REVIEW ARTICLE

THE ROLE OF PUMPKIN SEED OIL AS A THERAPY FOR TYPE 2 DIABETES MELLITUS

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ABSTRACT

Background: Type 2 diabetes mellitus is a very common non-communicable disease; the prevalence of diabetes is growing every year. Treatments of diabetes are based on lifestyle modification and oral and injectable drug therapy. Drug therapies have a negative impact on the body. Most patients began to switch to natural ingredients as antihyperglycemic, namely pumpkin seeds. The content of pumpkin seed oil is fatty acids, consisting of oleic acid, linoleic acid, lauric acid, palmitic acid, and stearic acid. ***Objective:*** To explore the potential of pumpkin seed oil and especially as a therapy for type 2 diabetes mellitus. ***Methods:*** The is a narrative review done through extensive literature search, identification, search, and download of national and international journal references. Literature studies were conducted through several portals, such as PubMed, Elsevier, ScienceDirect, and Google Scholar. The references that had been found were in accordance with the predetermined inclusion criteria. Articles were not used if the topic was not relevant. The search for references was in the form of research journals published on the internet for the last 10 years from 2013-2024. ***Results:*** (1) pumpkin and content, the results of the Cucurbitaceae family pumpkin, has a fatty acid content (linoleic, oleic, stearic, and palmitic). (2) linoleic acid on protein tyrosine phosphatase inhibition, the results can provide antidiabetic effects to prevent type 2 diabetes. (3) oleic acid on insulin hormone balance, the results of protection in diabetes mellitus by accelerating GLP-1 secretion. (4) Oleic acid on pancreatic beta cell function, results in securing insulin sensitivity by suppressing ROS formation and regulating MMP-2 activity in cell line 1.1B4. (5) Oleic acid on antioxidant, protective results on structural damage and function of antioxidant enzymes associated in hyperglycemia. (6) lauric acid stimulates GLP-1, results in increased proliferation activity and decreased apoptosis of beta cells. (7) lauric acid as diabetic wound healing, results play a role in improving wound healing because it can stimulate angiogenesis and suppress inflammatory markers. (8) palmitic acid on insulin and beta cell activity, results palmitic acid plays an important role in insulin control and beta cell activity. (9) stearic acid as a tyrosine phosphatase 1B inhibitor, the results of stearic acid increase receptor signaling to stimulate glucose uptake. ***Conclusion:*** Pumpkin seed oil contains potential fatty acids and acts as a therapy for diabetes mellitus. The potential and role as a therapy for diabetes is due to the content of pumpkin seed oil known to have activity in balancing insulin hormones, pancreatic beta cell function, antioxidants, stimulating Glucagon like peptide-1, and healing diabetic wounds.

Keywords: Pumpkin seed, type 2 diabetes mellitus, fatty acid, beta cell activity

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INTRODUCTION

A disease that is known to grow in prevalence from year to year both in the world and in Indonesia is diabetes mellitus. Type 2 diabetes mellitus is a common disease that accounts for 90% of all diabetes mellitus patients in the world[1]. Based on the International Diabetes Federation (IDF) there were 424 million people with diabetes mellitus in 2017, where people with diabetes aged 20-79 years. The number of people with diabetes mellitus is predicted to increase to 686 million by 2045. The number of people with diabetes mellitus in Southeast Asia in 2017 was 82 million, an increase in 2045 of 151 million. Indonesia ranks 7th out of the top 10 countries predicted in 2045 to have 5.4 million people with diabetes mellitus[2]. Meanwhile, the world health

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organization (WHO) report in 2000 predicted that the number of diabetics was 8.4 million, increasing to 21.3 million in 2030[3].

Type 2 diabetes mellitus is a disease characterized by disturbances in carbohydrate, fat, and protein metabolism caused by insulin resistance and insulin secretion in pancreatic beta cells[4,5]. Insulin secretion by pancreatic beta cells depends on three main factors, namely blood glucose levels, ATP-sensitive K channels and voltage- sensitive Calcium Channels of pancreatic beta cells[6]. Insulin resistance is a condition associated with the failure of target organs under normal conditions to respond to the activity of the hormone insulin. Insulin resistance causes insulin- mediated glucose utilization in peripheral tissues to be reduced. Insulin deficiency or insulin resistance causes failure to phosphorylate the insulin receptor substrate (IRS) complex, decreased translocation of glucose transporter-4 (GLUT-4) and decreased glucose oxidation so that glucose cannot enter cells and hyperglycemia conditions occur which result in diabetes mellitus[6].

Patients with diabetes mellitus make efforts in prevention and treatment using modern drug therapy, as for modern drug therapy, including: oral antidiabetic drugs (sulfonylura group, glinid, biguanid, thiazolidinedion (TZD), alpha glucosidase inhibitors, DPP-IV inhibitors). Antidiabetic drugs used by injection (insulin, GLP analogs, and amylin analogs). Sulfonylura class oral antidiabetic drugs such as glibenclamide are often used in patients with type 2 diabetes mellitus. The mechanism of action of glibenclamide is to inhibit ATP sensitive K+ channels in pancreatic beta cells. This inhibition causes depolarization of the cell membrane and will open the Ca channel. so that the opening of the Ca channel, Ca++ ions will enter the pancreatic beta cells and stimulate granules containing insulin to secrete insulin[7]. The side effects of sulfonylurea oral antidiabetic drugs have an impact on allergies. Hypoglycemia can result in shock, seizures, coma and even death. The side effect of hypoglycemia on glibenclamide occurs in elderly patients who have been taking glibenclamide for a long time and have hepatic and renal disorders[8].

By reviewing the many side effects caused and not expected by most sufferers, most sufferers began to switch to other alternative treatments, by utilizing natural ingredients to reduce blood glucose levels without or little side effects. Therefore, a study was conducted on the potential of Indonesian medicinal plants that have antidiabetic activity without causing side effects of hypoglycemia. Indonesia is rich in medicinal plant sources that can be utilized as diabetes therapy. One of the Indonesian plants that can be utilized is pumpkin seeds. The content in pumpkin seed oil is fatty acids. Types of fatty acids in pumpkin seed oil include oleic acid, linoleic acid, lauric acid, palmitic acid, and stearic acid[9]. Research conducted by Azzawi et al that pumpkin seed oil plays a role in reducing blood glucose levels, increasing insulin levels in rabbit diabetes models due to streptozotocin induction, but the mechanism of action of pumpkin oil to reduce blood glucose levels, and increase insulin is not presented in the article[10]. In addition, this review will present the content of pumpkin seed oil and its mechanism of action to increase antioxidant levels in the body, ward off free radicals, and wound healing. Based on the above background, this review article aims to determine the Potential of Pumpkin Seed Oil and its Role as a Therapy for Type 2 Diabetes Mellitus.

METHODS

The narrative review was done through extensive literature review, identification, search, and download of national and international journal references. Literature studies were conducted through several portals, such as PubMed, Elsevier, ScienceDirect, and Google Scholar. This narrative review presents information about the potential of pumpkin seed oil and its role as a therapy for type 2 diabetes mellitus. The literature study was carried out by summarizing material from journal article references into relevant publications, then presented in the form of a review of scientific literature studies. The search for references used PICO strategies such as: "antihyperglycemic", "pumpkin seed oil", "type 2 diabetes mellitus", "pumpkin oil as an antihyperglycemic agent" or combining keywords searched using boolean operators. The keywords use boolean operators such as: "pumpkin seed oil effect" AND "antihyperglycemic". The references that have been found in full text are in accordance with the predetermined inclusion criteria, these inclusion criteria if the discussion is pumpkin seed oil and its role as a therapy for type 2 diabetes mellitus. Articles were not used if the topic was not

relevant and full text was not available. The search was refereed to research journals published on the internet in the last 10 years from 2014- 2024.

Results and Discussion

1. Pumpkin and its active compounds: Pumpkin belongs to the genus *Cucurbita*, ordo *Cucurbitales*, family *Cucurbitaceae*, subfamily *Cucurbitoideae*[11]. The *Cucurbitaceae* family consists of 115 genera and has more than 960 species[12]. Its distribution is dominated by tropical climates, only a few in temperate climates. In general, it is a climbing liana with most herbaceous lianas and there are also soft woody lianas, and there are additional tools on the shoots in the form of tendrils[13]. Tendrils will clump together so that they help support the plant. Varieties of pumpkin include the species *Cucurbita pepo, Cucurbita maxima, Cucurbita moschata, and Cucurbita mixta*[14]. Other species include *Citrulus lanatus, Cucumis sativus, Lutffa acutangula, Momordica charantia*, and *Cucurbita digiata*. The most widely cultivated species of pumpkin globally are the species of Cucurbita moschata, Cucurbita maxima, and Cucurbita pepo[15]. The characteristics of *Cucurbita moschata* seeds have an elliptical shape[16], while according to OECD, pumpkin seeds can be oval or oval-elliptical[15]. There are variations the colors of pumpkin seeds include creamy yellow, yellow-white, brown, white, and light brown. Pumpkin seeds have a weight of 8.38 to 14.34 g in 100 pumpkin seeds[17].

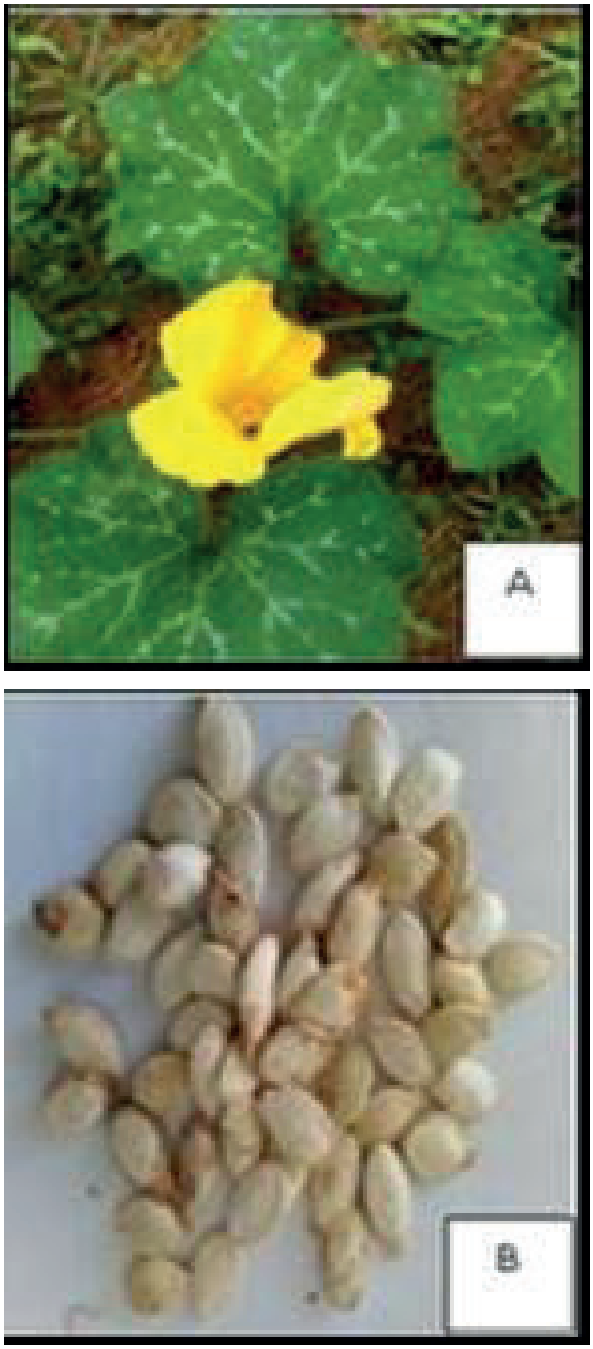

Figure 1: A) Pumpkin flower; B) Pumpkin seeds (Source: Ezin et al.)[11]

Oil Pumpkin seeds contain fatty acids. The types of fatty acids in pumpkin seeds are linoleic, oleic, stearic, and palmitic which account for more than 95% of the total saturated fatty acids and about 75% of them are unsaturated fatty acids (UFA)[18-22]. Small concentrations of arachidic and linolenic acids have also been reported[23-25]. The following fatty acid profile of pumpkin seed oil can be presented in Table 1.

Table 1. Fatty acid profile (mg/100 g) of pumpkin seeds (Source: Dotto & Chacha)[26]

Nutrients	Nutritional value
Capric acid (C10:0)	0.45
Lauric acid (C12:0)	1.34
Myristic acid (C14:0)	0.01 — 0.2
Palmitic acid (C16:0)	1.57 — 27.78
Stearic acid (C18:0)	0.78 — 13.46
Oleic acid (C18:1)	2.93 — 42.80
Linoleic acid (C18:2)	4.59 — 69.12
Linolenic acid (C18:3)	0.20 — 2.25
Palmitoleic (C16:1)	0.13 — 0.20
Arachidic acid (C20:0)	0.30 — 2.20

2. Linoleic acid against protein tyrosine phosphatases (PTP) inhibition: Protein tyrosine phosphatase (PTP) hydrolytically removes phosphate groups from tyrosine residues of target proteins, regulating signal transduction[27]. Regulation of protein tyrosine phosphorylation by

protein tyrosine kinase (PTK) and PTP is involved in intracellular signaling pathways associated with cell proliferation, differentiation, migration, and metabolism[28]. Disruption of PTP function causes various diseases, one of which is diabetes. Several specific PTPs, including PTPN1, PTPN2, PTPN9, PTPN11, PTPRF, PTPRS, and DUSP9, are associated with negative regulation of insulin signaling and induce insulin resistance relevant to the development of type-2 diabetes, indicating that PTPs may represent a new class of therapeutic targets[29].

AMP-activated protein kinase (AMPK) is an intracellular energy sensor that regulates glucose and lipid metabolism, and its activation stimulates glucose uptake and lipid oxidation in skeletal muscle and adipose tissue[30]. PTP, type 1 non-receptor (PTPN1 called PTP1B) is associated with negative regulation of insulin action, suggesting that PTPN1 inhibition may be a therapeutic strategy for the treatment of type 2 diabetes[31]. Previously, identified PTP type 9 non-receptor (PTPN9 called PTP-MEG2) and PTP type 11 non-receptor (PTPN11 called SHP-2) as potential antidiabetic targets and discovered a targeting inhibitor, chebulinic acid[32]. Since inhibitors for PTPs associated with insulin resistance have been shown to improve insulin sensitivity, the use of inhibitors against PTPN1, PTPN9, or PTPN11 is considered an effective strategy for treating type 2 diabetes. The results by Yoon et al. showed that linoleic acid inhibited the catalytic activity of PTPN1, PTPN9 and PTPN11 in vitro, indicating that linoleic acid targets PTPN1, PTPN9, and PTPN11[33]. In addition, 40 μM linoleic acid treatment increased glucose uptake through activation of AMPK and Akt signaling pathways. Taken together, these findings suggest that linoleic acid, a multi-targeting inhibitor of PTPN1, PTPN9, and PTPN11, may exert antidiabetic effects to prevent type 2 diabetes.

3. The role of oleic acid on insulin hormone balance: It is known that intestinal L-cells secrete a hormone called Glucagon-like peptide-1 (GLP-1), in response to nutrients[34]. This hormone has an influence on diabetes mellitus by increasing satiety, through delaying gastric emptying. It also increases insulin secretion from pancreatic islet β-cells[35]. Studies also show that GLP-1R, leads to an increase in mitochondrial UCP2, which is a key mitochondrial biogenesis regulator. Thus, GLP-1R mediates an important role in mitochondrial metabolism. For this reason, GLP-1 therapy is successful and routinely used to control diabetes mellitus[36].

Moreover, results showed that GLP-1RA promoted mitochondrial biogenesis in PC12 cells treated with glycation end products (AGEs)[37]. As a result, GLP-1RA has recently received attention to be considered as a better target to improve IR and reverse diabetes mellitus[38]. Oleic acid has also demonstrated its protective effect on diabetes mellitus by accelerating GLP-1 secretion. Studies have indicated that oleic acid stimulates GLP-1 secretion from intestinal L cells. Nonetheless, oleic acid stimulates GLP-1 secretion requiring the intracellular enzyme PKCζ, which is found mainly in fetal rat intestinal L cells and also in the mGLUTagL cell line[39,40]. Leptin has also shown anti-diabetic effects mainly by activation of AMPK. One study has found that leptin levels can be increased by oleic acid treatment in mice[41].

4. Oleic acid in pumpkin seed oil on pancreatic beta cell function: β-cell dysfunction is a contributing factor to type 2 diabetes mellitus[42]. The occurrence of β-cell dysfunction is due to an increase in pro-apoptotic proteins compared to anti-apoptotic proteins. In vitro and cell culture studies of insulinoma showed increased levels of caspase-3 (apoptotic protein) associated with the pathogenesis of IR and type 2 diabetes mellitus[43]. Matrix metalloproteinases 2 (MMP-2) plays a role in β-cell formation in the pancreas thereby improving tissue function to increase insulin sensitivity and reduce insulin resistance. Oleic acid decreased protective effect significantly decreased the level of activated caspase-3 in vascular smooth muscle cells from rat thoracic aortic artery also interfered with apoptosis through activation of PI3k pathway in β-cells. Moreover, oleic acid further secures insulin sensitivity by suppressing ROS formation and regulating MMP-2 activity in cell line 1.1B4[44]. Moreover, studies have shown that oleic acid treatment in insulin-releasing β-cell lines significantly increased the protein expression of superoxide dismutase 2 (SOD2), an important mitochondrial enzyme that is mainly involved in suppressing ROS.

5. Oleic acid against antioxidants: Increased ROS production and oxidative stress are important predictors of type 2 diabetes mellitus and IR. This oxidative stress is further implicated in the development of IR and type 2 diabetes

mellitus by disrupting stress signaling pathways, increasing β-cell dysfunction through apoptosis and autophagy, intensifying inflammatory responses and also by exacerbating endothelial cell dysfunction. Thus, antioxidants are the best therapeutic targets for the treatment of IR and type 2 diabetes mellitus and other metabolic induced ROS. Since, antioxidants are potential therapeutic options against ROS and possess radical scavenging activity, it can be the best target for the treatment of IR and type 2 diabetes mellitus[45].

In addition, oxidative stress plays a role in mitochondria-mediated disease processes, leading to the development of insulin resistance and type 2 diabetes mellitus. Since then, evidence suggests that impaired mitochondrial function induces insulin insensitivity in various cell types. Thus, targeting antioxidants that target mitochondria is the best strategy to regulate mitochondrial function in diabetes mellitus[46].

Some studies suggest that changes in the amount of antioxidant enzymes such as glutathione peroxidase, superoxide dismutase and catalase also potentiate oxidative stress and ultimately lead to type 2 diabetes mellitus[47]. Recently, studies have proven that oleic acid has a protective on the structural damage and function of antioxidant enzymes associated in a hyperglycemic environment. In the same way, Praoxonase-1 (PON1) is a potent antioxidant that negates ROS formation and oxidative stress, thereby exerting protective effects in type 2 diabetes mellitus[48]. Other studies have also shown a similarly influential role of PON1 in altering pathogenesis in DM and suggested a remarkable decrease in PON1 levels as a potential target for DM treatment in diabetic patients. Interestingly, oleic acid treats its safeguarding effect in this aspect by optimizing PON1 and thus altering type 2 diabetes mellitus.

6. Lauric acid stimulates Glucagon like peptide-1: Lauric acid content in pumpkin seed oil plays a role in stimulating GLP-1 (Glucagon like peptide-1). GLP-1 is secreted by L cells located in the intestine, especially in the distal ileum[49]. GLP-1 binds to G protein receptors on the beta cell membrane. This binding activates adenyl cyclase and increases intracellular cAMP. This increase will close K+ channels followed by an increase in intracellular calcium levels thus stimulating insulin secretion[50]. GLP-1 can increase proliferation activity and decrease beta cell apoptosis, so GLP-1 also has the ability to repair pancreatic beta cells. Lauric acid has strong antihyperglycemic potential for streptozotocin-induced beta cell regeneration. Lauric acid can reduce blood glucose levels by acting directly on the liver, activating insulin signaling in the liver which then causes a decrease in gluconeogenesis or the formation of new glucose and increases glycogenesis or the process of glycogen breakdown through the action of insulin in the liver[51].

The active and inactive mechanisms on GLP-1 are affected by glucagon suppression and stimulation. This mechanism is particularly interesting as GLP-1 appears to play a role in restoring glucose sensitivity of pancreatic B cells, with the mechanism possibly involving increased expression of GLUT2 (Glucose transporter 2) and glucokinase. GLP-1 hormone is also known as a hormone that can inhibit pancreatic B cell apoptosis, stimulate proliferation and insulin secretion from pancreatic B cells. In addition, GLP-1 plays a role in inhibiting gastric secretion and motility. This is important for delaying or slowing down carbohydrate absorption and contributes to the satiating effect. GLUT2 proteins are found in the liver, pancreatic B cells, hypothalamus basolateral membrane and brush border of the small intestine as well as the basolateral membrane of renal tubular cells. GLUT2 has a high capacity but low affinity, is a glucose sensor in pancreatic B cells. GLUT2 is very efficient as a glucose carrier with glucosamine carrier[52].

7. Lauric acid as diabetic wound healing: The active compound in pumpkin seed oil is lauric acid which plays a role in diabetic wound healing. The mechanism of action of lauric acid as an antibacterial has been known by its ability to disrupt bacterial cell membranes through fatty acid penetration which causes disruption of the bacterial enzymatic system. The anti-inflammatory action of lauric acid can be attributed to the inhibition of NF- kappa B and activation of the cascade on mitogen- activated protein kinase. The results of Safar researc that the use of pumpkin seed oil can repair damage to blood vessel walls, and increase the release of blood platelets in wound healing in mice[53]. Nuclear Factor Kappa B (NF-κB) is a protein molecule located in the cytoplasm and is in an inactive form and bound in cells. This molecule is responsible for regulating inflammation or swelling, wound

healing, immune response, and apoptosis and cell function. The activation pathway in NF-κB occurs very quickly and is an acute response (stress) to signals in cells which will then damage DNA. So that excessive and deregulated activation of NF-κB causes uncontrolled inflammation[54].

Pumpkin seed oil containing lauric origin plays a role in improving wound healing because it can stimulate angiogenesis and suppress inflammatory markers, this makes the nutrients and oxygen needed in the wound healing process can be fulfilled properly[55]. Pumpkin seed oil can increase the formation of new blood vessels in the wound. Good flow of nutrients and oxygen can accelerate wound healing.

8. Palmitic acid on insulin and beta cell activity: Palmitic acid is part of saturated fatty acids or Free fatty acids (FFAs) play an important role in insulin control and beta cell activity. Palmitic acid has been shown to stimulate mTOR signaling in hepatocytes[56]. Increased palmitic acid concentration affects insulin biosynthesis secretion, cell content, and also causes cell stress. This causes lipotoxicity, which can lead to loss of cell function, and plays a direct role in the pathophysiology of type 2 diabetes mellitus disease[57].

Palmitic acid affects insulin control through binding to its major receptor, FFA receptor 1 (FFAR1) known as GPR40[58]. The G-protein-coupled receptor FFAR1, which is mainly expressed in pancreatic beta cells, has seven transmembrane domains[59]. Different medium- and long-chain (C12-C22) FFAs activate cells, causing an increase in intracellular calcium levels and stimulation of insulin secretion, which enhances the insulinotropic ability of glucose and strengthens glucose-stimulated insulin secretion (GSIS). However, it is still unknown how exactly FFAR1 works.

9. Stearic acid as Protein Tyrosine Phosphatase 1B Inhibitor: Receptor tyrosine kinases (RTKs) including insulin receptors are linked to signal transduction pathways along the RTK/IRS/PI3K/PDK1/Akt axis[60,61]. Activated RTK phosphorylates RTK and insulin receptor substrate (IRS) on tyrosine residues, to dissociate IRS from the receptor and activate PI3K. Activated PI3K generates phosphatidylinositol (3,4,5)-triphosphate [PI(3,4,5)P3] by phosphorylating phosphatidylinositol 4,5-bisphosphate [PI(4,5)P2], and in turn, PI(3,4,5) P3 activates PDK1 through its binding. Activated PDK1 activates Akt by phosphorylating at Thr308 and Ser473 for Akt. The results of Tsuchiya et al that saturated FFA stearic acid markedly reduced PTP1B activity. The linoleic acid derivative DCP-LA suppresses PTP1B activity and directly binds to PTP1B (unpublished data). This raises the possibility that stearic acid may inhibit PTP1B through direct binding[62].

Protein tyrosine phosphatase 1B (PTP1B) functions as a negative regulator of the insulin receptor signaling pathway by dephosphorylating the receptor[63,64]. Stearic acid, thus, may enhance insulin/insulin receptor signaling by preventing tyrosine dephosphorylation of insulin receptor and IRS-1 due to PTP1B inhibition. In support of this, stearic acid significantly increased insulin-induced insulin receptor phosphorylation at Tyr1185 in 3T3-L1-GLUT4myc adipocytes and did not significantly increase receptor basal tyrosine phosphorylation. Stearic acid also increased basal phosphorylation and insulin-induced phosphorylation on Akt at Thr308 and Ser473, but not significantly. Taken together, these results suggest that stearic acid enhances insulin/insulin receptor signaling by suppressing insulin receptor tyrosine dephosphorylation in conjunction with PTP1B inhibition, although stearic acid is unable to induce full activation of Akt.

Insulin stimulates glucose uptake into 3T3-L1-GLUT4myc adipocytes in a concentration-dependent manner (0.1-100 nM). Remarkably, stearic acid stimulated glucose uptake into the cells in the absence of insulin, although the acid did not induce an additional increase in insulin-stimulated glucose uptake. Taken together, the results of this study lead to the conclusion that FFA-saturated stearic acid has the potential to inhibit PTP1B, which might lead to increased insulin receptor signaling by preventing tyrosine dephosphorylation at the receptor to stimulate glucose uptake.

The facilitating effect of stearic acid on glucose uptake into adipocytes interprets that stearic acid may protect against insulin resistance. In support of this, short-term treatment (15 min) with stearic acid or palmitic acid was shown to stimulate glucose uptake into adipocytes. In contrast, long-term treatment (4 hours) with palmitic acid showed the opposite effect, i.e. inhibition of

glucose uptake[62]. The glucose assay data here were obtained from a 2-hour treatment with stearic acid at a concentration of 30μM. In addition, glucose uptake was not significantly inhibited by the 4-hour treatment with stearic acid. Most previous studies have shown that saturated FFAs induce or accelerate insulin resistance associated with type 2 diabetes[65]. It is currently unknown why saturated FFAs show bidirectional effects on glucose uptake. This may be due to the different concentrations used. In studies to support saturated FFA-induced insulin resistance, saturated FFAs were used at very high concentrations ranging from 0.125 to 2 mM compared to those used here (1-30μM)[66].

CONCLUSION

Pumpkin seed oil contains linoleic, oleic, stearic, and palmitic acids. The content of these fatty acids in pumpkin seed oil has the potential and role as a therapy for diabetes mellitus. The potential and role as diabetes therapy due to the content of pumpkin oil is known to have activities in the balance of insulin hormones, pancreatic beta cell function, antioxidants, stimulating Glucagon like peptide-1, and diabetic wound healing. Therefore, therapy in diabetics can switch to using therapy from natural ingredients, namely pumpkin seeds as a therapy for people with diabetes mellitus.

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