Article

The Promising Mechanisms of Low Molecular Weight Compounds of *Panax Ginseng C.A. Meyer* in Alleviating COVID-19: A Network Pharmacology Analysis

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Abstract: *Panax Ginseng C.A. Meyer* (PGCAM) is a well-known phytomedicine, but most of its compounds, such as ginsenoside derivatives, have poor absorption and bioavailability profile due to high molecular weight (≥ 500 Daltons), which is the major hurdle for their clinical application. Hence, this research explored the efficiency of low molecular weight compounds (LMWCs) (< 500 Daltons) screened from PGCAM and their anti-COVID-19 mechanisms through network pharmacology. Molecular compounds from PGCAM were identified using public databases and filtered out by the drug-likeness evaluation. Genes interacted with these filtered compounds, and COVID-19-related genes were extracted from public databases. In addition, overlapping genes between compounds and interactive genes were identified using the Venn diagram. In parallel, the networking between compounds and overlapping genes was analyzed by RStudio. The pathway enrichment analysis of overlapping genes was determined by STRING. Finally, the key bioactive compounds were documented through virtual screening. The bubble chart suggested that the mechanisms of PGCAM against COVID-19 were related to 28 signaling pathways. The key molecular anti-COVID-19 mechanisms might be the anti-inflammation, anti-permeability, and pro-apoptosis by inactivating the PI3K-Akt signaling pathway. The six key genes and the five compounds related to the PI3K-Akt signaling pathway were RELA-paeonol, NFKB1-frutininone A, IL6-nepetin, MCL1-ramalic acid, VEGFA-trifolirhizin, and IL2-trifolirhizin. The docking between these key genes and compounds demonstrated promising binding affinity with a good binding score. Overall, our proposed LMWCs from PGCAM provide a fundamental basis with noteworthy pharmacological evidence to support the therapeutic efficacy of PGCAM in relieving the main symptoms of COVID-19.

Keywords: *Panax Ginseng C.A. Meyer*; low molecular weight compounds (< 500 Daltons); COVID-19; PI3K-Akt signaling pathway; anti-inflammation and anti-permeability; pro-apoptosis

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1. Introduction

Due to the intense efforts made by clinicians and researchers, only one human infection, “smallpox”, has been successfully eradicated from the world [1]. However, the recent outburst of a new type of pneumonia caused by a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2] is not likely to disappear from the globe completely, even after the quick development of a sustainable vaccine. This indicates one certain thing: that the world needs novel treatment plans and possible therapeutic interventions to combat the highly infectious disease (COVID-19), no matter what else happens next.

In late December 2019, a life-threatening contagious disease with unknown etiology was first reported in Wuhan, Hubei province, China [3]. Although infectious disease experts identified the new coronavirus (SARS-CoV-2) spread from the animal host, concerns remained over how the first person might have been infected [4]. Viral genomics and epidemiological studies evidenced that the animal-to-human shifted SARS-CoV-2 can rapidly transmit from one person to another through interaction or respiratory droplets [5,6].

Hence, the World Health Organization (WHO) initially declared a global emergency on 22 January 2020, as the Wuhan coronavirus spread. On 20 August 2020, the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University reported a health crisis with intensifying global case numbers (22,260,000) and fatalities [7,8]. COVID-19 predominantly attacks the respiratory system, even though other organ systems are compromised. Lower respiratory tract infection (LRTI) associated with fever, shortness of breath, and dry cough were reported as the symptoms with the first case from Wuhan, China [9]. Additionally, muscle aches, chills, sore throat, runny nose, headache, and chest pain were observed [10]. Currently, COVID-19 symptoms are similar to pneumonia, though a significant number of COVID-19 infected cases are asymptomatic, which can affect others as silent spread [11]. Importantly, patients with underlying diseases, such as asthma, diabetes, and hypertension, are more susceptible to COVID-19 [12,13].

A report suggests that around 40% of those infected with SARS-CoV-2 might remain asymptomatic and thus, the transmission might carry a greater risk than expected [11]. At present, endeavors to develop medications for COVID-19 by repositioning existing drugs have been pursued, as well as vaccine development. However, the efforts have been hampered by the lack of scientific evidence on how COVID-19 attacks human hosts [14]. On the other hand, phytochemicals have always played a pivotal role in providing potential therapy against diverse diseases [15], including fighting a mutant coronavirus [16]. From folk remedy times, medicinal plants provided many outstanding bioactive compounds, which led to great drug discoveries, such as aspirin from *Salix*, taxol from *Taxus brevifolia*, and artemisinin from *Artemisia annua* [17–19]. During the 2003 SARS outbreak, a series of Chinese herbal treatments were effectively implemented to control the pandemic situation [20], and even now, the Chinese government impulses traditional remedies aimed at COVID-19 prevention. According to the state administration of traditional Chinese medicine (TMC), 85.2% of the country's COVID-19 patients (total: 60,107) until 17 February 2020 had been recovered with the treatment of TMC [21]. Although researchers race to develop a vaccine, the rigorous validation of traditional medicine for identifying the wide-spectrum antiviral active components can also be a viable way to control the COVID 19 disease. Therefore, an attempt to explore novel antiviral compounds with the underlying mechanism of action should not be halted.

Korean traditional medicine literature, “Donguibogam”, established about 400 years ago, illustrates that *Panax Ginseng* C.A. Meyer (PGCAM) is a very potent herbal plant with multiple pharmacological activities, particularly strengthening the immune system against some pathogens [22]. According to an experiment, ginseng interrupted cellular oxidative damage induced by a respiratory syncytial virus (RSV) and downregulated pro-inflammatory gene expression level induced by RSV in the human alveolar epithelial cell [23]. Additionally, potential bioactive compounds of ginseng extracts, including ginsenoside derivatives (Rg1, Rg3, Rb1, Rb2, Rb3, Re, Rd, Rh2) and compound K, are renowned for therapeutic efficacy against several infectious diseases [24]. However, the major drawback of these compounds is their high molecular weight and low bioavailability; even the absorption and transportation rate of intact ginsenosides and their metabolites from the intestines are very poor [25]. In addition, some reports studied via Caco-2 permeability assay indicated the low permeability of ginsenoside derivatives ($<2.59 \pm 0.17 \cdot 10^{-7}$ cm/s) and compound K ($<8.65 \cdot 10^{-7}$ cm/s) [26,27]. It is evident that low permeable compounds have poor bioavailability profiles, which do not reach the intended biological system; thus, therapeutic efficacy is not well consistent [28]. Therefore, these findings suggest that the pharmacological value of low molecular weight compounds (LMWCs) in ginseng should be strengthened to provide therapeutic evidence against immune dysfunction, especially in treating COVID-19 infection during an urgent pandemic outbreak.

Network pharmacology (NP), a new paradigm and combined analytical system, can efficiently explore the interaction networking of diverse factors, such as ligands, protein targets, diseases, and genes [29]. NP can unveil the target prediction and mechanism of drug action with a multidimensional perspective, which highlights shifting of the

approach from “one target, one ligand” to “multiple targets, multivariate therapeutics” [30]. Importantly, it widely contributes to drug discovery by providing 40% of the recent active candidates with successful clinical evidence [31]. Currently, network pharmacology has been utilized broadly to decipher bioactive compounds and mechanisms of phytochemicals against diverse diseases [32]. In this research, we implemented network pharmacology to analyze LMWCs and mechanisms of PGCAM against COVID-19. Firstly, LMWCs in PGCAM were identified using browsing literature and public database and then filtered through Lipinski’s rule for drug-likeness compounds. Afterwards, genes that interacted with selected compounds or COVID-19-related genes were screened using public databases, and the overlapping genes between compounds and COVID-19 target genes were identified. Thirdly, KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway enrichment analysis of overlapping genes was employed to explore the molecular mechanisms of PGCAM against COVID-19. Finally, the potential bioactive compounds and key genes of PGCAM against COVID-19 were selected by analyzing the binding affinity energy in virtual mode. The overall workflow is presented in Figure 1.

Figure 1. Workflow of network pharmacology analysis of PGCAM against COVID-19.

2. Results

2.1. Potential Low Molecular Weight Bioactive Compounds from PGCAM

The public databases identified a total of 121 compounds in PGCAM, and the drug-likeness properties of 107 compounds were selected by Lipinski’s rule, which is presented in Table 1.

2.2. Target Genes Associated with the 107 Compounds or COVID-19

As shown in Supplementary Table S1, a total number of 1197 genes (STP + SEA) related to 107 compounds was identified and, among them, the overlapped 399 genes between SEA and STP were screened (Figure 2). The 399 genes (Supplementary Table S2) were again analyzed with COVID-19-related genes (356 genes) (Supplementary Table S3). Finally, the Venn diagram (Figure 3) showed the 27 overlapping genes (Supplementary Table S4) between the 399 genes and the 356 genes. Overall, the final 27 genes were selected from 107 LMWCs of PGCAM through COVID-19-related genes.

Table 1. A final list of the selected 107 compounds in PGCAM for network analysis based on Lipinski's rule.

No.	Compound	Molecular Weight (g/mol)	Pubchem ID	No.	Compound	Molecular Weight (g/mol)	Pubchem ID
1	pisol	186.33	8193	55	protopanaxadiol	460.7	9920281
2	3691-11-0	204.35	94275	56	3,5-dimethyl-p-anisic acid	180.2	88944
3	ϵ -cadinene	204.35	12302130	57	3-methylheptane	114.23	11519
4	δ -elemene	204.35	12309449	58	4-methyldodecane	184.36	521958
5	(+)-maalioidide	222.37	6452862	59	5-(E)-heptadec-12-enyl benzene-1,3-diol	346.5	5318012
6	(20S)-protopanaxatriol	476.7	11468733	60	7-tetradecyne	194.36	141979
7	3,4-dimethylheptane	128.25	13534	61	nepetin	316.26	5317284
8	3-ethyl-3-methylheptane	142.28	140213	62	ZINC8680004	456.7	7048528
9	acetal	118.17	7765	63	3'-biotin	244.31	5315463
10	MAV	194.14	446145	64	celabenzine	379.5	442847
11	γ -selinene	204.35	521334	65	(R)-(+)-citronellal	154.25	75427
12	ginsenoside A	258.35	5317632	66	dianthramine	289.24	441562
13	ginsenoside B	294.8	5317633	67	diterbutyl phthalate	278.34	121712
14	ginsenoside C	276.4	5317634	68	arachidonate	304.5	444899
15	ginsenoside D	262.4	5317635	69	frutinine A	264.23	441965
16	panaxytriol	278.4	93484	70	folienetriol	460.7	11048822
17	methylselenocysteine	182.09	147004	71	(20S)-protopanaxadiol	460.7	11213350
18	vulgarin	264.32	94253	72	ginsenoside E	258.35	5320336
19	palmitic acid	256.42	985	73	girinimbim	263.3	96943
20	linoleic acid	280.4	5280450	74	L-erythro-isocitric acid	192.12	439238
21	tetradecane	198.39	12389	75	D-erythro-Isocitric acid	192.12	447805
22	α -gurjunene	204.35	15560276	76	malvic acid	280.4	10416
23	α -cadinol	222.37	10398656	77	beta-D-mannose	180.16	439680
24	loxanol V	214.39	8209	78	methyl tricosanoate	368.6	75519
25	9-hexadecenoic acid	254.41	4668	79	NN-dimethyldecanamide	199.33	26690
26	methyl myristate	242.4	31284	80	stearyl acetate	312.5	69968
27	pentadecyclic acid	242.4	13849	81	panaxadiol	460.7	73498
28	methyl linoleate	294.5	5284421	82	panaxatriol	476.7	73599
29	2,6-dimethyl-3,7-octadiene-2,6-diol	170.25	5352451	83	pancratistatin	325.27	441597
30	hydron-propanedioate	104.06	23511544	84	2-formylpyrrole	95.1	13854
31	methyl stearate	298.5	8201	85	ramalic acid	346.3	5320886
32	methyl palmitelaidate	268.4	638303	86	suchilactone	368.4	132350840
33	methyl pentadecanoate	256.42	23518	87	trifolirhizin	446.4	442827
34	panaxynol	244.37	5281149	88	pangamic acid	476.6	57346693
35	bicyclogermacrene	204.35	13894537	89	D-pantothenic Acid	219.23	6613
36	neocnidilide	194.27	3083857	90	β -elemene	204.35	6918391
37	OCT	114.23	356	91	β -santalol	220.35	6857681
38	L-adenosine	267.24	448374	92	dammarane	414.7	9548714
39	elemicin	208.25	10248	93	methyl margarate	284.5	15609
40	diop	390.6	33934	94	oleanane	412.7	9548717
41	β -humulene	204.35	5318102	95	p-glucosyloxymandelonitrile	311.29	441465
42	stigmaterol	412.7	5280794	96	darutoside	484.6	44715524
43	β -sitosterol	414.7	222284	97	dibutyl phthalate	278.34	3026
44	β -caryophyllene	204.35	5281515	98	fumarine	353.4	4970
45	inermine	284.26	91510	99	paeonol	166.17	11092
46	methyl (Z)-icos-11-enoate	324.5	5463047	100	methyl palmitate	270.5	8181
47	kaempferol	286.24	5280863	101	N9-formylharman	212.25	129650345
48	α -humulene epoxide	220.35	14038843	102	adenosine	267.24	60961
49	TDA	214.34	12530	103	maltol (3-hydroxy-2-methyl-4-pyrone)	126.11	8369
50	n-heptadecanol	256.5	15076	104	salicylic acid	138.12	338
51	1-hexadecyne	222.41	12396	105	p-hydroxycinnamic acid	164.16	637542
52	13-tetradecenyl acetate	254.41	521718	106	gomisin N	400.5	158103
53	2,6,10,15-tetramethylheptadecane	296.6	41209	107	gomisin A	416.5	3001662
54	2-methyltridecane	198.39	15269				

2.3. Potential Molecular Pathways of PGCAM against COVID-19

The gene–gene networking analysis through overlapping 27 genes was visualized by STRING, which includes 24 nodes and 122 edges (Figure 4). The 3 (PTPRS, CPA3, and S1PR3) out of 27 genes were not associated with each other. The KEGG pathway enrichment analysis via STRING suggested that 27 overlapping genes were significantly enriched in 28 signaling pathways (Figure 5). Detailed descriptions of the 28 signaling pathways are listed in Table 2. Among them, both RELA and NFKB1 connected directly to 21 signaling pathways out of 28 signaling pathways and were noted as hub genes of PGCAM against the COVID-19 (Figure 6). Coincidentally, both RELA and NFKB1 play vital roles in all 21 signaling pathways by the PI3K-Akt signaling pathway, indicating that the PI3K-Akt signaling pathway might be a hub signaling pathway of PGCAM against COVID-19.

Figure 2. Overlapping genes (399 genes) between SEA (672 genes) and STP (924 genes).

Figure 3. Overlapping genes between 399 overlapping genes from two databases (A) and COVID-19-related genes (356 genes) (B). * Both human and mouse ACE2 gene included in Venn diagram, thus indicating a total of 355 genes (B).

Figure 4. Gene-gene interaction with 27 nodes and 117 edges in PGCAM against COVID-19.

Figure 5. Bubble chart of 28 signaling pathways in PGCAM against COVID-19.

Table 2. Target genes in 28 signaling pathways enrichment related to COVID-19.

KEGG ID	Description	Target Genes
hsa04933	AGE-RAGE signaling pathway in diabetic complications	RELA, MAPK8, NFKB1, IL1B, JUN, VEGFA, CXCL8
hsa04657	IL-17 signaling pathway	RELA, MAPK8, NFKB1, IL1B, JUN, IL6, CXCL8, MAP3K7
hsa04620	Toll-like receptor signaling pathway	RELA, MAPK8, NFKB1, IL1B, JUN, IL6, CXCL8, MAP3K7
hsa04621	NOD-like receptor signaling pathway	RELA, MAPK8, NFKB1, IL1B, JUN, IL6, CXCL8, MAP3K7
hsa04668	TNF signaling pathway	RELA, MAPK8, NFKB1, IL1B, JUN, IL6, MAP3K7
hsa05120	Epithelial cell signaling in Helicobacter pylori infection	RELA, JUN, MAPK8, NFKB1, CXCL8
hsa04622	RIG-I-like receptor signaling pathway	RELA, NFKB1, MAPK8, MAP3K7, CXCL8
hsa04010	MAPK signaling pathway	RELA, MAPK8, NFKB1, IL1B, JUN, VEGFA, MAP3K7
hsa04064	NF-kappa B signaling pathway	RELA, NFKB1, IL1B, CXCL8, MAP3K7
hsa04660	T cell receptor signaling pathway	RELA, NFKB1, JUN, IL2, MAP3K7
hsa04071	Sphingolipid signaling pathway	RELA, NFKB1, MAPK8, S1PR1, S1PR3
hsa04926	Relaxin signaling pathway	RELA, NFKB1, JUN, MAPK8, VEGFA
hsa04920	Adipocytokine signaling pathway	RELA, NFKB1, MAPK8, PPARA
hsa04151	PI3K-Akt signaling pathway	RELA, NFKB1, IL6, MCL1, VEGFA, IL2
hsa04024	cAMP signaling pathway	RELA, NFKB1, JUN, MAPK8, PPARA
hsa04066	HIF-1 signaling pathway	RELA, NFKB1, IL6, VEGFA
hsa04722	Neurotrophin signaling pathway	RELA, NFKB1, JUN, MAPK8
hsa04917	Prolactin signaling pathway	RELA, NFKB1, MAPK8
hsa04662	B cell receptor signaling pathway	RELA, NFKB1, JUN
hsa03320	PPAR signaling pathway	PPARA, PPARG, FABP2
hsa04014	RAS signaling pathway	RELA, NFKB1, MAPK8, VEGFA
hsa04068	FoxO signaling pathway	IL6, MAPK8, S1PR1
hsa04310	Wnt signaling pathway	JUN, MAPK8, MAP3K7
hsa04630	Jak-STAT signaling pathway	IL2, IL6, MCL1
hsa04062	Chemokine signaling pathway	RELA, NFKB1, CXCL8
hsa04012	ErbB signaling pathway	JUN, MAPK8
hsa04912	GnRH signaling pathway	JUN, MAPK8
hsa04152	AMPK signaling pathway	PPARG, MAP3K7

Figure 6. Degree values of 17 genes in 28 signaling pathways.

2.4. Key Genes and Bioactive Compounds of PGCAM against COVID-19

Based on the PI3K-Akt signaling pathway, six key genes (RELA, NFKB1, IL6, MCL1, VEGFA, and IL2) and 24 potential key bioactive compounds were identified in PGCAM against COVID-19. The 24 compounds are associated with six key genes on PI3K-Akt signaling pathway. The 24 compounds (Figure 7) are classified as follows: eight aliphatic acyclic compounds (NN-dimethyldecanamide, linoleic acid, methyl palmitelaidate, methyl linoleate, methyl myristate, methyl stearate, methyl margarate, and methyl pentadecanoate), eight aromatic heteropolycyclic compounds (frutinone A, nepetin, L-adenosine, adenosine, N9-formylharman, inermin, trifolirhizin, and kaempferol), five aromatic ho-

monocyclic compounds (paeonol, p-hydroxycinnamic acid, dibutyl phthalate, salicylic acid, and ramalic acid), one aliphatic heteromonocyclic compound (beta-D-mannose), one aliphatic heteropolycyclic compound (darutoside), and one aromatic heteromonocyclic compound (p-glucosyloxymandelonitrile). The interactions between each gene and potential active compound were visualized with RStudio (Supplementary Figure S1).

Figure 7. Chemical structures of potential bioactive compounds in PGCAM against COVID-19.

2.5. Affinity Score on Six Key Genes of Potential Bioactive Compounds in PGCAM against COVID-19

The potential bioactive compounds were docked against six genes (RELA, NFKB1, IL6, MCL1, VEGFA, IL2) to measure the binding energy. The molecular docking figure is presented in Figure 8.

Docking simulation of the affinity between R1-R2 and RELA protein in the “*Homo sapiens*” setting was analyzed. Based on the docking score, the order of priority of binding

Docking simulation of the affinity between R1-R2 and RELA protein in the “*Homo sapiens*” setting was analyzed. Based on the docking score, the order of priority of binding

energy is given as: R2, R1. The two-binding energy of R1-RELA and R2-RELA demonstrated -3.9 and -5.3 kcal/mol, respectively. Interaction analysis of the best-docked compound, namely “Paeonol”, resulted in four hydrogen bonds (Arg-174, Val-163, Thr-164, Arg-95) and seven hydrophobic bonds (Pro-176, Leu-175, Pro-177, Gln-162, Arg-73). The detailed information is listed in Table 3. Docking simulation of the affinity between N1-N4 and NFKB1 protein in the “*Homo sapiens*” setting revealed promising binding affinity, and the order of priority of binding energy is as follows: N1, N3, N2, N4. The binding energy of N1-NFKB1, N2-NFKB1, N3-NFKB1, and N4-NFKB1 exposed -7.2 , -5.2 , -5.6 , and -4.6 kcal/mol, respectively. Interaction analysis of the best-docked compound, namely “Frutinone A”, resulted in one hydrogen bond (Ser-113) and seven hydrophobic bonds (Val-145, Val-61, Leu-143, Arg-157, Ala-156, Thr-153, Lys-149). The detailed information is listed in Table 4. Docking simulations of the affinity between L1-L3 and IL6 protein in the “*Homo sapiens*” setting showed good binding energy, and the order of priority is given as: L3, L2, L1. The five-binding energy of L1-IL6, L2-IL6, and L3-IL6 were -5.0 , -5.7 , and -8.0 kcal/mol, respectively. Interaction analysis of the best-docked compound, namely “Nepetin”, resulted in two hydrogen bonds (Glu-165, Gln-166) and seven hydrophobic bonds (Lys-103, Phe-83, Glu-81, Ser-168, Pro-80, Ile-106, Pro-40). The detailed information is listed in Table 5. Docking simulation of the affinity between M1-M8 and MCL1 protein in the “*Homo sapiens*” setting was investigated, and the order of priority of binding energy is as follows: M7, M1, M2 = M8, M3, M6, M5, M4. The eight-binding energy of M1-MCL1, M2-MCL1, M3-MCL1, M4-MCL1, M5-MCL1, M6-MCL1, M7-MCL1, and M8-MCL1 unveiled -6.8 , -6.5 , -5.3 , -4.2 , -4.4 , -4.7 , -6.9 , and -6.5 kcal/mol, respectively. Interaction analysis of the best-docked compound, namely “Ramalic acid”, resulted in three hydrogen bonds (Asp-313, Arg-201, Arg-310) and five hydrophobic bonds (Gly-311, Glu-284, Thr-191, Glu-288, Arg-187). The detailed information is listed in Table 6.

Table 3. Binding energy of potential active compounds on RELA (PDB ID:1NFI).

Protein	Ligand	PubChem ID	Symbol	Binding Energy (kcal/mol)	Hydrogen Bond Interactions	Hydrophobic Interactions
					Amino Acid Residue	Amino Acid Residue
1NFI	NN-dimethyldecanamide	26690	R1	-3.9	Thr-67	Gly-68, Pro-69 Lys-314, Arg-166 Pro-317, Tyr-66 Asp-167
	Paeonol	11092	R2	-5.3	Arg-174, Val-163 Thr-164, Arg-95	Pro-176, Leu-175 Pro-177, Gln-162 Arg-73

Docking simulation of the affinity between V1-V11 and VEGFA protein in the “*Homo sapiens*” setting was explored, and the order of priority of binding energy is as follows: V4, V3, V2 = V6 = V7, V5, V9, V1, V11, V8 = V10. The eleven-binding energy of V1-VEGFA, V2-VEGFA, V3-VEGFA, V4-VEGFA, V5-VEGFA, V6-VEGFA, V7-VEGFA, V8-VEGFA, V9-VEGFA, V10-VEGFA, and V11-VEGFA revealed -5.0 , -7.1 , -7.5 , -8.1 , -6.8 , -7.1 , -7.1 , -3.9 , -5.1 , -3.9 , and -4.4 kcal/mol, respectively. Interaction analysis of the best-docked compound, namely “Trifolirhizin”, resulted in two hydrogen bonds (Asp-41, Glu-42) and five hydrophobic bonds (Asn-75, Glu-38, Tyr-39, Ser-95, Leu-97). The detailed information is listed in Table 7.

Table 4. Binding energy of potential active compounds on NFKB1 (PDB ID: 1SVC).

Protein	Ligand	PubChem ID	Symbol	Binding Energy (kcal/mol)	Hydrogen Bond Interactions	Hydrophobic Interactions
					Amino Acid Residue	Amino Acid Residue
1SVC	Frutinone A	441965	N1	−7.2	Ser-113	Val-145, Val-61 Leu-143, Arg-157 Ala-156, Thr-153 Lys-149
	Paeonol	11092	N2	−5.2	Ser-113, Arg-157 Thr-153	His-144, Lys-149 Ala-111, His-112 Leu-143, Val-145 Val-61
	P-hydroxycinnamic acid	637542	N3	−5.6	Ala-111, Ser-113 Arg-157	His-144, Lys-149 Leu-143, Thr-146 Thr-153, His-112 Val-145, Val-61
	Dibutyl phthalate	3026	N4	−4.6	Lys-337	Lys-278, Phe-301 Ile-281, Pro-303 Gly-299, Phe-298 Gln-282

Table 5. Binding energy of potential active compounds on IL6 (PDB ID: 4CNI).

Protein	Ligand	PubChem ID	Symbol	Binding Energy (kcal/mol)	Hydrogen Bond Interactions	Hydrophobic Interactions
					Amino Acid Residue	Amino Acid Residue
4CNI	Linoleic acid	5280450	L1	−5.0	Lys-39	Glu-81, Pro-80 Ser-168, Phe-83 Gln-105, Leu-104 Gln-166, Lys-103 Glu-165, Pro-40
	β-d-mannose	439680	L2	−5.7	Val-170, Asp-167 Asn-138, Asp-170 Ser-168, Gly-169	His-171, Lys-169
	Nepetin	5317284	L3	−8.0	Glu-165, Gln-166	Lys-103, Phe-83 Glu-81, Ser-168 Pro-80, Ile-106 Pro-40

Table 6. Binding energy of potential active compounds on MCL1 (PDB ID: 5JSB).

Protein	Ligand	PubChem ID	Symbol	Binding Energy (kcal/mol)	Hydrogen Bond Interactions	Hydrophobic Interactions
					Amino Acid Residue	Amino Acid Residue
5JSB	L-adenosine	448374	M1	−6.8	Gly-192, Ser-202 Tyr-116, Gln-189 Glu-188	Arg-201, Glu-115 Arg-222, Gln-221 Lys-276, Asp-218
	Adenosine	60961	M2	−6.5	Ser-202, Gly-192 Glu-188, Tyr-116 Asp-218, Gln-189	Lys-276, Arg-222
	Salicylic acid	338	M3	−5.3	Ala-193, Thr-191	Glu-173, Asp-195 Arg-184, Arg-187 Glu-188
	Methyl palmitelaidate	638303	M4	−4.2	Lys-102	Tyr-106, Arg-101 Ala-99, Glu-98 Lys-11, Ala-14 Val-18, Leu-95 Glu-15

Table 6. *Cont.*

Protein	Ligand	PubChem ID	Symbol	Binding Energy (kcal/mol)	Hydrogen Bond Interactions	Hydrophobic Interactions
					Amino Acid Residue	Amino Acid Residue
	Methyl pentadecanoate	23518	M5	−4.4	Tyr-106	Val-18, Ala-99 Glu-98, Arg-101 Lys-11, Glu-15 Ala-14, Leu-95 Lys-102
	Methyl linoleate	5284421	M6	−4.7	Lys-102, Tyr-106	Glu-15, Ala-99 Leu-95, Glu-98 Lys-11, Ala-14 Arg-101, Val-18
	Ramalic acid	5320886	M7	−6.9	Asp-313, Arg-201 Arg-310	Gly-311, Glu-284 Thr-191, Glu-288 Arg-187
	N9-formylharman	129650345	M8	−6.5	n/a	Arg-187, Asp-195 Glu-188, Arg-184 Ala-193, Glu-173 Arg-201, Thr-191

Table 7. Binding energy of potential active compounds on VEGFA (PDB ID: 4KZN).

Protein	Ligand	PubChem ID	Symbol	Binding Energy (kcal/mol)	Hydrogen Bond Interactions	Hydrophobic Interactions
					Amino Acid Residue	Amino Acid Residue
4KZN	β-d-mannose	439680	V1	−5.0	Asn-75, Ser-95 Tyr-39, Glu-38	Phe-96, Leu-97
	Darutoside	44715524	V2	−7.1	Asp-41, Ser-95	Glu-42, Ile-43 Glu-38, Tyr-39 Phe-96
	Inermin	91510	V3	−7.5	Glu-38, Leu-97 Asp-41	Phe-96, Ser-95 Pro-40, Tyr-39
	Trifolirhizin	442827	V4	−8.1	Asp-41, Glu-42	Asn-75, Glu-38 Tyr-39, Ser-95 Leu-97
	P-glucosyloxymandelonitrile	441465	V5	−6.8	Leu-97, Asn-75 Asp-41, Glu-38	Pro-40, Glu-42 Ser-95, Phe-96 Tyr-39
	Nepetin	5317284	V6	−7.1	n/a	Asp-41, Tyr-39 Phe-96, Leu-97
	Kaempferol	5280863	V7	−7.1	Asn-75	Phe-96, Ser-95 Tyr-39, Asp-41
	Methyl myristate	31284	V8	−3.9	n/a	Asn-75, Glu-38 Tyr-39, Ser-95 Leu-97
	Methyl stearate	8201	V9	−5.1	n/a	Glu-42, Asp-41 Glu-38, Asn-75 Leu-97, Ser-95 Tyr-39
	Methyl pentadecanoate	23518	V10	−3.9	n/a	Tyr-39, Glu-38 Leu-97, Ser-95 Asn-75
	Methyl margarate	15609	V11	−4.4	n/a	Glu-73, Tyr-39 Asn-75, Leu-97

Finally, docking simulation of the affinity between P1-P6 and IL2 protein in the “*Homo sapiens*” setting was investigated, and the order of priority of binding energy is as follows: P2, P5, P1 = P4, P3, P6. The six-binding energy of P1-IL2, P2-IL2, P3-IL2, P4-IL2, P5-IL2, and P6-IL2 indicated −7.0, −8.5, −6.3, −7.0, −7.4, and −5.2 kcal/mol, respectively. Interaction analysis of best-docked compound, namely “Trifolirhizin”, resulted in six hydrogen bonds

(Asp-68, Ser-129, Ile-128, Ala-131, Arg-15, Gln-70) and six hydrophobic bonds (Ser-69, Asp-84, His-79, Leu-80, Ser-132, His-133). The detailed information is listed in Table 8.

Table 8. Binding energy of potential active compounds on IL2 (PDB ID: 2ERJ).

Protein	Ligand	PubChem ID	Symbol	Binding Energy (kcal/mol)	Hydrogen Bond Interactions Amino Acid Residue	Hydrophobic Interactions Amino Acid Residue
2ERJ	Darutoside	44715524	P1	−7.0	Ile-63, Gln-46 Val-88, Arg-85 Trp-90, Thr-47 Asn-61	Gln-34, Cys-48
	Trifolirhizin	442827	P2	−8.5	Asp-68, Ser-129 Ile-128, Ala-131 Arg-15, Gln-70	Ser-69, Asp-84 His-79, Leu-80 Ser-132, His-133
	P-glucosyloxymandelonitrile	441465	P3	−6.3	Asn-61, Arg-85 Trp-90, Glu-49	Cys-48, Ile-63 Gln-34
	Nepetin	5317284	P4	−7.0	Pro-109, Gln-199	Ile-110, Leu-112 Met-107, Pro-196 Trp-197, Ala-108 Ser-198
	Kaempferol	5280863	P5	−7.4	Asp-20, Arg-15 His-133	Leu-85, Asp-84 Ser-69, Gln-70 Arg-81, His-79 Ala-66, Asp-68 Met-23
	Methyl linoleate	5284421	P6	−3.7	n/a	Cys-60, Cys-48 Leu-51, Glu-49 Ile-63, Asn-61

This result illustrated that the five bioactive compounds might be anti-inflammatory agents against COVID-19 (Figure 9).

Figure 9. Illustration of key findings in this study.

3. Discussion

Compounds–genes network indicated that the clinical efficacy of PGCAM on COVID-19-associated genes was directly involved in 27 genes. Of these, both RELA and NFKB1

genes were more significant genes than any other kind of genes. On top of that, based on the pathway enrichment, the PI3K-Akt signaling pathway is found as the topmost mechanism of PGCAM against COVID-19. Accordingly, the docking score through virtual screening on the six genes related to the PI3K-Akt signaling pathway suggested that five bioactive compounds (paeonol, frutinone A, nepetin, ramalic acid, trifolirhizin) were considered the most significant compounds of PGCAM against COVID-19. Meanwhile, the consequence of the KEGG pathway enrichment analysis of 27 genes might be an anti-COVID mechanism. The relationships of 28 signaling pathways with anti-virus properties were discussed as follows.

PPAR signaling pathway: Triggered PPAR- α regulates immunity of cytoplasmic DNA, blocks interferon production, and boosts vulnerability to viral infection [33].

MAPK (Mitogen-Activated Protein Kinase) signaling pathway: Virus-infected cells cause severe reactions that activate the MAPK signaling cascades to shield from virus attack. They can also be used by viruses to facilitate viral replication [34]. Furthermore, the p38 MAPK signaling pathway is a potent inflammatory pathway in lung and heart damage in COVID-19 patients [35].

ErbB signaling pathway: A great number of prime oncogenic virus infections are associated with ErbB signaling pathway. The Hepatitis B Virus (HBV) also induces overexpression of the Epidermal Growth Factor Receptor (EGFR) gene and protein [34,36–38].

RAS signaling pathway: Inhibition of RAS can curtail tissue damage severity in COVID-19 patients. Additionally, ACE (Angiotensin-converting enzyme) blockers cause a reduction in the response of the RAS system [39].

cAMP signaling pathway: cAMPs might have a viral-resistant effect by curbing viral replication and interrupting viral entry. On the other hand, they might have an inimical role by decreasing HIV antiviral immune responses, thus halting the removal of the virus and causing T cell malfunction [40].

Chemokine signaling pathway: Elevation of chemokines (CXCL10 and CXCL8) is clinically characteristic of COVID-19 infection. Moreover, its expression level indicated different clinical acuteness among the COVID-19 patients [41].

NF- κ B signaling pathway: Activation of NF- κ B signaling pathway shows acute inflammation induced after SARS-CoV attack, and NF- κ B blockers are favorable antivirals in the disorder caused by COVID-19 [42].

HIF-1 signaling pathway: HIF-1 α expression supports SARS-CoV-2 replication and sustainability, and it intensifies the cytokine production level in monocytes [43].

FOXO signaling pathway: Reduction of FOXO3 in T cells interrupted apoptosis, elevated multifunction of CD8 cells, and enhanced viral control [44].

Sphingolipid signaling pathway: Sphingolipids play a major protective role in the lungs against pulmonary and lung damage, and the control of their pathways may provide effective and improved therapeutic tactics [45]. Regulation of sphingolipids can be very advantageous and can have an effect on anti-inflammation, preservation of neuronal integrity, and anti-coagulant effects [46,47]. All of these favorable features might be utilized to counterbalance the involved disorders of COVID-19 [48].

PI3K-Akt signaling pathway: Activating of PI3K-Akt signaling is an important mechanism to prolong viral replication in both acute and constant infection, thus, virus-infected Vero E6 cells are activated by PI3K-Akt pathway [49,50].

AMPK signaling pathway: In both HBV and HBC viral infections, the AMPK activation is advantageous, but in others, such as the Ebola virus, dengue virus, and even human cytomegaloviral infections, AMPK plays a counteracting role [51].

Wnt signaling pathway: Controlling Wnt signaling could be a critical process in affecting the sustainability of viral pathogenesis [52].

Toll-like receptor signaling pathway: TLR-7 agonists may inhibit the onset of acute COVID-19 in indicative patients and synergy effects with antiviral treatment [53].

NOD-like receptor signaling pathway: NLRs may regulate inflammatory response via NF- κ B inhibition and block the viral defense system via interaction with mitochondrial antiviral-signaling protein (MAVS) [54].

RIG-I-like receptor signaling pathway: A report shows that SARS-CoV-2 ORF6 blocks RIG-I-like receptor signaling pathway, thus leading to the interruption of the host's innate immune system [55].

JAK/STAT signaling pathway: JAK/STAT pathway is linked to the induction of multiple molecular immune pathways. The interruption of this pathway may lead to the blockade of several cellular responses [56].

IL-17 signaling pathway: IL-17 blockers are immunologically probable as a strategy to inhibit severe respiratory symptoms in COVID-19 patients [57].

T cell receptor signaling pathway: It remains uncertain whether T cell responses are beneficial or detrimental in COVID-19, and whether T cell responses have minimal or maximal effects in COVID-19 infection [58].

B cell receptor signaling pathway: B cells have a crucial role in fighting viral infections; however, B cells are triggered after viral infection and before the production of immunoglobulin G (IgG) [59].

TNF signaling pathway: Anti-TNF α monoclonal antibodies are likely to weaken inflammatory disorders occurring in COVID-19 infection, lessening the release of other inflammatory-aggravating triggers [60].

Neurotrophin signaling pathway: A report shows that neurofilament light chain (NFL)—a biomarker of astrocytic and neuronal damage—was elevated in the blood of patients with COVID-19 [61]. It is evident that COVID-19 infection might dampen the neurological signaling pathway.

GnRH signaling pathway: When viral infections disturb the Blood–Brain Barrier (BBB), circulating immune cells, such as B and T cells, monocytes, and granulocytes, can enter the brain parenchyma to produce cytokines, and thus, it might be able to negatively alter the functions of GnRH neurons [62].

Prolactin signaling pathway: Patients with HIV have a higher prolactin amount compared to the healthy. Additionally, prolactin is considered as a cytokine in its response in the immune system [63,64].

Adipocytokine signaling pathway: Adipose tissue can react to proinflammatory inducement triggered in the lung through systemic circulation adipocytokines and other inflammatory factors [65].

Relaxin signaling pathway: The dysfunction of the relaxin signaling pathway might bring respiratory disorders recognized in COVID-19 patients. Moreover, SARS-CoV-2 NSP7 protein renders relaxin receptors very much weaker [66].

AGE-RAGE signaling pathway in diabetic complications: AGE-RAGE can also act as an innate immune sensor, including in respiratory viruses. As a consequence, the blocking of RAGE curtails the inflammatory level and progression of cardiovascular diseases [67].

Epithelial cell signaling in *Helicobacter pylori* infection: *Helicobacter pylori* downregulates T and B cell signaling to initiate the immune system [68]. It is obvious that COVID-19 patients with *Helicobacter pylori* might be vulnerable to inflammatory responses.

Based on the pathway enrichment analysis, both RELA and NFKB1 were considered as hub genes in PGCAM against COVID-19. Two genes of each were directly enriched in 21 out of 28 signaling pathways by the PI3K-Akt signaling pathway, indicating that PI3K-Akt signaling pathway might be a hub signaling pathway in PGCAM against COVID-19. The other four genes (IL6, MCL1, VEGFA, and IL2) directly related to the PI3K-Akt signaling pathway might be the significant genes to exert synergistic effects against COVID-19. Liu et al. [69] showed that inhibition of both RELA and/or NFKB1 reduces cytokine secretion and thus alleviates inflammation severity. A report specified that MCL-1 inhibition in mitochondrial membrane stimulates BAX, Cytochrome C, Caspase-9, and Caspase-3, and thus it leads to cell death [70,71]. Noticeably, a report indicated that vascular endothelial growth factor A (VEGFA) was inhibited by angiotensin-converting enzyme 2 (ACE2) and

upregulated by the attack of COVID-19, since COVID-19 interrupts the expression of ACE2. Consequently, VEGFA elevates vascular permeability and aggravation of endothelial damage [72]. Most recently, it has been reported that a higher level of both IL-2 and IL-6 was detected in COVID-19 patients [73]. Endothelial cell inflammation is also a major severity in COVID-19 infection, and its unmanageable cytokine production in tissues and cells aggravates severe immune reaction, which is defined as “cytokine storm”, resulting in worsening pneumonia. On top of that, the inhibition of six genes (RELA, NFKB1, IL6, MCL1, VEGFA, and IL2) associated with the PI3K-Akt signaling pathway contributes to the anti-proinflammation, anti-vascular permeability, and pro-apoptosis against COVID-19.

Therefore, the key mechanism of PGCAM against COVID-19 might be to block inflammation and vascular permeability, and trigger pro-apoptosis in tissues and/or cells by inactivating the PI3K-Akt signaling pathway.

4. Materials and Methods

4.1. Selective Compound Construction and Drug-Likeness Evaluation

The LMWCs information of PGCAM was collected by TCMSP (<https://tcmspw.com/tcmsp.php>), literature, SMILES, and Pubchem CID. The molecular formula of selective compounds was identified using ChemSpider (<https://www.chemspider.com/StructureSearch.aspx>, accessed on 13 October 2021) or Pubchem (<https://pubchem.ncbi.nlm.nih.gov>, accessed on 14 October 2021). The drug-likeness properties of the identified compounds were selected through Lipinski's rule (molecular weight ≤ 500 g/mol; Moriguchi octanol-water partition coefficient ≤ 4.15 ; the number of nitrogen or oxygen ≤ 10 ; and the number of NH or OH ≤ 5) in SwissADME (<http://www.swissadme.ch>, accessed on 14 October 2021). The compound structures were drawn by PubChem Sketcher V2.4 (<https://pubchem.ncbi.nlm.nih.gov/edit3/index.html> accessed on 14 October 2021).

4.2. Target Genes Related to Selected Compounds or COVID-19

Based on SMILES, target genes associated with screened compounds were selected through both SEA (<http://sea.bkslab.org>, accessed on 15 October 2021) and STP (<http://www.swisstargetprediction.ch>, accessed on 15 October 2021) with “Homo Sapiens” mode. The COVID-19-related genes were identified through PubChem (<https://pubchem.ncbi.nlm.nih.gov>, accessed on 17 October 2021). The overlapping genes between compounds and COVID-19 target genes were identified and visualized by VENNY 2.1 (<https://bioinfogp.cnb.csic.es/tools/venny>, accessed on 18 October 2021).

4.3. Bubble Chart of Enrichment Pathway Analysis of Overlapping Genes

Genes–genes interaction figure was drawn by STRING (<https://string-db.org>, accessed on 22 October 2021). RStudio plotted the bubble chart of KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway enrichment analysis of overlapping genes. The results of KEGG pathway enrichment provide a hint at the promising molecular mechanism of PGCAM against COVID-19.

4.4. Binding Affinity Energy Value of Key Bioactive Compounds on Genes In Silico

The binding affinity energy measurement of the uttermost potential bioactive compounds on key genes was determined by Autodock (<http://autodock.scripps.edu>, accessed on 25 October 2021), Vina (<http://vina.scripps.edu/> accessed on 25 October 2021), Pymol (<https://pymol.org/2/> accessed on 25 October 2021).

5. Conclusions

The efficiency of LMWCs extracted from PGCAM and their anti-COVID-19 mechanisms were firstly analyzed by using network pharmacology. The findings of this research indicated that potential bioactive compounds are paenol, frutinone A, ramalic acid, nepetin, and trifolirhizin, and the target genes are RELA, NFKB1, MCL1, VEGFA, IL2, and IL6 of PGCAM against COVID-19. The mechanism(s) of PGCAM against COVID-19 might

be inhibited inflammation, vascular permeability, and induction of cell apoptosis against COVID-19 by inactivating the PI3K-Akt signaling pathway. This research provides a scientific indication to support the therapeutic effect of PGCAM on COVID-19, and thus, the proper application of five bioactive compounds against COVID-19 might have potential synergistic effects, such as anti-inflammation, anti-vascular permeability, and pro-apoptosis of the infected cells to prevent COVID-19 vulnerability.

Still, there are also limitations to our analysis. The incompleteness of the herbal natural products database, COVID-19-related genes and protein–protein interaction network might bring bias about target gene findings. Moreover, our approach is dependent on GSEA analysis and molecular docking simulation, either agonist or antagonist. Thus, our predicted result would need to be further improved, through in vitro and in vivo.

The current study did not verify the LMWCs of PGCAM, whose efficacy needs to be validated via clinical test. However, our approach is a holistic perspective and integrated gene–compound interaction, which might be good and promising hints against COVID-19.

Finally, our analysis did not consider the target gene expression level practically after treatment of the selected compounds, which should be implemented in the future.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/pr10020333/s1>, Table S1: 1:197 genes (STP + SEA) related to 107 compounds. Table S2: The overlapping genes of SEA and STP: 399 Genes. Table S3: COVID 19-related genes: 356 genes. Table S4: Final 27 overlapping genes related to COVID-19. Figure S1: (A) Interactions between two bioactive compounds and RELA (PDB ID: 1NFI). (B) Interactions between four bioactive compounds and NFkB1 (PDB ID: 1SVC). (C) Interactions between three bioactive compounds and IL6 (PDB ID: 4CNI). (D) Interactions between nine bioactive compounds and MCL1 (PDB ID: 5JSB). (E) Interactions between eleven bioactive compounds and VEGFA (PDB ID: 4KZN). (F) Interactions between six bioactive compounds and IL2 (PDB ID: 2ERJ).

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Abbreviations

ACE2	Angiotensin-Converting Enzyme 2
AGE	Advanced Glycation Endproducts
AMPK	AMP-activated Protein Kinase
Caco-2 cell	Human intestinal epithelial cell
cAMP	Cyclic Adenosine MonoPhosphate
cAMPs	Cyclic Adenosine MonoPhosphates
CD8	Cluster of Differentiation 8
COVID-19	SARS-CoV-2 virus
EGFR	Epidermal Growth Factor Receptor
FOXO	Forkhead box protein O
GnRH	Gonadotropin-Releasing Hormone
<i>ErbB</i>	Erythroblastic Leukemia Viral Oncogene Homolog

HIF-1	Hypoxia-Inducible Factor-1
HIF-1 α	Hypoxia-Inducible Factor-1 alpha
HIV	Human Immunodeficiency Virus
IL2	Interleukin 2
IL6	Interleukin 6
KEGG	Kyoto Encyclopedia of Genes and Genomes
LMWCs	Low Molecular Weight Compounds (<500 Daltons; accepted by Lipinski's rule)
LRTI	Lower Respiratory Tract Infection
MAPK	Mitogen-Activated Protein Kinase
MAVS	Mitochondrial AntiViral-Signaling protein
MCL1	Myeloid Cell Leukemia 1
NFKB1	Nuclear Factor Kappa B Subunit 1
NF-KB	Nuclear Factor Kappa-light-chain-enhancer of activated B cells
NfL	Neurofilament Light chain
NOD	Nucleotide-binding Oligomerization Domain
NP	Network Pharmacology
ORF6	Open Reading Frame 6
PGCAM	Panax Ginseng C.A. Meyer
PI3K-Akt	Phosphatidylinositol 3-kinase—protein kinase B
PPAR	Peroxisome Proliferator-Activated Receptors
PPAR- α	Peroxisome Proliferator-Activated Receptor-alpha
RAGE	Receptor for Advanced Glycation Endproducts
RELA	Transcription factor p65
RAS	Renin-Angiotensin System
RIG-I	Retinoic acid-Inducible Gene I
RSV	Respiratory Syncytial Virus
SEA	Similarity Ensemble Approach
SMILES	Simplified Molecular Input Line Entry System
STP	Swiss Target Prediction
TCMSP	Traditional Chinese Medicine Systems
TLR	Toll-Like Receptor
TNF	Tumor Necrosis Factor
VEGFA	Vascular Endothelial Growth Factor A
WHO	World Health Organization

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