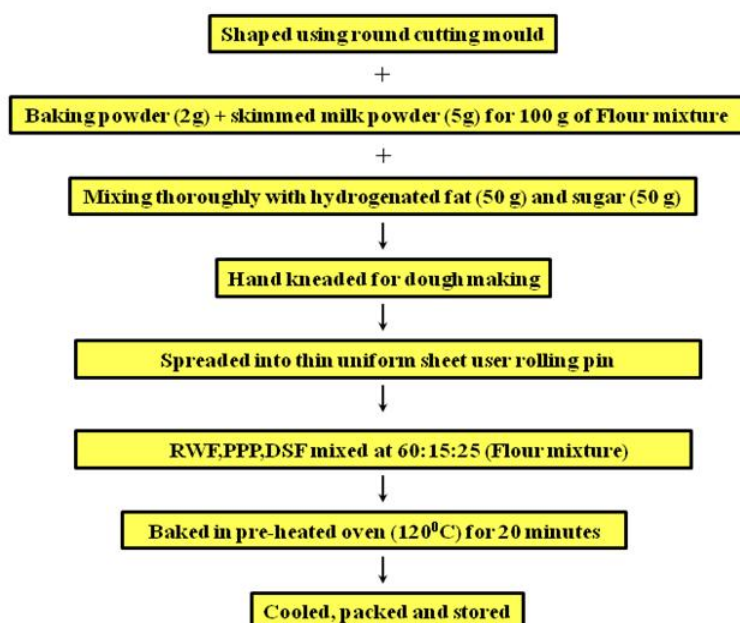


Fig. 1. Preparation of PSP and DSF incorporated cookies

Table 1. Treatment details of pomegranate peel powder and defatted soybean flour incorporated cookies

Group	Treatment	Dose (g/rat/day)	No. of rats	Duration
G ₁	Laboratory diet	-	6	21 days
G ₂	Laboratory diet + PPP and DSF cookies	5	6	21 days
G ₃	Laboratory diet + PPP and DSF cookies	10	6	21 days
G ₄	Laboratory diet (Control) + STZ	-	6	21 days
G ₅	STZ + Laboratory diet + PPP and DSF cookies	5	6	21 days
G ₆	STZ + Laboratory diet + PPP and DSF cookies	10	6	21 days

2.4 Blood Sample Collection and Preparation

Blood samples were collected from all six groups of rats on the 0th, 7th, and 21st days (after 72 hours of injection in diabetic rats) in clean, sterilized, and labelled 2ml capped centrifuge tubes using the retro-orbital plexus puncture method using micro-hematocrit capillary tubes. Immediately after collection, the blood samples were centrifuged at 3000 rpm for 10 min and kept in a slanting position for 1-2 h to facilitate serum separation at ambient conditions. The clear, non-haemolysed serum was then transferred into a clean, sterilised screw-capped vial and used for further analysis.

2.5 Estimation of Serum Glucose, Cholesterol, and Hemoglobin Levels

For this analysis, a sufficient quantity of test tubes were labelled as standard, control, and sample to be tested for all parameters.

Serum glucose estimation in rats was done by Trinder's method [7]. Glucose reagent (500 l) was pipetted into each test tube, and 5 l of blood samples were added to appropriate test tubes, mixed well, and incubated at 37° C for 10 min. The absorbance of the reaction mixture was measured at 525 nm against water as a blank using a UV spectrophotometer. The glucose content in the blood is expressed as mg/dL.

The PEG-CHOD-PAP method was used for the estimation of serum cholesterol [8]. Cholesterol reagent (500 l) was pipetted into each test tube, and 5 l of blood was added to the appropriate tube, mixed well, and incubated at 37° C for 10 min. The absorbance was read at 505 nm on a UV spectrophotometer, calculated using the following formula, and expressed as mg/dL.

$$\text{Total cholesterol } \left(\frac{\text{mg}}{\text{dL}} \right) = \frac{\text{Absorbance of test}}{\text{Absorbance of standard}} \times 100$$

The serum haemoglobin concentration in all blood samples was measured according to the cyanomethemoglobin method using Drabkin's reagent [9]. Blood samples were analysed for serum haemoglobin at the City Diagnostic Centre, Bagalkot.

The serum glucose, cholesterol, and haemoglobin of blood samples collected on the 0th, 7th, and 21st days were compared with their respective rat samples.

2.6 Statistical Analysis

In this present study, the sixuplicate data obtained on serum glucose, cholesterol, and haemoglobin levels in each experimental group were analysed by completely randomised design using one-way analysis of variance (ANOVA) and Fisher's Least Significant Difference at 1% level ($p = 0.01$). The entire analysis was performed using the online statistical programme called Graphpad Prism (version 8.0).

3. RESULTS AND DISCUSSION

Both defatted soybean flour and pomegranate peel powder have a low glycemic index by nature. Both ingredients were utilised in the production of cookies in place of the conventional carbohydrate-rich wheat flour since cookies are consistently taken as a regular evening snack by all age groups.

3.1 Serum Glucose Level

In Table 2, it is shown how different dosages of cookies combined with PPP and DSF affected the blood glucose levels of both diabetic and

non-diabetic rats. In the non-diabetic and diabetic rat groups, the initial serum glucose levels varied from 92.43 to 92.58 mg/dL and 179.43 to 286.05 mg/dL, respectively. Regardless of the feed treatments, the blood glucose level in non-diabetic rats rose at the 7th day and fell by the end of the trial, or the 21st day. But during the course of the trial, the blood glucose levels in the diabetic rat groups steadily decreased (Table 2). The serum glucose level of diabetic control rats (G₄) was significantly higher than those of non-diabetic rats (G₁, G₂ and G₃).

The effect of PPP and DSF incorporated cookies on diabetic rats' serum glucose levels from the 0th to the 21st day revealed a significant reduction in G₆ (-30.53%) followed by G₅ (-28.72%) compared to diabetic control, *i.e.*, G₄ (+1.16%) (Table 3). In the case of non-diabetic rat groups, though the PPP and DSF incorporated cookies increased the glycemic activity at the rate of 2.8 % and 10.9% invariable to its dose (G₂ & G₃ respectively), the serum glucose level was maintained in the normal recommended range of 140 mg/dL [10]. The results obtained in this study with respect to the serum glucose level of diabetic rats are in line with the findings of [11] who reported that pomegranate aqueous extract significantly decreased blood glucose and increased insulin levels in normal and diabetic treated rats. In their review, [12] reported that fasting blood glucose levels were decreased significantly by puniceic acid, methanolic seed extract, and pomegranate peel extract. Pomegranate peel extract is a potent drug for the reduction of diabetes induced by streptozotocin-induced guinea pigs [13]. [14] reported that an extract containing pomegranate peel and glibenclamide significantly reduced the blood glucose level from the 7th day onwards. [15] found that both pomegranate peel powder (PPP) and whey powder (WP) exhibited antioxidant activity.

3.2 Serum Cholesterol Level

The data on cookies incorporated with pomegranate peel powder and defatted soybean flour on the serum cholesterol level (mg/dl) of streptozotocin induced wistar rats as influenced by the different treatments is presented in Table 2.

During the experimental period, the non-diabetic control rats (G₁) showed a gradual increase in

serum cholesterol levels from 29.58 to 33 mg/dL (Table 2). There was a considerable decline in blood cholesterol levels in the other rat groups (G₂ to G₆). On the 21st day, the PPP and DSF incorporated cookies, *i.e.*, 5 g/rat/day and 10 g/rat/day, respectively, and reduced serum cholesterol levels in non-diabetic rats by 26.21% and 18.21% (Table 3). In diabetic rat groups, the PPP and DSF cookies (5 and 10g/rat/day) had the impact of reducing serum cholesterol levels at the rates of 42.21% and 43.70%, respectively (Table 3). The results obtained are in concordance with the findings of [16] who reported that dried pomegranate seeds and peel treatments improved and alleviated the harmful effects of hyperlipidemia and hypercholesterolemia. [17] reported that pomegranate peel and juice extract have a strong impact on reducing total lipids and total cholesterol. [18] revealed that administration of crude pomegranate husk in alloxan (120 mg/kg body weight) induced diabetic rats reduced the concentration of glucose, cholesterol, low density lipid cholesterol, very low density lipid cholesterol, and raised the level of high density lipid cholesterol.

3.3 Serum Haemoglobin Level

Except for the G₁ group, which was fed only laboratory diet, there was an increase in serum haemoglobin content in both STZ-induced diabetic and non-diabetic rats fed with cookies containing pomegranate peel powder and defatted soybean flour from the 0 day to the 21st day interval (Table 2).

Group 6 [10 g/rat/day] had a significant increase in serum haemoglobin content [10.85 mg/dl, 13.08 mg/dl, and 14.75 mg/dl for the 0th, 7th, and 21st days of intervals], which was followed by G₅ [5 g/rat/day] had a significant increase in serum haemoglobin content [10.90 mg/dl, 11.00 mg/dl, and 13.38 mg/dl for the 0th, 7th, and 21st days of intervals]. The rates of increase in serum haemoglobin levels in the respective treatments were 35.94% and 22.75% (Table 3). The results obtained are in concordance with the findings of [11] who reported that haemoglobin and red blood cells of the diabetic induced rat were shown to have a significant difference by the application of pomegranate peel extract. Normal haemoglobin levels of alloxan-induced diabetic rats were maintained with the administration of husk extract of pomegranate [18].

Table 2. Effect of fortified cookies on glucose, cholesterol and haemoglobin at serum level in STZ induced diabetic rats

Treatments	Serum glucose level (mg/dl)			Serum cholesterol level (mg/dl)			Serum haemoglobin level (mg/dl)		
	0 th day	7 th day	21 st day	0 th day	7 th day	21 st day	0 day	7 th day	21 st day
G ₁	92.58	95.93	94.78	29.58	30.65	33.00	14.55	13.85	13.70
G ₂	92.13	94.03	94.85	26.30	23.60	19.38	12.78	14.55	14.60
G ₃	92.43	120.55	103.85	23.33	21.43	19.08	11.13	11.58	12.93
G ₄	286.05	280.30	289.38	60.38	54.78	44.15	10.83	11.08	11.45
G ₅	227.53	197.98	162.18	40.55	32.88	23.43	10.90	11.00	13.38
G ₆	179.43	153.20	124.65	34.25	28.40	19.28	10.85	13.08	14.75
Mean	161.69	157.00	144.95	35.73	31.95	26.38	11.84	12.52	13.47
S.Em±	29.10	29.38	27.32	1.97	2.08	1.92	0.39	0.43	0.42
CD at 1%	118.47	119.61	111.22	8.03	8.50	7.82	1.61	1.75	1.73

Table 3. Effect of fortified cookies in altering the glucose, cholesterol and haemoglobin at serum level in STZ induced diabetic rats at 21st day compared with 0th day

Treatments	0 day	21 st day	% decrease from 0 day to 21 st day	% Decrease in PPP cookies over control on 21 st day
G ₄ : LD (Control) + STZ	286.05	289.38	-1.16	-
G ₅ : LD + STZ + PPP cookies (5g/rat/day)	227.53	162.18	28.72	43.95
G ₆ : LD + STZ + PPP cookies (10 g/rat/day)	179.43	124.65	30.53	56.92
Serum cholesterol level (mg/dl)				
G ₄ : LD (Control) + STZ	60.38	44.15	26.87	-
G ₅ : LD + STZ + PPP cookies (5g/rat/day)	40.55	23.43	42.21	46.93
G ₆ : LD + STZ + PPP cookies (10 g/rat/day)	34.25	19.28	43.70	56.33
Serum haemoglobin level (mg/dl)				
G ₄ : LD (Control) + STZ	10.38	11.45	5.72	-
G ₅ : LD + STZ + PPP cookies (5g/rat/day)	10.90	13.38	22.75	14.42
G ₆ : LD + STZ + PPP cookies (10 g/rat/day)	10.85	14.75	35.94	22.37

LD – Laboratory diet; STZ- Streptozotocin; PPP- Pomegranate peel powder



Fig. 2. Picture showing hypoglycaemic studies of cookies incorporated with pomegranate peel powder and defatted soybean flour in STZ induced diabetic rats

4. CONCLUSION

Although pomegranate peels are full of bioactive compounds, their raw form is not very valuable commercially. Encapsulated PPP is sold by several pharmaceutical companies for a high price that is beyond the reach of those with middle-class and lower incomes. Therefore, a substitute form such as extrudates, cakes, cookies, and other confectioneries that can be afforded by a variety of customers is necessary right now. So, in the present investigation, the oral administration of cookies incorporated with pomegranate peel powder and defatted soybean flour to STZ-induced male wistar rats showed decreased reduction and normalisation of elevated serum glucose and serum cholesterol with normalisation of haemoglobin levels compared to normal untreated rats. Therefore, it can be concluded that cookies incorporated with pomegranate peel powder and defatted soybean flour have shown hypoglycemic and hypocholesterolemic effects in STZ-induced wistar rats.

ETHICS APPROVAL

This work was carried out after the approval taken from Animal Ethical Committee (Ref. No: IAEC/HSKCOP/April 2019/UHS 2).

DATA AVAILABILITY

The datasets used and analyzed during the current study are available from the corresponding author.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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