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Swertiamarin and sweroside are potential inhibitors of COVID-19 based on the silico analysis

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Abstract

The severity of the respiratory disease caused by the severe acute respiratory syndrome coronavirus 2 has escalated rapidly in recent years, posing a significant threat to global health. Sweroside and swertiamarin are bioactive iridoid glycosides extracted mainly from *Swertia davidii* Franch. It remains unclear how *Swertia davidii* Franch. Specifically affects COVID-19 and its underlying mechanisms. We first employed network pharmacology and molecular docking techniques to investigate how sweroside and swertiamarin affect COVID-19 in order to explore its potential mechanism. We found that 35 potential target genes can be used for the treatment of COVID-19, with androgen receptor (AR), HSP90AA1, RAC-alpha serine/threonine–protein kinase, cyclin-dependent kinase 1, epidermal growth factor receptor, and glycogen synthase kinase-3 beta emerging as particularly promising candidates. Additionally, sweroside and swertiamarin demonstrated unambiguous interactions with the 3CL protease AR through molecular docking research. At the active site, sweroside and swertiamarin can bind to AR (1T65), the main protease (5R82), and 3CL protease (6M2N), showing therapeutic potential.

Abbreviations: AKT1 = RAC-alpha serine/threonine–protein kinase, AR = androgen receptor, CDK1 = cyclin-dependent kinase 1, EGFR = epidermal growth factor receptor, GSK3B = glycogen synthase kinase-3 beta, PPI = protein–protein interaction, SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Keywords: COVID-19, molecular docking, network pharmacology, sweroside, swertiamarin

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was responsible for the coronavirus disease (COVID-19) in 2019.[1] The disease has escalated worldwide, placing enormous pressure on health care systems. Individuals who contract the disease can develop acute respiratory distress, multiorgan failure, and death.[2] Therefore, it is crucial to identify new preventive and therapeutic agents as quickly as possible.[3,4] SARS-CoV-2 genome contains 4 structural proteins: spike (S), membrane (M), envelope (E), and nucleocapsid (N). 3CL proteinase (6M2N) and the main protease (5R82) are essential for the viral life cycle.[5]

Herbal medicines may have protective effects in SARS-CoV-2-infected patients with comorbidities.[6] Sweroside and swertiamarin (Fig. 1) are the main iridoid glycosides extracted from *Swertia davidii* Franch of Gentianaceae possess many pharmacological properties.[7,8] Moreover, many researchers have revealed that sweroside exhibits antivirus properties.[9,10]

The development of new drugs is crucial for the prevention and treatment of epidemics. Nevertheless, drug discovery is inherently time-consuming and costly, underscoring the urgent need for effective therapeutic agents against SARS-CoV-2.[11] There are no effective therapeutic drugs for SARS-CoV-2 other than vaccines. In this study, we utilized a network pharmacology strategy to investigate the potential properties of sweroside and swertiamarin against COVID-19. The experimental procedure is illustrated in Figure 2.

2. Material and methods

2.1. Target proteins related to sweroside, swertiamarin, and COVID-19

Identifying and validating drug-target interactions is a critical step in drug development.[12] We utilized an in silico model to identify the potential protein targets of sweroside and swertiamarin. The target genes related to sweroside and swertiamarin

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The author have no conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

There was no ethical approval required for this study.

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were identified using the Swiss Target Prediction databases[13] set with the "Homo sapiens" species. The UniProt database acquires gene names, gene IDs, and organisms. Our target profile for COVID-19 was identified by searching for "coronavirus 2019" and "COVID-19" in the GeneCards database. Venn plots were visualized using the Venny online tool. There were 35 unique targets related to sweroside, swertiamarin, and COVID-19 were identified.

2.2. PPI and enrichment analysis

The protein–protein interaction (PPI) network was constructed using STRING 11.0 platform by analyzing target proteins related to COVID-19.[14] To investigate the PPI network, those COVID-19 related genes were imported into STRING 11.0 and "Homo sapiens" was the limiting species. Targets with interaction scores ≥ 0.4 were chosen for enrichment analysis. Cytoscape 3.7.0 was used to construct, analyze, and visualize the PPI network.[15] Based on the Metascape database, we performed gene ontology analysis and pathway enrichment analyses.[16] Similarly, a smaller *P* value indicates greater enrichment levels, according to the Metascape database.

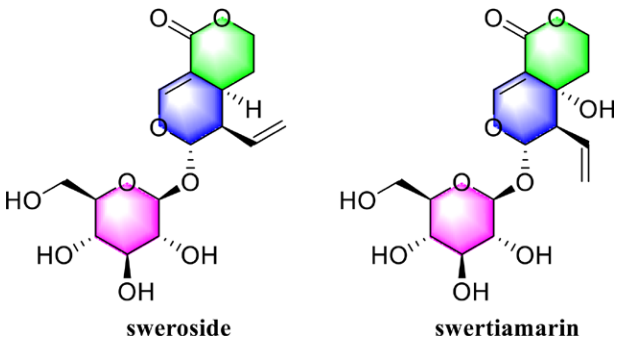

Figure 1. The structures of sweroside and swertiamarin.

2.3. Molecular docking

The RCSB PDB database was used to acquire the structural data for the selected targets. The Maestro 11.1 software was applied to verify network pharmacology assumptions. Candidate compounds in SDF format were obtained from PubChem, and candidate targets were selected for molecular docking. It is generally accepted that a docking score of ≥4.25 is meaningful.[17] To investigate the binding capacity of sweroside and swertiamarin with the proteins associated with COVID-19, 6 critical targets and 3 common receptors were selected. Ligands for related protein targets were used as positive controls.

3. Results

3.1. Potential target proteins prediction of sweroside and swertiamarin

The results revealed that sweroside and swertiamarin were compliant with Lipinski Rule of Five. Moreover, 134 target proteins of sweroside (Table S1, Supplemental Digital Content, http://links.lww.com/MD/N872) and 120 target proteins of swertiamarin (Table S2, Supplemental Digital Content, http://links.lww.com/MD/N872) were acquired from the PharmMapper Server and Swiss Target Prediction databases, respectively.

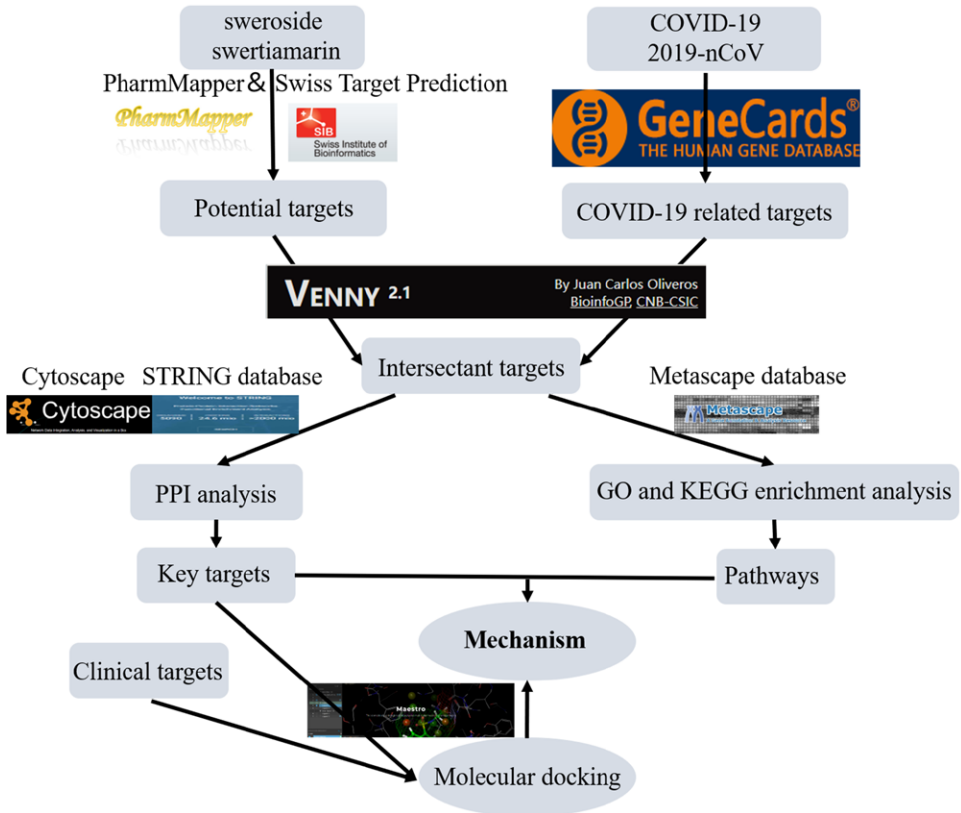

Figure 2. A flowchart of this study.

3.2. Acquisition of potential therapeutic targets for COVID-19

About 734 related target proteins of COVID-19 were collected from the database (Table S3, Supplemental Digital Content, http://links.lww.com/MD/N872). Venn analysis revealed 35 common proteins and potential therapeutic targets of sweroside and swertiamarin in COVID-19. The Venn analysis diagram is shown in Figure 3. Information related to the common targets is presented in Table 1.

3.3. The PPI network

A diagram of the PPI network is shown in Figure 4. To identify the key genes, we used the topological properties of each node in the network. The 6 targets, AR, HSP90AA1, RAC-alpha serine/threonine–protein kinase (AKT1), cyclin-dependent kinase 1 (CDK1), epidermal growth factor receptor (EGFR), and glycogen synthase kinase-3 beta (GSK3B), were pivotal nodes and ranked with a degree > 10 (Table 2), indicating that they may have a role in COVID-19.

3.4. Analysis of enrichment analysis of common targets

A total of 618 gene ontology enrichment entries ($P < .01$, top 10 are displayed based on P values, Fig. 5 and Table S4, Supplemental Digital Content, http://links.lww.com/MD/N872) of which 537 entries were related to biological processes (the top 20 are shown according to P values), mainly including regulation of kinase activities, protein kinase activities, and protein serine/threonine kinase activities. About 41 terms mainly included ficolin-1-rich granules and cytoplasmic vesicle lumen in the context of molecular functions (the top 20 are shown according to P values), and 40 entries were involved in endopeptidase activity, serine hydrolase activity, and protein serine/threonine kinase activity belonging to cell component entries (the top 20 are shown according to P values).

To further elucidate the relationship between target proteins and metabolic pathways, 86 pathways associated with 35 target proteins were identified through KEGG analysis using the Metascape database (Table S5, Supplemental Digital Content, http://links.lww.com/MD/N872) with the top 20 pathways presented based on P values < 0.01 (Fig. 6), mainly including the IL-17 pathway, human cytomegalovirus infection, PI3K-Akt pathway, and human immunodeficiency virus 1 infection.

Based on these findings, sweroside and swertiamarin appear to have the potential to treat COVID-19 through the regulation of biological processes, cellular functions, and signaling pathways.

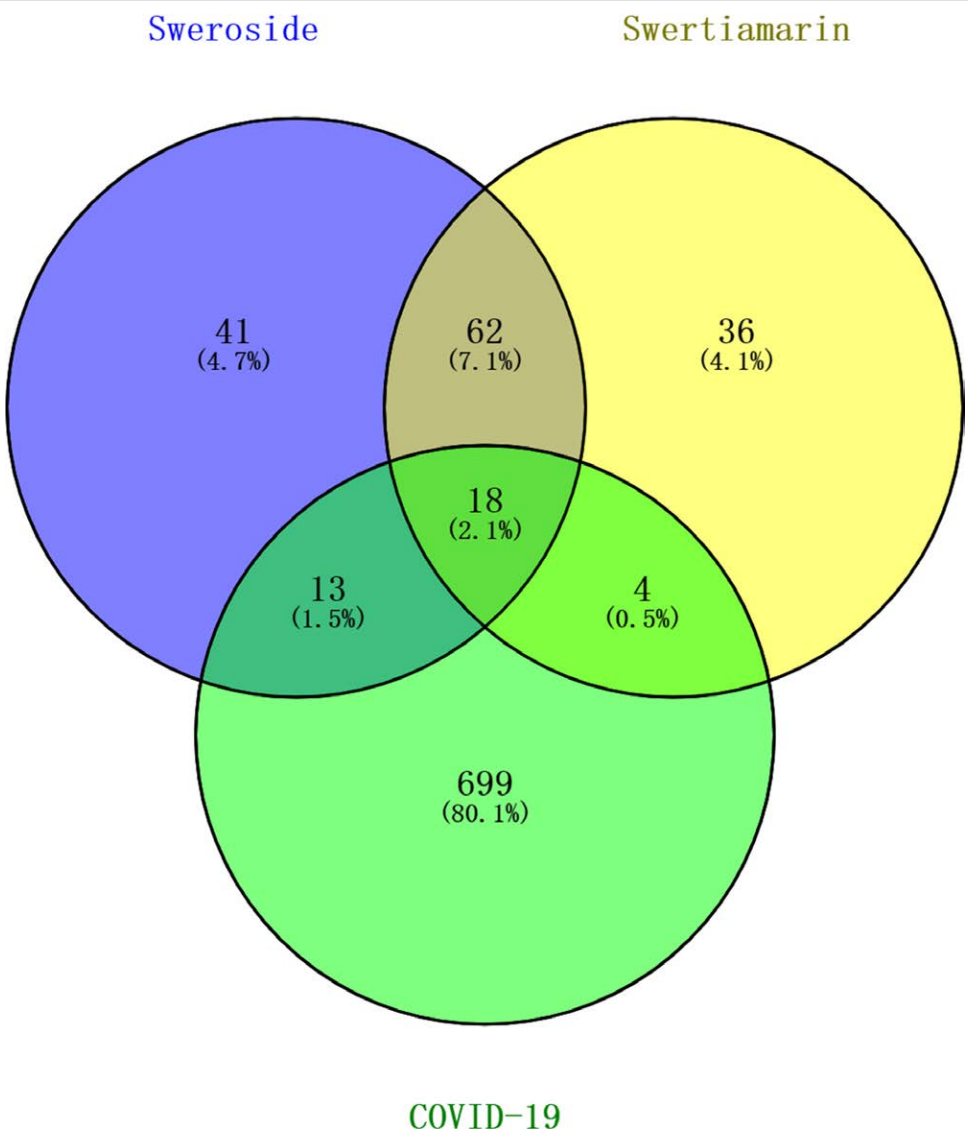

Figure 3. Intersection of targets of sweroside, swertiamarin and COVID-19.

3.5. Compounds–targets–pathways network analysis

A component–targets–pathways network was constructed using KEGG analysis to identify the potential targets (Fig. 7). This network revealed that sweroside and swertiamarin interacted with 18 targets implicated in COVID-19. Among these 18 target proteins, AR, HSP90AA1, AKT1, EGFR, and GSK3B are particularly noteworthy for their potentially significant roles in the progression of COVID-19.

Table 1

The potential targets of swertiamarin.

Gene names	UniProt ID	Protein names
CASP3	P42574	Caspase-3
ADAM17	P78536	Disintegrin and metalloproteinase domain-containing protein 17
F2	P00734	Prothrombin
PPARG	P37231	Peroxisome proliferator-activated receptor gamma
NOS3	P29474	Nitric oxide synthase, endothelial
MTHFD1	P11586	C-1-tetrahydrofolate synthase
CSNK2A1	P68400	Casein kinase II subunit alpha
ELANE	P08246	Neutrophil elastase
GAPDH	P04406	Glyceraldehyde-3-phosphate dehydrogenase
HSPA5	P11021	Endoplasmic reticulum chaperone BiP
MCL1	Q07820	Induced myeloid leukemia cell differentiation protein Mcl-1
CDK1	P06493	Cyclin-dependent kinase 1
CCNB1	P14635	G2/mitotic-specific cyclin-B1
MMP12	P39900	Macrophage metalloelastase
RNASE3	P12724	Eosinophil cationic protein
REN	P00797	Renin
ICAM2	P13598	Intercellular adhesion molecule 2
GBA	P04062	Lysosomal acid glucosylceramidase
PPIA	P62937	Peptidyl-prolyl cis-trans isomerase A
CCNA2	P20248	Cyclin-A2
TREM1	Q9NP99	Triggering receptor expressed on myeloid cells 1
EGFR	P00533	Epidermal growth factor receptor
F10	P00742	Coagulation factor X
HSP90AA1	P07900	Heat shock protein HSP 90-alpha
AR	P10275	Androgen receptor
AKT1	P31749	RAC-alpha serine/threonine-protein kinase
MMP3	P08254	Stromelysin-1
CTSB	P07858	Cathepsin B
GSK3B	P49841	Glycogen synthase kinase-3 beta
RHOA	P61586	Transforming protein RhoA
DPP4	P27487	Dipeptidyl peptidase 4
MAPK14	Q16539	Mitogen-activated protein kinase 14
LGALS3	P17931	Galectin-3
LGALS9	O00182	Galectin-9
ADA	P00813	Adenosine deaminase

3.6. Molecular docking

In this study, molecular docking simulations were conducted to model the interactions between sweroside, swertiamarin, and 6 key target proteins (AR, HSP90AA1, AKT1, CDK1, EGFR, and GSK3B) and 3 clinical targets (ACE2, Main protease, and 3CL protease), and the docking scores are listed in Table 3. We obtained the potential 3 target proteins (1 target proteins based on PPI network and 2 clinical targets) according to the docking score and the most underlying model is displayed in Figure 8 (3D) and Figure 9 (2D). The results indicated that sweroside formed hydrogen bonds with ASN 705, THR 877, LEU 704, and GLN 711 residues on AR (1T65), GLN 189 and GLU166 residues on the main protease (5R82), and GLY143 and HIS 41 residues on 3CL protease (6M2N). Swertiamarin forms hydrogen bonds with GLN 711 residues on AR, GLU166 and GLN 189 residues on the main protease (5R82), and ASN 142, HIS 41, and ARG 188 residues on 3CL protease (6M2N) (Fig. 10).

4. Discussion

An acute respiratory infectious disease, now known as COVID-19, has been reported in multiple hospitals since December 2019. While contemporary pharmacological agents have provided protection to vulnerable populations,[18] the notable therapeutic efficacy of traditional Chinese medicine and natural products in the context of COVID-19 warrants significant attention. Currently, the arsenal available to combat coronaviruses is limited. COVID-19 can be controlled or prevented by several options, such as interferon therapies and vaccines, but their approval can take months or years. In contrast, phytochemicals, particularly polyphenols, have demonstrated antiviral activity against various viral components and mechanisms.[19]

The field of network pharmacology combines bioinformatics and molecular biology to uncover potential targets, pathways, and interactions between drugs and their targets.[20–22] Additionally, network pharmacology can be used to explore the interplay between diseases, target proteins, and drugs.[23] It is possible to accelerate the process of screening and designing drugs through molecular docking.[24] In view of their unique roles in viral replication, the main protease and 3CL protease are considered potential targets.[25] This is particularly important because of its capacity to elucidate unique functions within the viral replication cycle. It is noteworthy that this technology

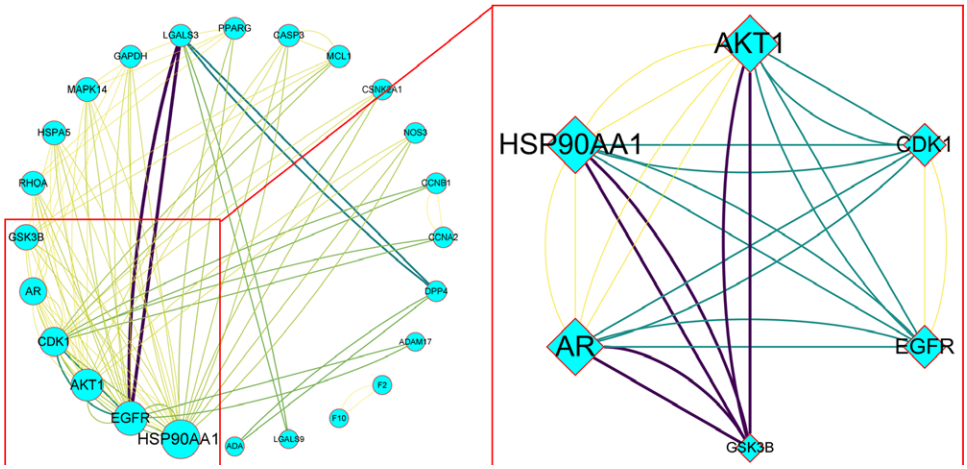

Figure 4. Protein–protein interaction network.

Table 2

The corresponding degree values of top 6 targets and 3 clinical targets.

Protein name	Gene name	PDB ID	Uniprot ID	Degree	Betweenness centrality	Closeness centrality	Neighborhood connectivity
Heat shock protein HSP 90-alpha	HSP90AA1	2YI7	P07900	26	0.280,635	0.636,364	4.769,231
Epidermal growth factor receptor	EGFR	3POZ	P00533	20	0.450,794	0.636,364	5.4
RAC-alpha serine/threonine-protein kinase	AKT1	3CQU	P31749	18	0.079683	0.538,462	5.666,667
Cyclin-dependent kinase 1	CDK1	6GU7	P06493	14	0.243,016	0.538,462	5.428,571
Androgen receptor	AR	1T65	P10275	12	0.026984	0.525	7.833,333
Glycogen synthase kinase-3 beta	GSK3B	2JDO	P49841	10	0.020556	0.4375	7
angiotensin I converting enzyme 2	ACE2	1R4L	Q9BYF1				
COVID-19 main protease	main protease	5R82	P0DTD1				
SARS-CoV-2 3CL protease	3CL protease	6M2N	P0DTD1				

**Note*: ACE2, main protease, and 3CLpro are common receptors related to COVID-19.

Figure 5. The selected target proteins underwent the GO enrichment analysis of biological processes (A), cell composition (B), and molecular function (C). GO = gene ontology.

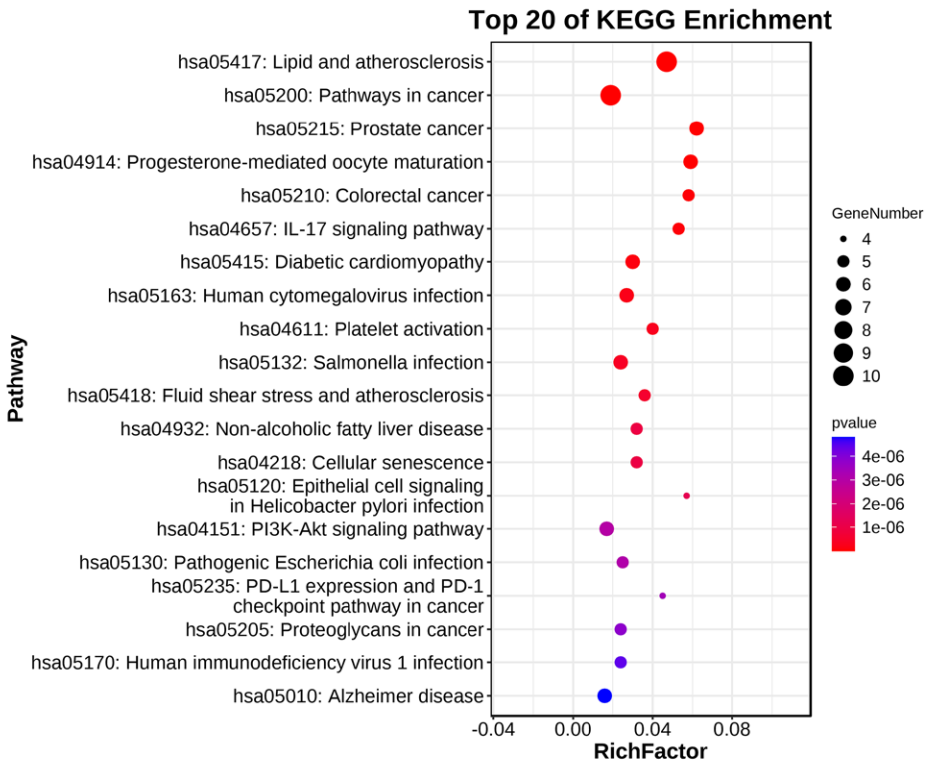

Figure 6. Potential targets for COVID-19 underwent the KEGG analysis. KEGG = Kyoto Encyclopedia of Genes and Genomes.

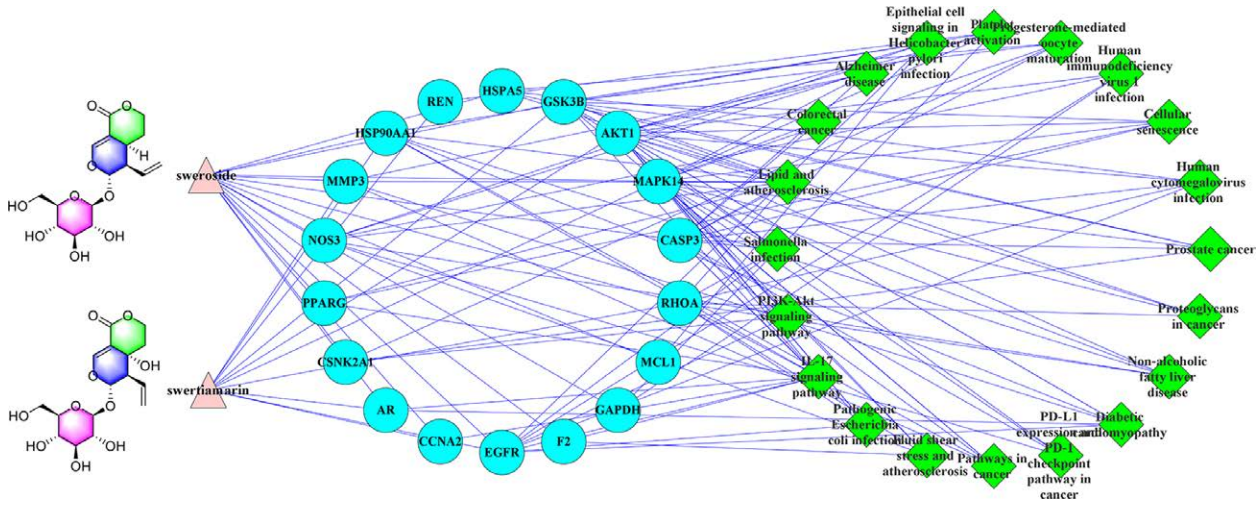

Figure 7. The construction of components–targets–pathways network.

Table 3

The docking scores of sweroside and swertiamarin with related targets.

Proteins	Compounds	Glide gscore	Glide hbond	Glide Evdw	Glide ecoul	Glide energy
HSP90AA1 (2YI7)	Contrast	-9.146	-0.469	-44.18	-15.245	-59.425
	Sweroside	-5.4	0	-24.515	-15.164	-39.679
	Swertiamarin	-5.511	0	-23.987	-16.076	-40.063
AKT1 (3CQU)	Contrast	-9.465	-0.608	-46.455	-7.047	-53.503
	Sweroside	-4.649	0	-14.35	-7.936	-22.285
	Swertiamarin	-4.091	0	-15.624	-9.548	-25.172
EGFR (3POZ)	Contrast	-12.931	-0.528	-64.991	-12.567	-77.558
	Sweroside	-5.551	0	-22.786	-18.634	-41.42
	Swertiamarin	-5.901	0	-25.635	-12.392	-38.027
CDK1 (6GU7)	Contrast	-8.152	-0.337	-40.572	-9.148	-49.72
	Sweroside	-5.919	0	-20.701	-19.491	-40.192
	Swertiamarin	-5.099	0	-26.042	-15.881	-41.924
GS3KB (2JDO)	Contrast	-9.068	-0.289	-51.521	-17.425	-68.946
	Sweroside	-4.501	-0.273	-14.811	-19.45	-34.262
	Swertiamarin	-5.481	-0.32	-15.417	-25.863	-41.28
AR (1T65)	Contrast	-10.064	0	-43.826	-3.041	-46.867
	Sweroside	**-7.612**	-0.32	-24.233	-7.3	-31.532
	Swertiamarin	**-7.193**	0	-29.768	-3.662	-33.43
ACE2 (1R4L)	Contrast	-8.602	-0.874	-39.865	-17.627	-57.492
	Sweroside	-5.718	-0.202	-27.686	-16.873	-44.559
	Swertiamarin	-5.25	-0.188	-28.238	-16.104	-44.342
Main protease 5R82	Contrast	-5.559	-1.324	-0.320	0.000	-2.696
	Sweroside	**-5.535**	-0.32	-22.084	-16.837	-38.921
	Swertiamarin	**-5.287**	-0.205	-23.642	-15.82	-39.462
3CL protease 6M2N	Contrast	-7.732	-0.391	-34.23	-9.564	-43.793
	Sweroside	**-6.73**	-0.305	-40.126	-8.863	-48.989
	Swertiamarin	**-5.932**	0	-35.815	-9.625	-45.44

Bold values presented the docking scores is similar to the contrast compound.

has proved useful during the recent SARS-CoV-2 pandemic when assessing the efficacy and potential mechanism of various drugs and compounds. When using molecular docking, significant binding interactions between ligands and proteins can be predicted, thereby indicating which proteins are inhibited by the ligands.[26]

Consequently, we investigated the interactions between sweroside, swertiamarin, the main protease, and 3CL protease. Sweroside and swertiamarin were both highly functional within the 3CL protease, highlighting their potential as antiviral agents. The main protease and 3CL protease are crucial receptors for coronaviruses, facilitating endocytosis of SARS-CoV-2 and playing a crucial role in drug profiling aimed at curbing the progression of COVID-19.[23] To inhibit viral RNA translation, the structural theory and current research consistently point to the main protease and 3CL protease as viable therapeutic targets. Consequently, we conducted a screening to evaluate the interactions between sweroside, swertiamarin, the main protease, and 3CL protease. Through these analyses, we were able to identify the active sites of swerosides and swertiamarin dock with the main proteases and 3CL proteases. Moreover, mutations in the amino acids that interact with the major viral protease may lead to inactivation of its function. Based on these findings, sweroside and swertiamarin may be used clinically. Based on the binding pattern demonstrated here, sweroside and swertiamarin could be useful against COVID-19, and several

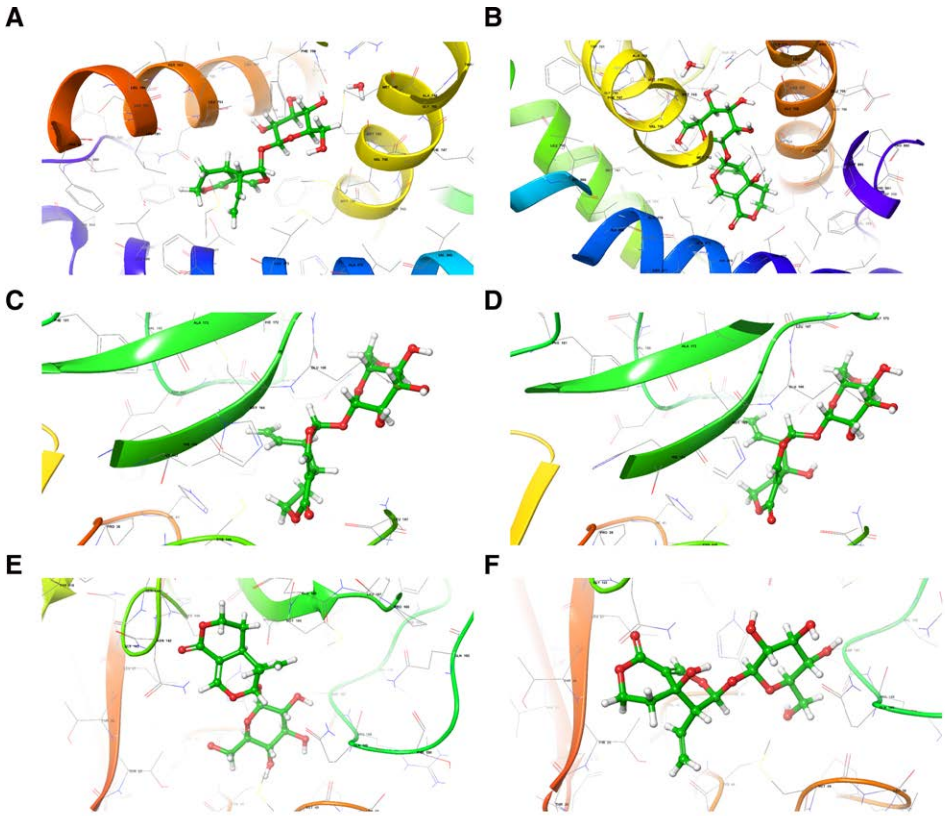

Figure 8. Molecular docking of sweroside, swertiamarin and key targets (3D): (A) sweroside with AR (1T65); (B) swertiamarin with AR (1T65); (C) sweroside with main protease (5R82); (D) swertiamarin with main protease (5R82); (E) sweroside with 3CL protease (6M2N); and (F) swertiamarin with 3CL protease (6M2N).

amino acid mutations in COVID-19 could hinder the functional activation of major viral proteases.

Despite presenting several intriguing findings, our study had certain limitations. Our conclusions are likely inaccurate and unreliable because of the absence of a comprehensive database of Chinese herbal medicines. Second, Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform offers active components with oral bioavailability ≥ 30% and drug-likeness ≥ 0.18, which may not accurately reflect their absorption profiles. Moreover, all results of this study were based on in silico analyses, so they may reflect false positives or false negatives. Further validation through basic experiments and clinical trials is essential to substantiate these predictions.

5. Conclusion

The potential therapeutic effects and molecular mechanisms of sweroside and swertiamarin for treating COVID-19 were revealed by combining a network pharmacology approach and molecular docking. The AR, HSP90AA1, AKT1, CDK1, EGFR, and GSK3B genes can improve COVID-19 by regulating the PI3K-Akt pathway, IL-17 signaling pathway, and human immunodeficiency virus 1 infection. These results also revealed that modulating the inflammatory response and antivirus effects could be the potential mechanisms by which sweroside and swertiamarin act on COVID-19. Sweroside and swertiamarin have potential activity against SARS-CoV-2. Further research will unambiguously elaborate the effective targets of sweroside and swertiamarin against COVID-19.

Author contributions

Conceptualization: Wenxiang Wang, Wei Xiong.
Data curation: Wenxiang Wang, Ying Tan, Jingxin Mao, Wei Xiong.
Funding acquisition: Wenxiang Wang.
Writing – original draft: Wenxiang Wang, Wei Xiong.
Writing – review & editing: Wenxiang Wang.

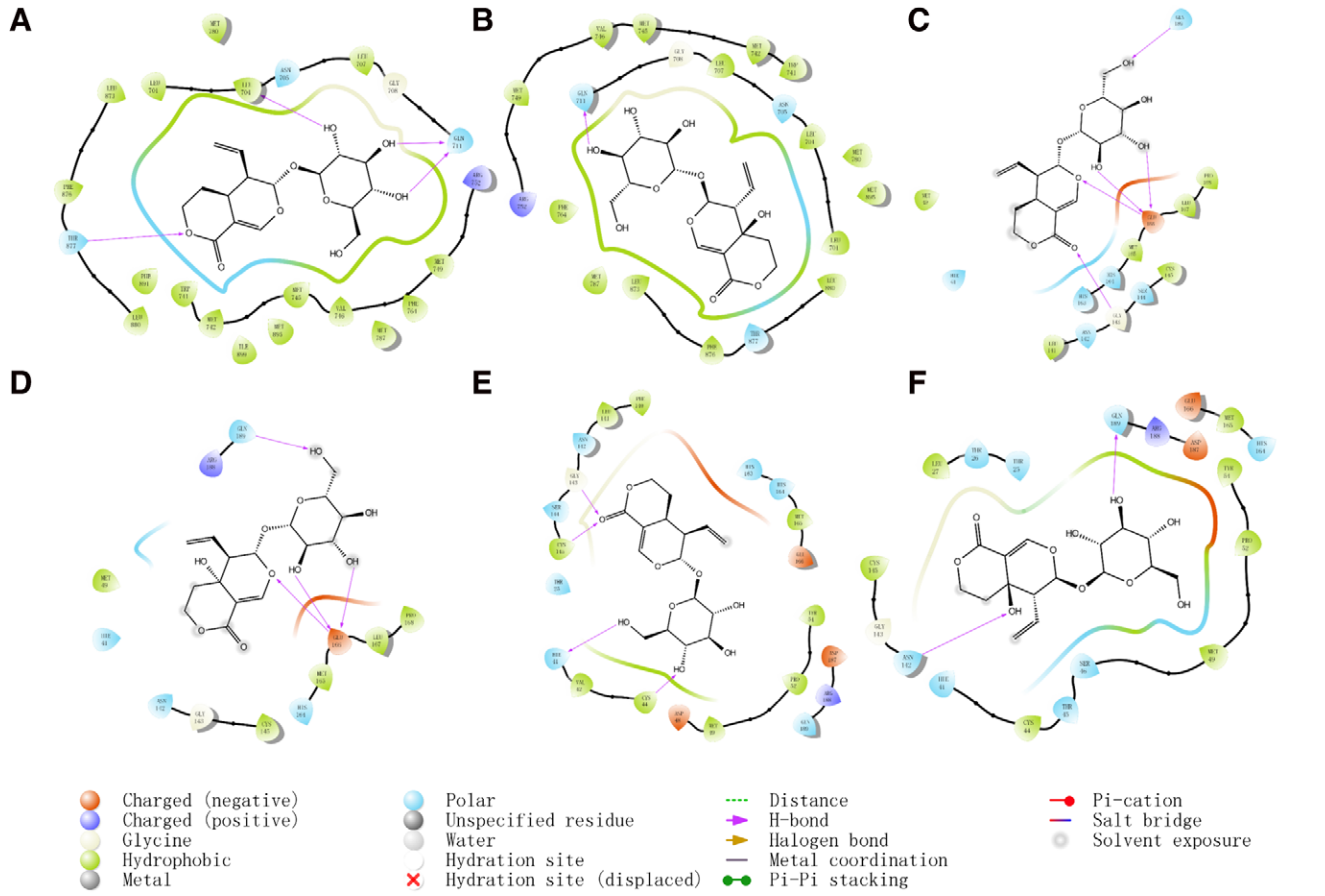

Figure 9. Molecular docking of sweroside, swertiamarin, and key targets (2D): (A) sweroside with AR (1T65); (B) swertiamarin with AR (1T65); (C) sweroside with main protease (5R82); (D) swertiamarin with main protease (5R82); (E) sweroside with 3CL protease (6M2N); and (F) swertiamarin with 3CL protease (6M2N).

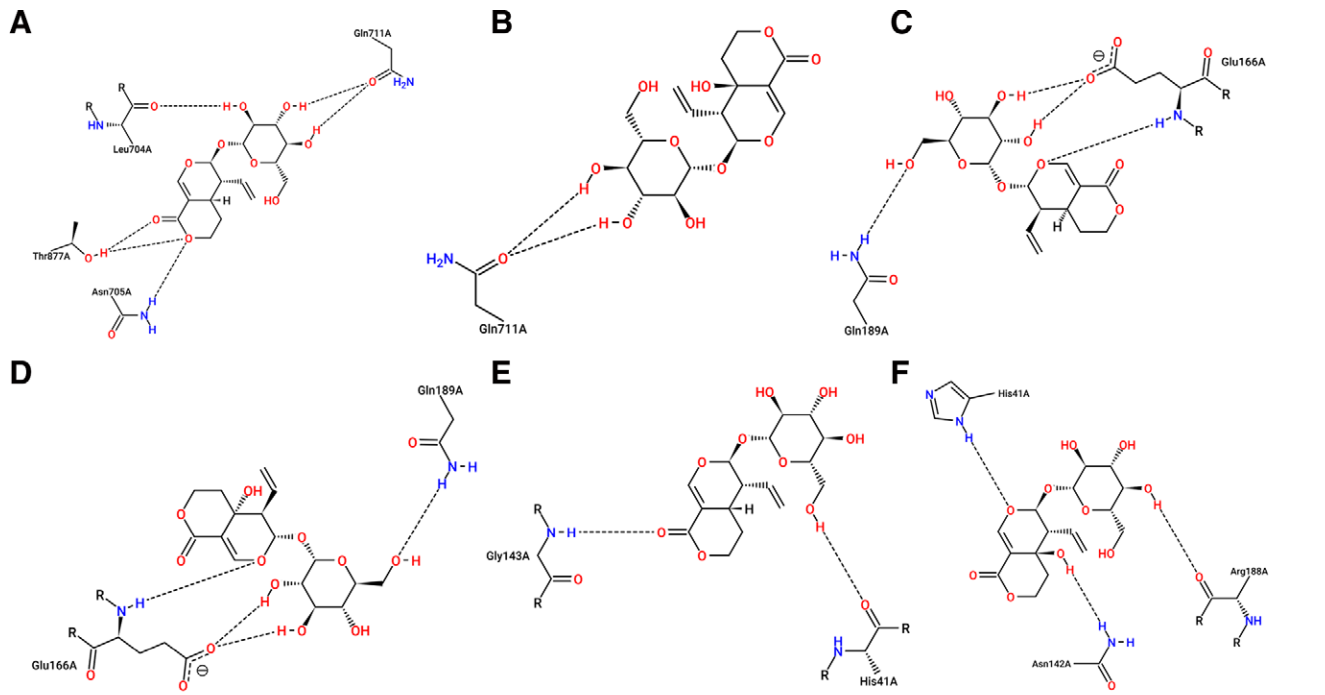

Figure 10. The crucial amino acids in these protein targets, the key sites of sweroside and swertiamarin: (A) sweroside with AR (1T65); (B) swertiamarin with AR (1T65); (C) sweroside with main protease (5R82); (D) swertiamarin with main protease (5R82); (E) swerosid with 3CL protease (6M2N); and (F) swertiamarin with 3CL protease (6M2N).

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