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, secretagogues (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
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 play a principal role in scavenging the free radicals and preventing the oxidative stress (Croft, 1998; Ross and Kausum, 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 Prabhu, 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., 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.

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

**Fig. 2:** Basic structure of I. Flavonoids; II. Naringenin; III. Naringin.
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). Naringenin also causes a reduction in glucose level in experimental animal studies by regulating the enzyme activities (Parmar et al., 2012) (Table 1).

Naringenin 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 naringenin 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).
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 a 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 Lahnuntluangi, 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

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

<table>
<thead>
<tr>
<th>Derivative, Dose &amp; duration</th>
<th>Mechanism of action</th>
<th>Outcome</th>
<th>Disease</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naringin 50 mg/kg for 42 days</td>
<td>↓ oxidative stress, modification of growth factor (TGF-β) pathway, prohibition of the transformation of perisinusoidal cells of liver leading to ↓ collagen synthesis.</td>
<td>↑ reduced glycosgen content in liver and plasma malondialdehyde content. ↓ increased level of serum acetoacetate.</td>
<td>Hyperglycaemia, oxidative stress</td>
<td>Guh et al., 2009</td>
</tr>
<tr>
<td>Naringin 50 mg/kg for 45 days</td>
<td>↓ VLDL and ↑ hepatic depuration of LDL precursors, reduction of Rho- pathways with renewing of PPAR-α and ↓ cholesteryl ester transfer protein (CETP).</td>
<td>Lower plasma LDL, increase plasma HDL, ↓ the hepatic triglyceride and total cholesterol level.</td>
<td>Obesity, Hyperlipidaemia, Hyperglycaemia</td>
<td>Bodas et al., 2011</td>
</tr>
<tr>
<td>Naringin 100 mg/kg for 56 days</td>
<td>↓ amount of resistin and ↑ amount of a diponecint by abolishing the biological activity and making of cytokines</td>
<td>↓ fat deposition and plasma lipid concentration, prevention of insulin resistance, decrease the systolic blood pressure</td>
<td>Obesity, hypertension, oxidative stress</td>
<td>Parmar et al., 2012</td>
</tr>
<tr>
<td>Naringin 200mg/kg for 70 days</td>
<td>Abolishes the ↑ level of nitric oxide, Superoxide dismutase is increased by the free radical scavenging ability of naringin.</td>
<td>↓ FBS and serum insulin, ↑ level of TNF-α, ↓ level of LDL and plasma MDA, ↑ level of superoxide dismutase, Glutathione, catalase</td>
<td>Hyperlipidaemia, obesity, hyperglycaemia, oxidative stress</td>
<td>Ikemura et al., 2012</td>
</tr>
<tr>
<td>Naringin 80mg/kg for 42 days</td>
<td>↓ amount of Hba1c and fasting blood glucose, ↑ the amount of insulin through β cells proliferation.</td>
<td>↑ level of insulin, normalise the ↓ level of plasma glutathione, vitamin</td>
<td>Hyperglycaemia, Oxidative stress</td>
<td>Kapoor and Kakkar, 2014</td>
</tr>
<tr>
<td>Naringin 50mg/kg for 30 days</td>
<td>↑ glycosgen content in liver and muscle by decreasing the activities of phosphoenolpyruvate carboxykinase and glucose-6-phosphatease. HMG-CoA reductase activity is inhibited which again inhibit the cholesterol homeostasis, prevents oxidative damage and pro-inflammatory cytokine release.</td>
<td>↓ serum insulin, amount of HbA1c is improved. ↑ hepatic &amp; muscle glycosgen content. ↓ total cholesterol, triglycere, LDL, VLDL level, ↑ HDL, ↑ amount of glutathione of and ↓ quantity of vit-c, TNF-α and IL-6.</td>
<td>Hyperglycaemia, Hyperlipidaemia, Oxidative stress</td>
<td>Chanet et al., 2012</td>
</tr>
<tr>
<td>Naringin 40 mg/kg for 10 days</td>
<td>Inhibition in the serum levels of DPP-IV activity, ↓ quantity of random glucose.</td>
<td>↑ insulin level, ↓ fasting serum and pancreatic nitrate concentration.</td>
<td>Hyperglycaemia</td>
<td>Bhattacharya et al., 2014</td>
</tr>
<tr>
<td>Naringin 100-1000µM for 1 &amp; 72 hour</td>
<td>↑ expression of many β cell genes.</td>
<td>↑ glucose stimulates insulin secretion, ↑ sensitivity of glucose &amp; protect β cells from cell death.</td>
<td>Hyperglycaemia,</td>
<td>Danja et al., 2019</td>
</tr>
</tbody>
</table>
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/m² is known as overweight and a BMI of >30.0 kg/m² 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 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


