

# A Mini Review: Phenolic Compounds in Diets for Managing Type II Diabetes

Suryawati<sup>1</sup>, Firdausa Sarah<sup>2</sup>, Mulia Dewi Vera<sup>3</sup>, Vonna Azizah<sup>4</sup>, Sakdiah<sup>5</sup>

<sup>1</sup>Department of Pharmacology, Faculty of Medicine, Syiah Kuala University, Indonesia

<sup>2</sup>Department of Internal Medicine, Faculty of Medicine, Syiah Kuala University, Indonesia

<sup>3</sup>Department of Patology Anatomy, Faculty of Medicine, Syiah Kuala University, Indonesia

<sup>4</sup>Department of Pharmacy, Faculty of Math and Science, Syiah Kuala University, Indonesia

<sup>5</sup>Department of Biochemistry, Faculty of Medicine, Syiah Kuala University, Indonesia

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Abstract: Diet management help to prevent or reduce the progress of diabetes mellitus, one of metabolic disorder potentially lead to serious complications such as retinopathy, nephropathy, heart and vascular diseases. This mini review highlights the hypoglycemic effect of natural supplemented diets evaluated in animals and humans. Several phenolic compounds from natural origins comprise of *Mangifera indica*, *Peperomia pellucida*, *Sesamum indicum*, *Passiflora edulis* and *Aegle marmelos* are briefly described. Mode of action observed in isolated phenolic compounds in improving diabetes are including free radical scavengers, inhibition of glucose regulating enymes and disruptions expression of glucose transporter genes.

## 1 INTRODUCTION

### 1.1 Diabetes Mellitus

Diabetes mellitus is a metabolic disorder characterized by chronic hyperglycemia caused by absolute or relative insulin deficiency, and sometime accompanied by insulin resistance (Robertson, 2004). DM drives the body to a condition in which the cells are exposed to an increase of oxidative stress. Conversely, it has been suggested that oxidative stress lead to chronic complication in which the level of oxidative stress in diabetic subject is advance. Hyperglycemia is a widely known etiology of enhanced free radical concentrations and decreased antioxidant defense system (Ahmed, 2005).

Free radicals are singlet oxygen comprising superoxide anion radical, hydroxyl, alkoxy, peroxy radical, hydrogen peroxide, and lipid hydroperoxide. These species are resulted from biochemical reaction in the body or environmental exposure. Cells injuries which lead to many diseases such as cancer, diabetes mellitus, developed due to the action of free

radicals on PUFA, amino acids, or DNA (Nimse & Pal, 2015).

Chronic hyperglycemia leads to toxic effects on structure and function of organs, including  $\beta$ -cell in pancreas. Islet cells of pancreas are among the tissues that have the lowest level of antioxidant defense. In chronic hyperglycemic state, reactive oxygen species accumulate in an excess amount and cause chronic oxidative stress in the islet cell. This condition damages the cell progressively (Robertson, 2004).

The pathophysiology of DM is complex and multi factorials, including the interaction of genetic and environmental factors. Three main pathophysiology factors involve in development DM, which are insulin resistance, decreased insulin secretion and increased glucose production (Polonsky & Burant, 2016).

Several biochemical pathways and mechanisms on how hyperglycemia causes cell damage have been explained in many studies which include increased glycolysis, activation of sorbitol pathway, glucose autoxidation, glycation (Ahmed, 2005), hexosamine metabolism, protein kinase C activation, and oxidative phosphorylation (Robertson, 2004). Therapy is targeted to increase insulin production,

decrease insulin resistance and stimulate cells glucose uptake. Several key factors targeted for combating diabetes are stimulator for insulin secretion (glucagon like peptide, GLP), inhibitor for GLP degradation (dipeptidyl peptidase), glucose regulating enzymes (amylase, glucosidase, etc), glucose transporter (GLUT 2, GLUT 4), and activated receptor for gene expression (peroxisome proliferator-activated receptor) (Tiwari, Thakur, Kumar, Dey, & Kumar, 2014).

To achieve a controlled glucose level, pharmacotherapy should be carried out with physical activities and diet management. Physical activity to reduces weight more than 5% was essential to achieve normal HbA1c and nutrition management was recommended strategy for type II diabetes patients (Franz, Boucher, Rutten-Ramos, & VanWormer, 2015)

## 1.2 Supplemented-diet

Enriched supplements with hypoglycemic agents help to prevent risk of hyperglycemia and normalize glucose level in diabetic patients. Diet for diabetic could be modulated with fibre, vitamins and natural antioxidants comes from plants (Radmila, Pavle, Dean, & Ljupco, 2013). Mediteranian food consist of fruits, leaves, oil etc show activity to neutralize free radicals, inhibit inflammation, prevent glucose absorption and lipid production (Alkhatib et al., 2017). Several studies had shown efficacy of compounding natural origin in diet to maintain normal glucose level.

### 1.2.1 *Mangifera indica*

*M. indica* is tropical plants consumed for its tasteful fruits. Leaves, stem bark and fruits are utilized for their health benefits due to high content of vitamin A and C, flavonoid and phenolic compounds. The seeds of *M. indica* displayed an inhibitory activity against alpha-amylase and glucosidase, two enzymes involved in carbohydrate digestion. Additionally, it prevented diabetes complication by interrupt alpha reductase (Irondi, Oboh, & Akindahunsi). Leaves extract suppress dipeptidyl peptidase- IV which resulted in insulin secretion (Muthukumaran, Srinivasan, Venkatesan, Ramachandran, & Muruganathan).

Due its lowering effects on blood glucose level, mangifera should be consumed routinely in daily life based on scientific evidence. A study of diet modulation using mangifera indica seeds conducted by Irondi et al. (2016) . Seeds were dried and grounded to produce kernell flour. The administration of diet supplemented with 10-20% of *M. indica*-kernell flour decreased fasting blood

glucose in streptozosin induced-diabetic rats, 3-fold higher than diabetic rats received non-supplemented food on day 21. Glycosilated haemoglobin value was improved in treated rats at 6%, whereas diabetic rats value was 10%. The kernell flour contained flavonoid and phenolic acids, essential metabolites for antihyperglycemic activity. Catechin, rutin, quercetin, quercitrin, kaempferol, gallic acid, caffeic acid, ellagic acid, and cholorogenic acid were metabolites identified in mangifera seeds (Irondi et al., 2016).

Consumption of diet containing catechin for 76 day decreased serum glucose in rats. In glucose tolerance test, rats fed with catechin showed lowered glucose amount after 120 minutes of glucose feeding. Biomarkers for oxidative stress, albumin and 8-hydroxy deoxyguanosine (8-OH dG) were less excreted in urin showing catechin activity as scavenger for free radicals (Igarashi, Honma, Yoshinari, Nanjo, & Hara, 2007). Catechin was observed to stimulated peroxisome proliferator activated receptor (PPAR)  $\gamma$ , other key to treat hyperglycemia (Shin et al., 2009).

There were numbers of studies reported that using rutin 5-100 mg/kg in diabetic rats reduced FBG and random glucose level. Rutin protected neuron, kidney and liver from damage. It also benefited on impairment of sexual function (Gullón, Lú-Chau, Moreira, Lema, & Eibes, 2017). This advantage might be correlated with its antioxidant activity (Ghorbani, 2017).

Quercetin (15 mg/kg bw day) stimulated endogenous antioxidant enzymes, superoxide dismutase (SOD), catalase and glutathione peroxidase (GSP) in STZ-induceddiabetic rats (Abdelmoaty, Ibrahim, Ahmed, & Abdelaziz, 2010).

The mechanism on how a flavonols like quercetin works involving the formation of complex with Cu that neutralizes hydroxyl radical, singlet oxygen and hydrogen peroxide which cause encountered oxidative stress in diabetes (Nimse & Pal, 2015).

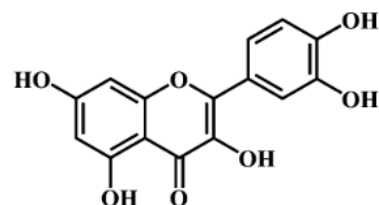


Figure 1. Quercetin

Kaempferol given for 30 days at dose 5 and 10 mg/kg to STZ induced-diabetic rats benefit in reducing glucose level and restoring neuron conduction by neutralized oxidative stress. This finding showed evidence that kaempferol enabled to correct neuropathy as complication of chronic hyperglycemia (Kishore, Kaur, & Singh, 2017)

### 1.2.2 *Peperomia pellucida*

*P. pellucida* in Indonesia, is known as kaca-kaca, tumpangan air, rangu-rangu atau gofu goroho. Leaves contained minerals, cardenolides, saponin, alkaloid, tannin (Egwuche, Odetola, & Erukainure, 2011). A methanol extract showed the existence of flavonoids and phenolic compounds and inhibit oxidative reactions (Nirosa & Raman, 2012).

As nutrients in diets, a study conducted by Hamzah *et al* showed the benefit of *P. pellucida* in controlling diabetes. Fresh leaves were dried at room temperature and processed to produce fine powder. Diabetic animals induced by intraperitoneal alloxan were fed with diet contained 10 and 20% of *Peperomia pellucida* leaves. The glucose level was measured after 28 days feeding and compared to the negative and positive controls. The result showed 60% decrease in blood glucose level which was close to positive control received glibenclamide. The antioxidant activity was confirmed by the increase of superoxide dismutase, CAT and GSH, the endogenous antioxidants. Lipid peroxidation which is abundant in diabetes was reduced. (Hamzah, Odetola, Erukainure, & Oyagbemi, 2012).

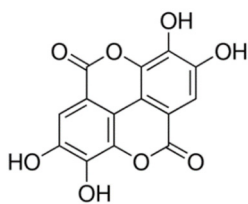


Figure 2. Ellagic acid

Susilawati *et al* succeeded to isolated ellagic acid, an antihyperglycemic agent from *peperomia pellucida* (Susilawati *et al.*, 2017). In different study, ellagic acid showed antioxidant activity in DPPH assay and inhibitory activity of lipid peroxidation. As alpha-amylase inhibitors, ellagic acid displayed a better potency compared to rosiglitazone, glimepiride and metformin (Mehta *et al.*, 2017)

Ellagic acid tightly interacted with glycogen phosphorylase, an enzyme that stimulate breakdown of glycogen. The interaction cause the inhibition of glucose production in hepar (Kyriakis *et al.*, 2015).

Administration of 10 mg/kg BW ellagic acid with 10 mg/kg BW pioglitazone showed more potent effect as hypoglycemic agents compared to a single agent use in diabetic rats. The combination influenced positively on gene expression for GLUT 4 and PPAR gamma (Nankar & Doble, 2017).

### 1.2.3 *Sesamum Indicum*

In *in vitro* study, butanol extract of black sesame inhibited alpha glucosidase higher than inhibitory against alpha amylase with activity superior compared to acarbose, a standard drug. Phytochemical screening identified glycosides, tannin, terpenoids and steroids (Amutha & Godavari).

Clinical trials revealed that sesame seeds stimulated the activity of enzymatic antioxidants, such as SOD, as well as non-enzymatic antioxidants, vitamin E (Vittori Gouveia, Cardoso, de Oliveira, Rosa, & Moreira, 2016).

Akanya, Isa, Adeyemi, and Ossamulu (2015) showed that 10%- 20% sesame seed in diet lowered blood glucose about 35-37%. Zhou, Lin, Abbasi, and Zheng (2016) found that black sesame contained more phenolic acid compared to white sesame, whereas flavonoid found to be more in white sesame rather than in black sesame. The existence of phenolic and flavonoid was correlated with the antioxidant activity. Sesamol, sesamin and sesamolin were lignant identified in a large amount in black sesame which explained its superior antioxidant activity (oxygen radical absorbance capacity (ORAC) value :132.33  $\mu\text{mol TE/g}$ ). Sesamin decreased blood glucose level and stimulated cardiac function in STZ induced diabetes rats after given orally 100 and 200 mg/kg for 4 week (Thuy *et al.*, 2017). Since hydroxyl functional group is important to react with radicals, sesamin and sesamolin with 4 OH showed more potent activity against free radical compared to sesamol that only pose 2 OH group (Jeng & Hou, 2005).

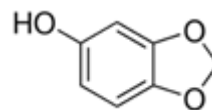
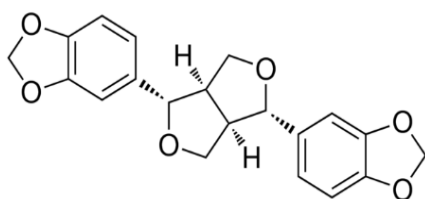


Figure 3. Sesamol



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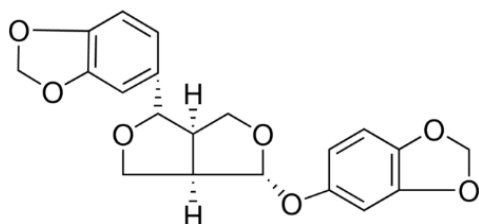


Figure 4. Sesamol

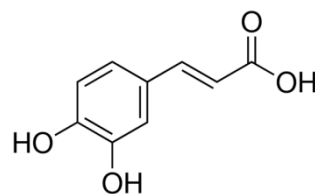


Figure 5. Caffeic acid

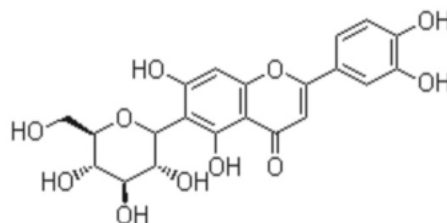


Figure 6. Isoorientin

#### 1.2.4 *Passiflora edulis*

Feeding 0.5–25 mg/kg of pectin from *P. edulis* to alloxan induced-diabetic rats reduced blood glucose (Silva et al., 2011). Extract of *P. edulis* peel were given at dose 250 and 500 mg/kg to diabetic rats induced by STZ for 15 days. The result showed a controlled blood glucose level with an increase of SOD level which reflected its antioxidant effect. Additionally, histopathology evaluation revealed the organ protective effects (Kandandapani, Balaraman, & Ahamed, 2015)

Peel flour was also tested in 43 diabetic respondents. Each volunteer consumed 30 g/day for two months. The result showed a decrease in blood glucose (de Queiroz et al., 2012). Supplemented diet with 30% of peel-flour of *Passiflora edulis* prevented insulin resistance in mice induced by 8 week-administration of 10% fructose. The study identified two phenolic compounds, caffeic acid and isoorientin (Goss et al., 2018).

Caffeic acid affected the expression of genes including glucose transporter 2 (Glut 2), insulin 1 (Ins 1) and some proteins played roles in increasing insulin production (Bhattacharya, Oksbjerg, Young, & Jeppesen, 2014). Caffeic acid is one of hydroxycinnamates that scavenge free radicals by giving its hydroxyl hydrogen to inhibit cells destruction (Nimse & Pal, 2015).

In a study using murine and human adipocyte, it was revealed the mode of action how isorientin worked as antidiabetic agent which affected insulin signal transduction. Normally, insulin binds to insulin receptor (IR) which then caused phosphorylation of the receptor, followed by activation of phosphatidylinositol 3 kinase (PI3K). PI3K phosphorylate protein kinase B resulted in a movement of glucose transporter (GLUT 4) to membrane to start glucose absorption. Isoorientin stimulated phosphorylation important protein IR, PI3K and protein kinase B (Alonso-Castro, Zapata-Bustos, Gómez-Espinoza, & Salazar-Olivo, 2012).

#### 1.2.5 *Aegle Marmelos*

*A. marmelos*, known as maja in Indonesia, is classified into *Rutaceae*. In a clinical study, consumption of *Aegle Marmelos* Correa leaf 20 g/100 mL reduce fasting blood glucose and HbA1c about 20%, observed after 4 weeks. The leaves contained aegelin 2, scopoletin and sitosterol (Nigam & Nambiar, 2018).

Identification using UHPLC-PDA showed the presence of aegeline (alkaloid), umbelliferone, scopoletin, marmesinin, 8-hydroxypsoralen, angelicin and marmelosin (simultaneous, avula). Phenolic compounds identified using RP-HPLC analyses were gallic acid (GA), p-coumaric acid (p-CA), vanillic acid (VA), p-hydroxy benzoic acid (p-HBA), syringic acid (SA), ferulic acid (FA) and chlorogenic acid (ChA) (Wali, Gupta, Mallick, Guleria, & Sharma, 2015)

GA and p-CA restored glucose regulation indicated by decreased glucose level and HbA1c and inclined insulin. Degeneration of neuron function in brain of diabetic rats was improved by affecting expression of protein Bax and Bcl-2 (abd moneim, gallic acid).

In vivo study on streptozosin-induced diabetic rats, given 100 mg/kg b.w of p-CA, showed the suppression of stimulant enzymes in gluconeogenesis along with improvement of serum lipids contributed for hiperglicemia. Administration of p-CA disrupted expression of protein GLUT 2 (Amalan, Vijayakumar, Indumathi, & Ramakrishnan, 2016) which facilitate glucose transportation across cell membrane and stimulate insulin secretion (Thorens, 2015).

Diabetic rats treated with GA (20 mg/kg b.wt. per day) and p-CA (40 mg/kg b.wt. per day) for 6 weeks displayed the hepatoprotective effects reflected by the controlled level of alanin transferase and aspartate aminotransferase (Moneim, El-Twab, Ashour, & Yousef, 2016) . GA and p-CA affected expression of tumour necrosis factor (TNF $\alpha$ ) and PPAR  $\gamma$  (Abdel-Moneim, El-Twab, Yousef, Reheim, & Ashour, 2018). TNF $\alpha$  is a cytokine known to induced insulin resistance and found overproduced in adipocytes. Inhibition of its gene expression was believed to induce insulin sensitivity (Moller, 2000).

In a study evaluating phenolic compounds as antidiabetic agents showed that glucose was maximally absorbed into cells when VA was applied. In diabetic rats given 30 mg/kg bw of VA for 3 weeks the glucose and insulin level were decreased showing activity against insulin resistance (Chang et al., 2015).

SA improved hyperglycemia by inhibiting formation of glycoprotein, a complex of protein and carbohydrate. In diabetic organism, the unutilized glucose was bonded to protein. The administration of SA 50 mg/kg bw in alloxan induced diabetic rats for 30 days effectively normalized the amount of glycoprotein including hexose, hexosamine, fucose and sialic acid Muthukumaran et al. (2013).

Narasimhan, Chinnaiyan, and Karundevi (2015) found that FA countered expression of GLUT 2 by inhibiting the binding of GLUT 2 transcription factors with their promotors. The transcription factors including sterol response element-binding protein (SREBP)-1c and Hepatocyte nuclear factor (HNF). These molecules made complex with promotor at specific site which then induced expression of gene for GLUT 2. Hiperglycemia stimulate the interaction of SREBP)-1c with promotor (Im et al., 2005)

## 2 CONCLUSIONS

In diabetes mellitus treatment, supplemented diet is essential to provide active agents which play roles in inhibiting glucose absorption, stimulating insulin production and increasing cells glucose uptake.

## REFERENCES

- Abdel-Moneim, A., El-Twab, S. M. A., Yousef, A. I., Reheim, E. S. A., & Ashour, M. B. (2018). Modulation of hyperglycemia and dyslipidemia in experimental type 2 diabetes by gallic acid and p-coumaric acid: The role of adipocytokines and PPAR $\gamma$ . *Biomedicine & Pharmacotherapy*, 105, 1091-1097.
- Abdelmoaty, M. A., Ibrahim, M., Ahmed, N., & Abdelaziz, M. (2010). Confirmatory studies on the antioxidant and antidiabetic effect of quercetin in rats. *Indian Journal of Clinical Biochemistry*, 25(2), 188-192.
- Ahmed, R. G. (2005). The physiological and biochemical effects of diabetes on the balance between oxidative stress and antioxidant defense system. *Medical Journal of Islamic World Academy of Sciences*, 15(1), 31-42.
- Akanya, H., Isa, U., Adeyemi, H., & Ossamulu, I. (2015). Effect of Sesamum indicum (Linn) seeds supplemented diets on blood glucose, lipid profiles and serum levels of enzymes in alloxan induced diabetic rats. *J. Appl. Life Sci. Int*, 2, 134-144.
- Alkhatib, A., Tsang, C., Tiss, A., Bahorun, T., Arefanian, H., Barake, R., . . . Tuomilehto, J. (2017). Functional Foods and Lifestyle Approaches for Diabetes Prevention and Management. *Nutrients*, 9(12), 1310.
- Alonso-Castro, A. J., Zapata-Bustos, R., Gómez-Espinoza, G., & Salazar-Olivo, L. A. (2012). Isoorientin reverts TNF- $\alpha$ -induced insulin resistance in adipocytes activating the insulin signaling pathway. *Endocrinology*, 153(11), 5222-5230.
- Amalan, V., Vijayakumar, N., Indumathi, D., & Ramakrishnan, A. (2016). Antidiabetic and antihyperlipidemic activity of p-coumaric acid in diabetic rats, role of pancreatic GLUT 2: In vivo approach. *Biomedicine & Pharmacotherapy*, 84, 230-236.
- Amutha, K., & Godavari, A. (2016). In-Vitro-Antidiabetic Activity of N-Butanol Extract Of Sesamum Indicum. *In-Vitro*, 9(4).
- Bhattacharya, S., Oksbjerg, N., Young, J., & Jeppesen, P. (2014). Caffeic acid, naringenin and quercetin enhance glucose-stimulated insulin secretion and glucose sensitivity in INS-1E cells. *Diabetes, Obesity and Metabolism*, 16(7), 602-612.
- Chang, W.-C., Wu, J. S.-B., Chen, C.-W., Kuo, P.-L., Chien, H.-M., Wang, Y.-T., & Shen, S.-C. (2015). Protective effect of vanillic acid against hyperinsulinemia, hyperglycemia and hyperlipidemia

- via alleviating hepatic insulin resistance and inflammation in high-fat diet (HFD)-fed rats. *Nutrients*, 7(12), 9946-9959.
- De Queiroz, M. d. S. R., Janebro, D. I., da Cunha, M. A. L., dos Santos Medeiros, J., Sabaa-Srur, A. U., Margareth de Fatima, F., & Dos Santos, S. C. (2012). Effect of the yellow passion fruit peel flour (*Passiflora edulis* f. *flavicarpa* deg.) in insulin sensitivity in type 2 diabetes mellitus patients. *Nutrition journal*, 11(1), 89.
- Egwuche, R., Odetola, A., & Erukainure, O. (2011). Preliminary investigation into the chemical properties of *Peperomia pellucida* L. *Research Journal of Phytochemistry*, 5(1), 48-53.
- Franz, M. J., Boucher, J. L., Rutten-Ramos, S., & VanWormer, J. J. (2015). Lifestyle weight-loss intervention outcomes in overweight and obese adults with type 2 diabetes: a systematic review and meta-analysis of randomized clinical trials. *Journal of the Academy of Nutrition and Dietetics*, 115(9), 1447-1463.
- Ghorbani, A. (2017). Mechanisms of antidiabetic effects of flavonoid rutin. *Biomedicine & Pharmacotherapy*, 96, 305-312.
- Goss, M., Nunes, M., Machado, I., Merlin, L., Macedo, N., Silva, A., . . . Santin, J. (2018). Peel flour of *Passiflora edulis* Var. *Flavicarpa* supplementation prevents the insulin resistance and hepatic steatosis induced by low-fructose-diet in young rats. *Biomedicine & Pharmacotherapy*, 102, 848-854.
- Gullón, B., Lú-Chau, T. A., Moreira, M. T., Lema, J. M., & Eibes, G. (2017). Rutin: a review on extraction, identification and purification methods, biological activities and approaches to enhance its bioavailability. *Trends in Food Science & Technology*, 67, 220-235.
- Hamzah, R. U., Odetola, A. A., Erukainure, O. L., & Oyagbemi, A. A. (2012). *Peperomia pellucida* in diets modulates hyperglycemia, oxidative stress and dyslipidemia in diabetic rats. *Journal of Acute Disease*, 1(2), 135-140.
- Igarashi, K., Honma, K., Yoshinari, O., Nanjo, F., & Hara, Y. (2007). Effects of dietary catechins on glucose tolerance, blood pressure and oxidative status in Goto-Kakizaki rats. *Journal of nutritional science and vitaminology*, 53(6), 496-500.
- Im, S.-S., Kang, S.-Y., Kim, S.-Y., Kim, H.-i., Kim, J.-W., Kim, K.-S., & Ahn, Y.-H. (2005). Glucose-stimulated upregulation of GLUT2 gene is mediated by sterol response element-binding protein-1c in the hepatocytes. *Diabetes*, 54(6), 1684-1691.
- Ironi, E. A., Oboh, G., & Akindahunsi, A. A. (2016). Antidiabetic effects of *Mangifera indica* Kernel Flour-supplemented diet in streptozotocin-induced type 2 diabetes in rats. *Food science & nutrition*, 4(6), 828-839.
- Jeng, K., & Hou, R. (2005). Sesamin and sesamol: nature's therapeutic lignans. *Current Enzyme Inhibition*, 1(1), 11-20.
- Kandapani, S., Balaraman, A. K., & Ahamed, H. N. (2015). Extracts of passion fruit peel and seed of *Passiflora edulis* (Passifloraceae) attenuate oxidative stress in diabetic rats. *Chinese Journal of Natural Medicines*, 13(9), 680-686. doi: [https://doi.org/10.1016/S1875-5364\(15\)30066-2](https://doi.org/10.1016/S1875-5364(15)30066-2)
- Kishore, L., Kaur, N., & Singh, R. (2017). Effect of Kaempferol isolated from seeds of *Eruca sativa* on changes of pain sensitivity in Streptozotocin-induced diabetic neuropathy. *Inflammopharmacology*, 1-11.
- Kyriakis, E., Stravodimos, G. A., Kantsadi, A. L., Chatzileontiadou, D. S., Skamnaki, V. T., & Leonidas, D. D. (2015). Natural flavonoids as antidiabetic agents. The binding of gallic and ellagic acids to glycogen phosphorylase b. *FEBS letters*, 589(15), 1787-1794.
- Mehta, V., Verma, P., Sharma, N., Sharma, A., Thakur, A., & Malairaman, U. (2017). Quercetin, ascorbic acid, caffeine and ellagic acid are more efficient than rosiglitazone, metformin and glimepiride in interfering with pathways leading to the development of neurological complications associated with diabetes: A comparative in-vitro study. *Bulletin of Faculty of Pharmacy, Cairo University*, 55(1), 115-121.
- Moller, D. E. (2000). Potential role of TNF- $\alpha$  in the pathogenesis of insulin resistance and type 2 diabetes. *Trends in Endocrinology & Metabolism*, 11(6), 212-217.
- Moncim, A. A., El-Twab, S. M. A., Ashour, M. B., & Yousef, A. I. (2016). Hepato-renal protective effects of gallic acid and p-coumaric acid in nicotinamide/streptozotocin-induced diabetic rats. *International Journal of Bioassays*, 5(6), 4641-4649.
- Muthukumar, J., Srinivasan, S., Venkatesan, R. S., Ramachandran, V., & Muruganathan, U. (2013). Syringic acid, a novel natural phenolic acid, normalizes hyperglycemia with special reference to glycoprotein components in experimental diabetic rats. *Journal of Acute Disease*, 2(4), 304-309.
- Nankar, R. P., & Doble, M. (2017). Hybrid drug combination: Anti-diabetic treatment of type 2 diabetic Wistar rats with combination of ellagic acid and pioglitazone. *Phytomedicine*, 37, 4-9.
- Narasimhan, A., Chinnaiyan, M., & Karundevi, B. (2015). Ferulic acid regulates hepatic GLUT2 gene expression in high fat and fructose-induced type-2 diabetic adult male rat. *European journal of pharmacology*, 761, 391-397.
- Nigam, V., & Nambiar, V. S. (2018). Aegle Marmelos Leaf Juice As A Complementary Therapy To Control Type 2 Diabetes-Randomised Controlled Trial In Gujarat, India. *Advances in Integrative Medicine*.
- Nimse, S. B., & Pal, D. (2015). Free radicals, natural antioxidants, and their reaction mechanisms. *Rsc Advances*, 5(35), 27986-28006.
- Nirosa, A., & Raman, P. (2012). Isolation of Chemical Compounds From Methanol Extract of *Peperomia pellucida*: Fak Sains dan Teknol Univ Malaysia Trengg.
- Polonsky, K. S., & Burant, C. F. (2016). Type 2 Diabetes Mellitus. In S. Melmed, K. S. Polonsky, P. R. Larsen & H. M. Kronenberg (Eds.), *Williams Textbook of*

- Endocrinology* (pp. 1386-1450). Philadelphia: Elsevier Health Sciences.
- Radmila, C.-N., Pavle, S., Dean, J., & Ljupco, A. (2013). The influence of nutrition (diet treatment) in streptozotocin-induced diabetic rats. *Macedonian Veterinary Review*, 36(1), 41-47.
- Robertson, R. P. (2004). Chronic Oxidative Stress as a Central Mechanism for Glucose Toxicity in Pancreatic Islet Beta Cells in Diabetes. *Journal of Biological Chemistry*, 279(41), 42351-42354. doi: 10.1074/jbc.R400019200
- Shin, D. W., Kim, S. N., Lee, S. M., Lee, W., Song, M. J., Park, S. M., . . . Hong, J.-H. (2009). (-)-Catechin promotes adipocyte differentiation in human bone marrow mesenchymal stem cells through PPAR $\gamma$  transactivation. *Biochemical pharmacology*, 77(1), 125-133.
- Silva, D. C., Freitas, A. L., Pessoa, C. D., Paula, R. C., Mesquita, J. X., Leal, L. K., . . . Viana, G. S. (2011). Pectin from *Passiflora edulis* shows anti-inflammatory action as well as hypoglycemic and hypotriglyceridemic properties in diabetic rats. *Journal of medicinal food*, 14(10), 1118-1126.
- Susilawati, Y., Nugraha, R., Krishnan, J., Muhtadi, A., Sutardjo, S., & Supratman, U. (2017). A New Antidiabetic Compound 8, 9-dimethoxy Ellagic Acid from Sasaladaan (*Peperomia pellucida* L. Kunth). *Research Journal of Pharmaceutical Biological And Chemical Sciences*, 8, 269-274.
- Thorens, B. (2015). GLUT2, glucose sensing and glucose homeostasis. *Diabetologia*, 58(2), 221-232.
- Thuy, T. D., Phan, N. N., Wang, C.-Y., Yu, H.-G., Wang, S.-Y., Huang, P.-L., . . . Lin, Y.-C. (2017). Novel therapeutic effects of sesamin on diabetes-induced cardiac dysfunction. *Molecular medicine reports*, 15(5), 2949-2956.
- Tiwari, N., Thakur, A., Kumar, V., Dey, A., & Kumar, V. (2014). Therapeutic targets for diabetes mellitus: an update. *Clinical Pharmacology & Biopharmaceutics*, 3(1), 1-10.
- Vittori Gouveia, L. d. A., Cardoso, C. A., de Oliveira, G. M. M., Rosa, G., & Moreira, A. S. B. (2016). Effects of the Intake of sesame seeds (*Sesamum indicum* L.) and derivatives on oxidative stress: A systematic review. *Journal of medicinal food*, 19(4), 337-345.
- Wali, A., Gupta, M., Mallick, S., Guleria, S., & Sharma, M. (2015). Antioxidant potential and phenol profile of Bael leaf (*Aegle marmelos*). *Indian Journal of Agricultural Biochemistry*, 28(2), 138-142.
- Zhou, L., Lin, X., Abbasi, A. M., & Zheng, B. (2016). Phytochemical contents and antioxidant and antiproliferative activities of selected black and white sesame seeds. *BioMed research international*, 2016.