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# A Review of Naringenin's Nutraceutical Properties: A boon in the Sustainable Food System

# Una revisión de las propiedades nutracéuticas de la naringenina: una bendición en el sistema alimentario sostenible

Dr Dipali Saxena[1*], Dr Uttam Sharma[2] and Anita Rawat[3]

[1] Assistant Professor, Shri Vaishnav Institute of Home Science, Shri Vaishnav Vidyapeeth Vishwavidyalaya Indore, Madhya Pradesh, India.

[2] Coordinator, Shri Vaishnav Institute of Home Science, Shri Vaishnav Vidyapeeth Vishwavidyalaya Indore, Madhya Pradesh, India

[3] Senior Quality Assurance Executive, Choksi Laboratory Limited Indore, Madhya Pradesh, India.

Corresponding author: Dr Dipali Saxena & Email: dipalisaxena@svvv.edu.in

ABSTRACT

Many of the medications on the market today are derived from natural sources. Apart from their physiological roles in plants, flavonoids are vital components of the human diet, despite not being classified as nutrients. Flavonoids are an important class of secondary metabolites found in plants that perform a variety of activities, including pigmentation and antioxidant activity. Naringenin is a flavanone (flavonoid) that occurs naturally and is known to have a bioactive influence on human health. It is mostly found in fruits (grapefruit and oranges) and vegetables. This phytochemical has been linked to a variety of biological activities, including antioxidant, anticancer, antiviral, antibacterial, anti-inflammatory and cardioprotective properties. Although few clinical trials have been conducted, the primary focus has been on naringenin bioavailability and cardioprotective effect and memory enhancement. Many molecular pathways underpinning its positive effects have been identified. This review also intends to bring newer insights, which will undoubtedly usher in a new era of flavonoid-based nutraceutical properties for the treatment of numerous infectious and degenerative disorders.

Keywords: Naringenin, flavonoids, biological, antioxidant, antibacterial, nutraceutical etc.

RESUMEN

Muchos de los medicamentos en el mercado hoy en día se derivan de fuentes naturales. Aparte de sus funciones fisiológicas en las plantas, los flavonoides son componentes vitales de la dieta humana, a pesar de no estar clasificados como nutrientes. Los flavonoides son una clase importante de metabolitos secundarios que se encuentran en las plantas y que realizan una variedad de actividades, incluida la pigmentación y la actividad antioxidante. La naringenina es una flavanona (flavonoide) que se produce de forma natural y se sabe que tiene una influencia bioactiva en la salud humana. Se encuentra principalmente en frutas (pomelos y naranjas) y

verduras. Este fitoquímico se ha relacionado con una variedad de actividades biológicas, que incluyen propiedades antioxidantes, anticancerígenas, antivirales, antibacterianas, antiinflamatorias y cardioprotectoras. Aunque se han realizado pocos ensayos clínicos, el enfoque principal ha sido la biodisponibilidad de la naringenina y el efecto cardioprotector y la mejora de la memoria. Se han identificado muchas vías moleculares que sustentan sus efectos positivos. Esta revisión también pretende aportar nuevos conocimientos, que sin duda marcarán el comienzo de una nueva era de propiedades nutracéuticas basadas en flavonoides para el tratamiento de numerosos trastornos infecciosos y degenerativos.

Palabras clave: Naringenina, flavonoides, biológico, antioxidante, antibacteriano, nutracéutico, etc.

## INTRODUCTION

Plants have been used by humans since antiquity for a variety of purposes, including food and medicinal. Many of today's medications are derived from natural sources. More than 25% of the medications given globally are derived from plants, and 121 active phytoconstituents are utilised to treat various illnesses. Polyphenolic substances (e.g., flavonoids, anthocyanins, and phenolic acids) derived from plants have been shown to provide potential health advantages in the treatment of obesity, hypertension, cardiovascular disease, and metabolic syndrome.

The term flavonoid is derived from the Latin word "flavus," which means yellow. It is a plant secondary product with properties like red, blue, and purple pigments found in plant tissues. Aside from their physiological roles in plants, Flavonoids are vital components of the human diet, despite not being classified as nutrients. Flavonoids account for a significant fraction of these bioactive chemicals (K Martin & C Appel., 2010). Flavonoids are abundant in citrus plants. The most important flavonoids identified from citrus fruits thus far are naringin, naringenin, nobelitin, narirutin, and hesperidin (Tripoli et al., 2007).

Naringenin is a flavonoid that has no flavour, colour, or texture. Naringenin are also name as Naringetol, Salipurol and Salipurpol. It is the most abundant flavanone in grapefruit and can be found in a wide range of fruits and herbs *(*Felgines et al., 2000). Naringenin has attracted increasing attention due to its positive health benefits in the human body. It has been reported to have several biological effects, such as monoamine oxidase inhibitory (Olsen at al., 2008) and neuroprotective activities (Zbarsky., 2005). Monoamine oxidase inhibitory and neuroprotective activities of naringenin may provide protection against oxidative neurodegeneration and alleviate central nervous system disorders such as depression, inflammatory and anti-ischemic activities (Muhammad 1t al., 2015; Trimech et al., 2008) which are closely related with their free radical scavenging activities.

## STRUCTURE OF NARINGENIN

The flavonoid fundamental structure consists of two benzene rings (A and B) linked by an oxygen-containing pyrene ring (C). Almost 6000 flavonoids have been found to date. Flavonoids have a wide range of

biological activities, including antibacterial, antiviral, anti-inflammatory, and anti-ischemic properties that are closely related to their free radical scavenging abilities. Naringenin has a simple 15-carbon-atom flavonoid skeleton, which comprises three rings. Among them, two benzene rings are linked to a three-carbon chain. The chemical nomenclature of naringenin is 2,3-dihydro-5,7-dihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one or 4',5,7-trihydroxyflavanone, with a molar mass of 272.3 (Klein et al. 2008).

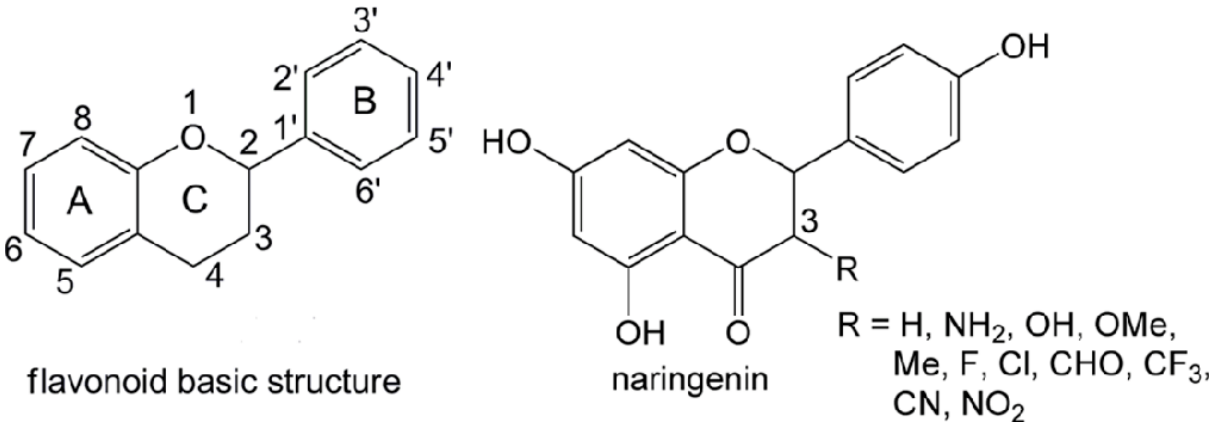


Figure 1: Basic structure of flavonoids (I), and naringenin (II).

## SOURCES AND BIOAVAILABILITY OF NARINGENIN

Naringenin is one of the most important naturally occurring flavonoid, predominantly found in some edible fruits, like *Citrus* species and tomatoes, and figs belonging to smyrna-type *Ficus carica*. Naringenin is a dietary flavonoid found in citrus fruits, honey, and bee pollen.

Naringenin and its glycoside have been discovered in several plants and fruits, including grapefruit, sour orange, tart cherries, tomatoes, chocolate, Greek oregano, water mint, and beans. The naringenin-to-naringenin ratio varies by source, as do the enantiomeric ratios. The aglycol form of naringenin-7-glucoside appears to be more bioavailable than the glucoside form (Minoggioet., 2003*)*. Grapefruit juice has substantially greater naringenin plasma concentrations than orange juice. The similar molecule kaempferol, which has a hydroxyl group adjacent to the ketone group, can also be found in grapefruit.

Cooked tomato paste contains naringenin, which can be absorbed. 150 grammes of tomato paste contain 3.8 milligrams of naringenin *(*Bugianesi et al.,2002*)*. Tomatoes and tomato-based products contain trace amounts of naringenin (Jadeja and Devakr 2014) . Fresh tomatoes, particularly tomato skin, contain naringenin chalcone, which is transformed to naringenin during the tomato ketchup manufacturing process.

Figure 2: Sources of naringenin

## NARINGENIN CONTENT

Table 1: Various citrus species and naringin concentrations found in juice (WC Ooghe et., 2010)

| Sources | Nargenin Content (*µg/mL)* |
|---|---|
| *Citrus* (*C.*) *sinensis* | 21.3 |
| Orange (blond), pure juice | 7.0 |
| Grapefruit, juice from concentrate | 37.8 |
| Pummelo, pure juice | 84.8 |
| Grapefruit, pure juice | 30.8 |
| Grapefruit/pummelo hybrid, pure juice | 45.1 |
| Grapefruit, raw (color not specified) *C. paradise* | 53.0 |
| Grapefruit, raw, pink and red, all areas (*C. paradisi*) (naringenin) | 32.6 |
| Grapefruit, raw, white, all areas (*C. paradisi*) | 21.3 |
| Grapefruit juice, white, raw | 18.2 |

## METABOLISM OF NARINGENIN

Naringenin has been shown to be quickly absorbed by the gastrointestinal tract, making it immediately accessible in circulation. It is the most pharmacologically efficacious version of naringin due to its fast absorption (Shakeel et al. 2007). Naringin is degraded into prunin and rhamnose by naringinase and -L-rhamnosidase, as shown in Figure 3. Prunin is subsequently degraded by -d-glucosidase into "Naringenin," which is absorbed into the intestinal system after being processed by naringinase (Mir et al., 2015).

Grapefruits are the richest source of naringenin, which is found as an inactive glycone form termed "naringin." Wanget al. (2005) define naringin as a 4',5,7-trihydroxyflavonone 7-rhamnoglucoside that is hydrolyzed by the intestine bacterial naringinase enzyme shortly after intake,

producing two intermediates, rhamnose and naringenin (4',5,7-trihydroxyflavonone—the more active aglycone form).

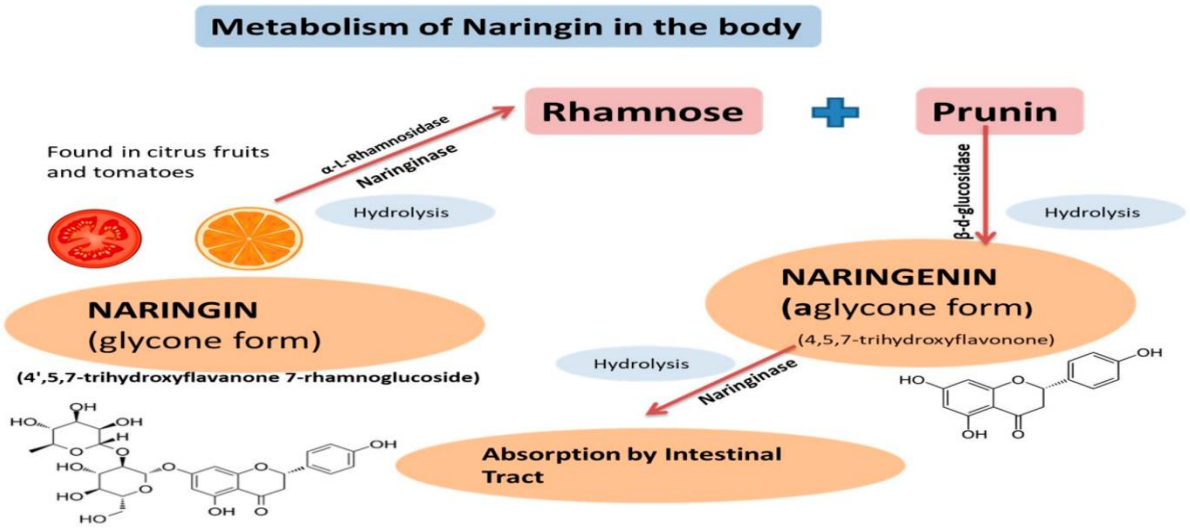


Figure 3: Metabolism of Naringenin

Nutraceutical Properties of Naringenin: Only a few clinical trials on naringin or naringenin have been filed, showing that significant efforts are necessary to move this natural substance from preclinical to clinical use. Information from several study reports was compiled and presented in various pertinent parts.

Antioxidant activity: Naringenin possesses antioxidant effects that have been demonstrated. It has been found in vitro and in animal tests to prevent oxidative damage to DNA (Gorinstein., 2005). The antioxidant activity of phenolic compounds is determined by their ability to withstand the damaging effects of free radicals. Antioxidant activity and structural characteristics are inextricably linked. The substituent effect is one of the most important structural aspects that influences the antioxidant capabilities of phenolic compounds.

The primary method by which naringenin exerts its different bioactivities is by suppressing oxidative stress, which is generated by various free radical species produced in organisms as by-products of aerobic metabolism. The studies on the influence of the substituent effect can be used to synthesize and select novel compounds with better antioxidant activity. Till far, numerous research has focused on the amount and position of hydroxyl groups in relation to biological activity.

Anticancer Activity: Cancer is one of the world's major causes of death. DNA mutations in normal cells generated by any exogenous stimulation or inherent aberration can result in unregulated cell proliferation, leading to tumour growth and progression. Chemotherapeutic drugs appear to have anti-cancer action via promoting cell death. The catastrophic effects of chemotherapy on the living system, on the other hand, are massive; that is, every healthy cell and especially quickly dividing cells, including stomach mucosa, hair follicle,

and bone marrow cells, are adversely affected in this process, limiting their normal functioning (Ravishankar at al., 2013). Therefore, toxicity appears to be the most limiting feature associated with the chemotherapeutic agents of synthetic origin.

Therapeutically active plant-derived products/components, on the other hand, are deemed mildly hazardous while possessing strong pharmacological properties. The anti-cancer potential of the flavonoid "naringenin" has been highly disputed around the world. Stefani et al., 1999 in Uruguay found that naringenin treatment reduced cancer risk in the oesophagus, larynx, oral cavity, and throat by around 70%.

Anti-Diabetic Activity*:* Diabetes is an endocrine metabolic condition characterised by high blood glucose levels. Diabetes is characterised by hyperglycemia, or elevated blood glucose levels in the body. Glucose and maltose are catabolic by-product's of starch that are processed by -glucosidase and -amylase (Barrett et al., 2010). It has been observed that inhibiting the activity of these important enzymes can result in lower blood glucose levels. The use of these enzyme targets may serve as prospective treatments for diabetes-related diseases.

Naringenin has been shown to have anti-diabetic properties, which are due to its capacity to inhibit -glucosidase and -amylase. According to scientific evidence, naringenin administration lowers blood glucose levels in streptozotocin-induced diabetic rats, improves insulin sensitivity in insulin-resistant rats given fructose, and reduces insulin resistance in mice fed high-fat diets but lacking LDL receptors (Priscilla et al., 2014). In type 2 diabetics, the mechanism of action of naringenin is comparable to that of the standard antidiabetic metformin. Naringenin-treated Wistar rats demonstrated reduced pain and allodynic consequences of streptozotocin-induced diabetic neuropathy. Naringenin has also been shown to have analgesic properties in an experimental model of neuropathic pain (Mulvihill et al., 2009).

Hepatoprotective activity: Naringenin, like silymarin, has been found to have hepatoprotective properties. Lee YS et al. (1998) revealed that turmeric protects the liver from a range of hepatotoxic insults, including carbon tetrachloride (CCl4), galactosamine, acetaminophen (paracetamol), and Aspergillus aflatoxin. Turmeric's hepatoprotective benefits are mostly due to its antioxidant capabilities and capacity to reduce the generation of pro-inflammatory cytokines. The ability of naringenin to protect against dimethyl nitrosamine (DMN)-induced liver damage in rats was examined. When the weight of the liver, as well as alanine transaminase (ALAT), aspartate transaminase (ASAT), alkaline phosphatase (ALP), and bilirubin levels, were assessed, oral treatment of naringenin (20 and 50 mg/kg daily for 4 weeks) significantly reduced DMN-induced damage. Naringenin also restored natural protein levels in serum and albumin, as well as hepatic function.

Anti-inflammatory activity: Naringenin is a flavonoid that occurs naturally and may be derived from citrus fruits, tomatoes, cherries, grapefruit, and chocolate. Naringenin, like most flavonoids, has been found to have numerous pharmacological potentials, including anti-inflammatory actions due to its capacity to create sufficient hydroxyl (-OH) substitutions, which allows it to scavenge ROS (Middleton E, et al.,1992). Consequently, it has been proposed that naringenin may alleviate and/or enhance pathological situations in which oxidation or inflammation is thought to be important.

Cardiovascular activity: Naringenin exhibited a variety of cardiovascular-protective effects, including antihypertensive, lipid-lowering, insulin-sensitizing, anti-oxidative, and anti-inflammatory properties. Naringin reduced the age-related rise in systolic blood pressure in stroke-prone spontaneously hypertensive rats, enhanced nitric oxide generation, improved endothelial function, and reduced the risk of cerebral thrombosis (Rajadurai M, et al, 2009). In addition, naringenin reduced oxidative stress in rats with isoprenaline-induced myocardial infarction.

Naringenin boosts immunity: Naringenin Improves Immunity Natural killer (NK) cells may recognise and kill tumour cells as well as virus-infected cells without being sensitised. NK cells have activating and inhibitory receptors and can tell the difference between normal and tumour cells. Salim S, et al. (2013) revealed the impact of NKG2D ligand expression on the Burkitt's lymphoma cell line Raji in boosting NK cell cytolytic activity. Different flavonoids were utilised as stimulants to increase NKG2D ligand expression. Pre-treatment of naringenin with luteolin, kaempferol, taxifolin, and hesperidin had no effect on NK cell lysis activity against Raji. Nevertheless, naringenin treatment increased susceptibility to NK cell lysis compared to untreated control cells. The increased NKG2D activity was responsible for naringenin's activity. These findings show that naringenin's anticancer action may be related to targeting of NKG2D ligand expression and point to a potential immunotherapeutic role in cancer treatment.

Antimicrobial activity*:* Natural products are currently gaining popularity due to their powerful antibacterial properties and less adverse effects than chemically manufactured substances. Natural goods are regarded safe and preferable to antibiotics due to the lower risk of drug resistance connected with them. Because of their many modes of action on bacterial cells, bacterial strains are less likely to acquire resistance to a natural chemical (Gorniak et al.,2019). Natural compounds show antibacterial activity by interfering with and disrupting the integrity of the bacterial membrane, inhibiting enzymes required for bacterial membrane production, inhibiting anti-biofilm activity, or inhibiting auto inducer-mediated cell-cell signalling.

Naringenin possesses a wide spectrum of antimicrobial activities, including antifungal and antibacterial. Naringenin has a broad range of antimicrobial properties, including antifungal and antibacterial activity (Duda et al., 2020). Naringenin has been shown to be effective against methicillin-resistant Staphylococcus aureus (Tran et al., 2020) and resistant Helicobacter pylori strains (Vikram et al., 2010). Naringenin's antibacterial activity is achieved by an inhibition of the autoinducer-mediated cell signalling pathway.

## CONCLUSIONS AND FUTURE PROSPECTS

The use of phytochemicals, particularly flavonoids, in illness prevention and treatment is extensively documented. Flavonoids can be found naturally in fruits and vegetables. A wide range of flavonoids found in nature each have distinct physical, chemical, and physiological properties. Dietary flavonoids and their analogues biological properties have been linked to a variety of mechanisms of action, including free radical scavenging, activation of survival genes and signalling pathways, transition metal ion chelation, regulation of mitochondrial function and bioenergetics, modulation of inflammation response, and even interactions with

microbiota. Nevertheless, flavonoids' activity extends beyond their health-promoting advantages to a wide range of plant ecological interactions, including serving as a signal and defence molecule. Several flavonoids have medicinal value as antibacterial agents.

We have given extensive nutraceutical properties of naringenin based on the most recent studies in this review. According to research, naringenin possesses various important nutraceutical benefits, including antioxidant, anti-inflammatory, antibacterial, anti-diabetic, and anticancer capabilities. There are multiple molecular mechanisms crucial to naringenin's pleotropic effects, which entail the fusion of cellular signalling pathways at various stages of different illnesses. Despite its enormous promise for treating various ailments, naringenin, like other polyphenols, is hampered by a bioavailability issue. To improve the efficacy of naringenin as a treatment, methods to increase its bioavailability must be researched. Further active study is needed to uncover the remarkable nutraceutical potentials of naringenin in terms of promoting better human health.

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