Research Paper

Revealing the targets and mechanisms of vitamin A in the treatment of COVID-19

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19), an epidemic disease characterized by rapid infection and a high death toll. The clinical diagnosis of patients with COVID-19 has risen sharply, especially in Western countries. Globally, an effective treatment for COVID-19 is still limited. Vitamin A (VA) exhibits pharmacological activity in the management of pneumonia. Thus, we reason that VA may potentially serve as an anti-SARS-CoV-2 regimen. In this study, bioinformatics analysis and computation assays using a network pharmacology method were conducted to explore and uncover the therapeutic targets and mechanisms of VA for treating COVID-19. We identified candidate targets, pharmacological functions, and therapeutic pathways of VA against SARS-CoV-2. Bioinformatics findings indicate that the mechanisms of action of VA against SARS-CoV-2 include enrichment of immunoreaction, inhibition of inflammatory reaction, and biological processes related to reactive oxygen species. Furthermore, seven core targets of VA against COVID-19, including *MAPK1, IL10, EGFR, ICAM1, MAPK14, CAT*, and *PRKCB* were identified. With this bioinformatics-based report, we reveal, for the first time, the anti-SARS-CoV-2 functions and mechanisms of VA and suggest that VA may act as a potent treatment option for COVID-19, a deadly global epidemic.

INTRODUCTION

Coronavirus disease 2019 (COVID-19), a deadly disease induced by the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first discovered in China, and is accompanied by a high degree of morbidity and mortality [1]. The virus has spread across the world and infected very large populations, especially in the United States [2]. Clinical features of COVID-19 may include pyrexia, asthenia, dyspnea, as well as acute respiratory distress syndrome, septic shock, and coagulation dysfunction in critically ill patients [3]. It is believed that, due to its high fatality rate, SARS-CoV-2 may strongly bind to angiotensin-converting enzyme 2 (ACE2), which is a key factor in the pathological pathway of SARS-CoV infection in the host [4]. The latest research findings have indicated that the affinity of SARS-CoV-2 to ACE2 may be 10 to 20 times greater than that of SARS-CoV [5]. In the SARS-CoV-2-infected population, it has been reported that people aged over 65 years have the highest rate of death [6]. Clinically, an effective and accurate diagnosis of SARS-CoV-2 has been achieved. However, the medical pharmacotherapy to treat COVID-19 is still insufficient

[7]. Accordingly, it is necessary to explore and develop bioactive compounds to treat COVID-19. Vitamins are considered as a food supplement and have been reported to play an important role in the immune system [8]. Vitamin A (VA) has potent physiological functions, such as promoting growth and reproduction and maintaining bone, epithelial tissue, vision, and normal secretion of mucosal epithelium. VA and its derivatives can prevent precancerous lesions [9]. An increasing number of reports indicate that VA is necessary to maintain immune function and that it is responsible for immune cell differentiation and proliferation [10]. It has been reported that VA can improve the ability of immune cells to produce antibodies and induce T lymphocytes to release functional lymphokines through modulation of target genes via nuclear receptors [11]. Additionally, VA is extremely important for maintaining sufficient levels of natural "killer cells" (showing antiviral activity) in circulating blood [12]. VA adjuvant therapy may enhance body immune function by increasing IgM and IgG levels and activating T lymphocytes [13]. More importantly, vitamin A was reported to play a significant role against pneumonia. It is evidenced that low VA content is linked to neonatal pneumonia [14]. Clinical data show that VA deficiency is implicated in fatal mycoplasma-induced pneumonia in children [15]. In addition, VA supplementation contributes to the reduction of clinical complications and shortening of in-hospital time for children with pneumonia [16]. All these pieces of evidence suggest that vitamin A may be an optional treatment for COVID-19; however, to date there has been no investigation of VA against SARS-CoV-2, especially its pharmacological mechanism. In this report, we aimed to determine and identify the curative effect of VA for treating COVID-19 and to utilize a network pharmacology approach to uncover the mechanisms underlying the therapeutic role of VA.

RESULTS

Identification of SARS-CoV-2- and vitamin A-associated genes

In order to determine the SARS-CoV-2-associated and VA-pharmacological action genes, we conducted a series of bioinformatic analyses. We assayed and identified 393 SARS-CoV-2-associated genes from the Genecard and OMIM datasets. In addition, 122 VA-pharmacological action genes were identified following data correction using the UniProt tool (Figure 1). When we compared the target (VA-associated and SARS-CoV-2-associated) genes, 15 VA-associated targets against SARS-CoV-2 were identified, and the common genes were subjected to target-function-protein interaction network analysis (Figure 1). By setting the median degree of freedom to 2.923, the maximum degree

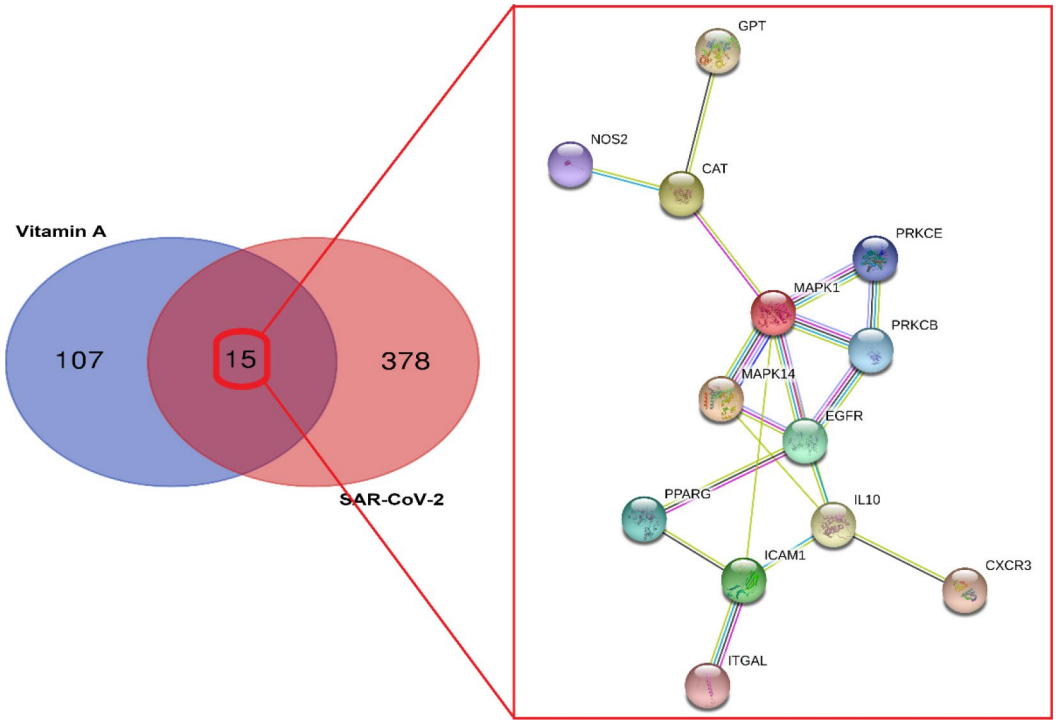

Figure 1. Identification of vitamin A and SARS-CoV-2 associated genes. Venn diagram showing the intersection targets of vitamin A against SARS-CoV-2 with an identified PPI network.

of freedom to 7, and the core target screening condition ranged to 3–7), seven core targets of VA against SARS-CoV-2 were identified, namely MAPK1, IL10, EGFR, ICAM1, MAPK14, CAT, and PRKCB (Figure 2).

Biological role of vitamin A against SARS-CoV-2

The core targets were subjected to gene ontology (GO) biological process and KEGG pathway enrichment analysis to understand the possible biological role of VA and the signaling pathway against SARS-CoV-2. The GO results highlighted that VA mediated a number of biological processes related to cellular response to the virus, immunity, cytokine production and secretion, and inflammatory response (Figure 3A and Supplementary Table 1). Immune responses are mediated by different classes of immune cells, such as neutrophils and lymphocytes, through the immune response-activating cell surface receptor signaling pathway. The VA-mediated immune response is also regulated by immunoglobulin production (Figure 3A and Supplementary Table 1). In addition, VA played a role in both acute and chronic inflammatory responses against SARS-CoV-2 (Figure 3A and Supplementary Table 1).

Vitamin A-mediated signaling pathway and network against SARS-CoV-2

We conducted a KEGG pathway analysis to further understand the possible mechanism underlying the anti-SARS-CoV-2 role of vitamin A. Our results highlighted that vitamin A might regulate a series of signaling pathways related to viral infections, such as human cytomegalovirus, influenza A, Kaposi sarcoma-associated herpes virus, human immunodeficiency virus 1, hepatitis C, Epstein-Barr, and human papilloma virus (Figure 4 and Online Resource 2). In addition, we also found that vitamin A was involved in many important cell signaling pathways such as FoxO, VEGF, TNF, Ras, nuclear factor kappa B (NF-κB), phospholipase D, mTOR, and JAK-STAT (Figure 4 and Supplementary Table 2). More importantly, we found the involvement of vitamin A in immune responses such as T cell receptor signaling pathway, leukocyte transendothelial migration, natural killer cell mediated cytotoxicity, Fc epsilon RI signaling pathway, B cell receptor signaling pathway, Th1 and Th2 cell differentiation, Fc gamma R-mediated phagocytosis, IL-17 signaling pathway, Toll-like receptor signaling pathway, Th17 cell differentiation, and human T-cell leukemia virus 1 infection (Figure 4 and Supplementary Table 2). Vitamin A regulates cytokine production via NOD-like receptor signaling pathway and chemokine signaling pathway (Figure 4 and Supplementary Table 2). These findings suggest that vitamin A could be a potential treatment for COVID-19. Finally, we used Cytoscape software to construct the gene network diagram of VA-target-GO-KEGG-SARS-CoV-2 (Figure 5).

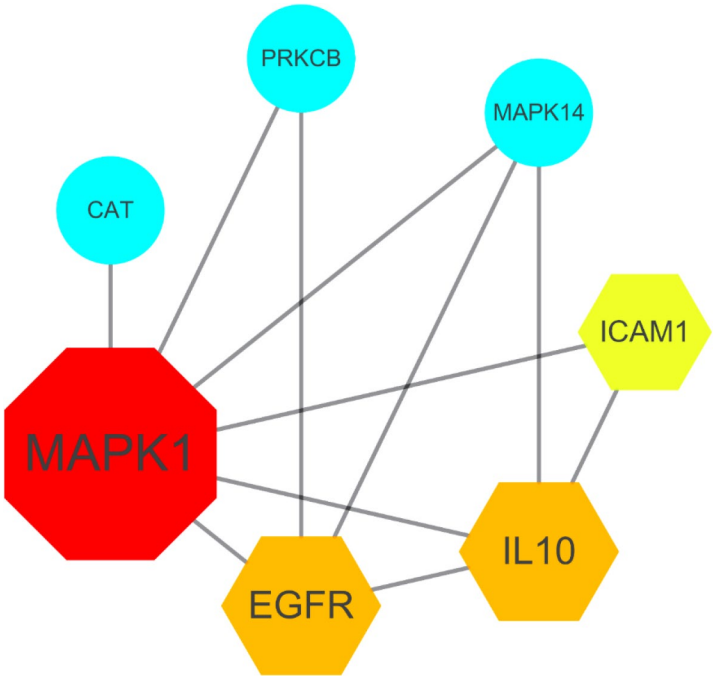

Figure 2. Gene network of the seven core targets of vitamin A against SARS-CoV-2

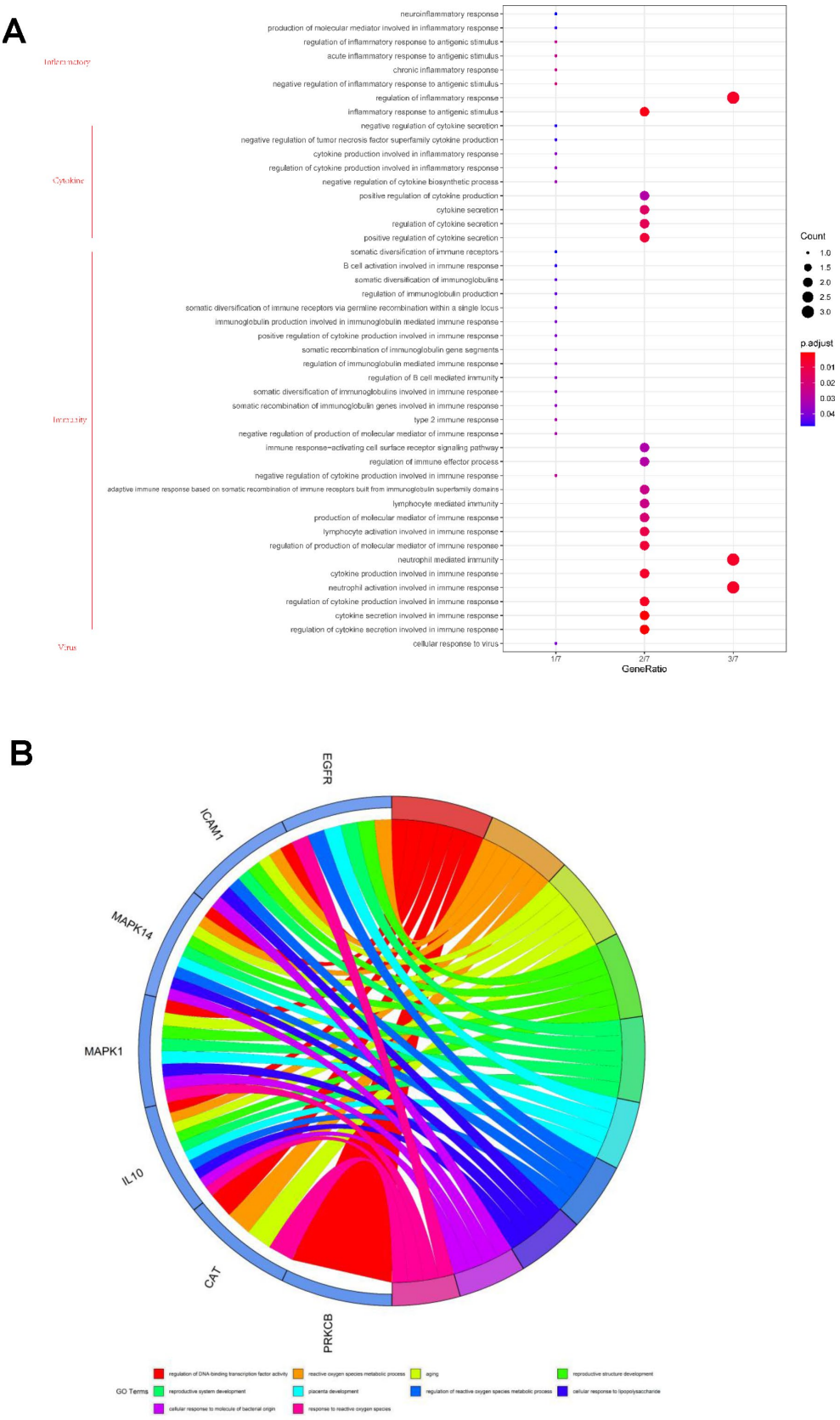

Figure 3. Gene ontology analysis of the seven core targets of vitamin A against SARS-CoV-2. (**A**) Bubble diagram showing the vitamin A-mediated biological process against SARS-CoV-2. (**B**) All core biotargets of vitamin A against SARS-CoV-2 were linked to the top 10 most enriched GO terms in Circro diagrams.

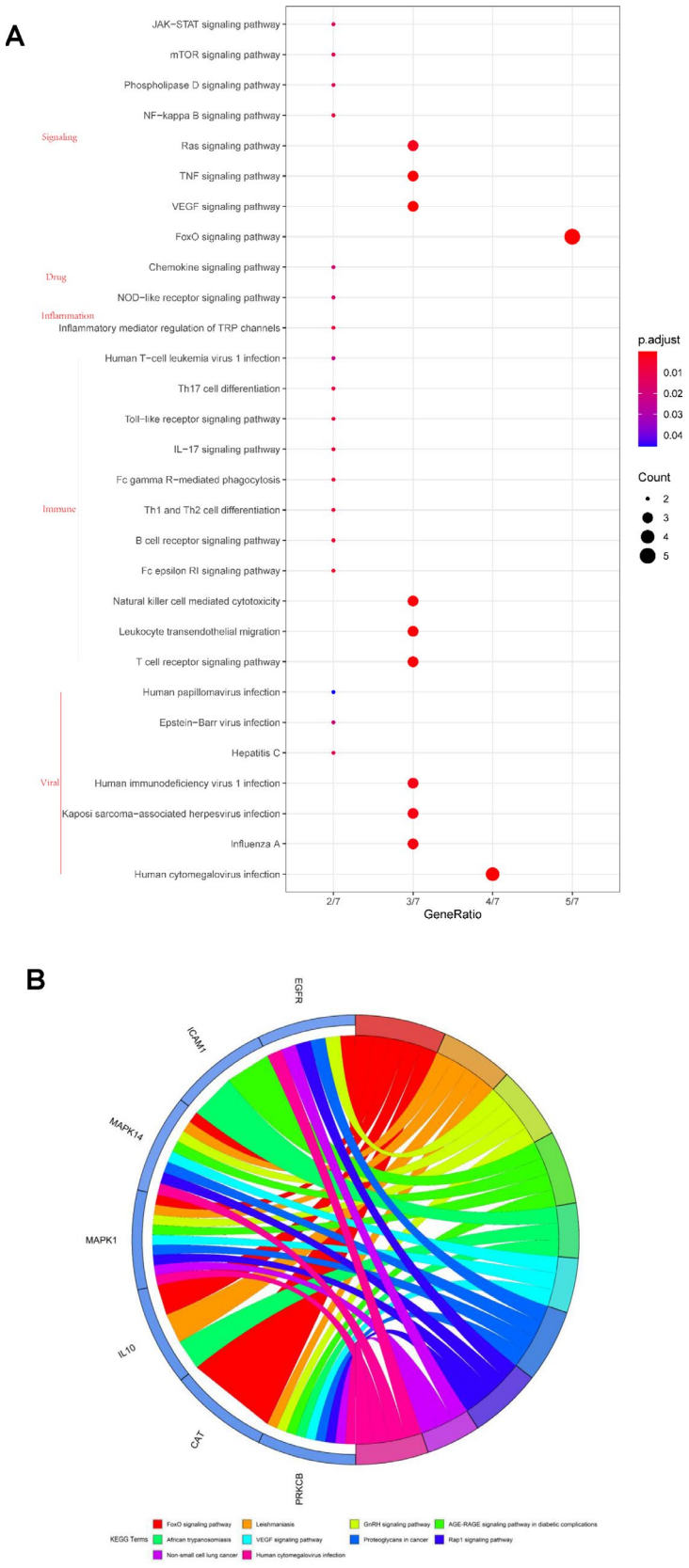

Figure 4. Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis of the seven core targets of vitamin A against SARS-CoV-2. (**A**) Bubble diagram showing the vitamin A-mediated cell signaling pathways against SARS-CoV-2. (**B**) Identified core biotargets of vitamin A against SARS-CoV-2 were associated with the 10 most enriched KEGG terms in Circro diagrams.

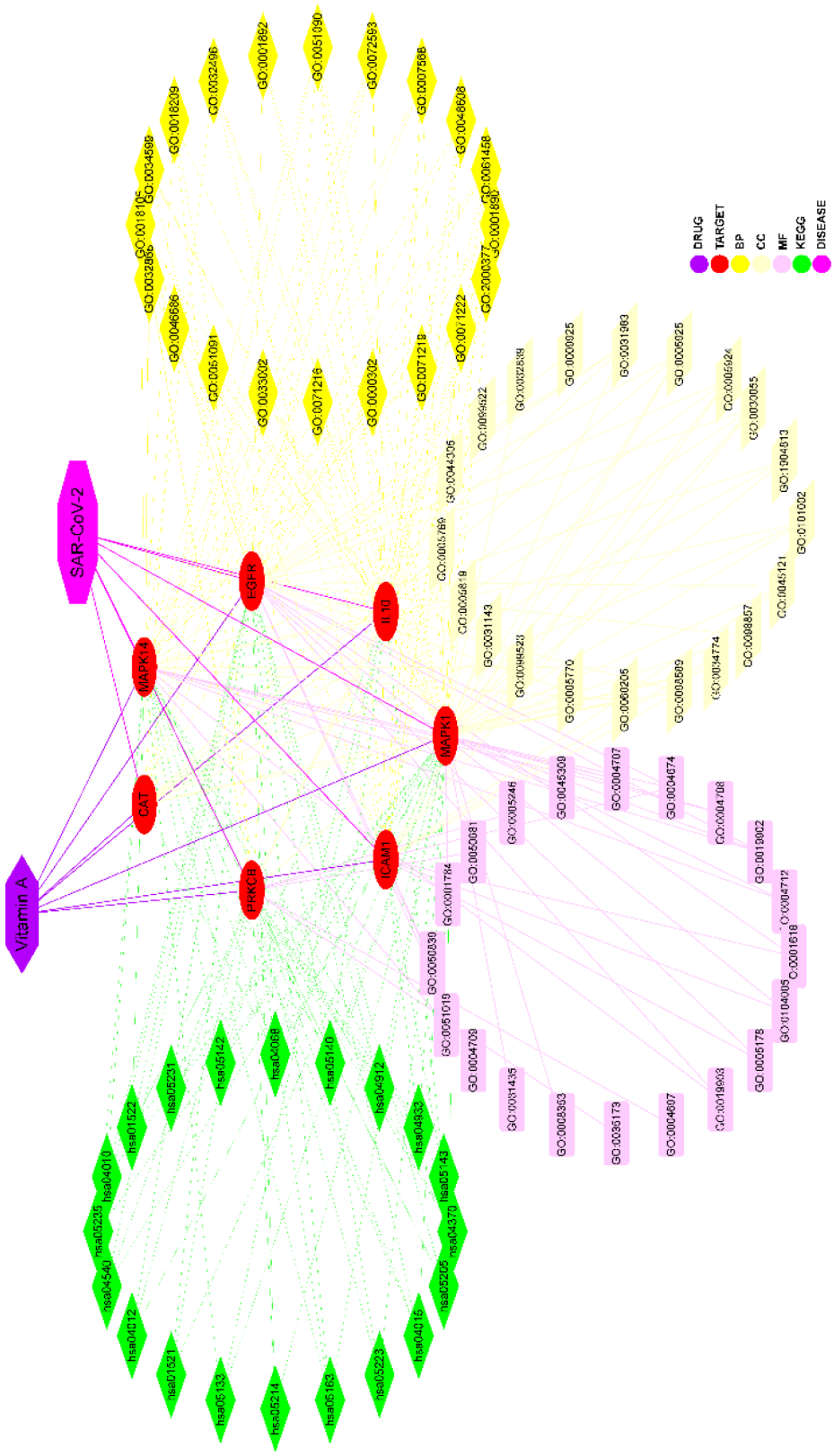

Figure 5. Interaction network of the target-KEGG pathways of VA against SARS-CoV-2. The middle part represented the anti-SARS-CoV-2 targets of vitamin A, and the enriched top 20 biological functions and KEGG pathways.

DISCUSSION

Recently, the prevalence and mortality of SARS-CoV-2 has increased sharply worldwide, especially in developed countries in 2020 [17]. However, there are few existing drug treatments for COVID-19, and some of the immunotherapy treatments and antiviral drugs used in clinical practice have shown limited therapeutic effectiveness [18]. Thus, further investigation and development of potential therapeutic agents is warranted. In this bioinformatics report, we aimed to identify and reveal the anti-SARS-CoV-2 targets and molecular mechanisms of VA through an emerging approach to network pharmacology. VA may exert potent, beneficial pharmacological activity for the treatment of COVID-19 via associated cytoprotection, anti-viral and anti-inflammatory effects, and immunoregulation. By using the network pharmacology strategy to uncover the molecular functions, the anti-SARS-CoV-2 effects of VA could be shown to be modulated by some key molecules and corresponding genes, including *MAPK1*, *IL10*, *EGFR*, *ICAM1*, *MAPK14*, *CAT*, and *PRKCB*. In our previous report, we demonstrated that vitamin C could also modulate a cluster of core targets against SARS-CoV-2 [19]. When we compared the findings, we found that two core targets, MAPK1 and EGFR, were found in the effect of both vitamin A and vitamin C. MAPK1, a functional protein kinase, is a key connection in the switch from extracellular irritation to intracellular signaling. Changes in the signaling pathway are evidenced in complex diseases, including cancers [20]. It has been reported that anti-pneumonia action exerted by VA is related to specific suppression of the MAPK signaling pathway, including MAPK1 activity [21]. EGFR, a tyrosine kinase receptor, plays important roles in modulating cell proliferation, division, differentiation, survival, and oncogenesis [22]. It has been reported that EGFR-mutated patients are likely to have hospital-acquired pneumonia [23]. IL-10, a pivotal anti-inflammatory cytokine, can effectively control inflammatory Th cells and immunopathology and secure cellular homeostasis [24]. Some reports have shown that inactivation of IL-10 is linked to an increased risk of developing pneumonia [25–26]. ICAM-1, a transmembrane glycoprotein receptor, can

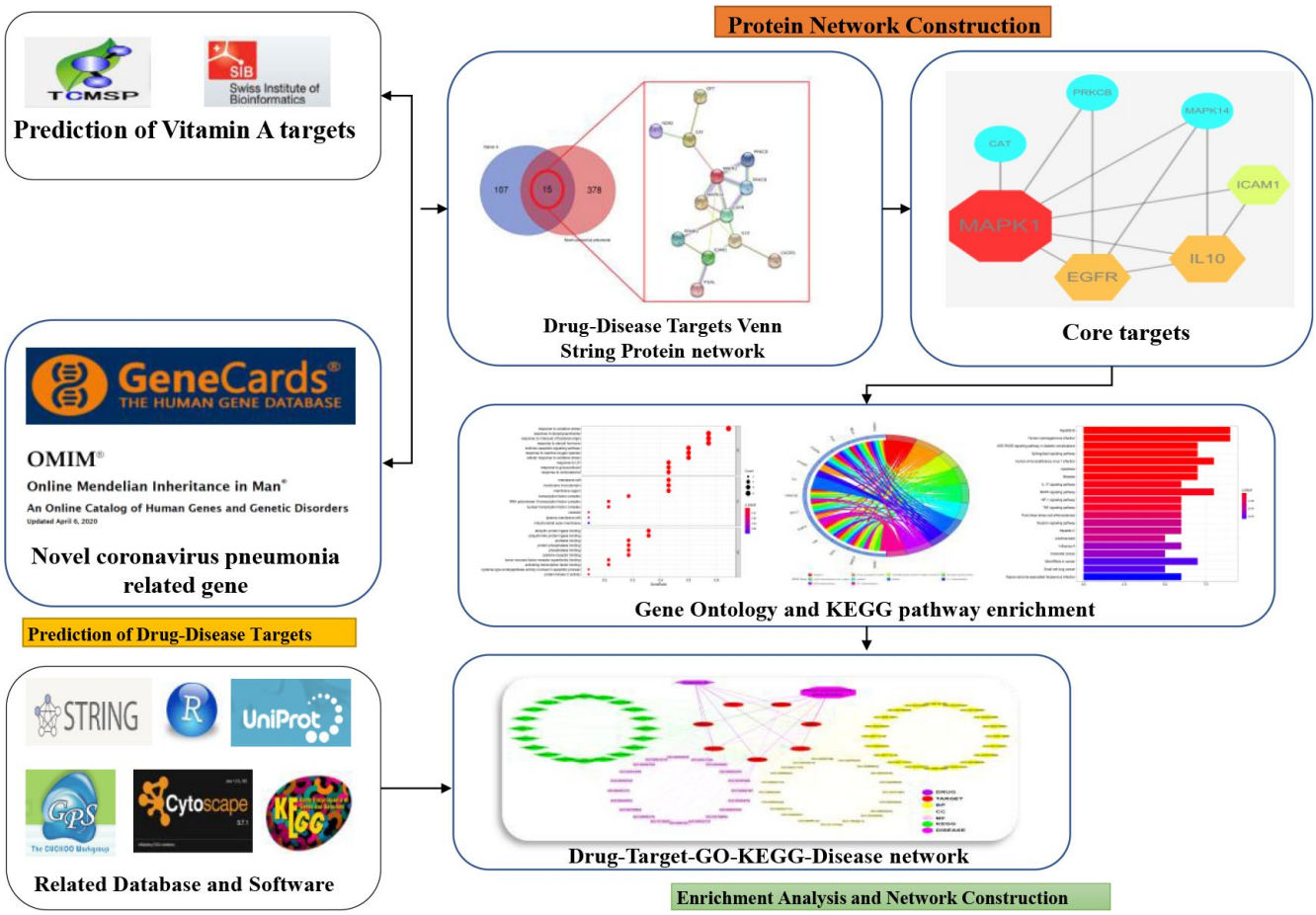

Figure 6. A schematic diagram to summarize the workflow of the study.

recruit inflammatory cells and cytokines to target tissue [27]. Reportedly, blood ICAM-1 content may function as a potent biomarker of patients with pneumonia [28], including pediatric pneumonia [29]. Catalase, a well-known antioxidant enzyme, acts as an oxidative catalyst for some biological functions [30]. Biologically, catalase is found to have potential therapeutic effectiveness against influenza-induced pneumonia [31]. PRKCB, an important regulator of B cells, can regulate metabolic and mitochondrial reprogramming responsible for B cell fate [32]. Some evidence indicates that PRKCB overexpression is associated with the development of pneumonia via activation of the NF-κB pathway [33]. Collectively, these predictive peptides may be used as potential markers for detecting SARS-CoV-2 and may serve as pharmacological targets against SARS-CoV. In further bioinformatics and computational assays, the therapeutic mechanisms of VA for managing COVID-19 could be conjunctively actualized through collective regulation of the FoxO signaling pathway, GnRH signaling pathway, PD-L1 expression, and PD-1 checkpoint pathway. Accordingly, VA demonstrates several pharmacological mechanisms against SARS-CoV, namely, cytoprotective action, anti-viral activity, anti-inflammatory effects, and immunity-based immunomodulation. The anti-coronavirus benefits may be the dual efficacy of a nutrient agent and bioactive compound to treat complex disease by synergistically modulating all presumptive multi-targets and multi-pathways. Adjuvant supplementation of VA may enhance the therapeutic efficacy of current clinical anti-viral agents and immunotherapy to treat potentially fatal COVID-19. However, the current findings should be further validated clinically.

In conclusion, the bioinformatics and computational findings from this study highlight the role of vitamin A in anti-viral, anti-inflammatory, and immunomodulatory effects via different biological processes and cell signaling pathways, as revealed by network pharmacology analysis. More importantly, VA may be used clinically for the treatment of COVID-19, as evidenced by the identified biological processes—which indicate pharmacological functions—and the signaling pathways, which suggest therapeutic mechanisms (Figure 6).

MATERIALS AND METHODS

Identification of candidate genes activated by VA

By using online datasets, in particular TCMSP, Drugbank, SuperPred, Swiss Target Prediction, ChemMapper, and BATMAN TCM, all target genes activated by VA were obtained. The genes activated by VA were collected for target correction from reviewed (Swiss-Prot) and Uniprot databases. The Genecard and OMIM datasets were employed to harvest SARS-CoV-2 genes. All the shortlisted genes and targets of VA and SARS-CoV-2 were subjected to intersection analysis via an online platform with graphical output (http://bioinformatics.psb.ugent.be/webtools/Venn/) in the form of Venn diagrams were plotted to display the relational VA-activated genes and targets of VA against SARS-CoV-2 [34, 35].

Gene Ontology (GO) and KEGG pathway enrichment analyses

The *R*-language package ClusterProfiler, ReactomePA, org.Hs.eg.Db, and GOplot were applied in the assay and visualization of the relational targets. GO analysis was conducted with the use of org.Hs.eg.Db, with a p-value cutoff of 0.05 in enriched output of bubble charts and Circos-circle charts. The Pathview package in *R*-language was used to merge the relational targets of enriched KEGG pathways by drawing pathway diagrams [36, 37].

Construction of network visualization in core targets

The software Cytoscape (v3.7.1) was used to plot the component-target-pathway network and the GO biological process and KEGG pathway-based visual graphics of VA against SARS-CoV-2 [38, 39].

Establishment of the biological process and KEGG molecular pathway of VA

To compare the anti-SARS-CoV-2 effects of VA, bioinformatics data of top biological functions and KEGG-enriched pathways were applied for pairwise comparison, including the value of -log10 (p-adjust) as the heat-map parameter, and the heat-map was drawn using HemI 1.0 software [19, 40].

Construction of construction of protein-protein interaction (PPI) network graphics of core targets

The relational targets of VA against SARS-CoV were employed as inputs to the software STRING for plotting target-to-target network interactions and target interaction PPI network diagram. The NetworkAnalyzer setting in Cytoscape software was applied to analyze topology parameters, such as median degrees of freedom and maximum degrees of freedom in the network. The optimal targets were collected based on degree values (DV). The upper limit of the filtering range was the maximum DV in the topology data, and the lower limit was twice the median of freedom, as previously reported [41, 42].

Abbreviations

CAT: Catalase; EGFR: Epidermal growth factor receptor; ICAM1: Intercellular Adhesion Molecule 1; IL10: Interleukin 10; KEGG: Kyoto Encyclopedia of Genes and Genomes; MAPK1: Mitogen-Activated Protein Kinase 1; MAPK14: Mitogen-activated protein kinase 14; OMIM: Online Mendelian Inheritance in Man; PRKCB: Protein kinase C beta type; TCMSP: The traditional Chinese medicine systems pharmacology database and analysis platform.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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SUPPLEMENTARY MATERIALS

Supplementary Tables

Please browse Full Text version to see the data of Supplementary Table 1.

Supplementary Table 1. Gene ontology analysis (biological process) using the identified seven core targets of VA against SARS-CoV-2.

Supplementary Table 2. KEGG pathway enrichment analysis using the identified seven core targets of VA against SARS-CoV-2.

ID	Description	GeneRatio	BgRatio	pvalue	p.adjust	qvalue	geneID	Count	remark
hsa05163	Human cytomegalovirus infection	4/7	225/8025	1.97E-05	0.000313	8.71E-05	MAPK1/EGFR/MAPK14/PRKCB	4	viral
hsa05164	Influenza A	3/7	170/8025	0.000307	0.00132	0.000367	MAPK1/ICAM1/PRKCB	3	viral
hsa05167	Kaposi sarcoma-associated herpesvirus infection	3/7	186/8025	0.0004	0.001632	0.000454	MAPK1/ICAM1/MAPK14	3	viral
hsa05170	Human immunodeficiency virus 1 infection	3/7	212/8025	0.000588	0.002175	0.000605	MAPK1/MAPK14/PRKCB	3	viral
hsa05160	Hepatitis C	2/7	155/8025	0.007304	0.012354	0.003435	MAPK1/EGFR	2	viral
hsa05169	Epstein-Barr virus infection	2/7	201/8025	0.012066	0.019176	0.005332	ICAM1/MAPK14	2	viral
hsa05165	Human papillomavirus infection	2/7	330/8025	0.030868	0.045444	0.012636	MAPK1/EGFR	2	viral
hsa04660	T cell receptor signaling pathway	3/7	104/8025	7.13E-05	0.000515	0.000143	MAPK1/IL10/MAPK14	3	immune
hsa04670	Leukocyte transendothelial migration	3/7	112/8025	8.89E-05	0.000524	0.000146	ICAM1/MAPK14/PRKCB	3	immune
hsa04650	Natural killer cell mediated cytotoxicity	3/7	131/8025	0.000142	0.000705	0.000196	MAPK1/ICAM1/PRKCB	3	immune
hsa04664	Fc epsilon RI signaling pathway	2/7	68/8025	0.001446	0.00442	0.001229	MAPK1/MAPK14	2	immune
hsa04662	B cell receptor signaling pathway	2/7	82/8025	0.002095	0.005552	0.001544	MAPK1/PRKCB	2	immune
hsa04658	Th1 and Th2 cell differentiation	2/7	92/8025	0.00263	0.006744	0.001875	MAPK1/MAPK14	2	immune
hsa04666	Fc gamma R-mediated phagocytosis	2/7	93/8025	0.002687	0.00678	0.001885	MAPK1/PRKCB	2	immune
hsa04657	IL-17 signaling pathway	2/7	94/8025	0.002744	0.006817	0.001895	MAPK1/MAPK14	2	immune
hsa04620	Toll-like receptor signaling pathway	2/7	104/8025	0.003348	0.007293	0.002028	MAPK1/MAPK14	2	immune
hsa04659	Th17 cell differentiation	2/7	107/8025	0.003541	0.007608	0.002115	MAPK1/MAPK14	2	immune

hsa05166	Human T-cell leukemia virus 1 infection	2/7	219/8025	0.014222	0.021743	0.006046	MAPK1/ICAM1	2	immune
hsa04750	Inflammatory mediator regulation of TRP channels	2/7	100/8025	0.0031	0.007142	0.001986	MAPK14/PRKCB	2	inflammation
hsa04621	NOD-like receptor signaling pathway	2/7	181/8025	0.009861	0.016164	0.004494	MAPK1/MAPK14	2	drug
hsa04062	Chemokine signaling pathway	2/7	189/8025	0.010718	0.01739	0.004835	MAPK1/PRKCB	2	drug
hsa04068	FoxO signaling pathway	5/7	131/8025	2.20E-08	3.49E-06	9.71E-07	MAPK1/IL10/EGFR/MAPK14/CAT	5	signaling
hsa04370	VEGF signaling pathway	3/7	59/8025	1.29E-05	0.000298	8.29E-05	MAPK1/MAPK14/PRKCB	3	signaling
hsa04668	TNF signaling pathway	3/7	112/8025	8.89E-05	0.000524	0.000146	MAPK1/ICAM1/MAPK14	3	signaling
hsa04014	Ras signaling pathway	3/7	232/8025	0.000766	0.002767	0.000769	MAPK1/EGFR/PRKCB	3	signaling
hsa04064	NF-kappa B signaling pathway	2/7	104/8025	0.003348	0.007293	0.002028	ICAM1/PRKCB	2	signaling
hsa04072	Phospholipase D signaling pathway	2/7	148/8025	0.006676	0.011819	0.003286	MAPK1/EGFR	2	signaling
hsa04150	mTOR signaling pathway	2/7	155/8025	0.007304	0.012354	0.003435	MAPK1/PRKCB	2	signaling
hsa04630	JAK-STAT signaling pathway	2/7	162/8025	0.007957	0.013179	0.003664	IL10/EGFR	2	signaling