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REVIEW

Prospects for the use of flavonoid substances in pulmonary fibrosis (review of experimental studies)

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ABSTRACT

Pulmonary fibrosis develops both spontaneously and as a result of lung damage by radiotherapy and chemotherapy, infectious diseases, and inhalation of harmful substances and particulate matter. In this case, normal tissue repair is disturbed: instead of regeneration of normal lung cells, the damaged tissue is replaced by fibrotic one consisting of dense collagen fibers. This leads to loss of lung tissue elasticity and impairment of its function, which significantly reduces the quality of patients' lives. The search for drugs for interstitial fibrotic lung diseases remains an urgent task, since the existing antifibrotic drugs only slow down disease progression and have side effects that significantly reduce the patients' quality of life. It is believed that natural polyphenolic substances, in particular flavonoids, can be used for the treatment of pulmonary fibrosis. Flavonoids present in various fruits, vegetables, tea and wine show a wide range of biological activities. They have antioxidant, anti-inflammatory and immunomodulatory properties, making them promising for the treatment of various diseases, including pulmonary fibrosis. Some studies have shown that flavonoids can inhibit myofibroblast activation and collagen production, which is directly related to the fibrotic process. Flavonoids are safe and can influence the hallmarks of fibrosis: oxidative stress, inflammation, cell proliferation and differentiation. To date, a large amount of experimental data confirming the antifibrotic effect of flavonoids has been accumulated. In recent years, clinical studies have been conducted to investigate the efficacy and safety of flavonoids in patients with pulmonary fibrosis. For example, quercetin and curcumin are being explored and have shown encouraging results in reducing markers of inflammation and fibrosis in the lung. However, the main obstacle to the widespread introduction of flavonoid substances into clinical practice remains their low oral bioavailability and rapid metabolism. The experimental data on the effect of flavonoids on the development of pulmonary fibrosis is analyzed in this review. The perspectives for improving their bioavailability using modern delivery systems (nanoparticles, liposomes, etc.), as well as dosage forms for topical application, are discussed in this paperwork.

Keywords: pulmonary fibrosis, flavonoids, experimental models

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ОБЗОР

Перспективы применения веществ флавоноидного ряда при фиброзе легкого (обзор экспериментальных исследований)

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РЕЗЮМЕ

Фиброз легкого развивается как спонтанно, так и вследствие воздействия повреждающих факторов, включая лучевую и химиотерапию, инфекционные заболевания, вдыхание вредных веществ и твердых частиц. При этом происходит нарушение нормальной репарации тканей: вместо регенерации нормальных клеток легкого происходит замещение поврежденной ткани фиброзной, состоящей из плотных коллагеновых волокон. Этот процесс ведет к утрате эластичности легочной ткани и нарушению ее функции, что существенно снижает качество жизни пациентов. Поиск средств для лечения интерстициальных фиброзирующих заболеваний легкого остается актуальной задачей, т. к. существующие антифибротические препараты лишь замедляют их прогрессирование и обладают побочными эффектами, существенно снижающими качество жизни пациентов. Считается, что природные вещества полифенольной природы, в частности, флавоноиды, могут применяться для лечения фиброза легкого. Флавоноиды, присутствующие в различных фруктах, овощах, чае и вине, демонстрируют широкий спектр биологических активностей. Они обладают антиоксидантными, противовоспалительными и иммуномодулирующими свойствами, что делает их перспективными для лечения различных заболеваний, включая фиброз легкого. Некоторые исследования показали, что флавоноиды могут ингибировать активацию миофибробластов и продукцию коллагена, что непосредственно связано с процессом фиброзирования. Флавоноиды нетоксичны и способны регулировать процессы, связанные с развитием фиброза: окислительный стресс, воспаление, пролиферацию и дифференцировку клеток. На сегодняшний день накоплено большое количество экспериментальных данных, подтверждающих антифибротическое действие флавоноидов. В последние годы проводятся клинические исследования, направленные на изучение эффективности и безопасности флавоноидов у пациентов с фиброзом легкого. Например, исследуются кверцетин и куркумин, которые показали обнадеживающие результаты в снижении маркеров воспаления и фиброза в легких. Однако основным препятствием для широкого внедрения флавоноидных веществ в клиническую практику остается их низкая биодоступность при пероральном применении и быстрый метаболизм. В данной работе проанализированы данные литературы о влиянии флавоноидов на развитие фиброза легкого в экспериментах и в клинических исследованиях, обсуждаются перспективы улучшения их биодоступности с помощью современных систем доставки (наночастицы, липосомы и др.), или использования лекарственных форм для местного применения.

Ключевые слова: фиброз легкого, флавоноиды, экспериментальные модели

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INTRODUCTION

The spectrum of interstitial fibrotic lung diseases is quite wide, but all of them lead to a gradual decrease in respiratory function, a significant decrease in the quality of patients' life and premature death [1]. Life expectancy after diagnosis in idiopathic pulmonary fibrosis (IPF) is on average 3–5 years [2], and the average five-year survival rate for this disease is 45.6 % [3]. Existing treatment methods and registered antifibrotic drugs somewhat slow down the progression of the disease and reduce the mortality rate, but have contraindications and side effects, so their long-term use is not always possible [4, 5]. Since the disease can occur for several years, finding drugs that can slow down or stop the progression of pulmonary fibrosis (PF) and are safe with long-term use, is an urgent task. In recent years, much attention has been paid in this regard to natural substances of polyphenolic nature, in particular, flavonoids.

These substances are found in various parts of plants and are an important component of traditional medicine and functional nutrition [6]. Flavonoids are nontoxic and are able to regulate the processes involved in the development of fibrosis: oxidative stress, inflammation, cell proliferation and differentiation (in particular, epithelial-mesenchymal transition), intercellular interactions [7, 8]. To the date, a substantial experimental evidence base has been accumulated justifying the use of flavonoids as antifibrotic agents. In addition, several pilot clinical trials have been conducted on patients with IPF [9, 10]. However, their low bioavailability prevents the widespread introduction of flavonoid substances into clinical practice. In this regard, the prospects of using dosage forms for topical use are being considered.

The purpose of the study was to analyze the literature data on the effect of flavonoid substances on the development of lung fibrosis in experiments with laboratory animals and in clinical studies, to identify prospects for increasing their bioavailability using modern delivery systems.

Pulmonary fibrosis: risk factors, occurrence, main mechanisms of pathogenesis

PF can occur as a manifestation of certain systemic diseases (systemic sclerosis, rheumatoid arthritis, etc.), interstitial lung diseases (nonspecific interstitial pneumonia, chronic pneumonitis on the background of hypersensitivity), because of viral and bacterial infections. These diseases are designated as chronic interstitial fibrotic lung diseases with a progressive course [11]. IPF, interstitial pneumonia, is isolated as a separate disease without clarified etiological factors [1]. Risk factors for the development of IPF include smoking, inhalation of particulate substances, viral infections, gastroesophageal reflux syndrome, genetic predisposition, the use of certain medications, ionizing radiation [2, 12].

In this paperwork, we will use the term "pulmonary fibrosis" in relation to all progressive fibrotic interstitial lung diseases, with clarifications if necessary.

The incidence of diseases in which PF occurs is relatively low. According to a 2021 study, the incidence of IPF (per 100,000 population per year) ranged from 3.5 to 13 in the Asia-Pacific region, from 0.9 to 4.9 in Europe and from 7.5 to 9.3 in North America [11]. In Russia, during 2018, an average of 7 new cases of IPF per 100,000 people per year were registered in women and 11 in men [2].

The incidence of other fibrosing interstitial lung diseases in the United States is about 52 patients per 100,000 people per year, of which 33 cases are with a progressive phenotype [14]. It is assumed that after the SARS-CoV19 epidemic, these figures may increase: after the coronavirus infection is cured, some patients experience a decrease in respiratory function and changes in the X-ray picture of the lungs, similar to that of PF [15].

Normally, epithelial damage is repaired by type II alveolocytes, capable of proliferating and differentiating into type I alveolocytes, which line most of the surface of the alveoli and carry out gas exchange. At the same time, in the places of damage, epithelial cells secrete profibrotic factors that cause the activation of resident fibroblasts and their differentiation into myofibroblasts [16]. Myofibroblasts are also formed from circulating bone marrow precursors, epithelial and endothelial cells [17]. The main function of these cells is the synthesis of the intercellular matrix, which is necessary for tissue repair at the site of injury, after which they normally undergo apoptosis, and the excess extracellular matrix is cleaved [18]. The literature describes several mechanisms that can interfere with the normal resolution of the reparative process.

Many authors consider excessive activation of the immune system and chronic inflammation to be the main factors in the development of PF [2, 19]. It has been shown that various cells of the immune system, e. g. neutrophils, macrophages, lymphocytes, contribute to the development of PF due to the activation of oxidative stress and the production of profibrotic growth factors, cytokines and chemokines [2, 20]. It is assumed that activation of the immune response makes a significant contribution to the development of PF associated with COVID-19 [15].

The mechanism of PF development is also described, in which the main role is given to the chronic epithelial damage, leading to an increase in the level of reactive oxygen species, apoptosis, activation of cellular aging, depletion of the stem cell pool and the so-called "phenotypic reprogramming" of the type II alveolocytes [16, 21], i. e. aberrant activation of normal repair pathways and the release of mediators activating fibroblasts [22, 23].

Another mechanism of tissue fibrotization is being considered due to positive feedback from the extracellular matrix [24]. It has been shown that with excessive deposition of the matrix, its densification occurs, which leads to tissue hypoxia and epithelial damage; the compacted matrix creates a profibrotic environment and promotes cellular aging [25, 26]. Thus, a so-called "fibrogenic niche" is created, and the fibrotic process is self-sustaining [24]. Shochet et al. [27] showed that while culturing normal fibroblasts on a "fibrotic" matrix obtained after culturing fibroblasts of patients with IPF (IPF), the expression of genes associated with the HIF1 signaling pathway is activated, which contributes to the differentiation of myofibroblasts and the progression of fibrosis.

Pulmonary fibrosis treatment

Medicinal and non-medicinal methods are used to treat PF. The latest ones include lung transplantation and the use of palliative methods (oxygen therapy, physical exercises, etc.) [28].

Initially, anti-inflammatory drugs, corticosteroids and immunosuppressive drugs were used to treat IPF, based on the hypothesis that chronic inflammation is the main mechanism of development of this disease. These drugs did not improve survival and pulmonary function, and combined therapy with prednisone, azathioprine and N-acetylcysteine increased mortality and hospitalization rates [4]. Two drugs have been registered for the treatment of IPF – nintedanib, an oral inhibitor of intracellular tyrosine kinases, and pirfenidone, a pyridone compound with anti-inflammatory, antifibrotic and antioxidant properties [4]. Both drugs reduce the risk of mortality by almost 2 times, and quintedanib also significantly reduces the risk of acute complications compared with patients who do not take drugs [29]. Nintedanib and pirfenidone have been recognized as effective for other fibrotizing lung diseases [1, 11]. Nevertheless, the long-term use of these drugs often becomes impossible due to the refusal of treatment due to the lack of effect and/or side effects [4, 5, 28].

To date, antibodies to the connective tissue growth factor (CTGF), pentraxin-2, an endothelin receptor antagonist, new small molecules (inhibitors of autotaxin phosphodiesterase, integrins, etc.), and others are being studied as potential antifibrotic drugs (check reviews [4, 30] for details).

The prospects for the use of substances of natural origin, in particular, flavonoids, are discussed, since such compounds have anti-inflammatory, antiproliferative and immunomodulatory effects, as well as low toxicity and can be used long-term. In addition, flavonoids (and polyphenols in general) reduce the toxicity of cytostatics, for example, cyclophosphamide, which is used in patients with PF as an immunosuppressant.

In a pilot study carried out on patients with IPF, it was shown that after 14 days of EGCG (epigallocatechin gallate, the most common catechin found in tea), the content of two biomarkers produced by fibroblasts, cartilage oligomeric matrixprotein (COMP) and periostin, was reduced in serum, as well as collagen I in lung biopsies, SNAI1, phosphorylated SMAD3 [9]. The same team of authors showed that in *ex vivo* lung tissue obtained from patients undergoing lung transplantation, EGCG suppresses the TGF-β1 signaling cascade and collagen accumulation, as well as activates its MMP-dependent decay [31].

In pilot trials on patients with IPF, it was shown that physical performance improved in the group of people taking a combination of dasatinib and quercitin. In addition, a decrease in the level of some markers of cellular aging in the blood was noted [10].

The use of flavonoids in experiments on laboratory animals

To study PF using laboratory animals, a wide range of models are used that reproduce the effect of the main etiological factors of disease development, i. e. genetic predisposition, drug use, radiation, inhalation of solid particles [19, 32]. If experiments with genetically modified or immunodeficient mice help to better understand the molecular genetic mechanisms of PF development, then cheaper and more convenient models of fibrosis induction using tissue-damaging light chemical agents, solid particles or irradiation are most often chosen for screening potential antifibrotic drugs [32]. The most commonly used well–characterized PF model using bleomycin, systemic administration of which leads to damage to the lung endothelium, inflammation, apoptosis of epithelial cells and the launch of reparative processes, and local – directly into the respiratory tract causes direct damage to the alveolar and bronchial epithelium, followed by pronounced inflammation and tissue fibrosing [33].

The relevance of these models is being discussed, however, they reproduce the main aspects of fibrotizing lung diseases in humans at the tissue (excessive deposition of extracellular matrix, decrease in respiratory volume), cellular (epithelial damage, fibroblast proliferation, epithelial-mesenchymal transition) and molecular (oxidative stress, secretion of profibrotic factors) levels.

Table 1 shows studies over the past 5 years that studied the effect of individual flavonoid compounds on the development of experimental lung fibrosis in mice and rats. In almost all the analyzed studies, it was shown that the use of flavonoid-type substances reduces the severity of PF at the morphological level; in two studies, no statistically significant decrease in the histopathological index [34] and relative lung mass [35] was revealed when quercetin was used, however, the drug influenced other studied indicators.

Compared with untreated animals, the use of flavonoids in the lungs reduces the synthesis of extracellular matrix proteins such as collagen and fibronectin [34, 36–38], the content of the myofibroblast marker α-SMA and markers of the epithelial-mesenchymal transition [37, 39, 40]. It was also revealed in experiments that flavonoid preparations contribute to a decrease in the production of profibrotic cytokines in the lung: TGF-β [41–43] and proinflammatory cytokines [35, 39, 42, 44]. The positive effect of the studied substances on the activity of enzymes of the antioxidant defense system and a decrease in markers of oxidative stress were found [35, 36, 43, 44]. Despite the fact that the antifibrotic effect of flavonoids has been studied in several experimental models, and the range of techniques used and the estimated indicators differed, the results of these studies show that flavonoids are able to affect the main mechanisms/aspects of fibrogenesis *in vivo*. The results of animal experiments are supported by data obtained in experiments using flavonoids *in vitro*. Thus, baicalin has been shown to reduce the proliferation of rat pulmonary fibroblasts induced by bleomycin [45].

Flavonoids also have a protective effect on models of chronic obstructive pulmonary disease induced by cigarette smoke or its components. The observed effects of flavonoids are consistent with the results obtained in lung fibrosis models: these substances reduce inflammation, activate antioxidant defense mechanisms, and prevent cellular aging and cell death of the alveolar epithelium [46].

Nevertheless, such experimental studies have been conducted for more than 10 years, and clinical studies remain isolated.

Thus, there is a significant gap between the stages of preclinical development and clinical trials for this class of compounds.

Prospects for the use of flavonoids for the treatment of lung fibrosis

The probable reason for the slow introduction of flavonoid preparations into clinical practice, in addition to the difficulties of standardization and commercial component, may be the limited bioavailability of flavonoids.

Unlike other molecules included in the composition of drugs, flavonoids in unchanged form do not reach target organs when administered orally. When ingested in the form of aglycones, flavonoids undergo metabolic transformation in the intestine (including with the participation of microorganisms) and the liver; the initial forms are practically not detected in blood plasma [54]. The antioxidant activity of conjugated products entering the systemic circulation after methylation, sulfation and

Table 1. Flavonoid-type substances with proven *in vivo* antifibrotic activity

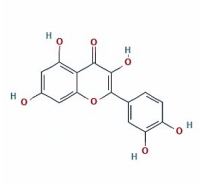
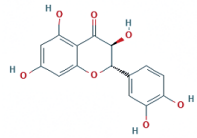
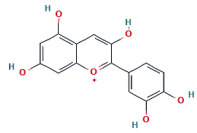
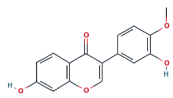
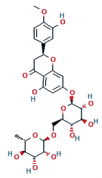
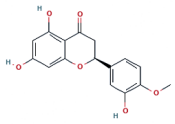
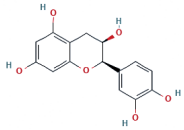
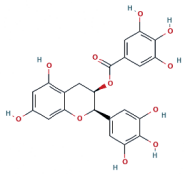
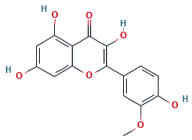
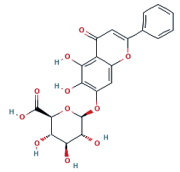
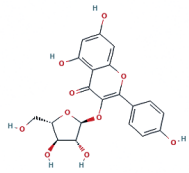
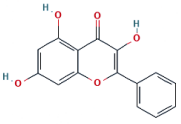
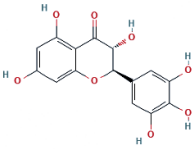
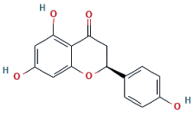
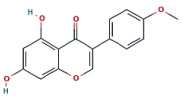
Substance formula	Substance	Model	Reference
	Quercetin	C57BL/6 mice; IT bleomycin	[34]
		Mice, SiO_2	[47]
		Wistar rats; IT bleomycin	[35]
	Dihydroquercetin	C57BL/6 rats; IT SiO_2	[48]
	Cyanidine	C57BL/6 mice; IT SiO_2	[49]
	Calicosin	C57BL/6 mice, IT bleomycin	[36]
	Hesperidin	Sprague-Dawley Rats; IP bleomycin	[42]
	Hesperidin	Wistar rats; IT SiO_2	[44]
	Epicatechin	NMRI mice; IT bleomycin	[43]
	Epigallocatechin gallate	C57BL/6 mice; solid particles intranasally	[50]
		Wistar rats; IT SiO_2	[51]

Table 1. Flavonoid-type substances with proven *in vivo* antifibrotic activity

Substance formula	Substance	Model	Reference
	Isoramnetin	C57BL/6 mice; IP bleomycin	[37]
	Baikal	Wistar rats; IT bleomycin	[45]
	Yuglanin	C57BL/6 mice; IT bleomycin	[40]
	Galangin	C57BL/6 mice; IT bleomycin	[52]
	Dihydromyricetin	C57BL/6 mice; IT bleomycin	[39]
	Naringenin	Balb/c mice; Mycoplasma infection	[53]
	Biochanin A	Wistar rats; IT bleomycin	[38]

Notes: IT stands for intratracheal, IP stands for intraperitoneal

glucuronidation is significantly reduced compared to that of the corresponding aglycones [7]; metabolites are rapidly excreted from the body. It is more likely that flavonoids, more precisely, the products of their metabolism, are able to activate the antioxidant defense system through the KEAP1-NRF2 pathway, which regulates the adaptive response to cellular stress [8].

Obviously, in order to increase the activity of flavonoids, it is necessary to provide ways and forms of administration that will avoid or minimize metabolic transformation in the intestine and liver. For the treatment of PF, these may be options for inhalation use or taking flavonoids in complexes with carriers. Such delivery systems include phytosomes (complexes of plant substances with phospholipids), lipid nanoparticles, polymer nanoparticles, and inorganic nanoparticles [7].

In particular, after administration of quercetin to mice as part of cationic lipid carriers, its higher content was observed in the lung, liver and kidneys compared with the control group that received free quercetin [55]. It was shown that apigenin more effectively inhibited the development of bleomycin-induced lung fibrosis in rats when it was administered to animals as part of polymer nanoparticles, compared with the substance in free form [56]

The use of dosage forms for inhalation has a number of advantages, such as the delivery of active substances directly to the lung, a relatively low content of substances in the systemic circulation, and ease of use [57]. In rats with induced PF, inhalation of pirfenidone or quintedanib gave the same therapeutic effect as oral administration, while the dose with topical application and, accordingly, the manifestations of side effects were significantly lower Rasooli et al. 2018; Surber et al. 2020, cit. according to [57]).

The bioavailability of naringenin complexes with hydroxypropyl-β-cyclodextrin was studied *in vivo*. It was found that the solubility of the flavonoid in the complex increases, and with intratracheal application, naringenin accumulates mainly in the lung [58]. It has also been shown that the bioavailability of naringenin in solid lipid particles is 2.5 times higher than in free form when administered intratracheal [59]. The effectiveness of naringenin-loaded phytoses based on the surfactant component dipalmitoyl phosphatidylcholine was demonstrated in a model of acute lung injury in rats [60].

Thus, the use of flavonoids in the composition of nanoparticles, liposomes and other carriers, including in the form of inhaled dosage forms, makes it possible to improve their bioavailability, as well as ensure the delivery of starting substances to the lung, rather than products of their metabolism.

CONCLUSION

Treatment of PF remains an urgent problem, because existing drugs only slow down the progression of this deadly disease, and their long-term use is often associated with serious side effects. In recent years, natural substances, in particular, flavonoids, have been studied as an alternative or accompanying therapy. Numerous animal and *in vitro* studies prove that flavonoids have antifibrotic properties. At the same time, due to the peculiarities of the metabolism of these substances in the mammalian body, with oral administration of flavonoids, they enter the lung only in small amounts in the form of secondary metabolites. The solution to this problem may be the development of delivery systems such as liposomes, as well as dosage forms for topical use.

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