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Review Article

"Pharmacological Activities of Naringenin and its Analogs: A Review"

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ABSTRACT

Phytochemicals are the compounds produced from the plants with different pharmacological actions. The primary groups of phytochemicals are flavonoids that are responsible for the different types of colors in plants parts and different pharmacological activities in humans. The different classes of flavonoids include flavanols, flavones, flavanones, and isoflavones. Naringenin is one of the most promising flavonoids that show a vast range of biological activities such as anticancer, anti-inflammatory, anti-allergic, antibacterial, and antiosteoporosis. This review emphasizes the role of naringenin that is useful in treating various chronic diseases.

Key words: Phytochemical, Flavonoids, Naringenin, Pharmacological activities.

1. INTRODUCTION

Many of the known and available drugs have been derived from plant sources. More than 121 active phytoconstituents derived from plants have been contributed to the drug discovery for different disorders so far [1]. It has been shown in epidemiological studies that diet rich in fruits and vegetables help the body to maintain its weight and provide protection against chronic illness [2].

Phytochemicals, being compounds produced from plants, primarily from the class of alkaloids, glycosides, polyphenols, and terpenes [3] that have a lot of promise as medicines, and they are being shown to have many different pharmacological actions. Antibacterial [4], antiasthma, anticancer [1], anti-Alzheimer, anti-inflammatory [5] antiarrhythmic, analgesic, and anti-hyperglycemic [2] actions are only a few of the pharmacological properties of phytochemicals.

Flavonoids are phytochemicals generated from plants that are responsible for the various hues of plant parts, such as in flowers different shades of yellow, orange, and red. Flavonoids such as flavanols, flavones, flavanols, flavanonols, flavanones, and isoflavones have been found in edible plants and are taken in the human diet daily [6]. Flavonoids, which are present in fruits and vegetables, provide some health advantages that include the reduction of some cancers such as breast, colon, lung, prostate, and pancreatic [7]. Some flavonoid compounds are also involved in cell cycle arrest, which ends up in blocking proliferation and inducing apoptosis of cancer cells. Through interaction with metabolic enzymes, flavonoids compounds can prevent oncogene activation, for example, inhibition of cytochrome P450 enzymes, such as CYP1A1 and CYP1A2 [7,8].

Flavonoids are oxygenated heterocycles made up of two aromatic rings connected by three carbon atoms [6]. Different types of flavonoid compounds result from variations in the fundamental structure of flavonoids (Figure 1). Flavonoids are a class of polyphenolic chemicals with a common benzo-pyrone structure that is widely dispersed [1].

The main sources of flavonoids are soybean (isoflavones), citrus (flavanones), tea, apple and cocoa (flavanols), celery (flavones), onions (flavanols), and berries (anthocyanins) [1].

2. NARINGENIN

Naringenin and hesperidin are the two common naturally occurring flavonoids, found in the form of aglycons and glycosides. Naringenin is a potent phenolic compound found in citrus fruits (Figure 2), most abundant in grapefruit (highest-43.5mg/100ml), and orange (2.13mg/100ml) (Figure 3) [2] are used in cosmetics, perfumes, and different medicinal drugs [1].

The pharmacological activities of naringenin has been reported for hypocholesterolemia, anti-estrogenic, anti-inflammatory, antihypertensive, anti-diabetic, anticancer, antimicrobial, and anti-inflammatory activities have been summarized (Figure 4) [1,2,10].

In recent studies, it is also found that naringenin appears as a powerful inhibitor of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. It also showed a strong antiviral against SARS-CoV-2 [11].

Naringenin has three hydroxyl groups in it. The 2-(4-hydroxy phenyl)- and 7-hydroxy groups can be easily modified; however, the 5-hydroxy group forms a hydrogen connection (H-bond) with the ketone at C-4, making it a little less approachable. Treatment of cancer cell lines with flavanones derivatives, such as the breast cancer cell line (MCF7), has shown different biological activities depending on the modifications at 2-(4-hydroxy phenyl)- and 7-hydroxy groups [12].

3. NARINGENIN ANALOGOUS ACTIVITY

3.1. Antioxidant Activity

Individual phenolic compound interactions, including naringenin interactions with others, were investigated for their antioxidant

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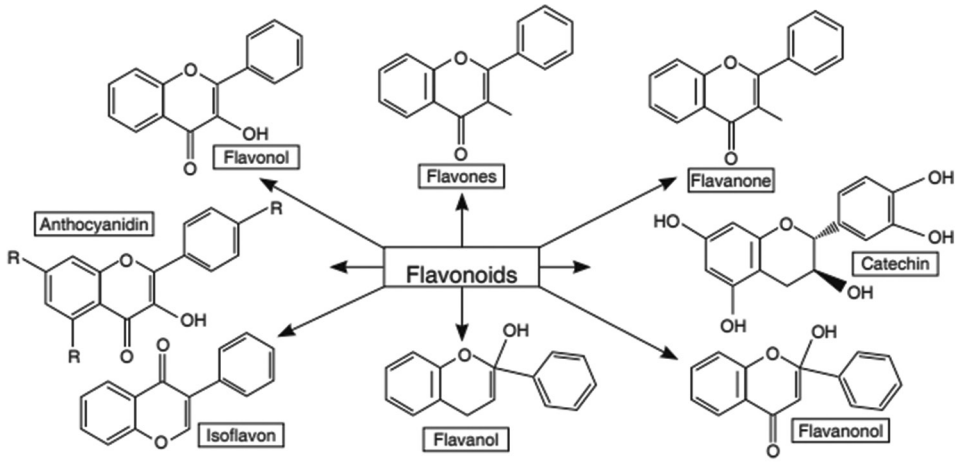


Figure 1: Chemical structures of different flavonoids [1].

Figure 2: Courtesy: Roberto Cannatar [9].

Dietary Sources	Phenol- Explorer mg/100 g–mg/100 ml	USDA mg/100 g–mg/100 ml
Rosemary	55.1	24.76
Grapefruit Juice	37.76	32.64
Red Wine	0.75	1.77
Orange Juice	0.07	1.63

Figure 3: Different concentration of naringenin in dietary sources [9].

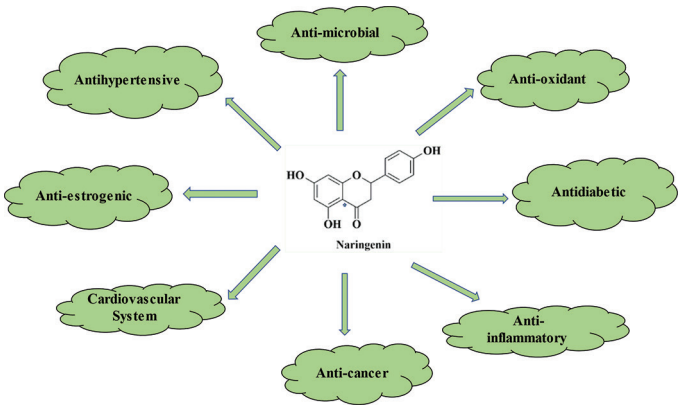


Figure 4: Pharmacological activities of naringenin.

ability to determine if they were antagonistic, additive, or synergistic. As a consequence of the findings, it was discovered that certain combinations had a synergistic impact when compared to the individual components. Several flavonoids, including naringenin, were tested *in vitro* for their ability to protect human plasma proteins against ONOO (-) or hemoglobin/$NaNO_2$/H_2O_2-mediated nitrative/oxidative damage. These flavonoids reduced ONOO (-)-induced protein oxidation dose-dependently, but had no impact on hemoglobin/$NaNO_2$/H_2O_2-triggered protein oxidation, suggesting that they may contribute to their protective action in part by blocking protein nitration [1].

3.2. Anti-diabetic Activity

Murine 3T3-L1 adipocytes and isolated mature human adipocytes were used in this study to determine the interaction of various flavonoids, including naringenin, with glucose absorption both in the baseline state and following insulin stimulation. According to the findings, naringenin increased glucose transfer from plasma to cells, which may be advantageous to diabetes patients [1,5].

3.3. In Neurodegenerative Disease

Naringenin is an anticholinesterase that helps diabetics with memory problems. Due to cholinergic neurotransmission loss, dementia patients in Parkinson disease and Alzheimer's disease typically show severe cholinergic abnormalities. Naringenin has been tried to treat both illnesses as a possible neuroprotective drug. Pre-treatment with naringenin may reduce neuronal damage and cognitive deficits caused by intracerebroventricular-streptozotocin, according to other research [5].

3.4. Anticancer Activity

A derivative of naringenin is proven to be effective in different cell lines of breasts, colon, stomach and uterus [5]. In the tested cells, upregulation of Fas/FasL expression, activation of caspase cascades, and inhibition of phosphoinositide 3-kinase (PI3K)/protein kinase B survival signaling pathways were found to induce apoptosis through upregulation of Fas/FasL expression, activation of caspase cascades, and inhibition of PI3K (48). The anticancer effect of naringenin was studied in a breast cancer resection model (metastases). The findings revealed that naringenin, when taken orally, inhibited the spread of metastases following surgery through modulating host immunity [1,13].

3.5. Anti-inflammatory Action

Regarding the systemic and cytokine storm during severe COVID-19 [14], naringenin can enhance lysosome-dependent cytokine

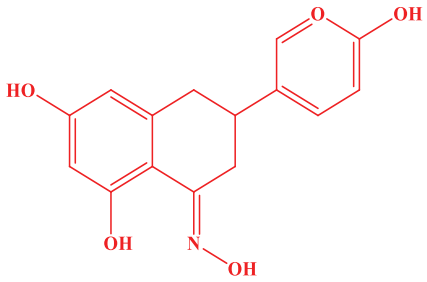
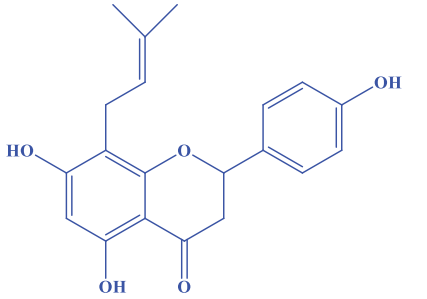
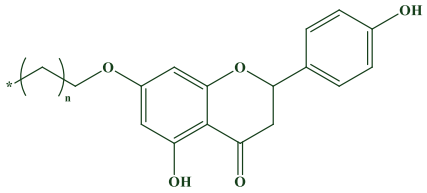
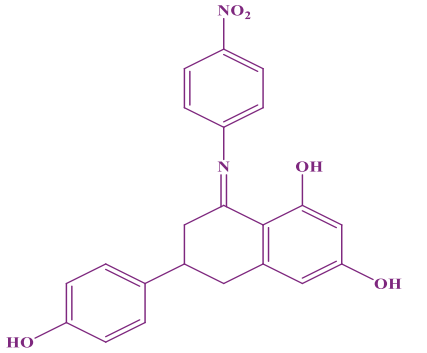
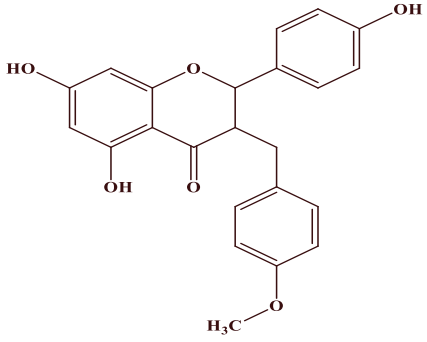
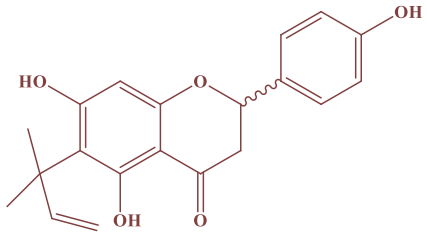
Derivatives of naringenin	Biological activity
	Anti-oxidant
	Anti-tumor
	Anti-proliferative Anti-ZIKA
	Antimicrobial
	Anti-cancer
	Anti-androgenic

Figure 5: Biologically active compounds of naringenin [4,16-19].

protein degradation, which may be significant in COVID-19 [15]. Naringenin-induced immunomodulation has been seen in patients with inflammatory airway diseases. Treatment with naringenin decreased airway hyperactivity and inflammation in a mouse asthma model, with the lower levels of Interleukin (IL-4) and IL-13 in bronchoalveolar lavage and serum IgE levels, as well as improved lung function. Furthermore, naringenin therapy decreased pulmonary eosinophilia to levels comparable to the non-asthmatic group [16].

3.6. Effect of Naringenin in the Cardiovascular System

By modulating the reactive oxygen species levels, mitochondrial potassium channels, and the estrogen-associated pathway, naringenin has a high rate of protective effect on the cell against damage caused due to ageing [15]. It also can improve the lipoprotein profile and increase cholesterol efflux [14]. In *in vitro* studies, it is proved that anti-fibrotic capacity of naringenin inhibited the proliferation of cardiac fibroblasts stimulated with transforming growth factor-β1 [15].

Some biologically active analogues of naringenin with their activities are tabulated below (Figure 5).

4. CONCLUSION

This review emphasizes the information about naringenin proves to be the most promising agent in developing drugs in the treatment of different pharmacological activities such as antiviral, antioxidant, anti-inflammatory, anti-proliferative, anti-diabetic, and anti-estrogenic activity. It also showed favorable effects against COVID-19. It was also shown that naringenin had beneficial benefits in oxidative stress diseases, both *in vivo* and *in vitro* experiments. For the overall health benefits of naringenin, including its usage as a nutraceutical and dietary supplement, further study and analysis are required. Because there is so little evidence on its safety and optimal dose level, additional research should also be done to evaluate the safety profile before it is used in humans.

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