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Dihydroquercetin as a potential immunonutrient in the complex therapy of COVID-19

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SUMMARY
The main aspects of the antiviral, anti-inflammatory, antioxidant and hepatoprotective properties of dihydroquercetin (DHA), which may affect the course of COVID-19, are considered. Given the low toxicity and a wide range of biological activity, aimed not only at suppressing enzymatic reactions with the participation of coronavirus, but also at eliminating the lesions caused by it in all major target organs, DHA can be recommended as an immunonutrient for inclusion in the complex therapy of the disease and in recovery period COVID-19.

KEYWORDS: *dihydroquercetin, antioxidant, COVID-19, SARS-CoV-2, coronavirus.*

CONFLICT OF INTERESTS. *The authors declare that they have no conflicts of interest.*
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Dihydroquercetin as potential immunonutrient in treatment of COVID-19

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SUMMARY
The main aspects of the antiviral, anti-inflammatory, antioxidant and hepatoprotective properties of dihydroquercetin (DHQ), which may affect the course of COVID-19, are considered. Given the low toxicity and a wide range of biological activity, aimed not only at suppressing enzymatic reactions with the participation of coronavirus, but also at eliminating the lesions caused by it in all the main target organs, dihydroquercetin can be recommended for inclusion in the complex therapy of the disease and during the recovery period of COVID-19.
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Introduction

The rapid outbreak of the coronavirus infection COVID-19 poses a global health problem around the world. To date, no special drugs have been developed for the treatment and prevention of COVID-19 caused by the new coronavirus*SARS-CoV-2*... In the context of a pandemic, the issue of creating effective antiviral drugs for the treatment of a new coronavirus infection is most acute, since effective treatment methods have not yet been developed and therapy is often reduced to symptomatic treatment, relying mainly on the repurposing of existing drugs (such as ritonavir, remdesivir, favipiravir) and antibiotics to treat secondary infections rapidly developing in the presence of COVID-19. The shortage of drugs with clinically proven efficacy contributed to the fact that natural products began to attract more and more attention due to their low toxicity and the absence of side effects [1-4].

Pleiotropic Properties of Dihydroquercetin

Dihydroquercetin (DHA) is a bioflavonoid found in some conifers that has a number of unique medicinal properties. DHA has attracted the attention of researchers due to its ability to prolong the life of those higher plants in which it was found.

In 1814, the French researcher Chevreul isolated the first flavonoid, later named quercetin. In Russia, the study of flavonoids was initiated by the famous botanist Ivan Parfenievich Borodin in 1873. A new stage in the study of bioflavonoids began in 1936, when American scientists of Hungarian origin Albert Szent-Györgyi and Istvan Rusnyak established that a complete cure for scurvy is possible only in the case of a combination of vitamin C with another substance that increases the resistance of capillaries, and isolated this substance (from citrus fruits), calling it vitamin P. Subsequently it turned out that

Дигидрокверцетин Эвалар

В России именно Дигидрокверцетин от Эвалар зарегистрирован как средство для поддержания в норме проходимости воздуха в бронхах, тонуса бронхиальной стенки, функций легких и бронхов[1]

Преимущества Дигидрокверцетин от Эвалар:

25mg

Высокая дозировка дигидрокверцетина – 25 мг в 1 таблетке[2]

Высококачественное сырье из лиственницы сибирской со степенью очистки – 98-100%[3]

GMP

Изготовлен в условиях фарм-производства по международному стандарту качества GMP

Наведите и узнайте больше

Эвалар

НЕ ЯВЛЯЕТСЯ ЛЕКАРСТВЕННЫМ СРЕДСТВОМ

[1] По данным Единого реестра свидетельств о государственной регистрации, октябрь 2020 г. [2] 100% от адекватного уровня суточного потребления. [3] По данным внутреннего входного контроля. Протоколы №С-754, С-966, С-96.

vitamin P is not just one substance, but a whole range of compounds, and the name "vitamin P" has been replaced by the term "bioflavonoids".

In the late 1940s, the Oregon Forest Products Laboratory in the Oregon Forest Products Laboratory began investigating the chemical composition of the bark of Western pine trees in order to determine its applicability. One of the first to study the bark of the Douglas fir (*Douglas fir*). DHA has been found to be a commercially important ingredient in the bark of Douglas fir (Pew, C. John, 1947).

Currently, the main raw material for the production of DHA on an industrial scale is Siberian larch wood (*Larix sibirica Ledeb*) and Daurian larch (*Larix dahurica Turcz*). Larch wood contains up to 2.5% of flavonoids, among which DHA accounts for up to 90–95% of the total amount of flavonoids [5, 6]. DHA is widely used in the medical, food, pharmaceutical and perfume industries [7–10]. As a preservative, DHA is added to milk powder, confectionery, butter, etc. For the manifestation of the antioxidant effect, DHA is added to various ointments.

Dihydroquercetin is a bioflavonoid with a wide range of pharmacological properties, has antiradical and antioxidant activity that exceeds the known natural analogs (vitamins B, C and others) by more than 10 times [11, 12], has antibiotic, radioprotective and immunomodulatory properties. Established bactericidal action against pathogenic bacteria, fungi and viruses and a positive effect on the intestinal lactic acid microflora [13].

In earlier studies, the antiviral properties of DHA were investigated *in vitro* [14, 15] and *in vivo* [15] in relation to a member of the picornavirus family, the Coxsackie B4 virus (one of the main causes of type 1 diabetes mellitus). It is noted that the effect of DHA in the treatment of viral pancreatitis was comparable to or exceeded the effect of ribavirin (previously approved for the treatment of COVID-19). In [16] it was found that the antiviral activity of dihydroquercetin against influenza A and B viruses is comparable or higher than that of remantadine.

DHA has a positive effect on the molecular mechanisms underlying the regulation of vascular permeability and vascular wall resistance, as well as on the metabolism of arachidonic acid, which makes it possible to use DHA in inflammatory diseases, allergic and hemorrhagic syndromes. DHA helps to reduce the level of circulating pro-inflammatory cytokines (tumor necrosis factor α, interleukin-1β, interleukin-6).

With long-term intake of DHA, it helps to maintain the functions of the immune system, prevents the exacerbation of chronic respiratory diseases and the occurrence of ARVI.

The first clinical trials of DHA in the treatment of patients with acute pneumonia were carried out more than 20 years ago [17, 18]. The use of DHA in complex therapy promoted the rapid relief of pulmonary inflammation. Acceleration of processes recorded normalization of the main indicators of blood circulation in the bronchial mucosa and a decrease in serum reactive oxygen species (ROS).

In patients with pneumonia, whose therapy included 90% DHA at a dose of 40–60 mg four times a day during the acute and subacute periods, 1.8 times more effective clinical and radiological recovery of pulmonary tissue, as well as a decrease in pneumofibrosis by 3.6 times compared with the control group of patients in whom DHA was not included in the therapy [19].

Similar results were obtained in a clinical study of endobronchial microcirculation of the bronchial mucosa in patients with chronic obstructive pulmonary disease (COPD) [20].

The membrane stabilizing effect of DHA and its redox properties contribute to the efficient functioning of tissue respiration enzymes, oxygen utilization and ATP synthesis in mitochondria. Along with the stabilization of erythrocyte membranes and improvement of the oxygen transport function of erythrocytes, these effects determine the antihypoxant, antihemolytic properties of DHA, which contribute to an increase in oxygen and energy supply of cells.

DHA blocks the removal of charge from erythrocytes, thereby preventing them from sticking together and the formation of blood clots.

The antiplatelet properties of DHA are widely known [19, 21]. In [22], it was shown*in vivo*that DHA can dose-dependently suppress platelet aggregation activated by various inducers.

DHA has a capillary-protective effect, reduces the permeability and fragility of capillaries, improves microcirculation, helps to inhibit the action of enzymes that loosen the connective tissue of the walls of blood vessels and other systems, but acids), thus maintaining strength, elasticity and normalizing the permeability of the vascular wall.

DHA is able to reduce capillary permeability by 1.3–1.4 better than quercetin, while decreasing the exudative phase of the inflammatory reaction [23].

As a ligand of the GABA-benzodiazepine complexes of the brain, DHA promotes the manifestation of sedative, hypotensive and analgesic effects.

Clinical trials of drugs with DHA, which have been conducted in Russia for more than 20 years, have shown the positive effect of DHA as a prophylactic agent to reduce the risks of cardiovascular diseases, as well as in rehabilitation after a number of diseases - coronary heart disease, discirculatory encephalopathy, cerebral atherosclerosis [24] , diabetes mellitus, lung diseases. [19]. Clinically confirmed dose-dependent inhibition of cholesterol synthesis, reaching 86% [25].

The positive properties of DHA are manifested in both intracellular and extracellular environments. Research on erythrocytes, leukocytes, macrophages

and hepatocytes have shown that DHA contributes to their greater resistance to membrane damage. DHA stabilizes cell membranes by inhibiting free radical processes of lipid peroxidation.

Points of application of dihydroquercetin in COVID-19

Oxidative stress is a key factor in the development of COVID-19 in a significant number of patients [26-28]. This is especially true for severe cases in which pulmonary dysfunction, cytokine storm (intense inflammatory response) and viral sepsis are manifested.

Today, the prospects of using DHA as a regulator of oxidative stress as part of complex therapy for COVID-19 and for the prevention of possible complications are being actively discussed [29].

The process of oxidative stress in COVID-19, accompanied by the formation of ROS, leads to deep damage and bilateral inflammation of the lung tissue, uncharacteristic of conventional inflammation. The results of diagnosing patients using radiography (including computed tomography), as well as the results of pathological studies of deceased patients showed that inflammation in COVID-19 has not only viral, but also biochemical etiology. The development of hypoxia against the background of the course of COVID-19 is associated with damage to hemoglobin molecules in erythrocytes, which come into contact with the surface proteins of the membrane*SARS-CoV-2*... This process is accompanied by the release of toxic iron ions from the hemoglobin heme into the blood, which in free form are carried throughout the body. Hemoglobin without iron, when passing through the lungs, is unable to form a bond with oxygen and deliver it to the tissues. As a result, hemoglobin ceases to perform its functions and becomes a carrier of the coronavirus. Free iron causes peroxidation, which leads to tissue degradation at the level of cellular components — lipids, DNA and proteins, which ultimately can lead to damage to the brain and nerve tissues. Part of the free iron binds to protein and forms ferritin, which is a kind of marker for COVID-19.

DHA as an antioxidant is capable of breaking the chain oxidation reaction [19, 30–34].

It is known that regular consumption of foods with DHA protects the liver from destruction by viruses and toxic substances, improves the elimination of toxins, radionuclides and heavy metal salts. Like all other flavonoids, DHA is a chelating agent and is able to bind to iron [34, 35], inhibiting its participation in ROS generation [36].

A number of studies show that DHA inhibits apoptosis processes caused by excess iron in the liver in rats [37]. DHA exhibits similar bioavailability in humans and rats [38, 39], and the level of iron in the liver of rats in the experiment was comparable to that for humans with iron overload. Excess iron leads to a significant increase in lipid and protein peroxidation, as well as a decrease in the total antioxidant capacity of liver tissue

Liver dysfunction associated with the accumulation of iron in it as a result of hemoglobin degradation is accompanied by the release of a specific enzyme alanine aminotransferase into the blood, which is a marker for the development of severe forms of COVID-19.

DHA, by reducing the iron content in the liver, enhances the regeneration of damaged tissues. The use of DHA improves the histopathological picture of the liver, a decrease in iron-induced inflammatory reactions is confirmed by a decrease in the activity of hepatic transaminases in the blood serum.

Studies carried out on volunteers have revealed an improvement in the stability of the psycho-emotional state of volunteers in the context of the COVID-19 pandemic, taking a carbohydrate product enriched with a freeze-dried DHA nanoemulsion. The volunteers were exposed to the stress factor due to the impact of information on the dynamics and consequences of the spread of coronavirus infection. Compared with the control group taking the placebo product, the volunteers taking the product with DHA showed a significantly lower increase in the leukocyte intoxication index (6.1 versus 40.9%), as well as a significantly smaller decrease in the lymphocyte index (3.8 versus 8.0%), indirectly indicating the state of stress in the body. Volunteers who took the product with DHA showed a 7.6% decrease in serum cortisol,

Conclusion

The biological activity of DHA is aimed at restoring the normal functioning of all major target organs *SARS-CoV-2* such as lungs, heart, liver and others. In addition, DHA is an anticoagulant and a powerful antioxidant, which helps to normalize blood hematological parameters. Positive results from clinical trials conducted earlier in the treatment of acute pneumonia suggest that DHA may also be used to treat pneumonia caused by the novel coronavirus infection, COVID-19. The ability of DHA to excrete toxic free iron, which is formed as a result of the degradation of hemoglobin under the influence*SARS-CoV-2*, can significantly reduce tissue degradation and reduce the burden on the liver against the background of COVID-19. All of the above allows us to consider DHA as a potential immunonutrient in complex therapy.*SARS-CoV-2* , significantly reduce tissue degradation and reduce the burden on the liver against the background of COVID-19.

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