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Therapeutic Natural Medicines against Thrombocytopenia Associated with COVID-19 Infection

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***Abstract*—** *There are many complications associated with the SARS CoV-2 i.e. a lung injury, neuro-inflammation and GI symptoms. Thrombocytopenia (Low platelet count) increase mortality rate of COVID-19 infected patients. The mechanisms by which this coronavirus affects the hematopoietic system, however, remain unknown. Fever, weakness, and a dry cough are the most common symptoms in COVID-19 patients. Abdominal pain, headaches, palpitations, and chest pain are uncommon signs. Reduced lymphocyte and platelet counts, but normal white blood cell counts, are typical haematological changes. The mechanisms by which this coronavirus affects the hematopoietic system remain unknown. We suggest some natural medicine that may help to prevent thrombocytopenia.*

***Keywords*—** *Thrombocytopenia; Platelet aggregation; Platelet consumption; Lung injury, COVID-19; Natural medicine.*

I. INTRODUCTION

A Novel corona virus found on December 2019 with the pneumonia, caused by severe acute respiratory syndrome corona virus 2 (SARS CoV-2) found in Wuhan, China, WHO named as COVID-19 [1]. There are many complications associated with the SARS CoV-2 i.e. a lung injury, neuro-inflammation and GI symptoms are reported.[2,13] Angiotensin converting enzyme 2 (ACE-2) act as a binding site for SARS CoV-2, due to presence of spike proteins on the surface of SARS CoV-2. It increases its binding affinity for ACE-2 10-20 times more than SARS CoV-1[3,4]. Transmission Human to human transmission of coronaviruses is primarily thought to occur among close contacts with respiratory droplets generated by sneezing and coughing.[23] Reported that thrombocytopenia (Low platelet count) increase mortality rate of COVID-19 infected patients. G. Lippi et al. performed meta-analysis to identify whether platelet count affected or not in COVID-19 patients found that the rate of thrombocytopenia, decrease in platelet count associated with increased risk of severe COVID-19. Platelet are the tiny, anucleated fragment important for several biological responses like homeostasis,[1,6] thrombosis, wound repair, angiogenesis, immunity and performed anti-inflammatory responses. Platelet perform important role in innate immunology within the lungs including defence against respiratory viruses such as platelets against pulmonary infection of H1N1 virus i.e. platelets engulfs the virions and secrets the antiviral molecule to destroy those virions.[1]

Fever, weakness, and a dry cough are the most common symptoms in COVID-19 patients, and dyspnea progresses gradually. Some patients have mild symptoms at the start of the illness and don't have a visible fever. Abdominal pain, headaches, palpitations, and chest pain are uncommon signs. Reduced lymphocyte and platelet counts, but normal white blood cell counts, are typical haematological changes in COVID-19 patients. Prolonged activated partial thromboplastin time, elevated D-dimer levels in 26% of patients, and normal prothrombin time (PT) in the majority of patients[7]. Two patients had thrombocytopenia and two had elevated D-dimer levels at the University of Hong Kong-Shenzhen Hospital (Shenzhen, Guangdong province, China)[8]. 82.1 percent of patients had lymphopenia, 36.2 percent had thrombocytopenia, and 33.7 percent had leukopenia, according to a study involving 1099 patients from 31 provinces/direct-controlled municipalities in China [9]. These anomalies in laboratory markers were more pronounced in extreme cases [9]. 72.5 percent of 13 patients from three Beijing hospitals developed thrombocytopenia[10]. According to data from 41 patients admitted to a designated hospital in Wuhan, 5% of patients had thrombocytopenia at the time of admission [11]. In the vast majority of instances, the platelet count did not drop to the point where bleeding began. The mechanisms by which this coronavirus affects the hematopoietic system, however, remain unknown. We summarised the haematological changes associated with thrombocytopenia in COVID-19 patients and suggested possible mechanisms by which COVID-19 induces thrombocytopenia in this paper and some natural medicine that may help to prevent thrombocytopenia.

Coronaviruses can cause abnormal hematopoiesis by infecting bone marrow cells[12]. The nucleotide homology between SARS-CoV-2 and human SARS-CoV is 82 percent[13]. Since SARS-CoV and HCoV-229E have similar antigen characteristics, it's possible that the antigens of SARS-CoV-2 and HCoV-229E are related. CD13 (human aminopeptidase N) is a metalloprotease found on the cell surfaces of epithelial cells in the stomach, kidneys, and lungs, and is an HCoV-229E receptor[14]. CD13 is a granulocyte and monocyte marker found in epithelial cells of the respiratory tract, smooth muscle cells, fibroblasts, kidney and small intestine epithelial cells, activated endothelial cells, lymphocytes, and platelets. Via CD13 receptors, HCoV-229E reaches bone marrow cells and

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platelets, causing growth inhibition and apoptosis in the bone marrow, resulting in aberrant hematopoiesis and thrombocytopenia[14]. SARS-CoV-2 infection causes thrombocytopenia close to that caused by SARS-CoV and HCoV-229E infection. SARS-CoV-2, based on this phenomenon, is thought to inhibit hematopoiesis in the bone marrow through certain receptors, resulting in decreased primary platelet formation and thrombocytopenia.

Secondary hemophagocytic lymphohistiocytosis (sHLH) is caused by excessive mononuclear macrophage proliferation and activation, which results in the release of a large number of inflammatory cytokines and the swallowing of a large number of blood cells. The basic characteristics of this reactive disease include recurrent fever, hyperferremia, cytopenia, and lung involvement, and it has a rapid response with a high mortality rate. Elevated ferritin was found to be one of the predictors of death in a retrospective study of 150 COVID-19 patients in Wuhan, China[15]. Wei Haiming's team discovered that T cells were overactivated to generate granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-6 after novel coronavirus infection after examining blood samples from 33 serious and vital COVID-19 patients (IL-6). CD14+CD16+ inflammatory mononuclear macrophages were stimulated to generate more interleukin-6 (IL-6) and other inflammatory factors by GM-CSF, resulting in an inflammatory storm and immune damage to the lungs and other organs[16]. The clinical manifestations and laboratory analysis of patients with sHLH are identical. Furthermore, studies[15] have shown that cytokine spectrums similar to sHLH are linked to the severity of COVID-19 disease. The hematopoietic progenitor cells in the bone marrow of patients with pneumonia infected by novel coronavirus were killed after the cytokine storm, the primary output of platelets decreased, and at the same time, too many blood cells were swallowed, resulting in a decrease in peripheral blood platelet count.

A significant number of megakaryocytes dynamically release platelets during pulmonary circulation, according to evidence[17]. Lung damage is exacerbated by persistent hypertension and oxygen toxicity, resulting in consolidation changes such as fibrosis. Damaged pulmonary capillary beds obstruct the mechanism of megakaryocyte rupture and platelet release, limiting platelet release into the pulmonary circulation and indirectly reducing platelet synthesis in the systemic circulation.

II. Infection with SARS-CoV-2 can Increase Platelet Destruction and Platelet Consumption

COVID-19 can raise levels of autoantibodies and immune complexes, causing the immune system to target platelets for destruction. Immune-mediated thrombocytopenia in HIV-1 infected patients is a common occurrence, according to a study[18]. Although the cause is unclear, it has been linked to platelet membrane components in circulating immune complexes as well as anti-platelet membrane GPIIIa49-66 IgG antibodies[18]. Cross-reactivity exists between anti-platelet membrane GPIIIa49-66 IgG antibodies and the HIV-1GP 160/120 antigen. Reticuloendothelial cells will recognise antibodies and immune complexes accumulated on platelet surfaces, and the platelets will be killed as target tissues, resulting in excessive platelet destruction. Anti-platelet antibodies and immune complexes can coat platelets with similar antigens, causing immune-mediated damage. Furthermore, via molecular mimicry, antibodies produced during viral infection can specifically bind to antigens on platelets, resulting in increased platelet destruction.

Lung damage is caused by viral infection and inflammation. Platelets in the lungs can be activated by damaged lung tissues and pulmonary endothelial cells, resulting in aggregation and the development of microthrombi, which increases platelet intake. The majority of COVID-19 patients with thrombocytopenia have elevated D-dimer levels and a shortened coagulation duration, proving the above hypothesis of low intravascular coagulation. As a result, it's still unknown which medications were used to treat patients with COVID-19 who had thrombocytopenia and recovered. - coronaviruses include SARS-CoV-2, MERS-CoV, and SARS-CoV. A patient with MERS was previously treated for thrombocytopenia with large doses of corticosteroids administered by intravenous infusion, and their platelet counts improved[19]. This traditional approach has been shown to improve thrombocytopenia in HIV patients[20]. As a result, it's possible that intravenous injections of human immunoglobulin, corticosteroids, and platelets may help patients in some situations. The prescribed dose of glucocorticoid may be used in a short period of time for patients with excessive activation of the inflammatory response, according to the treatment measures of Diagnosis and Treatment Protocol for COVID-19 (Trial Version 7)[21]. This is in line with the findings of the previous studies aimed at reducing thrombocytopenia. HIV-related thrombocytopenia can be treated with reverse transcriptase inhibitors. Zidovudine, for example, improved platelet synthesis. Furthermore, drug stimulation of megakaryocyte synthesis may boost platelet production. The chemokine CXCR4 has been found to be expressed in megakaryocytes. Reverse transcriptase inhibitors and chemokine receptor antagonists can help COVID-19 patients since SARS-CoV-2 and HIV are both RNA viruses. At the same time, in Diagnosis and Treatment Protocol for COVID-19 (Trial Version 7) [21], it is proposed that Shenmai injection can be used to treat immunosuppression in the treatment of traditional Chinese medicine. Shenmai injection acts as a scavenger for a variety of pathological substances. It can effectively boost anticoagulation and thrombocytopenia in COVID-19 patients. The immunotherapy scheme of "monoclonal antibody drug topirazumab + routine therapy" is also listed in the Diagnosis and Treatment Protocol for COVID-19 (Trial Version 7) [21] as a viable choice for treating serious and critical COVID-19 cases. Tocilizumab, a monoclonal antibody against the IL-6 receptor, effectively blocks COVID-19's inflammatory storm, enhancing prognosis[22].

III. Natural Medicine

Many studies reported that low platelet count increases severity in COVID-19 infected patient with increased

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mortality rate[5]. To overcome this complication we can focus on platelet biogenesis with some of natural/ herbal drugs.

Carica papaya

Carica papaya leaves are significantly inhibit the haemolysis. One study suggested that extract of papaya leaves increased thrombocyte count in mice. It is also reported that increased platelet production in patients suffering from dengue and viral infections after treating them with papaya leaves[24].

Actinida deliciosa

Kiwi is a vitamin-C rich fruit[25] increases immunity and platelet production. One study performed using kiwi fruit extract inhibited a platelet aggregation in response to ADP, collagen and arachidonic acid; inhibitory action shown by reducing TXA_2 synthesis.[26]

Tinospora cordifolia

The study performed by using methanolic extract obtained from *T. cordifolia* shown antithrombotic property/ effect due to inhibition of thrombin-induced platelet activation. Further study will reveal the actual constituent exhibiting antithrombotic activity[27].

Somewhat the platelets count enhancer drug will helps the COVID-19 infected patient to fight against the virus.

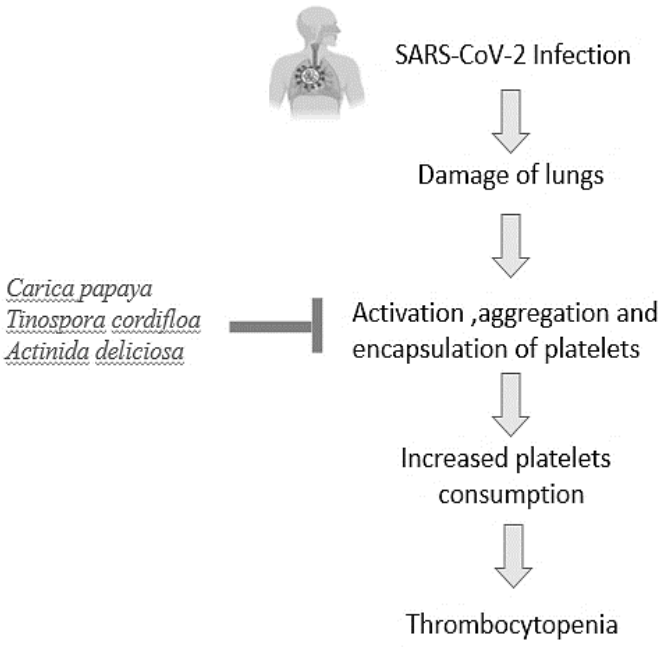

Figure showing Natural medicinal drugs inhibiting the thrombocytopenia[28]

IV. Conclusion

Low platelet count increase mortality rate of COVID-19 infected patients. To overcome this complication we can focus on platelet biogenesis with some of natural/ herbal drugs. Carica papaya leaves are significantly inhibit the haemolysis. Kiwi fruit extract inhibits a platelet aggregation in response to ADP, collagen and arachidonic acid; inhibitory action shown by reducing TXA2 synthesis. It is also reported that it increases platelet production in patients suffering from dengue and viral infections after treating them with papaya Leaves. Tinospora cordifolia shown antithrombotic property/ effect due to inhibition of thrombin-induced platelet activation. Platelets count enhancer drug will helps the infected patient to fight against the virus.

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