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Mini Review

The Promising Role of Flavonoids in Chronic Obstructive Pulmonary Disease

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Abstract

Background: Flavonoid-rich foods are beneficially associated with enhancing pulmonary function; however, the protective effects of flavonoids may have an impact on COPD through anti-inflammatory mechanisms. Chronic obstructive pulmonary disease (COPD) is a prevalent lung disease with a high death rate and multiple health problems. Recently, up to 7000 flavonoids have been identified as having anticancer, antioxidant, and anti-inflammatory properties. Various mechanisms of action of flavonoids have been implicated. ***Aim***: This review aims to identify and appraise various flavonoids used in managing COPD and reveal their mechanisms. ***Methods***: We searched the Web of Sciences, Google Scholar, PubMed, Scopus, and EMBASE databases from December 1975 to February 2022 by using the relevant keywords for this narrative review. ***Results***: Many flavonoids were found to be effective in the management of COPD, such as liquiritin apioside, quercetin, baicalin, naringin, hesperidin, silymarin, and casticin. The proposed mechanisms for these flavonoids could either be attributed to antioxidant or anti-inflammatory activity. ***Conclusion***: Flavonoids could be a promising alternative to be developed and tested for the treatment of COPD in clinical settings.

Keywords: COPD, Flavonoids, Antioxidant activity, Anti-inflammatory activity

الدور الواعد للفلافونويد في مرض الانسداد الرئوي المزمن

الخلاصة

الخلفية: ترتبط الأطعمة الغنية بالفلافونويد بشكل مفيد بتعزيز وظيفة الرئة. ومع ذلك، فإن الآثار الوقائية للفلافونويد قد يكون لها تأثير على مرض الانسداد الرئوي المزمن من خلال آليات مضادة للالتهابات. مرض الانسداد الرئوي المزمن **(COPD)** هو مرض رئوي منتشر مع ارتفاع معدل الوفيات ومشاكل صحية متعددة. في الآونة الأخيرة، تم تحديد ما يصل إلى 7000 من مركبات الفلافونويد على أنها ذات خصائص مضادة للسرطان ومضادة للأكسدة ومضادة للالتهابات من خلال آليات مختلفة من تأثير مركبات الفلافونويد. **الهدف**: تهدف هذه المراجعة إلى تحديد وتقييم مركبات الفلافونويد المختلفة المستخدمة في علاج مرض الانسداد الرئوي المزمن والكشف عن آلياتها. **الأساليب**: بحثنا في قواعد بيانات **Web of Sciences** و **Google Scholar** و **PubMed** و **Scopus** و **EMBASE** من ديسمبر 1975 إلى فبراير 2022 باستخدام الكلمات الرئيسية ذات الصلة لهذه المراجعة السردية. **النتائج**: تم العثور على العديد من مركبات الفلافونويد الفعالة في علاج مرض الانسداد الرئوي المزمن، مثل ليكويريتين أبيوسيد، كويرسيتين، بايكالين، نارينجين، هسبيريدين، سيليمارين، وكاستيسين. يمكن أن تعزى الآليات المقترحة لهذه الفلافونويد إما إلى نشاط مضاد للأكسدة أو مضاد للالتهابات. **الخلاصة**: يمكن أن تكون مركبات الفلافونويد بديلا واعدا ليتم تطويره واختباره لعلاج مرض الانسداد الرئوي المزمن في الممارسات السريرية.

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Overview

Chronic obstructive pulmonary disease (also known as COPD) is a progressive disease that affects the airways over time and is caused by a blockage in the airways that cannot be reversed [1]. This sickness is associated with a significantly increased rate of both death and morbidity [2]. More than three million fatalities occur each year as a direct result of COPD, which throws a tremendous strain on healthcare systems around the world [3].

Clinical signs and symptoms

The conventional idea states that prolonged exposure to cigarette smoke in a susceptible individual will result in an abnormal inflammatory response that will cause damage to the airways. This will ultimately lead to bronchitis and emphysema if the alveoli are affected. The typical decline in lung function that occurs with age will quicken as one gets older, which will ultimately result in a constriction of the airways and persistent symptoms of respiratory disease [4]. Emphysema, chronic bronchitis (CB), and even just a mild blockage of the airways could all fall under this category [5]. It is possible for symptoms to worsen without warning. It's possible that you'll start coughing for the first time, or that an existing cough could get worse or come back more frequently. There is a possibility that the amount of sputum generated could increase, or that it will change color from clear to a dark yellow, green, or brown. The alteration of mucus is typically the first symptom that there is a worsening of the condition. In addition, you may have a harder time falling asleep, wake up with headaches, feel confused, and have lower amounts of oxygen in your blood than you normally would. In addition, a change in the consistency of the mucus is typically the first clue that an exacerbation is occurring [6].

Diagnosis

The diagnosis is supposed to be made based on atypical pulmonary function tests as well as symptoms that are diagnostic of the condition, such as a cough, shortness of breath, inadequate physical activity, and recurrent airway infections. Spirometry is frequently all that is required to establish a reduction in airflow. The severity of the patient's dyspnea and respiratory restriction, the frequency of the patient's exacerbations, and the results of the clinical examination all factor into the development of a treatment plan. According to the findings of study conducted in Europe, patients with severe COPD exhibit the following symptoms of the disease in the following percentages: dyspnea (73%), expectoration (64%), coughing (59%), and wheezing (42%) [7].

Risk factors

Inflammation that occurs frequently, oxidative damage, an imbalance between protease and anti-protease, ecological damage, and human genes all have an impact on the complex mechanisms that are at play in COPD [5]. The most common cause of COPD is cigarette smoking; however, dust exposure in the workplace may also be a contributing factor in the development of the disease [2]. There are many different oxidizing agents that have been identified in cigarette smoke (CS), which contains up to 7000 different elements. Consuming tobacco messes up the usual balance of oxidants and antioxidants in the body, which in turn exacerbates the effects of oxidative stress in the lungs and the rest of the body. The oxidants that are present in cigarette smoke have the potential to cause severe damage to cells and tissues. In addition, oxidizing chemicals inhibit the body's natural defensive mechanisms and cause inflammation, all of which contribute to an overall increase in oxidative stress [5]. The risk of developing COPD varies not just with age but also with geographical location and sexual orientation. However, there are additional aspects that play a role, such as those that are connected to the working environment, the impact of infectious diseases, and the consequences of polluted environments. In addition, there is a link between this illness and a number of important consequences and comorbidities [1]. Chronic inflammation and persistent oxidative stress from natural exposures (such as smoking cigarettes) can be the cause of significant tissue damage and an exacerbation of sickness [5]. The formation of oxidants by these particles kicks off a chain reaction that leads to the reaction of cells, the expression of transcription factors, the generation of mediators, and inflammatory respiratory issues. Cigarette smoking is known to cause lipid peroxidation and carbonyl stress [8,9], both of which contribute to DNA damage [9] and speed up the aging process and death of epithelial cells [10,11]. All of the aforementioned are important mechanisms that have a role in the development of bronchial deformation as well as emphysema [5]. Some of research data suggests that the ultimate result of COPD, which includes aging, activities, and continual gene-environment interactions across a range of different physiological pathways [3,4], may have an effect on the development, maintenance, and function of the respiratory system.

Pathogenesis

According to the World Health Organization (WHO), chronic obstructive pulmonary disease (COPD) is the fourth most common cause of death across the globe, accounting for 2.75 million deaths annually [1]. There is a possibility that the genetic material of eukaryotic viruses such as anelloviruses, herpesviruses, papillomaviruses, and retroviruses is present in the lung. This could be the cause of the protracted asymptomatic infection as well as the prevalence of bacteriophages in the virome. COPD is

characterized by decreased immunological regulation [11], which can be attributed to the lung damage that is caused by environmental causes and inflammation. A common consequence of cellular senescence is a reduction in cell multiplication accompanied by maintenance of metabolic function. This can promote inflammation, slow the healing process, and even initiate cancer [3]. Oxidative stress is a significant factor in the development of lung cancer as well as chronic obstructive pulmonary disease (COPD), which is marked by inflammation. In addition, there is some evidence that inflammatory illnesses can lead to carcinoma, and there is also some evidence that there is a direct connection between chronic obstructive pulmonary disease (COPD) and lung cancer that is connected with inflammation [12]. Inflammatory mediators have been shown to be capable of preventing the development of cancer [13], both by encouraging the milieu favorable to cancer and by increasing the production of cytokines to increase the immune response. It is a condition that is still underdiagnosed despite the fact that it is occasionally discovered at an advanced stage. The current pharmaceutical treatments are unable to reverse the decline in respiratory function that is associated with COPD, hence the management of the disease needs to be improved so that early detection and early quitting of smoking are prioritized [1].

Flavonoids

Researchers from a variety of fields, including science and nutrition, are taking a comprehensive approach and focusing their attention on a wide range of dietary flavonoids [13]. Flavonoids are a wide-ranging class of polyphenolic compounds that are typically found in plants as either free aglycones or glycosides. Flavonoids can be broken down into two different types. They are the secondary metabolites that are found in the greatest abundance. It has been shown that the production of flavonoids requires participation from both the acetate metabolism and the shikimate pathway [14]. The 15-carbon skeleton of flavonoids is made up of two benzene rings that are connected together by a 3-carbon bridging chain. Flavonoids are usually classified as flavones, flavonols, flavanone, flavan, isoflavone, and chalcone [3]. Flavonoids are also known as flavanones. The flavonoid families are naturally occurring polyphenolic compounds that are composed of two aromatic rings (the A and B rings, which are essentially what make up the core structure of these molecules) joined by a pyran ring (or the C ring), which contains an oxygen atom [13]. Flavonoids can be found in a variety of plant-based foods and beverages, including tea, coffee, chocolate, and berries. There are several different phytonutrients that are abundant in flavonoids, and many fruits, vegetables, and even some natural plants contain these phytonutrients. In most cases, they are found in the form of free molecules, glycosides, or methylated metabolites [13]. There are a significant number of flavonoids present in nature, but only around 10,000 of them, most of which come from plant sources, have been described. Recent research that was released demonstrates that flavonoids have positive features such as anti-allergic, antiplatelet, anticancer, antioxidant, and anti-inflammatory actions against viruses. These properties have also been proven to be anti-inflammatory. As a result of this, there has been a recent uptick in interest in these chemicals since there is speculation that they may be beneficial to human health [15]. According to research, polyphenols are the most effective antioxidants for preventing an excessive generation of a variety of reactive oxygen species (ROS). Flavonoids, lignans, hydrocinnamic acids, hydroxybenzoic acids, and stilbenes are the most important subgroups of polyphenols. Out of all of the polyphenols, flavonoids are believed to be the best polyphenol-type compounds there are. Subclasses of flavonoids include flavonols, flavones, flavanones, isoflavones, and anthocyanidins. Flavonoids also contain anthocyanidins. It has been demonstrated that higher consumption of foods that are rich in flavonoids is closely correlated with improved lung function as well as a reduced risk of developing chronic diseases [13].

Role of flavonoids in COPD

According to the research that has been conducted, the preventative effects of flavonoids include the alleviation of symptoms and the improvement of pulmonary function. Flavonoids also play a role in the regulation of inflammation, which is an important therapeutic advantage for COPD patients, given that inflammation is the root cause of continuing cellular damage in COPD patients [3]. Flavonoids have been shown to offer multiple health benefits, the two most important of which are anti-inflammatory and antioxidant effects. These benefits have been backed up by extensive research in the scientific literature. The presence of an unsaturated C ring [2], the number of hydroxyl groups at the A and B rings and their placement, the presence of a carbonyl group at position C-4 at ring C, and frequently the absence of glycosylation of the molecule are the structural characteristics of active flavonoids that define their anti-inflammatory and anti-allergic effect against multiple respiratory diseases [13]. In order to produce an anti-inflammatory response, the activity of histone deacetylase 2 (HDAC2) is probably enhanced, and the nuclear factor-kappa B (NF-κB) pathway is probably repressed [16].

Flavonoid types

Liquiritin apioside

The major flavone found in the *radix* and *rhizoma* of the *Glycyrrhizae* plant is known as liquiritin apioside. In the human type II alveolar epithelial cell line (A549), it was discovered that liquiritin apioside was able to reduce the

levels of tumor necrosis factor alpha (TNF-α) and transforming growth factor beta (TGF-β) [17]. In addition, the use of liquiritin apioside in a rat model of the condition produced by cigarette smoke resulted in a significant reduction in the number of goblet cells that produce mucus in the air [3].

Quercetin

A study that was conducted in a preclinical model of chronic obstructive pulmonary disease showed that quercetin lowered markers of both lung inflammation and oxidative stress [18]. This was possible as a result of the high antioxidant and anti-inflammatory properties that quercetin possesses. Additionally, in a human model, treatment with quercetin reversed CSE-induced corticosteroid insensitivity in monocytic U937 cells and peripheral blood mononuclear cells (PBMC) from COPD patients. This was accomplished by initiating adenosine monophosphate-activated protein kinase (AMPK) and inducing the expression of nuclear factor erythroid 2-related factor 2. Therefore, quercetin, when taken with corticosteroids, has the potential to become a novel treatment for COPD [19].

Baicalin

Isolated from the root of the *Scutellariae radix*, baicalin is an isoflavone that possesses a wide variety of beneficial biological properties. In order to investigate the effects of baicalin on COPD, cell models, as well as models based on rats, were developed by using cigarette smoke (CS) and cigarette smoke extract (CSE). These studies revealed that baicalin blocked the NF-κB pathway, which resulted in significant anti-inflammatory effects on COPD and a decrease in the production of proinflammatory cytokines [11,20,21]. In addition, utilizing cigarette smoke extract (CSE) to produce type II pneumocytes in an in vitro cell model showed that baicalin had a strong anti-inflammatory effect. This caused inflammation to be significantly reduced. It is highly likely that the ability of baicalin to inhibit the NF-κB pathway is responsible for this decrease in inflammation. Its potency has been observed to be inversely associated with its concentration [16].

Naringenin

The ability of naringenin to diminish inflammation by inhibiting NF-κB was demonstrated in a study carried out on mice that had been subjected to CS [17]. In addition, the bronchial mucosa and bronchoalveolar lavage fluid (BALF) of COPD patients were found to express increased amounts of thymic stromal lymphopoietin (TSLP), chemokine interferon-inducible protein 10 kDa (CXCL10), C-C chemokine ligand 17 (CCL17), and CCL22 in clinical research [22]. In a human mast cell line, it was demonstrated that naringenin (100 mmol) blocked the receptor-interacting protein (RIP)-2 as well as caspase-1, which resulted in the production of TSLP being halted [23]. While all of this was going on, it was found that administering oral naringenin at a dose of 100 mg/kg reduced the concentrations of reactive oxygen species (ROS) in the BALF of mice with acute lung injury caused by LPS. These ROS included H2O2 and malondialdehyde (MDA). This finding indicates that naringenin has the potential to have an antioxidative effect on lung diseases [24].

Hesperidin

Mice were utilized in a study in which they were injected with cigarette smoke extract (CSE) to induce COPD and then given hesperidin to treat the symptoms of the disease. In mice with COPD brought on by CSE, hesperidin was able to lessen the effects of oxidative stress and inflammatory reactions [25]. These responses were connected to the signaling axis consisting of SIRT1, PGC-1, and NF-κB.

Silymarin

In a study where mice were used, CS was given to them twice a day for a total of two hours. The silymarin was administered intraperitoneally one hour previous to the CS administration. After receiving pretreatment with silymarin, the airway epithelial thickening and peribronchial inflammatory cell infiltration that were brought on by CS were significantly mitigated. In mice that had been given CS, the administration of silymarin resulted in a large decrease in the number of total cells, macrophages, and neutrophils, as well as the activity of myeloperoxidase (MPO). In addition, a pretreatment with silymarin was able to minimize the increase in malondialdehyde (MDA) levels and the decline in superoxide dismutase (SOD) activities that were caused by CS. According to the findings of this research, silymarin was able to reduce the oxidative stress and inflammation that were brought on by smoking. There is some speculation that the mitogen-activated protein kinases (MAPK) pathway plays a part in the anti-inflammatory effect [26].

Casticin (CST)

Casticin was demonstrated to improve lung functions in an animal study that was carried out on Wistar rats that were exposed to CS. This was accomplished by the attenuation of pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6), as well as the considerable inhibition of the inducible nitric oxide synthase and NF-κB. Casticin has been shown to protect the lungs against COPD by enhancing pulmonary function, reducing oxidative stress, and lowering inflammatory responses [27].

Conclusion

Many *in vivo* animal studies proved the effectiveness of flavonoids in the managements of COPD since they possess many properties like antioxidant and anti-inflammatory activities; these features render them a good candidate to be developed and tested in clinical settings.

Conflicts of interest

There are no conflicts of interest.

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Data sharing statement

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