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REVIEW ARTICLE

BIO-DYNAMIC ACTIVITY OF NARINGENIN – A REVIEW

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ABSTRACT

Flavonoids are important natural compounds with diverse biologic activities. Citrus flavonoids constitute an important series of flavonoids. Naringenin belong to this series of flavonoids and were found to display strong anti-inflammatory and antioxidant activities. Several lines of investigation suggest that naringenin supplementation is beneficial for the treatment of obesity, diabetes, hypertension, and metabolic syndrome. A number of molecular mechanisms underlying its beneficial activities have been elucidated. However, their effect on obesity and metabolic disorder remains to be fully established. Moreover, the therapeutic uses of these flavonoids are significantly limited by the lack of adequate clinical evidence. This review aims to explore the biologic activities of these compounds, particularly on lipid metabolism in obesity, oxidative stress, and inflammation in context of metabolic syndrome.

INTRODUCTION

Favonoids are a widely distributed group of phytochemicals having benzo-pyrone nucleus, and more than 4,000 different flavonoids have been described and categorized into flavonols, flavones, flavanones, isoflavones, catechins and anthocyanidins. Flavonoids occur naturally in fruits, vegetables, nuts, and beverages such as coffee, tea, and red wine, as well as in medical herbs. Flavonoids are responsible for the different colors of plant parts and are important constituents of the human diet. Flavanoids have different pharmacological activities, such as antioxidant, anti-allergic, antibacterial, anti-inflammatory, antimutagenic and anticancer activity. Naringenin belongs to the flavanones and is mainly found in fruits (grapefruit and oranges) and vegetables.

Pharmacologically, it has anti-cancer, anti-mutagenic, anti-inflammatory, anti-oxidant, anti-proliferative and anti-atherogenic activities. Naringenin is flavones a type of flavonoid, that is considered to have a bioactive effect on human health. It is the predominant flavones in grape fruit. An inverse association between flavonoid intake and oxidation effect has been suggested by a number of epidemiological studies [(1,2,3,4)].

Properties of naringenin

Naringenin is one of the most studied flavonoids abundant in citrus plants. Naringenin derived from plants are found to be highly beneficial to human health because of their intrinsic antioxidant potential. Recent research on these small molecules has expanded on their effects and the molecular mechanisms for their modes of action in the prevention of a wide range of diseases. Particularly, naringenin and their derivatives are known to exhibit strong anti-oxidant potential along with plenty of protective effects for the improvement of human health. Several in vitro and in vivo experimental results support their beneficial effects. Naringenin is used for the treatments of osteoporosis, cancer and cardiovascular diseases, and showed lipid-lowering and insulin-like properties. In the present review, detailed pharmacological and analytical aspects of naringenin have been presented, which revealed the impressive pharmacological profile and the possible usefulness in the treatment of different types of diseases in the future. The information provided in this communication will act as an important source for development of effective medicines for the dietary sources, bioavailability and biological activities of naringenin and its derivatives.

Chemistry

The chemical name of naringenin is 2, 3-dihydro-5, 7-dihydroxy-2-(4-hydroxyphenyl) - 4H-1-benzopyran-4-one (Figure 1), and it has a molecular weight of 272.26 (C_{15} H_{12} O_5). Naringenin is almost insoluble in water and is soluble in organic solvents such as alcohol. Naringenin is derived from the hydrolysis of glycone forms of this flavanone, such as naringin or narirutin[(5)]. Naringin (naringenin-7-rhamnoglucoside), the bitter principleof grapefruit (Citrus paradisi), is found in the juice, flower, and rind of the fruit and constitutes up to 10% of the dry weight. Naringin and other naringenin glycosides can be found in a variety of other sources including propolis[(6)] and Prunus davidiana[(7)]. Monotes engleri contains a prenylated form of naringenin (6-(1, 1-dimethylallyl) naringenin)[(8)].

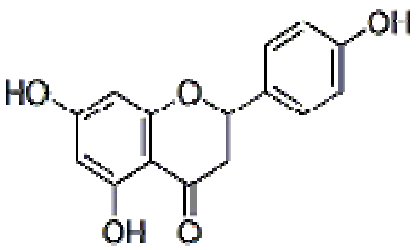

Figure 1 Naringenin

Pharmacokinetics

As naringenin is generally present in foods bound to sugars as β -glycosides (i.e., naringin), it was originally thought that absorption from the diet would be negligible. However, a number a studies have detected naringenin in human urine [9,10,11,12,13] and plasma[9,10] following oral doses of pure naringin[9,11] or grapefruit juice([9,10,12,13]). Furh *et al*.,[10] showed that excretion of naringenin glucuronides in humans reaches levels more than 100-fold higher than the concentration of naringenin excreted in the urine. Hackett *et al*.,[13] have shown that a major route for flavonoid metabolism in rats is excretion in the bile. This generally occurs following conjugation of flavonoid polar hydroxyl groups with glucuronic acid, sulfate, or glycine. Naringenin present in the bile may either be excreted or reabsorbed, therefore raising the possibility of enterohepatic recycling of naringenin.

Naringenin has been detected in the plasma following oral administration of naringin or grapefruit juice but is generally reported to be below accurate detection limits [9, 10] and has not been reported to exceed 4 m M[10]. However, due to the lipophilic nature of naringenin, it is possible that it accumulates within tissues, particularly membranes, and eventually reaches greater concentrations than those observed in the plasma. This accumulation would most likely occur in tissues such as the liver and intestine.

Mechanisms of Action

Anti-oxidant effect

The naringenin exhibited higher antioxidant capacity and hydroxyl and superoxide radical scavenger efficiency. The glycosylation attenuated the efficiency in inhibiting the enzyme xanthine oxidase and the aglycone could act like a more active chelator of metallic ions than the glycoside. Additionally, naringenin showed a greater effectiveness in the protection against oxidative damage to lipids in a dose-dependent manner. The flavanone was effective in reducing DNA damage[14].

Hepatoprotective effects

Naringenin has been found to have a hepatoprotective characteristic similar to silymarin. Animal studies have demonstrated turmeric's hepatoprotective effects from a variety of he-patotoxic insults, including carbon tetrachloride (CCl4), alactosamine, acetaminophen (paracetamol), and Aspergillus aflatoxin. Turmeric's hepatoprotective effect is mainly a result of its antioxidant properties, as well as its ability to decrease the formation of pro-inflammatory cytokines. The protective capacity of naringenin on dimethylnitrosamine (DMN) - induced hepatic damage in rats was investigated. Oral administration of naringenin (20 and 50 mg/kg daily over 4 wk) notably diminished DMN-induced dam-age when the weight of the liver was evaluated, as well as alanine transaminase (ALAT), aspartate transaminase (ASAT), alkaline phosphatase (ALP), and bilirubin levels. Naringerin also restored natural protein levels in serum and albumin and hepatic malondialdehyde (MDA) levels. The naringenin had antifibrinogenic and hepatoprotective effects, suggesting that it could be useful in the treatment of hepatic fibrosis[15].

Anti-inflammatory Effects

The pathogenesis of inflammatory bowel disease (IBD) such as ulcerative colitis (UC) is usually associated with reduced antioxidant capacity. Generation of free radicals like reactive oxygen species (ROS) leads to lipid per oxidation, which inhibits cellular antioxidant capability, resulting in prominent colonic inflammation. There is a great need to search for safe and tolerable compounds for the management inflammation to reduce patient compliance as well as the adverse effects of conventional treatments. Naringenin is a naturally occurring flavonoid that can be extracted from citrus fruits, tomatoes, cherries, grapefruit, and cocoa. Like most of the flavonoids, naringenin was experimentally found to have several pharmacological potentials, including anti- inflammatory because of naringenin has properties to produce sufficient hydroxyl (-OH) substitutions, which give it the capability to scavenge ROS. Thus, it has considered that naringenin may diminish and/or improve pathological conditions where oxidation or inflammation is deemed to play a vital role[16].

Anticarcinogenic effects

Animal studies involving rats and mice, as well as in vitro studies utilizing human cell lines, have demonstrated naringenin ability to inhibit carcinogenesis at three stages: tumor promotion, angiogenesis, and tumor growth. Naringenin is also known to cause cytotoxic and apoptotic effects in several cancer cell lines in a dose-dependent manner as well as inhibits tumor growth in sarcoma S-180 implanted mice, suggesting that naringenin can potentially be used to inhibit tumor growth (14-16). Cytotoxic effects were also induced in human cancer cell lines when high concentrations of naringenin were administered (50% effective concentration: 150-560 μM). However, the use of flavonoids as cancer chemo preventive or chemotherapeutic agents requires the development of novel flavonoids or naringenin derivatives that can induce cytotoxicity at low concentrations in a cell type-dependent manner[17].

Cardiovascular Effects

Naringin showed a range of properties that help protect the cardiovascular system, including antihypertensive, lipid-lowering, insulin-sensitising, anti-oxidative and anti-inflammatory properties. Naringin prevented the age-related increase in systolic blood pressure in stroke-prone spontaneously hypertensive rats, increased nitric oxide production, improved endothelial function and decreased

cerebral thrombotic tendency . Further, naringin prevented oxidative stress in the hearts of rats with isoprenaline-induced myocardial infarction [(18)]. Obesity, an important component of metabolic syndrome, is a chronic low-grade inflammatory condition leading to adipocyte differentiation and growth in adipose tissues [(19)]. In mice fed a high fat diet, naringin decreased visceral adiposity and lowered plasma lipid concentrations, probably by activation of AMP kinase.

Gastro-intestinal effect

Pre-administration of naringenin significantly reduced the severity of colitis and resulted in down-regulation of pro-inflammatory mediators (inducible NO synthase (*iNOS*), intercellular adhesion molecule-1 (*ICAM-1*), monocyte chemoattractant protein-1 (*MCP-1*), cyclo-oxygenase-2 (*Cox2*), *TNF*-α and *IL-6* mRNA) in the colon mucosa. The decline in the production of pro-inflammatory cytokines, specifically TNF-α and IL-6, correlated with a decrease in mucosal Toll-like receptor 4 (*TLR4*) mRNA and protein. Phospho-NF-κB p65 protein was significantly decreased, which correlated with a similar decrease in phospho-IκBα protein. Consistent with the *in vivo* results, naringenin exposure blocked lipopolysaccharide-stimulated nuclear translocation of NF-κB p65 in mouse macrophage RAW264.7 cells. In addition, *in vitro* NF-κB reporter assays performed on human colonic HT-29 cells exposed to naringenin demonstrated a significant inhibition of TNF-α-induced NF-κB luciferase expression[(20, 21)].

Naringenin enhances immunity

Natural killer (NK) cells are capable of identifying and killing tumor cells as well as virus infected cells without pre-sensitization. NK cells express activating and inhibitory receptors, and can distinguish between normal and tumor cells. The present study was designed to demonstrate the importance of the expression level of NKG2D ligands on the Burkitt's lymphoma cell line, Raji, in enhancing NK cell cytolytic activity. Various flavonoids were used as stimulants to enhance the expression of NKG2D ligands. NK cell lysis activity against Raji was not changed by pre-treatment of naringenin with luteolin, kaempferol, taxifolin and hesperetin. However, treatment with naringenin showed increased sensitivity to NK cell lysis than untreated control cells. The activity of naringenin was due to enhanced NKG2D ligand expression. These results provide evidence that narigenin's antitumor activity may be due to targeting of NKG2D ligand expression and suggests a possible immunotherapeutic role for cancer treatment[(22)].

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