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Antidiabetic and Antihypertensive Properties of Naringin: A Review

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Abstract: Despite the availability of various medications that successfully lower blood glucose levels and blood pressure, diabetes mellitus (DM) and hypertension (HTN) continue to place a tremendous strain on global medical resources. The prevention of numerous complications, which remain the leading cause of mortality due to these diseases, is a key challenge in the management of these two disorders. Phytochemicals are a rich source of plant-derived molecules that are critical for the discovery of substances with medicinal potential. Flavonoids have a history of being important natural components with a variety of biological functions. Naringin, a flavanone glycoside found mostly in grapefruit and citrus fruits, is a natural flavanone glycoside. Obesity, diabetes, high blood pressure, and metabolic syndrome can all be treated with naringin. A few molecular pathways underpinning its beneficial properties have been discovered. Naringin has a wide spectrum of pharmacological properties, including anti-inflammatory and cancer-fighting properties.

Keywords: Naringin, Diabetes, Hypertension, Flavonoid, Insulin

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Introduction

The use of herbal medicine for the treatment of various ailments has expanded dramatically (Frishman *et al.*, 2009). This is due to several causes, the most important of which is that herbal medication is a less expensive option with less unwanted side effects (Susalit *et al.*, 2011). Around 80% of the population in several Asian and African nations rely on indigenous traditional treatments for their primary health care requirements, which primarily consist of crude

herbal concoctions (Santé Omdl, 2005). According to studies, India has over 20,000 medicinal herbs, but only 7,000–7,500 of these are used by traditional practitioners to treat various ailments (Samy *et al.*, 2008). Compounds that give plants their colour, flavour, and smell are known as phytochemicals. The therapeutic characteristics and health benefits of medicinal herbs are regarded to be mostly due to these substances. Poisonous and toxic compounds are also found in

phytochemicals. Despite the burgeoning scientific interest in the development of novel chemicals to treat diabetes and hypertension, the incidence of these diseases and their complications remain high, underscoring the unmet and urgent need for novel candidate chemicals with significant efficacy. Phytochemicals derived from plants are currently being investigated as potential therapeutic candidates for the prevention and treatment of a variety of metabolic diseases, including diabetes and hypertension. Naringin is a flavanone glycoside made up of the flavanone naringenin and the disaccharide neohesperidose. It is also found in citrus fruits (Wong *et al.*, 2013) and gives citrus juices a bitter taste (Chtourou *et al.*, 2015). Flavonoids are a class of secondary metabolites found in plants that are a source of bioactive chemicals (Ghasemzadeh and Jaafar, 2013). Naringin has antioxidant, anti-inflammatory, anti-apoptotic, anti-ulcer, anti-osteoporotic, anti-diabetic, anti-hypertensive, and anti-carcinogenic activities (Wang *et al.*, 2013).

Diabetes mellitus (DM) has become more common in recent years as a result of sedentary lifestyles and dietary changes in many nations, particularly developing ones. This disease, which accounts for about 90% of all cases of DM, is likely to increase in terms of the number of diabetic persons, which is also expected to rise dramatically, reaching over 80 million cases by 2025 (Zimmet *et al.*, 2001). Hypertension, along with pre-hypertension and other hazardously high blood pressure, is responsible for 8.5 million deaths from stroke, ischaemic heart disease, other vascular diseases, and renal disease worldwide (Olsen *et al.*, 2016; NCD-RisC, 2021).

Global scenario of diabetes and hypertension:

Diabetes mellitus (DM) is becoming one of the most significant burdens on world health and economies, with a prevalence of 8.8% in adults (20–79 years) (Bommer *et al.*, 2017). Diabetes mellitus (all kinds) is ranked ninth among the leading causes of morbidity and mortality with a significant impact on life expectancy (G.B.D. Mortality, 2015). Although the exact classification

of diabetes is still debated due to the complicated nature of its pathophysiology, three basic subtypes are universally recognised: type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), and gestational diabetes mellitus (GDM) (American Diabetes, 2019). The present epidemic of T2DM has demonstrated a strong global escalation, accounting for nearly 90% of diabetes cases (Hu and Jia, 2019), along with the increasing influence of genetic abnormalities, chemical toxicity, sedentary lifestyle, and ageing.

Hypertension, often known as high blood pressure, is a leading cause of atherosclerosis, coronary artery disease, myocardial infarction, heart failure, stroke, and renal insufficiency (Oparil, 1999). According to the first comprehensive global analysis of trends in hypertension prevalence, detection, treatment, and control, the number of adults aged 30–79 years with hypertension has increased from 650 million to 1.28 billion in the last thirty years. Nearly half of the patients in this study were unaware that they had hypertension (NCD-RisC, 2021).

Source, structure, and bioavailability of naringin:

Naringin is predominantly found in grapefruit *Citrus paradisi*. It is also present in other plants (Table 1) including *Citrus sinensis*, *Citrus unshiu*, *Citrus nobilis*, *Citrus tachibana*, *Citrus junos*, *Artemisia selengensis*, *Artemisia stolonifera*, roots of *Cudrania cochinchinensis*, aerial parts of *Thymus herba barona*, fruits of *Poncirus* and related citrus species (Ting *et al.*, 2008).

Naringin (naringenin-7-rhamnoglucoside) (Fig. 1) is a flavanone glycoside that mainly exists in grapefruit and citrus fruits. It possesses the distinct bitter taste of grapefruit juice (Arnao *et al.*, 1990). The molecular formula of naringin is C₂₇H₃₂O₁₄ and the molecular weight is 580.4 g/mol. Two units of rhamnose are found to be attached to its aglycone part, naringenin at the 7-carbon position (Wang *et al.*, 2006).

It is known that oral bioavailability of naringin is very low. Naringin is converted to absorbable

Table 1: Naringin concentrations found in various citrus species juice

Plant species	Naringin Content (mg/ml)	Reference
<i>Citrus (C.) sinensis</i>	21.3	Kawaii <i>et al.</i> (1999)
<i>Citrus aurantium</i>	19.7	de Lourdes <i>et al.</i> (2007)
<i>Citrus reticulata</i>	3383.6	Dhuique-Mayer <i>et al.</i> (2005)
<i>Citrus clementina</i>	8.0	Dhuique-Mayer <i>et al.</i> (2005)
<i>Citrus bergamia</i>	22.3	de Lourdes <i>et al.</i> (2007)
<i>Citrus paradisi</i>	230.0	de Lourdes <i>et al.</i> (2007)

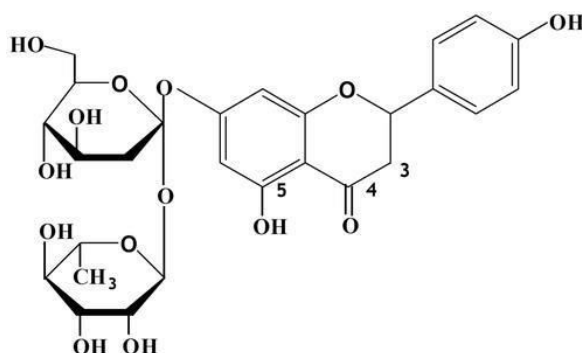


Fig. 1: Chemical structure of naringin.

naringenin by biotransformation through enzymes such as α -rhamnosidase and β -glucosidase (Kim *et al.*, 1998). When naringin is administered by the oral route, very low amounts of naringenin are encountered. This can be explained by the fact that naringin is hydrolyzed to naringenin just before absorption.

Antidiabetic properties of naringin:

Diabetes is characterised by hyperglycemia and insulin resistance. Insulin resistance is characterised as a reduction in the peripheral tissues' responsiveness to insulin. In experimental obesity models, inflammatory cytokines such as TNF- α may produce insulin resistance (Hotamisligil *et al.*, 1993). Furthermore, IL-6 and TNF- α concentrations were found to be higher in people with insulin resistance and type 2 diabetes in various investigations (Kado *et al.*, 1999; Pickup *et al.*, 2000). Naringin's hypoglycemic effect has been

thoroughly documented (Jung *et al.*, 2004; Ali and Kader, 2004). Cotreatment of streptozotocin-induced diabetes in rats with naringin (30 mg/kg) and vitamin C (50 mg/kg) improved insulin concentration and reduced oxidative stress (Punithavathi, 2008). At a supplementation level of 0.2 g/kg of meal, it also enhanced insulin concentration and pancreatic architecture in db/db mice (Jung *et al.*, 2004). The glucose-lowering action of naringin in experimental animals is also influenced by changes in glucose-regulating enzyme activity (Jung *et al.*, 2004). In db/db mice, naringin significantly reduced the activity of hepatic glucose-6-phosphatase and phosphoenolpyruvate carboxy kinase relative to control mice (Jung *et al.*, 2004). It has also been revealed that hypoglycemic activity of naringin is mediated through glucose absorption in skeletal muscle (Zygmunt *et al.*, 2010). In skeletal muscle cells, increased glucose absorption is mediated by AMPK

overexpression (Zygmunt *et al.*, 2010). In a model of high-fat-diet-fed mice, naringin supplementation (0.2 g/kg of diet) decreased glucose intolerance and insulin resistance (Pu *et al.*, 2010).

In albino male rats, naringin administration at 40 mg/kg twice daily for 10 days lowered blood dipeptidyl peptidase-4 (DPP-IV) enzyme activity and random glucose concentrations while increasing insulin levels. Fasting glucose concentrations, on the other hand, showed no significant decrease (Parmar *et al.*, 2012). Naringin, given at doses of 50 and 100 mg/kg for 28 days, improved diabetic rats' glucose utilisation and insulin sensitivity. In diabetic rats, naringin at 100 mg/kg for 28 days improved the impaired β -cell function (Sharma *et al.*, 2011). Naringin administration at a dose of 50 mg/kg for four weeks alleviated diabetic rats' increased blood glycosylated haemoglobin (HbA1C). In diabetic rats, however, naringin administration resulted in a considerable increase in serum insulin levels. In diabetic rats, therapy with 50 mg/kg naringin for four weeks improved their increased oral glucose tolerance (Mahmoud *et al.*, 2013). The increased oral glucose tolerance test (OGTT) and HbA1C in diabetic rats improved dramatically after 30 days of naringin administration at a dose of 50 mg/kg. Furthermore, treatment with naringin at a dose of 50 mg/kg for 30 days resulted in a rise in serum insulin levels (Ahmed *et al.*, 2012). In diabetic rats, naringin at a dose of 50 mg/kg for 56 days considerably reduced high fasting and significantly improved hepatic glycogen content, but did not alter OGTT levels (Sinethemba, 2014). Treatment with naringin at a dose of 0.2 g/kg for 10 weeks reduced the increased HOMA-IR score (an evaluation of insulin resistance) in high diet fed mice by 20.3 per cent. Furthermore, naringin administration at a dose of 0.2 g/kg for 10 weeks resulted in a considerable reduction in fasting blood glucose and serum insulin levels (Pu *et al.*, 2012). The STZ-induced rats' fasting blood insulin and hepatic glycogen levels were considerably improved after 42 days of therapy with 50 mg/kg naringin (Murunga *et al.*, 2016). Naringin administration of 50 mg/kg for 56 days

dramatically reduced polydipsia in diabetic rats compared to untreated diabetic rats (Adebiyi *et al.*, 2016a). Naringin treatment of rats at 50 mg/kg for 56 days resulted in a considerable reduction in fasting blood glucose and an increase in plasma insulin concentrations (Adebiyi *et al.*, 2016b). Diabetic rats given naringin at a dose of 80 mg/kg for 42 days kept their increased blood glucose levels while having lower plasma insulin levels (Pari and Suman, 2010).

Antihypertensive properties of naringin:

Naringin supplementation improved hypertension in obese rats fed a high-carbohydrate/high-fat diet (Alam *et al.*, 2013) and stroke-prone hypertensive rats (Ikemura *et al.*, 2012). Furthermore, utilising thoracic aortic ring preparations, naringin dramatically boosted the synthesis of NO metabolites in urine and improved acetylcholine-mediated endothelium function by NO production (Ikemura *et al.*, 2012). In comparison to sham rats, naringin therapy at a dose of 40 mg/kg resulted in an increase in systolic and diastolic blood pressure at 15, 30, 45, 60, and 90 min. In addition, naringin at an oral dose of 80 mg/kg for four weeks restored systolic and diastolic blood pressure at 15, 30, 45, 60, and 90 min, compared to sham rats. Furthermore, when naringin 80 mg/kg was given to rats for 15, 30, 45, 60, and 90 minutes, the increase in mean arterial blood pressure was reduced compared to sham rats (Visnagr *et al.*, 2015). Naringin (250, 500, and 1000 mg/kg) significantly reduced the increase in systolic blood pressures in spontaneously hypertensive rats after 4 weeks of treatment (Ikemura *et al.*, 2012). The therapy of naringin at a dose of 100 mg/kg for 8 weeks lowered the increased systolic blood pressure in high diet fed rats (Alam *et al.*, 2013).

Conclusion

Naringin supplementation has proven to be efficacious for the treatment of diabetes and hypertension in animal models. The dose used in animal studies may not be achieved in human trials and emphasis should be given to establish a dietary recommendation of citrus fruit

consumption or for the pure compound naringin. The use of naringin in clinical therapy has a few drawbacks. The available scientific data about the use of naringin in humans to treat diabetes and hypertension is extremely minimal. To determine a conclusive role for naringin in human treatments, more clinical research is required. It is also uncertain how long naringin should be supplied for. Short-term naringin administration is unlikely to improve therapeutic outcomes. Moreover, further clinical investigations should be carried out with naringin in metabolic diseases.

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