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PREVENTIVE ROLE OF NARINGIN IN DIABETES MELLITUS AND ITS MECHANISM OF ACTION : A REVIEW

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Abstract

Diabetes is a chronic metabolic ailment that causes abnormal metabolism of carbohydrates and shows high blood glucose level which is due to either deficiency in insulin secretion or there is an impairment in insulin action. The traditional and plant based remedies for the management of diabetes has been approved by the world health organization. Over the last three decades the use of herbal medicines is increased enormously worldwide. From the plant source most of the synthetic drugs were discovered from different regions of the world to meet the need. The objective of this review was to provide information about the most useful anti-diabetic compounds from plants available through numerous literature sources from various databases. Many researches confirmed the benefits of phytoconstituents with anti-diabetic effects in the management of diabetes mellitus. Thus, drugs from plants may control all pathological aspects of diabetes, either by increasing insulin production by the pancreas, helping to lower the body's insulin requirements, or reducing gluconeogenesis in the liver. One of the factor involved in the development of diabetic complications is the damage occurred by free radicals and hence an anti-diabetic compound with anti-oxidant properties would be more beneficial. The present review article is designed to potentiate the activity of a plant based product naringin for its anti-diabetic potential and for other metabolic diseases also. This compound is broadly available in Orange peels and hence its application in treatment of diabetes especially type two diabetes mellitus is found to be cost effective.

Key words: Diabetes, Naringin, Herbal product, phytochemical constituents, metabolic disorder.

Introduction

Diabetes is an endocrine disease which affects large number of peoples worldwide occurs due to lower in insulin secretion or there is a deterioration in insulin action along with a disorder of carbohydrate, lipid and protein metabolism (Mahmoud *et al*., 2015). Recent studies also proposed that a high-fat diet is the main cause of the development of a metabolic ailment both in humans and animal (Bruce and Hanson, 2010; Despres and Lemieux, 2006). Ailments such as hypertension, insulin-resistant diabetes, obesity, dyslipidemia are included as metabolic diseases (*Alberti et al*., 2006). Various remedies such as, biguanides, alpha-glucosidase inhibitors, insulin therapy, thiazolidinediones, sulphonylureas, non-sulphonylureas, secretogogues (Rapaglinide, Nateglinide) are there for treatment of diabetes (White, 2008). However, many side effects including insulin resistance, minor influence on glycosylated hemoglobin (HbA1c), obesity, less control over postprandial glucose levels and atherosclerosis are known to be associated with such remedies. Previous studies elucidated that diet rich in fruits and vegetables helps in regulating body weight and also provide protection against various chronic ailments like cancer and diabetes (Estaquio *et al*., 2008; Liu *et al*., 2004; Vieiera *et al*., 2016; Kuzuma *et al*., 2017; Stefan *et al*., 2018). Many studies reveal that polyphenolic compounds like flavonoids, anthocyanines and phenolic acids shows effective health benefits in prevention of obesity, hypertension, cardiovascular and other metabolic diseases. Flavonoids are the chief bioactive compound comprise of a large proportion among all (Martin and Appel, 2010). Research from various studies showed significant anti-diabetic, cardio protective, antioxidant, hepatoprotective and anti-inflammatory effects of flavonoids (Mahmoud, 2013; Mahmoud and Soliman, 2013; Mahmoud, 2014; Mahmoud *et al*., 2014). Citrus fruits contains many important flavonoids such as naringin, naringenin, narirutin, hesperidin and nobelitin (Tripoli *et al*., 2007). Previous studies reveal that the flavonoids established to have

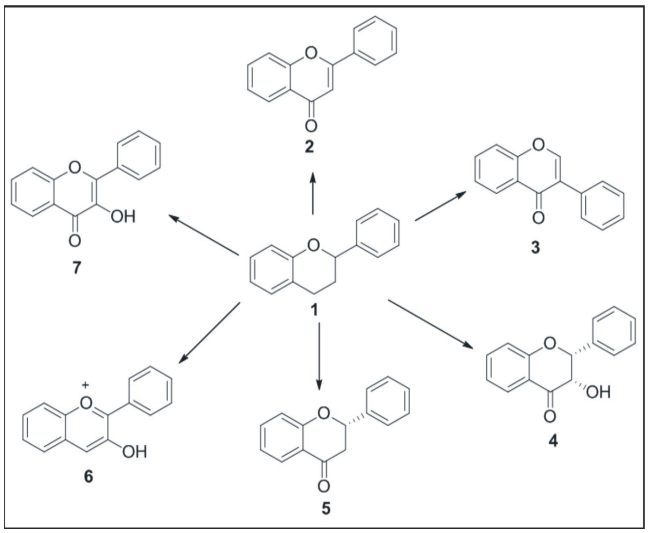

Fig. 1: Basic structure of Flavonoids; 2: Flavone; 3: Isoflavone; 4: Flavan-3-ol; 5: Flavanone; 6: Anthrocyanidine; 7: Flavonol.

antioxidant properties along with other effects such as regulating enzymes through different mechanisms which are effective against curing many diseases (Lagouge *et al*., 2006; Amor *et al*., 2018; Yahfoufi *et al*., 2018).

Flavonoids

A category of soluble polyphenolic contents are present as plant metabolite in flavonoid. The basic structure of flavonoid comprise of 15 carbon atoms and out of which two benzene rings are connected with a 3-carbon chain (Croft, 1998). Flavones, isoflavones, anthocyanidins, flavanols and flavanones, are the varieties of flavonoids fount in plant extracts (Peterson and Dwyer, 1998) (Fig. 1). All these flavonoids plays a principal role in scavenging the free radicals and preventing the oxidative stress (Croft, 1998; Ross and Kasum, 2002).

Naringenin

Naringenin (4, 5, 7-trihydroxy-flavanone) is a largest class of polyphenol from the group of flavonoids with approximately 6000 types have so far been discovered. It is a subclass of flavonoids, which constitute a saturated three carbon chain and an oxygen atom at carbon four (Kumar and Pandey, 2013). Citrus fruits mainly composed of naringenin, with greatly high volume present in grapefruit juice (43.5 mg/100 mL), less quantity present in orange juice (2.13 mg/100 mL), whereas very less amount available in lemon juice (0.38 mg/100 mL) (Erlund, 2004; Gattuso *et al*., 2007). Both naringin and naringenin possess secure antioxidant properties (Renugadevi and Prabu, 2009; Jung *et al*., 2003); but naringin is less potent as compared to naringenin due to the steric hindrance of the scavenging group caused by the sugar content of naringin. It has been proved from previous studies that naringenin express many pharmacological properties which include antioxidant, nephroprotective, anti-immunomodulatory,atherosclerotic, neuroprotective, hepatoprotective, anti-cancer, anti-inflammatory and anti-diabetic (Zaidun *et al*., 2018; Sharma *et al*., 2015; Coelho *et al*., 2013; Rani *et al*., 2016; Zeng *et al*., 2018; Hernandez and Muriel, 2018; Mulvihill *et al*., 2010; Orhan *et al*., 2015; Mulvihill *et al*., 2016; Testai and Calderone, 2017; Assini *et al*., 2013). There are also very few research works executed with a complete study of pharmacokinetic properties of naringin and naringenin. Naringenin undergoes high-speed metabolism in liver and transformed into many glucuronide intermediates and this metabolism process may restrict its bioavailability in plasma (Fuhr and Kummert, 1995; Ishii *et al*., 1997).

Naringin on Hyperglycaemia and diabetes mellitus

Naringenin exhibits hyperglycaemic activity by inhibiting the enzyme α-glucosidase, inhibiting glucose uptake *in vitro* and also interfering with genes linked with metabolism of lipid (Priscilla *et al*., 2014; Li *et al*., 2006). Hyperglycaemia and insulin resistance (decreased response of the tissues towards insulin) are usual characteristics of metabolic syndrome. Few inflammatory cytokines like TNF-α may responsible in increasing the insulin resistance in obesity experimental models (Hotamisligil *et al*., 1993) (Fig. 3). Individuals with insulin resistance and type two diabetes shows increased amount of TNF-α and IL-6 (Pickup *et al*., 2000; Kado *et al*., 1999). Inflammatory cytokines like TNF-α (decreased response of tissues towards insulin) and IL-6 also may responsible for deterioration of insulin resistance and outlying insulin receptor that leads to elevation of glucose concentrations in plasma (Krogh *et al*., 2006; Dandona

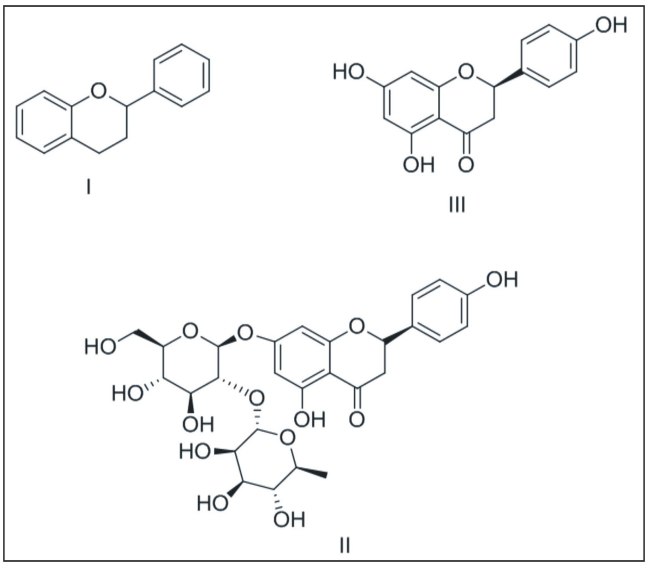

Fig. 2: Basic structure of I. Flavonoids; II. Naringenin; III. Naringin.

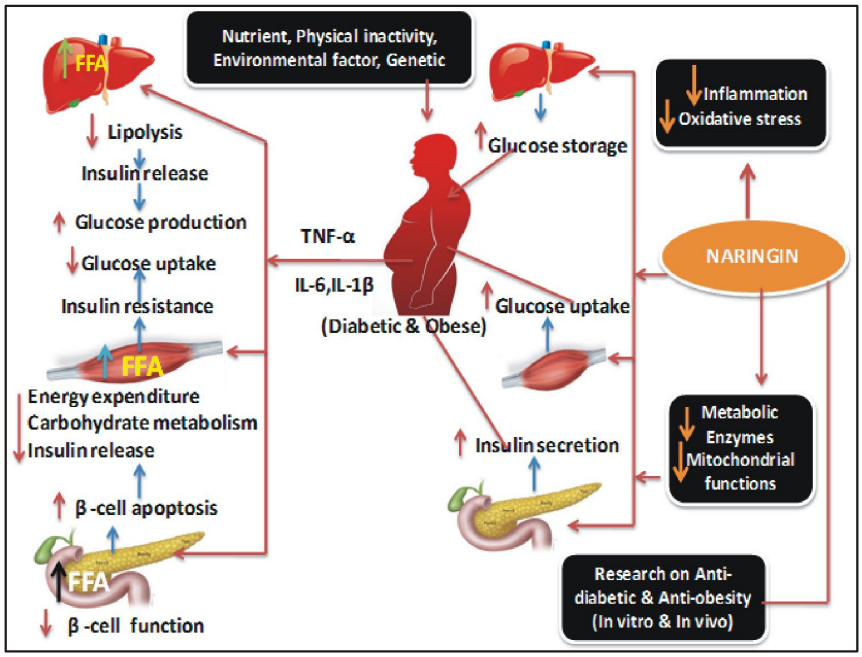

Fig. 3: Mechanism of action of Naringin in many metabolic ailments

et al., 2004) (Fig. 3). Inflammatory cytokine levels are increased by a high-fat diet which leads to insulin resistance and hyperglycaemia (Terra *et al*., 2009; Lee *et al*., 2010). Naringenin also causes an increase in phosphorylation of 5'adenosine monophosphate-activated protein kinase (AMPK) which is an enzyme that plays an important role in improving insulin sensitivity and cellular energy homeostasis in type two diabetes and other metabolic ailments (Zygmunt *et al*., 2010). In addition to this naringenin increases the amount of Sirtuin1 and peroxisome proliferator-activated receptor gamma co-activator (PGC)-1α that links to cellular glucose metabolism, insulin sensitivity and mitochondrial function (Mutlur *et al*., 2017).

Insulin resistance occurs due to the exposure of palmitic acid to L6 myotubes can be reduced by treatment with naringenin of 50 μM and 75 μM for 16 h by significant restoration of glucose uptake and translocation of GLUT-4 (Jung *et al*., 2004) (Fig. 3). Naringin also causes a reduction in glucose level in experimental animal studies by regulating the enzyme activities (Parmar *et al*., 2012) (Table 1).

Naringin at a dose of 40 mg/kg twice daily for 10 days remarkably reduces the activity of serum dipeptidyl peptidase-4 (DPP-IV) enzyme and also the concentrations of random glucose with elevated levels of insulin in albino male rats but there is non-significant reduction in concentrations of fasting glucose was observed (Sharma *et al*., 2011). A dose of 50-100 mg/kg of naringin treated for 28 days express an improvement in utilization of glucose and also the function of insulin along with it also improves the minimized beta-cell function in diabetic rats (Mahmoud *et al*., 2013). A dosage of 50 mg/kg naringin for 28 days treatment remarkably improves the increased oral glucose tolerance and elevated HbA1C in diabetic rats (Adebiyi *et al*., 2016). Rats when given with naringin at a dosage of 50 mg/kg for 56 days remarkably shows reduction in fasting blood sugar and elevated concentration of plasma insulin (Pari and Suman, 2010). Rats having diabetes when given with naringin at a dosage of 80 mg/kg for 42 days remarkably maintain the increase amount of blood sugar and also causes a reduction in plasma insulin (Kapoor and Kakkar, 2014) (Table 1). Naringenin at a dose of 50 mg/kg for 30 days decreases blood sugar quantity, hepatocyte ROS and lipid peroxidation in streptozotocin persuade diabetic rats (Bravo, 1998).

Naringin on hyperlipidaemia

Naringin helps in lowering increased lipid concentrations in plasma (Xulu *et al*., 2012). The hepatic triglyceride, cholesterol levels, activity of Acyl-CoA cholesterol acyltransferase, HMG-CoA reductase, were remarkably decreases when treated with naringin compared to the non-diabetic rats in table 1 (Bodas *et al*., 2011). Naringin at a dosage of 1.5 g per kg for 49 days express a reduction in the amount of cholesterol and plasma triglyceride compared to the controlled ones (Sharma *et al*., 2011) and also the triglyceride, nonessential fatty acid and total cholesterol amounts in plasma of the naringin given groups were decreased after 56 days. Naringin at a dosage of 50 and 100 mg per kg for 28 days remarkably decreases triglyceride, LDL, total cholesterol and increased amount of HDL in diabetic rats (Pu *et al*., 2012). Naringin at a dosage of 0.2 g/kg for 70 days significantly reduces the cholesterol and LDL levels with increase in amount of HDL of high-fed diet mice without changing the level of triglyceride as shown in table 1 (Ikemura *et al*., 2012.

Naringin on hypertension

Many studies elucidated that Naringin was found to have anti-hypertensive effect in high-fat-diet-fed rats with obesity and hypertensive rats liable to stroke. It causes remarkably increase in making nitric oxide metabolites in urine and causes increase in acetylcholine induced endothelium function with the help of thoracic aortic ring preparations by making nitric oxide (Visnagri *et al*., 2015).

Table 1: Effect of Naringin and their action in many metabolic ailments.

Derivative, Dose & duration	Mechanism of action	Outcome	Disease	Reference
Naringin 50 mg/kg for 42 days	↓oxidative stress, modification of growth factor (TGF-β) pathway, prohibition of the transformation of perisinusoidal cells of liver leading to ↓ collagen synthesis.	↑ reduced glycogen content in liver and plasma malondialdehyde content. ↓ increased level of serum acetoacetate.	Hyperglycaemia, oxidative stress	Guh *et al.*, 2009
Naringin 50 mg/kg for 45 days	↓ VLDL and ↑ hepatic depuration of LDL precursors, reduction of Rho- pathways with renewing of PPAR-α and ↓ cholesteryl ester transfer protein (CETP).	Lower plasma LDL, increase plasma HDL, ↓ the hepatic triglyceride and total cholesterol level.	Obesity, Hyperlipidaemia, Hyperglycaemia	Bodas *et al.*, 2011
Naringin 100 mg/kg for 56 days	↓ amount of resistin and ↑ amount of a diponectin by abolishing the biological activity and making of cytokines	↓ fat deposition and plasma lipid concentration, prevention of insulin resistance, decrease the systolic blood pressure	Obesity, hypertension, oxidative stress	Parmar *et al.*, 2012
Naringin 200mg/kg for 70 days	Abolishes the ↑ level of nitric oxide, Superoxide dismutase is increased by the free radical scavenging ability of naringin.	↓ FBS and serum insulin, ↓ level of TNF- α, ↓ level of LDL and plasma MDA. ↑ level of superoxide dismutase, Glutathione, catalase	Hyperlipidaemia, obesity, hyperglycaemia, oxidative stress	Ikemura *et al.*, 2012
Naringin 80mg/kg for 42 days	↓ amount of Hba1c and fasting blood glucose, ↑ the amount of insulin through β cells proliferation.	↑ level of insulin, normalise the ↓ level of plasma glutathione, vitamine	Hyperglycaemia, Oxidative stress	Kapoor and Kakkar, 2014
Naringin 50mg/kg for 30 days	↑ glycogen content in liver and muscle by decreasing the activities of phosphoenolpyruvate carboxykinase and glucose-6 -phosphatase. HMG-CoA reductase activity is inhibited which again inhibit the cholesterol homeostasis, prevents oxidative damage and pro-inflammatory cytokine release.	↑ serum insulin, amount of HbA1c is improved. ↑ hepatic & muscle glycogen content. ↓ total cholesterol, triglyceride, LDL, VLDL level, ↑ HDL, ↑ amount of glutathione of and ↓ quantity vit-c, TNF- α and IL-6	Hyperglycaemia, Hyperlipidaemia, Oxidative stress	Chanet *et al.*, 2012
Naringin 40 mg/kg for 10 days	Inhibition in the serum levels of DPP-IV activity. ↓ quantity of random glucose.	↑ insulin level. ↓ fasting serum and pancreatic nitrate concentration.	Hyperglycaemia	Bhattacharya *et al.*, 2014
Naringin 100-1000 μM for 1 & 72 hour	↑ expression of many β cell genes.	↑ glucose stimulates insulin secretion, ↑ sensitivity of glucose & protect β cells from cell death.	Hyperglycaemia,	Danja *et al.*, 2019

Naringin at a dosage of 40 mg per kg causes an increase in both systolic and diastolic blood pressure at different time interval as compared to controlled rats but at an increased dose of 80 mg per kg for 28 days it shows a remarkably antihypertensive effects by restoration of the blood pressure at different time interval and also there is an decrease in mean arterial blood pressure as compared to controlled rats (Ikemura *et al*., 2012). Naringin at a dosage of 250, 500 and 1000 mg per kg for 28 days remarkably reduces the increased systolic blood pressures in hypertensive rats (Jagetia and Lalnuntluangi, 2016).

Naringin on oxidative stress

It shows effective free radical scavenging activity by raising the glutathione-s-transferase, superoxide dismutase, catalase and glutathione quantity with decreased lipid peroxidation in doxorubicin induced oxidative stress rats in fig. 3 (Cavia-saiz *et al*., 2010). Previous studies elucidated that Naringin and Naringenin both helps in inhibiting the enzyme xanthine oxidase in vitro which are the sources of superoxide anions (Russo *et al*., 2000; Pu *et al*., 2012). Oxidative stress is inhibited at a dosage of 0.2 g/mg for 70 days with an increasing

activity of glutathione peroxidase, catalase, superoxide dismutase, antioxidant capacity, glutathione and reduced activity of malondialdehyde in high-fat diet mice (Akondi *et al*., 2011). A dosage of 10 mg/kg of Naringin for 46 days reduces the quantity of malondialdehyde and increases the amount of superoxide dismutase as well as catalase in diabetic rats (Murunga *et al*., 2016). A dosage of 50 mg/kg of Naringin for 42 days crucially showed improvement in amount of hepatic malondialdehyde, glutathione, nitric oxide and serum in diabetic rats (Guh *et al*., 2009) (Table 1).

Naringin on obesity

Increased energy intake compared to its expenditure leads to deposition of fat and weight gain which are risk factor for many diseases like diabetes, hyperlipidaemia, hypertension, arteriosclerosis and other metabolic ailments (WHO, 2002). As per WHO, a BMI in between 25.0-30.0 kg/m^2 is known as overweight and a BMI of >30.0 kg/m^2 is known as obesity in adults (Alam *et al*., 2013). Naringin at a dosage of 95.4±2.2 mg/kg/day for 8 weeks helps in reducing the fat deposition including circumference of abdomen (Ahmed *et al*., 2012).

Conclusion

Phytoconstituents such as flavonoids, alkaloids, terpenes, glycosides and tannins, saponins, are of plant origin with anti-diabetic principles. These phytoconstituents act through various mechanisms which include elevated insulin secretion, reduction in glucose output in liver, regulation of few enzymes responsible for carbohydrate metabolism such as α-glucosidase inhibitors, intonation of molecules such as PPARγ, antioxidant activities, involvement in the activities of some glycolytic enzymes such as phosphoenolpyruvate carboxykinase, improvement in HbA1c, hypolipidaemic activities, increased expression of glucose transporters and many others to potentiate their anti-diabetic activity. Among all phytoconstituents, flavonoids were proved to be with most favoured anti-diabetic concept. These naturally transpire secondary plant products showed a great capability in making of marketable, novel and effective anti-diabetic drugs. Numerous studies disclosed that naringin proved to be effective against hypertension, hyperlipidaemia, hyperglycaemia and obesity. Many studies also showed a fruitful effect of naringenin in the pancreas, recovery activity of β cells and improving their sensitivity and response towards glucose.

References

Am, M. and H. Oe (2015). Anti-Diabetic Effect of Naringin: Insights into the Molecular Mechanism. Diabetes Obes. *Int. J.*, **35:** 250-263.

Adebiyi, O.A., O.O. Adebiyi and P.M.O. Owira (2016). Naringin reduces hyperglycemia-induced cardiac fibrosis by relieving oxidative stress. *PLoS One*, **11:** 136-144.

Alberti, K.G.M.M., P. Zimmet and J. Shaw (2006). Metabolic syndrome - A new world-wide definition. A consensus statement from the International Diabetes Federation. *Diabet. Med*., **23:** 469-480.

Amor, S., P. Châlons, V. Aires and D. Delmas (2018). Polyphenol Extracts from Red Wine and Grapevine: Potential Effects on Cancers. *Diseases*., **6:** 106.

Assini, J.M., E.E. Mulvihill and M.W. Huff (2013). Citrus flavonoids and lipid metabolism. *Curr. Opin. Lipidol*., **24:** 34-40.

Akondi, R.B., P. Kumar, A. Annapurna and M. Pujari (2011). Protective Effect of Rutin and Naringin on Sperm Quality in Streptozotocin (STZ) Induced Type 1 Diabetic Rats. *Iran. J. Pharm. Res. (IJPR).*, **10:** 585.

Alam, M.A., K. Kauter and L. Brown (2013). Naringin improves diet-induced cardiovascular dysfunction and obesity in high carbohydrate, high fat diet-fed rats. *Nutrients*., **5:** 637-650.

Ahmed, O.M., A.M. Mahmoud, A. Abdel-Moneim and M.B. Ashour (2012). Antidiabetic effects of hesperidin and naringin in type 2 diabetic rats. *Diabetol. Croat.*, **41:** 53-67.

Bodas, R., Ó. López-Campos, N. Prieto, F.J. Giráldez and S. López S. Andrés and (2011). The effect of naringin on plasma lipid profile and liver and intramuscular fat contents of fattening lambs. *Options Mediterraneennes*, **A:** 223-226.

Bravo, L. (2009). Polyphenols: Chemistry, Dietary Sources, Metabolism and Nutritional Significance. *Nutr. Rev*., **56:** 317-333.

Bruce, K.D. and M.A. Hanson (2010). The Developmental Origins, Mechanisms and Implications of Metabolic Syndrome. *J. Nutr.*, **140:** 648-652.

Bhattacharya, S., N. Oksbjerg, J.F. Young and P.B. Jeppesen (2014). Caffeic acid, naringenin and quercetin enhance glucose-stimulated insulin secretion and glucose sensitivity in INS-1E cells. *Diabetes, Obes. Metab*., **16:** 602-612.

Coelho, R.C.L.A., H.H.M. Hermsdorff and J. Bressan (2013). Anti-inflammatory Properties of Orange Juice: Possible Favorable Molecular and Metabolic Effects. *Plant Foods Hum. Nutr*., **68:** 1-10.

Chanet, A., P. Wizinska, S. Polakof, A. Mazur, C. Bennetau-Pelissero, C. Morand, A.M. Bérard and D. Milenkovic (2012). Naringin at a nutritional dose modulates expression of genes related to lipid metabolism and inflammation in liver of mice fed a high-fat diet. *Nutr. Aging*., **1:** 113-121.

Chandra Jagetia, G. and V. Lalnuntluangi (2016). The Citrus Flavanone Naringin enhances Antioxidant Status in the Albino Rat Liver treated with Doxorubicin. *Biochem. Mol. Biol. J.*, **2:** 1-9.

Croft, K.D. (1998). The chemistry and biological effects of flavonoids and phenolic acids, in: Annals of the New York Academy of Sciences. *New York Academy of Sciences*, **854:** 435-442.

Després, J.P. and I. Lemieux (2006). Abdominal obesity and metabolic syndrome. *Nature*, **444:** 881-887.

Dandona, P., A. Aljada and A. Bandyopadhyay (2004). Inflammation: The link between insulin resistance, obesity and diabetes. *Trends Immunol*., **25:** 4-7.

Estaquio, C., K. Castetbon, E. Kesse-Guyot, S. Bertrais, V. Deschamps, L. Dauchet, S. Péneau, P. Galan and S. Hercberg. The French National Nutrition and Health Program Score Is Associated with Nutritional Status and Risk of Major Chronic Diseases, *J. Nutr*., **138:** 946-53.

Fuhr, U. and A.L. Kummert (1995). The fate of naringin in humans: A key to grapefruit juice-drug interactions? *Clin. Pharmacol. Ther*., **58:** 365-373.

Gattuso, G., D. Barreca, C. Gargiulli, U. Leuzzi and C. Caristi (2007). Flavonoid composition of citrus juices. *Molecules*., **12:** 1641-1673.

Guh, D.P., W. Zhang, N. Bansback, Z. Amarsi, C.L. Birmingham and A.H. Anis (2009). The incidence of co-morbidities related to obesity and overweight: A systematic review and meta-analysis. *BMC Public Health*, **9:** 88.

Hartogh, D.J.D. and E. Tsiani (2019). Antidiabetic properties of naringenin: A citrus fruit Polyphenol. *Biomolecules*, **9:** 99.

Hernández-Aquino, E. and P. Muriel (2018). Beneficial effects of naringenin in liver diseases: Molecular mechanisms. *World J. Gastroenterol*., **24:** 1679-1707.

Hotamisligil, G.S., N.S. Shargill and B.M. Spiegelman (1993). Adipose expression of tumor necrosis factor-α: Direct role in obesity-linked insulin resistance. *Science*, **259:** 87-91.

Ikemura, M., Y. Sasaki, J.C. Giddings and J. Yamamoto (2012). Preventive Effects of Hesperidin, Glucosyl Hesperidin and Naringin on Hypertension and Cerebral Thrombosis in Stroke-prone Spontaneously Hypertensive Rats. *Phyther. Res*., **26:** 1272-1277.

Ikemura, M., Y. Sasaki, J.C. Giddings and J. Yamamoto (2012). Preventive effects of hesperidin, glucosyl hesperidin and naringin on hypertension and cerebral thrombosis in stroke-prone spontaneously hypertensive Rats. *Phyther. Res*., **26:** 1272-1277.

Ishii, K., T. Furuta and Y. Kasuya (1997). Determination of naringin and naringenin in human urine by high-performance liquid chromatography utilized solid-phase extraction. *J. Chromatogr. B Biomed. Appl*., **704:** 299-305.

Jung, U.J., H.J. Kim, J.S. Lee, M.K. Lee, H.O. Kim, E.J. Park, H.K. Kim, T.S. Jeong and M.S. Choi (2003). Naringin supplementation lowers plasma lipids and enhances erythrocyte antioxidant enzyme activities in hypercholesterolemic subjects. *Clin. Nutr*., **22:** 561-568.

Jung, U.J., M.K. Lee, K.S. Jeong and M.S. Choi (2004). The Hypoglycemic Effects of Hesperidin and Naringin Are Partly Mediated by Hepatic Glucose-Regulating Enzymes in C57BL/KsJ-db/db *Mice. J. Nutr*., **134:** 2499-2503.

Kumar, S., A.K. Pandey, K.P. Lu and J. Sastre (2013). Chemistry and Biological Activities of Flavonoids: An Overview. *Sci. World J*., **2013:** 16.

Kuzma, J.N., K.A. Schmidt and M. Kratz (2017). Prevention of metabolic diseases: Fruits (including fruit sugars) vs. vegetables. *Curr. Opin. Clin. Nutr. Metab. Care*., **20:** 286-293.

Kado, S., T. Nagase and N. Nagata (1999). Circulating levels of interleukin-6, its soluble receptor and interleukin-6/interleukin-6 receptor complexes in patients with type 2 diabetes mellitus. *Acta Diabetol*., **36:** 67-72.

Krogh-Madsen, R., P. Plomgaard, K. Møller, B. Mittendorfer and B.K. Pedersen (2006). Influence of TNF-α and IL-6 infusions on insulin sensitivity and expression of IL-18 in humans. *Am. Journal Physiol. - Endocrinol. Metab*., **291:** E108-114.

Kapoor, R. and P. Kakkar (2014). Naringenin accords hepatoprotection from streptozotocin induced diabetes in vivo by modulating mitochondrial dysfunction and apoptotic signaling cascade. *Toxicol. Reports*, **1:** 569-581.

Li, J.M., C.T. Che, C.B.S. Lau, P.S. Leung and C.H.K. Cheng (2006). Inhibition of intestinal and renal Na+-glucose cotransporter by naringenin. *Int. J. Biochem. Cell Biol*., **38:** 985-995.

Liu, S., M. Serdula, S.J. Janket, N.R. Cook, H.D. Sesso, W.C. Willett, J.A.E. Manson and J.E. Buring (2004). A prospective study of fruit and vegetable intake and the risk of type 2 diabetes in women. *Diabetes Care*, **27:** 2993-2996.

Lagouge, M., C. Argmann, Z. Gerhart-Hines, H. Meziane, C. Lerin, F. Daussin, N. Messadeq, J. Milne, P. Lambert, P. Elliott, B. Geny, M. Laakso, P. Puigserver and J. Auwerx (2006). Resveratrol Improves Mitochondrial Function and Protects against Metabolic Disease by Activating SIRT1 and PGC-1α. *Cell*, **127:** 1109-1122.

Lee, I.S., G. Shin and R. Choue (2010). Shifts in diet from high fat to high carbohydrate improved levels of adipokines and pro-inflammatory cytokines in mice fed a high-fat diet. *Endocr. J*., **57:** 39-50.

Martin, K.R. (2009). Polyphenols as dietary supplements: A double-edged sword. *Nutr. Diet. Suppl*., **2:** 1.

Mahmoud, A.M. (2013). Hematological alterations in diabetic rats - Role of adipocytokines and effect of citrus flavonoids. *E.X.C.L.I. J*., **12:** 647-657.

Murunga, A.N., D.O. Miruka, C. Driver, F.S. Nkomo, S.Z.Z. Cobongela and P.M.O. Owira (2016). Grapefruit Derived Flavonoid Naringin Improves Ketoacidosis and Lipid Peroxidation in Type 1 Diabetes Rat Model. *PLoS One*, **11:** e0153241.

Mulvihill, E.E., J.M. Assini, B.G. Sutherland, A.S. Dimattia, M. Khami, J.B. Koppes, C.G. Sawyez, S.C. Whitman and M.W. Huff (2010). Naringenin decreases progression of

atherosclerosis by improving dyslipidemia in high-fat-fed low-density lipoprotein receptor-null mice. *Arterioscler. Thromb. Vasc. Biol.*, **30:** 742-748.

Mahmoud, A.M. (2014). Hesperidin protects against cyclophosphamide-induced hepatotoxicity by upregulation of pparγ and abrogation of oxidative stress and inflammation. *Can. Journal Physiol. Pharmacol*., **92:** 717-724.

Mulvihill, E.E., A.C. Burke and M.W. Huff (2016). Citrus Flavonoids as Regulators of Lipoprotein Metabolism and Atherosclerosis. *Annu. Rev. Nutr*., **36:** 275-299.

Mutlur Krishnamoorthy, R. and A. Carani Venkatraman (2017). Polyphenols activate energy sensing network in insulin resistant models. *Chem. Biol. Interact*., **275:** 95-107.

Orhan, I., S. Nabavi, M. Daglia, G. Tenore, K. Mansouri and S. Nabavi (2015). Naringenin and Atherosclerosis: A Review of Literature. *Curr. Pharm. Biotechnol*., **16:** 245-251.

Parmar, H.S., P. Jain, D.S. Chauhan, M.K. Bhinchar, V. Munjal, M. Yusuf, K. Choube, A. Tawani, V. Tiwari, E. Manivannan and A. Kumar (2012). DPP-IV inhibitory potential of naringin: An in silico, *in vitro* and *in vivo* study. *Diabetes Res. Clin. Pract*., **97:** 105-111.

Peterson, J. and J. Dwyer (1998). Flavonoids: Dietary occurrence and biochemical activity. *Nutr. Res*., **18:** 1995-2018.

Pu, P., D.M. Gao, S. Mohamed, J. Chen, J. Zhang, X.Y. Zhou, N.J. Zhou, J. Xie and H. Jiang (2012). Naringin ameliorates metabolic syndrome by activating AMP-activated protein kinase in mice fed a high-fat diet. *Arch. Biochem. Biophys*., **518:** 61-70.

Pickup, J.C., G.D. Chusney, S.M. Thomas and D. Burt (2000). Plasma interleukin-6, tumour necrosis factor α and blood cytokine production in type 2 diabetes. *Life Sci*., **67:** 291-300.

Priscilla, D.H., D. Roy, A. Suresh, V. Kumar and K. Thirumurugan (2014). Naringenin inhibits α-glucosidase activity: A promising strategy for the regulation of postprandial hyperglycemia in high fat diet fed streptozotocin induced diabetic rats. *Chem. Biol. Interact*., **210:** 77-85.

Russo, A., R. Acquaviva, A. Campisi, V. Sorrenti, C. Di Giacomo, G. Virgata, M.L. Barcellona and A. Vanella (2000). Bioflavonoids as antiradicals, antioxidants and DNA cleavage protectors. *Cell Biol. Toxicol*., **16:** 91-98.

Ross, J.A. and C.M. Kasum (2002). D IETARY F LAVONOIDS/ : Bioavailability, Metabolic Effects and Safety. *Annu. Rev. Nutr*., **22:** 19-34.

Rani, N., S. Bharti, B. Krishnamurthy, J. Bhatia, C. Sharma, M. Amjad Kamal, S. Ojha and D.S. Arya (2016). Pharmacological Properties and Therapeutic Potential of Naringenin: A Citrus Flavonoid of Pharmaceutical Promise. *Curr. Pharm. Des*., **22:** 4341-4359.

Renugadevi, J. and S.M. Prabu (2009). Naringenin protects against cadmium-induced oxidative renal dysfunction in rats. *Toxicology*., **256:** 128-134.

Stefan, N., H.U. Häring and M.B. Schulze (2018). Metabolically healthy obesity: the low-hanging fruit in obesity treatment? *Lancet Diabetes Endocrinol*., **6:** 249-258.

Sharma, A.K., S. Bharti, S. Ojha, J. Bhatia, N. Kumar, R. Ray, S. Kumari and D.S. Arya (2011). Up-regulation of PPARγ, heat shock protein-27 and-72 by naringin attenuates insulin resistance, â-cell dysfunction, hepatic steatosis and kidney damage in a rat model of type 2 diabetes. *Br. J. Nutr*., **106:** 1713-1723.

Sharma, M., N. Akhtar, K. Sambhav, G. Shete, A. Bansal and S. Sharma (2014). Emerging Potential of Citrus Flavanones as an Antioxidant in Diabetes and its Complications. *Curr. Top. Med. Chem*., **15:** 187-195.

Tripoli, E., M. La Guardia, S. Giammanco, D. Di Majo and M. Giammanco (2007). Citrus flavonoids: Molecular structure, biological activity and nutritional properties: A review. *Food Chem*., **104:** 466-479.

Testai, L. and V. Calderone (2017). Nutraceutical value of citrus flavanones and their implications in cardiovascular disease. *Nutrients*, **9:** 502.

The world health report (2002). Reducing Risks, Promoting Healthy Life," (2013)

Terra, X., G. Montagut, M. Bustos, N. Llopiz, A. Ardèvol, C. Bladé, J. Fernández-Larrea, G. Pujadas, J. Salvadó, L. Arola and M. Blay (2009). Grape-seed procyanidins prevent low-grade inflammation by modulating cytokine expression in rats fed a high-fat diet. *J. Nutr. Biochem*., **20:**210-218.

Vieira, A.R., S. Vingeliene, D.S.M. Chan, D. Aune, L. Abar, D. Navarro Rosenblatt, D.C. Greenwood and T. Norat (2015). Fruits, vegetables and bladder cancer risk: A systematic review and meta-analysis. *Cancer Med*., **4:** 136-146.

Visnagri, A., M. Adil, A.D. Kandhare and S.L. Bodhankar (2015). Effect of naringin on hemodynamic changes and left ventricular function in renal artery occluded renovascular hypertension in rats. *J. Pharm. Bioallied Sci*., **7:** 121-127.

White, J.R. (2008). Dipeptidyl peptidase-IV inhibitors: Pharmacological profile and clinical use. *Clin. Diabetes*., **26:** 53-57.

Xulu, S. and P.M. Oroma Owira (2012). Naringin ameliorates atherogenic dyslipidemia but not hyperglycemia in rats with type 1 diabetes. *Jour. Cardiovasc. Pharmacol*., **59:** 133-141.

Yahfoufi, N., N. Alsadi, M. Jambi and C. Matar (2018). The immunomodulatory and anti-inflammatory role of polyphenols. *Nutrients*, **10:** 1618.

Zaidun, N.H., Z.C. Thent and A.A. Latiff (2018). Combating oxidative stress disorders with citrus flavonoid: Naringenin. *Life Sci*., **208:** 111-122.

Zeng, W., L. Jin, F. Zhang, C. Zhang and W. Liang (2018). Naringenin as a potential immunomodulator in therapeutics. *Pharmacol. Res*., **135:** 122-126.

Zygmunt, K., B. Faubert, J. MacNeil and E. Tsiani (2010). Naringenin, a citrus flavonoid, increases muscle cell glucose uptake *via* AMPK. *Biochem. Biophys. Res. Commun*., **398:** 178-183.