Review Article

Naringenin and its Beneficial Effect in Human Health

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Chettinad Health City Medical Journal 2021; 10(1): 38 - 41

DOI: https://doi.org/10.36503/chcmj10(1)-06

Abstract

Polyphenols are compounds naturally found in many fruits and vegetables which have been known to exert many health benefits. Among the different types of polyphenols, naringenin is an important polyphenol which has been evidenced to have many health benefits in diseases like cancer, obesity, cardiovascular diseases, diabetes etc. Naringin is the glycosidic form of naringenin which is also useful to protect us from some diseases. The different category of polyphenols and some of the health benefits of naringenin and naringin is discussed in this article.

Introduction

Polyphenols are a huge group of ubiquitous and different molecules which are present in almost every vascular plants and a range of marine organisms as secondary metabolites. The structure of polyphenols range from most simple up to complex frameworks constituted of benzene cycles. Polyphenols are known to have important role in combating pathogenic diseases, growth promotion, reproduction etc. Among the polyphenols, phytochemicals are responsible for the color of the plants as well as contribute to their organoleptic characteristics.[1]

Classification of polyphenols

The different classes of polyphenols are as follows:[2]

(i) Tannins
(ii) Coumarins
(iii) Stilbenes
(iv) Flavonoids

Among these polyphenols, flavonoids are classified further into the subgroups given below:[3]

(i) Flavones
(ii) Chalcones
(iii) Flavanones
(iv) Isoflavones
(v) Flavonols
(vi) Flavanols and proanthocyanidin
(vii) Anthocyanidins

All these flavonoids have very low solubility in water and low bioavailability. The above subgroups also have further subgroups which are given in Fig 1, Fig 2 and Fig 3.

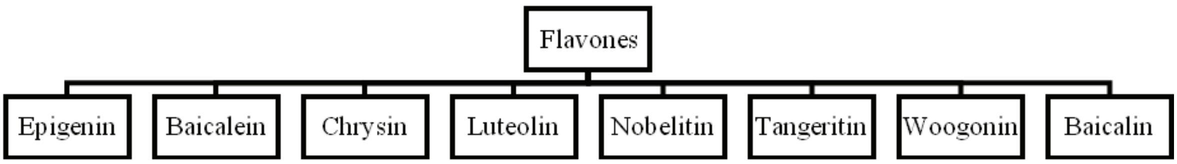

Figure 1: The different subgroups of flavones

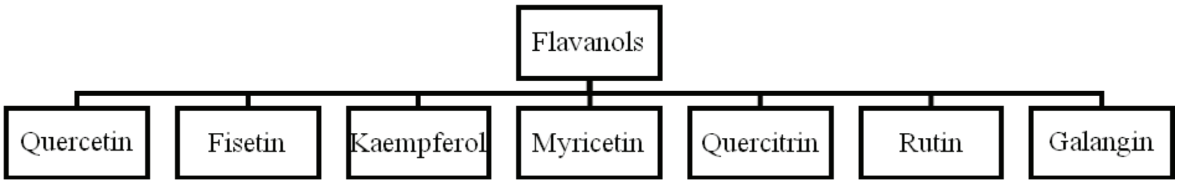

Figure 2: The different subgroups of flavanols

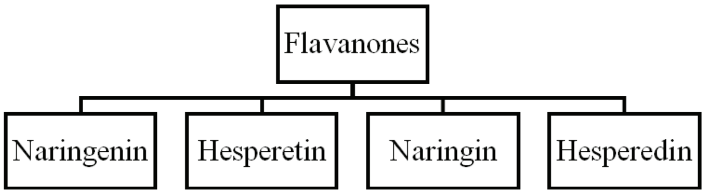

Figure 2: The different subgroups of flavanones

Bioavailability of different polyphenols

The previous 97 studies have established that bioavailability varies greatly from one polyphenol to another. The available polyphenols in our diet may not be essentially present at the maximum concentrations of the active metabolites in the target tissues. Average values for the maximal plasma concentration, the time it takes to reach the maximum of plasma concentration, the area under the curve of plasma concentration versus time graph, the excretion half-life, and the relative excretion of polyphenols in urine were computed for major polyphenols. The researchers also investigated the kinetics and extent of absorption of polyphenol in adults, after oral administration of a single dose of pure polyphenol provided, extracts from plant, or whole food/beverage. The blood metabolites, resulting from digestion of food and hepatic activity, usually vary from the native compounds. The plasma concentrations of total metabolites ranged proportionately after ingestion of a glycone, and the variable urinary excretion varied mostly depending on the ingested dose and also the polyphenol. The mostly absorbed polyphenols are Gallic acid and isoflavones.4Catechins, flavanones, and quercetin glucosides, are also absorbed with different kinetics. The least absorbed polyphenols are proanthocyanidins, the galloylated tea catechins, and the anthocyanins. The statistical data shows that they are finite for assessing the absorption rate of hydroxycinnamic acids and other polyphenols. These data can be helpful for designing, interpretation of intervention studies and examination of the health benefits of polyphenols.[4]

Naringenin

The chemical name of Naringenin is 2,3-dihydro-5,7-dihydroxy-2-(4-hydroxyphenyl)-4H-1-benzopyran-4-one having a molecular weight of 272.26 with formula $C_{15}H_{12}O_5$. It is very important flavonoid which occurs naturally and is found predominantly in citrus fruits and tomatoes, some types of figs (Smyrna-type) Ficuscarica.[5-9] The health effects of naringenin is been shown widely with a reduction of lipid peroxidation biomarkers, reduction in protein carbonylation, increasing metabolism of carbohydrates, enhanced antioxidant defense, reactive oxygen species (ROS) scavengers, has anti-atherogenic effect, it can modulate the immune system and also has anti-inflammatory effects.[5,10] The fatty acid metabolism signaling pathways are also modulated by naringenin which can perturb the lipid accumulation in the liver and impair the plasma lipids.[10] Some of the beneficial effects of naringenin and its glycosidic form naringin in human health is discussed below.

Inhibition of TNF-α induced Vascular Smooth Muscle Cell (VSMC) proliferation

A study by Siyu Chenet al., reported that Vascular Smooth Muscle Cell (VSMC) proliferation and migration that is generated by different inflammatory stimuli plays a significant role in atherosclerosis as well as restenosis. As we know that naringenin is a citrus flavonoid having both lipid-reducing and similar properties like insulin. In this study, they examined whether naringenin influences TNF-α -induced VSMC proliferation and migration. In that case to find out how and whether Heme Oxygenase-1 (HO-1) was involved or not, rat VSMCs were treated with naringenin alone or in consolidation with TNF-α stimulation. It was established that naringenin could induce HO-1 at mRNA and protein levels, in VSMCs also. Naringenin attenuated the level of TNF-α in a dose dependent fashion which was induced by VSMC proliferation and their migration. Naringenin blocked the ERK/MAPK and Akt phosphorylation, however p38 MAPK and JNK pathways remained unchanged. Naringenin also blocked the rise of ROS generation which was induced by TNF-α. Particularly, the specific HO-1 inhibitor ZnP P IX or HO-1 siRNA partially eradicated the useful effects of Naringenin on VSMCs. The results offered that naringenin may play a vital role as a new drug in the treatment of these kind of pathologies by inducing HO-1 expression. Hence it will decrease VSMC proliferation as well as migration.[11]

Naringin could induce anti-atherosclerotic effect

A study by Tun-Pin Hsueh et al., showed that naringin, a glycosidic form of naringenin has an anti-atherosclerotic effect but the basic mechanism was not described vividly. Their study aimed to assess the effect of naringin on the TNF α-induced expressions of cell adhesion molecules (CAMs), chemokines and NF-KB signaling pathway in Human Umbilical Vein Endothelial Cells (HUVEC). The results showed that naringin, at sub lethal concentrations could constrain the adhesion of THP-1 monocytes to the TNF-α stimulated HUVECs in a dose dependent manner. The TNF α-could induce the expressions of different CAMs, including VCAM-1, ICAM-1 and E- selectin , at the level of both mRNA and protein. These levels were suppressed by naringin significantly in a dose dependent way. Moreover, the TNF α induced mRNA as well as protein levels of chemokines, including Fractalkine /CX3CL1, MCP-1 and RANTES, were eventually decreased to some extent by naringin. Most notably naringin subdued the translocation of NF-KB induced by TNF-α. This resulted from the inhibition of phosphorylation of IKKα/β, IKB-α and NFKB. Briefly, the study proposed that naringin regulated TNF α induced expressions of CAMs and chemokines, mediated by the inhibition of TNF α-induced activation of IKK/NF-KB signaling pathway. These data supported that naringin had an anti-atherosclerotic effect.[12]

Naringenin can inhibit Adipogenesis and decreases Insulin Sensitivity

Naringenin is one of the most abundant citrus flavonoids found in citrus foods and mainly exist in its glycosidic form naringin. It has been reported that naringenin has many therapeutic potential.[5] Allison J. Richard et al., studied the relationship between obesity and the metabolic syndrome. When the adipose tissues are incapable of increasing their lipid storage at obese state, the condition leads to metabolic dysfunction. After screening 425 botanicals, naringenin was found to inhibit adipocyte differentiation and also have hyperlipidemic capacity. The effect of naringenin in liver cell line showed that it can curb adipogenesis in a dose dependent manner and debilitates mature fat cell action. It inhibited the adipocyte marker protein expression which was responsible for lipid accumulation. Naringenin reduced the capacity of insulin to induce IRS-1 tyrosine phosphorylation in mature 3T3-L1 adipocytes. Consequently it inhibited insulin-stimulated uptake of glucose in a dose-dependent manner over a longer time frame. Naringenin exposure to mature murine and human adipocytes hindered Adiponectin protein expression. This study has revealed that naringenin can have an unfavourable impact on diseases related to adipocyte by narrowing differentiation of pre adipocytes and significantly inducing insulin resistance. Similar action was also noted by diminishing expression of adiponectin in mature fat cells.[13]

Naringenin can exhibit antiproliferative activity in Human Epidermoid Carcinoma Cells

Md. Sultan Ahmed et al., explored the antiproliferative agents which reduce skin carcinoma. The anti-proliferative activity was studied using MTT assay as well as the apoptotic activities of naringenin was studied using apoptotic hallmarks like DNA fragmentation, nuclear condensation, cell cycle kinetics, change in mitochondrial membrane potential, and caspase-3 as biomarkers. They also investigated the capability of naringenin to activate ROS, which in turn initiates the apoptotic cascade using human epidermoid carcinoma A431 cells. The results showed that naringenin exposure could reduce the viability of A431 cells significantly and the reason for cell death was apoptosis as evidenced by enhancement of nuclear condensation, mitochondrial depolarization, increment in caspase 3 activity and fragmentation of DNA in a dose dependent manner. The intracellular ROS production also increased after exposure to naringenin in a dose-dependent fashion. Cell cycle study showed that naringenin could induce cell cycle arrest in G0/G1 phase. The outcome of this study assured that naringenin can lead to cell death in epidermoid carcinoma cells by generating ROS, apoptotic induction by mitochondrial depolarization, caspase 3 elevation, nuclear condensation, DNA fragmentation and G0/G1 phase cell cycle arrest.[14]

Conclusion

Phytochemicals are the most abundantly found and safe supplement from our diet and aims to show the future pathways of alternative medicine because of their profound protective properties towards many kinds of diseased conditions. A small discussion is being made in this manuscript about some of the beneficial effects of naringenin and naringin. Many more studies are being done to support the efficacy of these molecules towards preventing or partially curing certain human diseases. Combinational therapies with different phytochemicals along with traditional treatment has also been developed recently. Although the poor solubility and bioavailability of phytochemicals creates a small hindrance in their applications many nano formulations, nano encapsulations are enumerated for better solubility as well as bioavailability. Thus, the future research is awaited to explore the possible applications of combinational therapies and enhanced applicability of phytochemicals.

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