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Network pharmacology and molecular docking reveal the mechanisms of action of *Panax notoginseng* against post-COVID-19 thromboembolism

Shouli Yuan[1,†], Ismael Obaidi[2,3,†], Tao Zhang[4], Maria Pigott[2], Shibo Jiang[5], Helen Sheridan[2], Junying Liu[2,*]

[1]Academy for Advanced Interdisciplinary Studies, Peking University, Beijing, China
[2]NatPro Centre for Natural Products Research, School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin, Dublin, Ireland
[3]College of Pharmacy, University of Babylon, Hillah, Iraq
[4]School of Food Science & Environmental Health, Technological University Dublin, Grangegorman, Dublin, Ireland
[5]Key Laboratory of Medical Molecular Virology (MOE/NHC/CAMS), School of Basic Medical Sciences, Shanghai Institute of Infectious Disease and Biosecurity, Fudan University, Shanghai, China
[†]These authors contributed equally to this work

***Corresponding author:** Junying Liu, NatPro Centre for Natural Products Research, School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin, Dublin, Ireland; Tel.: +353-(0)871233798
E-mail: juliu@tcd.ie

Abstract

Panax notoginseng (PNGS) is a potent folk therapy for blood-related diseases. However, further research is required to fully elucidate the mechanisms of its pharmacological activities and to explore its therapeutic potential for treating thromboembolism (TE) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This study aimed at analysing the molecular mechanisms of PNGS and at clarifying their potential role in treating TE induced by COVID-19, by employing network pharmacology and molecular docking. To this end, a network pharmacological approach was combined with expression profiling by high-throughput sequencing of GSE156701 so as to elucidate the compound constituents of PNGS for treating TE caused by SARS-CoV-2 at a systemic level. Protein-protein interaction network, Gene Ontology, and Kyoto Encyclopedia of Genes and Genomes analyses were employed in order to decipher the associated drug-target interactions. The integration of these results suggested that five targets, including the angiotensin-converting enzyme (ACE), the coagulation factor III (F3), interleukin-1 beta (IL-1β), the mitogen-activated protein kinase 1 (MAPK1), and the plasminogen activator inhibitor-1 (SERPINE1), represent major genes involved in thromboembolism. The data suggest that PNGS exerts collective therapeutic effects against TE caused by SARS-CoV-2, and provides a theoretical basis for further laboratory study of the active drug-like ingredients and the potential mechanisms of PNGS in TE treatment.

KEYWORDS

Panax notoginseng, SARS-CoV-2, post-acute COVID-19, thromboembolism, network pharmacology

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1. INTRODUCTION

While the containment of coronavirus disease 2019 (COVID-19) through the provision of various vaccines and the rise of herd immunity is ongoing, the understanding and management of the long-term sequelae of COVID-19 in survivors of acute disease has become a focal point of research. Many patients experience persistent or prolonged effects. Indeed, post-acute COVID-19 can be defined as persistent symptoms and delayed or long-term complications beyond four weeks from the onset of the symptoms. Following six months of the disease, the risk of thromboembolism (TE) in hospitalized COVID-19 survivors is sevenfold more significant than that of non-hospitalized COVID-19 patients. At the same time, those in the intensive care unit face an eighteen-fold higher substantial risk than all other survivors [1]. In addition, various adverse events following vaccination have been reported, ranging from mild symptoms to more specific organ failures. Post-vaccine thrombosis, including cerebral venous thrombosis, has become a major concern in patients, particularly women, who have received adenovirus-based vaccines [2]. *Panax notoginseng* (Burk) F. H. Chen (PNGS), as a traditional Chinese medicine, has been documented to possess anti-inflammatory, anti-oxidative, inhibitory of platelet aggregation, regulatory of blood glucose and blood pressure, inhibitory of neuronal apoptosis, and neuroprotective properties [3]. Ginseng and its major active constituents, ginsenosides and saponins, are known to improve the immune system and exert anti-inflammatory effects by targeting the inflammasome stimulation [4]. This study aimed at analysing the molecular mechanisms of action of PNGS and at clarifying their potential role in treating TE induced by COVID-19, by using network pharmacology and molecular dynamics.

2. MATERIALS AND METHODS

This study explores the molecular mechanisms underlying the effects of PNGS on COVID-19-associated TE, by employing network pharmacology and molecular docking. Furthermore, it provides a new strategy for developing a novel way to alleviate thromboembolism. To this end, a network pharmacological approach was combined with expression profiling by the high-throughput sequencing of GSE156701, so as to elucidate the compound constituents of PNGS for treating TE caused by SARS-CoV-2 at a systemic level.

3. RESULTS

Target fishing resulted in 508 targets related to 14 bioactive PNGS compounds. The overlapping targets between the PNGS-related and the TE-dysregulated genes resulted in a drug-disease target set with 51 genes (Figure 1). These overlapping genes were then used in order to perform herb-compounds-targets-disease network, protein-protein interaction network, Gene Ontology (GO), and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses. The integration of these results suggested that five targets, including the angiotensin-converting enzyme (ACE), the coagulation factor III (F3), interleukin-1 beta (IL-1β), the mitogen-activated protein kinase 1 (MAPK1), and the plasminogen activator inhibitor-1 (SERPINE1), represent major genes involved in TE. These targets involve more than four pathways, including the AGE/RAGE signalling pathway in diabetic complications, the fluid shear stress and atherosclerosis pathway, the complement and coagulation cascades, and COVID-19. Molecular docking and molecular dynamics simulation were applied so as to validate these results, indicating a stable combination between two compounds (quercetin and ginsenoside) and five targets (ACE, F3, IL-1β, MAPK1, and SERPINE1) with the following binding affinities being some examples: (i) ginsenoside-ACE: -9.7 kcal/mol, (ii) quercetin-SERPINE1: -8.7 kcal/mol, (iii) quercetin-MAPK1: -8.5 kcal/mol, and (iv) quercetin-ACE: -8.3 kcal/mol.

4. DISCUSSION

Based on our analysis, the major PNGS targets are ACE, MAPK1, and SERPINE1. ACE is part of the renin-angiotensin-aldosterone system, which regulates blood pressure. The S proteins of SARS-CoV2 allow the virus to enter the cells by interacting directly with ACE2. As such, ACE2 is arguably one of the primary targets for drugs aiming to exert therapeutic effects on COVID-19 [5]. MAPK1 participates in the MAPK and PI3-Akt signalling pathways. This might suggest that PNGS may target COVID-19-induced TE *via* a direct inhibition of MAPK1, thus suppressing the PI3K-Akt and MAPK signalling pathways [6]. This also suggests potential novel therapeutic targets for long COVID-19. SERPINE1, a serpin peptidase inhibitor, encodes for the plasminogen activator inhibitor 1 (PAI-1), which plays an integral role in COVID-19-induced endothelial dysfunction and thrombosis [7]. It has been reported that the PAI-1 levels are high in COVID-19 patients when compared to those of healthy individuals.

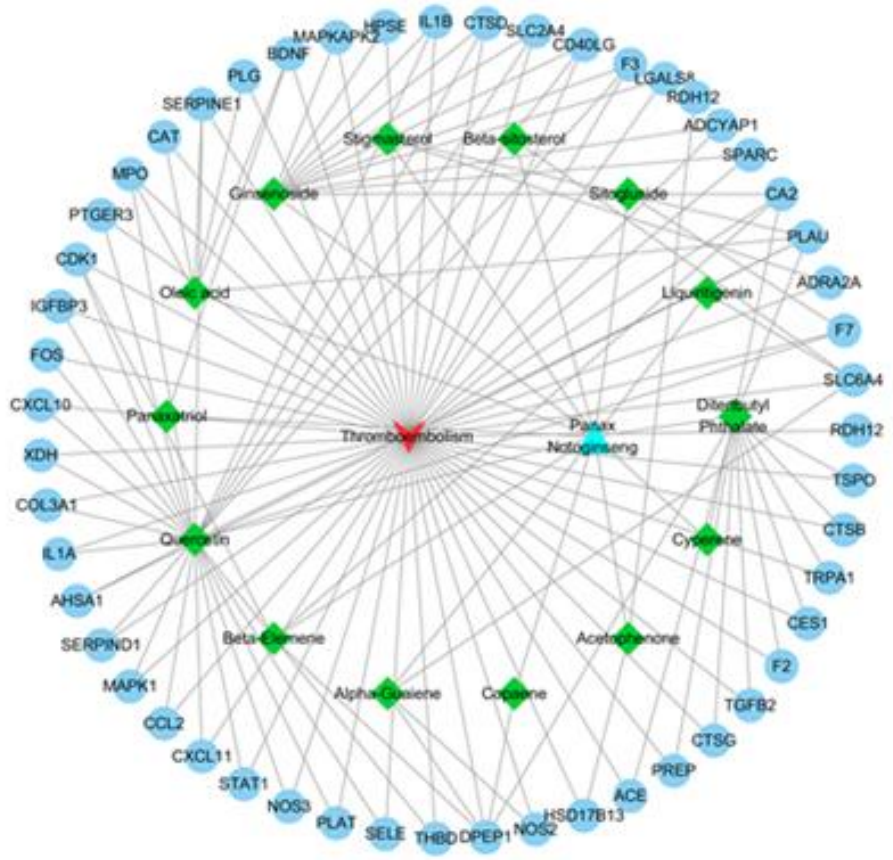

Figure 1. The overlapping gene symbols between the drug and the disease, and the herb-compounds-targets-disease (HCTD) network of *Panax notoginseng*. The HCTD visual network explained: green and blue nodes stand for bioactive components and related targets, respectively; azure nodes stand for targets; red nodes stand for disease.

Moreover, these patients have a strong correlation between their PAI-1 levels and their neutrophil activation, respiratory distress, and mortality rate. Therefore, both the efficacy and the safety of thromboprophylaxis by natural products in post-COVID-19 survivors depend on an enhanced understanding of the pathophysiology and the mechanisms of such complications. Our results have confirmed the top two out of 14 bioactive components in PNGS to be “quercetin” and “ginsenoside”. Ginsenoside demonstrates blood pressure-regulating activity with little or no effect on respiration. Ginseng saponin shows vasoactive results *via* the releasing of nitric oxide [8]. One proposed anti-COVID-19 mechanism of ginsenosides is *via* the suppression of the inflammasome activation. Thus, they facilitate the host’s immune status and exert anti-inflammatory activities [4]. Moreover, ginsenosides have been reported to reduce the cardiovascular insults associated with COVID-19. They maintain blood pressure, minimize the incidence of myocardial infarction, heart failure, and arrhythmia, and they also improve vascular and cardiac integrity [9]. Quercetin, on the other hand, has antiviral activity against many enveloped viruses, including the meningitis and the herpes simplex viruses. It can inhibit the H^+-ATPase of the lysosomal membrane, thereby preventing virus coat removal. In addition to its antioxidant and anti-inflammatory activities, it inhibits the expression of the human ACE2 receptors and SARS-CoV-2 enzymes, including MPro, PLPro, and RdRp [10].

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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