UNIVERSITI PUTRA MALAYSIA

EFFECT OF POMEGRANATE ON METABOLIC INDICES AND INFLAMMATORY BIOMARKERS IN STREPTOZOTOCIN-NICOTINAMIDE INDUCED DIABETIC RATS

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SEYEDEH ZEINAB TAHERI ROUHI

Thesis submission to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of

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October 2015

Chair: Professor Asmah Rahmat, PhD
Faculty: Medicine and Health Sciences

Type 2 Diabetes Mellitus (T2DM) is a persistent health and lifestyle difficulty in affluent societies worldwide. T2DM is associated not only with hyperinsulinaemia and hyperglycemia, but also with other disorders such as atherosclerosis, hypertension, inflammatory disorders and abnormal lipid profile. Fruits have been applied universally in the treatment of these side effects, since they are natural, safe, and available. The therapeutic potential of pomegranate sections has been stated by multitudinous scientists using various *in vitro* assays, which is through the attendance of particular bioactive compounds. The present study aimed to determine the effect of pomegranate juice (PJ) and pomegranate seed (PS) consumption, and their potential effect on treatment of diabetes and its associated complications such as abnormalities in plasma glucose, insulin, inflammatory factors, lipid profile, and pancreatic islets of Langerhans in T2D rats. Moreover, the identification of the bioactive compounds and antioxidant activity of PJ and PS were studied. Accordingly forty (n= 40) adult healthy male Sprague Dawley rats, were randomly divided into five groups of control (diabetic and non –diabetic) and experimental (diabetic), and T2DM was induced in four groups by administration of streptozotocin-nicotinamide; As they received one intraperitioneal injection of 60 mg/kg b.w of streptozotocin (STZ) each. The dose of 120 mg/kg b.w i.p nicotinamide (NAD) was administered 15 min before STZ. Diabetic animals in PJ, PS , and glibenclamide treated groups (n=8 each) received 1 ml of PJ, 100 mg PS powder diluted in 1 ml of distilled water, and 5 mg/ kg b.w respectively, every day for 21 days through oral gavage. Rats in all groups were sacrificed on day 22. The obtained data was analyzed by SPSS software (v: 20) using One-way analysis of variance (ANOVA). The outputs demonstrated that PJ and PS treatment had slight reducing effect on plasma glucose concentration, with no statistically significant difference comparing to diabetic control (DC) group ($P>0.05$). Moreover, no impact on plasma insulin was observed. While PS treatment did not show any considerable changes in the size and number of islets of Langerhans, PJ treated group showed significant repair and restoration signs of islets of Langerhans ($P<0.05$). The outputs demonstrated that PJ administration lowered the

parameters of plasma total cholesterol and triglyceride significantly, and LDL-c non-significantly less than those of DC group; In contrast, PS treatment significantly raised plasma total cholesterol, LDL-c, and HDL-c levels compared to the DC rats ($P<0.05$). PJ and PS significantly reduced the levels of plasma inflammatory biomarkers, which were actively raised in T2D rats ($P<0.05$). Although further studies should investigate the biochemical mechanisms underlying PS activities as future research plans, the present data suggests that PJ has a protective effect against lipid abnormalities and overexpression of inflammatory cytokines as diabetes side effects. High antioxidant flavonoids and polyphenolic active constituents present in PJ are possibly responsible for its anti-hyperlipidemic and anti-inflammatory effect, as well as the restoration effect on the damaged islet cells of Langerhans in experimental rats. Hence, the pharmacological, biochemical, and histopathological profiles of PJ treated rats obviously indicated its helpful effects in amelioration of diabetes-associated complications, which can help to management of diabetes.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia
sebagai memenuhi keperluan untuk ijazah Sarjana Sains

KESAN DELIMA KE ATAS INDEKS METABOLIK DAN BIOMARKERS KERADANGAN DALAM *STREPTOZOTOCIN-NICOTINAMIDE* TIKUS TERARUH DIABETIK

Oleh

SEYEDEH ZEINAB TAHERI ROUHI

Oktober 2015

Pengerusi: Profesor Asmah Rahmat, PhD
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Diabetes Mellitus Jenis 2 (T2DM) adalah gejala gangguan kesihatan dan gaya hidup, dalam masyarakat di seluruh dunia. T2DM bukan sahaja dikaitkan dengan hiperinsulinaemia dan hiperglisemia, tetapi juga dengan gangguan lain seperti aterosklerosis, tekanan darah tinggi, gangguan keradangan dan profil lipid yang tidak normal. Buah-buahan telah digunakan secara universal dalam rawatan kesan-kesan sampingan, kerana mereka adalah sumber semula jadi, selamat, dan sentiasa ada. Potensi terapeutik buah delima telah dinyatakan oleh ramai ahli-ahli saintis dengan menggunakan *in vitro* asai, iaitu melalui kehadiran sebatian bioaktif tertentu. Kajian ini bertujuan untuk mengenalpasti kesan penggunaan jus delima (PJ) dan biji delima (PS), dan kesan potensi mereka dalam merawat penyakit kencing manis dan komplikasi yang berkaitan dengannya seperti keabnormalan dalam glukosa plasma, insulin, faktor-faktor radang, profil lipid, dan islets pankreas Langerhans pada tikus teraruh T2D. Selain itu, pengenalpastian sebatian bioaktif dan aktiviti antioksidan PJ dan PS juga telah dikaji. Empat puluh ekor (n = 40) tikus jantan Sprague Dawley, telah dibahagikan secara rawak kepada lima kumpulan kawalan (-diabetik kencing manis dan bukan) dan eksperimen (kencing manis), dan T2DM telah diaruh dalam empat kumpulan dengan streptozotocin-nikotinamid; a setiap tikus menerima satu suntikan intraperitioneal 60 mg / kg berat badan daripada streptozotocin (STZ). Dos 120 mg / kg berat badan ip nikotinamid (NAD) diaruh 15 min sebelum STZ. Tikus diabetes di PJ, PS, dan kumpulan rawatan glibenclamide (n = 8 setiap satu) menerima 1 ml PJ, 100 serbuk mg PS dicairkan dalam 1 ml air suling, dan 5 mg / kg berat badan masing-masing, setiap hari selama 21 hari melalui *oral gavage*. Tikus dalam semua kumpulan dibunuh pada hari ke- 22. Data yang diperolehi dianalisis dengan menggunakan perisian SPSS (v: 20) dengan menggunakan analisis varians satu hala (ANOVA). Hasil menunjukkan bahawa kumpulan rawatan PJ dan PS telah mengurangkan sedikit kesan pada kepekatan glukosa plasma, tanpa perbezaan statistik yang signifikan apabila dibandingkan dengan kumpulan kawalan diabetes (DC) (P> 0.05). Malah tidak ada kesan yang dapat diperhatikan kepada plasma insulin. Walaupun kumpulan rawatan PS tidak

menunjukkan apa-apa perubahan besar dalam saiz dan bilangan Langerhans, kumpulan rawatan PJ menunjukkan pembaikan dan pemulihan tanda-tanda besar Langerhans ($P < 0.05$). Hasil menunjukkan bahawa hasil rawatan dengan PJ telah mengurangkan parameter plasma kolesterol dan trigliserida dengan ketara, dan LDL-c berbanding dengan kumpulan DC; Sebaliknya, rawatan PS telah meningkatkan aras plasma kolesterol, LDL-c, dan HDL-c berbanding tikus DC ($P < 0.05$). PJ dan PS dengan ketara telah mengurangkan aras plasma penanda biologi radang, yang dihasilkan secara aktif dalam tikus T2D ($P < 0.05$).Walaubagaimanapun, kajian lanjut perlu dijalankan untuk mengkaji aktiviti mekanisme biokimia asas PS sebagai pelan kajian masa depan, data ini menunjukkan bahawa PJ mempunyai kesan perlindungan terhadap keabnormalan lipid dan radang sitokin iaitu kesan sampingan diabetes. antioksidan Flavonoid yang tinggi dan komponen-komponen polifenolik aktif di dalam PJ mungkin bertanggungjawab untuk menghasilkan kesan anti-hiperlipidemik dan anti-radang, serta kesan pemulihan pada sel-sel Langerhans yang rosak pada tikus eksperimen. Oleh itu, farmakologi, biokimia, dan histopatologi profil dalan kumpulan rawatan tikus PJ jelas menunjukkan kesan yang berguna dalam mengurangkan komplikasi diabetes yang boleh membantu untuk mengawal diabetes.

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I certify that a Thesis Examination Committee has met on 30th October, 2015 to conduct the final examination of seyedeh zeinab taheri rouhi on her thesis entitled "Effect Of Pomegranate On Metabolic Indices And Inflammatory Biomarkers In Streptozotocin-Nicotinamide Induced Diabetic Rats." in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Master of Science.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

ALX	Alloxan
ANOVA	Analysis of variance
AOAC	Association Of Analytical Communities
BCE	Before the Christian Era
BHA	Butylated hydroxyanisole
BWG %	Body Weight Gain percent
CAT	Catalase
COX-2	Cyclooxygenase 2
CRH	Corticotropin Releasing Hormone
D	Drug
DALYs	Disability-Adjusted Life Year
DM	Diabetes Mellitus
DNA	Deoxyribonucleic acid
DPPH	2,2-diphenylpicrylhydrazyl
DPX	Distrene, Plasticiser, Xylene
DW	Distilled Water
e.g.	For example
EC_{50}	Efficient Concentration
EDTA	Ethylene diamine tetraacetic acid
ELISA	Enzyme Linked Immune-Sorbent Assay
FBS	Fasting Blood Sugar
FFA	Free Fatty Acid
Ft	Feet
g	Gram
G	Glibenclamide
GAEs	Gallic Acid Equivalents
GDM	Gestational diabetes mellitus
H&E	hematoxylin & eosin
HbA1c	Hemoglobin A1c
HDL	High-density lipoprotein
i.e.	That is
i.p	Intraperitoneal
IBD	Inflammatory bowel disease
IDDM	Insulin Dependent Diabetes Mellitus
IDF	International Diabetes Federation
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
IL-6	Interleukin 6
IR	Insulin Resistance
IRS-1	Insulin Receptor Substrate-1
Iv	Intravenous
KATP	ATP-sensitive potassium channels
KATP	ATP-sensitive potassium channels
Kg	Kilogram
L	Litre
LA	Linoleic Acid

LCMS/MS	Liquid Chromatography-Tandem Mass Spectrometry
LDL	Low-density lipoprotein
LD_{50}	Median Lethal Dose
LSD	Least Significant Difference
Mg	Milligram
Ml	Milliliter
Mmol	Millimol
Mrna	Messenger Ribonucleic acid
N	Negative control
NAD	Nicotinamide Adenine Dinucleotide
NF-κB	Nuclear Factor kappa-light-chain-enhancer of activated B cells)
NHMS	National Health and Morbidity Survey
NIDDM	Non-Insulin Dependent Diabetes Mellitus
NSP	Non-starch polysaccharides
Ox-LDL	Oxidized LDL
P	Positive control
PAMPs	Pathogen-associated molecular patterns
PFE	Pomegranate Flower Extract
PG	Pomegranate
PGE2	Prostaglandin E2
PGE2	Prostaglandin E2
PJ	Pomegranate juice
PPAR	Peroxisome Proliferator-Activated Receptors
PRRs	Pattern Recognition Receptors
PS	Pomegranate seed
PSO	Pomegranate seed oil
ROS	Reactive Oxygen Species
S.D	Standard Deviation
SOD	Superoxide dismutase
STZ-NAD	Streptozotocin-Nicotinamide
SUR1	Sulfonylurea Receptor 1
T2DM	Type 2 Diabetes Mellitus
TG	Triglycerides
TLRs	Toll-Like Receptors
TNF-α	Tumor necrosis factor α
VLDL	Very-low-density-lipoprotein
vs.	Versus
WHO	World Health Organization
ZDF	Zucker Diabetic Fatty
ZL	Zucker Lean
µg	Microgram

CHAPTER ONE

INTRODUCTION

1.1 Background of Study

Diabetes Mellitus (DM) can be a common systemic ailment affecting a substantial quantity in the population internationally. Globally in 2013, it is estimated that almost 382 million people suffer from diabetes for a prevalence of 8.3% (Aguiree *et al*., 2013). A misbalance between the generation of reactive oxygen species (ROS) and antioxidant guarding in the body, leads to harden oxidative stress, which causes the cellular lesions. The antioxidant defense provide the arrangement of removing ROS in the body, and refund the dominant decreasing environment, as well as mending the tissue's failure (Gutteridge & Halliwell, 1999). Oxidative stress plays a vital role inside etiology along with pathogenesis of many chronic diseases such as cancers, diabetes mellitus, hypertension, and atherosclerosis (Krajcovicova-Kudlackova, Valachovicova, Mislanova, & Pribojova, 2012; Reuter, Gupta, Chaturvedi, & Aggarwal, 2010).

Oxidative stress could be prevented by dietary intake of antioxidants, which could delay and inhibit the oxidation of susceptible cellular substrates. Hence, fortifying the diet via antioxidants is important, as they can support our body versus many chronic diseases. Besides, owing to capability of barricade the lipids oxidative decline, antioxidants have the ability of increasing the food quality protection (Erukainure *et al*., 2012). The reason for the importance of antioxidants is because of their modulation the oxidation processes in the body (Lee *et al.*, 2002). Hence, the research to find cheap and plentiful resources of natural antioxidants is fascinating global interest. Regardless many studies about the positive effect of fruits and vegetables intake on chronic diseases, still the exact mechanisms are not known.

Free radicals neutralization by intake of phytochemicals and antioxidants combination trough the fruits and vegetables, conducts to health promotion (Benbrook, 2005). Previous studies (Broekmans *et al.*, 2000; Zino, Skeaff, Williams, & Mann, 1997) have shown not only great fruit and vegetables consumption causes the plasma carotenoids multiplication, as well as vitamin C (both with high antioxidant attributes), but also can reduce markers of oxidative stress for people with diabetes type 2 (Åsgård *et al.*, 2007). The high phytochemical content and other advantageous micronutrients in fresh fruits and vegetables has been ascribed to their role of human health improvement (Opara & Al-Ani, 2010). These phytochemicals mainly phenolics (similar to flavonoids, phenolic acids, diterpenes, tannins and saponins) have acknowledged for their high antioxidative activity by scavenging free radicals which cause oxidative

stress that can lead to cellular damage and many degenerative disorders (Boyer & Liu, 2004; Lampe, 1999). One of the most abundant and common phenolics are flavonoids, that have been found highly in vegetables and fruits (Schinella, Tournier, Prieto, De Buschiazzo, & Rıos, 2002; Tepe, Sokmen, Askin Akpulat, & Sokmen, 2005). They are involved in the treating process of some diseases such as diabetes (in which free radicals are mediated), because of their phenolic mechanism (Czinner *et al*., 2000).

Lots of intervention studies have added fruits and vegetables in the diet; However people have a little desire to consume fruits and vegetables (Hall, Moore, Harper, & Lynch, 2009). There is strong relation between reduction of occurrence of cancer and cardiovascular disease and consumption of fruits and vegetables (Pomerleau, Lock, & McKee, 2006; van't Veer, Jansen, Klerk, & Kok, 2000). Furthermore, a latter meta-analysis study determined that lifestyle intermediacy would have an effective role to ward off type 2 diabetes (Gillies *et al*., 2007). Diabetes is a strong independent risk factor for cardiovascular sickness (Gerstein *et al*., 2005), and often the conditions exist together, sharing common modifiable risk factors (Liu *et al*., 2000).

At this time, scientific community has considerable attention in the functional properties of some high antioxidant fruits such as pomegranate. *Punica granatum Linn. (Punicaceae)* which named pomegranate is a short tree, which grows in the warm valleys. Pomegranate cultivates in the Himalayas hills and throughout the India (Krishnamurthi, 1969). In the traditional medicine pomegranate (PG) is used for treatment of various sickness because of its bioactive compounds. The grown pomegranate fruit is used in earache and chest disturbances, bronchitis, and brain diseases, because of its special features (diuretic, fortifying, lenient, and styptic). Pomegranate peel and bark are taken orally to hinder biliousness, bronchitis, dysentery, piles, and diarrhea. The powdered sprouts of flower are admitted as interior to help the treatment of diarrhea, children dysentery and bronchitis. The gurgle of flowers extraction assists to reduce the throat and oral inflammation (Viuda-Martos, Fernández-López, & Pérez-Álvarez, 2010). In the Unani medicine, traditionally, the flowers of pomegranate have been used either as a solitary drug or in polyherbal formulizations to cure diabetes (Nandkarni, 1976). The eatable segment of pomegranate demonstrates 52% of whole fruit weight , containing 22% seeds and 78% juice (El-Nemr, Ismail, & Ragab, 1990). The presence of anti-oxidants has been reported from pomegranate in juice, peel, pulp and seed fractions (Yunfeng Li *et al*., 2006). Enormous antioxidant properties have been reported from pomegranate fruit, due to its several flavonoids, alkaloids, and other phenolic components, same as delphinidin, cyanidin and pelargonidin, as well as hydrolysable tannins like punicalagin, gallic acid, pedunculagin, ellagic acid, and punicalin (Du, Wang, & Francis, 1975). Various studies have been done from extracts of several sections of this fruit for ; The biological activities viz. antibacterial, antifungal (Charya, Reddy, Kumar, & Reddy, 1979), anthelmintic, antifertility (Gujral, Varma, & Sareen, 1960), antioxidant (Noda, Kaneyuki, Mori, & Packer, 2002), and antidiabetic (Jafri, Aslam, Javed, & Singh, 2000).

1.2 Problem statements

Type 2 Diabetes Mellitus (T2DM) which is a novel epizootic appearing quickly in developing societies (Wild, Roglic, Green, Sicree, & King, 2004), has been described as a universal significant health issue, that menaces both security and finance of any countries, mainly developing societies. Moreover, it is one of the main chronic diseases which increases the risk of future vascular disease, and regardless of geographic locality and socioeconomic position, it can affect all people (Oliveira *et al*., 2009). It is the fourth or fifth foremost reasons of death in most rich countries, and there is considerable indication that it is altering into an epidemic in many poor and middle-income societies (International Diabetes Atlas, 2011). The latest evaluations of International Diabetes Federation (IDF) show that universally 8.3% of adults have diabetes and the number of people who are living with this disease is going to be 592 million in future 25 years. About 175 million new cases still are not recognized and a majority of diabetic patients are going forward to complications (International Diabetes Atlas, 2011). Despite of these distressing configurations, public health decision makers and administrations in developing nations are not fully aware of the prevalent degree or, more seriously the better potential for enhancement in diabetes, as well as its critical problems in their nations (Oliveira *et al*., 2009). The increase in the burden of diabetes mellitus to population growth, genetics and environmental agents, as well as physical inactivity and growing urbanization, have ascribed by studies (Bener *et al.,* 2012; Bener, Zirie, & Al-Rikabi, 2005; Hu, 2011). Based on Malaysian Burden of Disease and Injury Study, there were 2,261 deaths related to diabetes in year 2000 (857 men and 1404 women). Malaysian diabetic females die quicker, and survivors had to tolerate more afflictions (Faudzi *et al*., 2004). According to Disability-Adjusted Life Year (DALYs) data, diabetes was rated 5th for women and 6th for men among the upside 10 total burden of diabetes in Malaysia (Faudzi *et al*., 2004).

At this time, diabetes treatment basically involves a maintained decline in hyperglycemia through application of thiazolidinediones, sulphonylureas, biguanides, meglitinides, D-phenylalanine derivatives and α-glucosidase suppressors plus insulin. Although, because of undesirable side effects, the affections of these products are arguable and the request regarding new compounds for treating the diabetes is increasing (Group, 1995; Moller, 2001). The patients' tendency for natural compounds with anti-hyperglycemic function is growing, due to the side effects affiliated with oral hypoglycemic drugs and insulin. Consequently, it is necessary to search an economical and a therapeutically efficient utilization of natural productions in prohibition and therapy, particularly in developing and underdeveloped societies. Hence, plants have been suggested as a healthy source of vitamins, fiber and antioxidants, which contain flavonoids and phenolics, as yet unknown origin of possibly beneficial antidiabetic compounds; but just some of them have been exposed to precise scientific consideration owing to a loss of mechanism-supported existing *in vitro* experiments (Fabricant & Farnsworth, 2001; Oubre, Carlson, King, & Reaven, 1997).

1.3 Significance of the Study

Differences in social structure, hormonal misbalance, mental stress, heredity and obesity are optimizing the development of diabetes pandemic which is an important metabolic disorder (Nasiruddin, Qasmi, & Rahmani, 2011). This research consider the changes in inflammatory biomarkers and other$_e$ metabolic indices in diabetes investigational scheme. Clinical trials and epidemiological studies have established an inverse correlation between intake of fruits and vegetables and the occurrence of diseases such as diabetes, inflammation, cardiovascular disease, cancer and aging- related disorders (Canene-Adams *et al*., 2007; Jilcott *et al*., 2007; McCann *et al.*, 2007; Morris, Evans, Tangney, Bienias, & Wilson, 2006; Ruxton, Gardner, & Walker, 2006). Biological actions also high phenolic content of pomegranate fruit lead it to be considered as a healthy fruit (Lansky & Newman, 2007). An analysis of the literature shows that duration of phytochemicals extraction and storage conditions may affect bioavailability of these phytochemicals that might be extracted from fruit juices. Hence to avoid this loss, we used freshly squeezed juice and separate the seeds of pomegranate fruits. In the other hand, there is no scientific publication evaluating impacts of fresh pomegranate juice in contrast with pomegranate seed powder. Regarding the fact that the majority of researches on hypoglycemic activity of pomegranate seed are concentrated on pomegranate seed oil, they may not be comparable with this work. Specific doses of pomegranate juice & seed have been applied in this study, make it different with previous studies.in addition, the controversial results in this study, might be the most notable part, which make new contributions necessary, for future researches. Therefore, remedial role evaluation of the several extracts from various parts of the pomegranate, such as fruit juice and seed were studied in this work against Streptozotocin-Nicotinamide (STZ-NAD) induced diabetic male rats.

1.4 Research Objectives

1.4.1 General Objective

To study the effect of pomegranate on metabolic indices and inflammatory biomarkers in Streptozotocin-Nicotinamide (STZ-NAD) induced diabetic rats.

1.4.2 Specific Objectives

Four specific study goals were proposed:

1. To identify the different types of chemical compositions in pomegranate juice and pomegranate seed by identification of the bioactive compounds

using LC-MS/MS technique, and assessment of antioxidant activity of pomegranate juice and seed separately using DPPH radical scavenging assay.

2. To evaluate of the changes of body weight, plasma levels of glucose, insulin, lipid profile (including cholesterol, triglyceride, LDL, HDL) and inflammatory biomarkers (including IL-6, NF-κB, TNF-α) of rats related to the type of treatments. Normal control group (NC), diabetic control group (DC), pomegranate juice treatment group (PJ), pomegranate seed treatment group (PS), and drug (glibanclamide) treatment group (G), at the end of the intervention period.
3. To assess any significant issues related to the histological features of H&E stained-section of pancreas in rats and the likely impact on what is happening in pancreatic islets of Langerhans before and after treatment.
4. To specify the pomegranate parts in which further treatment could be supported and provide advice on how this might be therapeutically useful.

1.5 Limitations of the Study

There were several limitations in this study that might be considered for further researches:

- The variety of pomegranate fruit used in this study is unknown.
- Since LC-MS/MS can only detect the bioactive compounds present in the sample, it is recommended to use HPLC to quantify the detected compounds in future studies.
- *In vivo* anti-oxidant effect of samples by measuring oxidative stress in blood or tissue should be part of the future measurement. A measurement of anti-oxidant defense enzymes in blood or tissue could also be used.
- The pancreatic beta cell mass did not assessed- Future research should examine the beta cell mass in pancreatic islets of Langerhans, after completing the trial to show difference of the functional beta cells in different groups.
- Further studies should measure the postprandial glucose and insulin levels or perform a GTT to see how islets of Langerhans in pancreas in different groups response to challenge.

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