行政院國家科學委員會專題研究計畫 成果報告

以活體試驗探討香瓜茄對於氧化、醣化及脂質代謝之影響（第 3 年）
研究成果報告(完整版)

計 畫 類 別 ：個別型
計 畫 編 號 ：NSC 97-2313-B-040-001-MY3
執 行 期 間 ：99 年 08 月 01 日至 100 年 07 月 31 日
執 行 單 位 ：中山醫學大學營養學系（所）

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處 理 方 式 ：本計畫涉及專利或其他智慧財產權，2 年後可公開查詢

中 華 民 國 100 年 09 月 07 日

前言

「糖尿病」一直是國人十大死因之一， 長期以來高居十大死因第四位，而糖尿病之死亡原因常常是因其所導致的併發症所引起。而糖尿病併發症的發生與血糖過高(hyperglycemia)有密切的相關性，因此良好的血糖控制對於減緩糖尿病患併發症的發生是很重要的。

糖尿病是一種慢性新陳代謝失調的疾病，主要是因胰臟β-cell無法分泌足量的胰島素或體內無法有效利用胰島素有關，在胰島素缺乏情狀下，使血液中葡萄糖濃度增加超過標準時稱之為糖尿病(Diabetes Mellitus，DM)。在臨床上發現糖尿病患會有多吃、多喝、多尿及體重減輕的典型症狀出現。目前對於糖尿病診斷標準是根據美國糖尿病學會(American diabetes association，ADA)在1997 年6月對糖尿病診斷所做的最新修訂標準:

1.隨機血糖值≧200 mg/dl，合併有多吃、多喝、多尿及體重減輕症狀。

2.空腹血糖值有兩次≧126 mg/dl。

3.OGTT 兩小時後血糖值≧200 mg/dl。

以上三項只要有一項符合即可診斷為糖尿病(1)。

醛糖還原酶(Aldose reductase)大部分存在於人體的神經細胞、水晶體及視網膜等組織中，醛糖還原酶為多元醇路徑(polyol pathway)的關鍵酵素。當人體處於高血糖狀況下醛糖還原酶即被活化，增加葡萄糖代謝成山梨醇，同時又因為山梨醇去氫酶(Sorbitol Dehydrogenase)的活性並不與醛糖還原酶等比例增加，因此細胞內山梨醇濃度就會大量增加。山梨醇本身為極性分子，不易通透細胞膜;故在細胞內堆積，進而影響細胞滲透壓調節導致細胞代謝與功能的損傷，因而造成糖尿病併發症之發生。

香瓜茄（Pepino Melonpear）， 學名 Solanum Muricatum Ait ;屬茄科植物， 台灣以澎湖產量最多， 屬於澎湖地區高經濟價值之農作物(2)。目前有關此農作物之生理功能的報告並不多見， 所以本研究的目標之一就是要探討香瓜茄的補充是否能影響醛糖還原酶的活性， 進而下降糖尿病併發症之傷害。

研究方法

使用體重約25g的雄性Balb/c小白鼠， 空腹一夜後由尾靜脈注射溶於以1M檸檬酸緩衝之生理食鹽水(pH 4.2)的Streptozotocin(200mg/kg)(3)或改以低劑量腹腔連續注射(4)。在注射後第7~10天利用血糖機檢測血糖反應，判定是否成功誘發糖尿病。控制組則以1M 檸檬酸緩衝之生理食鹽水(pH 4.2)替代STZ進行注射。老鼠分別餵食含有香瓜茄及其水萃物之飼料，待犧牲後取其血液及肝、腎等組織做各項分析，觀察香瓜茄及其水萃物改善血糖及臨床症狀之效果。

分析測定項目:

1. 血液: a)血糖測定 b)血漿胰島素(Insulin)濃度測定 c)Aldose reductase 測定
2. 肝臟: a) Aldose reductase測定 b)抗氧化功能成分Glutathione (GSH) 及 Glutathione Peroxidase酵素活性 c) malondialdehyde (MDA)濃度測定
3. 腎臟: a) Aldose reductase測定 b)抗氧化功能成分Glutathione (GSH) 及 Glutathione Peroxidase酵素活性 c) malondialdehyde (MDA)濃度測定
4. 實驗數據之統計分析

   實驗結果以mean ± SD 表示，以student`s *t*-test 比較不同處理組間的差異，$p < 0.05$ 表統計上具有顯著的差異。

第一年

香瓜茄對糖尿病小鼠血糖及insulin之影響

在第一年的研究模式中以STZ 誘發高血糖下，飲食中添加香瓜茄對糖尿病小鼠血糖具有明顯下降作用。而此作用機轉是否與增加胰臟β-cell 分泌胰島素有關，以本實驗測量血清insulin 結果發現香瓜茄應不具有此生理效應，但對於糖尿病小鼠血糖的控制仍具有良好的效果而且以生食香瓜茄部分較具此功效。而且在體重減輕的典型症狀之控制上也具有抑制作用。

香瓜茄對糖尿病小鼠血清TBARs之影響

在生理正常情況下，生物體內具有抗氧化系統以清除體內產生過多的自由基，而在長期處於高血糖情況下將導致體內氧化壓力昇高，增加細胞及組織器官的損傷。在本實驗結果中發現飲食中添加香瓜茄對糖尿病小鼠體內氧化壓力昇高具有一定程度的下降作用，可緩解體內的高氧化壓力狀態。因此推論香瓜茄中所具有的活性成分可能具有節省GSH 含量消耗的功能，進而增加體內的抗氧化能力。

香瓜茄對糖尿病小鼠血清Aldose reductase之影響

在疾病狀態下，身體組織間長期處於高血糖之狀態，將會導致體內許多的蛋白質進行糖化作用，生成不可逆性構造體（advanced glycation end product；AGE，糖化終產物）。而此產物會使體內之氧化壓力增加造成組織之傷害。而醛糖還原酶即為此多元醇路徑的關鍵酵素，在本實驗結果中發現飲食中添加香瓜茄對糖尿病小鼠體內醛糖還原酶的活性的上升具有抑制作用。因此抑制此關鍵酵素的活性將可對於糖尿病後續併發症之發生具有延緩之作用。因此第一年的研究結果證實，飲食中添加香瓜茄對STZ 誘發糖尿病小鼠血糖的控制、體重下降之延緩、氧化壓力的下降、糖尿病相關併發症的延緩等具有實質的幫助，其對於第1型糖尿病小鼠具有保護的作用。

第二年

在第2年的研究模式中仍以STZ 誘發高血糖，飲食中則是添加經減壓及凍乾濃縮後之香瓜茄水萃物對糖尿病小鼠的血糖控制上仍然具有改善作用。因此證實香瓜茄中所具有的活性成分應具有促進葡萄糖代謝利用的功能，但仍須進一步證實。而第2年的實驗結果亦發現在水萃物之水層中有較好的降血糖效果，因此推論香瓜茄中所含有的活性物質可能具有較高的水溶性。

由本實驗監測的指標發現飲食中添加濃縮萃取之香瓜茄水萃物對糖尿病小鼠的血清與腎臟中的aldose reductase 活性及腎臟中的TBARs值均有下降作用。顯示香瓜茄中所具有的活性成分可能具有降低氧化傷害並能延緩腎臟併發症的發生，與第一年的初步結果一致。而且同樣是在水萃物之水層中有較好的效果。香瓜茄水萃物之初步分析結果顯示經由水萃取後之粗萃物再經由Partition處理之後發現幾乎為高極性之水溶性物質，其餘部分則含量甚微。因此推斷香瓜茄中所具有的活性成分可能是屬於高水溶性之物質。而用NMR 分析的結果發現，除一般常見的營養成分（如：單糖、雙糖、脂肪酸、三酸甘油酯）之外，尚含有不少的未知物質待進一步釐清，而這些較為複雜的成分可能與抗糖尿病的活性有關。將進一步大量純化分析，並證實其抗糖尿病的功效。

第三年

在第三年中，則將其應用至第2型糖尿病中，結果亦顯示仍然可以有效下降因胰島素阻抗所產生的血糖升高的情形。並且也可以下降發生葡萄糖耐受不良的情形，而以胰島素阻抗性指標HOMA-Index來觀察時，也同樣發現香瓜茄水萃物具有降低胰島素阻抗及增進周邊組織在胰島素刺激下對葡萄糖的利用。而第2型糖尿病所伴隨的肥胖及血脂異常，在餵食香瓜茄水萃物後，其肝臟及脂肪組織中也有明顯改善的情形。而且同樣地，在多元醇路徑及糖化終產物（AGEs）的抑制作用上也同樣具有實質的幫助。另外，當長期處於血糖偏高（即高於正常；≧200mg/dl）的情形下，體內氧化壓力亦會增高；而在餵食香瓜茄水萃物後，也可以下降體內的氧化壓力，具有緩和體內升高的氧化壓力的效果。

國科會補助專題研究計畫成果報告自評表

請就研究內容與原計畫相符程度、達成預期目標情況、研究成果之學術或應用價值（簡要敘述成果所代表之意義、價值、影響或進一步發展之可能性）、是否適合在學術期刊發表或申請專利、主要發現或其他有關價值等，作一綜合評估。

1. 請就研究內容與原計畫相符程度、達成預期目標情況作一綜合評估

■達成目標

說明：

本計畫已達成預期目標，已發表期刊論文 1 篇，後續仍持續撰寫投稿中。

□ 未達成目標（請說明，以 100 字為限）

□ 實驗失敗

□ 因故實驗中斷

□ 其他原因

2. 研究成果在學術期刊發表或申請專利等情形：

論文：■已發表 □未發表之文稿 □撰寫中 □無

專利：□已獲得 ■申請中 □無

技轉：□已技轉 □洽談中 □無

其他：(以 100 字為限)

目前已發表期刊論文 1 篇，後續仍持續撰寫投稿中。

3. 請依學術成就、技術創新、社會影響等方面，評估研究成果之學術或應用價值（簡要敘述成果所代表之意義、價值、影響或進一步發展之可能性）（以500 字為限）

香瓜茄（Pepino），屬於茄科植物，台灣以澎湖產量最多，屬於澎湖地區高經濟價值之農作物。但目前對於香瓜茄之生理功能的確實研究報告仍相當缺乏，因有關香瓜茄的生理功能及應用還有許多研究與探討的空間。

本研究結果發現以 STZ 誘發高血糖模式下，飲食中添加香瓜茄水萃物對糖尿病小鼠血糖調控具有明顯下降作用。而在正常生理情況下，生物體內具有抗氧化系統，以清除體內所產生過多的自由基，但長期處於高血糖的情況下則會導致體內氧化壓力升高，增加細胞及組織器官的損傷。

而經由添加香瓜茄水萃物對糖尿病小鼠體內氧化壓力升高具有降低作用，可緩解體內的高氧化壓力狀態，進而增加體內的抗氧化能力。另一方面也經由 LPS(lipopolysaccharide)的投予誘發氧化壓力的情況下也具有抗氧化的效果。

而在長期處於高血糖之疾病狀態下，體內因多元醇路徑（polyol pathway）的活化將導致許多併發症的發生包括：腎病變、視網膜病變、神經病變、血管病變等。而醛糖還原酶即為此多元醇路徑的關鍵酵素，本研究結果中發現飲食中添加香瓜茄水萃物對糖尿病小鼠體內醛糖還原酶的活性具有抑制作用。所以抑制此關鍵酵素的活性將可對於糖尿病併發症之發生具有延緩之作用。因此證實香瓜茄水萃物具有抗氧化作用及多元醇路徑的抑制作用。

國科會補助計畫衍生研發成果推廣資料表

日期：100 年 8 月 日

<table>
<tr><td>國科會補助計畫</td><td colspan="3">計畫名稱：
以活體試驗探討香瓜茄對於氧化、醣化及脂質代謝之影響
計畫主持人：　徐成金
計畫編號：NSC-97-2313-B-040-001-MY3　領域：保健暨營養食品</td></tr>
<tr><td rowspan="2">研發成果名稱</td><td colspan="3">（中文）
香瓜茄及香瓜茄水萃物之抗氧化活性及對於多元醇路徑之抑制作用</td></tr>
<tr><td colspan="3">（英文）
The effect of pepino(Solanum muricatum Ait) on antioxidant activity and inhibition of polyol pathway</td></tr>
<tr><td>成果歸屬機構</td><td>中 山 醫 學 大 學</td><td>發明人
（創作人）</td><td>徐成金</td></tr>
<tr><td rowspan="2">技術說明</td><td colspan="3">（中文）
1. 香瓜茄具有的抗氧化作用。
2. 香瓜茄對多元醇路徑的抑制作用。目前許多的多元醇路徑抑制劑均屬於化學合成，而香瓜茄屬於天然植物，其成分對於多元醇路徑的抑制作用將有利於更進一步的開發。</td></tr>
<tr><td colspan="3">（英文）</td></tr>
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註：**本項研發成果若尚未申請專利，請勿揭露可申請專利之主要內容。**

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Research Article

Received: 15 October 2010 Revised: 26 December 2010 Accepted: 25 January 2011 Published online in Wiley Online Library:

(wileyonlinelibrary.com) DOI 10.1002/jsfa.4345

Protective effects of an aqueous extract from pepino (*Solanum muricatum* Ait.) in diabetic mice

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Abstract

BACKGROUND: This study analysed the content of ascorbic acid, phenolic acids and flavonoids in aqueous and ethanol extracts of pepino (*Solanum muricatum* Ait.), and examined the protective effects of pepino aqueous extract (PAE) in a mouse model of diabetes. PAE at 1, 2 and 4% was supplied for 5 weeks.

RESULTS: Aqueous and ethanol extracts had similar levels of total phenolic acids, but PAE had a higher content of ascorbic acid and total flavonoids than the ethanol extract. PAE treatments at 2% and 4% significantly lowered plasma glucose level ($P < 0.05$); however, only the 4% PAE significantly elevated plasma insulin level at week 5 ($P < 0.05$). PAE treatments significantly decreased the levels of malonyldialdehyde and reactive oxygen species in kidney ($P < 0.05$); however, only the 2% and 4% treatments significantly reduced oxidised glutathione formation, increased glutathione level, and retained renal glutathione peroxidase and catalase activities ($P < 0.05$). PAE treatments at 2% and 4% significantly lowered renal interleukin (IL)-6 and tumour necrosis factor-α levels ($P < 0.05$); however, only the 4% treatments significantly diminished renal IL-1β and levels of monocyte chemoattractant protein-1 ($P < 0.05$). PAE treatments at 4% significantly decreased aldose reductase activity and sorbitol production in kidney ($P < 0.05$).

CONCLUSION: These findings support the suggestion that pepino aqueous extract could attenuate the progression of diabetes via its antioxidative, anti-inflammatory and antiglycative effects.

Keywords: *Solanum muricatum* Ait; pepino; diabetes; oxidative stress; glycation; phytochemicals

INTRODUCTION

Pepino (*Solanum muricatum* Ait.) is a plant food with a sweet smell and yellow skin colour with purple stripes. The original cultivation of pepino extended along the Andes, from southern Colombia to Bolivia and the coast of Peru.[1] This plant food is considered as a fruit in Europe, and it has been cultivated as a new vegetable in Iran.[2] Pepino is a popular food in Penghu island, Taiwan. Local residents of that island always treat it as a vegetable. The volatile aromatic constituents of pepino have been analysed.[3] The authors reported that pepino contains terpenes and β-damascenone, which contributed to the exotic aromas of this food. So far, it remains unknown whether this plant food contains phenolic acids or flavonoids. If pepino is rich in these phytochemicals, this plant food may possess nutraceutical functions.

The anti-tumour effect of pepino has been reported.[4] The authors found that a lyophilised aqueous fraction extracted from pepino possessed cytotoxic activity against test tumour cell lines including prostate, stomach, liver, and breast cancer cells, and concluded that this plant food could target various tumour cells by triggering apoptosis. Although the active compound(s) responsible for the anti-tumour effects of pepino remain unclear, this previous study implied that pepino was a potent medicinal food. Based on safety and economic considerations, taking this plant food directly for consumers may be more practical than using its components. Therefore, the investigation and/or application of extracts from this plant food for preventing and alleviating the development of chronic diseases are reasonable and worthy.

Diabetes is a common chronic disease in Taiwan and other countries. Individuals with diabetes are encouraged to consume more fresh vegetables and fruits in order to obtain phenolic compounds and flavonoids because most of these phytochemicals possess bioactivities, and may modify glucose homeostasis.[5] Thus, an animal study was designed to examine the effect of pepino extract on glycaemic control in a mouse model of diabetes. Furthermore, it is well known that oxidative injury, inflammatory stress and activation of the polyol pathway are inter-related, and contributed to the pathological development

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of diabetes or deterioration due to the disease.[6–8] Therefore, the antioxidative, anti-inflammatory and antiglycative effects from pepino extract were determined by measuring the variation of reactive oxygen species, glutathione, inflammatory cytokines, and activity of certain enzymes responsible for antioxidant defence and the polyol pathway in a mouse model of diabetes.

In our present study, the content of phenolic acids and flavonoids in both aqueous and ethanol extracts of pepino was analysed. The possible protective effects and actions from this plant food against the progression of diabetes were examined. These results could enhance understanding regarding the composition and application of pepino.

MATERIALS AND METHODS

Materials

Fresh pepino (*Solanum muricatum* Ait.), harvested in spring 2008, was obtained from farms in Penghu island, Taiwan. A 50 g edible portion of pepino was chopped and mixed with 150 mL sterile distilled water, or 50% ethanol at 25 °C for 12 h, followed by homogenising in a Waring blender. After filtration through Whatman No. 1 filter paper, the filtrate was further freeze dried to a fine powder. Pure standards of several phenolic acids and flavonoids were purchased from Sigma-Aldrich Chemical Co. (St Louis, MO, USA).

Determination of ascorbic acid, phenolic acids and flavonoids content

The ascorbic acid content in aqueous and ethanol extracts of pepino was analysed by the method of Zapata and Dufour.[9] The total phenolic acids content was determined by the Folin–Ciocalteu method.[10] A 0.5 mL sample of the extract was mixed with 2.5 mL of 0.2 mol L^{-1} Folin–Ciocalteu reagent for 5 min, and further mixed with 2 mL of 75 g L^{-1} sodium carbonate. After 2 h incubation, the absorbance was measured at 760 nm and result was expressed as gallic acid equivalents. Total flavonoids content was measured using the method of Zhishen *et al.*[11] A 0.5 mL sample was mixed with 0.5 mL of 2% $AlCl_3$ ethanol solution. After 1 h incubation, the absorbance was measured at 420 nm and the result was expressed as quercetin equivalents. The content of caffeic acid, cinnamic acid, coumaric acid, ellagic acid, ferulic acid, rosmarinic acid, epicatechin, myricetin, naringenin, quercetin and rutin in aqueous and ethanol extracts of pepino was determined by HPLC methods described by Sellappan *et al.*[12] HPLC equipped with a diode array UV–visible detector and a Phenomenex Prodigy 5-*m*, ODS-2, RP C18 column was used, and UV spectra were recorded from 220 to 450 nm. Quantification was performed based on external standards (six phenolic acids and five flavonoids) with known concentrations. Calibration curves of these standards ranging from 10 to 200 ng mL^{-1} were used with good linearity and R^2 values exceeding 0.98 (peak areas vs. concentration), and peak areas were used to quantify the content of each phenolic acid or flavonoid in the sample.

Animals and diets

Male Balb/cA mice, 3–4 weeks old, were obtained from National Laboratory Animal Center (National Science Council, Taipei City, Taiwan). The use of mice was reviewed and approved by Chung Shan Medical University Animal Care Committee. To induce diabetes, mice with body weight of 22.1 ± 1.2 g were treated with streptozotocin (50 mg kg^{-1} body weight in 0.1 mol L^{-1} citrate buffer, pH 4.5) i.p. for three consecutive days. The blood glucose level was monitored on day 10 from the tail vein using a one-touch blood glucose meter (Lifescan Inc., Milpitas, CA, USA). Mice with fasting blood glucose levels ≥14.0 mmol L^{-1} were used for this study. After diabetes had been induced, mice were divided into several groups (10 mice per group).

Table 1. Content of ascorbic acid, total phenolic acids, total flavonoids, caffeic acid, cinnamic acid, coumaric acid, ellagic acid, ferulic acid, rosmarinic acid, epicatechin, myricetin, naringenin, quercetin and rutin in pepino aqueous extract (PAE) or 50% ethanol extract (PEE)

Compound (mg 100 g^{-1} dry weight)	PAE	PEE
Ascorbic acid	43.8 ± 8.3[b]	6.6 ± 1.3[a]
Total phenolic acids	1217 ± 188[a]	1073 ± 245[a]
Total flavonoids	875 ± 62[b]	461 ± 53[a]
Caffeic acid	– [c]	–
Cinnamic acid	75.7 ± 3.1[b]	23.0 ± 1.5[a]
Coumaric acid	14.5 ± 2.3[a]	23.9 ± 1.7[b]
Ellagic acid	9.2 ± 1.4[a]	6.8 ± 2.1[a]
Ferulic acid	82.3 ± 2.6[b]	11.8 ± 1.3[a]
Rosmarinic acid	47.2 ± 1.6[b]	8.4 ± 0.7[a]
Epicatechin	–	–
Myricetin	31.7 ± 3.8[a]	28.9 ± 1.8[a]
Naringenin	57.2 ± 5.5[b]	14.7 ± 4.2[a]
Quercetin	126.5 ± 10.7[b]	90.3 ± 6.2[a]
Rutin	30.8 ± 7.1[a]	32.4 ± 4.3[a]

Data are expressed as mean ± SD ($n = 9$).
[ab] Means in a row without a common letter differ, $P < 0.05$.
[c] Means too low to be detected.

Design of the experiment

Because pepino aqueous extract (PAE) contained more ascorbic acid and total flavonoids (as shown in Table 1), this extract was used for the antidiabetic study. Powder of PAE at 1, 2 or 4 g was mixed with 99, 98 or 96 g standard powder diet. After 5 weeks supplementation, kidney from each mouse was collected and weighted. Blood was also collected, and plasma was separated from erythrocytes immediately. A 0.1 g sample of kidney was homogenised on ice in 2 mL phosphate-buffered saline (PBS, pH 7.2). The protein concentration of plasma and kidney homogenate was determined by the method of Lowry *et al.*[13] using bovine serum albumin as a standard. In all experiments, the sample was diluted to a final concentration of 1 g protein L^{-1}.

Blood glucose and insulin analyses

The plasma glucose level (mmol L^{-1}) was measured by a glucose HK kit (Sigma Chemical Co.) The plasma insulin level (nmol L^{-1}) was measured by using a rat insulin kit (SRI-13K; Linco Research Inc., St Charles, MO, USA).

Glutathione and oxidised glutathione levels, catalase and glutathione peroxidase activities assay

Glutathione (GSH) and oxidised glutathione (GSSG) concentrations (nmol mg $protein^{-1}$) in kidney were determined by commercial colorimetric GSH and GSSG assay kits (OxisResearch, Portland, OR, USA). Catalase and glutathione peroxidase (GPX) activities (U mg^{-1} protein) in kidney were determined by catalase and GPX assay kits (Calbiochem, EMD Biosciences, Inc., San Diego, CA, USA).

Determination of lipid oxidation and reactive oxygen species

Lipid oxidation was determined by measuring the level of malondialdehyde (MDA, mmol L^{-1}) via an HPLC method[14] in kidney. The method described in Gupta *et al.*[15] was used to measure the amount of reactive oxygen species (ROS) in kidney.

Analyses of cytokines

Kidney was homogenised in 10 mmol L^{-1} Tris-HCl buffered solution (pH 7.4) containing 2 mol L^{-1} NaCl, 1 mmol L^{-1} ethylenediaminetetraacetic acid, 0.01% Tween 80, 1 mmol L^{-1} phenylmethylsulfonyl fluoride, and centrifuged at 9000 × *g* for 30 min at 4 °C. The resultant supernatant was used for cytokine determination. The levels of interleukin (IL)-1β, IL-6, tumour necrosis factor (TNF)-α and monocyte chemoattractant protein (MCP)-1 were measured by ELISA using cytoscreen immunoassay kits (BioSource International, Camarillo, CA, USA).

Measurement of aldose reductase and sorbitol dehydrogenase activities

Kidney homogenate was centrifuged and the supernatant was used for analysis. The method of Nishinaka and Yabe-Nishimura[16] was used to measure renal aldose reductase (AR) activity by monitoring the decrease in absorbance at 340 nm due to oxidation of nicotine adenine dinucleotide phosphate (NADPH). Sorbitol dehydrogenase (SDH) activity was assayed according to the method of Bergmeyer[17] by mixing 100 mL kidney homogenate, 200 mL NADPH (12 mmol L^{-1}) and 1.6 mL triethanolamine buffer (0.2 mol L^{-1}, pH 7.4).

Determination of renal sorbitol and fructose content

Kidney was homogenised with PBS (pH 7.4) containing U-[^{13}C]-sorbitol as an internal standard. The supernatant was lyophilised, and the content of sorbitol and fructose in each lyophilised sample was determined by liquid chromatography with tandem mass spectrometry, according to the method of Guerrant and Moss.[18]

Statistical analyses

The effect of each treatment was analysed from 10 mice in each group. Data were subjected to analysis of variance (ANOVA) and computed using the SAS General Linear Model procedure.[17] Differences with $P < 0.05$ were considered to be significant.

RESULTS

The content of ascorbic acid, total phenolic acids, total flavonoids, caffeic acid, cinnamic acid, coumaric acid, ellagic acid, ferulic acid, rosmarinic acid, epicatechin, myricetin, naringenin, quercetin and rutin in pepino extracts is shown in Table 1. Caffeic acid and epicatechin were not detectable in either aqueous or ethanol extract. Aqueous and ethanol extracts had similar content of total phenolic acids. Aqueous extract had more ascorbic acid, total flavonoids, cinnamic acid, ferulic acid, rosmarinic acid, quercetin and naringenin than ethanol extract. As shown in Table 2, compared with DM control groups, mice with 2% or 4% PAE treatments had significantly lower water intake, lower feed intake and higher body weight at week 5 ($P < 0.05$). Plasma levels of glucose and insulin are presented in Fig. 1. When compared with the DM control group, PAE treatments at 2% and 4% significantly reduced plasma glucose level at week 5 ($P < 0.05$); however, PAE treatments only at 4% significantly elevated plasma insulin level at week 5 ($P < 0.05$).

As shown in Table 3, PAE treatments dose-dependently decreased MDA level in kidney ($P < 0.05$). The renal ROS level was lowered by PAE treatments ($P < 0.05$); but without a dose-dependent effect. PAE treatments, at 2% and 4%, significantly reduced GSSG formation, increased GSH level, and retained GPX and catalase activities in kidney ($P < 0.05$). Renal levels of inflammatory cytokines are presented in Table 4. PAE treatments at 2% and 4% significantly declined IL-6 and TNF-α levels in kidney ($P < 0.05$); however, PAE treatments at 4% only significantly decreased IL-1β and MCP-1 levels in kidney ($P < 0.05$). The effects of PAE upon the renal levels of sorbitol and fructose, and activity of aldose reductase and sorbitol dehydrogenase are presented in Table 5. PAE treatments, only at 4%, significantly diminished aldose reductase activity, and decreased sorbitol and fructose production in kidney ($P < 0.05$).

DISCUSSION

Pepino is consumed as a vegetable in Taiwan and Iran. The results of our present study revealed that both aqueous and ethanol extracts from pepino contained ascorbic acid, phenolic acids and flavonoids. These findings indicated that pepino, at least via the presence of these phytochemicals, could provide healthy benefits. Hyperglycaemia, oxidative stress, inflammation and glycation are

Table 2. Water intake, feed intake and body weight of mice without induced diabetes (non-DM), and a mouse model of diabetes in which the mice consumed a normal diet (DM), or 1, 2, 4% pepino aqueous extract at weeks 2 and 5

		Non-DM	DM	DM+PAE, 1%	DM+PAE, 2%	DM+PAE, 4%	
Water intake (mL mouse^{-1} d^{-1})							
	2	2.1 ± 0.6^{a}	3.7 ± 1.0^{b}	3.4 ± 1.3^{b}	3.6 ± 0.7^{b}	3.2 ± 1.0^{b}	
	5	2.3 ± 1.1^{a}	5.4 ± 1.5^{c}	5.2 ± 1.2^{c}	4.3 ± 0.6^{b}	4.0 ± 0.9^{b}	
Feed intake (g mouse^{-1} d^{-1})							
	2	1.9 ± 0.7^{a}	2.7 ± 1.0^{a}	2.8 ± 0.8^{a}	2.5 ± 1.0^{a}	2.6 ± 1.1^{a}	
	5	2.2 ± 1.0^{a}	4.8 ± 1.2^{c}	4.5 ± 1.4^{c}	3.3 ± 0.9^{b}	3.1 ± 0.7^{b}	
Body weight (g mouse^{-1})							
	2	23.0 ± 1.2^{b}	19.5 ± 0.9^{a}	20.2 ± 1.3^{a}	19.1 ± 0.6^{a}	20.4 ± 1.4^{a}	
	5	26.7 ± 2.3^{c}	15.0 ± 1.4^{a}	15.3 ± 0.9^{a}	17.0 ± 1.0^{b}	17.5 ± 1.3^{b}	

Data are expressed as mean ± SD, $n = 10$.
[a–c] Means in a row without a common letter differ, $P < 0.05$.
PAE, pepino aqueous extract.

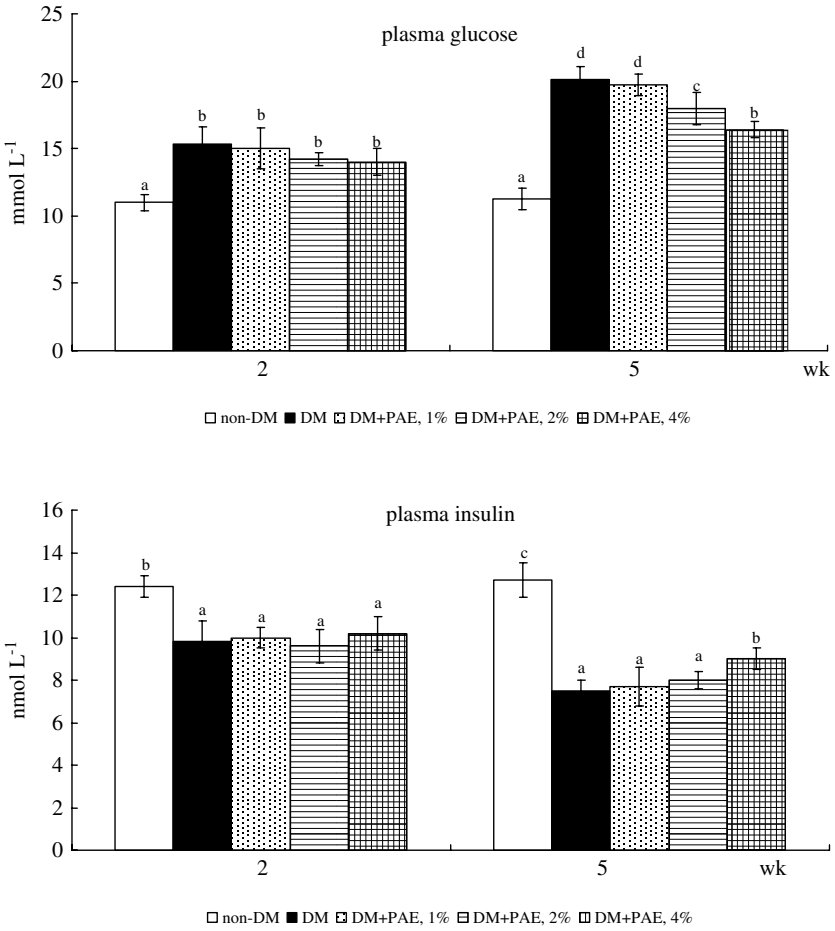

Figure 1. Plasma levels of glucose (mmol L^{-1}) and insulin (nmol L^{-1}) of mice without induced diabetes (non-DM), and a mouse model of diabetes in which the mice consumed a normal diet (DM) or 1%, 2%, 4% pepino aqueous extract (PAE) at weeks 2 and 5. Data are expressed as mean ± SD, $n = 10$. [a–d]Means among bars without a common letter differ, $P < 0.05$.

Table 3. Level of MDA, ROS, GSSG, GSH and activity of catalase and GPX in kidney from mice without induced diabetes (non-DM), and a mouse model of diabetes in which the mice consumed a normal diet (DM), or 1, 2, 4% pepino aqueous extract at 5 weeks

	non-DM	DM	DM+PAE, 1%	DM+PAE, 2%	DM+PAE, 4%
MDA (μmol L^{-1})	1.03 ± 0.10^{a}	3.89 ± 0.40^{e}	3.14 ± 0.27^{d}	2.67 ± 0.20^{c}	2.10 ± 0.23^{b}
ROS (nmol mg^{-1} protein)	0.42 ± 0.06^{a}	1.19 ± 0.16^{c}	0.81 ± 0.13^{b}	0.76 ± 0.08^{b}	0.74 ± 0.05^{b}
GSSG (nmol mg^{-1} protein)	0.31 ± 0.08^{a}	1.23 ± 0.16^{c}	1.20 ± 0.17^{c}	0.82 ± 0.13^{b}	0.73 ± 0.11^{b}
GSH (U mg^{-1} protein)	10.9 ± 1.1^{c}	5.2 ± 1.2^{a}	5.5 ± 0.9^{a}	7.1 ± 1.2^{b}	7.4 ± 1.0^{b}
Catalase	17.4 ± 1.4^{c}	9.2 ± 1.0^{a}	8.9 ± 1.3^{a}	11.3 ± 0.8^{b}	12.0 ± 1.2^{b}
GPX	20.1 ± 2.2^{c}	12.9 ± 1.5^{a}	13.2 ± 1.0^{a}	14.9 ± 1.3^{b}	15.4 ± 1.8^{b}

Data are expressed as mean ± SD, $n = 10$.
[a–e] Means in a row without a common letter differ, $P < 0.05$.
PAE, pepino aqueous extract.

important factors responsible for the development of diabetic complications.[6–8] In our current study, intake of pepino aqueous extract, especially at 2% and 4%, markedly improved body weight loss, hyperglycaemia, hypoinsulinaemia, renal oxidative, inflammatory and glycative stress in a mouse model of diabetes. These results suggest that the aqueous extract of pepino could attenuate the progression the progression of diabetes via multiple actions, and also partially explained the possibility of pepino as a medicinal food.

Our present study found that the aqueous extract of pepino could mitigate renal oxidative stress via reducing the formation of MDA, ROS and GSSG; and enhance antioxidant defence via retaining GSH level and activity of GPX and catalase. The antioxidative effects of ascorbic acid, ferulic acid, rosmarinic acid, naringenin and rutin in humans or in animal models of diabetes have been reported.[20–22] Thus the observed antioxidative protection in diabetic mice with pepino consumption could be partially ascribed to the presence of ascorbic acid, phenolic acids

Table 4. Renal level* of inflammatory cytokines in mice without induced diabetes (non-DM), and a mouse model of diabetes in which the mice consumed a normal diet (DM), or 1, 2, 4% pepino aqueous extract at 5 weeks

Cytokine	non-DM	DM	DM+PAE, 1%	DM+PAE, 2%	DM+PAE, 4%
IL-6	19 ± 5^{a}	257 ± 24^{d}	239 ± 21^{d}	187 ± 16^{c}	149 ± 10^{b}
TNF-α	14 ± 4^{a}	230 ± 28^{d}	219 ± 13^{d}	174 ± 17^{c}	141 ± 11^{b}
IL-1β	15 ± 3^{a}	221 ± 21^{c}	217 ± 18^{c}	208 ± 16^{c}	178 ± 10^{b}
MCP-1	18 ± 5^{a}	213 ± 18^{c}	209 ± 20^{c}	201 ± 16^{c}	165 ± 15^{b}

Data are expressed as mean $\pm$ SD, $n = 10$.
* Results are given as pg mg^{-1} protein.
$^{a-d}$ Means in a row without a common letter differ, $P < 0.05$.
PAE, pepino aqueous extract.

and flavonoids in this aqueous extract. In addition, it is noted that the intake of pepino effectively maintained renal activity of GPX and catalase. This finding implied that pepino might spare these antioxidant enzymes or be able to mediate these enzymes.

It has been documented that the excessive production of IL-6 and TNF-α in type I diabetes facilitated deterioration due to the disease because IL-6 increased platelet sensitivity to thrombin activation, TNF-α impaired beta-cell function, and both IL-6 and TNF-α increased the generation of intracellular ROS.[23] The results of our present study indicated that supplementation with pepino extract at 2% and 4% declined the production of these two pro-inflammatory cytokines, which might in turn slow down the inflammatory response, inflammation-oriented coagulation and oxidative deterioration. The inhibitory effects of ellagic acid, rutin and naringenin upon IL-6 and TNF-α release in mast cell or mouse tissue have been reported.[24,25] Thus, the anti-inflammatory effects from pepino aqueous extract might be partially resulted from the contribution of these compounds. In addition, MCP-1 is a chemotactic factor for activating monocytes and macrophages, and could recruit monocytes to the sites of injury.[26] We found that the renal MCP-1 level could be reduced by pepino aqueous extract only at 4%. Thus, a 4% pepino extract might be able to suppress the activation of monocytes and macrophages, and consequently diminish inflammatory stress. These results suggested that pepino extract at 4% might provide anti-inflammatory protection via both lowering the production of pro-inflammatory cytokines and deactivating monocytes and macrophages.

Hyperglycaemia facilitates glucose metabolism via the polyol pathway and leads to the formation of advanced glycation endproducts and exacerbates diabetes-induced microvascular abnormalities.[27,28] Aldose reductase, the first and rate-limiting enzyme in this polyol pathway, reduces glucose to sorbitol, which could be further metabolised to fructose by sorbitol dehydrogenase, the second enzyme in the polyol pathway.[28] In our present study, the renal aldose reductase activity could be effectively reduced by the 4% pepino extract, which consequently lowered renal sorbitol production. These findings suggest that pepino at 4% could suppress the polyol pathway and alleviate diabetes-associated glycative injury in kidney. The inhibitory effects of phytochemicals, such as quercetin, upon aldose reductase activity and sorbitol production in a rat model of diabetes have been reported.[29] We also notified that pepino aqueous extract had marked quercetin content. Thus, the observed anti-aldose reductase effect from this extract could be partially ascribed to the presence of this phytochemical in this extract. Since aldose reductase activity had been diminished, the lower production of sorbitol in kidney could be explained. Pepino treatment failed to affect renal sorbitol dehydrogenase activity. It is possible that the decreased fructose production in kidney as we observed was simple due to the lower available sorbitol for sorbitol dehydrogenase. Since oxidative, inflammatory and glycative stress had been mitigated in the pepino-treated mouse model of diabetes, it was reasonable to observe the improved glycaemic control and body weight loss in these mice.

Our present study enhanced understanding about the composition of pepino, and we also notified that the sum of ascorbic acid, total phenolic acids and total flavonoids in this aqueous extract was about 2140 mg, only a small proportion of 100 g of freeze-dried powder. Although the combination of ascorbic acid, phenolic acids and flavonoids might offer synergistic protective effects toward these mice with induced diabetes, it was hard to conclude that the observed antioxidative, anti-inflammatory and antiglycative effects from pepino extract only resulted from these components. The other possibility is that other component(s) in pepino also contributed to its antidiabetic benefits. Further study is necessary to analyse and ensure the active compounds in pepino for its protection against diabetes. Oxidative, inflammatory and glycative injury is also involved in the pathological development of other chronic diseases such as cardiac and neurodegenerative diseases.[30,31] Since the aqueous extract of pepino is able to decrease these pathogenic stresses, the application of pepino might be helpful to attenuate the progression of other diseases.

In conclusion, our present study provided several novel findings to elucidate the composition and antidiabetic effects of pepino (*Solanum muricatum* Ait.). This plant food contained ascorbic acid, phenolic acids and flavonoids. The aqueous extract of pepino exhibited antioxidative, anti-inflammatory and

Table 5. Activity of aldose reductase, sorbitol dehydrogenase, and level of sorbitol and fructose in kidney from mice without induced diabetes (non-DM), and a mouse model of diabetes in which the mice consumed a normal diet (DM), or 1, 2, 4% pepino aqueous extract at 5 weeks

	non-DM	DM	DM+PAE, 1%	DM+PAE, 2%	DM+PAE, 4%
Aldose reductase (nmol min^{-1} mg^{-1} protein)	1.09 ± 0.19^{a}	2.48 ± 0.30^{c}	2.51 ± 0.22^{c}	2.33 ± 0.16^{c}	1.83 ± 0.18^{b}
Sorbitol dehydrogenase (U g^{-1} protein)	3.9 ± 0.5^{a}	8.2 ± 1.2^{b}	8.4 ± 1.5^{b}	8.0 ± 1.0^{b}	7.7 ± 0.8^{b}
Sorbitol (nmol mg^{-1} protein)	2.8 ± 0.5^{a}	21.4 ± 1.6^{c}	22.0 ± 1.2^{c}	20.3 ± 1.4^{c}	15.1 ± 1.0^{b}
Fructose (nmol mg^{-1} protein)	10.2 ± 1.4^{a}	78.5 ± 4.2^{c}	75.2 ± 5.2^{c}	76.9 ± 3.6^{c}	64.5 ± 4.9^{b}

Data are expressed as mean $\pm$ SD, $n = 10$.
$^{a-c}$ Means in a row without a common letter differ, $P < 0.05$.
PAE, pepino aqueous extract.

antiglycative protection in a mouse model of diabetes. These findings suggest that pepino could be developed as a functional food for the prevention and/or alleviation of diabetes.

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國科會補助計畫衍生研發成果推廣資料表

日期:2011/09/07

國科會補助計畫	計畫名稱: 以活體試驗探討香瓜茄對於氧化、醣化及脂質代謝之影響
	計畫主持人: 徐成金
	計畫編號: 97-2313-B-040-001-MY3　　學門領域: 食品及農化

無研發成果推廣資料

97 年度專題研究計畫研究成果彙整表

計畫主持人：徐成金	計畫編號：97-2313-B-040-001-MY3
計畫名稱：以活體試驗探討香瓜茄對於氧化、醣化及脂質代謝之影響	

成果項目			量化			單位	備註（質化說明：如數個計畫共同成果、成果列為該期刊之封面故事...等）
			實際已達成數（被接受或已發表）	預期總達成數(含實際已達成數)	本計畫實際貢獻百分比		
國內	論文著作	期刊論文	0	0	100%	篇	
		研究報告/技術報告	0	0	100%		
		研討會論文	1	0	100%		
		專書	0	0	100%		
	專利	申請中件數	1	0	100%	件	
		已獲得件數	0	0	100%		
	技術移轉	件數	0	0	100%	件	
		權利金	0	0	100%	千元	
	參與計畫人力（本國籍）	碩士生	2	0	100%	人次	
		博士生	1	0	100%		
		博士後研究員	0	0	100%		
		專任助理	0	0	100%		
國外	論文著作	期刊論文	1	0	100%	篇	
		研究報告/技術報告	0	0	100%		
		研討會論文	0	0	100%		
		專書	0	0	100%	章/本	
	專利	申請中件數	0	0	100%	件	
		已獲得件數	0	0	100%		
	技術移轉	件數	0	0	100%	件	
		權利金	0	0	100%	千元	
	參與計畫人力（外國籍）	碩士生	0	0	100%	人次	
		博士生	0	0	100%		
		博士後研究員	0	0	100%		
		專任助理	0	0	100%		

其他成果 (無法以量化表達之成果如辦理學術活動、獲得獎項、重要國際合作、研究成果國際影響力及其他協助產業技術發展之具體效益事項等，請以文字敘述填列。)	無

	成果項目	量化	名稱或內容性質簡述
科教處計畫加填項目	測驗工具(含質性與量性)	0	
	課程/模組	0	
	電腦及網路系統或工具	0	
	教材	0	
	舉辦之活動/競賽	0	
	研討會/工作坊	0	
	電子報、網站	0	
	計畫成果推廣之參與（閱聽）人數	0	

國科會補助專題研究計畫成果報告自評表

請就研究內容與原計畫相符程度、達成預期目標情況、研究成果之學術或應用價值（簡要敘述成果所代表之意義、價值、影響或進一步發展之可能性）、是否適合在學術期刊發表或申請專利、主要發現或其他有關價值等，作一綜合評估。

1. 請就研究內容與原計畫相符程度、達成預期目標情況作一綜合評估 ■達成目標 □未達成目標（請說明，以 100 字為限） □實驗失敗 □因故實驗中斷 □其他原因 說明：
2. 研究成果在學術期刊發表或申請專利等情形： 論文：■已發表 □未發表之文稿 □撰寫中 □無 專利：□已獲得 ■申請中 □無 技轉：□已技轉 □洽談中 ■無 其他：(以 100 字為限)
3. 請依學術成就、技術創新、社會影響等方面，評估研究成果之學術或應用價值（簡要敘述成果所代表之意義、價值、影響或進一步發展之可能性）(以 500 字為限)