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Naringenin: a potential bioactive compound and pathways of biosynthesis – a review

by ***Nguyen Anh Dung*** *and* ***Nguyen Thanh Thuan*** *(Thu Dau Mot University)*

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Corresponding author: Dungna@tdmu.edu.vn
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ABSTRACT

Naringenin is a member of the flavonoid family. This natural compound represents a large proportion of secondary metabolites produced by higher plants and is a rich part of the human diet. Naringenin also has been used in the pharmaceutical and medical fields as an effective drug for anti-oxidative, anti-cancer, anti-obesity, and anti-inflammatory activities. Naringenin is also a typical plant metabolite, that has never been reported to be produced in prokaryotes. Recently, many papers reported that various members of the Streptomyces family, a genus of actinobacteria, had a novel pathway to produce naringenin. As a result, this review focuses on some clinical pharmacological effects and promising applications in the medical of naringenin, also its pathways of biosynthesis.

Keywords: *biosynthesis of naringenin, naringenin, naringenin in pharma and medical*

1. Introduction

Naringenin is a member of the flavonoid family, of which the molecular formula is $C_{15}H_{12}O_5$ and named as 5,7-dihydroxy-2-(4-hydroxyphenyl)-2,3-dihydrochromen-4-one by the International Union of Pure and Applied Chemistry (IUPAC) (Wilcox, Borradaile, & Huff, 1999) (Fig. 1). Naturally, naringenin is a secondary metabolite biosynthesized by the grapefruit and citrus family, and known as a glycosylated form of the naringin which is a flavonoid and rapidly transformed into naringenin by the actions of enzymes such as α-L-rhamnosidase and β-glucosidase (Mbaveng, Zhao, & Kuete, 2014; Zobeiri et al., 2018). Recently, it was reported to be produced by *Streptomyces*

clavuligerus, a member of actinobacteria (Rubén Alvarez et al., 2015). In the medical and pharmaceutical fields, naringenin showed its abilities in the treatments for anti-oxidative, anti-cancer, anti-obesity, and anti-inflammatory activities (Felgines, Texier, & Morand, 2000; Ke et al., 2017; Nasr Bouzaiene et al., 2016).

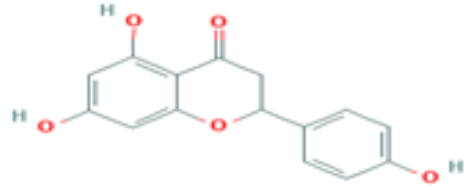

Figure 1. *Chemical Structure Depiction of Naringenin (Wilcox et al, 1999)*

2. Findings and Discussion

Applications of naringenin in the medical and pharmaceutical fields

The naringenin and L-rhamnose were obtained from naringin hydrolysis reaction under the catalysis activities of α-rhamnosidase and β-glucosidase enzymes. Naturally, naringin was responsible for the bitterness in grapefruit, citrus fruits and others (Rajadurai, Stanely, & Prince, 2006). As a result, naringenin was one of the most common flavonoids absorbed and detected in human serum (Palma-Duran et al., 2015). The mentioned flavanone aglycones also underwent the conversion into phenolic acids by employing the cleavage of the C-ring by enzymes of the intestinal microflora (Kim et al., 1998). Recently, many papers on the potential pharmacological and therapeutic effects of naringenin have been published by scientists. Six healthy volunteers received orally 135 mg of naringenin, under fasting conditions. Blood samples were collected at 14 different time points over a 12 hours period. Urine was collected over 24 hours, in five sequential timed intervals. Plasma and urine naringenin concentrations, after enzymatic hydrolysis of their conjugated forms, were measured using validated high-pressure liquid chromatography methods. Pharmacokinetic analysis on human plasma showed that naringenin had been absorbed rapidly after 20 minutes of dosing and its concentration had got to the highest after 3,5-4hrs of the experiment process (Kanaze, Bounartzi, Georgarakis, & Niopas, 2007). Ultra-fast liquid chromatography-quadrupole-time-of-flight tandem mass spectrometry (UFLC-Q-TOF-MS/MS) was used to assess the urinary excretion of flavonoids in Chinese 23–30 years old volunteers, after 250mL orange juice consumption (containing 31μM of naringenin). An overall 22% recovery was detected in 4 to 12hrs that evidenced a phase II metabolism (especially sulfation and glucuronidation) of the aglycone after intestinal hydrolysis (Zeng et al., 2017). Some studies investigated the comparative pharmacokinetics of naringin and its aglycone, naringenin. To find a pharmacokinetic basis for the detected difference, naringenin and naringin were administered orally (25mg/kg) and (225mg/kg) in rabbits, respectively. After oral administration of naringenin and naringin to rabbits, mean concentration-time profiles in serum were calculated. The maximum serum

concentration of naringin and its conjugates occurred after almost 90 mins, whereas the naringenin administration occurred after 10 min. Since a similar flavonoid glycoside such as rutin demonstrated delayed absorption than its aglycone, naringin was poor to be absorbed than naringenin (Hsiu et al., 2002).

The potential treatment of naringenin in cardiovascular disease has been researched clearly by scientists for a long time. The cardiovascular system is susceptible to many chronic diseases such as hypertension and myocardial infarction which are the acute conditions for necrosis of the myocardium that occurs as a result of an imbalance between coronary blood supply and myocardial demand. Due to the generation of toxic reactive varieties such as superoxide radicals, myocardial cells get damaged. A common mechanism of molecular and cellular damage in cardiovascular disease is, directly and indirectly, related to oxidative stress. When compared to vitamin C and E, flavonoids had stronger antioxidant capacity. Orally administered naringin was hydrolyzed to a major metabolite naringenin by the intestinal microflora (Testai, & Calderone, 2017; Jagetia et al., 2005). Since naringenin was obtained from the hydrolysis of naringin (a naringenin glycoside), both pure naringenin and naringin were used for studies on the ability of cardiovascular disease prevention (Onakpoya, O'Sullivan, Heneghan, & Thompson, 2017). In a double-blind cross-over study, 12 patients with stage I hypertension received alternatively 500mL/day of a fruit juice containing 593μM naringin or a juice with lower content (143μM naringin) for 5 weeks. Systolic blood pressure decreased in both groups, but no significant differences were found, while diastolic blood pressure was more effectively reduced in the high-dose naringin group (Reshef et al., 2005). Another evidence showed that dyslipidemic patients had been observed to have better lipoprotein profile and the reduction of blood lipid when they had used a kind of medicine containing about 95μM naringin for each capsule for six months (Toth et al., 2015). A study also resulted that by using 400mg naringin/capsule/day for 8 weeks, patients' low-density lipoprotein (LDL) cholesterol levels decreased, in contrast, their antioxidant enzyme activities (i.e., superoxide dismutase and catalase) increased. A result of decrease in triglycerides total and LDL cholesterol levels was also reported in a group of 237 hyperlipidemic volunteers using bergamot extract containing several flavonoids (including naringin) during 30 days (Mollace et al., 2011). A recent study reported that ischemia/reperfusion (I/R) injury impaired cardiovascular function also caused cellular apoptosis and myocardial infarction (MI). Naringenin treatment provided protection against I/R injury by stimulating mitochondrial biogenesis and preserving mitochondrial function through the AMP-activated protein kinase/Sirtuin-3 (AMPK-SIRT3) signaling pathway (Yu et al., 2019). In a related study, the potential effects of naringin for altering lipoproteins, lipids, and lipid metabolizing enzymes were investigated in isoproterenol-induced MI in Wistar rats. It was reported that there had been a significant reduction in the levels of

total and free cholesterol, free fatty acids, cholesterol ester, and triglycerides in serum, heart and elevated phospholipids in the heart. Naringin inhibited the activity of β-Hydroxy β-methylglutaryl-CoA (HMG-CoA) reductase which could lead to lower cholesterol effectively, resulting in protecting the myocardium against lipid accumulation (Rajadurai, Stanely, & Prince, 2006).

Biosynthesis pathways of naringenin

Naringenin was obtained by hydrolysis of naringin (a flavonoid glycoside) from citrus peels (Mamma, Kourtoglou, & Christakopolulos, 2008). The albedo of citrus fruits also was used to obtain the naringin by extraction with methanol 50% in water solution (Caccamese & Chillemi, 2010). Under the enzymatic treatment of α-L-rhamnosidase (EC 3.2.1.40), the obtained naringin was converted into prunin and L-rhamnose and on the next step, the β-galactosidase enzyme catalyzed the β–galactoside hydrolysis of prunin to produce naringenin and D -glucose (Puri, Kaur, Schwarzc, Singh, & Kennedy, 2011).(Fig. 2).

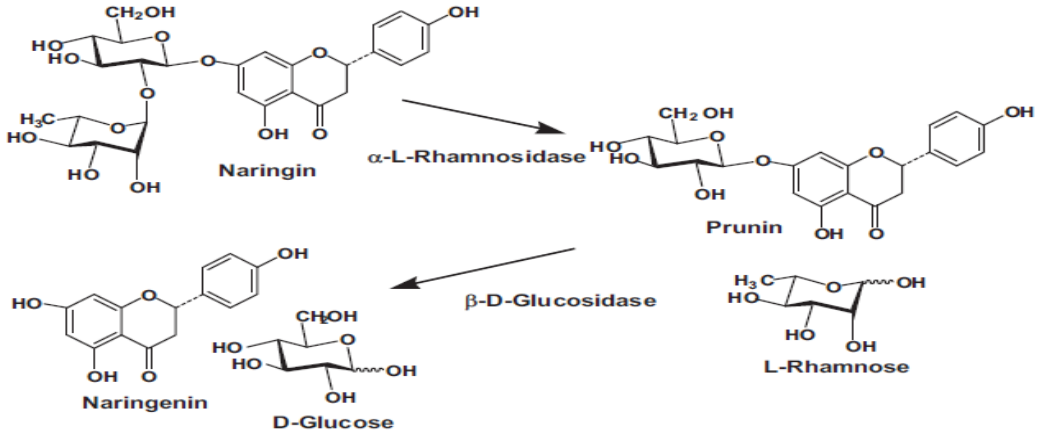

Figure 2. *Naringin and its degraded products (Puri, Kaur, Schwarzc, Singh, & Kennedy, 2011)*

Naringenin is naturally produced in several plants, especially in grapefruit, and its biosynthesis has been studied in *Medicago*, parsley and other plants but it is unknown if the same pathway occurs in *S. clavuligerus and S. coelicolor* (Yu et al., 2019). The 4-coumaroyl-CoA is the starter unit of the naringenin biosynthesis pathways in both dicotyledonous and monocotyledonous plants. In dicotyledonous plants, it is converted from phenylalanine under the activation of the enzyme Phenylalanine ammonia-lyase (PAL), Cinnamate-4-hydroxylase, CoA-dependent ligase, Chalcone synthase and Chalcone isomerase, respectively (Koopman et al., 2012; Kyndt, Meyer, Cusanovich, & Van Beeumen, 2002). The condensation between 4-coumaroyl-oA and three units of malonyl-CoA with the activation of Chalcone synthase enzyme to produce naringenin chalcone which is ready to be catalyzed to change into naringenin by Chalcone isomerase enzyme (Jeandet et al., 2018) (Fig. 3). In monocotyledonous plants, they may also use tyrosine as main substrate and directly produce p-Coumaric acid without the need for

Cinnamate-4-hydroxylase activity (Nasr Bouzaiene et al., 2016; Eichenberger et al., 2017).

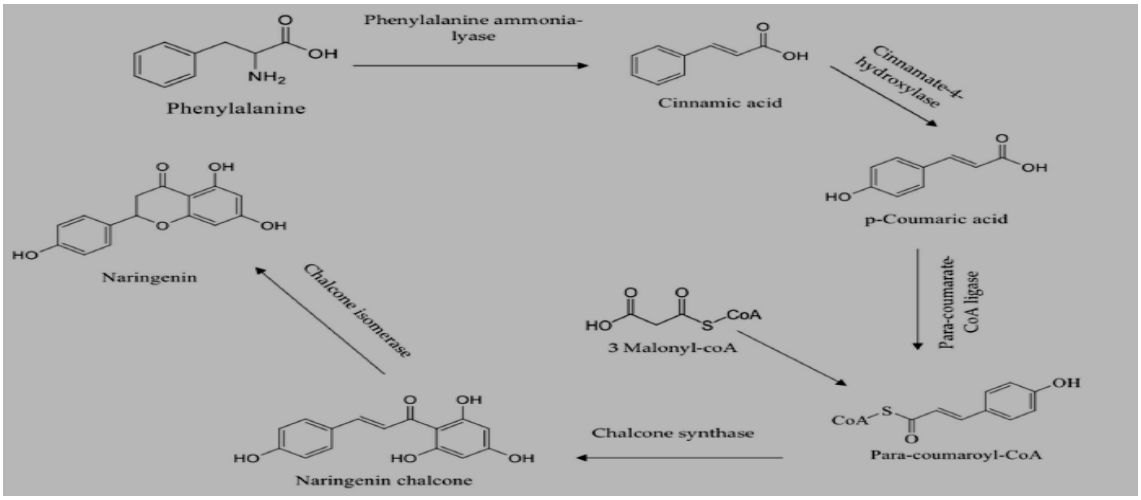

Figure 3.*The biosynthesized pathway of natural naringenin in dicotyledonous plants (Salehi et al., 2019)*

Recently, scientists discovered the *encP* gene in *S. maritimus* encodes an enzyme with the ability to catalyze hydrolyzed reaction to convert phenylalanine to cinnamic acid, required for biosynthesis, without cinnamate-4-hydroxylase (Kyndt, Meyer, Cusanovich, & Van Beeumen, 2002). Similarly, *S. clavuligerus* was reported to produce a compound revealed by Liquid chromatography–mass spectrometry (LC-MS), nuclear magnetic resonance (NMR), and high-performance liquid chromatography (HPLC) coelution as naringenin standard. The genomic analysis of this strain showed the presences of side by side genes ncs and ncyP encoding chalcone synthase and naringenin cytochrome P450, respectively. Moreover, both PAL and TAL enzymes for using Phenylalanine and Tyrosine also were encoded by Tal gene separated from the above genes (Alvarez et al., 2015). (Fig.4)

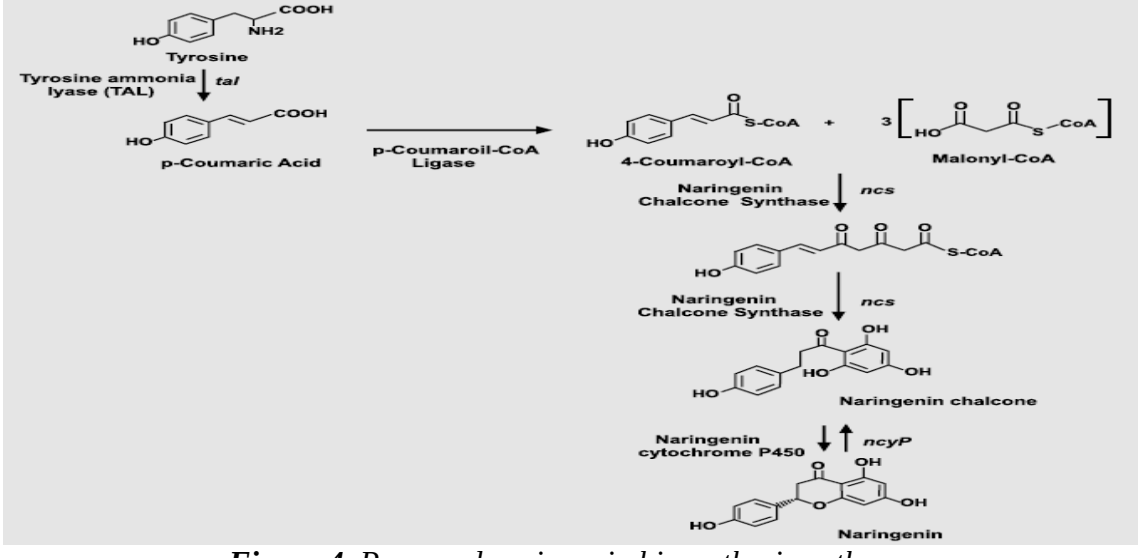

Figure 4*. Proposed naringenin biosynthesis pathway in Streptomyces clavuligerus (Xiang, & Moore, 2002)*

3. Conclusion

Naringenin and naringin (a naringenin glycoside), spontaneously present in the citrus family, grapefruit and others. Naringin is able to convert into naringenin by the enzymatic treatment. Besides, naringenin also has been detected to be biosynthesized by actinobacteria especially the genus *Streptomyces*. Many studies and clinical trials have proved that both naringenin and naringin are consumed and metabolized by animals and humans easily. Moreover, scientists have shown that naringenin seems to be a promising medicine to reduce the plasmatic lipid, lipoprotein, total and LDL-cholesterol levels, resulting in the healths of patients with hypertension, dyslipidemia and myocardial infarction, the pre-symptoms of cardiovascular disease. Further clinical studies are needed to better address naringenin safety, efficacy, delivery and bioavailability in humans.

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