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Review Article

COVID-19 and *Panax ginseng*: Targeting platelet aggregation, thrombosis and the coagulation pathway

Yuan Yee Lee [a, b, c], Yixian Quah [d], Jung-Hae Shin [a, b, c], Hyuk-Woo Kwon [e], Dong-Ha Lee [f], Jee Eun Han [b], Jin-Kyu Park [b], Sung Dae Kim [b], Dongmi Kwak [b], Seung-Chun Park [b], Man Hee Rhee [a, b, c, *]

[a] *Ginseng Circulatonic Laboratory, College of Veterinary Medicine, Kyungpook National University, Daegu, Republic of Korea*
[b] *College of Veterinary Medicine, Kyungpook National University, Daegu, Republic of Korea*
[c] *Cardiovascular Research Institute, Kyungpook National University, Daegu, Republic of Korea*
[d] *Development and Reproductive Toxicology Research Group, Korea Institute of Toxicology, Daejeon, Republic of Korea*
[e] *Department of Biomedical Laboratory Science, Far East University, Eumseong, Republic of Korea*
[f] *Department of Biomedical Laboratory Science, Namseoul University, Cheonan, Republic of Korea*

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ABSTRACT

Coronavirus disease 2019 (COVID-19) not only targets the respiratory system but also triggers a cytokine storm and a series of complications, such as gastrointestinal problems, acute kidney injury, and myocardial ischemia. The use of natural products has been utilized to ease the symptoms of COVID-19, and in some cases, to strengthen the immune system against COVID-19. Natural products are readily available and have been regularly consumed for various health benefits. COVID-19 has been reported to be associated with the risk of thromboembolism and deep vein thrombosis. These thrombotic complications often affects mortality and morbidity. *Panax ginseng*, which has been widely consumed for its various health benefits has also been reported for its therapeutic effects against cardiovascular disease, thrombosis and platelet aggregation. In this review, we propose that *P. ginseng* can be consumed as a supplementation against the various associated complications of COVID-19, especially against thrombosis. We utilized the network pharmacology approach to validate the potential therapeutic properties of *P. ginseng* against COVID-19 mediated thrombosis, the coagulation pathway and platelet aggregation. Additionally, we aimed to investigate the roles of *P. ginseng* against COVID-19 with the involvement of platelet-leukocyte aggregates in relation to immunity-related responses in COVID-19.

1. Introduction

Coronavirus disease 2019 (COVID-19) is a respiratory disease. The coronavirus of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is known to target angiotensin-converting enzyme 2 (ACE2), and the priming of spike protein and cellular serine protease TMPRSS2 is required for cell entry. Therefore, both ACE2 and TMPRSS2 are needed for the entry of the coronavirus into the cells.

ACE2 is a component of the renin-angiotensin system (RAS) that plays a role in the cardiovascular system. It is expressed in various organs in the body, including the arterial and venous endothelial cells and the arterial smooth muscle cells [1,2]. ACE2 functions to degrade angiotensin 1–7, activating the angiotensin II type 1 receptor (AT1R) that is detected in cardiovascular disease [3]. COVID-19 causes extrapulmonary complications affecting the neurological, renal, hepatic, gastrointestinal, cardiac, endocrine, and dermatological functions as well as thromboembolism [4]. Recently, it has been reported that SARS-CoV-2 binds to platelet ACE2, increasing thrombus formation in COVID-19 patients [5]. On the other hand, platelet activation was more common in platelets from patients with COVID-19 compared with that in healthy donors when stimulated with agonists like collagen, thrombin or adenosine diphosphate (ADP) [6–8]. Manne et al. (2020) had also stated that circulating platelets in patients with COVID-19 had elevated platelet-neutrophil, platelet-monocyte and platelet-T cell

* Corresponding author. College of Veterinary Medicine, Kyungpook National University, Daegu, 41566, Republic of Korea.
E-mail address: rheemh@knu.ac.kr (M.H. Rhee).

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aggregates [6]. Therefore, platelets are an important target to prevent thromboembolism in patients with COVID-19.

2. Thrombosis in COVID-19

Microvascular and macrovascular thromboembolism in the spleen, brain, gut and lungs are often found in patients with COVID-19 [9–12]. Deep vein thrombosis and pulmonary embolism were also noted in critically ill patients [13]. It is evident that thrombosis often originates from an inflamed vascular endothelium [14,15]. Hanff et al. (2020) has summarized mechanisms leading to thrombosis in COVID-19, which includes disseminated intravascular coagulation (DIC), cytokine storm, complement activation, macrophage activation syndrome and renin angiotensin system overactivation, all of which would cause thrombosis [16]. Disseminated intravascular coagulation causes the activation of the coagulation pathway, depositing platelet-fibrin thrombi, leading to the consumption of platelets and procoagulant factors which results in bleeding disorders. The levels of D-dimers and fibrin degradation products (FDP) were potential markers of DIC and these markers were highly related to the mortality and morbidity of patients with COVID-19 [17]. Another study had shown a slight increase in prothrombin time (PT) and activated partial thromboplastin time (aPTT) in patients with COVID-19, but the levels of fibrinogen and factor VIII were markedly elevated [18]. Hence, thrombosis and its related side effects are a result of COVID-19 other than pulmonary complications.

2.1. The role of platelets in thrombosis

Vessel injury causes the secretion of the agonists of platelet activation such as collagen, von Willebrand factor (vWF), activating platelets and allowing them to adhere to the vessel wall [19,20]. Whenever the vessels are damaged, platelets communicate with immune cells to initiate the host defense response [21,22]. However, the recruitment of immune cells to the vessel wall may also initiate an inflammatory response that contributes to the formation of foam cells. The accumulation of foam cells will form a necrotic core and finally a vulnerable plaque [23,24]. Plaque rupture leads to the formation of a platelet-rich thrombus [25].

2.2. Fibrinolysis in COVID-19

The balance between thrombosis and injury is maintained by fibrinolysis and coagulation factors [26]. The relationship between fibrinolysis and COVID-19 has been widely reported. A report had indicated that COVID-19 causes the impairment of fibrinolysis and hypercoagulability, further causing venous thromboembolic events, stroke, and renal failure [27]. Patients with COVID-19 have an elevated amount of D-dimers, which may indicate a crippling fibrinolytic system. However, SARS-CoV-2 may take advantage of the fibrinolytic system to increase infectivity. Hence, it should be carefully considered whether a treatment that targets to increase fibrinolysis is advantageous [28]. Elevated D-dimer and decreased fibrinolysis has also been related to a high mortality rate and Ibañez et al. (2020) has also suggested the D-dimer could originate from the lungs [29]. In a recent study, acute fibrinolysis shutdown has also been observed in septic shock patients [30]. Another recent report suggested the possible relationship between sepsis and COVID-19 due to the high similarity in pathophysiological and clinical characteristics [31]. Multiorgan failure is also common in COVID-19 patients, which is also a characteristic of sepsis [32]. Furthermore, we observed an important role of the immune system in thrombus formation and the activation of platelets and fibrinolysis, and their relationship may be intertwined.

2.3. Platelet-leukocyte aggregates

The relationship between platelet-leukocyte aggregates and their contribution to thrombosis have already been studied. As previously reviewed by Cerletti et al. (2012), the main receptor responsible for the formation of aggregates is the P-selectin on platelets and P-selectin glycoprotein ligand-1 (PSGL-1) on leukocytes, that causes the activation of the integrin $\alpha M\beta 2$ (Mac-1), enforcing the binding between the aggregates [33]. This reveals the connectivity of thrombosis and the progression of inflammation. Mac-1 can be activated by fibrinogen [34], which increases the stability of the aggregates. Moreover, the tethering of monocytes on the vascular endothelium expressing P-selectin may induce the activation of nuclear factor-kappa B (NFκB) [35]. A review by Koupenova et al. (2018) have suggested that platelets interact with neutrophils, monocytes, eosinophils and leukocytes. Platelet-neutrophil interactions play an important role in neutrophil extracellular trap (NET) formation, platelet-monocyte aggregates were associated with vascular thromboembolism and myocardial infarction and platelet-eosinophil aggregates were mediated via platelet P-selectin and PSGL-1 on eosinophils. Platelet-lymphocyte interaction formation encourages the secretion of platelet factor 4 (regulation of immunity via the inhibition of Th17 differentiation), while serotonin secreted by platelets encourage the proliferation and activation of naïve T cells [36].

As mentioned above, platelets are important players in thrombosis and the activation of the innate immune system, including the trafficking of immune cells to the site of injury. COVID-19 has been widely reported to be associated with the risk of thrombosis. Hottz et al. (2020) had found an increased level of tissue factor (TF) expressed in monocytes that had increased the interaction between platelets and monocytes while increasing the levels of fibrinogen and D-dimer in patients with severe COVID-19, which are signs of impaired fibrinolysis [37]. In another study, a correlation was found between the increased platelet-monocyte aggregates (PMAs), platelet-neutrophil aggregates (PNAs) and inflammation, corresponding to the severity of COVID-19 [38]. Leppkes et al. (2020) has also reported the occurrence of vascular occlusion caused by NETs in the microvessels of COVID-19 patients, possibly causing organ damage [39]. In another study, the populations of PMAs, PNAs, platelet-CD4 T-cell aggregates and platelet-CD8 T-cell aggregates were found to be significantly elevated in the whole blood of COVID-19 patients compared with those in healthy donors [6]. As previously reported, platelet-leukocyte aggregates (PLAs) cause the formation of a fibrin clot with platelets via PSGL-1 on the leukocyte-derived microparticles with tissue factor [40]. Therefore, PLAs are contributors of thrombosis and inflammation in COVID-19.

3. Herbal supplementations and their proposed role for the treatment of COVID-19

Patients with COVID-19 may have to live with various side effects even after recovery. Despite the use of drugs and medication, herbs may be used to ease or relieve the associated complications of COVID-19. A review by Fuzimoto et al. (2020) has summarized 43 reports and reviews of herbs and herbal decoctions that exhibit antiviral activities against SARS-coronavirus, with 31 of them revealing the mechanisms of action. These herbs were mostly reported to exhibit antiviral activities via the inhibition of proteins in various phases of viral replication [41]. Cloves, cinnamon, garlic and basil were amongst the many natural products that have potential antiviral and immune enhancing properties, which can be used in the treatment of COVID-19 [42]. Another review by Panyod et al. (2020) had evaluated various herbs that were used as dietary therapy against the prevention of COVID-19. *Portulaca olaracea* L.

and *Eucalyptus polybractea* have also been used to prevent H11N9 virus infection in Madin–Darby Canine Kidney (MDCK) cells, whereas *P. ginseng* was shown to prevent H1N1 virus infection in mice and MDCK cells, and its ginsenosides are potentially effective against atherosclerosis [43]. Several traditional medicine concoctions have also been widely reported for their therapeutic effect against COVID-19. Ang et al. (2020) have also summarized the herbal formulae that are recommended for use in the medical observation period of COVID-19, which includes an array of herbs [44]. In another review, herbs like *Houttyunia cordata* (water extract) and the phenolic compounds of *Istatis indigotica* were proposed to be SARS-CoV1 3CL protease inhibitors, and an array of mushrooms have been shown to have potential therapeutic effects against COVID-19 [45]. Natural products are comparatively more accessible and potentially beneficial against COVID-19. Considering the high risk of thromboembolism in COVID-19, the consumption of herbs that are potentially antiviral and immune boosters may not be fully effective against the associated complications of COVID-19. Therefore, it is important to further investigate the role of natural products that target thrombosis and platelet aggregation.

Several reports have suggested that natural products targeting thrombosis or possessing anti-platelet activity may be beneficial against COVID-19 [46,47]. However, further studies are required to assess the effectiveness of natural products targeting thrombosis in relation to COVID-19 due to experimental restrictions. In this review, we will focus on the potential targets of *P. ginseng* against hypercoagulability and platelet activation and COVID-19.

3.1. Targeting the associated complications of COVID-19 via the inhibition of platelet aggregation and thrombus formation

3.1.1. Platelet hyperactivity

As mentioned above, platelet activation is one of the main drivers of thrombus formation. Therefore, the prevention of platelet activation will inhibit the downstream mechanisms of clot formation. Platelets are activated when their agonists are released from the vascular endothelium due to injury or inflammation. The GPIb-IX-V complex binds to vWF, and GPVI to collagen. GPIIb/IIIa activation on platelets causes the formation of the prothombinase complex and generation of thrombin to convert fibrinogen into fibrin. This is regarded as the classical haemostasis of platelets [48]. Moreover, ginsenoside Rg3, Rp3 and gintonin from *P. ginseng* had been shown to inhibit platelet aggregation, targeting the collagen-, ADP-, and thrombin-induced platelet aggregations [49–51].

3.1.2. P-selectin

It is evident that platelet P-selectin was increased in patients with COVID-19 and represents the activated platelet population [6,52,53]. *P. ginseng* has been widely studied for its antiplatelet activity [54–56]. P-selectin was also shown to be inhibited by the total saponin, ginsenoside Ro and Rg3, and the ginseng berry of *P. ginseng* [49,57–59]. P-selectin also allows the binding of platelets to PSGL-1 on various immune cells. Since the effect of *P. ginseng* against PLAs, PMAs, and PNAs is still unclear, future studies are required to confirm the same.

3.1.3. Integrin αIIbβ3

A high number of COVID-19 cases were reported to negatively affect ST-segment elevation myocardial infarction (STEMI), or also known as the classical heart attack [60]. A case report had suggested that COVID-19 could have encouraged platelet aggregation resulting in an increased risk of stent thrombosis. The authors suggest the use of P2Y12 inhibitors and GPIIb/IIIa inhibitors to reduce the dangers of acute stent thrombosis [61].

The activation of integrin αIIbβ3, with the help of fibrinogen, allows platelets to bind with each other to form aggregates. Although solid evidence is required to confirm the relationship between COVID-19 and integrin αIIbβ3, *P. ginseng* has been widely reported to exhibit antiplatelet activities via the inside-out and outside-in signaling of integrin αIIbβ3. Korean Red Ginseng (steamed roots of *P. ginseng*), ginsenoside Rp1, Rp3, and Rp4; gintonin; and the crude saponin fraction of Korean Red Ginseng was reported to inhibit the binding of fibrinogen to integrin αIIbβ3 in rat platelets, whereas Rk1 inhibited the inside-out signaling in human platelets [50,51,62–66]. Outside-in signaling was inhibited by ginsenoside Rk1 (human platelets) and Rp3 and gintonin (rat platelets) [50,51,63]. This indicates that *P. ginseng* and its ginsenosides are evidently effective in preventing the activation of integrin αIIbβ3.

As mentioned above, *P. ginseng* effectively inhibited the outside-in signaling in rat and human platelets. The downstream pathway of the outside-in signaling causes platelet spreading, clot retraction, and thrombus consolidation [67]. When the outside-in signaling is activated, the fibrin matrix is connected and a retraction force was exerted in between the actin–myosin cytoskeleton of the platelets and the fibrin outside the cells [68]. Clot retraction increases clot density, making it a stable clot that prevents further bleeding. In patients with COVID-19, increased clot formation had been observed in several groups [69–71]. Several reports had shown that ginsenoside Rg3 and Rp3, and gintonin had inhibited thrombus formation *in vivo* [49–51], suggesting the potential beneficial effects of *P. ginseng* against the associated complications of COVID-19.

3.1.4. Thromboxane A2 (TXA2)

An upregulated amount of TXA2 was reported in patients with COVID-19 with observable hypoalbuminemia. The authors suggested the role of immune-inflammatory pathways and platelet aggregation that increased the risk of venous thromboembolism and hypercoagulability [72]. Conti et al. (2020) have also summarized the proposed pathway in relation to inflammation and microthrombi formation, wherein TXA2 plays a vital role in platelet aggregation and thrombi formation. TXA2 will also be converted into thromboxane B2 (TXB2) which is its stable metabolite [73]. The activation of platelets via collagen or vWF induces the activation of the arachidonic acid pathway, causing platelets to secrete TXA2, that will be taken up by the TXA2 receptor on platelets further inducing platelet activation [74]. TXB2 can be detected as it is a stable metabolite of TXA2. Studies had shown that Korean Red Ginseng and ginsenosides Rk1 had shown effective inhibition of TXB2 in platelets [63,66].

3.1.5. PI3K/Akt pathway

One of the vital pathways of the activation of platelets is the PI3K/Akt pathway. A report had shown that patients admitted to the ICU with COVID-19 had increased protein expression of phosphorylated PI3K and Akt expressions in platelets and the sera of patients with COVID-19 had induced increased phosphorylation of PI3K and Akt in the platelets of healthy donors. The authors have also shown that the activation of the PI3K/Akt pathway by SARS-CoV-2 is dependent on Fc-gamma-RIIA but independent of GPIIb/IIIa [75]. On the other hand, some reports had suggested that the PI3K/Akt/mTOR pathway is a potential target pathway, modulating the immune reponse against COVID-19 [76,77]. As summarized by Irfan et al. (2020), various ginsenosides were reported to inhibit the PI3K/Akt pathway in platelets (Rg1, Rg2, Rg3, 2HRg3, Rp1, Rp3, Rp4, and gintonin) but activate the PI3K/Akt pathway in endothelial cells (Rb1, Rc, and Re) encouraging vasorelaxation [55].

4. The potential therapeutic effects of *P. ginseng* via network pharmacology

4.1. Network construction

Cytoscape is an analysis and visualization tool for managing large biological data that can be easily interpreted with nodes and edges, where the nodes are biological molecules and edges connect the nodes to depict their relationship [78]. This method has been widely utilized for drug discovery. The networks in this study were all constructed using Cytoscape 3.9.0 (http://www.cytoscape.org). The StringApp in Cytoscape (http://apps.cytoscape.org/apps/stringapp) provides various functions to input networks, where it provides automatic text-mining of biomedical literature [79]. The yfiles plugin was used to construct the organic layouts of the networks.

4.2. Potential gene identification of COVID-19 targeted by P. ginseng

The (1) COVID-19 network was imported using the STRING: disease query using the query "COVID-19" where "*Homo sapiens*" was selected for the species. Network (2), which is the target genes of *P. ginseng* was acquired using the STRING: PubMed query with "*Panax ginseng*" yielding 3363 search results. A total of 100 genes were imported with a confidence level of 0.700 for both networks. To visualize the potential target genes of *P. ginseng* against COVID-19, the *Merge Networks tool* in Cytoscape was used to create a union of network (1) and (2) as shown in Supplementary Figure 1 and 2. The resultant network was identified as (3) the target genes of *P. ginseng* against COVID-19 (Fig. 1). Network (1) had a total of 605 edges and 645 edges for network (2). The union of the both networks (network 3) had a total of 188 nodes and 1195 edges. Singleton nodes were removed for better visualization, yielding a total of 159 nodes and 1195 edges. The confidence level was then increased to 0.990 using STRING to visualize high potential target genes of *P. ginseng* against COVID-19. After the removal of singleton nodes, 89 nodes and 109 edges remain. Even when using a high confidence level, a few visible clusters of genes could still be observed, along with a cluster containing vWF, F2, F3, F8, ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin motifs 13) and SERPINC1 (serpin family C member 1), as shown in Fig. 1. Prothrombin is encoded by F2, tissue factor is encoded by F3, while the coagulation factor FVIII is encoded by F8; they have been reported to be prognostic genetic markers for thrombosis in patients with COVID-19 [80]. ADAMTS13, also known as vWF-cleaving protease, had been reported to inhibit platelet aggregation by inducing the cleavage of the ultralarge vWF multimers, which are released by Weibel–Palade bodies when fluid shear stress is present [81]. It also plays an important role in thrombosis and inflammation [82]. SERPINC1, is the gene of antithrombin and its mutation has been reported to be related to antithrombin deficiency [83]. Thus, it can be indicated that the potential target of *P. ginseng* against COVID-19 is related to the coagulation cascade, which may possibly be related to platelet aggregation.

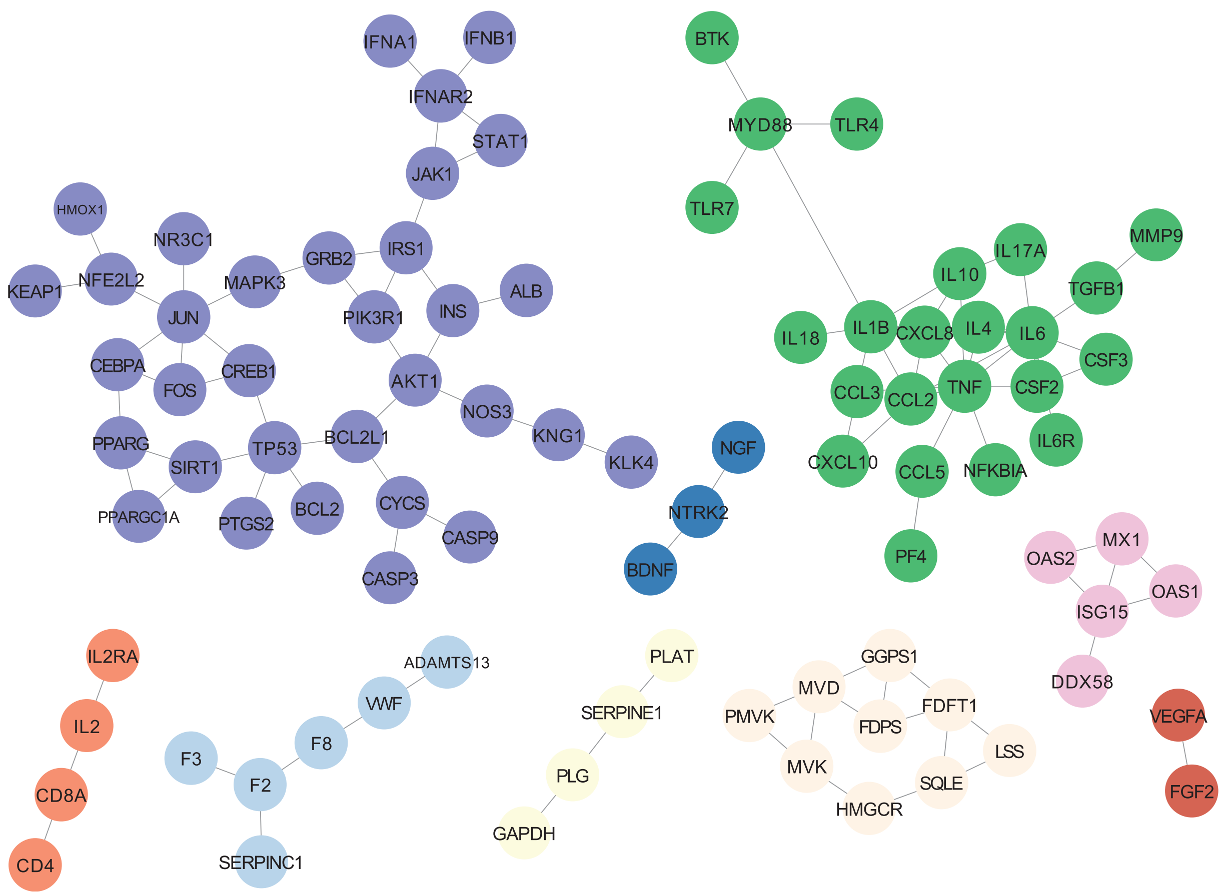

Fig. 1. The merged network of the COVID-19 network from STRING: disease query using the StringApp (http://apps.cytoscape.org/apps/stringapp) in Cytoscape 3.9.0 (http://www.cytoscape.org) and the *Panax ginseng* network from STRING: PubMed query showing the possible target proteins of *Panax ginseng* against COVID-19. The network contains 89 nodes and 109 edges when set to a confidence of 0.990.

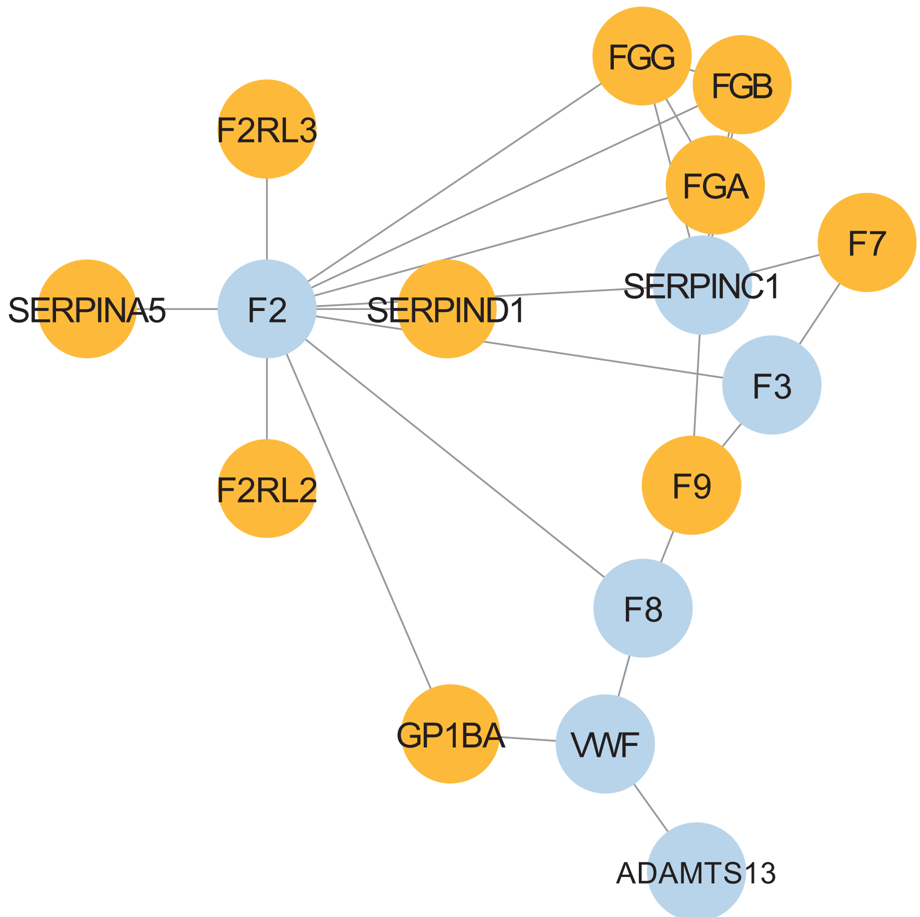

Fig. 2. Expanding the network related to the coagulation pathway. The cluster related to the coagulation pathway was expanded with the help of StringApp (http://apps.cytoscape.org/apps/stringapp). The added proteins were marked as yellow while original proteins were shown in blue. Network was constructed using Cytoscape 3.9.0 (http://www.cytoscape.org).

We expanded the cluster to visualize possible related genes via the StringApp by 10 interactions (species: "*Homo sapiens*") and selectivity of interactors as 0.5, giving us network (4) with suggested possible proteins shown in yellow (Fig. 2) [80]. Proteins, such as coagulation factor II thrombin receptor like 2 (F2RL2), F2R like thrombin or trypsin receptor 3 (F2RL3), serpin family A

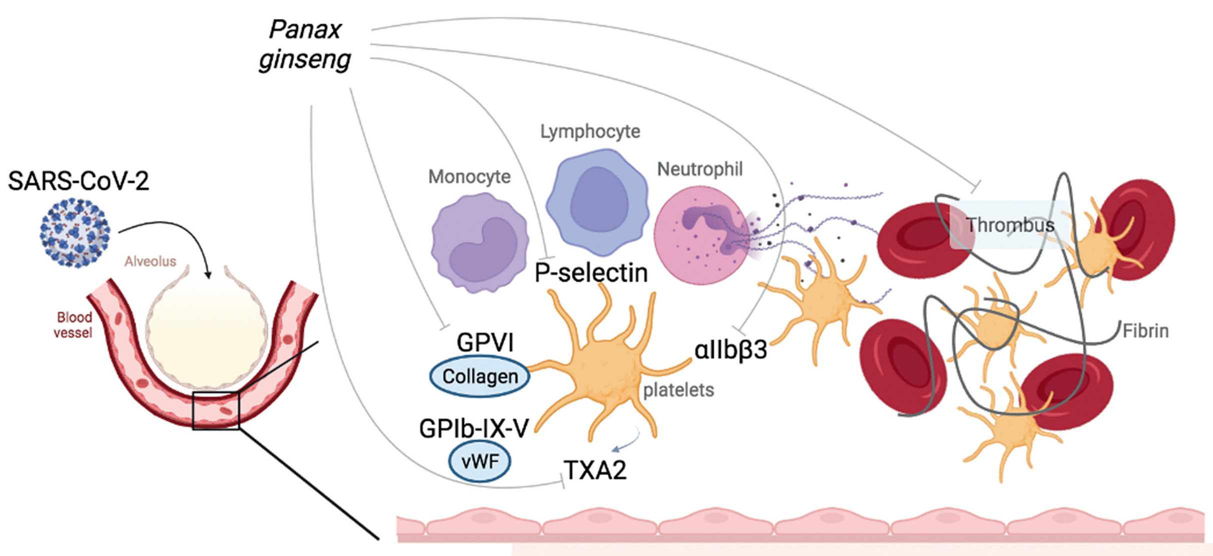

Fig. 3. The proposed target pathway of *Panax ginseng* against COVID-19. GPVI, glycoprotein VI; GPIb-IX-V, Glycoprotein Ib-IX-V complex; TXA2, thromboxane A2; αIIbβ3, integrin αIIbβ3; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

member 5 (SERPINA5), serpin family D member 1 (SERPIND1), fibrinogen gamma chain (FGG), fibrinogen beta chain (FGB), fibrinogen alpha chain (FGA), coagulation factor VII (F7), coagulation factor IX (F9) and glycoprotein Ib platelet subunit alpha (GP1BA), were added into the network. F2RL2 and F2RL3 are also known as proteinase activated receptor (PAR) 3 and PAR4, both of which are expressed on platelets. This suggests that *P. ginseng* may target platelet aggregation via the GP1BA and PAR on platelets and the coagulation cascade against COVID-19, corresponding to the discussion above.

Previous literature on natural products and network pharmacology have obtained information on the bioactive compounds of various herbs from databases like TCMSP (https://tcmsp-e.com) [84] and BATMAN (http://bionet.ncpsb.org.cn/batman-tcm/) [85]. We sought to also investigate whether the bioactive compounds of *P. ginseng* from TCMSP can provide further information on the predicted targets against COVID-19. Twenty-one bioactive compounds (oral bioavailability $\geq$30; drug-likeness $\geq$ 0.18) were included, and the target genes were also determined by Kim et al. (2021) [86]. The network was imported and constructed using Cytoscape 3.9.0 (Supplementary Figure 3) and addressed as network (5). Networks (1) and (5) were merged to identify whether the bioactive compounds were reported against the target genes in COVID-19 (network (6); Supplementary Figure 4). However, no overlapping genes were present in the merged network. Based on our findings in Fig. 2, it was suggested that *P. ginseng* may target the coagulation pathway, corresponding to our discussion on platelet hyperactivity.

5. Current pharmacological approaches

Various antiplatelet drugs were repurposed to control SARS-CoV-2. In a study by Liu et al. (2020), the drug diapyridamole had significantly suppressed the levels of D-dimer in COVID-19 patients and improved the conditions of severely ill patients [87]. Aspirin exhibits antithrombotic activity by targeting the COX-1/arachidonic acid pathway, thereby inhibiting the platelet production of TXA2 [88]. Aspirin was reported to show lower in-hospital deaths by COVID-19 [89], and the preexisting prescription of aspirin in veterans infected with SARS-CoV-2 resulted in a lower 14-day mortality [90]. However, a meta analysis had shown no significant difference in the mortality rates between COVID-19 patients that are aspirin users and nonaspirin users [91]. Several trials involving a combination of antithrombotic drugs, such as apixaban and argatroban were conducted as summarized by Moroni et al. (2021) [92]. This suggests the potential of anticoagulants or antithrombotic agents in treating the associated complications of COVID-19.

6. Future perspectives

It is evident that COVID-19 not only affects the respiratory system but involves an array of events involving the immune system, vascular endothelium, platelet aggregation and thrombus formation. To date, no effective medication for COVID-19 is available. Therefore, we can only target the associated complications of COVID-19 to reduce mortality in infected patients. Although the efficacy of natural products against COVID-19 has yet to be investigated due to experimental restrictions, we propose *P. ginseng* as a potential candidate to be supplemented to patients with COVID-19, which can potentially prevent thrombosis (Fig. 3). Recently, Kim et al. (2021) have also proposed a nanoencapsulation method to further improve the antithrombotic effects of red ginseng extract. Moreover, further studies are required to evaluate the efficacy of *P. ginseng* in lowering the elevated levels of PLAs, PMAs and PNAs.

Declaration of competing interest

The authors declare no conflict of interest.

Acknowledgments

The illustrations in this study were created with BioRender.com.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgr.2022.01.002.

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