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The potential mechanism of Astragali Complanati Semen in the Treatment of Cancer-related fatigue Based on Network Pharmacology, Molecular Docking and Molecular Dynamics Simulation

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ABSTRACT: *Modern pharmacological studies confirm that Astragali Complanati Semen possesses antioxidant, anti-inflammatory, and anti-fatigue properties; however, its mechanism of action in treating cancer-related fatigue remains unclear. This study uses network pharmacology to investigate the potential mechanisms by which the major components of Astragali Complanati Semen treat cancer-related fatigue, and validates these findings through molecular docking and molecular dynamics simulationsThrough network pharmacology screening, 10 bioactive compounds and 89 overlapping targets were identified in Astragali Complanati Semen. The GO and KEGG enrichment results primarily involved apoptosis processes, ATP binding, and mitochondria, as well as the PI3K-Akt signaling pathway, the AMPK signaling pathway, and others. Following two rounds of molecular docking screening of the bioactive compounds against core targets, it was determined that the bioactive molecules in Astragali Complanati Semen bound well primarily to the targets SIRT1, PARP1, PTGS2, KDR, PPARG, EGFR, ABCB1, MMP2, and MAPK3. Molecular dynamics simulations showed that Calycosin-7-O-β-D-glucoside-SIRT1, complanatuside-PARP1, and Laricitrin-PARP1 remained stable throughout the simulation. The results indicated that Astragali Complanati Semen exerted its therapeutic effects against cancer-related fatigue through the synergistic action of multiple components, targets, and pathways. This study provides a theoretical basis for its molecular mechanisms and offers more effective treatment options for patients with cancer-related fatigue in the future.*

KEY WARDS: *Astragali Complanati Semen, Cancer-related fatigue, Molecular docking, Molecular dynamics*

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I. INTRODUCTION

Cancer-related fatigue (CRF) is one of the most common symptoms among cancer patients. It refers to a persistent, debilitating sense of fatigue caused by cancer or its treatment, encompassing emotional, physical, or cognitive aspects[1-2]. Cancer-related fatigue is characterized by persistent, extreme fatigue that is disproportionate to the level of activity, and it significantly impacts patients' quality of life and treatment outcomes[3]. According to statistics, more than 80% of cancer patients experience cancer-related fatigue during or after treatment, and for some patients, these symptoms of fatigue can persist for several years[4]. Currently, there are various interventions for alleviating CRF, such as exercise interventions, mind-body therapies, and psychoeducation; however, standardized treatment methods are still lacking[5]. Therefore, identifying safe and effective new treatment strategies has become a priority in current research. Studies have shown that traditional Chinese medicine (TCM) and its active ingredients offer unique advantages in alleviating cancer-related fatigue and can improve symptoms through multiple targets and pathways.

Astragali Complanati Semen consisted of the dried, mature seeds of the leguminous plant Astragalus compressus. The main components of Astragali Complanati Semen included polysaccharides, flavonoids, and triterpenoids. Studies confirmed that Astragali Complanati Semen and its extracts possessed significant anti-

exercise fatigue, antitumor, anti-inflammatory, free radical scavenging, and antioxidant effects[6-8]. Furthermore, Astragali Complanati Semen could maintain energy supply in exercising rats, delay the onset of exercise-induced fatigue, and promote post-exercise recovery[9]. Although previous studies reported that Astragali Complanati Semen and its extracts had anti-exercise fatigue effects, the mechanisms of action and relevant targets of Astragali Complanati Semen and its components in combating cancer-related fatigue remain unclear. Therefore, computational methods such as network pharmacology, molecular docking, and molecular dynamics simulations[10]were employed to investigate the pharmacological mechanisms by which drugs treat diseases.

In this study, we aim to employ a combined approach involving network pharmacology, molecular docking, and molecular dynamics simulations to elucidate the potential of Astragali Complanati Semen components to intervene in cancer-related fatigue, identify their targets, explore their mechanisms of action, and demonstrate the potential value of Astragali Complanati Semen in treating cancer-related fatigue.

II. MATERIAL AND METHODS

2.1 Active Ingredients and Target Predictions for Astragali Complanati Semen

A search for "Astragali Complanati Semen" was conducted in the TCMSP database (https://tcmspw.com/tcmsp.php)[11] to screen for active components of Astragali Complanati Semen, using the criteria of oral bioavailability (OB) ≥ 30% and drug-like properties (DL) ≥ 0.18. Using Swiss Target Prediction (https://swisstargetprediction.ch/)[12], we set the species to *Homo sapiens*, selected targets with a probability probability > 0, and then merged and deduplicated the results to identify protein targets associated with the active components of Astragali Complanati Semen. Gene names were standardized using the UniProt database (https://www.uniprot.org)[13].

2.2 *Prediction of Disease Targets for Cancer-Related Fatigue*

A search was conducted using the keyword "cancer-related fatigue" in the OMIM (https://www.omim.org/)[14] and GeneCards database (https://www.genecards.org/)[15] to identify targets associated with cancer-related fatigue; targets were then filtered based on the median relevance score to obtain the most relevant targets. Finally, disease-related targets associated with "cancer-related fatigue" were extracted, and duplicates were removed to obtain the relevant target dataset.

2.3 Identification of Common Targets Between Astragali Complanati Semen and Cancer-Related Fatigue

Using the Venny 2.1.0 online tool (https://bioinfogp.cnb.csic.es/tools/venny/)[16], we identified the targets of the active components in Astragali Complanati Semen by intersecting them with the targets for cancer-related fatigue, thereby identifying the targets for Astragali Complanati Semen in the treatment of cancer-related fatigue.

2.4 Construction of Protein-Protein Interaction Networks and Screening of Key Targets

The set of common targets was imported into the STRING database (https://stringdb.org)[17], the species was set to Homo sapiens, the minimum interaction threshold was set to ≥0.40, isolated targets were removed, protein-protein interaction (PPI) analysis was performed, and the results were imported into Cytoscape 3.10.0 to construct a PPI network. The MCC method in the CytoHubba plugin was used to identify 20 key targets.

2.5 GO and KEGG Pathway Enrichment Analysis of Common Targets

The set of common target genes was imported into the DAVID database (https://david.ncifcrf.gov/)[18], with the species set to *Homo sapiens*. GO and KEGG pathway enrichment analyses were performed on the common target genes to investigate the potential biological functions and major signaling pathways through which Astragali Complanati Semen acts on cancer-related fatigue. Furthermore, the online platform Weishengxin (https://www.bioinformatics.com.cn/)[19] was used to visualize the GO and KEGG pathway enrichment results to clarify the potential mechanisms of action.

2.6 Molecular Docking of the Major Components and Key Target Molecules of Astragali Complanati Semen

Molecular docking was performed between the 10 major bioactive compounds in Astragali Complanati Semen and their core targets. The chemical structures of the compounds in Astragali Complanati Semen were downloaded from the TCMSP database, and the protein structures were obtained from the PDB (https://www.rcsb.org/)[20]. Topological optimization of the proteins and ligands was performed using AutoDock Vina (http://vina.scripps.edu/)[21] and BIOVIA Discovery Studio 2019 to remove hydrogen bonds and solvent molecules prior to molecular docking. Subsequently, LibDock was used to perform a second round of molecular docking on the targets, and active molecules and proteins that failed the LibDock docking were excluded. After two rounds of molecular docking screening, active molecules with high affinity for the target protein and their corresponding binding sites were ultimately identified.

2.7 Molecular Dynamics Simulation

Based on the molecular docking results, this study conducted a 100 ns molecular dynamics simulation analysis on complex systems with high docking scores (LibDock > 143) to gain a deeper understanding of the interaction strength and stability of the receptor-ligand complexes obtained from molecular docking. The molecular dynamics simulations of the protein-ligand complexes were performed using the GROMACS 2022 software package, and the simulation systems and topology files were constructed using software commands. Solvation was performed using the AMBER03 force field and the TIP3P water model. The system was placed in a periodic cubic box, and after energy minimization and NVT/NPT equilibration, a 100 ns simulation was conducted. During trajectory extraction, jumps were corrected to ensure the integrity of the complex, and the periodic boundary conditions were removed. The analysis included key metrics such as root-mean-square deviation (RMSD), root-mean-square fluctuation (RMSF), solvent-accessible surface area (SASA), and the number of protein-ligand hydrogen bonds, along with visualizations of the results.

III. RESULTS AND DISCUSSIONS

3.1 Astragali Complanati Semen and Screening for Disease Targets in the Treatment of Cancer-Related Fatigue

By searching the GeneCards and OMIM databases, we identified a total of 1,313 disease targets associated with cancer-related fatigue. By combining these results with the Swiss Target Prediction database, we identified 302 target molecules for the active components of Astragali Complanati Semen. The drug targets were then intersected with the targets obtained from the disease databases, ultimately identifying 89 common targets for Astragali Complanati Semen in the treatment of cancer-related fatigue, as shown in Figure 1.

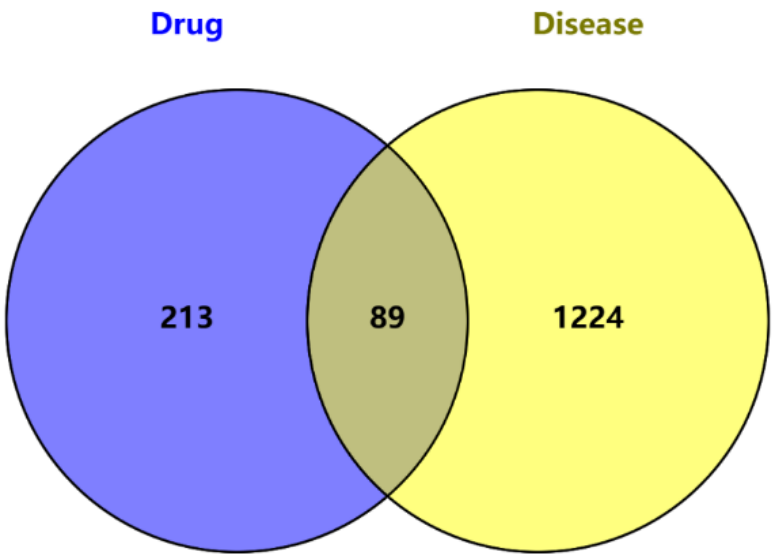

Figure 1: Venn diagram showing the intersection of predicted target molecules of Astragali Complanati Semen and CRF-related target molecules

3.2 Key Components of Astragali Complanati Semen

A screening of the TCMSP database identified 10 bioactive compounds in Astragali Complanati Semen, as shown in Table 1. These included kaempferid, formononetin, calycosin, quercetin, kaempferol, calycosin-7-O-β-D-glucoside, NSC6355, β-sitosterol, laricitrin, and complanatuside. These active components might be essential for the therapeutic effects of Astragali Complanati Semen in treating cancer-related fatigue.

Table I. **Key Components of Astragali Complanati Semen**

Mol ID	Molecule Name	OB (%)	DL
MOL004564	Kaempferid	73.41	0.27
MOL000392	formononetin	69.67	0.21
MOL000417	Calycosin	47.75	0.24
MOL000098	quercetin	46.43	0.28
MOL000422	kaempferol	41.88	0.24

MOL009289	Calycosin-7-O-β-D-glucoside	41.6	0.81
MOL000184	NSC63551	39.25	0.76
MOL000358	β-sitosterol	36.91	0.75
MOL009278	Laricitrin	35.38	0.34
MOL009293	complanatuside	32.52	0.64

3.3 Analysis of Common Target Protein Interaction Networks

We constructed a PPI network of 89 overlapping targets using the STRING database and visualized it using Cytoscape 3.10.0 software, as shown in Figure 2a. The PPI network consisted of 88 nodes and 1,087 edges; node size and color varied according to their degree values. The degree value represented the number of edges connected to a node, indicating its importance. Using the MCC method in the Cytohubba plugin, 20 potential key targets were identified, as shown in Figure 2b: BCL2, CTNNB1, HSP90AA1, AKT1, EGFR, ESR1, HIF1A, SRC, MMP9, TNF, PTGS2, KDR, MMP2, PARP1, MAPK3, MCL1, ABCB1, SIRT1, IGF1R, and PPARG. The results suggested that Astragali Complanati Semen might play an important role in alleviating cancer-related fatigue by acting on these targets.

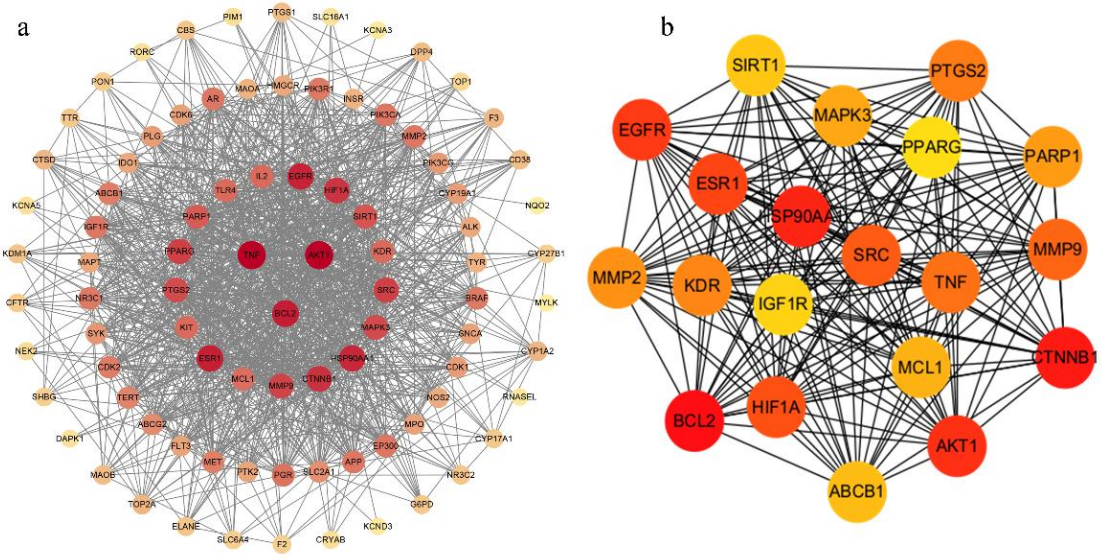

Figure 2: PPI network analysis of common targets ((a) Network diagram of 89 common targets; (b) Network diagram of 20 core targets)

3.4 GO and KEGG Pathway Enrichment Analysis

Based on the database, GO function and KEGG pathway enrichment analyses were performed using a significance threshold of $P < 0.01$. At the GO function level, 78 biological processes, 35 cellular components, and 65 molecular functions were identified as enriched based on $P < 0.01$. For the dataset generated from the DAVID database, the top 10 entries were selected to construct a GO function network. As shown in Figure 3a, BP was primarily enriched in the negative regulation of apoptosis, the positive regulation of phosphoinositide 3-kinase/protein kinase B signaling, the negative regulation of gene expression, the hypoxic response, the positive regulation of nitric oxide biosynthesis, the positive regulation of cell proliferation, and the positive regulation of apoptosis. MF was primarily enriched in homologous protein binding, protein kinase activity, enzyme binding, and ATP binding. CC was primarily enriched in protein complexes, signal receptor complexes, the cytoplasm, the cell membrane microdomain, the cell surface, the cytosol, the plasma membrane, the perinuclear region of the cytoplasm, mitochondria, and extracellular exosomes.

At the KEGG pathway level, a total of 114 signaling pathways significantly associated with target function were identified. Pathways unrelated to the disease were excluded based on a Pvalue < 0.01, and the top 20 signaling pathways were selected after sorting by enrichment score. As shown in Figure 3b, the pathways were primarily enriched in cancer pathways, glycan pathways in cancer, the PI3K-Akt signaling pathway, the HIF-1 hypoxia-inducible factor signaling pathway, central carbon metabolism in tumors, the estrogen signaling pathway, the FoxO transcription factor signaling pathway, the VEGF signaling pathway, the AMPK signaling pathway, and apoptosis, among others.

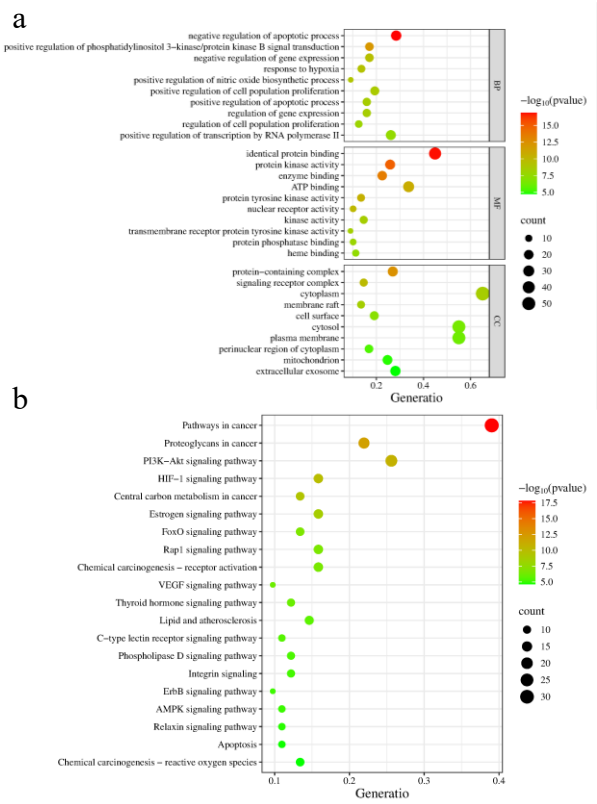

Figure 3: Enrichment Analysis of Common Target Genes ((a) GO Enrichment Analysis of Common Target Genes; (b) KEGG Enrichment Analysis of Common Target Genes)

The PI3K-AKT pathway was shown to be a central regulator of mitochondrial function and muscle cell homeostasis in CRF, and the AMPK-SIRT1 axis was also identified as a key mediator of improvement in CRF. Previous studies demonstrated that targeting these pathways could reduce myoblast apoptosis, oxidative stress, and mitochondrial dysfunction. Shenqi Fuzheng Injection could alleviate cancer-related fatigue by activating AMPK and inhibiting the PI3K/AKT signaling pathway, thereby improving mitochondrial function and reducing apoptosis in skeletal muscle cells[22]. Chemotherapy drugs could cause similar symptoms of skeletal muscle fatigue; among them, oxaliplatin was shown to disrupt mitochondrial and energy homeostasis during the treatment of colorectal cancer. It could activate apoptotic pathways in cancer cells, but it also led to mitochondrial dysfunction and disruption of energy homeostasis in non-cancerous cells, a phenomenon that was particularly pronounced in skeletal muscle[23][24]. Research confirmed that Cistanche extract could induce mitochondrial autophagy, clear mitochondria from skeletal muscle damaged by chemotherapy, reduce levels of oxidative stress and apoptosis, and alleviate cancer-related fatigue. This indirectly confirmed the impact of natural medicinal interventions on mitochondrial homeostasis and apoptosis processes in relation to cancer-related fatigue[25].

The results of GO and KEGG enrichment analyses indicated that these targets and pathways might play a significant role in the alleviation of cancer-related fatigue by Astragali Complanati Semen.

3.5 Molecular Docking Results

Molecular docking was used to preliminarily evaluate the binding affinities of 10 components of Astragali Complanati Semen to 20 key target genes. The lower the docking score, the stronger the affinity; a score of < -7.0 kcal/mol indicated strong binding affinity. As shown in Figure 4, the binding energies of these key targets with the ligands ranged from -5.80 to -10.30 kcal/mol, indicating that these active components all bound effectively to the proteins. Compounds and protein combinations with binding energies ≤ -9 kcal/mol for each receptor were selected for a second round of LibDock molecular docking. This yielded LibDock scores for the active molecules and their targets, with binding scores ranging from 99.67 to 158.39. Active compounds and protein combinations with scores ≥ 120 were selected for plotting, as shown in Table 2. The results indicated that the active molecules from Astragali Complanati Semen, identified through two rounds of molecular docking, bound well primarily to the targets SIRT1, PARP1, PTGS2, KDR, PPARG, EGFR, ABCB1, MMP2, and MAPK3.

This suggested that the active molecules from Astragali Complanati Semen might alleviate cancer-related fatigue by influencing these potential targets.

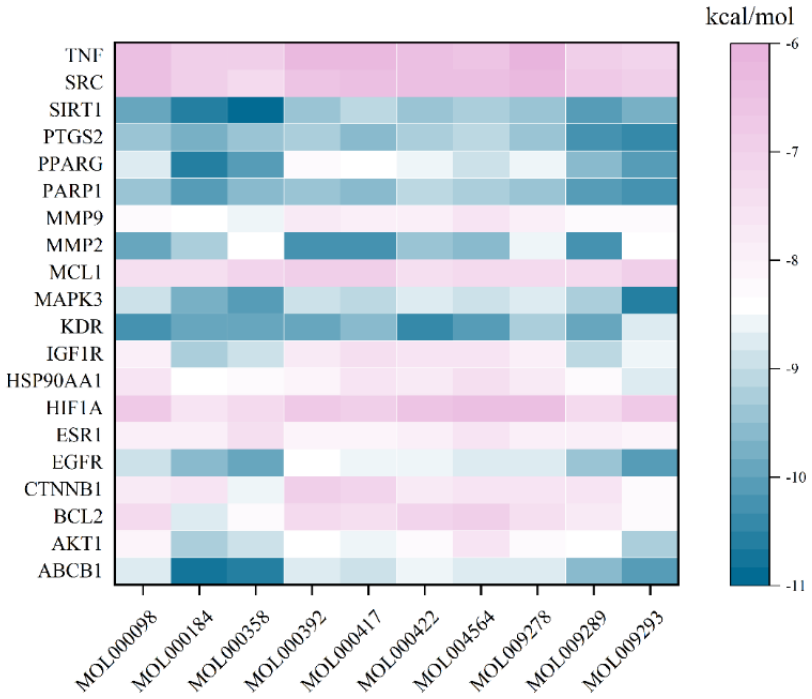

Figure 4: Heatmap of binding energies for key components of Astragali Complanati Semen and key targets in AutoDock

***Table II*. Key Components of Astragali Complanati Semen and LibDock Scores for Key Targets**

MOL	Target	LibDock_score	MOL	Target	LibDock_score
MOL009289	SIRT1	158.393	MOL009289	KDR	140.615
MOL000184	SIRT1	141.539	MOL000184	KDR	133.389
MOL000358	SIRT1	139.392	MOL009289	PPARG	138.296
MOL009278	SIRT1	132.809	MOL009293	PPARG	128.450
MOL004564	SIRT1	125.663	MOL000184	PPARG	120.164
MOL000098	SIRT1	125.110	MOL000358	EGFR	133.88
MOL009293	PARP1	143.734	MOL000184	EGFR	125.124
MOL009278	PARP1	143.518	MOL009289	ABCB1	133.058
MOL000358	PARP1	137.288	MOL000417	MMP2	130.647
MOL009289	PARP1	134.525	MOL004564	MMP2	129.758
MOL000184	PARP1	131.055	MOL000422	MMP2	126.984
MOL000098	PARP1	128.192	MOL000392	MMP2	125.927
MOL000417	PARP1	127.758	MOL000098	MMP2	124.297
MOL000184	PTGS2	142.682	MOL000358	MAPK3	127.203
MOL000358	PTGS2	142.675	MOL000184	MAPK3	125.810
MOL000098	PTGS2	124.826			

Based on the molecular docking results, the top three complexes were selected for visualization, as shown in Figure 5. The binding pockets of SIRT1 and PARP1 were tightly occupied by different small molecules. In the SIRT1 protein, Arg 446 formed a strong conventional hydrogen bond with MOL009289, while also forming carbon-hydrogen bonds with Ala 262, Ile 270, Val 412, Phe 413, and Phe 414; Ile 347 and Val 445 exhibited strong hydrophobic interactions with MOL009289 (Figure 5a). In the PARP1 protein, Asp105 and Arg217 formed strong conventional hydrogen bonds with MOL009293, while Glu102 and His248 exhibited strong hydrophobic interactions with MOL009293 (Figure 5b). In the PARP1 protein, Gly 202, Tyr 228, and Ser 243 formed strong conventional hydrogen bonds with MOL009278, while also forming carbon-hydrogen bonds with His 201 and Phe 236; His 201, Tyr 235, and Tyr 246 exhibited strong hydrophobic interactions with MOL009278 (Figure 5c)..

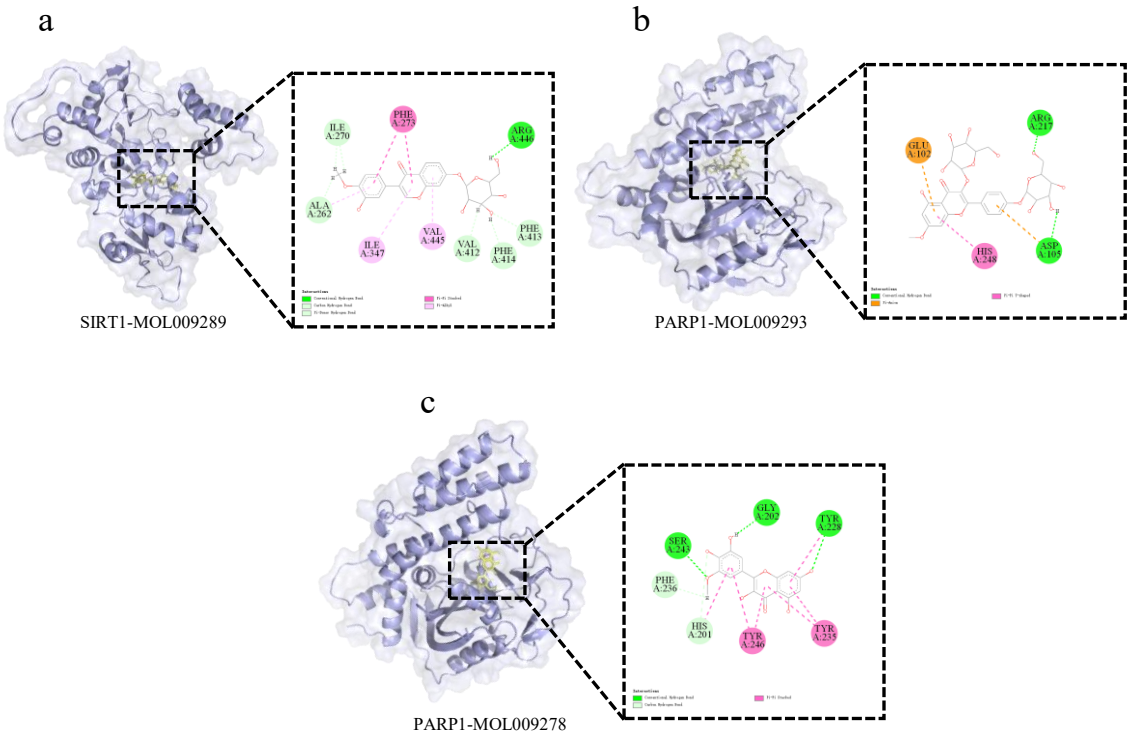

Figure 5: Molecular docking of active components from Astragali Complanati Semen with target proteins ((a) SIRT1-MOL009289 molecular docking results; (b) PARP1-MOL009293 molecular docking results; (c) PARP1-MOL009278 molecular docking results)

Several studies confirmed that SIRT1, as a key regulator of energy metabolism and mitochondrial function, mediated the treatment of CRF through the AMPK-SIRT1 pathway[22,26]. Previous studies confirmed that Calycosin-7-O-β-D-glucoside could alleviate oxidative stress, improve mitochondrial function, and reduce apoptosis by upregulating SIRT1 protein expression and activating the SIRT1/FOXO1/PGC-1α signaling pathway [27-28]. This suggested that Calycosin-7-O-β-D-glucoside could improve CRF-related energy metabolism disorders and mitochondrial dysfunction by activating SIRT1 and its associated signaling pathways. PARP1 is involved in DNA repair and oxidative stress responses and is associated with muscle atrophy related to cancer cachexia. Studies showed that inhibiting PARP1 could reverse markers of muscle wasting in colorectal cancer models[29]. Furthermore, based on molecular docking and kinetic simulation results for PARP1-MOL009293 and PARP1-MOL009278, complanatuside and laricitrin from Astragali Complanati Semen might reduce muscle wasting and alleviate cancer-related fatigue by modulating PARP1 and alleviating oxidative stress. These results indicated that the Astragali Complanati Semen compounds MOL009289, MOL009293, and MOL009278 effectively bound to key targets primarily through hydrogen bonding and hydrophobic interactions, further validating the reliability of the key targets for Astragali Complanati Semen in the treatment of cancer-related fatigue, as identified through network pharmacology methods. This suggests that the components of Astragali Complanati Semen may alleviate cancer-related fatigue mainly by regulating signaling pathways involving SIRT1 and PARP1.

3.6 Molecular Dynamics Results

To further investigate the stability of protein-ligand interactions, molecular dynamics simulations were performed. Based on the results of molecular docking analysis, molecular dynamics simulations were conducted on the SIRT1-MOL009289, PARP1-MOL009293, and PARP1-MOL009278 protein-ligand complexes.

As shown in Figure 6a, during the 100 ns simulation, the RMSD of the free SIRT1 protein remained stable within a range of 0.3 nm to 0.5 nm. The RMSD of the SIRT1-MOL009289 complex increased rapidly in the early stages of the simulation, then stabilized after 40 ns, fluctuating over the long term within the range of 0.3 nm to 0.6 nm without a sustained upward trend. Compared to the free protein, the overall mean RMSD of the

complex was slightly higher, but this value remained within a reasonable range, indicating that the overall conformation of the complex remained stable. The overall RMSD of the free PARP1 protein remained stable within the range of 0.1–0.3 nm. The RMSD of both complexes increased rapidly during the early stages of the simulation; subsequently, both stabilized after 20 ns and fluctuated over the long term within the range of 0.1–0.3 nm, showing no sustained upward trend. The trends in RMSD for both complexes were highly consistent with those of the free proteins (with overlap in most regions), indicating that ligand binding did not significantly affect the overall conformational stability of the protein backbone. The results suggested that the binding of small-molecule ligands did not significantly affect the overall conformational stability of the SIRT1 and PARP1 proteins.

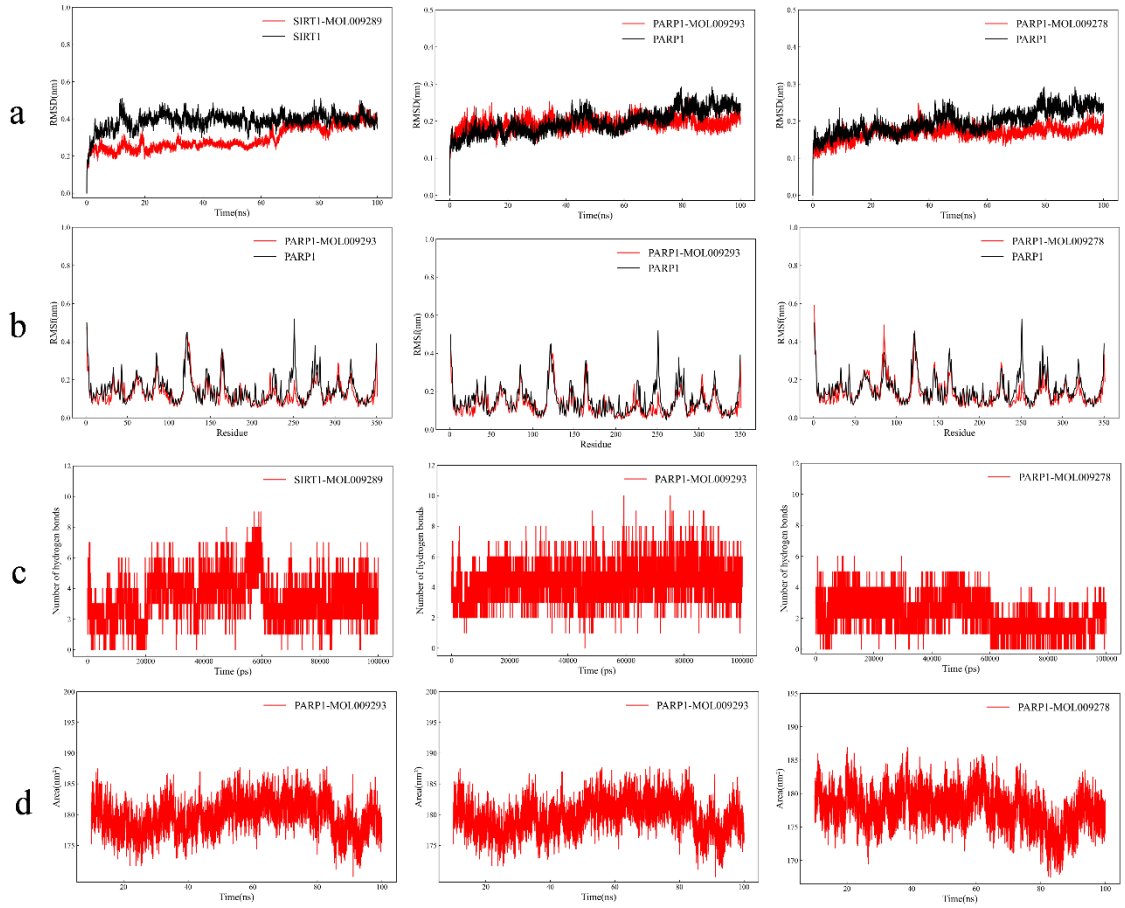

Figure 6: Results of molecular dynamics simulations ((a) Root-mean-square deviation (RMSD) values for the three complexes; (b) Root-mean-square fluctuation (RMSF) of residues for the three complexes; (c) Number of hydrogen bonds for the three complexes; (d) Solvent-accessible surface area (SASA) for the three complexes)

As shown in Figure 6b, during the 100 ns simulation, RMSF analysis revealed that the average RMSF values for the individual proteins SIRT1 and PARP1 were approximately 0.18 nm and 0.15 nm, respectively. Among these, the SIRT1-MOL009289 complex had an average RMSF value of approximately 0.20 nm, which was higher than that of the individual proteins and exhibited greater fluctuations. This indicated that ligand binding to the protein resulted in an overall increase in local flexibility and a decrease in structural rigidity. The average RMSF value of the PARP1-MOL009293 complex was approximately 0.13 nm, which was lower than that of the individual proteins, and it exhibited lower fluctuations in certain amino acid regions, indicating that ligand binding to the protein increased the stability of the complex. The PARP1-MOL009278 complex had an average RMSF value of approximately 0.13 nm, which was lower than that of the protein alone, and exhibited lower fluctuations

in certain amino acid regions, indicating that ligand binding had a certain enhancing effect on the conformational stability of this complex.

As shown in Figure 6c, during the 100 ns simulation, hydrogen bond analysis revealed that the average hydrogen bond numbers of the protein-ligand complexes SIRT1-MOL009289, PARP1-MOL009293, and PARP1-MOL009278 were approximately 4, 4, and 2, respectively, and the maximum numbers of hydrogen bonds formed throughout the simulation were 9, 10, and 6, respectively. The three complex systems maintained stable hydrogen bond interactions throughout the simulation. Although the number of hydrogen bonds fluctuated to some extent in each system, it generally remained within a stable range, and no prolonged disappearance occurred, indicating that the ligands exhibited good binding stability within the binding pocket.

As shown in Figure 6d, during the 100 ns simulation, SASA analysis revealed that the SASA values of the protein-ligand complexes SIRT1-MOL009289, PARP1-MOL009293, and PARP1-MOL009278 fluctuated within the ranges of 165.15–190.73 nm², 169.92–187.84 nm², and 167.45–186.921 nm², respectively, without sustained expansion, and remained stable overall. These results further supported the stability of the molecular docking conformations.

IV. CONCLUSIONS AND RECOMMENDATIONS

Modern pharmacology indicates that Astragali Complanati Semen possesses antioxidant, anti-inflammatory, free radical-scavenging, and anti-fatigue effects[6]. Through network pharmacology and molecular docking screening, a total of nine targets including SIRT1, PARP1, PTGS2, KDR, PPARG, EGFR, ABCB1, MMP2, and MAPK3 were ultimately identified as having good binding affinity with the active components of Astragali Complanati Semen. This suggests that Astragali Complanati Semen targets these pathways synergistically through multiple active components, potentially involving signaling pathways such as the PI3K-AKT pathway, the AMPK pathway, and apoptosis, which collectively mediate the improvement of CRF symptoms. Molecular docking and dynamics simulations reveal that the combinations of Astragali Complanati Semen components exhibiting the highest binding affinities for their target proteins are SIRT1-MOL009289, PARP1-MOL009293, and PARP1-MOL009278. The results suggest that these compounds may exert their anti-CRF effects by directly targeting SIRT1 and PARP1.

In summary, through network pharmacology combined with molecular docking and molecular dynamics studies, the potential mechanism of action of Astragali Complanati Semen in treating CRF was elucidated. Key components in Astragali Complanati Semen exhibit strong binding affinity with key therapeutic targets such as SIRT1 and PARP1. Astragali Complanati Semen may exert its effects on CRF by acting on the PI3K-AKT and AMPK signaling pathways to influence energy metabolism, mitochondrial function, and apoptosis. Further in vitro and in vivo experiments are needed to validate its specific regulatory effects on key pathways and targets, as well as the efficacy of its individual components, in order to provide more effective treatment options for patients with cancer-related fatigue.

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