Seaweed Sulfated Polysaccharides

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Seaweed sulfated polysaccharides (PSs) has wide therapeutic potential, including anticoagulant, thrombolytic, and fibrinolytic activities, opens up new possibilities for their study in experimental and clinical trials. These natural compounds can be important complementary drugs for the recovery from hemostasis disorders due to their natural origin, safety, and low cost compared to synthetic drugs.

seaweed polysaccharides fucoidans carrageenans ulvans anticoagulants thrombolytics fibrinolytics thrombin inhibitors hemostasis disorders blood coagulation COVID-19 associated coagulopathy SARS-CoV-2

1. Introduction

Hemostasis disorders play an important role in the pathogenesis, clinical manifestations, and outcome of COVID-19. First of all, the hemostasis system suffers due to a complicated and severe course of COVID-19. In the initial stage of the disease, a significant number of COVID-19 patients develop signs of hypercoagulation, and in the later stages, signs of disseminated intravascular coagulation (DIC) syndrome. Coagulation disorders and their clinical manifestations have a number of differences from the classic DIC syndrome, and are named COVID-associated coagulopathy [1][2][3].

Patients with severe COVID-19 have a tendency toward thrombotic complications in the venous and arterial systems, which is the leading cause of death in this disease [1][4][5][6].

The treatment of COVID-19 patients and, in particular, correction of the hemostasis disorders is a difficult problem. Despite the data on the effectiveness of heparin drugs in reducing mortality in severe COVID-19 patients, and despite thromboprophylaxis [7][8], the development of venous and arterial thromboembolic complications has been reported. There is also a problem with the optimal dosage of anticoagulant agent [5][9][10][11]. Thus, there are a number of unresolved issues regarding the use of these drugs.

In this regard, there is a need to use the effective anticoagulants and antithrombotic drugs, as well as their optimal dosages, in the treatment of COVID-19 patients and for the prevention of thrombotic complications [7][12][13].

Despite the success achieved in SARS-CoV-2 therapy, the development of more effective treatment regimens for this infection with the inclusion of anticoagulants, thrombolytics, and fibrinolytics, as well as the search for new

effective drugs of this pharmacological group, does not lose relevance. The wide therapeutic potential of seaweed sulfated polysaccharides (PSs), including anticoagulant, thrombolytic, and fibrinolytic activities, opens up a new possibilities for their study in experimental and clinical trials.

2. Treatment Strategies of COVID-19-Induced Hypercoagulation and the Potency of Seaweed Sulfated PSs for the Correction of Hemostasis Disorders

The treatment of COVID-19 patients, and in particular hemostasis disorders, is challenging and a difficult issue, since the pathogenesis of the disorders is not completely clear.

Addressing the need for the use of anticoagulants, their optimal dosage in the prevention and treatment of patients with COVID-19, and the control of anticoagulant therapy are important issues. Heparin drugs are often used as anticoagulants in the treatment of patients with COVID-19. There is unfractionated heparin (UFH)—first-generation preparations called heparin, which are a mixture of PSs with a molecular weight (MW) in the range of 2–30 kDa (with a predominance of high-molecular fractions of glycosaminoglycan), and low-molecular-weight heparin (LMWH), obtained by chemical or enzymatic hydrolysis of UFH and having a molecular weight of 3–7 kDa.

The mechanism of anticoagulant action of heparin is to inhibit the activity of thrombin (clotting factor IIa), which catalyzes the conversion of fibrinogen to fibrin and some other reactions in the hemostatic system. The antithrombin activity of heparin depends on the presence of the plasma protein antithrombin III (AT III). When heparin binds to AT III, conformational changes occur in the latter molecule, which allow it to quickly connect to the active center of thrombin and other serine proteases (factors IXa, Xa, XIa and XIIa, kallikrein, and plasmin) [14]. Therefore, heparin inhibits thrombosis, contributing to the inactivation of thrombin by its physiological inhibitor AT III. In the presence of heparin, the inactivation of thrombin by antithrombin III is accelerated about 1000-fold. Slightly less important for the manifestation of the anticoagulant effect of heparin is the “heparin II cofactor” (HC II), the second heparin-dependent thrombin inhibitor other than AT III, which neutralizes thrombin only at high concentrations of heparin in the blood plasma [15][16].

Both UFH and LMWH form complexes with AT III. However, if the UFH-AT III complex equally inhibits thrombin (factor IIa) and factor Xa, as well as other enzyme blood-clotting factors (Hageman factor, factors IX, XI, XII, etc.), then the anti-Xa activity prevails in LMWH [14][17][18][19].

Among the direct acting parenteral anticoagulants, it is recommended to give preference to LMWH compared to UFH, since the inhibitory activity of LMWH is stronger toward factor Xa, and LMWH rarely causes such complications as heparin—induced thrombocytopenia and osteoporosis. Qian et al. [20] observed a reduction of treatment duration in patients with acute exacerbation of chronic obstructive pulmonary disease receiving ventilatory support using LMWH. ISTH interim guidance recommends LMWH as a first-line therapy for the prophylaxis of VTE in hospitalized patients with COVID-19 [8]. The synthetic drug fondaparinux has also been shown to be effective for the prevention of VTE in older acute medical patients and in reducing total mortality [21].

According to Tang et al. [7], LMWH contributed to a decrease in mortality in patients with sepsis-induced coagulopathy. The same author has shown the effectiveness of enoxaparin for prophylactic coagulation abnormalities in COVID-19 patients.

With regard to the dosage of heparin, a prophylactic dose of LMWH is recommended for the prevention of VTE in hospitalized patients with COVID-19, and a therapeutic dose of LMWH is recommended for patients with significantly elevated D-dimer concentrations [22].

Therefore, taking into account the pathogenesis, prevention, and treatment regimens for severe complications of COVID-19, LMWH are included in the treatment protocols for all hospitalized patients. LMWH is also recommended for use in the outpatient setting. The administration of LMWH, the duration of its use, and the dose should be determined taking into account the risk factors for each patient in combination with laboratory monitoring.

Prospective clinical trials are ongoing to confirm the benefits of using anticoagulants to improve the survival of COVID-19-patients.

In addition, direct oral anticoagulants are used in COVID-19 patient therapy. However, as Testa et al. [23] have shown, when used concomitantly with antiviral agents, the latter, especially those that interact with P-glycoprotein and/or cytochrome P450-based metabolic pathways, can alter the pharmacokinetic and pharmacodynamic profiles, hence altering their anticoagulant activity and increasing the risk of bleeding. In this regard, although direct oral anticoagulants are convenient for the outpatient management of COVID-19 patients, caution is recommended, given their interaction with other drugs used to treat COVID-19 [24][25].

The use of heparins as anticoagulants is also indicated when taking into account the additional mechanisms of their action. In particular, heparin exhibits anti-inflammatory activity by inhibiting the recruitment of neutrophils into tissues, binding and neutralizing inflammatory cytokines and acute phase proteins, and potentially having a protective effect on the endothelium [26][27][28][29]. It also has been hypothesized that heparin may interfere with the interaction between the virus and the host cell via a nonspecific ion bond, and thus may contribute to reducing the frequency of infected cells in COVID-19 [27]. A number of studies have reported that the use of heparins in critically ill COVID-19 patients contributed to a decrease in the production of elevated cytokines (IL-6 and TNF-α) [30]. Additionally, heparin protects the endothelium [31]. There are also data that heparin interacts with spike proteins of several viruses, including the SARS-CoV-2 spike protein receptor-binding domain, suggesting that it may be able to modulate protein's interactions with the endothelium [32]. Due to these characteristics, LMWH remains as the best choice of anticoagulant for hospitalized patients with severe COVID-19.

However, despite evidence that heparin in prophylactic doses is effective in reducing mortality in severe COVID-19 patients, a number of studies have reported a high incidence of venous and even arterial thromboembolic complications (deep vein thrombosis, pulmonary embolism or in situ thrombosis in the pulmonary arteries, and arterial thrombosis), despite thromboprophylaxis, which raises the issue of increasing anticoagulant doses. Prospective studies are currently in progress to try to answer this question [5][33][34].

White et al. [35] also reported heparin resistance in COVID-19. According to the authors, out of 14 patients with COVID-19 associated coagulopathy and with a high risk of thrombosis, who were treated with LMWH or UFH, resistance to UFH was documented in 8/10 (80%) patients, and suboptimal peak anti-Xa following therapeutic LMWH in 5/5 (100%) patients.

There is also the problem of anticoagulants' optimal dose strategy. For example, a reduction in mortality in hospitalized patients with COVID-19 is shown when using a therapeutic, but not a preventive, dose of anticoagulants [12][13][36].

Taking into account the high frequency of thromboembolic complications, the International Society on Thrombosis and Haemostasis' guidelines continue to recommend thromboprophylaxis for all hospitalized patients, and in most patients with COVID-19, thromboprophylaxis should be continued after hospital discharge [9].

The Expert Group of American Society of Hematology recommended the use of prophylactic-intensity anticoagulation compared to moderate-intensity or therapeutic-intensity anticoagulants for critical COVID-19-related patients or acute COVID-19 patients who do not have a confirmed VTE [37]. Taking into consideration their activation and their role in the clot formations, platelets are a potential target for the prevention of complications in SARS-CoV-2 infection [38][39][40][41]. The most commonly used antiplatelet agents are aspirin, clopidogrel, lopinavir/ritonavir, vorapaxar, and dipyridamole [41][42][43][44]. Among the antiplatelet agents, aspirin and clopidogrel are associated with decreased risk of ARDS, as well as decreased mortality among critically ill COVID-19 patients [43][44].

Vorapaxar and dipyridamole are considered promising antiplatelet agents for the treatment of COVID-19. Vorapaxar exhibits its antiplatelet activity through the antagonism of protease-activated receptor 1 (PAR-1), which plays an important role in thrombin-induced platelet aggregation, and is associated with blood clotting and inflammation [45].

For example, Liu et al. [42] used dipyridamole with a positive clinical effect. However, these authors note that there are a number of questions regarding the use of antiplatelet drugs in COVID-19 treatment, and therefore additional clinical trials are needed [42].

The data presented above indicate that anticoagulant and antithrombotic therapy play a key role in the treatment of hemostasis disorders in COVID-19, but there are still a number of unresolved issues regarding the use of these drugs. Thus, the optimal effective anticoagulant and antithrombotic agents, as well as their doses, remain uncertain.

A separate problem is the interaction of antithrombotic and anticoagulant drugs with specific drugs in COVID-19 treatments, since not all drugs are compatible. An individual approach to the patient is recommended, aimed at the optimal risk/benefit ratio of various antithrombotic strategies, taking into account the underlying hypercoagulable state.

Therefore, the treatment of patients and prevention of thrombosis in COVID-19 requires solving issues related to the need to find new effective anticoagulants, as well as their optimal dosage. In this regard, the search for new effective anticoagulants remains relevant. In this aspect, the sulfated PSs of seaweed are of interest.

3. Conclusions

Seaweed sulfated polysaccharides (PS) possess anticoagulant, antithrombotic, and fibrinolytic properties. These activities depends on the structural features (content and position of sulfate groups on the main chain of the PSs, molecular weight, monosaccharide composition and type of glycosidic bonds, the degree of PS chain branching, etc.). Sulfated PSs act on the hemostasis system both directly and indirectly and affect the factors of the extrinsic and intrinsic coagulation pathways, as well as the final stage of coagulation or the conversion of fibrinogen to fibrin under the thrombin influence. Anticoagulant activity of PS can be associated with plasma AT III, and antithrombotic activity—with an increase in the level of t-PA and competitive binding to the t-PA-PAI-1 complex.

The combination of the anticoagulant, antithrombotic, and fibrinolytic properties allows us to consider seaweed sulfated PSs as alternative sources of new anticoagulant and antithrombotic compounds. In this regard, and along with the low toxicity and relative low cost of their production, sulfated PSs are promising for clinical use and represent an alternative to heparin. The wide therapeutic potential of seaweed sulfated PSs, including anticoagulant, thrombolytic, and fibrinolytic activities, opens up new possibilities for their study in experimental and clinical trials. These natural compounds can be important complementary drugs in the fight against coronaviruses due to their natural origin, safety, and low cost compared to synthetic drugs. However, further investigations are needed regarding the use of seaweed PSs as potential anticoagulants, thrombolytics, and fibrinolytics aimed to correct hemostasis disorders in COVID-19 patients.

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