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Assessment of glycemic index of the unripe green papaya in mice

Yu-Hsing Lin [1, #], Pi-Hsin Chen [2, #], Ya-Ling Cyue [2], Keng-Chia Hsu [2], Ya-Peng Wang [2], Yu-Ying Fang [2], Tsung-Han Wu [2], Shih-Yi Guo [2], Chia-Ying Lin [2], Jhih-Yun Wang [2] and Shao-Wen Hung [2, 3, *]

[1] *Department of Pet Healthcare, Yuanpei University of Medical Technology, Xiangshan, Hsinchu 300, Taiwan*
[2] *Division of Animal Industry, Animal Technology Research Center, Agricultural Technology Research Institute, Xiangshan, Hsinchu 300, Taiwan*
[3] *Department of Nursing, Yuanpei University of Medical Technology, Xiangshan, Hsinchu 300, Taiwan*
[#] *Contributed equally to this work.*

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Abstract

Papaya (*Carica papaya* L.) is a rich-nutrition fruit include vitamins (A, B and C), carbohydrates, proteins, alkaloids, proteolytic enzymes, and benzyl isothiocyanate. Papaya contains papain, which helps strengthen the constitution of diabetes patients. Its water-soluble fiber can stabilize blood sugar levels, reducing the risk of complications. Papaya has benefits such as lowering blood lipids and softening blood vessels due to the fruit acids it contains, which is advantageous for patients with diabetes complicated by hypertension, arteriosclerosis, and dyslipidemia. Additionally, the proteolytic enzymes in papaya are beneficial for the digestive system. Unripe green bananas have been found to contain a significant amount of resistant starch, giving them potential as a low glycemic index (GI) food. Therefore, the aim of this study was to determine the effects of unripe green papaya on blood glucose regulation. The blood glucose values were measured in C57BL/6 mice before and within 120 minutes after consuming 50 mg of glucose and the grated unripe green papaya containing 50 mg of starch was conducted to calculate the incremental area under the curve (IAUC) for blood glucose changes post-consumption of glucose and the grated unripe green papaya. The results showed that the average IAUC for the grated unripe green papaya was 11,176.67, while the average IAUC for glucose was 7,666.25. According to the GI calculation formula, GI of the grated unripe green papaya was determined to be 146. Therefore, based on the results of this study, these results will be used as the basis for the development of related blood glucose regulation products of the unripe green papaya (*Carica papaya* L.) in the future.

Keywords: Blood glucose; *Carica papaya* L.; *In vivo*; Papaya; Regulation

1. Introduction

Diabetes is one of the top ten causes of death among Taiwanese. Nearly, 10,000 people die of diabetes every year in Taiwan. According to the statistics, there are more than 2 million diabetic patients in the country, and the number continues to increase at a rate of 25,000 cases per year. Diabetes and its related complications affect Taiwanese's health and cannot be underestimated, and the medical burden is quite huge. Diabetes can be divided into type I diabetes (destroyed islet cells, resulting in insulin deficiency), type II diabetes (insulin resistance, and combined relative insulin deficiency), other types of diabetes, gestational diabetes, etc. Its diagnostic criteria include the following 4 items [(1) Glycosylated hemoglobin (HbA1c)≧6.5%; (2) Fasting plasma glucose ≧126 mg/dL; (3) Plasma blood glucose ≧200 mg/dL in the second hour of oral glucose tolerance test (OGTT); (4) Typical symptoms of hyperglycemia (eating, drinking, polyuria and weight loss) and random plasma glucose ≧ 200 mg/dL], as long as one of the items is met in non-pregnancy conditions, it can be diagnosed as diabetes (the first three items need to be verified more than 2 times). Diabetes is a complex chronic disease. Diabetes lovers should receive regular treatment and follow-up, and learn to

* Corresponding author: Shao-Wen Hung

implement a good lifestyle and manage their own blood sugar. This is the only way to delay and avoid complications [1-3]. When the blood glucose is high, the body is usually asymptomatic. Usually, it is only known by means of blood glucose testing, or when there are symptoms of three excesses and one deficiency (eating too much, drinking too much, urinating too much, and losing weight), you will doubt whether you have diabetes. Diabetic patients are also less prone to symptoms of physical discomfort when their blood glucose is not well controlled, because of this makes it easy for diabetics to ignore blood glucose control [1-2].

Papaya (*Carica papaya* L.) is well known for its exceptional nutritional and medicinal properties throughout the world. The whole plant including its fruit, leaves, seed, root, bark, juice and latex obtain from papaya plant used as nutritionally, medicinally and for various other purposes. Base on literatures, papaya seeds contained a significant amount materials of anti-cancer activities. *In vitro* study shows that it can treat many cancer cell line. Papaya seeds contain a significant amount materials (isothiocyanate) of anti-cancer activities for suppressing tumor growth of colon, breast, lung, leukemia and prostate cancer [4-6]. Therefore, theses functional compounds of Papaya (*Carica papaya* L.) have indicated that many biological effects is effective against and attenuating the metabolic syndrome, heat-shock, hypertension, diabetes, liver disease, muscle and/or joint pains, hyperglycemia, inflammation, oxidant activity, free radical scavenging effects, acute and chronic hepatitis, and caner growth [7-10]. Therefore, the objective of this study was to evaluate the *in vivo* effects of papaya (*Carica papaya* L.) on the regulation of blood glucose.

2. Materials and Methods

2.1. Chemicals and Reagents

Phosphate-buffered saline (PBS; Sigma-Aldrich, Cat. No. P3813), D-(+)-glucose (Sigma-Aldrich, Cat. No. 50-99-7), saline (Taiwan Biotech Co., LTD, Cat. No. 100-120-1101), and Zoletil 50 (Virbac, Carros, France) were applied in this experiment.

2.2. Procession of the Unripe Green Papaya

The unripe green papaya in block form are chopped with a blade and placed in a mortar. Liquid nitrogen is added for grinding. After grinding, the mixture is sieved through a fine mesh to make the banana particles suitable for administration with a mouse gavage needle. According to the information of the unripe green papaya, the available starch (non-resistant starch) content of the unripe green papaya is 18.37%. To ensure each mouse consumes 50 mg of carbohydrates, each mouse needs to consume 272.18 mg of the test sample. Therefore, 272.18 mg of the test sample is taken, and 1,000 μL of ddH_2O is added to adjust the consistency for gavage needle aspiration and feeding.

2.3. Experimental Animals, Experimental Design, and Sample Collection

Adult female 20 C57BL/6 mice [6 weeks old; body weight (BW) between 19-21 g] with specific pathogen-free (SPF) conditions were used for this study, were purchased from BioLASCO Taiwan Co., Ltd. (Yilan, Taiwan). Before the experiment, all mice were housed in the animal room for 7 days. The environment was maintained room temperature (24-27°C) and 60%-70% humidity with a photoperiod of 12-hr light/12-hr dark cycle. The study will begin after a week acclimation. The Institutional Animal Care and Use Committee (IACUC) of Agricultural Technology Research Institute inspected all animal experiments and this study comply with the guidelines of protocol IACUC 112001 approved by the IACUC ethics committee. The female 20 BALB/c mice were divided respectively the glucose-treated group (n = 10) and the unripe green papaya-treated group (n = 10). The experiment was divided into two stages. Before the experiment begins, the daily diets (No. 5053, LabDiet®; PMI Nutrition International, St. Louis, MO, USA) were removed from the mouse cages to induce fasting. After a fasting period of 6 hours, the first blood glucose measurement was taken, which is recorded as the fasting blood glucose value. Next, all mice were gavaged with 50 mg of glucose, and blood glucose values are measured immediately after feeding. Subsequent blood glucose measurements are taken every 15 minutes, five times in total, then every 30 minutes until the final measurement at 120 minutes post-feeding. After the measurements are completed, the mice are returned to their cages and reared. The process is repeated 2 days later, but with the test sample replacing the glucose for the second stage. The 2-day interval ensures that the glucose administration from the first stage does not affect the data for the test sample in the second stage.

2.4. Blood Glucose Measurement

Blood glucose values are monitored at the scheduled time points. At the specified time points, blood samples are taken from the tail vein of the mice, and blood glucose values are measured using a chip-based glucose meter (Accu-Chek®, Taiwan).

2.5. Statistical Analysis

The data were expressed as mean ± SEM (standard error of the mean). Data calculations were performed using Excel, a built-in software in the Office commercial suite. The glycemic index (GI) value of the sample were calculated using the GI calculation formula: Average incremental area under the curve (IAUC) of unripe green papaya / IAUC of glucose × 100%. Quantitative plotting of the data was done using GraphPad Prism 5.

3. Results

The blood glucose values were measured in female C57BL/6 mice before and within 120 minutes after consuming 50 mg of glucose and the grated unripe green papaya containing 50 mg of starch was conducted to calculate IAUC for blood glucose changes post-consumption of glucose and the grated unripe green papaya. The results showed that the average IAUC for the grated unripe green papaya was 11,176.67, while the average IAUC for glucose was 7,666.25. According to the GI calculation formula: Average IAUC of unripe green papaya / IAUC of glucose × 100%, GI of the grated unripe green papaya was determined to be 146 (Table 1).

Table 1 Changes in blood glucose levels in the glucose-treated and the unripe green papaya-treated mice. Measure the blood glucose levels of mice at specified times and record the blood glucose values for each mouse. Calculate the average blood glucose level for the mice at each time point. All values are expressed as mean ± SEM (standard error of the mean), with each group consisting of n = 10**.**

Blood glucose measurement time (min)	**Groups**	
	Glucose	Unripe green papaya
0	153.39 ± 6.23	136.89 ± 4.89
15	341.39 ± 22.85	274.67 ± 10.28
30	297.06 ± 17.62	287.28 ± 15.46
45	250.72 ± 16.74	276.28 ± 15.73
60	183.67 ± 9.34	254.78 ± 13.93
90	153.33 ± 7.16	192.61 ± 9.85
120	144.89 ± 7.26	156.44 ± 5.82

4. Discussion

Controlling blood glucose levels is of utmost importance due to its profound impact on overall health. High blood glucose levels can wreak havoc on the body by damaging endothelial cells lining blood vessels, leading to a cascade of complications, both acute and chronic. The emphasis on diabetes treatment in recent years stems from the recognition that uncontrolled diabetes poses significant risks to health and well-being. While diabetes itself may not be inherently terrifying, the consequences of chronically elevated blood glucose levels are dire. (1) High blood glucose levels can damage the endothelial cells lining blood vessels throughout the body. This damage compromises the function of blood vessels, leading to impaired circulation and tissue perfusion. (2) Endothelial cell damage and impaired circulation can compromise the function of vital organs such as the kidneys, eyes, heart, and nervous system. Over time, this dysfunction can lead to a range of acute and chronic complications. (3) Acute complications of uncontrolled diabetes include ketoacidosis and hyperglycemic hyperosmolar syndrome, both of which can be life-threatening if not promptly treated. (4) Elevated blood glucose levels can contribute to various eye diseases such as cataracts, glaucoma, and diabetic retinopathy, which can lead to vision impairment or even blindness if left untreated. (5) Diabetes is a leading cause of kidney diseases, including diabetic nephropathy. These conditions can progress to kidney failure, requiring lifelong dialysis or transplantation. (6) Diabetic individuals are at increased risk of developing cardiovascular diseases, including coronary artery disease, which can lead to heart attacks and strokes. (7) Chronic high blood glucose levels can damage nerves, leading to neuropathy characterized by motor, sensory, and autonomic dysfunction. (8) Neuropathy and impaired circulation increase the risk of foot lesions in diabetic individuals. Loss of sensation and poor wound healing can lead to severe complications such as ulcers, gangrene, and the need for amputation. These complications are often irreversible and progressive, ultimately leading to a significant decline in quality of life and, in severe cases, premature death. Therefore, meticulous control of blood glucose levels is essential to mitigate the risk of these complications and ensure overall health and well-being in individuals with diabetes [11-15].

Papaya is renowned for its exceptional nutritional and medicinal properties. Every part of the papaya plant, from its fruit to its leaves, seeds, roots, bark, juice, and latex, has been utilized for various purposes, including nutrition and medicine. Research has demonstrated the functional effects of different parts of the papaya plant in maintaining liver health, preventing diseases, and even treating various conditions [4-6; 16-17]. Studies have indicated that papaya black seed extracts possess potent anti-fungal activity against pathogens such as *Aspergillus flavus*, *Candida albicans*, and *Penicillium citrinum*. Additionally, these extracts have exhibited anti-parasitic effects against *Trypanosoma cruzi*, including both blood trypomastigote and amastigote stages. Furthermore, papaya black seed extracts have shown promising inhibition of sperm motility, increased gastroprotection, and potential anti-cancer activities [6]. According to our previous experiment, papaya black seeds may have a potential to inhibit the growth of colorectal cancer cells. We hope that papaya black seed extracts will be more deeply researched and developed in the R&D of new anti-colorectal cancer drug in the future [4-5]. The multifaceted benefits of papaya underscore its importance not only as a delicious fruit but also as a valuable source of medicinal compounds with diverse therapeutic applications.

In our previous experiment, we successfully established a mouse model with hyperglycemia [4-5]. The weight gains of mice in both the negative control group and the group treated with herbal tea were significantly lower compared to those in the normal control group. Moreover, fasting blood glucose levels in the negative control group were significantly higher than those in the normal control group, while the herbal tea group showed a trend towards lowering fasting blood glucose levels. Notably, the postprandial blood glucose levels in the herbal tea group, after 8 weeks of administration, differed significantly from those in the negative control group. Results from the oral glucose tolerance test (OGTT) indicated that blood glucose levels in the negative control group were notably higher than those in the normal control group. Calculation of the area under the OGTT curve revealed a significantly higher area under the curve in the negative control group compared to the normal control group. However, at the 8th and 12th weeks, the herbal tea group exhibited significantly lower results compared to the negative control group. These findings suggest that herbal tea may have beneficial effects on hyperglycemia, as evidenced by improvements in weight gain, fasting and postprandial blood glucose levels, and OGTT outcomes [4-5].

In this experiment, the results showed that the average IAUC for the grated unripe green papaya was 11,176.67, while the average IAUC for glucose was 7,666.25. According to the GI calculation formula, GI of the grated unripe green papaya was determined to be 146. Therefore, based on the results of this study, these results will be used as the basis for the development of related blood glucose regulation products of the unripe green papaya in the future.

5. Conclusion

The aim of this study was to determine the effects of unripe green papaya on blood glucose regulation. According to the GI calculation formula, GI of the grated unripe green papaya was determined to be 146. Therefore, based on the results of this study, these results will be used as the basis for the development of related blood glucose regulation products of the unripe green papaya (*Carica papaya* L.) in the future.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare no conflict of interest.

Statement of ethical approval

The Institutional Animal Care and Use Committee (IACUC) of Agricultural Technology Research Institute inspected all animal experiments and this study comply with the guidelines of protocol IACUC 112001 approved by the IACUC ethics committee.

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