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**University of Basrah College
of pharmacy**



Department of pharmaCognosy

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**The use of hesperidin supplements in flu, hay fever,
COVID-19 and other viral conditions.**

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4 BENEFITS OF HESPERIDIN

 <p>Prevents Bruising</p> <p>Hesperidin is one of the two most active bioflavonoids in citrus fruits, which, in combination with vitamin C, maintain the thin walls of small capillary blood vessels, preventing bruising and bleeding and can mitigate excessive menstrual bleeding. Hesperidin is also common in the treatment of athletic injuries for bruising and swelling.</p>	 <p>May Combat Heart Disease, Cancer</p> <p>Hesperidin may assist in protecting the body from circulatory issues, heart disease and cancer. Studies have shown that bioflavonoids can be helpful in treating blood clotting disorders. They can also assist in preventing cellular damage caused by free radicals — unstable molecules that form when the body burns oxygen. Hesperidin also facilitates vitamin C complex formation in support of healthy immune function.</p>	 <p>Stabilizes Blood Pressure</p> <p>Various randomized trials have shown the beneficial effects of hesperidin, mainly resulting from anti-inflammatory and anti-atherogenic actions. A 2004 study in the Journal of Nutrition found that hesperidin, in combination with the compound naringin, is a potential aid to blood pressure stabilization (x). Hesperidin may potentially have chemoprotective properties, however there is no proof currently that it is able to prevent cancer.</p>	 <p>Healthy Skin</p> <p>Hesperidin is also being incorporated into skin health regimens due to its vasoprotective (blood-vessel protecting) qualities. While previously popularized skin care and anti-aging products were focused on plumping or reducing wrinkles, another factor of youthful and healthy skin appearance is related to even skin tone.</p>
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Abstract

There has been increasing interest in the research on flavonoids from plant sources because of their versatile health benefits reported in various epidemiological studies. Since flavonoids are directly associated with human dietary ingredients and health, there is need to evaluate structure and function relationship. The bioavailability, metabolism, and biological activity of flavonoids depend upon the configuration, total number of hydroxyl groups, and substitution of functional groups about their nuclear structure. Fruits and vegetables are the main dietary sources of flavonoids for humans, along with tea and wine. Most recent researches have focused on the health aspects of flavonoids for humans. Many flavonoids are shown to have antioxidative activity, free radical scavenging capacity, coronary heart disease prevention, hepatoprotective, anti-inflammatory, and anticancer activities, while some flavonoids exhibit potential antiviral activities. In plant systems, flavonoids help in combating oxidative stress and act as growth regulators. For pharmaceutical purposes cost-effective bulk production of different types of flavonoids has been made possible with the help of microbial biotechnology. This review highlights the structural features of flavonoids, their beneficial roles in human health, and significance in plants as well as their microbial production. Hesperidin is a plant chemical that is classified as a “ bioflavonoid ” . It is found primarily in citrus fruits. Hesperidin alone, or in combination with other citrus bioflavonoids(Diosmin , for example), is most often used for blood vessel conditions such as hemorrhoids, various vein, and poor circulation (venous stasis). It is also used to treat lymphedema, a condition involving fluid. Hesperidin is a flavone-on glycoside found in citrus fruits. Its aglycone form is called hesperetin. Its name is derived from the word "hesperidium", for fruit produced by citrus trees. It was first isolated in 1828 by French chemist Lebreton from the white inner layer of citrus peels (mesocarp, albedo). It is Hesperidin is believed to play a role in plant defense. Hesperidin is a naturally occurring bioflavonoid, a compound in plants with antioxidant properties. Bioflavonoids also provide the color, flavor and aroma to plants. While hesperidin and other similar bioflavonoids are commonly referred to as vitamin P, they are not actual vitamins. Hesperidin does not naturally occur in the body; you can only get it through foods or synthetic supplements.

Introduction:

Flavonoids are a group of more than 10,000 polyphenolic compounds that are found in foods of plant origin. Broadly they can be divided into six major classes, namely, flavanones, anthocyanidins, flavan-3-ols, flavonols, isoflavones, and flavones. The growing evidence of the versatile health benefits of flavonoids including cancer prevention has generated a tremendous interest in the research related to dietary sources of flavonoids[1,2,3]...Flavonoids are a group of plant metabolites thought to provide health benefits through cell signalling pathways and antioxidant effects. These molecules are found in a variety of fruits and vegetables.

Food sources

Flavonoids are the most common and widely distributed group of plant phenolic compounds, occurring virtually in all plant parts, particularly the photosynthesising plant cells. They are a major coloring component of flowering plants. Almost all fruits, vegetables and herbs contain a certain amount of flavonoids. They can also be found in other food sources including dry beans, grains, red

wine and green and black teas. The general rule is that the more colorful a food item is, the richer it will be in flavonoids. Oranges, however are an exception to the rule because the flavonoids contained in this fruit are mainly found in the white and pulp interior of the skin. The best way to ensure a good intake of flavonoids is to consume plenty of fresh fruit and vegetables on a daily basis. Experts advise eating five servings of vegetables and four of fruit. Regarding the intake of red wine, men are advised not to drink more than two glasses per day and women should not drink more than one glass per day. Flavonoid supplements are also available, but people who buy these should note that experts have not confirmed what the ideal flavonoid intake is and an excess intake may even be harmful. Flavonoids are an integral part of human and animal diet. Some food sources containing different classes of flavonoids, flavonoids cannot be synthesized by humans and animals [4]. Thus flavonoids found in animals are of plant origin rather than being biosynthesized in situ. Flavonols are the most abundant flavonoids in foods. Flavonoids in food are generally responsible for colour, taste, prevention of fat oxidation, and protection of vitamins and enzymes [5]. Flavonoids found in the highest amounts in the human diet include the soy isoflavones, flavonols, and the flavones. Although most fruits and some legumes contain catechins, the levels vary from 4.5 to 610 mg/kg [6]. Preparation and processing of food may decrease flavonoid levels depending on the methods used. For example, in a recent study, orange juices were found to contain 81–200 mg/L soluble flavanone, while the content in the cloud was 206 – 644 mg/L which suggest that the flavanone are concentrated in the cloud during processing and storage. Flavonoids are abundant in plants, in which they perform several functions. They are essential pigments for producing the colors needed to attract pollinating insects. In higher order plants, flavonoids are also required for UV filtration, nitrogen fixation, cell cycle inhibition, and as chemical messengers. Flavonoids secreted by a plant's roots aid the symbiotic relationship between rhizobia and certain vegetables such as peas, clover and beans. The rhizobia present in soil produce Nod factors in response to the presence of flavonoids. These Nod factors are then recognized by the plant, which induces certain responses such as ion fluxes and root nodule formation. Some flavonoids also inhibit certain spores to protect against certain plant diseases. Flavonoids are ubiquitous in plants and are the most common type of polyphenolic compound found in the human diet. The abundance of flavonoids coupled with their low toxicity relative to other plant compounds means they can be ingested in large quantities by animals, including humans. Examples of foods that are rich in flavonoids include onions, parsley, blueberries, bananas, dark chocolate and red wine .

Hesperidin :

is a flavonoid found in the rinds of citrus fruits. Flavonoids are a type of polyphenol, which are antioxidants found in plants and are essential to human health. Hesperidin is one of the flavonoids that give citrus fruits their color and taste. It is also sold as a health supplement to repair and prevent damage from cardiovascular degeneration and disease. Hesperidin is also referred to by names like bioflavonoid, citrus bioflavonoid, and hesperin methyl-chalcone. It is often present in multi-vitamins, though it can also be found as a pure extract. It is so abundant in citrus fruits that it is an inexpensive by-product of citrus production, and adequate amounts of the flavonoid can usually be obtained by eating citrus fruits and drinking citrus juices with pulp. Flavonoids like hesperidin used to be called “vitamin P.” This term is now obsolete, but flavonoids and vitamins are essential to each other. Hesperidin is most commonly found in foods that are high in vitamin C, and it is an essential component in vitamin C absorption. Vitamin C actually consists of a chain of

molecules, so flavonoids complete the chain and make the vitamin more soluble for easy absorption into the body. People with vitamin absorption disorders, such as those with elevated levels of copper in the blood, often benefit from taking hesperidin supplements along with extra Vitamin C. In addition to its antioxidant properties, hesperidin can also be used as an anti-inflammatory and anti-carcinogenic compound. It seems to reduce the symptoms of allergies and hay fever by inhibiting histamine production in the blood, and early clinical trials with female mice showed that this antioxidant decreased the bone loss associated with aging. In clinical tests, hesperidin taken as a supplement has shown promising results in increasing the strength and elasticity of vascular walls. It can also reduce or slow vascular degeneration associated with liver disease, aging, and lack of exercise. Hesperidin increases blood flow and helps reduce problems associated with vascular swelling such as hemorrhoids and varicose veins. Like other polyphenols, such as the compounds found in olive oil, hesperidin can be used to reduce cholesterol levels in the blood. It is safe for most people to take hesperidin supplements. Some people, especially those who are allergic to citrus fruits, might have a reaction to the compound. Pregnant women, nursing mothers, and people taking blood thinners should not use hesperidin supplements without professional guidance.

Health Benefits of Hesperidin:

1- anti oxidant : The ability to scavenge free radicals is essential and beneficial for human health, since excess of free radicals leads to oxidative stress that adversely affects cell structure and function. Oxidative stress triggers inflammation, which further potentiates oxidative stress in a vicious cycle, triggering various life threatening diseases ranging from cardiovascular and neurodegenerative disorders to diabetes and cancer. Hesperidin not only scavenges free radicals but can also stimulate the endogenous antioxidant defense mechanisms. These mechanisms include enhanced activity and production of cellular antioxidant enzymes such as superoxide dismutase (SOD), heme oxygenase-1 (HO-1), catalase, etc., and elevation of the predominant cellular antioxidant called glutathione [7] Hence, hesperidin provides valuable support in conditions associated with oxidative stress and provides protection against stress inducing treatments such as chemotherapy and radiation therapy.

2-Inflammation: Often oxidative stress in the body is accompanied by systemic inflammation characteristic of many chronic conditions. Numerous studies indicate that hesperidin and hesperetin are able to reduce various pathologically elevated inflammatory markers [8]. This inhibitory effect has been predominantly associated with their antioxidant activity and ability to inactivate the pro-inflammatory cascade initiated by free radicals. These compounds were also effective in decreasing the synthesis of pro-inflammatory cytokines e.g. tumor necrosis factor - alpha (TNF- α) as well as pro-inflammatory enzymes such as inducible nitric oxide synthase (iNOS, that yields nitric oxide - NO).

3-- rheumatoid arthritis. One of the conditions associated with elevated inflammatory response is **rheumatoid arthritis**. Though this autoimmune disorder mainly affects joints, other organs such as lung and heart may also be affected which often results in death. The anti-inflammatory properties of hesperidin have been confirmed in animal model of rheumatoid arthritis and also in

clinical trials in patients suffering from this disease [9].

4-Cardiovascular health: Hesperidin is a well-known cardiovascular protective and strengthening agent. It demonstrates several benefits to the cardiovascular system due to its ability to affect various cellular mechanisms. For instance, due to its anti-oxidant properties hesperidin can prevent LDL oxidation and protect the cell membrane of erythrocytes (red blood cells) from oxidative damage[10]. It also acts as an inhibitor of two main enzymes in cholesterol metabolism – HMGCoA reductase and ACAT that regulate total (so called “bad” cholesterol ”) and “ good cholesterol ” (HDL) levels. .

5-High Blood Pressure: Another health benefit of hesperidin has been associated with its antihypertensive effect. It is believed that hesperidin is responsible for blood pressure lowering effect of orange juice since it promotes nitric oxide production resulting in vasodilation (widening of blood vessels) [11] Moreover, hesperidin can enhance relaxation of the endothelial cells (cells of the inner blood vessel wall) induced by acetylcholine (a neurotransmitter) and can inhibit secretion of endothelium-derived vasoconstricting factor endothelin-1 (ET-1) [12]. All aforementioned mechanisms aid in blood pressure normalization.

6-Blood viscosity: In addition, hesperidin exerts anti-platelet activity. Both in vitro and in vivo studies have shown the efficacy of hesperidin in suppression of platelet aggregation induced by different stimuli (e.g. collagen, arachidonic acid, thrombin)[7].

7-Nervous system: Several studies have linked the lower intake of some flavonoids including hesperidin to dementia, Parkinson's and Alzheimer's diseases[13]. Hesperidin and hesperetin have also demonstrated the ability to cross the blood-brain barrier making them ideal candidates in the natural treatment of different central nervous system disorders The neuroprotective effect of hesperidin has been widely studied in the last decade and mainly attributed to its antioxidant and anti- inflammatory properties as seen by an increased level of antioxidant enzymes, decreased level of oxidative stress, inflammatory markers, and pro-apoptotic proteins in neurons.[14]...

8--Diabetes: Impaired glucose metabolism and diabetes type 2 often leads to severe complications such as neuropathy and cardiovascular diseases. Animal studies demonstrate that hesperidin can normalize glucose metabolism by influencing enzymes regulating glucose metabolism and reducing lipid levels in the blood and liver. This was confirmed in a human study in 36 female patients with type 2 diabetes[15]. Dietary supplementation with Daflon (hesperidin containing supplement) for 45 days resulted in a significant reduction in blood glucose levels accompanied by a decrease in total and LDL cholesterol, triglycerides, oxidative stress, and inflammation.

9-Cancer: A number of studies have been conducted to elucidate the anticancer effects of hesperidin and its aglycone hesperetin. Unlike conventional chemotherapeutics these flavonoids can inhibit tumor growth by targeting multiple cellular processes at the same time[16].through prevent growth step of tumor cancer such as use for breast cancer through protecting against oxidative stress and inhibiting cell proliferation ...[17]

10-Infections: Hesperidin in citrus fruits acts mainly as an antifungal agent, however, research studies support its efficacy also against viral and bacterial infections[18].... One study examined the antibacterial and antifungal activity of ethanolic extract of grapefruit seed and pulp against 20 bacterial and 10 yeast strains .The strongest antibacterial effect was seen against Salmonella enteritidis with minimum inhibitory concentration (MIC) of 2.06% (extract concentration), while MIC for other tested bacteria and yeasts ranged from 4.13% to 16.5%. A recent study with Aeromonas hydrophila, a human pathogen that causes intestinal and extra-intestinal infections, demonstrated that hesperidin had bactericidal and immunomodulating effects. .Both in vitro and in vivo experiments indicate that hesperidin displays anti parasitic activity against adult worms of Schistosomamansonii that are responsible for the tropical disease schistosomiasis which affects millions of people especially children worldwide... In addition, hesperidin has been proposed as a potential contraceptive microbicide for sexually transmitted diseases [19]... based on its hyaluronidase inhibiting activity (an enzyme that increases tissue permeability). Since hyaluronidase plays a essential role in sperm and microbe penetration into the substrate/target, the ability of hesperidin to inhibit hyaluronidase gave an indication toward its contraceptive effects. (Not required) Hesperidin was also found to inhibit various sexually transmitted pathogens including Neisseria gonorrhoeae, Chlamydia trachomatis, . Moreover hesperidin had no toxic effects on the host cells as well as on the growth of normal vaginal lactobacilli .Hesperetin (aglycone) displays marked inhibitory activity against Helicobacter pylori a bacterium linked to the development of stomach ulcers .. [20]..An interesting finding was noticed regarding the influence of hesperidin on human intestinal microbiota While hesperidin had no impact on the tested bacteria (Bacteroides galacturonicus, Lactobacillus sp., Enterococcus coccae, Bifidobacterium catenulatum, Ruminococcus gauvreauii, Escherichia coli), its aglycone , hesperidin inhibited growth of almost all of them. This means that hesperetin can modulate the intestinal flora and indirectly interfere with its own bioavailability..

Hesperdin use for Allergy:

Allergy is an overreaction of the immune system to a substance (e.g., pollen, certain food, dust, fur, etc.) that normally causes little or no problem. Hay fever, asthma and food and skin allergies are well known examples of allergy. The symptoms of allergy include a runny nose, itchy rash, shortness of breath and/or swelling. The underlying mechanism of allergy involves immunoglobulin E (IgE) antibodies that bind to the allergen and trigger the release of inflammatory chemicals such as histamine which in turn increases the permeability of capillaries and exacerbates the symptoms. Hesperidin has been shown to inhibit both synthesis and release (degranulation) of histamine from mast cells and basophils (white blood cells)[21]. Moreover, it can reduce another permeability promoting substance called vascular endothelial growth factor (VEGF) as well as the level of IgE] The results from a study in the animal model of allergic asthma show that hesperidin is effective in suppressing airway inflammation and sensitivity to bronchoconstrictors(narrowing the airway passages) and also in decreasing infiltration and accumulation of leukocytes in the lungs. In addition, oral administration of hesperidin is effective in ameliorating allergic rhinitis (hay fever) symptoms in laboratory mice (134). In vitro study on human basophils, collected from patients

suffering from seasonal allergic rhinitis, also confirmed anti-histamine effects of hesperetin. Hence, taking into account the above facts hesperidin can be useful in the management of allergy symptoms....[7].

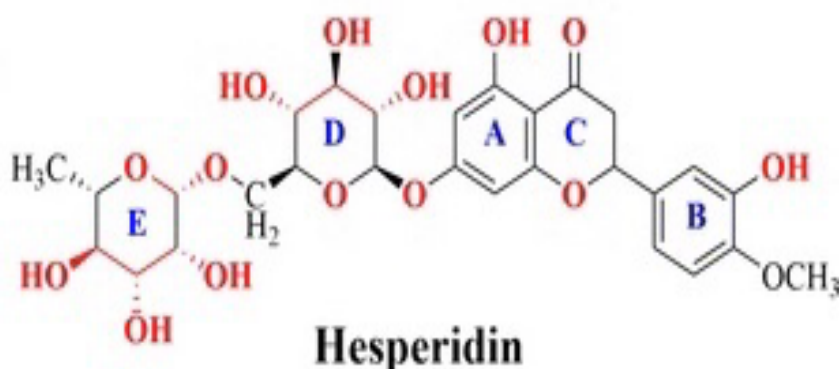
The antiviral activity of hesperidin:

The anti-inflammatory activity of hesperidin was mainly attributed to its antioxidant defense mechanism and suppression of pro-inflammatory cytokine production. Hesperidin exhibited anti-viral activity against the influenza virus through a significant reduction of virus replication..[22]

Hesperidin and Its aglycone, hesperetin, have properties including **antiviral activity**. There is a study showed hesperidin to be effective against human rotavirus, which is causative agent of diarrhea in infants and young children. Also, hesperidin inhibited replication of influenza (flu) virus in vitro and decreased the number of infected cells[22].

Hesperidin could alleviate H1N1-induced impairment of pulmonary function by inhibiting cytokine production in pulmonary microvascular endothelial cells through **MAPK**(mitogen-activated protein kinase) signalling pathways..

Hesperetin has shown anti-influenza virus activity, Specific antiviral activity of hesperidin and its aglycone hesperetin has long been known, based on in vitro studies, especially towards influenza virus and some herpes viruses. Hesperetin was attributed inhibition activity against the replication of the same herpes viruses. It showed also a potent inhibitory effect on the infectivity of rotavirus, in some experiments hesperidin, at a dose of 100 mg per kg of body weight and with intragastric administration, was found to effectively inhibit influenza A virus replication and spread, by up-regulating certain cell-autonomous immune responses, **In particular, flavonoids possessing an ability of anti- influenza virus replication have a double hydrogen bond between C2 and C3 and a replaced group at C2, or a double bond between C2 and C3 and a replaced group at C3.**[22].



The effect of hesperidin on SARS-CoV and COVID-19.

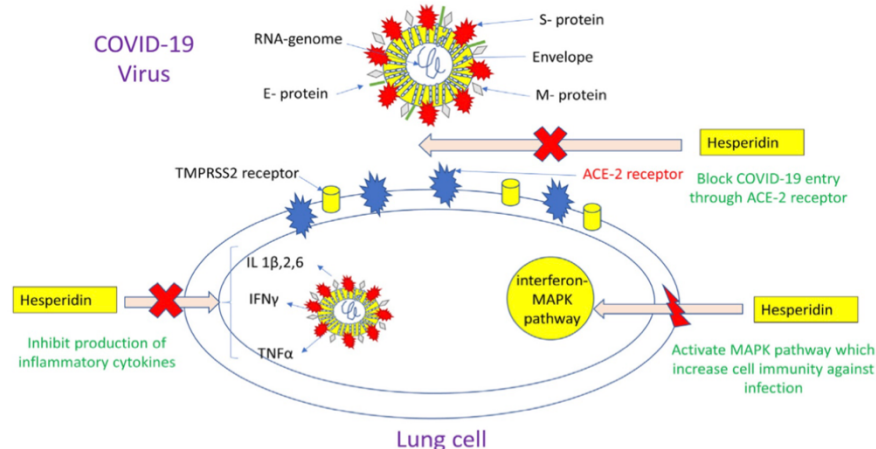
Hesperidin, a flavonoid abundant in citrus peels, was identified as a potentially very interesting molecule in the **fight against COVID-19**. Its antiviral activity was proven for other viruses, in particular SARS-CoV, thus it could reveal useful also in case of further mutations of SARS-CoV-2. In the therapeutic use, hesperidin has the advantage of strong binding affinity to all the main viral and cellular targets, outperforming not only other natural molecules, but also antiviral drugs recommended for clinical trials on COVID-19 inpatients. These targets correspond to different stages of the infection, from the entry of the virus into the host human cell, to the transcription of viral genome and virus replication. According to recent studies, hesperidin showed remarkable binding affinity to the three main protein receptors of SARS-CoV-2, i.e., the SARS-CoV-2 protease domain, the receptor binding domain of the spike glycoprotein (RBD-S), and the receptor binding domain of the ACE2 at the protease domain (RBD-ACE2), responsible for cell infection and virus replication. {The spike protein of SARS-CoV was identified as a general target for vaccines and therapeutic treatments [27]. A subunit (S1) of the spike protein contains a receptor-binding domain (RBD) that engages with the host cell receptor ACE2, while the other subunit (S2) mediates fusion between the viral and host cell membranes.}

So we seen that the binding affinity to the three main targets was considered representative of the inhibitory activities of hesperidin against viral infection, by either inhibiting the latching of the virus to the ACE2, or inhibiting the virus replication in the cells. Thus, hesperidin could be a promising active substance for drugs potentially useful to prevent or treat COVID-19[28], possibly along with other citrus flavonoids. they are seen that hesperidin was the only compound that could target the binding interface between the spike protein and human ACE2, so that by superimposing the RBD–ACE2 complex to the hesperidin–RBD complex, a distinct overlap of hesperidin with the interface of ACE2 was observed. This suggests that hesperidin may disrupt the interaction of ACE2 with RBD and prevent the virus from entering the cell[22].

Based on virtual screening, hesperidin may disrupt the interaction of ACE2 with RBD of SARS-CoV-2 thus block its entry into the lung cells Therefore, hesperidin can be used as a promising prophylactic agent against COVID-19 infection.[28].

Patients infected with COVID-19 exhibited what is called “cytokine storm” which initiated primarily as an inflammatory response and resulted in uncontrolled over-production of soluble markers of inflammation. Available evidence showing that cytokine storm, is a major cause for the development of ARDS. Cytokine storm involves the release of various immune-active molecules such as Interferons (e.g. $\text{IFN } \gamma$), interleukins (e.g. $\text{IL-1 } \beta$, IL-2 , IL-6), chemokines, and tumor necrosis factor-alpha ($\text{TNF-}\alpha$)

Hesperidin with its high anti-inflammatory activity inhibited the secretion of pro-inflammatory cytokines such as $\text{IFN-}\gamma$ and IL-2 . Besides, hesperidin inhibited $\text{IL-1 } \beta$ - stimulated inflammatory responses by inhibiting the activation of the $\text{NF- } \kappa\text{B}$ signaling cascade. It also played a major role in suppressing the release of inflammatory markers such as ($\text{TNF } \alpha$ and IL-6) in type 2 diabetic patients Therefore, it can be used as adjuvant therapy to control the severe inflammatory reaction against COVID-19.[29]



The solubility and bioavailability of hesperidin..

According to the studies , hesperidin is slightly soluble in water, and this may limit the bioavailability of hesperidin, as well as its metabolic stability and spreading to tissues and organs. So The therapeutic efficacy of orally administrated hesperidin depends on its bioavailability which in turn is dependent on its ability to dissolve in water and be absorbed through the intestinal mucosa.. And The low bioavailability level (<25%) of hesperidin was attributed to its irregular absorption in the gastrointestinal tract, as well as to the hydrolysis into aglycone hesperetin under gastric pH conditions, and enzymatic degradation .. The crystal structure of hesperidin, and the respective aglycones, hesperetin , was deemed responsible for poor water solubility, along with the hydrophobic nature of the molecule itself and the primary particle size (generally greater than 5 μ m). The remarkable size of primary particles is due, in turn, to the tendency of hesperidin to form complex crystals with other similar glucosides, which makes also difficult to obtain it in a pure state . The solubility of hesperidin in water, pure or aggregated with other glucosides, is lower than 20 mg/L .[23]

Due to poor water solubility and the presence of the sugar rutinose moiety the ingested hesperidin must proceed to the colon where gut microorganisms liberate it as the aglycone hesperetin which can indicates a shift in the absorption site from colon to small intestine be either absorbed or further degraded concentration of hesperetin up to 7-7.4 hours. Its modified form called hesperetin-7-glucoside (with glucose moiety instead of rutinose) has good absorption and bioavailability reaching the maximum plasma concentration within 36 minutes of its ingestion. This explains the delay in plasma (blood) peak systemic blood circulation, hesperetin absorbed in the intestine or colon undergoes further metabolic transformation in these organs as well as in the liver. These metabolic changes include mainly glucuronidation and sulfation .since the circulating forms of hesperetin metabolites found in plasma were glucuronides (87%) and sulfoglucuronides (13%) [23]...

The most common method to enhance the bioavailability of hesperidin, as well as of other poorly available drugs, was to enhance their dissolution rate by coupling the bioactive compound with a suitable carrier able to destroy the crystalline structure, and forming solid fine dispersions, associated with larger available surface and more rapid wetting and dissolution . This way, the drug can be released efficiently as very fine colloidal particles with a size less than 1 μ m...

Another method consists in processing bioactive molecules in order to obtain more soluble molecules, while retaining the original properties. This is the case of **glucosyl hesperidin**, obtained by regioselective transglycosylation of hesperidin with cyclodextrin glucanotransferase from *Bacillus stearothermophilus*, which showed ten thousand times higher water solubility (around 200

g/L) and about 3.7 higher bioavailability, also they can use polymeric carrier with adequate coating properties, able to protect hesperidin in the gastric medium. Avoiding gastric degradation, and increasing the solubility[22].

***Review on some flavonoids & hesperidin supplements to treat ,
prevent some conditions and enhancement of immune system..***

Flavonoids, widely exist in plant kingdom, including our daily diets such as vegetables and fruits, are also important components of many traditional herb medicines[24]. The better understanding of the functions of flavonoids, the better taking advantages of flavonoids in our daily lives and health care industry. For example, we can choose fruits and vegetables rich in hesperidin as our main food source during influenza seasons to promote our autonomous immunity to defend influenza virus infection. because Our immune system is our most important defence against pathogens – viruses, bacteria, fungi and germs, hence it plays essential role in protecting our bodies against illness and disease[25]. Additionally, many traditional antiviral drugs are made from plant extracts containing some antiviral components. some products contain diosmin— another flavonoid glycoside that act as against hypertension as well as inflammation conditions. For example, the agent **Daflon** 500 mg (diosmin 90%, hesperidin 10%) was demonstrated to improve multiple histological aspects of the acute inflammatory reaction as well as of the chronic inflammation. The sulphonated and phosphorylated hesperidin compounds proved to be extremely potent inhibitors of the hyaluronidase enzyme, which causes a breakdown of hyaluronic acid, thereby increasing tissue permeability and favoring the penetration of certain harmful bacteria[26]. Also there is a repatriation-ship with VC and flavonoids, The peel and rind of citrus fruits contain bioflavonoids in abundance. Bioflavonoids are a vibrant substance often found in foods that contain vitamin C that are essential for its correct absorption. In addition to helping our systems absorb vitamin C, bioflavonoids have antioxidant properties that prevent cell damage from free radicals, maintain collagen, and improve capillary strength. Hesperidin is an antioxidant flavonoid that is part of the bioflavonoid complex but is added in higher concentration to this formula for increased efficacy[24].

Here there are some products of hesperidin:

1- Swanson premium hesperidin

Swanson Premium is a high-quality supplement company that produces very good supplements. Their hesperidin product is one of the top ones on the market.

Specs and Highlights:

500mg Hesperidin per serving.



2- Swanson hesperidin & diosmin

This blend provides the optimal balance of nutrients for people who want to get a little more benefit from their supplements. It's also a less common combination of two antioxidants that are normally hard to find. It's derived from sweet orange skin and carefully extracted to maintain the beneficial nutrients.

Specs and Highlights:

100mg Hesperidin & 500mg Diosmin A powerful antioxidant combination.



3-Jarrow Formulas Venous Optimizer

This is a powerful supplement that contains a blend of some of the most important supplements. Vitamin C is used to increase bioavailability.

Specs and Highlights:

50mg Hesperidin, 450mg Diosmin, 200mg Vitamin C

Contains a proprietary mix of herbs and substances to help increase the delivery of the supplement

Suitable for vegetarians and vegans.[27].



References

- 1-Agati G, Azzarello E, Pollastri S, Tattini M (2012) Flavonoids as antioxidants in plants: location and functional significance. Plant Sci 196:67–76 .
- 2-Aherne AS, Obrien NM (2002) Dietary flavonols: chemistry, food content and metabolism. Nutrition 18:7581.
- 3-Brodowska KM (2017) Natural flavonoids: classification, potential role, and application of flavonoid analogues. Eur J Biol Res 7(2):108–123.

- 4-E. Wollenweber and V. H. Dietz, (2014)“Occurrence and distribution of free flavonoid aglycones in plants,” *Phytochemistry*,vol.20,no.5,pp.869–932,1981.
- 5-R. Koes, W. Verweij, and F. Quattrocchio, (2005)“Flavonoids: a colorful model for the regulation and evolution of biochemical pathways,” *Trends in Plant Sciences*, vol. 10, no. 5, pp. 236–242,
- 6-L. H. Yao, Y. M. Jiang, J. Shi et al.,(2004)“Flavonoids in food and their health benefits,” *Plant Foods for Human Nutrition*, vol. 59, no. 3, pp. 113 – 122,.
7-<https://www.drrathresearch.org/attachments/education/Phytobiology/Hesperidin.pdf>.
- 8-25-Agrawal YO et al.,(2014), Hesperidin produces cardioprotective activity via PPAR- γ pathway in ischemic heart disease model in diabetic rats. *PLoS One*.(65):78-99.
- 9-Kometani T et al.(2008), Effects of alpha-glucosylhesperidin, a bioactive food material, on collagen-induced arthritis in mice and rheumatoid arthritis in humans. *Immunopharmacol Immunotoxicol*.(40):67
- 10-Kalpana KB et al.(2009), Evaluation of antioxidant activity of hesperidin and its protective effect on H₂O₂ induced oxidative damage on pBR322 DNA and RBC cellular membrane. *Mol Cell Biochem*.(49):43
- 11-Rizza S et al. (2011),Citrus polyphenol hesperidin stimulates production of nitric oxide in endothelial cells while improving endothelial function and reducing inflammatory markers in patients with metabolic syndrome. *J Clin Endocrinol Metab*.(64):93.
- 12-Nelson ER et al. The oxysterol, (2012),27-hydroxycholesterol, links cholesterol metabolism to bone homeostasis through its actions on the estrogen and liver X receptors. *Endocrinology*. 2011.
- 13-Gao X et al. Habitual intake of dietary flavonoids and risk of Parkinson disease. *Neurology*(42):18.
- 14-Choi EJ, Ahn(2008) WS.Neuroprotective effects of chronic hesperetin administration in mice.*Arch Pharm Res* (53):31.
- 15-Rizk S M, Sabri NA. (2009)Evaluation of clinical activity and safety of Daflon 500 mg in type 2 diabetic female patients. *Saudi Pharm J*.(54):78
- 16-Meiyanto E.,(2012) al. Natural products for cancer-targeted therapy: citrus flavonoids as potent chemopreventive agents. *Asian Pac J Cancer Prev*.(63):89.
- 17-Kamaraj S.,(2009). al. Antioxidant and anticancer efficacy of hesperidin in benzo(a)pyrene induced lung carcinogenesis in mice. *Invest New Drugs*.(54):73
- 18-martin L. ,(2015),Bioavailability of dietary polyphenols and gut microbiota metabolism: antimicrobial properties. *Biomed Res Int*.(22)18.
- 19-Garg,A.,(2005),Biological activity assessment of a novel contraceptive antimicrobial agent. *J Androl*.(75):32
- 20-De Clercq E.,(2006), Potential antivirals and antiviral strategies against SARS coronavirus infections. *Expert Rev Anti Infect Ther*.(68):32.
- 21-Han NR,. (2020),Pyeongwee-San extract (KMP6): a new anti-allergic effect. *J Pharm Pharmacol*.(61):79.
- 22-Francesco,M.,Rosaria,C., Federica,Z.,and Mario,P.(2020). Review of Evidence Available on Hesperidin-Rich Products as Potential Tools against COVID-19 and Hydrodynamic Cavitation-Based Extraction as a Method of Increasing Their Productio.MDPI journal processes.
- 23-Repon ,K., Tadanobu ,T., and Takashi ,S.,(2009). Glucosyl Hesperidin Prevents Influenza A Virus Replication in Vitro by Inhibition of Viral SialidaseArticle in Biological & Pharmaceutical Bulletin ·research gate.7(32):2

- 24-Saha RK, Takahashi T, Suzuki T.(2009) Glucosyl hesperidin prevents influenza a virus replication in vitro by inhibition of viral sialidase. *Biol Pharm Bull* ; 32: 1188-1192.
- 25-Wahlgren J. Influenza A viruses: an ecology review. *Infect Ecol Epidemiol*,(2011); 10.(3402):89.
- 26-Thunström, L.; Newbold, S.C.; Finnoff, D.; Ashworth, M.; Shogren, J.F.(2020), The benefits and costs of flattening the curve for COVID-19. 1–17, doi:10.2139/ssrn.3561934.
- 27-Yusuf A. ,Haggaga,I, Nahla E. El-Ashmawyb, Kamal M. Okasha,(2020)'Is hesperidin essential for prophylaxis and treatment of COVID-19 Infection?',*ELSEVIR*, 0306:2-3
- 28-<https://top10supps.com/best-hesperidin-supplements>