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ORIGINAL RESEARCH

Promotion of Hair Regrowth in Androgenetic Alopecia with Supplemented Erzhi Wan: Exploring Its Mechanism Using Network Pharmacology and Molecular Docking

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Purpose: Supplemented Erzhi Wan (SEZW) is a Traditional Chinese Medicine commonly used in the treatment of androgenetic alopecia (AGA). This study aims to verify the effectiveness of SEZW for the treatment of AGA in mice and explore the potential molecular mechanisms underlying its function using network pharmacology and molecular docking.

Methods: Forty mice were divided into five groups: Control, AGA-model, AGA-Positive, SEZW Low Dose, and SEZW High Dose. Hair regrowth in mice was evaluated by scoring hair on days 0, 14, and 28 post-treatment and weighing mouse hair on day 28 post-treatment. The targets of the active compounds of SEZW were obtained using the Traditional Chinese Medicine Database. AGA-related targets were downloaded from five databases. Then, the overlapping genes were identified. A protein-protein interaction network was constructed using the STRING database. Hub targets were determined through analysis. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were performed. Finally, molecular docking of active compounds and hub targets was performed.

Results: Hair regrowth in mice in the SEZW treatment groups was significantly enhanced relative to that in the AGA-model mice. A total of 59 potential drug-disease targets were identified. Based on the GO/KEGG analysis results, oxidative stress and gland development were identified as potential mechanisms of action of SEZW in AGA treatment. The PI3K-Akt and AGE-RAGE signaling pathways and seven hub targets were identified as the potential underlying mechanism of SEZW function. Molecular docking results showed that the most active SEZW compounds bind stably to several of the candidate disease targets.

Conclusion: SEZW is effective in the treatment of AGA in a mouse model. Combined with network pharmacological analysis, the potential mechanisms, signaling pathways, and hub targets of SEZW in the treatment of AGA were identified, providing new ideas for further studies.

Keywords: Chinese herbal formulas, hair loss, hair regeneration, mechanism prediction

Introduction

Androgenetic alopecia (AGA), also known as male- or female-pattern alopecia, involves the miniaturization of hair follicles resulting in progressive hair thinning and shedding. Male-pattern alopecia primarily manifests as a receding frontal hairline with an M-shaped pattern, while female-pattern alopecia mainly manifests as diffuse hair thinning in a Christmas tree-like pattern on the top of the head. AGA can be accompanied by lighter hair color, higher oil production, and scalp inflammation, among other symptoms.[1] The mechanism underlying AGA involves the shortening of the hair

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follicle anagen phase, premature entry into the telogen phase, and eventual miniaturization of hair follicles, resulting in slow hair growth and hair loss.[2]

AGA is a major type of alopecia affecting 60–70% of the population.[3] In China, the prevalence of AGA is as high as 21.3% in men and 6.0% in women.[4] Recently, there has been increasing evidence indicating that AGA, as a chronic progressive disease, not only affects the appearance of patients but also causes psychological disorders.[5] Hence, early interventions and effective treatments of androgenetic baldness are vital.

To date, only two drugs have been approved by the United States Food and Drug Administration (FDA) and European Medicines Agency for the treatment of AGA: finasteride and minoxidil. However, finasteride is not recommended for women according to the FDA. Moreover, both drugs have side effects and are effective in <50% of patients.[3] A variety of other treatments exist, such as dutasteride, low-level laser therapy, stem cell-based therapy, platelet-rich plasma, microneedles, and hair transplants. These treatments mainly focus on improving symptoms, and their effectiveness is intrinsically related to their maintenance.[1] In addition, as these treatments are still under research and require further validation, we should consider their potential limitations regarding their effectiveness and side effects. Alternatively, various traditional Chinese herbs, including their monomers, have been reported to alleviate hair loss.[6–8] Furthermore, since herbs are typically reported to have fewer side effects, they are promising treatments.[9]

In Traditional Chinese Medicine (TCM), hair loss is closely related to kidney and blood deficiencies. Kidney deficiency is a pathological change in the kidney with insufficient essence and impaired function. If the kidney essence and blood production are insufficient, the hair lacks nutrition, resulting in hair fall. Therefore, the TCM treatment of hair loss is based on tonifying the kidneys and nourishing the blood.

SEZW is a Chinese medicinal formula consisting of ErZhi Wan (EZW) plus Cornus officinalis (CO) and Rehmanniae Radix Praeparata (RRP), which have tonifying effects on the kidneys and blood. EZW is a commonly used formula in TCM composed of two Chinese herbs, Ecliptae Herba (EH) and Fructus Ligustri Lucidi (FLL), whose names originate from the specific seasons when the two herbs are harvested: winter and summer solstices, respectively. EH and FLL have similar efficacies in treating AGA and according to historical documents, they can also darken the hair when used in combination. Research has shown that the proliferation, differentiation, and death of follicular melanocytes occur along the hair cycle progresses.[10] Furthermore, follicular melanogenesis includes the melanogenic activity of follicular melanocytes, migration of melanin granules, and pigmentation of the hair shaft.[11] Therefore, we hypothesize that EZW not only can deepen hair color but also can promote hair growth. Even when CO, RRP, EH, and FLL are commonly used to treat AGA, the mechanism underlying the function of SEZW in alleviating hair loss remains unclear.

Since the current Western medicines for AGA have limited efficacy and applicability, it is worthwhile to consider TCM as an entry point for research and development of new treatments. In this study, we validated the efficacy of SEZW in the treatment of AGA by constructing an AGA mouse model. Network pharmacology was used to identify potential key targets and signaling pathways to explore the mechanism of action of SEZW in AGA treatment. Finally, the results were validated using molecular docking.

Materials and Methods

Materials

FLL granules (1 g, 10 g/bag), EH granules (1 g, 10 g/bag), RRP granules (4 g, 10 g/bag), and CO granules (1 g, 6 g/bag) were purchased from Zhangjiagang Traditional Chinese Medicine Hospital (Jiangyin Tianjiang Pharmaceutical Co., Ltd., Wuxi, China). Finasteride Tablets were obtained from Hangzhou MSD Pharmaceutical Co. Ltd. (1 mg/tablet, Hangzhou, China). Testosterone propionate injections were bought from Tianjin Jinyao Pharmaceutical Co. (1 mL × 25 mg, Tianjin, China).

One bag each of EH, FLL, RRP, and CO were added to pure water to obtain low (1 g/mL) and high concentration (2 g/mL) treatment solutions. Finasteride was powdered, added to a 0.5% sodium carboxymethylcellulose solution and mixed thoroughly to obtain a 0.1 mg/mL finasteride suspension. The testosterone propionate injection was diluted with injectable corn oil to a concentration of 5 mg/mL. Each solution was prepared weekly and stored at 4 °C. The solutions were warmed to room temperature before being administered.

Animals

Forty 6–8 weeks old males C57BL/6 mice, weighing 18–22 g, were purchased from the Suzhou Hengxingchen Biomedical Co. (Suzhou, China). The experiments were approved by the Animal Ethics Committee of Zhangjiagang TCM Hospital Affiliated to Nanjing University of Chinese Medicine according to guidelines for the ethical review of laboratory animal welfare People's Republic of China National Standard GB/T 35892-2018. The 40 mice were fed adaptively with free access to food and water for one week, after which a 2×3 cm area was marked on their dorsal side. The hair in this area was removed with an electric razor, and residual hair was removed with a depilatory cream. The dorsal skin of all mice was pink, suggesting that the hair follicles had entered the telogen phase. All mice except those in the control group were injected subcutaneously with 0.1 mL of 5 mg/mL testosterone propionate on the back every day for 28 days to obtain the AGA-model mice.[12]

Treatments

The 40 mice were randomly divided into five groups of eight mice each: Control, AGA-model, AGA-Positive, SEZW low dose (SEZW-L), and SEZW high dose (SEZW-H) groups. Mice in the AGA-Positive group were treated with 0.1 mL of 0.1 mg/mL finasteride suspension, while mice in the SEZW-L and SEZW-H groups were given 10 g/kg/d and 20 g/kg/d SEZW solution, respectively, via intragastric administration for 28 days. The mice were photographed on days 0, 14, and 28 during the dosing period to record hair growth and score the results (Figure 1A). Two trained technicians blindly measured hair regrowth ratios (%) according to the proportion of dorsal skin that turns black. As hairs enter the telogen phase the skin is pink, while in the anagen phase it is black. The evaluation criteria for hair regrowth were as follows: score 0=no growth observed; 1=up to 20% growth; 2=20–40% growth; 3=40–60% growth; 4=60–80% growth; and 5=80% to full growth.[13] On day 28 of the experiment, all hair in the previously marked area on the dorsal side was removed using an electric razor. Subsequently, hair was weighed using a balance.

Active Ingredients and Potential Targets Identification

Four Chinese herbs, EH, FLL, CO, and RRP, were searched for in the Traditional Chinese Medicine Database and Analysis Platform (TCMSP, https://tcmsp-e.com/). The active compounds in each herb were screened with the conditions of oral bioavailability (OB) ≥ 30% and drug-like properties (DL) ≥ 0.18. All potential targets corresponding to the ingredients in SEZW were collected. The names of the targets were normalized using the UniProt database (https://www.uniprot.org/). We selected targets that had been reviewed previously and removed duplicates and non-human targets. Finally, the compound-related targets were identified.

Identification of AGA-Related Targets

To obtain AGA-related targets, we used "Androgenetic alopecia" and "Alopecia seborrheic" as keywords to search in five gene databases: GeneCards (https://www.genecards.org/), OMIM (https://omim.org/), DrugBank (https://go.drugbank.com/), PharmGKB (https://www.pharmgkb.org/), and TTD (http://db.idrblab.net/ttd/). On the GeneCards database, genes with scores >0.5 were identified as those closely associated with AGA and were included in the study. Subsequently, we merged the AGA-related targets retrieved from the five databases.

Construction of Protein-Protein Interaction (PPI) Network for Drug-Disease Hub Targets

The Venn package in R was used to determine the overlap between the drug targets and disease-related genes, which were SEZW-AGA common targets. The PPI network was constructed by uploading candidate genes to the STRING database (https://string-db.org/). Subsequently, we imported the obtained results into the Cytoscape3.9.1 software for further analysis. CytoNCA, a Cytoscape plugin, was used to identify potential hub targets based on the analysis of six parameters: betweenness, closeness, degree, eigenvector, Local Average Connectivity-based method, and network. The top three active compounds in terms of the number of targets in the network and OB values were considered major active compounds.

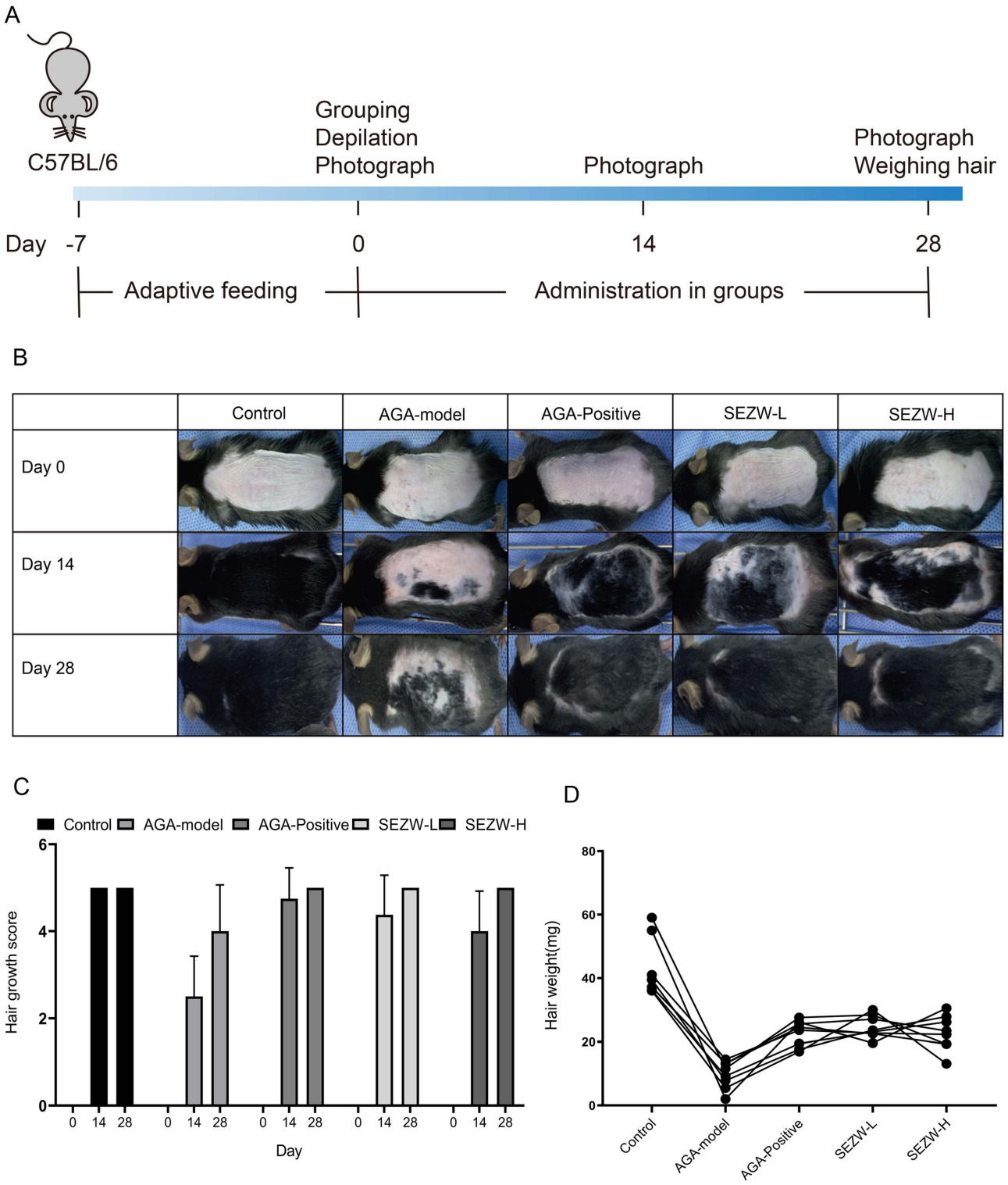

Figure 1 Pharmacodynamic study of SEZW in AGA-model mice. (**A**) A Schematic diagram of the pharmacodynamic experiment. (**B**) Dorsal photographs of mice in Control, AGA-model, AGA-Positive, SEZW-L, and SEZW-H groups at day 0, 14, and 28. (**C**) Changes in hair regrowth scores of the Control, AGA-model, AGA-Positive, SEZW-L, and SEZW-H groups at day 0, 14, and 28, represented as the mean. (**D**) Regrowth hair weight from the dorsal section of the mice in each of the five groups at day 28, represented as the mean. **Abbreviations**: SEZW, Supplemented Erzhi Wan; AGA, androgenetic alopecia; SEZW-L; SEZW low dose; SEZW-H; SEZW high dose.

GO and KEGG Enrichment Analyses

GO and KEGG enrichment analyses were performed to explore the potential functions of the candidate targets and crucial signaling pathways using the ClusterProfiler package in R4.2.1. Regarding the GO analysis, functions across the

three categories, biological process (BP), cellular component (CC), and molecular function (MF), were considered statistically significant at P<0.05. Regarding the KEGG analysis, terms with P<0.05 were considered potential signaling pathways.

Molecular Docking Technology

The SEZW-AGA hub targets were considered receptor proteins, whereas the major active compounds were considered ligands. We obtained the core receptor protein and ligand structures from the Protein Data Bank (PDB) (http://www.rcsb.org/pdb/home/home.do) and PubChem databases (https://pubchem.ncbi.nlm.nih.gov/), respectively. The receptor proteins were pretreated via dehydration and hydrogenation using the PyMOL (https://pymol.org/2/) and AutoDockTools software (https://autodock.scripps.edu/download-autodock4/). Molecular ligands were converted into 3D structures using ChemOffice software (https://www.chemdraw.com.cn/). Subsequently, the receptor proteins and ligands were docked, and the docking fractions were calculated using AutoDockVina (https://vina.scripps.edu/). The lower the binding energy of the interactions, the better the binding ability between the receptors and ligands.[14] Finally, the receptor-ligand complexes were visualized using PyMoL.

Results

Pharmacodynamic Study of SEZW on AGA-Model Mice

After 28 days of treatment, hair regrowth on the dorsal side of the mice in the AGA-model group was significantly slower than that of the mice in the other groups, indicating that the AGA-model mice had been constructed successfully (Figure 1B). After 2 weeks, hair regeneration reached more than 80% in the control group (Figure 1C), and there was a significant difference in hair regeneration scores between the control and the AGA-model group (P<0.01) (Figure 1C). The hair regeneration scores of mice in both the SEZW-L and SEZW-H groups were significantly higher than those of mice in the AGA-model group (P<0.01) (Figure 1C). Moreover, the mice in the AGA-Positive group showed faster hair growth, and their scores were significantly different from those of the mice in the AGA-model group (P<0.01) (Figure 1C). The hair regeneration scores of the mice in the Control, AGA-Positive, SEZW-L, and SEZW-H groups did not differ significantly (P>0.05) (Figure 1C), and mice in all these groups showed more than 80% hair regrowth after 28 days. The statistically significant difference between the hair scores of mice in the AGA-model and the other groups was maintained at 28 days (P<0.05) (Figure 1C). The results based on the hair weights of the mice supported these differences: The AGA-model mice had the lowest hair weight and the control group had the highest regenerated hair weight (Figure 1D). Compared to the AGA-model group, mice in the AGA-Positive, SEZW-L, and SEZW-H groups showed a significant increase in hair weight (P<0.01) (Figure 1D).

Prediction of the Targets of SEZW

By setting thresholds of OB ≥30% and DL ≥0.18, we identified 10, 13, 20, and 2 active compounds for FLL, EH, CO, and RRP, respectively, from the TCMSP database. The corresponding targets for each active compound were also downloaded from the TCMSP database (Table 1). After deduplication and integration, we obtained 200 molecules targeted by the active compounds present in SEZW.

AGA-Related Target Prediction

We obtained 657, 12, 11, 745, and 0 candidate AGA-related genes from GeneCards, OMIM, DrugBank, PharmGKB, and TTD, respectively. Targets related to AGA in the GeneCards database were sorted and selected based on a relevance score greater than 0.5, which was considered a strong correlation. After removing duplicates, we obtained a final set of 1385 AGA-related genes (Figure 2A).

Construction of PPI Networks for Drug-Disease Targets

A total of 59 shared targets of drug compounds and diseases were found (Figure 2B). Based on these, a PPI network consisting of 59 nodes and 592 edges was constructed. Network edges were added based on evidence collected through

Table 1 Active compounds and targets selected for SEZW

Drug	MolId	MolName	Symbol
Mohanlian	MOL001689	Acacetin	NOS2
Mohanlian	MOL001689	Acacetin	PTGS1
Mohanlian	MOL001689	Acacetin	AR
Mohanlian	MOL001689	Acacetin	PTGS2
Mohanlian	MOL001689	Acacetin	DPP4
Mohanlian	MOL001689	Acacetin	HSP90AB1
Mohanlian	MOL001689	Acacetin	CDK2
Mohanlian	MOL001689	Acacetin	PRSS1
Mohanlian	MOL001689	Acacetin	NCOA2
Mohanlian	MOL001689	Acacetin	NCOA1
Mohanlian	MOL001689	Acacetin	CAMKMT
Mohanlian	MOL001689	Acacetin	CHEK1
Mohanlian	MOL001689	Acacetin	ADRB2
Mohanlian	MOL001689	Acacetin	RELA
Mohanlian	MOL001689	Acacetin	BCL2
Mohanlian	MOL001689	Acacetin	CDKN1A
Mohanlian	MOL001689	Acacetin	BAX
Mohanlian	MOL001689	Acacetin	CASP3
Mohanlian	MOL001689	Acacetin	TP53
Mohanlian	MOL001689	Acacetin	CASP8
Mohanlian	MOL001689	Acacetin	FASN
Mohanlian	MOL001689	Acacetin	FASLG
Mohanlian	MOL001689	Acacetin	CYP19A1
Mohanlian	MOL002975	Butin	PTGS1
Mohanlian	MOL002975	Butin	PTGS2
Mohanlian	MOL002975	Butin	RXRA
Mohanlian	MOL002975	Butin	HSP90AB1
Mohanlian	MOL002975	Butin	DPEP1
Mohanlian	MOL003378	1,3,8,9-tetrahydroxybenzofurano[3,2-c]chromen-6-one	HSP90AB1
Mohanlian	MOL003389	3'-O-Methylorobol	NOS2
Mohanlian	MOL003389	3'-O-Methylorobol	PTGS1
Mohanlian	MOL003389	3'-O-Methylorobol	ESR1
Mohanlian	MOL003389	3'-O-Methylorobol	AR
Mohanlian	MOL003389	3'-O-Methylorobol	PPARG
Mohanlian	MOL003389	3'-O-Methylorobol	PTGS2
Mohanlian	MOL003389	3'-O-Methylorobol	ESR2
Mohanlian	MOL003389	3'-O-Methylorobol	MAPK14
Mohanlian	MOL003389	3'-O-Methylorobol	GSK3B
Mohanlian	MOL003389	3'-O-Methylorobol	HSP90AB1
Mohanlian	MOL003389	3'-O-Methylorobol	CDK2
Mohanlian	MOL003389	3'-O-Methylorobol	CHEK1
Mohanlian	MOL003389	3'-O-Methylorobol	PRSS1
Mohanlian	MOL003389	3'-O-Methylorobol	CCNA2
Mohanlian	MOL003389	3'-O-Methylorobol	NCOA1
Mohanlian	MOL003389	3'-O-Methylorobol	CAMKMT
Mohanlian	MOL003398	Pratensein	NOS2
Mohanlian	MOL003398	Pratensein	PTGS1
Mohanlian	MOL003398	Pratensein	ESR1
Mohanlian	MOL003398	Pratensein	AR

(*Continued*)

Table 1 (Continued).

Drug	MolId	MolName	Symbol
Mohanlian	MOL003398	Pratensein	PPARG
Mohanlian	MOL003398	Pratensein	PTGS2
Mohanlian	MOL003398	Pratensein	ESR2
Mohanlian	MOL003398	Pratensein	DPP4
Mohanlian	MOL003398	Pratensein	MAPK14
Mohanlian	MOL003398	Pratensein	GSK3B
Mohanlian	MOL003398	Pratensein	HSP90AB1
Mohanlian	MOL003398	Pratensein	CDK2
Mohanlian	MOL003398	Pratensein	CHEK1
Mohanlian	MOL003398	Pratensein	PRSS1
Mohanlian	MOL003398	Pratensein	CCNA2
Mohanlian	MOL003398	Pratensein	NCOA2
Mohanlian	MOL003398	Pratensein	CAMKMT
Mohanlian	MOL003402	Demethylwedelolactone	PTGS2
Mohanlian	MOL003402	Demethylwedelolactone	GSK3B
Mohanlian	MOL003404	Wedelolactone	ESR1
Mohanlian	MOL003404	Wedelolactone	PPARG
Mohanlian	MOL003404	Wedelolactone	ESR2
Mohanlian	MOL003404	Wedelolactone	GSK3B
Mohanlian	MOL003404	Wedelolactone	HSP90AB1
Mohanlian	MOL003404	Wedelolactone	CDK2
Mohanlian	MOL003404	Wedelolactone	IKBKB
Mohanlian	MOL003404	Wedelolactone	AR
Mohanlian	MOL000006	Luteolin	PTGS1
Mohanlian	MOL000006	Luteolin	AR
Mohanlian	MOL000006	Luteolin	PTGS2
Mohanlian	MOL000006	Luteolin	HSP90AB1
Mohanlian	MOL000006	Luteolin	PRSS1
Mohanlian	MOL000006	Luteolin	NCOA2
Mohanlian	MOL000006	Luteolin	DPP4
Mohanlian	MOL000006	Luteolin	RELA
Mohanlian	MOL000006	Luteolin	EGFR
Mohanlian	MOL000006	Luteolin	AKT1
Mohanlian	MOL000006	Luteolin	VEGFA
Mohanlian	MOL000006	Luteolin	CCND1
Mohanlian	MOL000006	Luteolin	BCL2L1
Mohanlian	MOL000006	Luteolin	CDKN1A
Mohanlian	MOL000006	Luteolin	CASP9
Mohanlian	MOL000006	Luteolin	MMP2
Mohanlian	MOL000006	Luteolin	MMP9
Mohanlian	MOL000006	Luteolin	MAPK1
Mohanlian	MOL000006	Luteolin	IL10RA
Mohanlian	MOL000006	Luteolin	RB1
Mohanlian	MOL000006	Luteolin	CDK4
Mohanlian	MOL000006	Luteolin	TNFAIP6
Mohanlian	MOL000006	Luteolin	JUN
Mohanlian	MOL000006	Luteolin	IL6R
Mohanlian	MOL000006	Luteolin	CASP3
Mohanlian	MOL000006	Luteolin	TP53
Mohanlian	MOL000006	Luteolin	NFKBIA

(*Continued*)

Table 1 (Continued).

Drug	MolId	MolName	Symbol
Mohanlian	MOL000006	Luteolin	TOP1
Mohanlian	MOL000006	Luteolin	MDM2
Mohanlian	MOL000006	Luteolin	APP
Mohanlian	MOL000006	Luteolin	MMP1
Mohanlian	MOL000006	Luteolin	PCNA
Mohanlian	MOL000006	Luteolin	ERBB2
Mohanlian	MOL000006	Luteolin	PPARG
Mohanlian	MOL000006	Luteolin	HMOX1
Mohanlian	MOL000006	Luteolin	CASP7
Mohanlian	MOL000006	Luteolin	ICAM1
Mohanlian	MOL000006	Luteolin	MCL1
Mohanlian	MOL000006	Luteolin	BIRC5
Mohanlian	MOL000006	Luteolin	IL2RA
Mohanlian	MOL000006	Luteolin	CCNB1
Mohanlian	MOL000006	Luteolin	TYR
Mohanlian	MOL000006	Luteolin	IFNG
Mohanlian	MOL000006	Luteolin	IL4
Mohanlian	MOL000006	Luteolin	TOP2A
Mohanlian	MOL000006	Luteolin	GSTP1
Mohanlian	MOL000006	Luteolin	XIAP
Mohanlian	MOL000006	Luteolin	SLC2A4
Mohanlian	MOL000006	Luteolin	INSRR
Mohanlian	MOL000006	Luteolin	CD40LG
Mohanlian	MOL000006	Luteolin	PTGES
Mohanlian	MOL000006	Luteolin	NUF2
Mohanlian	MOL000006	Luteolin	ADCY2
Mohanlian	MOL000006	Luteolin	MET
Mohanlian	MOL000098	Quercetin	PTGS1
Mohanlian	MOL000098	Quercetin	AR
Mohanlian	MOL000098	Quercetin	PPARG
Mohanlian	MOL000098	Quercetin	PTGS2
Mohanlian	MOL000098	Quercetin	HSP90AB1
Mohanlian	MOL000098	Quercetin	NCOA2
Mohanlian	MOL000098	Quercetin	DPP4
Mohanlian	MOL000098	Quercetin	AKR1B1
Mohanlian	MOL000098	Quercetin	PRSS1
Mohanlian	MOL000098	Quercetin	KCNH2
Mohanlian	MOL000098	Quercetin	SCN5A
Mohanlian	MOL000098	Quercetin	ADRB2
Mohanlian	MOL000098	Quercetin	MMP3
Mohanlian	MOL000098	Quercetin	F7
Mohanlian	MOL000098	Quercetin	RXRA
Mohanlian	MOL000098	Quercetin	ACHE
Mohanlian	MOL000098	Quercetin	GABRA1
Mohanlian	MOL000098	Quercetin	MAOB
Mohanlian	MOL000098	Quercetin	RELA
Mohanlian	MOL000098	Quercetin	EGFR
Mohanlian	MOL000098	Quercetin	AKT1
Mohanlian	MOL000098	Quercetin	VEGFA
Mohanlian	MOL000098	Quercetin	CCND1

(*Continued*)

Table 1 (Continued).

Drug	MolId	MolName	Symbol
Mohanlian	MOL000098	Quercetin	BCL2
Mohanlian	MOL000098	Quercetin	BCL2L1
Mohanlian	MOL000098	Quercetin	FOS
Mohanlian	MOL000098	Quercetin	CDKN1A
Mohanlian	MOL000098	Quercetin	EIF6
Mohanlian	MOL000098	Quercetin	BAX
Mohanlian	MOL000098	Quercetin	CASP9
Mohanlian	MOL000098	Quercetin	PLAU
Mohanlian	MOL000098	Quercetin	MMP2
Mohanlian	MOL000098	Quercetin	MMP9
Mohanlian	MOL000098	Quercetin	MAPK1
Mohanlian	MOL000098	Quercetin	IL10RA
Mohanlian	MOL000098	Quercetin	EGF
Mohanlian	MOL000098	Quercetin	RB1
Mohanlian	MOL000098	Quercetin	TNFAIP6
Mohanlian	MOL000098	Quercetin	JUN
Mohanlian	MOL000098	Quercetin	IL6R
Mohanlian	MOL000098	Quercetin	AHSA1
Mohanlian	MOL000098	Quercetin	CASP3
Mohanlian	MOL000098	Quercetin	TP53
Mohanlian	MOL000098	Quercetin	ELK1
Mohanlian	MOL000098	Quercetin	NFKBIA
Mohanlian	MOL000098	Quercetin	POR
Mohanlian	MOL000098	Quercetin	ODC1
Mohanlian	MOL000098	Quercetin	CASP8
Mohanlian	MOL000098	Quercetin	TOP1
Mohanlian	MOL000098	Quercetin	RAF1
Mohanlian	MOL000098	Quercetin	SOD1
Mohanlian	MOL000098	Quercetin	PRKCA
Mohanlian	MOL000098	Quercetin	MMP1
Mohanlian	MOL000098	Quercetin	HIF1A
Mohanlian	MOL000098	Quercetin	STAT1
Mohanlian	MOL000098	Quercetin	RUNX1T1
Mohanlian	MOL000098	Quercetin	CDK1
Mohanlian	MOL000098	Quercetin	HSPA5
Mohanlian	MOL000098	Quercetin	ERBB2
Mohanlian	MOL000098	Quercetin	PPARG
Mohanlian	MOL000098	Quercetin	ACACA
Mohanlian	MOL000098	Quercetin	HMOX1
Mohanlian	MOL000098	Quercetin	CYP3A4
Mohanlian	MOL000098	Quercetin	CYP1A2
Mohanlian	MOL000098	Quercetin	CAV1
Mohanlian	MOL000098	Quercetin	MYC
Mohanlian	MOL000098	Quercetin	F3
Mohanlian	MOL000098	Quercetin	GJA1
Mohanlian	MOL000098	Quercetin	CYP1A1
Mohanlian	MOL000098	Quercetin	ICAM1
Mohanlian	MOL000098	Quercetin	IL1B
Mohanlian	MOL000098	Quercetin	CCL2
Mohanlian	MOL000098	Quercetin	SELE

(*Continued*)

Table 1 (Continued).

Drug	MolId	MolName	Symbol
Mohanlian	MOL000098	Quercetin	VCAM1
Mohanlian	MOL000098	Quercetin	PTGER3
Mohanlian	MOL000098	Quercetin	CXCL8
Mohanlian	MOL000098	Quercetin	PRKCB
Mohanlian	MOL000098	Quercetin	BIRC5
Mohanlian	MOL000098	Quercetin	DUOX2
Mohanlian	MOL000098	Quercetin	NOS3
Mohanlian	MOL000098	Quercetin	HSPB1
Mohanlian	MOL000098	Quercetin	SULT1E1
Mohanlian	MOL000098	Quercetin	IL2RA
Mohanlian	MOL000098	Quercetin	NR1I2
Mohanlian	MOL000098	Quercetin	CYP1B1
Mohanlian	MOL000098	Quercetin	CCNB1
Mohanlian	MOL000098	Quercetin	PLAT
Mohanlian	MOL000098	Quercetin	THBD
Mohanlian	MOL000098	Quercetin	SERPINE1
Mohanlian	MOL000098	Quercetin	COL1A1
Mohanlian	MOL000098	Quercetin	IFNG
Mohanlian	MOL000098	Quercetin	ALOX5
Mohanlian	MOL000098	Quercetin	IL1A
Mohanlian	MOL000098	Quercetin	MPO
Mohanlian	MOL000098	Quercetin	TOP2A
Mohanlian	MOL000098	Quercetin	NCF1
Mohanlian	MOL000098	Quercetin	ABCG2
Mohanlian	MOL000098	Quercetin	HAS2
Mohanlian	MOL000098	Quercetin	GSTP1
Mohanlian	MOL000098	Quercetin	NFE2L2
Mohanlian	MOL000098	Quercetin	NQO1
Mohanlian	MOL000098	Quercetin	PARP1
Mohanlian	MOL000098	Quercetin	AHR
Mohanlian	MOL000098	Quercetin	PSMD3
Mohanlian	MOL000098	Quercetin	SLC2A4
Mohanlian	MOL000098	Quercetin	COL3A1
Mohanlian	MOL000098	Quercetin	CXCL11
Mohanlian	MOL000098	Quercetin	CXCL2
Mohanlian	MOL000098	Quercetin	DCAF5
Mohanlian	MOL000098	Quercetin	NR1I3
Mohanlian	MOL000098	Quercetin	CHEK2
Mohanlian	MOL000098	Quercetin	INSRR
Mohanlian	MOL000098	Quercetin	CLDN4
Mohanlian	MOL000098	Quercetin	PPARA
Mohanlian	MOL000098	Quercetin	PPARD
Mohanlian	MOL000098	Quercetin	HSF1
Mohanlian	MOL000098	Quercetin	CXCL10
Mohanlian	MOL000098	Quercetin	CHUK
Mohanlian	MOL000098	Quercetin	SPP1
Mohanlian	MOL000098	Quercetin	RUNX2
Mohanlian	MOL000098	Quercetin	RASSF1
Mohanlian	MOL000098	Quercetin	E2F1
Mohanlian	MOL000098	Quercetin	E2F2

(*Continued*)

Table 1 (Continued).

Drug	MolId	MolName	Symbol
Mohanlian	MOL000098	Quercetin	ACP3
Mohanlian	MOL000098	Quercetin	CTSD
Mohanlian	MOL000098	Quercetin	IGFBP3
Mohanlian	MOL000098	Quercetin	IGF2
Mohanlian	MOL000098	Quercetin	CD40LG
Mohanlian	MOL000098	Quercetin	IRF1
Mohanlian	MOL000098	Quercetin	ERBB3
Mohanlian	MOL000098	Quercetin	PON1
Mohanlian	MOL000098	Quercetin	DIO1
Mohanlian	MOL000098	Quercetin	PCOLCE
Mohanlian	MOL000098	Quercetin	NPEPPS
Mohanlian	MOL000098	Quercetin	HK2
Mohanlian	MOL000098	Quercetin	RASA1
Mohanlian	MOL000098	Quercetin	GSTM1
Mohanlian	MOL000098	Quercetin	GSTM2
Nvzhenzi	MOL000358	Beta-sitosterol	PGR
Nvzhenzi	MOL000358	Beta-sitosterol	NCOA2
Nvzhenzi	MOL000358	Beta-sitosterol	PTGS1
Nvzhenzi	MOL000358	Beta-sitosterol	PTGS2
Nvzhenzi	MOL000358	Beta-sitosterol	HSP90AB1
Nvzhenzi	MOL000358	Beta-sitosterol	KCNH2
Nvzhenzi	MOL000358	Beta-sitosterol	DRD1
Nvzhenzi	MOL000358	Beta-sitosterol	CHRM3
Nvzhenzi	MOL000358	Beta-sitosterol	CHRM1
Nvzhenzi	MOL000358	Beta-sitosterol	SCN5A
Nvzhenzi	MOL000358	Beta-sitosterol	CHRM4
Nvzhenzi	MOL000358	Beta-sitosterol	ADRA1A
Nvzhenzi	MOL000358	Beta-sitosterol	CHRM2
Nvzhenzi	MOL000358	Beta-sitosterol	ADRA1B
Nvzhenzi	MOL000358	Beta-sitosterol	ADRB2
Nvzhenzi	MOL000358	Beta-sitosterol	CHRNA2
Nvzhenzi	MOL000358	Beta-sitosterol	SLC6A4
Nvzhenzi	MOL000358	Beta-sitosterol	OPRM1
Nvzhenzi	MOL000358	Beta-sitosterol	GABRA1
Nvzhenzi	MOL000358	Beta-sitosterol	BCL2
Nvzhenzi	MOL000358	Beta-sitosterol	BAX
Nvzhenzi	MOL000358	Beta-sitosterol	CASP9
Nvzhenzi	MOL000358	Beta-sitosterol	JUN
Nvzhenzi	MOL000358	Beta-sitosterol	CASP3
Nvzhenzi	MOL000358	Beta-sitosterol	CASP8
Nvzhenzi	MOL000358	Beta-sitosterol	PRKCA
Nvzhenzi	MOL000358	Beta-sitosterol	PON1
Nvzhenzi	MOL000358	Beta-sitosterol	MAP2
Nvzhenzi	MOL000422	Kaempferol	NOS2
Nvzhenzi	MOL000422	Kaempferol	PTGS1
Nvzhenzi	MOL000422	Kaempferol	AR
Nvzhenzi	MOL000422	Kaempferol	PPARG
Nvzhenzi	MOL000422	Kaempferol	PTGS2
Nvzhenzi	MOL000422	Kaempferol	HSP90AB1
Nvzhenzi	MOL000422	Kaempferol	NCOA2

(*Continued*)

Table 1 (Continued).

Drug	MolId	MolName	Symbol
Nvzhenzi	MOL000422	Kaempferol	DPP4
Nvzhenzi	MOL000422	Kaempferol	PRSS1
Nvzhenzi	MOL000422	Kaempferol	PGR
Nvzhenzi	MOL000422	Kaempferol	CHRM1
Nvzhenzi	MOL000422	Kaempferol	ACHE
Nvzhenzi	MOL000422	Kaempferol	SLC6A2
Nvzhenzi	MOL000422	Kaempferol	CHRM2
Nvzhenzi	MOL000422	Kaempferol	ADRA1B
Nvzhenzi	MOL000422	Kaempferol	GABRA1
Nvzhenzi	MOL000422	Kaempferol	F7
Nvzhenzi	MOL000422	Kaempferol	CAMKMT
Nvzhenzi	MOL000422	Kaempferol	RELA
Nvzhenzi	MOL000422	Kaempferol	IKBKB
Nvzhenzi	MOL000422	Kaempferol	AKT1
Nvzhenzi	MOL000422	Kaempferol	BCL2
Nvzhenzi	MOL000422	Kaempferol	BAX
Nvzhenzi	MOL000422	Kaempferol	TNFAIP6
Nvzhenzi	MOL000422	Kaempferol	JUN
Nvzhenzi	MOL000422	Kaempferol	AHSA1
Nvzhenzi	MOL000422	Kaempferol	CASP3
Nvzhenzi	MOL000422	Kaempferol	MAPK8
Nvzhenzi	MOL000422	Kaempferol	MMP1
Nvzhenzi	MOL000422	Kaempferol	STAT1
Nvzhenzi	MOL000422	Kaempferol	CDK1
Nvzhenzi	MOL000422	Kaempferol	PPARG
Nvzhenzi	MOL000422	Kaempferol	HMOX1
Nvzhenzi	MOL000422	Kaempferol	CYP3A4
Nvzhenzi	MOL000422	Kaempferol	CYP1A2
Nvzhenzi	MOL000422	Kaempferol	CYP1A1
Nvzhenzi	MOL000422	Kaempferol	ICAM1
Nvzhenzi	MOL000422	Kaempferol	SELE
Nvzhenzi	MOL000422	Kaempferol	VCAM1
Nvzhenzi	MOL000422	Kaempferol	NR1I2
Nvzhenzi	MOL000422	Kaempferol	CYP1B1
Nvzhenzi	MOL000422	Kaempferol	ALOX5
Nvzhenzi	MOL000422	Kaempferol	HAS2
Nvzhenzi	MOL000422	Kaempferol	GSTP1
Nvzhenzi	MOL000422	Kaempferol	AHR
Nvzhenzi	MOL000422	Kaempferol	PSMD3
Nvzhenzi	MOL000422	Kaempferol	SLC2A4
Nvzhenzi	MOL000422	Kaempferol	NR1I3
Nvzhenzi	MOL000422	Kaempferol	INSRR
Nvzhenzi	MOL000422	Kaempferol	DIO1
Nvzhenzi	MOL000422	Kaempferol	PPP3CA
Nvzhenzi	MOL000422	Kaempferol	GSTM1
Nvzhenzi	MOL000422	Kaempferol	GSTM2
Nvzhenzi	MOL000422	Kaempferol	AKR1C3
Nvzhenzi	MOL000422	Kaempferol	SLPI
Nvzhenzi	MOL004576	Taxifolin	PTGS1
Nvzhenzi	MOL004576	Taxifolin	PTGS2

(*Continued*)

Table 1 (Continued).

Drug	MolId	MolName	Symbol
Nvzhenzi	MOL004576	Taxifolin	HSP90AB1
Nvzhenzi	MOL004576	Taxifolin	RXRA
Nvzhenzi	MOL004576	Taxifolin	AKR1B1
Nvzhenzi	MOL004576	Taxifolin	RELA
Nvzhenzi	MOL004576	Taxifolin	ICAM1
Nvzhenzi	MOL004576	Taxifolin	DGAT2
Nvzhenzi	MOL004576	Taxifolin	MTTP
Nvzhenzi	MOL004576	Taxifolin	APOB
Nvzhenzi	MOL005147	Lucidumoside D_qt	NOS2
Nvzhenzi	MOL005147	Lucidumoside D_qt	ESR1
Nvzhenzi	MOL005147	Lucidumoside D_qt	AR
Nvzhenzi	MOL005147	Lucidumoside D_qt	SCN5A
Nvzhenzi	MOL005147	Lucidumoside D_qt	PTGS2
Nvzhenzi	MOL005147	Lucidumoside D_qt	CA2
Nvzhenzi	MOL005147	Lucidumoside D_qt	ACHE
Nvzhenzi	MOL005147	Lucidumoside D_qt	ADRB2
Nvzhenzi	MOL005147	Lucidumoside D_qt	DPP4
Nvzhenzi	MOL005147	Lucidumoside D_qt	GSK3B
Nvzhenzi	MOL005147	Lucidumoside D_qt	HSP90AB1
Nvzhenzi	MOL005147	Lucidumoside D_qt	CDK2
Nvzhenzi	MOL005147	Lucidumoside D_qt	PRSS1
Nvzhenzi	MOL005147	Lucidumoside D_qt	CCNA2
Nvzhenzi	MOL005147	Lucidumoside D_qt	NCOA2
Nvzhenzi	MOL005190	Eriodictyol	PTGS1
Nvzhenzi	MOL005190	Eriodictyol	PTGS2
Nvzhenzi	MOL005190	Eriodictyol	HSP90AB1
Nvzhenzi	MOL005190	Eriodictyol	NCOA2
Nvzhenzi	MOL005190	Eriodictyol	HMOX1
Nvzhenzi	MOL005190	Eriodictyol	NFE2L2
Nvzhenzi	MOL005190	Eriodictyol	NQO1
Nvzhenzi	MOL005212	Olitoriside_qt	NR3C2
Nvzhenzi	MOL000006	Luteolin	PTGS1
Nvzhenzi	MOL000006	Luteolin	AR
Nvzhenzi	MOL000006	Luteolin	PTGS2
Nvzhenzi	MOL000006	Luteolin	HSP90AB1
Nvzhenzi	MOL000006	Luteolin	PRSS1
Nvzhenzi	MOL000006	Luteolin	NCOA2
Nvzhenzi	MOL000006	Luteolin	DPP4
Nvzhenzi	MOL000006	Luteolin	RELA
Nvzhenzi	MOL000006	Luteolin	EGFR
Nvzhenzi	MOL000006	Luteolin	AKT1
Nvzhenzi	MOL000006	Luteolin	VEGFA
Nvzhenzi	MOL000006	Luteolin	CCND1
Nvzhenzi	MOL000006	Luteolin	BCL2L1
Nvzhenzi	MOL000006	Luteolin	CDKN1A
Nvzhenzi	MOL000006	Luteolin	CASP9
Nvzhenzi	MOL000006	Luteolin	MMP2
Nvzhenzi	MOL000006	Luteolin	MMP9
Nvzhenzi	MOL000006	Luteolin	MAPK1
Nvzhenzi	MOL000006	Luteolin	IL10RA

(*Continued*)

Table 1 (Continued).

Drug	MolId	MolName	Symbol
Nvzhenzi	MOL000006	Luteolin	RB1
Nvzhenzi	MOL000006	Luteolin	CDK4
Nvzhenzi	MOL000006	Luteolin	TNFAIP6
Nvzhenzi	MOL000006	Luteolin	JUN
Nvzhenzi	MOL000006	Luteolin	IL6R
Nvzhenzi	MOL000006	Luteolin	CASP3
Nvzhenzi	MOL000006	Luteolin	TP53
Nvzhenzi	MOL000006	Luteolin	NFKBIA
Nvzhenzi	MOL000006	Luteolin	TOP1
Nvzhenzi	MOL000006	Luteolin	MDM2
Nvzhenzi	MOL000006	Luteolin	APP
Nvzhenzi	MOL000006	Luteolin	MMP1
Nvzhenzi	MOL000006	Luteolin	PCNA
Nvzhenzi	MOL000006	Luteolin	ERBB2
Nvzhenzi	MOL000006	Luteolin	PPARG
Nvzhenzi	MOL000006	Luteolin	HMOX1
Nvzhenzi	MOL000006	Luteolin	CASP7
Nvzhenzi	MOL000006	Luteolin	ICAM1
Nvzhenzi	MOL000006	Luteolin	MCL1
Nvzhenzi	MOL000006	Luteolin	BIRC5
Nvzhenzi	MOL000006	Luteolin	IL2RA
Nvzhenzi	MOL000006	Luteolin	CCNB1
Nvzhenzi	MOL000006	Luteolin	TYR
Nvzhenzi	MOL000006	Luteolin	IFNG
Nvzhenzi	MOL000006	Luteolin	IL4
Nvzhenzi	MOL000006	Luteolin	TOP2A
Nvzhenzi	MOL000006	Luteolin	GSTP1
Nvzhenzi	MOL000006	Luteolin	XIAP
Nvzhenzi	MOL000006	Luteolin	SLC2A4
Nvzhenzi	MOL000006	Luteolin	INSRR
Nvzhenzi	MOL000006	Luteolin	CD40LG
Nvzhenzi	MOL000006	Luteolin	PTGES
Nvzhenzi	MOL000006	Luteolin	NUF2
Nvzhenzi	MOL000006	Luteolin	ADCY2
Nvzhenzi	MOL000006	Luteolin	MET
Nvzhenzi	MOL000098	Quercetin	PTGS1
Nvzhenzi	MOL000098	Quercetin	AR
Nvzhenzi	MOL000098	Quercetin	PPARG
Nvzhenzi	MOL000098	Quercetin	PTGS2
Nvzhenzi	MOL000098	Quercetin	HSP90AB1
Nvzhenzi	MOL000098	Quercetin	NCOA2
Nvzhenzi	MOL000098	Quercetin	DPP4
Nvzhenzi	MOL000098	Quercetin	AKR1B1
Nvzhenzi	MOL000098	Quercetin	PRSS1
Nvzhenzi	MOL000098	Quercetin	KCNH2
Nvzhenzi	MOL000098	Quercetin	SCN5A
Nvzhenzi	MOL000098	Quercetin	ADRB2
Nvzhenzi	MOL000098	Quercetin	MMP3
Nvzhenzi	MOL000098	Quercetin	F7
Nvzhenzi	MOL000098	Quercetin	RXRA

(*Continued*)

Table 1 (Continued).

Drug	MolId	MolName	Symbol
Nvzhenzi	MOL000098	Quercetin	ACHE
Nvzhenzi	MOL000098	Quercetin	GABRA1
Nvzhenzi	MOL000098	Quercetin	MAOB
Nvzhenzi	MOL000098	Quercetin	RELA
Nvzhenzi	MOL000098	Quercetin	EGFR
Nvzhenzi	MOL000098	Quercetin	AKT1
Nvzhenzi	MOL000098	Quercetin	VEGFA
Nvzhenzi	MOL000098	Quercetin	CCND1
Nvzhenzi	MOL000098	Quercetin	BCL2
Nvzhenzi	MOL000098	Quercetin	BCL2L1
Nvzhenzi	MOL000098	Quercetin	FOS
Nvzhenzi	MOL000098	Quercetin	CDKN1A
Nvzhenzi	MOL000098	Quercetin	EIF6
Nvzhenzi	MOL000098	Quercetin	BAX
Nvzhenzi	MOL000098	Quercetin	CASP9
Nvzhenzi	MOL000098	Quercetin	PLAU
Nvzhenzi	MOL000098	Quercetin	MMP2
Nvzhenzi	MOL000098	Quercetin	MMP9
Nvzhenzi	MOL000098	Quercetin	MAPK1
Nvzhenzi	MOL000098	Quercetin	IL10RA
Nvzhenzi	MOL000098	Quercetin	EGF
Nvzhenzi	MOL000098	Quercetin	RB1
Nvzhenzi	MOL000098	Quercetin	TNFAIP6
Nvzhenzi	MOL000098	Quercetin	JUN
Nvzhenzi	MOL000098	Quercetin	IL6R
Nvzhenzi	MOL000098	Quercetin	AHSA1
Nvzhenzi	MOL000098	Quercetin	CASP3
Nvzhenzi	MOL000098	Quercetin	TP53
Nvzhenzi	MOL000098	Quercetin	ELK1
Nvzhenzi	MOL000098	Quercetin	NFKBIA
Nvzhenzi	MOL000098	Quercetin	POR
Nvzhenzi	MOL000098	Quercetin	ODC1
Nvzhenzi	MOL000098	Quercetin	CASP8
Nvzhenzi	MOL000098	Quercetin	TOP1
Nvzhenzi	MOL000098	Quercetin	RAF1
Nvzhenzi	MOL000098	Quercetin	SOD1
Nvzhenzi	MOL000098	Quercetin	PRKCA
Nvzhenzi	MOL000098	Quercetin	MMP1
Nvzhenzi	MOL000098	Quercetin	HIF1A
Nvzhenzi	MOL000098	Quercetin	STAT1
Nvzhenzi	MOL000098	Quercetin	RUNX1T1
Nvzhenzi	MOL000098	Quercetin	CDK1
Nvzhenzi	MOL000098	Quercetin	HSPA5
Nvzhenzi	MOL000098	Quercetin	ERBB2
Nvzhenzi	MOL000098	Quercetin	PPARG
Nvzhenzi	MOL000098	Quercetin	ACACA
Nvzhenzi	MOL000098	Quercetin	HMOX1
Nvzhenzi	MOL000098	Quercetin	CYP3A4
Nvzhenzi	MOL000098	Quercetin	CYP1A2
Nvzhenzi	MOL000098	Quercetin	CAV1

(*Continued*)

Table 1 (Continued).

Drug	MolId	MolName	Symbol
Nvzhenzi	MOL000098	Quercetin	MYC
Nvzhenzi	MOL000098	Quercetin	F3
Nvzhenzi	MOL000098	Quercetin	GJA1
Nvzhenzi	MOL000098	Quercetin	CYP1A1
Nvzhenzi	MOL000098	Quercetin	ICAM1
Nvzhenzi	MOL000098	Quercetin	IL1B
Nvzhenzi	MOL000098	Quercetin	CCL2
Nvzhenzi	MOL000098	Quercetin	SELE
Nvzhenzi	MOL000098	Quercetin	VCAM1
Nvzhenzi	MOL000098	Quercetin	PTGER3
Nvzhenzi	MOL000098	Quercetin	CXCL8
Nvzhenzi	MOL000098	Quercetin	PRKCB
Nvzhenzi	MOL000098	Quercetin	BIRC5
Nvzhenzi	MOL000098	Quercetin	DUOX2
Nvzhenzi	MOL000098	Quercetin	NOS3
Nvzhenzi	MOL000098	Quercetin	HSPB1
Nvzhenzi	MOL000098	Quercetin	SULT1E1
Nvzhenzi	MOL000098	Quercetin	IL2RA
Nvzhenzi	MOL000098	Quercetin	NR1I2
Nvzhenzi	MOL000098	Quercetin	CYP1B1
Nvzhenzi	MOL000098	Quercetin	CCNB1
Nvzhenzi	MOL000098	Quercetin	PLAT
Nvzhenzi	MOL000098	Quercetin	THBD
Nvzhenzi	MOL000098	Quercetin	SERPINE1
Nvzhenzi	MOL000098	Quercetin	COL1A1
Nvzhenzi	MOL000098	Quercetin	IFNG
Nvzhenzi	MOL000098	Quercetin	ALOX5
Nvzhenzi	MOL000098	Quercetin	IL1A
Nvzhenzi	MOL000098	Quercetin	MPO
Nvzhenzi	MOL000098	Quercetin	TOP2A
Nvzhenzi	MOL000098	Quercetin	NCF1
Nvzhenzi	MOL000098	Quercetin	ABCG2
Nvzhenzi	MOL000098	Quercetin	HAS2
Nvzhenzi	MOL000098	Quercetin	GSTP1
Nvzhenzi	MOL000098	Quercetin	NFE2L2
Nvzhenzi	MOL000098	Quercetin	NQO1
Nvzhenzi	MOL000098	Quercetin	PARP1
Nvzhenzi	MOL000098	Quercetin	AHR
Nvzhenzi	MOL000098	Quercetin	PSMD3
Nvzhenzi	MOL000098	Quercetin	SLC2A4
Nvzhenzi	MOL000098	Quercetin	COL3A1
Nvzhenzi	MOL000098	Quercetin	CXCL11
Nvzhenzi	MOL000098	Quercetin	CXCL2
Nvzhenzi	MOL000098	Quercetin	DCAF5
Nvzhenzi	MOL000098	Quercetin	NR1I3
Nvzhenzi	MOL000098	Quercetin	CHEK2
Nvzhenzi	MOL000098	Quercetin	INSRR
Nvzhenzi	MOL000098	Quercetin	CLDN4
Nvzhenzi	MOL000098	Quercetin	PPARA
Nvzhenzi	MOL000098	Quercetin	PPARD

(*Continued*)

Table 1 (Continued).

Drug	MolId	MolName	Symbol
Nvzhenzi	MOL000098	Quercetin	HSF1
Nvzhenzi	MOL000098	Quercetin	CXCL10
Nvzhenzi	MOL000098	Quercetin	CHUK
Nvzhenzi	MOL000098	Quercetin	SPP1
Nvzhenzi	MOL000098	Quercetin	RUNX2
Nvzhenzi	MOL000098	Quercetin	RASSF1
Nvzhenzi	MOL000098	Quercetin	E2F1
Nvzhenzi	MOL000098	Quercetin	E2F2
Nvzhenzi	MOL000098	Quercetin	ACP3
Nvzhenzi	MOL000098	Quercetin	CTSD
Nvzhenzi	MOL000098	Quercetin	IGFBP3
Nvzhenzi	MOL000098	Quercetin	IGF2
Nvzhenzi	MOL000098	Quercetin	CD40LG
Nvzhenzi	MOL000098	Quercetin	IRF1
Nvzhenzi	MOL000098	Quercetin	ERBB3
Nvzhenzi	MOL000098	Quercetin	PON1
Nvzhenzi	MOL000098	Quercetin	DIO1
Nvzhenzi	MOL000098	Quercetin	PCOLCE
Nvzhenzi	MOL000098	Quercetin	NPEPPS
Nvzhenzi	MOL000098	Quercetin	HK2
Nvzhenzi	MOL000098	Quercetin	RASA1
Nvzhenzi	MOL000098	Quercetin	GSTM1
Nvzhenzi	MOL000098	Quercetin	GSTM2
Shanzhuyu	MOL001494	Mandenol	PTGS1
Shanzhuyu	MOL001494	Mandenol	PTGS2
Shanzhuyu	MOL001494	Mandenol	NCOA2
Shanzhuyu	MOL001495	Ethyl linolenate	PTGS1
Shanzhuyu	MOL001495	Ethyl linolenate	NCOA2
Shanzhuyu	MOL001771	poriferast-5-en-3beta-ol	PGR
Shanzhuyu	MOL001771	poriferast-5-en-3beta-ol	NCOA2
Shanzhuyu	MOL002879	Diop	SCN5A
Shanzhuyu	MOL002879	Diop	ADRB2
Shanzhuyu	MOL002879	Diop	CHRM3
Shanzhuyu	MOL002883	Ethyl oleate (NF)	NCOA2
Shanzhuyu	MOL000358	Beta-sitosterol	PGR
Shanzhuyu	MOL000358	Beta-sitosterol	NCOA2
Shanzhuyu	MOL000358	Beta-sitosterol	PTGS1
Shanzhuyu	MOL000358	Beta-sitosterol	PTGS2
Shanzhuyu	MOL000358	Beta-sitosterol	HSP90AB1
Shanzhuyu	MOL000358	Beta-sitosterol	KCNH2
Shanzhuyu	MOL000358	Beta-sitosterol	DRD1
Shanzhuyu	MOL000358	Beta-sitosterol	CHRM3
Shanzhuyu	MOL000358	Beta-sitosterol	CHRM1
Shanzhuyu	MOL000358	Beta-sitosterol	SCN5A
Shanzhuyu	MOL000358	Beta-sitosterol	CHRM4
Shanzhuyu	MOL000358	Beta-sitosterol	ADRA1A
Shanzhuyu	MOL000358	Beta-sitosterol	CHRM2
Shanzhuyu	MOL000358	Beta-sitosterol	ADRA1B
Shanzhuyu	MOL000358	Beta-sitosterol	ADRB2
Shanzhuyu	MOL000358	Beta-sitosterol	CHRNA2

(*Continued*)

Table 1 (Continued).

Drug	MolId	MolName	Symbol
Shanzhuyu	MOL000358	Beta-sitosterol	SLC6A4
Shanzhuyu	MOL000358	Beta-sitosterol	OPRM1
Shanzhuyu	MOL000358	Beta-sitosterol	GABRA1
Shanzhuyu	MOL000358	Beta-sitosterol	BCL2
Shanzhuyu	MOL000358	Beta-sitosterol	BAX
Shanzhuyu	MOL000358	Beta-sitosterol	CASP9
Shanzhuyu	MOL000358	Beta-sitosterol	JUN
Shanzhuyu	MOL000358	Beta-sitosterol	CASP3
Shanzhuyu	MOL000358	Beta-sitosterol	CASP8
Shanzhuyu	MOL000358	Beta-sitosterol	PRKCA
Shanzhuyu	MOL000358	Beta-sitosterol	PON1
Shanzhuyu	MOL000358	Beta-sitosterol	MAP2
Shanzhuyu	MOL000359	Sitosterol	PGR
Shanzhuyu	MOL000359	Sitosterol	NCOA2
Shanzhuyu	MOL000359	Sitosterol	NR3C2
Shanzhuyu	MOL000449	Stigmasterol	PGR
Shanzhuyu	MOL000449	Stigmasterol	NR3C2
Shanzhuyu	MOL000449	Stigmasterol	NCOA2
Shanzhuyu	MOL000449	Stigmasterol	ADH1C
Shanzhuyu	MOL000449	Stigmasterol	IGHG1
Shanzhuyu	MOL000449	Stigmasterol	RXRA
Shanzhuyu	MOL000449	Stigmasterol	NCOA1
Shanzhuyu	MOL000449	Stigmasterol	PTGS1
Shanzhuyu	MOL000449	Stigmasterol	PTGS2
Shanzhuyu	MOL000449	Stigmasterol	ADRA2A
Shanzhuyu	MOL000449	Stigmasterol	SLC6A2
Shanzhuyu	MOL000449	Stigmasterol	SLC6A3
Shanzhuyu	MOL000449	Stigmasterol	ADRB2
Shanzhuyu	MOL000449	Stigmasterol	AKR1B1
Shanzhuyu	MOL000449	Stigmasterol	PLAU
Shanzhuyu	MOL000449	Stigmasterol	LTA4H
Shanzhuyu	MOL000449	Stigmasterol	MAOB
Shanzhuyu	MOL000449	Stigmasterol	MAOA
Shanzhuyu	MOL000449	Stigmasterol	CTRB1
Shanzhuyu	MOL000449	Stigmasterol	CHRM3
Shanzhuyu	MOL000449	Stigmasterol	CHRM1
Shanzhuyu	MOL000449	Stigmasterol	ADRB1
Shanzhuyu	MOL000449	Stigmasterol	SCN5A
Shanzhuyu	MOL000449	Stigmasterol	ADRA1A
Shanzhuyu	MOL000449	Stigmasterol	CHRM2
Shanzhuyu	MOL000449	Stigmasterol	ADRA1B
Shanzhuyu	MOL000449	Stigmasterol	GABRA1
Shanzhuyu	MOL005481	2,6,10,14,18-pentamethylicosa-2,6,10,14,18-pentaene	PTGS2
Shanzhuyu	MOL005503	Cornudentanone	PTGS2
Shanzhuyu	MOL005503	Cornudentanone	NCOA2
Shanzhuyu	MOL005530	Hydroxygenkwanin	NOS2
Shanzhuyu	MOL005530	Hydroxygenkwanin	PTGS1
Shanzhuyu	MOL005530	Hydroxygenkwanin	PTGS2
Shanzhuyu	MOL005530	Hydroxygenkwanin	DPP4

(*Continued*)

Table 1 (Continued).

Drug	MolId	MolName	Symbol
Shanzhuyu	MOL005530	Hydroxygenkwanin	HSP90AB1
Shanzhuyu	MOL005530	Hydroxygenkwanin	PRSS1
Shanzhuyu	MOL005530	Hydroxygenkwanin	NCOA2
Shanzhuyu	MOL005530	Hydroxygenkwanin	CAMKMT
Shanzhuyu	MOL005531	Telocinobufagin	NR3C2
Shanzhuyu	MOL005531	Telocinobufagin	NR3C1
Shanzhuyu	MOL008457	Tetrahydroalstonine	NOS2
Shanzhuyu	MOL008457	Tetrahydroalstonine	PTGS1
Shanzhuyu	MOL008457	Tetrahydroalstonine	DRD1
Shanzhuyu	MOL008457	Tetrahydroalstonine	CHRM3
Shanzhuyu	MOL008457	Tetrahydroalstonine	KCNH2
Shanzhuyu	MOL008457	Tetrahydroalstonine	CHRM1
Shanzhuyu	MOL008457	Tetrahydroalstonine	AR
Shanzhuyu	MOL008457	Tetrahydroalstonine	SCN5A
Shanzhuyu	MOL008457	Tetrahydroalstonine	PPARG
Shanzhuyu	MOL008457	Tetrahydroalstonine	CHRM5
Shanzhuyu	MOL008457	Tetrahydroalstonine	PTGS2
Shanzhuyu	MOL008457	Tetrahydroalstonine	ADRA2C
Shanzhuyu	MOL008457	Tetrahydroalstonine	CHRM4
Shanzhuyu	MOL008457	Tetrahydroalstonine	OPRD1
Shanzhuyu	MOL008457	Tetrahydroalstonine	ACHE
Shanzhuyu	MOL008457	Tetrahydroalstonine	ADRA1B
Shanzhuyu	MOL008457	Tetrahydroalstonine	ADRB2
Shanzhuyu	MOL008457	Tetrahydroalstonine	ADRA1D
Shanzhuyu	MOL008457	Tetrahydroalstonine	SLC6A4
Shanzhuyu	MOL008457	Tetrahydroalstonine	OPRM1
Shanzhuyu	MOL008457	Tetrahydroalstonine	DPP4
Shanzhuyu	MOL008457	Tetrahydroalstonine	HSP90AB1
Shanzhuyu	MOL008457	Tetrahydroalstonine	PRSS1
Shanzhuyu	MOL008457	Tetrahydroalstonine	CAMKMT
Shudihuang	MOL000359	Sitosterol	PGR
Shudihuang	MOL000359	Sitosterol	NCOA2
Shudihuang	MOL000359	Sitosterol	NR3C2
Shudihuang	MOL000449	Stigmasterol	PGR
Shudihuang	MOL000449	Stigmasterol	NR3C2
Shudihuang	MOL000449	Stigmasterol	NCOA2
Shudihuang	MOL000449	Stigmasterol	ADH1C
Shudihuang	MOL000449	Stigmasterol	IGHG1
Shudihuang	MOL000449	Stigmasterol	RXRA
Shudihuang	MOL000449	Stigmasterol	NCOA1
Shudihuang	MOL000449	Stigmasterol	PTGS1
Shudihuang	MOL000449	Stigmasterol	PTGS2
Shudihuang	MOL000449	Stigmasterol	ADRA2A
Shudihuang	MOL000449	Stigmasterol	SLC6A2
Shudihuang	MOL000449	Stigmasterol	SLC6A3
Shudihuang	MOL000449	Stigmasterol	ADRB2
Shudihuang	MOL000449	Stigmasterol	AKR1B1
Shudihuang	MOL000449	Stigmasterol	PLAU
Shudihuang	MOL000449	Stigmasterol	LTA4H
Shudihuang	MOL000449	Stigmasterol	MAOB

(*Continued*)

Table 1 (Continued).

Drug	MolId	MolName	Symbol
Shudihuang	MOL000449	Stigmasterol	MAOA
Shudihuang	MOL000449	Stigmasterol	CTRB1
Shudihuang	MOL000449	Stigmasterol	CHRM3
Shudihuang	MOL000449	Stigmasterol	CHRM1
Shudihuang	MOL000449	Stigmasterol	ADRB1
Shudihuang	MOL000449	Stigmasterol	SCN5A
Shudihuang	MOL000449	Stigmasterol	ADRA1A
Shudihuang	MOL000449	Stigmasterol	CHRM2
Shudihuang	MOL000449	Stigmasterol	ADRA1B
Shudihuang	MOL000449	Stigmasterol	GABRA1

text-mining, experiments, databases, co-expression, neighborhood, gene fusion, and co-occurrence, with the minimum required interaction score set as "medium confidence" (0.400). We imported the PPI into Cytoscape3.9.1 for further analysis and visualization (Figure 3A). After the first filtring through CytoNCA, 20 targets were identified (Figure 3B). After two filters, we identified numerous crucial targets within the network: AKT1, JUN, VEGFA, HIF1A, TP53, EGF, and PTGS2 (Figure 3C). According to the SEZW-AGA interaction network, quercetin (MOL000098), luteolin (MOL000006), and kaempferol (MOL000422) exhibited the highest degrees of interaction with 59 targets and acted on 45, 27, and 21 targets, respectively (Figure 4). Additionally, the OB values of quercetin, luteolin, and kaempferol were 46.43%, 36.16%, and 41.88%, respectively. Together, these findings suggest that quercetin, luteolin, and kaempferol are the primary active compounds in SEZW.

GO and KEGG Enrichment Analyses

GO and KEGG enrichment analyses were conducted, and 1298 BP, 28 CC, 91 MF, and 123 KEGG pathway terms were found to be enriched based on an adjusted P value <0.05. The top 10 terms in each category are listed in Table 2. From these enrichment results, the top five terms of each GO term and the top 10 KEGG pathways were chosen for visualization (Figure 5).

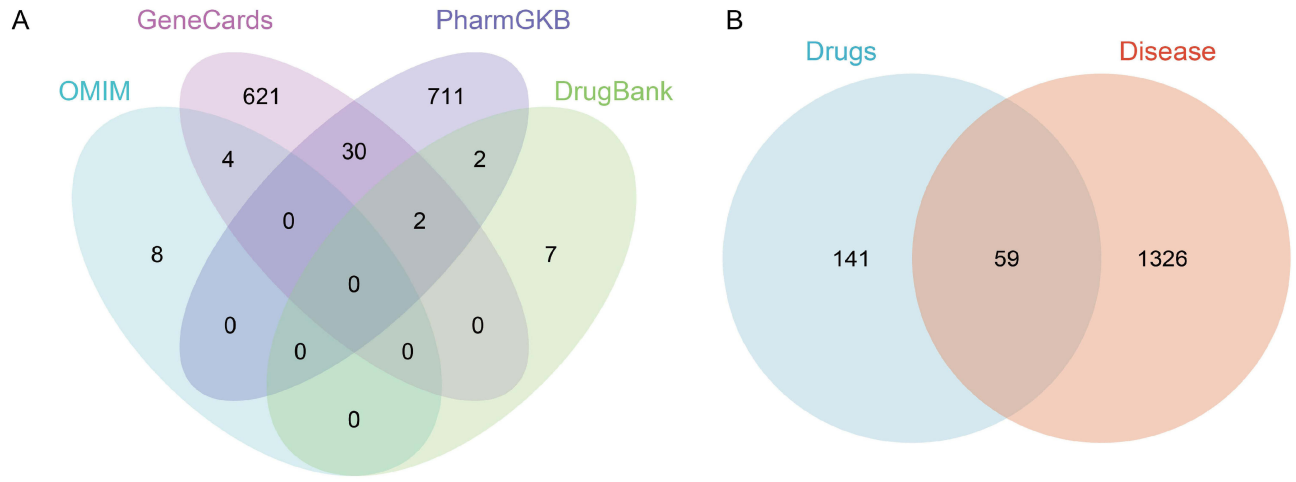

Figure 2 Venn diagram. (**A**) Venn diagram showing the AGA-related genes from the GeneCards, OMIM, DrugBank, and PharmGKB databases. (**B**) Venn diagram showing the targets of the active compounds in Drugs and Disease.
Abbreviation: AGA, androgenetic alopecia.

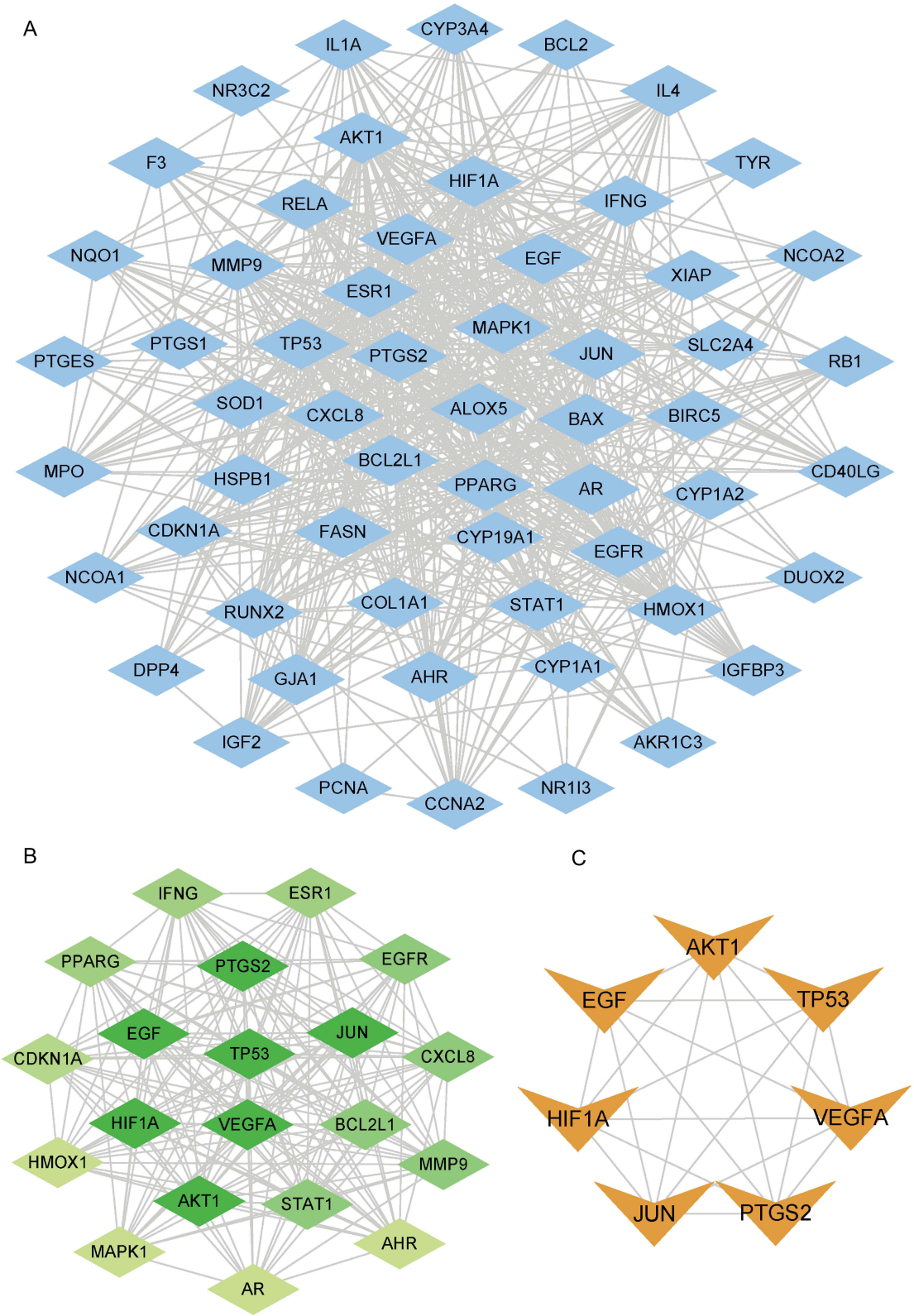

Figure 3 PPI network including the 59 hub genes and identified hub targets. (**A**) 59 SEZW-AGA common targets were identified. (**B**) After the first filtering through CytoNCA, 20 targets were identified. The darker the color, the greater the degree. (**C**) 7 hub targets were identified after a second filtering stage.
Abbreviations: PPI, protein-protein interaction; SEZW, Supplemented Erzhi Wan; AGA, androgenetic alopecia.

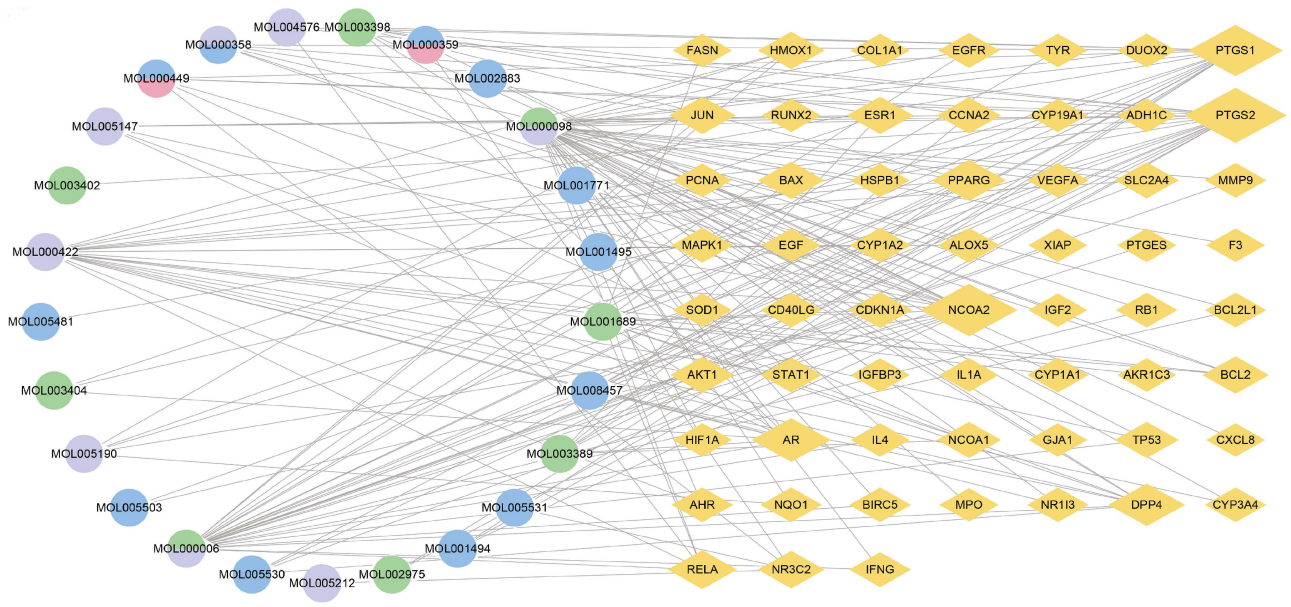

Figure 4 SEZW-AGA network. Circles represent the active compounds in SEZW and diamonds represent the SEZW-AGA common targets. Purple, green, blue, and pink represent the target compounds of FLL, EH, CO, and RRP, respectively.
Abbreviations: SEZW, Supplemented Erzhi Wan; AGA, androgenetic alopecia; FLL, Fructus Ligustri Lucidi; EH, Ecliptae Herba; CO, Cornus Officinalis; RRP, Rehmanniae Radix Praeparata.

Molecular Docking Technology

We selected candidate hub targets (AKT1, JUN, VEGFA, HIF1A, TP53, EGF, and PTGS2) as protein receptors and the three major active compounds (quercetin, luteolin, and kaempferol) as ligands for validation using molecular docking. A binding energy of less than −5 kcal/mol was used as the threshold for stable binding. In our study, all binding values were less than −6 kcal/mol, indicating a strong receptor-ligand affinity (Table 3). We selected the top nine stable receptor-ligand complexes for visualization (Figure 6).

Table 2 GO and KEGG enrichment analysis

ONTOLOGY	ID	Description	GeneRatio	p.Adjust
BP	GO:0006979	Response to oxidative stress	23/59	2.40052E-19
BP	GO:0000302	Response to reactive oxygen species	17/59	5.1564E-17
BP	GO:0048732	Gland development	21/59	5.22157E-17
BP	GO:0062197	Cellular response to chemical stress	19/59	1.60471E-16
BP	GO:0034599	Cellular response to oxidative stress	17/59	6.38749E-15
BP	GO:0048608	Reproductive structure development	19/59	1.48981E-14
BP	GO:0061458	Reproductive system development	19/59	1.48981E-14
BP	GO:0031667	Response to nutrient levels	18/59	3.94683E-13
BP	GO:0071276	Cellular response to cadmium ion	9/59	5.95164E-13
BP	GO:0046686	Response to cadmium ion	10/59	6.8524E-13
CC	GO:0005667	Transcription regulator complex	12/59	3.02528E-06
CC	GO:0045121	Membrane raft	7/59	0.00231201
CC	GO:0031983	Vesicle lumen	7/59	0.00231201
CC	GO:0098857	Membrane microdomain	7/59	0.00231201
CC	GO:0090575	rna polymerase II transcription regulator complex	6/59	0.00231201
CC	GO:0005641	Nuclear envelope lumen	2/59	0.008467042
CC	GO:0034774	Secretory granule lumen	6/59	0.008467042

(*Continued*)

Table 2 (Continued).

ONTOLOGY	ID	Description	GeneRatio	p.Adjust
CC	GO:0060205	Cytoplasmic vesicle lumen	6/59	0.008467042
CC	GO:0000307	Cyclin-dependent protein kinase holoenzyme complex	3/59	0.008467042
CC	GO:0005635	Nuclear envelope	7/59	0.0099996
MF	GO:0140297	Dna-binding transcription factor binding	16/59	3.05538E-10
MF	GO:0061629	Rna polymerase II-specific DNA-binding transcription factor binding	14/59	5.3385E-10
MF	GO:0020037	Heme binding	9/59	5.63989E-08
MF	GO:0046906	Tetrapyrrole binding	9/59	7.85358E-08
MF	GO:0001223	Transcription coactivator binding	6/59	1.77756E-07
MF	GO:0016705	Oxidoreductase activity, acting on paired donors, with incorporation or reduction of molecular oxygen	9/59	2.39541E-07
MF	GO:0016209	Antioxidant activity	7/59	4.21581E-07
MF	GO:0004879	Nuclear receptor activity	6/59	4.5763E-07
MF	GO:0098531	Ligand-activated transcription factor activity	6/59	4.5763E-07
MF	GO:0140296	General transcription initiation factor binding	6/59	4.5763E-07
KEGG	hsa05207	CHEMICAL carcinogenesis - receptor activation	18/59	7.77054E-13
KEGG	hsa05212	Pancreatic cancer	12/59	1.48736E-11
KEGG	hsa05161	Hepatitis B	15/59	2.07722E-11
KEGG	hsa04933	Age-RAGE signaling pathway in diabetic complications	12/59	2.21369E-10
KEGG	hsa05219	Bladder cancer	9/59	3.65377E-10
KEGG	hsa05208	Chemical carcinogenesis - reactive oxygen species	15/59	1.10354E-09
KEGG	hsa05215	Prostate cancer	11/59	2.00325E-09
KEGG	hsa01522	Endocrine resistance	11/59	2.00325E-09
KEGG	hsa04066	HIF-1 signaling pathway	11/59	5.74334E-09
KEGG	hsa05210	Colorectal cancer	10/59	8.90401E-09

Discussion

Network pharmacology is a new drug design strategy based on rapid systems biology and multidirectional pharmacology developments. Nogales[15] argued that diseases are currently diagnosed by phenotypes aimed at alleviating symptoms rather than by mechanisms and treatments, which often only have minimal transient effects. The approach to drug development has changed with the rise of network pharmacological research. Instead of focusing on a single symptom and target, we used a disease-multitarget-multidrug model. This involves the use of two or more drugs to synergistically target key network proteins, thereby addressing the underlying disease at the root cause. The "treatment based on syndrome differentiation" approach in TCM involves combining various drugs to target the underlying nature of pathological changes; therefore, aligns with the drug-multitarget-multidrug model in network pharmacological research.

Thus, network pharmacology is a valid method to analyze the mechanism of action of SEZW in the treatment of AGA. This treatment strategy is characteristic of the TCM "treatment based on syndrome differentiation" approach, which uses TCM theory to analyze relevant clinical data, clarify the essentiality of diseases, and identify the 'syndrome", which can reflect the combination of the cause, location, nature of the disease, and its tendency to develop and change. From this, treatment rules, methods, and prescriptions are formulated.

In this study, we obtained 200 SEZW targets from the TCMSP database and 1385 AGA-associated genes from the GeneCards, OMIM, DrugBank, PharmGKB, and TTD databases. Then, 59 candidate SEZW-AGA targets were identified at the intersection of these lists. The above results were imported into the STRING tool, and a PPI network was constructed with 59 nodes and 592 edges. In addition, we identified seven potential hub targets: AKT1, JUN, VEGFA, HIF1A, TP53, EGF, and PTGS2. Some of these genes have been investigated previously for their relevance in hair growth. For example, VEGFA (vascularization endothelial growth factor A) has been shown to regulate vascularization and vessel size around the hair follicle, thus altering the size of follicles as blood vessels are required to provide

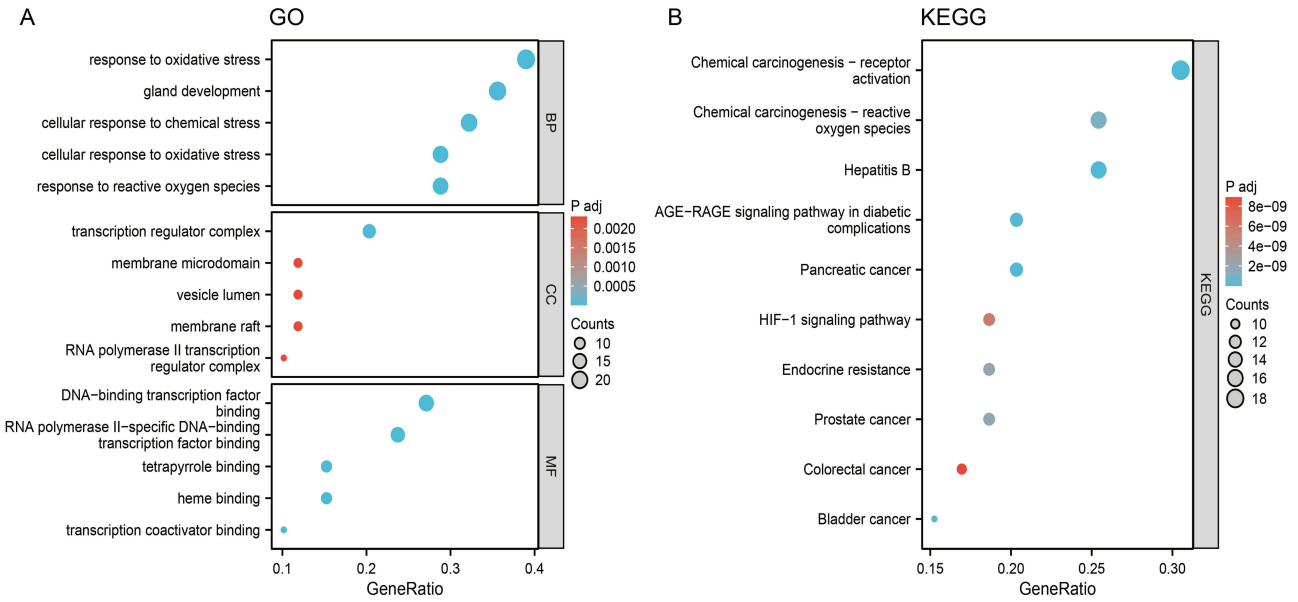

Figure 5 Results from GO and KEGG enrichment analyses. (**A**) Top 5 significant GO enrichment terms in the BP, CC, and MF categories across the 59 common targets. (**B**) Top 10 KEGG enrichment pathways across the 59 common targets.
Abbreviations: GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; BP, biological process; CC, cellular component; MF, molecular function.

nutrients.[13] In addition, Gaofeng Wang et al[16] found that activation of HIF1A signaling by inducing tissue hypoxia promoted wound-induced hair follicle neogenesis.

Quercetin, luteolin, and kaempferol were identified as the major active compounds in SEZW. They are flavonoids that can be identified in EZW through mass spectrometry.[17] Quercetin has previously been shown to stimulate melanogenesis in mice hair follicle melanocytes and promote hair shaft growth in cultured human hair follicles.[18,19]

Subsequently, GO and KEGG enrichment analyses were performed on the 59 candidate targets. These targets were mainly enriched for processes involving the response to oxidative stress, reactive oxygen species, gland development, cellular response to chemical stress, and cellular response to oxidative stress. Among these, oxidative stress, defined as the excess of reactive oxygen species relative to antioxidants, has been linked to neurodegenerative diseases, cardiovascular diseases, diabetes mellitus, and many other pathologies.[20] Studies have shown a close relationship between oxidative stress and AGA. For example, Bahta et al[21] found that the premature senescence of balding dermal papilla cells in vitro is associated with the expression of oxidative stress and DNA damage markers. Upton et al[22] further investigated the role of oxidative stress in the pathogenesis of AGA in relation to cell senescence, migration, and the secretion of hair follicle inhibitory factors. Moreover, AGA patients have shown increased oxidative stress in vivo.[23,24] However, few drugs used to treat AGA target the pathological mechanisms of oxidative stress, and those that do require further validation. EZW has been demonstrated to inhibit oxidative stress and regulate metabolism in a diabetic cardiomyopathy-related study.[25] Therefore, we hypothesized that the mechanism of action of SEZW in treating AGA may be related to oxidative stress. Experimental research is needed to investigate this further.

Table 3 The molecular docking of the active compounds to the core targets

Active Compound	Docking Score (kcal/mol)						
	AKT1	JUN	VEGFA	HIF1A	TP53	EGF	PTGS2
Quercetin	-8.1	-9.5	-7	-7.6	-7.2	-7.9	-9.2
Luteolin	-7.9	-8.2	-6.9	-	-7.3	-	-10
Kaempferol	-7.6	-8.1	–	-	-	-	-9.2

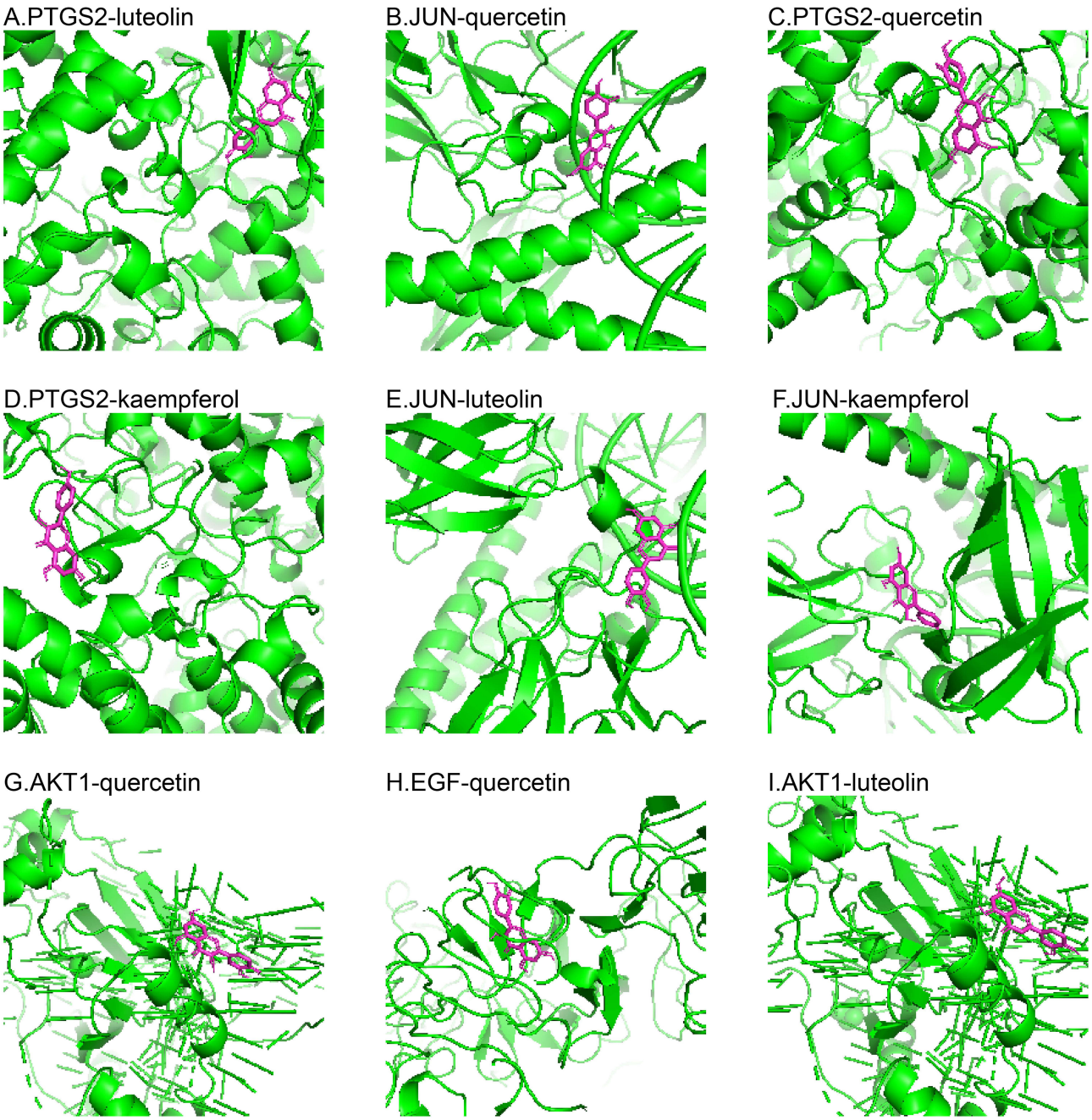

Figure 6 Results of molecular docking of active compounds and hub targets. Complexes are arranged from the lowest to the highest binding energy score: (**A**) PTGS2-luteolin. (**B**) JUN-quercetin. (**C**) PTGS2-quercetin. (**D**) PTGS2-kaempferol. (**E**) JUN-luteolin. (**F**) JUN-kaempferol. (**G**) AKT1-quercetin. (**H**) EGF-quercetin. (**I**) AKT1-luteolin.

The KEGG enrichment analysis identified 123 significantly enriched pathways, including the PI3K-Akt signaling pathway. Akt, which was previously identified as a hub target, is also a key downstream molecule in the PI3k/Akt signaling pathway. This pathway has a significant impact on cancer and neurological, metabolic, and cardiovascular diseases, among others.[26–29] Through activation or inhibition of downstream proteins, PI3K/Akt regulates signal transduction and is involved in numerous biological processes, such as cell proliferation, migration, differentiation, apoptosis, and metabolism.[30] Research by Yu Chen[31] has shown that the PI3K-Akt signaling pathway plays a crucial role in de novo hair follicle regeneration. This provides further theoretical support for exploring the possible involvement of the PI3K/AKT signaling pathway in the pathological process of AGA.

Our study has some limitations. We have demonstrated the promotion of hair growth by SEZW in AGA-model mice; however, large-scale clinical studies need to be conducted to confirm these results.

Conclusion

SEZW promoted hair growth in mice with AGA. Based on network pharmacology, we identified the possible mechanisms of action of SEZW in the treatment of AGA, finding that the response to oxidative stress, gland development, and chemical stress are critical targets. Further, the PI3K/Akt and AGE-RAGE signaling pathways were identified as potential signaling pathways through which SEZW exerts its therapeutic effects. AKT1, JUN, VEGFA, HIF1A, TP53, EGF, and PTGS2 were identified as hub molecules for the efficacy of SEZW in AGA treatment.

Abbreviations

AGA, androgenetic alopecia; BP, biological process; CC, cellular component; CO, Cornus officinalis; DL, drug-like properties; EH, Ecliptae Herba; FDA, the United States Food and Drug Administration; FLL, Fructus Ligustri Lucidi; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; MF, molecular function; OB, oral bioavailability; PDB, Protein Data Bank; PPI, Protein-Protein Interaction; RRP, Rehmanniae Radix Praeparata; SEZW, Supplemented Erzhi Wan; SEZW-H, SEZW high dose; SEZW-L, SEZW low dose; TCM, Traditional Chinese Medicine; TCMSP, Traditional Chinese Medicine Database and Analysis Platform.

Data Sharing Statement

All relevant data are contained within the article.

Ethics Approval

The network pharmacological analysis was approved by the Ethics Committee of the Affiliated Zhangjiagang Hospital of Soochow University. The experiments were approved by the Animal Ethics Committee of Zhangjiagang TCM Hospital Affiliated to Nanjing University of Chinese Medicine according to guidelines for the ethical review of laboratory animal welfare People's Republic of China National Standard GB/T 35892-2018.

Acknowledgments

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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