

Therapeutic Applications of Naringenin, a Flavanone Enriched in Citrus Fruits, for Disorders beyond Diabetes

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Abstract: In recent years, there has been an increase in epidemiological studies to highlight the health benefits of plant secondary metabolites. Flavonoids (polyphenolic plant secondary metabolites) are recently emerging as an important source for the discovery of new drugs increasing their pharmaceuticals, nutraceutical and medicinal applications. Naringenin is a flavanone, enriched in citrus fruits, tomatoes, bergamot, etc. which has been evaluated extensively for managing diabetes. However, in addition to this, naringenin had been ascribed to various important biological activities like antioxidant, antiviral, anticancer, anti-inflammatory, antiestrogenic, etc. This article aims at highlighting the therapeutic value of naringenin in managing disorders other than diabetes and its role in regulating gene expression by altering chromatin structure as histone deacetylase inhibitor. The understanding of these phenomena will increase the overall knowledge of the various health-promoting effects of citrus fruits.

Keywords: Naringenin; flavanone; anti-viral; hepatoprotective; anti-cancer; anti-estrogenic

1 Introduction

Many secondary metabolites are present in plants which enable them to fight stresses in terms of predators, microorganisms and environment. Flavonoids are an important class of plant secondary metabolites which are emerging as an imperative source for pharmaceuticals, nutraceuticals, and medicinal products [1]. Many flavonoids are under investigation by different research groups to evaluate their unknown effects on well-being and human health. Flavonoids are having polyphenolic structures and are enriched in various fruits, vegetables and herbs [2]. They are extracted from various parts of the plant-like leaf, roots, fruits, flowers, stem, etc., and provide a number of health benefits like anti-oxidant, anti-inflammatory and anti-microbial [3]. Flavonoids are a major class of plant polyphenols with more than 6000 identified different structures but with a common nuclear structure: A linear three-carbon chain forming an oxygenated heterocycle and joining two aromatic rings (Fig. 1). Flavonoids are further



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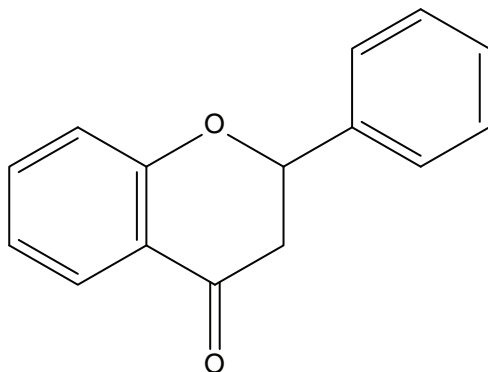


Figure 1: The basic structure of flavanone

divided on the basis of structural features into different subgroups of which major five subgroups are: flavanone, flavone, flavonols, isoflavones, chalcones, and anthocyanin [4].

The flavonoids are being synthesized by plants via shikimic acid and acylpolymalonate metabolic pathways [5]. The synthesis starts with the formation of aromatic rings followed by hydroxylation and methoxylation of the flavonoids. Besides other flavonoids, naringenin and hesperetin are most abundantly available in edible fruits and vegetables as glycosides and aglycone [6]. Naringenin is a flavanone enriched in citrus fruits like grapefruits, oranges, lemons, and fresh tomato skin; having an aromatic structure with hydroxyl and methoxy groups. Naringenin (4,5,7 trihydroxyflavanone) is an aglycone form of naringin that has been reported to be a bioactive molecule with many beneficial effects on humans such as, anti-oxidant, anti-inflammatory, anti-cancer, anti-tumorigenic and anti-estrogenic [7]. The flavanone glycoside naringin is less soluble in water and is also less potent anti-oxidant than naringenin due to the steric hindrance caused by sugar moieties on it for the scavenging group. Furthermore, it is broken down to its aglycon naringenin by the gut microflora which increases its absorbance from the gut [8].

Current treatment methods for complex diseases like cancer are centered on synthetic drugs that are rather expensive and loaded with side effects [9]. Although many of the available drugs, nowadays, have been derived from natural sources, and for many others, people are still not aware of their therapeutic significance [10]. Flavonoids, apart from being known to play important physiological roles in the plants, are important constituents of the human diet. Even though they are not considered as nutrients but play a major role in protecting against various pathological conditions. Multiple reports have highlighted the health beneficial effects of flavonoids and their uses [3]. This article aims at reviewing the various therapeutic implications of a flavanone naringenin, which can increase the scope of its applications.

The retrieval of potentially relevant studies was done by systematically searching for three databases (Google Scholar, Web of Science and PubMed) in September 2019. The keywords used as search terms were related to naringenin and disease protection. The search terms used were: naringenin and viral infection or naringenin and inflammation or naringenin and estrogen or naringenin and liver or naringenin and cancer or naringenin and Science or naringenin and histone. The selection of the studies was based on the following criteria: (1) written in English, (2) original research (i.e., no conference proceedings), and (3) no duplicates. The inconclusive studies were discussed between authors to reach consensus. The systematic search retrieved 585 papers that were potentially relevant and after selection procedure, 40 studies were included in this review and discussed below.

2 Naringenin

A polyphenol naringenin contains three hydroxyl groups and is also called 4,5,7-trihydroxy-flavanone which is a member of subclass 4 hydroxy flavanones. Its heterocyclic structure contains keto oxygen at 4th carbon (Fig. 2) and chiral center at carbon 2, which is responsible for its stereospecific profiles and varied bioactivities. It is a colorless flavanone with bitter taste which is particularly enriched in citrus fruits, with highest levels of naringenin are found in grapefruit (43.5 mg/100 ml), 2.13 mg/100 mL in orange-juice and the lowest 0.38 mg/100 ml in lemon-juice [11,12]. Various factors like genetics, soil/light environmental conditions, germination stage, ripeness, and storage conditions affect the synthesis of naringenin in different plant parts [13].

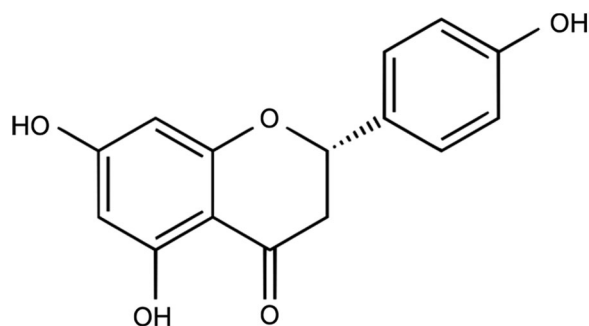


Figure 2: Structure of naringenin

Limited studies have also examined the pharmacokinetic properties and bioavailability of naringenin. Its oral absorption is very less and only 15% of naringenin is absorbed through the gastrointestinal tract mainly through small intestine and colon. The micromolar level of naringenin concentration in plasma can be achieved after intake of either grapefruit juice or pure naringenin. The plasma concentration of naringenin peaked with 0.7 μM –14.8 μM after administering 250 ml of grapefruit juice containing approximately 200 mg naringenin concentration [14]. Intake of 135 mg of pure naringenin increases its concentration to 0.7–2 $\mu\text{g/ml}$ in blood plasma [15]. The accumulation of naringenin had been observed in various tissues like liver, brain, kidney, large intestine, small intestine and feces after gastric administration of naringenin (2.5 mg) in Sprague–Dawley rats. Also, it shows increased kidney clearance and around 42.11% of absorbed naringenin was found to be excreted in urine [16]. Various pharmacological effects have been attributed to naringenin like antioxidant, immunomodulatory, anti-inflammatory, nephroprotective, hepatoprotective, neuroprotective, anti-diabetic, anti-cancer and anti-atherosclerotic. The anti-diabetic, anti-atherosclerotic and cardio-protective effects of naringenin are well discussed before [14,17–20] others are discussed as follows (Fig. 3).

2.1 Anti-Viral Properties of Naringenin

Naringenin had been proved to show anti-viral effects against the dengue virus strain (DENV-2) and was found to be up to 50% virucidal with $\text{IC}_{50} = 52.64 \mu\text{g/ml}$. These inhibitory effects were observed in every stage of viral infection during the *in vitro* studies on Vero cell line [21]. Naringenin because of its potent free radicle scavenging activity, had been recommended as a therapeutic adjunct to Nucleoside-reverse-transcriptase-inhibitors (NRTIs) for antiretroviral therapy (cARVs). The combination had been proposed to mitigate the mitochondrial toxicity of these drugs [22]. *In silico* docking studies with different flavonoids had demonstrated the blocking of neuraminidase site by naringenin and other flavonoids in Influenza Type A viruses [23].

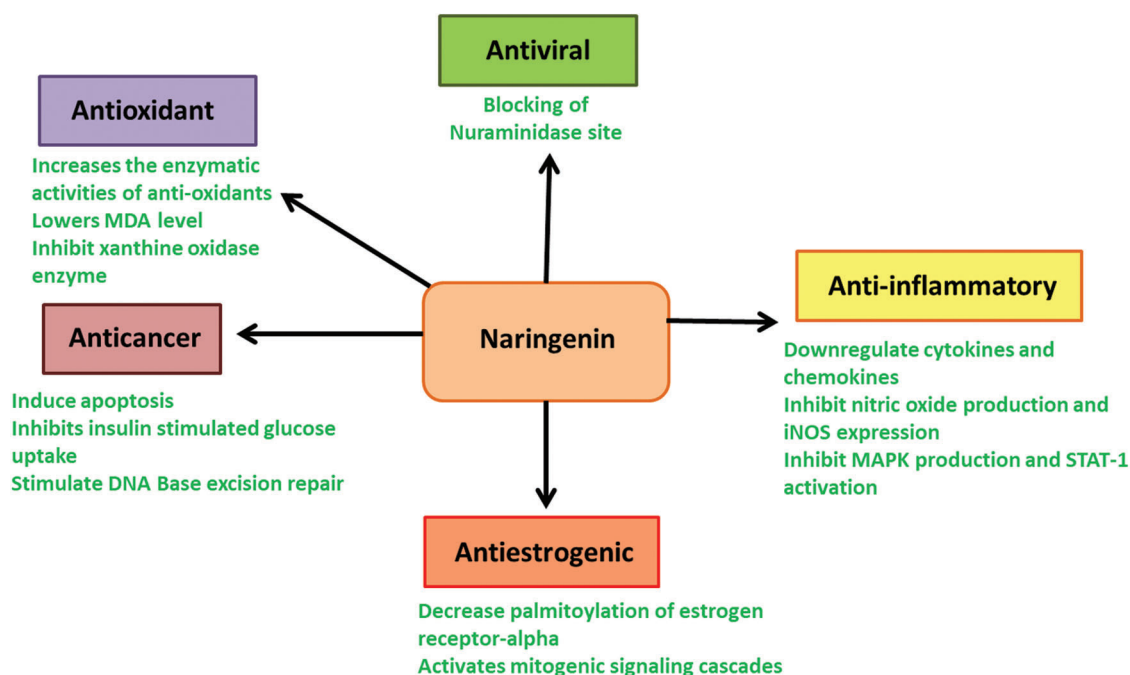


Figure 3: Therapeutic effects of naringenin

2.2 Anti-Inflammatory Properties of Naringenin

Naringenin was also evaluated for its anti-inflammatory and antioxidant effects in thermally burned rats [24]. In a study conducted on *Chlamydia trachomatis* infected macrophages which are responsible for causing either acute cervicitis, pelvic inflammatory infection or the asymptomatic chronic disorder, naringenin was demonstrated to produce anti-inflammatory effects by down-regulating the cytokines (TNF- α , IL-1 β , IL-1 α , IL-6, IL-10, IL-12p70) and chemokines (CCL4, CCL5, CXCL1, CXCL5 and CXCL10) [25,26].

Naringenin was found to inhibit inflammation-induced neuronal cell death by inhibiting nitric oxide production and iNOS expression induced by LPS/IFN- γ in glial cells. It also inhibited LPS/IFN- γ induced phosphorylation of MAPK (p38 mitogen-activated protein kinase) and activation of STAT-1 [27,28]. Naringenin was also found effective against trichloroethylene (TCE) (widely used industrial solvent which affects liver functioning) treated human epidermal keratinocytes (HaCaT). TCE had been attributed to the increase the production of intracellular Ca²⁺ which further elevates the free radical production and DNA fragmentation. Naringenin efficiently reverts back all the cytotoxic effects of TCE [29].

2.3 Anti-Estrogenic Properties of Naringenin

Naringenin is itself a weak estrogen and was also found to possess anti-estrogenic effects. Its administration (30 mg/kg) was shown to have anti-estrogenic effects on female SD rats which were suffering from increase wet uterine weight, increased DNA synthesis, increased progesterone binding receptor PR and peroxidase activity due to the treatment with 17 β -estradiol (E2). These effects were reversed by naringenin treatment with growth reduction. In-vitro studies conducted on the MCF-7 cell line also showed similar anti-estrogenic effects of naringenin [30]. Naringenin was observed to decrease the palmitoylation of estrogen receptor-alpha much faster than 17-beta-estradiol. This led to the rapid dissociation of estrogen receptor-alpha from caveolin-1 and activates the mitogenic signaling cascades

driving cancer cells to apoptosis. Naringenin thus plays an important role in preventing/curing cancer, osteoporosis and cardiovascular diseases [31,32].

2.4 Free Radical Scavenging Properties of Naringenin

Naringenin had been exhibited to possess higher antioxidant activity than its glycoside naringin. It effectively inhibits xanthine oxidase enzyme and actively chelates metal ions. It also protects lipids from oxidative damage in a dose-dependent manner however it was found un-protective against reduced glutathione (GSH) oxidation [33–35]. The oral administration of 50 mg/kg/day of naringenin to STZ induced diabetic rats was found to lower the fasting levels of glycosylated hemoglobin and fasting blood glucose levels. It also increases the enzymatic activities of anti-oxidants in the pancreas and lowers the MDA levels. Furthermore, it was found to lower the serum levels of alanine transaminase, aspartate transaminase and lactate dehydrogenase in the diabetic rats and thus show protective effects on pancreatic tissue of diabetic rats [36].

2.5 Hepatoprotective Properties of Naringenin

The hepatoprotective effects of naringenin have been well established. Its oral administration at dosage 20 mg/kg and 50 mg/kg per day for 4 weeks was found effective against dimethylnitrosamine (DMN) induced liver injury. It was also found to improve various parameters of liver functioning tests like aspartate transaminase, alanine transaminase, bilirubin, and alkaline phosphatase levels thereby improving liver weights. Naringenin treatment reduced the DMN-induced accumulation of collagen in the liver and thus protects against hepatic fibrosis [37,38]. Naringenin was also found effective against streptozotocin-induced hepatotoxicity in rats, thereby having implications in reducing diabetes-associated hepatopathy [39,40]. The formulation of a naringenin-loaded nanoparticle-system had been observed to improve the solubility and rate of naringenin release. It also exhibited more potent hepato-protective effects as compared to naringenin alone, with significant anti-apoptotic effects (via activation of caspase-3 and -9) [41].

2.6 Anti-Cancer Properties of Naringenin

Naringenin was found cytotoxic to different cancerous cell lines of human origin like MCF-7 (breast cancer), MDA-MB-231 (breast cancer), KATO III (stomach cancer), MKN-7 (stomach cancer), HepG2 (Liver cancer), Hep3B (Liver cancer), Hela/Hela-TG (Cervix Cancer), PK-1 (Pancreas cancer) and Caco-2 (Colon cancer). It is highly cytotoxic to leukemic cells like NALM-6, HL-60, Jurkat, and U937 and was found to induce apoptosis in a dose-dependent manner in these cell lines. Furthermore, naringenin was also found to inhibit the growth of tumors in sarcoma S-180-implanted mice [42]. It inhibits the insulin-stimulated glucose-uptake in breast cancer MCF-7 cells thereby resulting in their growth arrest and inhibiting proliferation. A study demonstrated that 25% inhibition in glucose uptake was observed with 10 μ M naringenin. This inhibitory effect is due to the inhibition of MAPK and PI3K signaling pathways and reduced GLUT4 translocation [43].

Naringenin prevents mutagenic changes in cancerous cell line by stimulating base excision repair of DNA. The exposure of prostate cancer cells to 10–80 μ mol/L of naringenin for 24 hours increased the mRNA expression of three important enzymes of DNA base excision repair i.e., apurinic/apyrimidinic endonuclease, DNA polymerase β and 8-oxoguanine-DNA glycosylase 1 thereby stimulating DNA repair [44]. Naringenin also inhibits breast cancer metastases by regulating host immunity in a breast cancer resection model. Oral administration of naringenin significantly increased the proportion of T cells expressing IFN- γ and IL-2. This proves its efficacy as a surgical adjuvant in breast cancer patients [45].

3 The Epigenetic Modifying Potential of Naringenin

Epigenetic modifications are heritable changes that occur at the molecular level (at DNA) without changing DNA sequence but include changes resulting in increased gene expression or gene silencing.

Furthermost these changes in gene expression will lead to phenotypic changes or will increase the incidence of serious conditions like cancer, diabetes mellitus, etc. In nucleosomal structure, negatively charged DNA is wrapped around the octamer protein called histone core which is again positively charged thus resulting in two states of DNA euchromatin (loosely bound hence open for transcription) and heterochromatin (tightly bound hence no transcription). The histone core has some residual tails like lysine residue which may get acetylated via enzymes like HAT (histone acetyltransferases) or deacetylated by enzymes HDAC (histone deacetylases). This phenomenon may lead to the up-regulation of gene expression or down-regulation respectively [46]. A histone deacetylase SIRT6 is an emerging potential therapeutic target for age-associated diseases and metabolic disorders. In an attempt to fish quercetin related structurally similar compounds that can modulate SIRT6 activity, SIRT6-coated magnetic beads were used by applying a candidate approach. Naringenin was found to be a potential SIRT6 inhibitor from seed extract of *T. foenum-graecum* [47]. Combination therapy of naringenin with SAHA (suberoylanilide hydroxamic acid), a histone deacetylase, was found to show synergistic effect for increasing transamidation activity and increasing the cytotoxicity of SAHA in neuroblastoma cells [48]. Naringenin is therefore presumed to possess potent histone deacetylase inhibitory activity but more detailed studies are required to confirm this.

4 Conclusions

Overall, naringenin is a potential molecule with widespread health benefits. It is a prime candidate for drug discovery and development because of its low toxicity and high bioavailability. Evidence suggests the anti-oxidant, anti-estrogenic, anti-viral and hepatoprotective effects of naringenin for which it can be used for curing complex diseases like diabetes and cancer. However limited studies are available to analyze the effect of naringenin administration on human subjects. Therefore more research is required to understand the preclinical/clinical effects of naringenin, particularly tissue-specific effects like on adipose tissue, pancreas, skeletal muscle, etc.

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Conflicts of Interest: The authors declare that they have no conflicts of interest to report regarding the present study.

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