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Naringenin: Present status and its future prospective

Sumit Kumar*

School of Life Science, Jawaharlal Nehru University, New Delhi, India 110067.

***Corresponding Author:** Email: sumguptabt_2006@rediffmail.com

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Abstract

The chief cause of the global burden of disease is the Inflammation led by Oxidative Stress (OS). The French paradox is the dietary anomaly embedded on the mediterranean diets. It made the great interest to search health beneficial compound present in the food. Naringenin, a flavonoids present in the citrus fruits, widely consumed around the world. Naringenin has shown to reduce the inflammation, obesity and oxidative stress in various studies. It also has shown posses a strong anticancerous property. Besides it also have a wide pharmacological property and due to that it protect the biological system against various types of cytotoxic damage and pathogenesis. The objective of this article is to discuss the current status of naringenin in protection against the different types of non-communicable diseases along with its pharmacokinetics. In the last part of review I focused on some unexplored area where naringenin may hold some good promise.

1. INTRODUCTION

"Nutrition is coming to the forefront as a major modifiable determinant of chronic disease"

(WHO Technical Report, No. 916)

Naringenin is a flavonoid abundantly presents in the citrus fruits (citrus paradise), propolis, prunus davidiana, tomato and orange (*Citrus sinensis*).Grape-fruits juice is a rich source of naringin, a glycon of naringenin which present up to 800 mg/liter of juice[1]. In *Acacia farnesiana,* naringenin it is present in association with the Gallic acid, known as naringenin gallate[2]. It has been ranges from 68-302 mg/kg in Grape fruit juice[3-4]. The highest concentration of naringenin was found in Grape-fruits, which is up to 53 mg/100 gram of juice[5]. Similarly in case of citrus fruits, it ranges from 11.6-20.1/100 gram of juice[3, 6]. In *Citrus paradisi* it's predominant in the form of naringin (naringenin 7-neohesperidoside) followed by narirutin (naringenin 7-rutinoside)[2]. Whereas in tomato fruits it is presents in the Free State or in the form of naringenin 7-rutinoside and naringenin 7-glucosides[2, 7]. Naringenin is abundantly present in tomato skin and its level increases considerably during the maturation period. The naringenin level in tomato has been found to range from 0.8 to 4.2 mg/100 gram of tomato[7].

Naringenin is a known by different names such as naringetol, pelargidanon, salipurpol, Salipurol, Asahina, 480-41-1, Naringenin, (S)-Naringenin, YSO1 (PubChem: SID 3792). Its molecular weight is 272.26 and the chemical formula is $C_{15}H_{12}O_5$ [(2S)-5,7-dihydroxy-2-(4-hydroxyphenyl)-2,3-dihydrochromen-4-one] (figure 1). It's insoluble in the water, while completely soluble in the organic solvent such as alcohol, DMSO etc. Unlike aglycone naringenin, naringin is fairly soluble in water up to 1 mg/ml in water at 40°C (Merck Index).

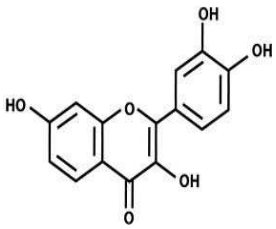

Figure 1: Chemical structure of naringenin (5, 7-dihydroxy-2-(4-hydroxyphenyl) chroman-4-one).

Plants possess a large number of secondary metabolites, play a critical role in cellular functions. Secondary metabolites are divided in to 3 major categories, flavonoids, terpenoids, nitrogen and sulphur-containing alkaloids[8]. Flavonoides are a group of plant polyphenolic secondary metabolites that have a common three ring structure (C6–C3–C6). Flavonoides play an important role in many functions in plants, like in floral pigmentation, UV filtration, symbiotic nitrogen fixation, photosynthesis and offer protection against the various disease[9]. Despite the scarce information on the regulation of the synthesis of naringenin in plants, Hanxiao and coworker[10], (2005) have successfully cloned the naringenin biosynthesis pathway gene from *Arabidopsis thaliana* and *Hypericum androsaemum* in *Saccharomyces cerevisiae* and observed that the naringenin flux is governed by the supply of L-tyrosine, although it may not be a compete study but has a significant impact in the industrial production of naringenin. Naringenin is rapidly build-up during the cell division and remains in a steady phase during the cell elongation. However, its synthesis again boosts up and reaches maximum in the fruits during the maturation phase[11-12]. Since it is derived from the phenylpropanoid pathway it has shown similarity with other flavonoid like genistein, apigenin, quercetin and hesperidins[13].

The information about the role of naringenin in the plant is very scant, although it may play an important role in protection against different pathogens. It further gets support from the different In-vitro studies that have shown its antibacterial and antifungal effects[14-16]. The other role ascribed to naringenin is in neutralizing free radicals in plants[17-18].

2. PHARMACOKINETICS

Previous studies have been shown that naringin a bound form of Naringenin with hexose sugar is unable to absorbe in body. It is absorbed into the body after breaking down into aglycone (naringenin) and monosaccharide by gut flora[19-22].The gut micro-flora of rat and humans have capacity to cleave off the glycosidic bond of naringin before being it is absorbed in the body[19-22]. In fact, Kim *et al.,* (1998)[23] have identified some bacterial strain such as Bacteroides JY-6, Eubacterium YK-4, and Fusobacterium K-60 in fecus, that have the capability to cleave the naringin to produce the naringenin[22]. Similarly, studies performed in nude animal or in germ free by administrating the the high dosees of antibiotics to animal, animal loss the capacity to absorb the naringenin in the body. When naringin was incubated with the gut flora in *in-vitro* system besides naringenin, other compounds like the p-hydroxyphenylpropionic acid, p-coumaric acid, p-hydroxybenzoic acid, and phenylpropionic acid were also formed[24-27]. The above observed compounds were also detected in the rat urine after administration of the naringenin or naringin[26-28].

Previous studies done by using 3-[14C]-flavonoids in rats indicated that the intestinal absorption of aglycone flavanones may be greater than 90% then its glycone[29]. The bioavailability of the naringenin and its glucoside was checked in rat after oral administration of naringenin (0.25%), naringenin-7-glucoside (0.38%) and naringenin-7-rhamnoglucoside and found that Glucurono and sulfoconjugated metabolites of naringenin have no relation with the type or form of naringenin administered[28]. Naringenin-7-rhamnoglucoside showed a delay in absorption in comparison to other 2 forms of naringenin in oral administration studies. In one study, it was observed that the different form of naringenin reached the peak in plasma at different time period and for naringenin it was 20-30 min. (Cmax: 0.021 µmol/L) and for naringenin glucuronide 20-30 min (Cmax: 0.09 µmol/L) [30].

In the distribution studies, it was observed that naringenin is widely distributed in the body, starting from the liver at highest conc. followed by stomach, small intestine, kidney, trachea, lung, testis, heart, ovary, spleen, muscle, and brain in succession, however in the brain it was almost negligible indicating its inability to cross the blood-brain barrier. Naringenin was also found to be excreted from the urine in the range from 8.5-8.8% of administrated dose[27]. In human case studies done by Fuhr *et al.,* (1995)[20], have shown that the presence of naringenin was detected after 8 hours of administration of naringin. Most administrated part was found to be excreted in urine, which was 57% molar equivalent of administrated naringin, beside naringenin they were also able to detect some other minor components like naringenin glucuronides, (<4 µmol/L). Urine and bile are the most preferred route for its elimination. Whereas in the case of bile it is again reabsorbed into the body from the intestine and again reappear into the body second time.

The grape juice is a rich source of naringin (glycone), and it was observed that the Cmax value for naringenin in plasma was highest after 5.5 hours in comparison to 4-4.8 hours when pure compound (naringin) was administrated[27]. Bugianesi *et al.,* (2002)[7] showed that C_{max} value for naringenin in plasma was reached as early as 2 hours after the ingestion of tomato paste, which is known to be a rich source of aglycone naringenin. In the case of grapefruits administration study, naringenin level reached up to 6 µM/liter in plasma after administration of the grapefruits juice equivalent of 200 mg of naringenin[4, 27]. Its bioavailability was found to be enhanced by associating it with the cyclodextrin[31]. Similarly, its effectiveness could be also enhanced by coating it over the nanoparticle[32].

3. TOXICOLOGICAL STUDIES

Flavonoids are generally considered to have low toxicity, but in the case of naringenin experimental data is very limited. First time a study done by Lisa *et al.,* in 1999[13] showed the IC_{50} value was > 1 mM but it varies cell to cells. Later another study done by Tundis and coworker (2011)[33] have shown that IC_{50} value for the naringenin was 2.2, 7.7, and 33.4 µM in C32, LNCaP, and COR-L23 cell lines respectively[33]. However, IC_{50} value for the Vero cells was found to be much higher (0.319 mM) [34]. *In-vivo* toxicity showed that medium lethal dose (LD50) for mice and rat is >5000 mg/kg body weight[35]. While as toxicity to embryonic tissue of mice was observed at 300 µM conc[36].

4. HEALTH PROMOTING EFFECTS OF NARINGENIN

Naringenin has potential to act as strong free radical scavenger due to the presence of the hydroxyl group over the phenolic ring since hydroxyl group are known to neutralize the free radicals by donating a proton from it and itself get oxidized. Furthermore, naringenin is itself stabilized by the delocalization of the unpaired electron over the phenolic rings[37]. Chetia *et al.* (2012)[38] have compared the hydroxyl radical scavenging of naringenin along with other compounds and found that the IC_{50} value was 29.66, 29.84 and 34.12 for the naringenin, β-carotene and N-acetylcysteine respectively. Similarly in case DPPH free radical scavenging assay they observed that free radical scavenging activity of naringenin was almost similar to β-carotene and N-acetylcysteine. However in the case of nitric oxide radical scavenging activity they found that naringenin has better capacity to scavenge the above radicals in comparison to the β-carotene.

4.1 PROTECTION AGAINST DNA DAMAGE

Naringenin has higher potential to protect against DNA damage in comparison to other flavonoids. Celik *et al.,* (2010)[39] have shown that Naringenin at 2 mM reduces DNA damage (plasmid pBR322) induced by idarubicin up to 31.8% in comparison to the 26.7% and 3.2 % offered by Resveratrol and Trolox., Naringenin had closer interaction with the DNA helix then other two flavonoids. The probable reason could be the presence of the hydroxyl group at 7th position or 5, 7 dihydroxy group in the flavonoids that may help in the closer interaction with the DNA helical strand[40-41]. It has also shown the similar type of effects in idarubicin-induced DNA damage in a cellular plasmid assay[39]. Meanwhile, a similar study done by Gao *et al.,* (2006)[42] have found that naringenin reduced the ferrous sulfate induced DNA damage in LNCaP human prostate cancer cells by inducing the expression of the 8-oxoguanine-DNA glycosylase1 (hOGG1), apurinic/apyrimidinic endonuclease and DNA polymerase beta (DNA poly beta) hOGG1 and DNA poly beta. A study done in murine melanoma cells, B16-F10, it was observed that it induced the melanin production via Wnt/β-catenin signaling, so it could be helpful in the reduction of the radiation-induced DNA damage by stimulating the production of melanin[43-45]. Naringenin also protects against the oxidative stress induced DNA damage in Wistar male rat liver[46]. In another study done in alloxan induced diabetic mice, have found that it protected against the DNA damage by lowering the oxidative stress[47]. Similarly, we have also found that it drastically reduced the radiation-induced DNA damage (pBR322) in an acellular system.

4.2 PROTECTION AGAINST INFLAMMATION

In an *in-vivo* study done in mice have shown that naringenin (50 mg/kg body weight) reduced the level of the proinflammatory cytokine, NF-κB and iNOS in the pancreatic tissue of *Streptozotocin nicotinamide* treated Wistar rats and improved the level of the RBC, WBC and platelets[48]. It has been shown that naringenin reduces the ethanol-induced inflammation in mice after a 30 days treatment (50 mg/kg body wt.) by lowering down the level of proinflammatory mediators such as TNF-α, IL-6, NF-κB, COX-2, MIP-2, CD-14 and iNOS. In renal protection studies, proved that it protects the diabetic mice against the renal injury by decreasing the plasma levels of glucose, creatinine and blood urea nitrogen, by enhancing the expression of the insulin and along with reducing the expression of the proinflammatory cytokines like TNF and IL 6 and inflammatory proteins like Cox-2, NF-kB, macrophage inflammatory protein-2 (MIF2)[49-50]. Beside these effects, naringenin also decreases the level of the serum aspartate and alanine transaminases[50]. NF-kB and iNOS is the main mediator of the inflammation and Naringenin has potential to inhibit their levels in various biological systems to reduce the level of inflammation[51-55].

Naringenin was found to reduce the severity of colitis by reducing the expression of pro-inflammatory mediators such as inducible NO synthase (iNOS), intercellular adhesion molecule-1 (ICAM-1), monocyte chemoattractant protein-1 (MCP-1), cyclo-oxygenase-2 (Cox2), TNF-α, TLR4 and phapso-NF-kB and IL-6 level in the colon mucosa[55]. TLR2 expression in the adipocytes is known to be the main cause of the obesity-induced inflammation and development of insulin resistance in the body. In this context, a study was done by Yoshida *et al.,* (2013)[56] have found that the naringenin reduced level of the inflammatory mediators i.e. TLR, TNF α and c jun NH2 terminal kinase in adipocytes after co-culturing it with the macrophage[56]. Naringenin inhabits the release of proinflammatory cytokines from macrophage via down-regulation of AP-1[57-58]. In another report it has shown that, it inhibited the LPS induced proinflammatory cytokines by inactivating the NF-kB and MAPK in the BV-2 microglia cells, A study done by Vafeiadou *et al.,* 2009[59] in glial cells, observed that naringenin protects against the LPS induced inflammation in the cells by inhibiting the iNOS and p38 expression into cells[59]. It has the potential to induce the cell proliferation of Chlamydia trachomatis, due to its immunomodulatory in nature[60].

4.3 PROTECTION AGAINST VARIOUS TYPES OF OXIDATIVE STRESS AND PATHOGENESIS

Oxidative stress is known to critically involve in the pathogenesis of various diseases such as Alzheimer's disease, Parkinson's disease, and other neurodegenerative diseases[61]. Previous studies have shown that oral administration of the dietary compound has the ability to overcome the diseases caused by oxidative stress[62]. Naringenin has shown to reduce the occurrence of Alzheimer's disease, Parkinson's disease in the animal model system by activating the key signaling pathway involved in the reduction of oxidative stress such as Nuclear factor E2-related factor 2 (Nrf2), Antioxidant response element (ARE) genes etc[63]. Some *in-vivo* studies have shown that it potential to scavenge the 1-methyl-3-nitro-1-nitrosoguanidine generated free radicals in the mice stomach and liver[64]. In other study done by Jain *et al.,* (2011)[65] has shown that it

reduces the arsenic-induced free radical formation in mice blood and protected the hematopoietic system against oxidative stress mediated cytotoxicity. Similarly oral administration of the naringenin (50 mg/kg body wt.) attenuated the oxytetracycline (200 mg/kg body wt. for 15 days) induced nephrotoxicity in rat by lowering down the level of serum urea and creatinine with improving the level of antioxidant enzyme[66]. It protected against the liver damage caused by the dimethylnitrosamine (DMNA) at 20 mg/kg body weight by lowering the level of the malondialdehyde formation[67]. Naringenin was shown to reduce the ROS formation in Alzheimer's disease model system and ameliorated the scopolamine-induced amnesia into the mice at a dose of 4.5 mg/kg body weight[68]. Reduction in the carbonyl induced neurotoxicity in the mouse neuroblastoma cell lines (Neuro 2A), was attributed to the reduction of the oxidative stress, apoptosis and maintaining the proper mitochondrial potential for the functioning of the system[69]. Naringenin reduced the oxidative stress induced by doxorubicin in mice by ROS scavenging and iNOS inhibition[70]. The reduction in the oxidative stress appears to be due to its ferrous ions chelating property and by this ways the formation of the hydroxyl radical via iron-dependent reaction is eliminated [71].

Oxidative stress is known to cause the membrane damage, and it has found that naringenin protects the cellular membrane against ROS by actively scavenging the free radicals with the closer membrane interaction due to the presence of the 4′-hydroxyl group[37]. Besides direct free radical scavenging, membrane protection offered by the naringenin could also be due to the glutathione, since it has shown to enhance the level of the oxidized glutathione[72]. The depletion of GSH seems to be a prime factor that permits free radical induced lipid peroxidation[73-74].

Naringenin is reported to behave as pro-oxidants in few studies, and this behavior could be due to its ability to oxidize NADH and production of the phenoxyl radicals in the presence of peroxidases and hydrogen peroxide[75-76]. However in the majority of cases it behaves as an antioxidant[77] and in one done in mice does not shows any pro-oxidant effects up to a dose of 120 mg/kg body weight[78].

Radiation is one of the agents that have shown to induce the oxidative stress. However in one in-vitro study done in HaCaT cell lines, it has shown to reduce the UV induce DNA damage[79]. Similarly in in-vivo studies done in mice model system, we observed that naringenin has the capacity to protect against the radiation-induced cytotoxic damage in animals by inhibition of NF-kB. The protective role of naringenin against NF-kB may depends on the radiation dose. At lower doses of radiation, NF-kB might be helpful in the protection against radiation by giving an adaptive response but the same could not be true at the high dose of radiation exposure, where it may itself act a potential source of radiation-induced inflammation[80]. Since it gives various let life complication in the body due to sustained oxidative stress and inflammation[81]. In different genotoxic studies done in the *in-vivo* system, naringenin has shown to reduce the oxidative damage caused by various compounds such as carbon tetrachloride, lead, cadmium, etc by inducing the cellular antioxidant defense machinery[70, 82-84].

In the year 2010, almost 340 million peoples were suffering from the diabetes, and it could be the 7th leading cause of the death globally by 2030s[85-86]. A relation between the citrus fruits and obesity reduction is long known. Recently it has been found that the antidiabetic property of the citrus fruits is mainly due to its constituent naringenin[87]. In streptozotocin induced, diabetic mice, naringenin has shown to reduce the blood glucose level and improved the level of plasma lipid[87]. Naringenin has shown to promote the glucose metabolism by behaving like insulin. Similarly, it also has batter controlling power to keep VLDL cholesterol under control[88].

4.4 PROTECT AGAINST THE CANCER AND TUMOR

Today cancer is one of the leading causes of the death worldwide although cancer registry is yet to available in all countries for the statistical purpose but according to WHO it causes the death of 8.2 million peoples across the globe every year[89]. Some *in-vitro* studies using various cancer cell lines such as in breast (MCF-7, MDA-MB-231), stomach (KATOIII, MKN-7), liver (HepG2, Hep3B, Huh7), cervix (Hela, Hela-TG), pancreas (PK-1), and colon (Caco-2) as well as leukemia (HL-60, NALM-6, Jurkat, U937), naringenin have shown growth inhibitory and cytotoxic effects on above cell lines[90-91]. Naringenin has the ability to blocks the cell cycle and induces apoptosis in the hepatocellular carcinoma cells (Hep G2) by overexpression of p53 and Bax[92]. Whereas in human lung cancer A549 cells, it enhanced apoptosis in mediated by TRAIL[93]. Naringenin enhanced the apoptosis in the AGS gastric cancer cells by inhibiting the β catenin/Tcf pathway, which is known to play an important role in carcinogenesis[94]. An another study done in the human promyelocytic leukemia HL-60 cell found that it enhances the cell death by the activation of the NF-kB which subsequently causes the intracellular ATP depletion and mitochondrial dysfunction[95].

Naringenin also suppresses the colorectal cancer by inhibiting the Cox 1, a key enzyme involved in carcinogenesis[96]. The protective effects of naringenin on DNA damage and inhibition of the cell proliferation in cancer cells could be due to its ability to inhibit the synthesis of the polyamines, which is essential for the regulation of protein, DNA and RNA synthesis, beside it also alter DNA–protein interactions, which disrupt certain cellular functions[64, 97-98]. Naringenin inhibits the growth of implanted C6 glioma cells in rat brain in 30 day treatment at a dose rate of 50 mg/kg by decreasing the expression of PK-C, NF-kappa B, cyclin D1 and CDK 4[99]. Naringenin decreased the number of metastatic property of tumor in a breast cancer resection mouse model system and extended the life span of the tumor-bearing mice by reducing the no. of TGF-β secreting Treg cells and at the same time enhanced the proportion of the IFN-γ and IL-2 secreting $CD4^+$ and $CD8^+$ cells[100]. It was observed that naringenin reduces the size of the implanted sarcomas-180 in mice after 5 days of oral administration[90]. In one study, it was observed that the naringenin reduced no. of implanted ascites carcinoma cells at 50 mg/kg dose rate in Ehrlich ascites carcinoma tumor model by down-regulating the expression of VEGF, HIF 1α, HSP 90 and pAKT[101]. Naringenin was found to reduce the DMBA induced oral carcinogen in Golden

Syrian hamsters[32]. Similarly, it also inhibited the carcinogenesis induced by the N-nitrosodimethylamine in mice[92]. Some epidemiological studies have shown the effect of naringenin in the indirect study where it was observed that the chance of breast cancer is lower in women consuming a high proportion of citrus fruits[5, 102].

In various reports by using patient data, Cancer and diabetes are often diagnosed within the same individual more frequently rather than by chance[102]. Naringenin which is known to reduce the diabetes by regulating the metabolism of the glucose in the body could be helpful in the prevention of the cancer linked with the diabetes. However, its effects against the diabetes led cancer either in lab or at the epidemiological level yet be known.

4.5 **MODULATION OF GENE EXPRESSION**

Some molecular studies have proved that naringenin affects the expression of the various important genes such as NF-kB, p21, p53, COX-2, iNOS, etc. in different model system[54, 104-105]. It affects signaling of the various important pathways, such as Akt/PI3K, β-catenin/Tcf, TGF-β1/Smad3, STAT 1, c-jun pathway mitogen-activated protein kinase (MAPK)/extracellular signal–regulated kinase (ERK) (MAPKerk) pathway etc in various cell lines and *in-vivo* studies[57, 94, 106-107]. Besides it also reduce the level of pro-inflammatory cytokines such as IL-1, IL-6, IL-8, IL-10, etc. in different model systems[57]**.** Due to its weak estrogenic activity, it was found to induce the apoptotic cascade in the cells after interaction with the ER-α and EP-β and induced the P38/MAPK pathway, beside it also up-regulated the Cx43, Bcl 2, p21. etc [99, 108-109]. Naringenin induces apoptosis in cancer cells by downregulation of the Akt/PI3K pathway in cancer cells. Whereas, in normal cells, it reduces the apoptosis by lowering down the expression of the AIF/endo G[110].

5. FUTURE PROSPECTIVE

In different studies, naringenin has shown to reduce the modern day diseases such as diabetes, cancer, inflammation, etc. in various animal model systems. Naringenin modulates a large numbers of pathways beside its antioxidative property, which leads to the reduction in the oxidative stress mediated pathogenesis. However in context to the effect of naringenin on human, no epidemiological study has been performed expect showing a link between the citrus fruits and lower rate of cancer in breast cancer patients. In many instance cancer is commonly observed in diabetic patients. Naringenin has shown to reduce the diabetes and also help in the prevention of the cancer in diabetic patients. Based on the experienced gain from different studies, it could be safely concluded that naringenin may potentiate the outcome of radiotherapy by overcoming the radio-diminished immune response and give a batter clearance of tumor by activating the host cytotoxic immune response. Beside it is also possible that naringenin may reduce the damage to the normal cells during radiotherapy due to its differential effects on the normal and cancer cells.

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