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Flavonoid: A review on Naringenin

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Abstract

Many of the currently available drugs have been derived from natural sources. Apart from their physiological roles in the plants, flavonoids are important components of the human diet, even though they are not considered as nutrients. Flavonoids are a major class of plant secondary metabolites that serves a multitude of functions including pigments and antioxidant activity. Naringenin is a naturally occurring flavanone (flavonoid) known to have a bioactive effect on human health and is mainly found in fruits (grapefruit and oranges) and vegetables. Naringenin possesses various biological activities such as antidiabetic, antiatherogenic, antidepressant, immunomodulatory, antitumor, anti-inflammatory, DNA protective, hypolipidaemic, antioxidant, peroxisome proliferator-activated receptors (PPARs) activator, and memory improving. A number of molecular mechanisms underlying its beneficial activities have been elucidated. Further this review aims to provide newer insights and will certainly lead to a new era of flavonoid based pharmaceutical agents for the treatment of many infectious and degenerative diseases.

Keywords: flavonoids, naringenin, flavone, flavanol

1. Introduction

Plants have been used by human being since antiquity for diverse purposes such as food and medicine. Many of the currently available drugs have been derived from natural sources. More than 25% of the drugs prescribed worldwide are derived from plants, and 121 such active phytoconstituents are used for different disorders^[1, 2]. The term flavonoid is derived from the Latin word "flavus", meaning yellow. It is a plant secondary product that has characteristics in red, blue, and purple pigments in plant tissues. Apart from their physiological roles in the plants, flavonoids are important components of the human diet, even though they are not considered as nutrients. Flavonoidal compounds share the same basic skeleton, the flavan-nucleus, consisting of two aromatic rings with six carbon atoms (ring A and B) interconnected by a hetero cycle including three carbon atoms (ring C)^[3-7]. Flavonoids are important natural compounds with diverse biologic activities. Citrus flavonoids constitute an important series of flavonoids.

Flavonoids are plant-derived phytochemicals responsible for the different colors of plant parts like shades of yellow, orange and red in flowers. More than 4,000 flavonoids, such as flavonols, flavones, flavanols, flavanonols, flavanones, and isoflavones have been reported in the edible plants and are consumed regularly in the human diet^[8]. Flavonoids, found in fruits and vegetables, have various health benefits^[9]. The biosynthesis of flavonoids occurs via the combination of shikimic acid and acylpolymalonate metabolic pathways.

A starting compound is phenylpropane, a cinnamic acid derivative derived from shikimic acid, in which three acetate residues are incorporated followed by ring closure. The chalcone structure is an intermediate to the flavone structures, which might be hydroxylated and reduced at different positions^[10]. Recent evidences have indicated that an adult human diet rich in flavonoids leads to a decrease of total cholesterol, low-density lipoproteins, and triglycerides in plasma, as well as a reduced incidence of cardiovascular diseases and osteoporosis^[8]. Among naturally occurring flavonoids, naringenin and hesperetin are very common in some edible fruits and vegetables as aglycons and glycosides. Naringenin is most abundant in grapefruit and are used in perfumery, cosmetic and in different pharmaceutical formulations. It has been reported for the hypocholesterolemic, antiestrogenic, hypolipidemic, antihypertensive, and anti-inflammatory activities^[11].

2. Importance of flavonoids

Plants produce a vast array of natural products including phenolic compounds, which are responsible for the major organoleptic characteristics of plant-derived foods and beverages. They play an important role in the color and taste properties of fruits and vegetables^[12, 13].

Flavonoids, a group of phytochemicals, have diverse beneficial biochemical and pharmacological properties, mainly presented in foods of plant origin, such as fruits, vegetables, tea, wine, seeds, herbs, spices, and whole grains [14]. Flavonoids are biological pigments responsible for the colors from red to blue in flowers, fruit and leaves [15].

3. Flavonoid biosynthesis

Flavonoids are a major class of plant secondary metabolites that serves a multitude of functions including pigments and antioxidant activity. Flavonoids are synthesized from phenylpropanoid derivatives by condensation with malonyl-CoA. For example, condensation of p-coumaroyl-CoA (C6-C3) with three malonyl-CoA (C3) molecules results in naringenin chalcone with a diphenylpropane (C6-C3-C6) unit, which is converted to naringenin with the flavone (2-phenylchromen-4-one) backbone by conjugate ring closure. These and further modifications yield a variety of structural forms including chalcones, flavanones, dihydroflavonols, and flavans, anthocyanins, flavones and flavonols, and isoflavonoids [52].

4. Chemistry

Flavonoids are composed of two aromatic rings linked through three carbon atoms that form an oxygenated heterocycle. Variations on the basic structure of flavonoids yield different classes of flavonoidal compounds [16]. Flavonoids are a widely distributed group of polyphenolic compounds characterized by a common benzo-pyrone structure. Over 4,000 different flavonoids have been described and categorized into flavonols, flavones, flavanones, isoflavones, catechins, and anthocyanidins [17]. Diverse biochemical properties of flavonoids including naringin, hesperidin, diosmin, and rutin have provoked interest in biology and medicinal chemistry. These compounds have exhibited a broad range of biological and pharmacological activities, such as antioxidant, anti-allergic, antibacterial, anti-inflammatory, antimutagenic and anticancer effects. Flavonoids represent one of the most prevalent classes of compounds in vegetables, nuts, fruits and beverages, as well as in medical herbs (e.g., *Silybum marianum*, *Alpina officinarum*, *Hypericum perforatum*) [18]. 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 [19-22]. 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 (C₁₅ H₁₂ O₅). 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 [23]. Naringin (naringenin-7-rhamnoglucoside), the bitter principle of 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 [24].

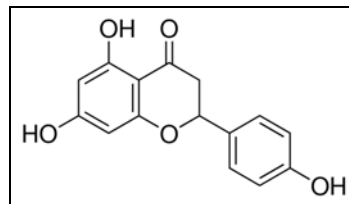


Fig 1: Structure of Naringenin

5. Properties of Naringenin

Low concentrations of naringenin are also found in tomatoes and tomato-based products. Fresh tomatoes, especially tomato skin, also contain naringenin chalcone, which is converted to naringenin during processing to tomato ketchup [25]. In vitro studies indicate a wide range of biologic activities for different flavonoids. These studies have mainly been performed with flavonoid aglycones or glycosides. Until very recently, flavonoid metabolites were rarely used, mainly because data about their identity were scarce; moreover, chemical standards for only a few potential metabolites are commercially available [26].

6. Sources of Naringenin



Fig 2: Sources of Naringenin

7. Metabolite description

Naringenin is a flavanone that is considered to have a bioactive effect on human health as antioxidant, free radical scavenger, anti-inflammatory, carbohydrate metabolism promoter, and immunity system modulator. This substance has also been shown to repair DNA. Scientists exposed cells to 80 mm of naringenin per litre, for 24 hours, and found that the amount of hydroxyl damage to the DNA was reduced by 24 percent in that very short period of time. Unfortunately, this bioflavonoid is difficult to absorb on oral ingestion. Only 15% of ingested naringenin will get absorbed, in the human gastrointestinal tract, in the best case scenario. A full glass of orange juice will supply about enough naringenin to achieve a concentration of about 0.5 mm per litre. But, one has to wonder, if given more time than 24 hours, would lower concentrations have similar effects [53].

8. Reported pharmacological activities on naringenin

8.1 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 [39].

8.2 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 damage when the weight of the liver was evaluated, as well as alanine transaminase (ALAT), aspartate transaminase (ASAT), alkaline phosphatase (ALP), and bilirubin levels. Naringenin 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 [40].

8.3 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 [41].

8.4 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 μ M). 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 [42].

8.5 Cardiovascular Effects

Naringin showed a range of properties that help protect the

cardiovascular system, including antihypertensive, lipidlowering, insulin-sensitising, anti-oxidative and antiinflammatory 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 [43].

8.6 Obesity

It is an important component of metabolic syndrome, is a chronic low-grade inflammatory condition leading to adipocyte differentiation and growth in adipose tissues (44). In mice fed a high fat diet, naringin decreased visceral adiposity and lowered plasma lipid concentrations, probably by activation of AMP kinase.

8.7 Gastro-intestinal effect

Pre-administration of naringenin significantly reduced the severity of colitis and resulted in down-regulation of proinflammatory 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- κ B p65 protein was significantly decreased, which correlated with a similar decrease in phospho-I κ B α protein. Consistent with the in vivo results, naringenin exposure blocked lipopolysaccharide-stimulated nuclear translocation of NF- κ B p65 in mouse macrophage RAW264.7 cells. In addition, in vitro NF- κ B reporter assays performed on human colonic HT-29 cells exposed to naringenin demonstrated a significant inhibition of TNF- α -induced NF- κ B luciferase expression [45].

8.8 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 naringenin's antitumor activity may be due to targeting of NKG2D ligand expression and suggests a possible immunotherapeutic role for cancer treatment [46].

9. Pharmacokinetics

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 [47-51] and plasma [47, 48] following oral doses of pure naringin [47, 49] or grapefruit juice [47-51]. The excretion of naringenin

glucuronides in humans reaches levels more than 100-fold higher than the concentration of naringenin excreted in the urine. 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 [47, 48] and has not been reported [48]. 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.

10. Summary

Naringenin is a naturally occurring flavanone (flavonoid) known to have a bioactive effect on human health. This phytochemical is the predominant flavanone in citrus fruits such as grapefruits, oranges, and tomatoes [54]. Naringenin possesses various biological activities such as antidiabetic [55], antiatherogenic [57], antidepressant [57], immunomodulatory [56], antitumor [58], anti-inflammatory [59], DNA protective [55], hypolipidaemic [60], antioxidant [59], peroxisome proliferator-activated receptors (PPARs) activator [56], and memory improving. Naringenin was found to decrease oxidative stress in rats by depleting elevated lipid peroxide and nitric oxide and elevating reduced glutathione levels. Cholinergic function was improved by Naringenin through the inhibition of elevated cholinesterase (CHE) activity, suggesting that it acted as an antioxidant and CHE inhibitor against type-2 diabetes-induced memory dysfunction [54]. Besides, it was shown that when administered to mice at 4.5 mg/kg, Naringenin significantly ameliorated scopolamine-induced amnesia strengthen its role as chemopreventive agent against Alzheimer disease [59]. It was also found that rats pretreated with Naringenin showed a clear protection of the number of tyrosine hydroxylase (TH)-positive cells in the substantia nigra and dopamine levels in the striata suggesting the ability of this compound to exhibit neuroprotection in the 6-hydroxydopamine model of Parkinson disease may be *via* its antioxidant capabilities and capability to penetrate into the brain [57]. Naringenin reduced the extent of cisplatin-induced nephrotoxicity, as evidenced by significant reduction in serum urea and creatinine concentrations, decreased polyuria, reduction in body weight loss, marked reduction in urinary fractional sodium excretion and glutathione *S*-transferase activity, and increased creatinine clearance. Naringenin also has a protective role in the abatement of doxorubicin-induced cardiac toxicity that resides, at least in part, on its antiradical effects and regulatory role on NO production [61].

11. Conclusion

Prevention and cure of diseases using phytochemicals especially flavonoids are well known. Fruits and vegetables are natural sources of flavonoids. Variety of flavonoids found in the nature possesses their own physical, chemical, and physiological properties. Structure function relationship of flavonoids is epitome of major biological activities [59]. The biological properties of dietary flavonoids and their analogues have been indicated to be due to multiple mechanisms of actions including free radical scavenging, activation of survival genes and signaling pathways, transition metal ion chelation, regulation of mitochondrial function and bioenergetics, modulation of inflammation response, and even

interactions with micro biota. Nevertheless, activity of flavonoids are not limited to their health promoting benefits but spread to a wide range of ecological interactions of plants, such as acting as a signal and defense molecule [62]. Medicinal efficacy of many flavonoids as antibacterial, hepatoprotective, anti-inflammatory, anticancer, and antiviral agents is well established. Therapeutic use of new compounds must be validated using specific biochemical tests. With the use of genetic modifications, it is now possible to produce flavonoids at large scale [59]. Their applications in industry are beyond the limit of nutraceuticals and drug candidate molecules. The heterogeneous biological activities of flavonoid compounds and its derivatives depend on their structural diversity [62]. In epidemiology, serum biomarkers, in addition to dietary intake data, could be used when studying the associations between flavonoids and risk of diseases. Most importantly, clinical studies on the health effects of both high and low doses of flavonoids are warranted. In these studies, bioavailability should be monitored, because marked interindividual variation could confound the results. Finally, it is emphasized that any bioactive compound could, at least in theory, also possess adverse effects or exhibit different effects at varying doses [26]. Further achievements will provide newer insights and will certainly lead to a new era of flavonoid based pharmaceutical agents for the treatment of many infectious and degenerative diseases [59]. This should be kept in mind when planning long-term human studies.

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