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Promising compounds from natural sources against COVID-19

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ABSTRACT. The epidemic associated with the new Sars-CoV-2 coronavirus has affected almost all countries of the world and no reliable treatment for this infection exists yet. Many laboratories in the world are currently conducting intensive experimental and theoretical/in silico studies to find effective drugs specific for this disease (COVID-19), but unfortunately, it may take a long time before new drugs appear in the clinical practice. One of the currently widely accepted approaches for finding active compounds is based on the possibility of using existing drugs approved by government medical organizations (as the FDA). Their choice is based on screening, based on the use of computer models that evaluate the specific binding (energy minimization) of such drugs to target molecules that are important for the life cycle. Thus, a few well-known antiviral drugs against HIV, hepatitis C and others selected on this basis exerted an antiviral effect in vitro, but their real effectiveness was far from expected. It should be emphasized that the severe clinical manifestation of the disease is an acute respiratory distress syndrome, mediated by oxidative stress and an aggressive immune attack on its own cells. In this regard, the use of compounds with high antioxidant activity could have advantages both prophylactically and medically. There is a huge range of natural compounds, including official and traditional medicine, which represent valuable unlimited potential for COVID-19 therapy, the advantage of such compounds in their low toxicity. In this review, we tried to focus on the clinical and pharmacological properties of natural substances, mainly flavonoids, which can become promising drugs for the treatment and prevention of COVID-19. The review includes information on possible virus targets and antiviral drugs. Much attention is paid to the question of inhibition of viral activity. Based on published data, including structural features of various compounds, a prediction is made about the prospects of using these compounds as inhibitors of viral activity, as well as anti-inflammatory drugs for the treatment of COVID-19. An important step in the analysis of compounds was the study of the possibility of their interaction with cellular targets of the virus, as well as the ability to bind to the proteins of the Sars-CoV-2 virus itself.

Keywords: COVID-19, SARS-CoV-2, antiviral drugs, flavonoids, treatment, antioxidants

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Перспективные соединения из природных источников для терапии COVID-19

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РЕЗЮМЕ. Эпидемия, связанная с новым коронавирусом Sars-CoV-2, поразила практически все страны земного шара, и надежных лечебных средств от этой инфекции пока не существует. Многие лаборатории в мире в настоящее время ведут интенсивные экспериментальные и теоретические исследования с целью поиска эффективных препаратов, специфичных для этого заболевания (COVID-19), но, к сожалению, может потребоваться много времени, прежде чем новые лекарства появятся в клинической практике. Один из самых популярных подходов основан на возможности использования для лечения существующих препаратов, одобренных правительственными медицинскими организациями. Их выбор основан на скрининге, в основе которого лежит использование компьютерных моделей, оценивающих специфическое связывание (минимизация энергии связывания) таких препаратов с молекулами-мишенями, важных для жизненного цикла. Так, ряд известных антивирусных препаратов против ВИЧ, гепатита С, выбранных подобным образом, оказывали противовирусный эффект in

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vitro, но их клиническая эффективность была невысокой. Следует подчеркнуть, что тяжелая форма клинического проявления заболевания представляет собой острый респираторный дистресс-синдром, опосредованный окислительным стрессом и агрессивной иммунной атакой на собственные клетки. В этой связи применение соединений с высокой антиоксидантной активностью может иметь преимущества как в профилактическом, так и в лечебном плане. Существует огромный спектр природных соединений, включая препараты официальной и традиционной медицины, которые представляют неограниченный потенциал, в том числе для терапии вирусных заболеваний. Основным преимуществом подобных соединений является их низкая токсичность. В данном обзоре мы постарались сделать акцент на клинические и фармакологические свойства природных веществ, преимущественно флавоноидов, которые могут стать перспективными препаратами для лечения и профилактики COVID-19. В обзор включена информация о возможных мишенях вируса и противовирусных препаратах. Большое внимание уделено вопросу ингибирования вирусной активности. На основе литературных данных, в том числе о структурных особенностях различных соединений, сделан прогноз о перспективности использования данных соединений в качестве ингибиторов вирусной активности, а также в качестве противовоспалительных средств для терапии COVID-19. Важным этапом при анализе соединений было изучение возможности их взаимодействия с клеточными мишенями вируса, а также способности связывания с белками самого вируса Sars-CoV-2.

Ключевые слова: COVID-19, SARS-CoV-2, противовирусные препараты, флавоноиды, лечение, антиоксиданты

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Introduction

Due to the epidemic that has covered almost the entire globe, many laboratories in the world are currently conducting intensive experimental and theoretical studies to try to find effective drugs specific to COVID-19. Since much is already known about the life cycle of the virus, the structure of the virion (Sars-CoV-2), cellular receptors and the mechanism of its entry into the cell, attempts are made experimental and theoretical (in silico) to calculate possible active drugs from existing ones approved by state medical organizations (such as FDA).

Suitable targets and possible known drugs for blocking SARS-CoV-2 infection

The enveloped SARS-CoV-2 virions (60–160 nm) contain single positive-stranded RNA and 4 structural proteins: S (spike), E (envelope), M (membrane) and N (nucleocapsid) where the S glycoprotein responsible for the virus/host cell binding and fusion [1]. This virus enters the cell using in the main the angiotensin converting enzyme 2 (ACE2) localized to the cell surface. The ACE-2 is expressed on the cells of various organs, heart, kidneys, blood vessels, and most importantly, on lung epithelial cells. The host proteases furin activates S protein by priming it for two subunits S1 and S2 since without this process the binding affinity would be low. This feature distinguishes the Sars-CoV-2 from other similar coronaviruses, Sars-CoV and Sers-CoV [1]. The S1 subunit comprises a receptor-binding domain (RBD) that has only a 40% amino acid identity with other SARS-CoVs, while S2 subunit is responsible for the fusion between the viral and cellular membranes. RBD of SARS-CoV-2 possesses about 10-20 times higher receptor binding affinity than that of SARS-CoV S protein [2]. It is likely that this may play a role in the reported higher permeability and contagiousness of SARS-CoV-2. The viral RNA (genome about 30 kb) encodes non-structural proteins the most important of which is main chymotrypsin-like protease (M^{pro}; 3CLpro, nsp5), papain-like protease (PL^{pro}, nsp3), helicase and RNA-dependent RNA polymerase (RdRp). The proteases M^{pro} and PL^{pro} are to process the viral polyprotein into functional units necessary for virus replication and packaging [3, 4]. Considerable interest is now attracted to the M^{pro} protease whose structure is relatively conservative [5] and to the ACE-2 as a main receptor.

Currently, researchers focus on the search and selection of inhibitors that can block the entry of the virus into the cell and enzymes that are important for the life cycle of the virus. First, the choice for patient treatment is made in favor of the FDA-approved drugs. They include numerous antiviral drugs, antibiotics and other compounds, the potential affinity of which is evaluated by computer simulations (docking and molecular dynamics) due to the lack of available experimental models. Among these selected drugs are IFN analogues, Lopinavir, Ritonavir, Simeprevir, Paritaprevir, Favipiravir, Remdesivir, Hydroxychloroquine, Azitromycin and others, with many of them being used to treat AIDS [6–9]. However, their actual activity against COVID-19 is being evaluated in clinical trials now [10]. In a recent work, comparative computational study of 2500 small molecules in the FDA-approved drug database using a rapid analytical protocol to find potential inhibitors of M^{pro} was carried out. As a result, 15 perspective compounds were identified with considerable activity, and among them Dipyridamole had the highest score [11]. Furthermore, the experiments on its binding to recombinant M^{pro} (technique based on Biacore sensorics) showed a high binding affinity. In addition, as proven experimentally, the drug reduced the inflammation caused by the SARS-CoV-19 mediated through a NF-kB

signaling mechanism. Clinical trials (1st round, 31 patients with COVID-19) demonstrated significant clinical results [11]. Dipyridamole is a coronary vasodilatator, but it was found to inhibit virus-induced cytopathic effect against a broad-spectrum of virus families [12, 13].

Iranian researchers screened 6654 compounds by molecular docking in a test for their binding to viral protease (binding threshold < –7.7 kcal/mol). The selection was further narrowed down by excluding the compounds that had strong side effects and were not easily available in the market. As a result, the drug with aromatic resonance structure, Cinanserin, was selected as a substance with the best affinity [14]. Baricitinib, Fedratinib, and Ruxolitinib are potent and selective JAK inhibitors approved for treatment of rheumatoid arthritis and myelofibrosis. All three are powerful anti-inflammation drugs that, as JAK–STAT signaling inhibitors, are likely to be effective against the negative effects of the elevated levels of cytokines (including interferon-γ) typically observed in the patients with Covid-19. Although these three drugs have similar JAK inhibitor potencies, Baricitinib seems to be the best choice, especially considering the possibility of oral administration (only once a day) and an acceptable side-effects profile. The most significant side-effect of Baricitinib observed during long-term clinical trial programs was only small infections of the upper respiratory tract, but the incidence of serious infections were rare, and in the case of using baricitinib for patients with Covid-19 there would be no serious complications [15, 16].

However, many of the drugs mentioned here have undesirable side effects and must be used with caution only for hospital care in case of clinical trials, while their activity against this virus remains uncertain. For example, drug Hydroxychloroquine used to treat systemic lupus erythematosus and certain types of malaria became widely known several weeks ago thanks to a study by French scientists as an anti-Covid-19 drug, did not show strong activity according to Chinese clinicians [17], and the drug can be unsafe for people with cardiac arrhythmias and kidney or liver problems. Although the FDA and the Ministry of Health of Russia recently improved the use of hydroxychloroquine as a drug for certain people who are hospitalized with COVID-19 (Hydroxychloroquine.Wikipedia).

Development of SARS-CoV-2-specific drug seems to be quite a complicated task requiring a lot of effort and time for all stages of the preclinical and clinical trials. On the other hand, knowing the specific features of the pathological mechanism of the coronavirus, we can try to use drugs for treatment that can block processes not at the virus level, but rather at the level of the host organism. Acute respiratory distress syndrome and lung damage caused by SARS-CoV-19 apparently depend on the activation of oxidative stress which triggers the production of pro-inflammatory cytokines, such as IL-1β, IL-8, IL-18, IL-6, IFN and TNF-α [18]. Neutrophils and macrophages generate special oxidizing molecules through the NADPH system to destroy foreign elements, but their redundancy results in damage of many normal cells [19]. The IL-1β and IL-18 together with caspase-1 trigger a form of cell death called pyroptosis which in contrast to apoptosis is proinflammatory [20, 21]. With influenza infection, pyroptosis also promoted by IFN is observed in the late stage of disease-causing death of epithelial cells [22]. A TLR4 signaling is a key disease pathway that controls the severity of induced acute lung injury, and production of oxidized phospholipids that may potentially induce lung injury and cytokine production by lung macrophages were observed in all tested SARS-infected human patients [23]. Unfortunately, the pathogenesis mechanism of COVID-19 and molecular processes of virus-induced acute lung injury remain unclear. But it is obvious, based on the analogy with older coronaviruses, that acute inflammation is always accompanied by mass production of pro-inflammatory cytokines, damage and death of pulmonary epithelial cells, which in severe cases leads to lethal outcome. Given the lack of real antiviral drugs against Sars-CoV-2, the identification of compounds that can inhibit the production of pro-inflammatory cytokines is highly desirable. In this regard, it makes sense to pay attention to known relatively non-toxic drugs and natural substances and their modifications, to substances of plant origin: polyphenols, terpenoids and carotenoids [24]. It should also be noted that some known antiviral drugs have aromatic/polyphenol structure and could also possess antioxidant activity [25]. Since ancient times, plants have been an invaluable source of traditional medicines and many of them have been tested for effectiveness by many generations of people.

Promising compounds from natural sources

The search for potential protease (M^{pro}) inhibitors from plants among terpenoid compounds using a docking model and molecular dynamics was undertaken by the Iranian researcher. As a result, 9 perspective substances from different plant sources were revealed and among them the Ginkgolide A from the tree *Gingko biloba* had a high score since calculations suggest that it can form specific bonds with the amino acids in the active center of M^{pro} [26].

In mid-March 2020, Chinese researchers published a preprint [27] about the discovery of another specific receptor, CD147, in addition to ACE-2. The anti-CD147 humanized antibody significantly inhibited the penetration of the virus into host cells, and verification of the interaction between CD147 and the virion spike protein showed high binding affinity (1.85×10^{-7} M). Data on co-immunoprecipitation, ELISA and immune-electronic microscopy also confirmed this fact. The discovery of new targets provides opportunities for the development of new specific drugs. The literature search for possible low molecular weight inhibitor ligands for CD147 undertaken by us (excluding exotic and unavailable ones) revealed natural compound with antioxidant activity:

baicalin, flavonoid component of the plant *Scutellaria baicalensis* [28]. Interestingly, it was shown earlier that Baicalin has an anti-inflammatory effect due to the suppression of the pro-inflammatory genes responsible for the production of nitric oxide, cyclooxygenase, lipoxygenase, cytokines production including IL-6, IL-1, TNF-α and also the monocyte chemotactic protein playing a critical role in inflammatory reactions (regulating leukocyte recruitment) [29]. The root extract is used in the traditional Chinese medicine as an anti-aging agent; moreover, baicalin stimulates brain performance, exhibits antitumor effects and improves cardiac activity. This property can be attributed to the phenolic moiety of baicalin, aglycon, bearing some similarities to the resveratrol molecule (see below), potent antioxidant which in turn showed pronounced activity against MERS-CoV infection [30, 31]. In addition to baicalin, *S. baicalensis* contains many other useful antioxidants. We do not exclude that such compounds as Vogonin, Oroxilin, Neobaikalein and Chrysin may have a protective effect in case of SARS-CoV-2 infection. Thus, *Scutellaria baicalensis* extract, in our opinion, can be a valuable source of potentially useful compounds for the prevention and treatment of COVID-19.

Surprisingly, after these lines were written, a preprint was published (April 10) by Chinese authors indicating that the main component of *Scutellaria baicalensis*, baicalein, strongly inhibits the activity of SARS-CoV-2 Mpro in vitro, with IC50 =0.39 μM. In addition, four others active compounds from various herbs were also described but their activity was slightly lower. The extract of *S. baicalensis* was also effective against SARS-CoV-2 infection [32]. It should be noted that 8 years ago the papers were published where similar compounds, Scutellarin and Myricetin, demonstrated activity against SARS-CoV-1 coronavirus helicase [33, 34]. It is possible that various other flavonoid compounds of *S. baicalensis* may have protective properties against SARS-CoV-2 infection.

Further evidence that flavonoids can inhibit coronavirus infection follows from an article published before the onset of Covid-19 epidemic. 3-isotheaflavin-3-gallate (TF), a potent natural antioxidant of black tea, was found to inhibit in vitro the SARS-CoV-1 protease $3CL^{Pro}$ (IC_{50} =7 μM); black tea extracts also had similar activity [35]. Since there is some evidence that SARS-CoV-2 infection can be initiated and transmitted through the intestinal tract, demonstration of the virus-neutralizing activity of black tea TF can be very important [36]. But it should also be noted that the degree of penetration of TF through the intestines into the bloodstream is quite low.

Resveratrol is a well-known antioxidant, and also anti-inflammatory and antitumor agent that protects plants from bacterial and fungal infections. Resveratrol testing for antiviral activity against MERS-CoV infection (in vitro) demonstrated significant effectiveness. The authors indicated that inhibition could be attributed to enhancing the signaling through Sirtuin 1 (histone deacetylase), DNA repair, and a decrease in apoptosis and inflammatory reactions caused by pro-inflammatory cytokines [37]. In other work, when analyzing possible repressors of ACE2 and FURIN genes whose translation products help the virus enter the cell, promising compounds from a set of existing drugs were identified and tested on transgenic models. The leading compound was Quercetin, a polyphenol from the flavonoid group found mainly in red-colored plants, especially in red onion. Quercetin appears to directly interfere with the binding of the SARS-CoV-2 virus to human ACE2 thereby inhibiting the penetration of the virus into cells [38, 39]. Earlier experiments demonstrated anti-inflammatory properties of Quercetin at a high level of oxidative damage [40].

Other promising compounds

Melatonin was discovered as a regulator of the circadian rhythm in various organisms including bacteria, protozoa, plants, fungi, invertebrates, and at the same time its most important function is antioxidant and free radical scavenging activities associated with modulation of both pro- and anti-inflammatory cytokines [41]. Due to these features' melatonin has also been found to be effective against viral infections in a variety of experimental animal and in vitro studies [42]. Its protective role was shown against influenza: melatonin significantly reduces production of TNF-α, IL-6, and IFN-γ and at the same time increases the levels of IL-10 and TGF-β [43].

In acute lung injury and respiratory distress syndrome, Melatonin alleviates symptoms by suppressing inflammation through the effect on the NLRP3 inflammasome. Melatonin disrupts the pathological cycle formed by the cytokine IL-1β coupled with the inflammasome inhibiting the activation of signaling via NF-κB and mitochondrial ROS production [44, 45]. Although obviously there are still no reports on the use of Melatonin in patients with COVID-19, its use for the treatment of other diseases has shown promising results, as it markedly reduced the levels of circulating cytokines [46]. Melatonin has been shown to successfully inhibit pneumonia and protect macrophages from pyroptosis, has a high safety profile which suggests that it can be an effective suppressor of COVID-19 mediated oxidative damage [45, 46].

Another promising agent is Dexpanthenol (provitamin of B_5) taking into consideration its marked inhibition ability of the LPS-induced neutrophiles influx, protein leakage, and release of TNF-α and IL-6 in bronchoalveolar lavage fluid and thus it can protect from acute lung injury due to its antioxidative activity [47]. In the recent publication, Chinese researchers reported that the rate of SARS-CoV-2 replication is 3–4 times higher than that of SARS-CoV, and recommended the use of antagonists against major inflammatory mediators, such as IL-6, along with effective antiviral agents, but avoid excessive suppression of the innate immune response [48].

Out of newly developed structures, fullerene carbon allotropes with strong electron withdrawing ability de-

spite synthetic origin have been also detected in nature. Fullerene C60 derivatives have shown prominent antiviral properties in different studies. Water-soluble fullerene derivatives are known to inhibit HIV protease, preventing virus from reproducing [49, 50]. Fullerene carbohydrate derivatives can affect Ebola virus pathogenicity by binding DC-SIGN lectin of human macrophages [51, 52]. Previously, we found that the aqueous solution of C60/N-methypyrrolidone complex (ASF) has antiviral activity in vitro and in vivo against herpes simplex virus (HSV-1) and human cytomegalovirus (HCMV) [53]. Although the mechanism is not well understood, the effects of fullerene may be associated with its antioxidant activity and partially with its direct virucidal effect. Furthermore, both native and amino-acid modified fullerenes have demonstrated antiviral effect for HSV 1 and 2, most likely by inhibiting cell lipid chain oxidation, required for viral penetration through cell membrane [54]. The water-soluble fullerene C60 in form of non-covalent complex with polyvinylpyrrolidone is known as a free radical scavenger. It significantly inhibited the production of proinflammatory cytokines induced by TNF-α in synovial fibroblasts, infiltrating lymphocytes, and macrophages in the rat model of arthritis [55]. The decrease in TNF-α, IL-6, IL-1 under the action of hydroxylated fullerene was also shown in an in vitro model of oxidative stress in cells with overexpression of TLR2 receptors in mouse peritoneal macrophage culture [56]. Moreover, ASF could modulate the expression of proinflammatory cytokines TNF-α and IL-6 that was shown in a wound model of inflammation [57]. While neither fullerene, nor its derivatives have been approved for medical use, the trials for currently registered antiviral drugs in COVID-19 therapy are still underway, this is likely to boost the search for new antiviral therapeutics.

Conclusion

Summing up, we want to note that natural antioxidants, and not only natural ones, can be considered as promising antiviral agents. The Sars-CoV-2-induced oxidative stress leads to significant interference with metabolic processes, especially with respect to the immune system. And probably, we do not yet know the full picture of these changes. Plant polyphenolic compounds, natural endogenous compounds (melatonin), and some synthetic substances (fullerene) have low toxicity combined with high antioxidant activity. Moreover, they are all substances with a wide spectrum of action, and the most important fact is that some of them are able to exhibit not only an antioxidant effect, but also specifically bind to important proteins involved in the life cycle of a cow virus. Thus, it is obvious that a therapy system including both inhibition of virus replication and suppression of proinflammatory cytokine production is highly desirable. If it is impossible to destroy the virus, then it is necessary to eliminate its destructive consequences.

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