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Research Article

Exploring the Mechanism of Antioxidant Action of Bitter Almond Based on Network Pharmacology and Molecular Docking Techniques

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Objective. A network pharmacology approach was used to investigate the main active ingredients, key targets, and mechanisms of action of bitter almond antioxidants, and preliminary validation of the relevant targets was performed using molecular docking techniques. *Methods*. The active ingredients of bitter almond were obtained through the traditional Chinese medicine systematic pharmacology database and analysis platform (TCMSP), and the main active ingredients were screened by bioavailability (OB) and drug-like properties (DL); the GeneCards database was used to search antioxidant-related disease targets through the traditional Chinese medicine systematic pharmacology database and analysis; building a "drug-disease-target" visual network map with Cytoscape 3.9.0 software; a protein interaction (PPI) network was constructed using STRING website and core targets were screened; GO function and KEGG pathway enrichment analysis were obtained using Metoscape. Finally, SailVina software was used to molecularly dock the major active ingredients and target proteins and visualize them using PyMOL software. *Results*. A total of 19 antioxidant active ingredients were obtained for bitter almond, mainly stigmasterol, glycyrol, and estrone. The targets regulated by their main active ingredients were intersected with oxidative targets, and 53 intersected targets were obtained by Venn diagram, with key targets involving NR3C2, NCOA2, MAOA, ADRA2A, and CHRM1; GO analysis yielded 3616 GO entries, including 2821 biological process (BP) entries, 316 cellular component (CC) entries, and 479 molecular function (MF) entries, and 184 signalling pathways were obtained from KEGG pathway enrichment screening. The molecular docking results showed that Stigmasterol-NR3C2 binding was better. *Conclusion*. Stigmasterol, glycyrol, estrone, and licochalcone B in bitter almond may be the material basis of antioxidant and have better antioxidant activity; therefore, bitter almond has the characteristics of multicomponent, multitarget and multipathway.

1. Introduction

Antioxidant is the abbreviation for antioxidant-free radicals [1]. When the human body is in contact with the outside world, influenced by its own respiration (oxidation) and external environmental factors, the body will constantly produce free radicals. Generally speaking, the number of free radicals in the human body is in a dynamic process of growth and decline, which will not cause harm to the human body, but when the balance is broken, a large number of free radicals will oxidize and damage the body's cells, thus causing various diseases, atherosclerosis, diabetes, rheumatoid arthritis, cancer, the aging process, and other diseases are closely related to the occurrence of free radicals [2]. More and more studies show that antioxidants are an important step in preventing aging, because free radicals or oxidants break down cells and tissues, affect metabolic functions, and can cause different health problems. Studies prove that the antioxidant system of the human body is a system with perfect and complex functions comparable to the immune system, and the stronger the body's antioxidant capacity, the healthier it is and the longer it lives [3]. Antioxidants are used to slow down the development of ageing and some chronic diseases by protecting the body's cells

from damage, bitter almonds are an excellent source of vitamin E, one of the most effective natural antioxidants.

Bitter almonds have a long history of use in medicine and are a common herb of medicinal and food origin, and have been recorded in the Materia Medica for generations. 2020 edition of the ≪Pharmacopoeia of the People's Republic of China ≫stipulates that the source of bitter almonds is Prunusarmeniacavar.ansu, Siberian apricot *P. sibirica*, Northeastern apricot *P. mandshurica,* or apricot *P. armeniaca* of the *Rosaceae* family *armeniaca* [4, 5]. Bitter amygdalin is the main efficacy component of bitter almond, with antioxidant, antibacterial, anti-inflammatory, immunomodulatory activities, and antitumour activity [6, 7]. Some studies have reported that bitter amygdalin has antitumour effects on solid tumours such as lung cancer, bladder cancer, and kidney cancer, and each species of almond has different strengths of reducing ability, all of which can participate in the reduction reaction of target sites and effectively scavenging site free radicals [8, 9].

Network pharmacology has emerged worldwide in recent years. It is based on the theories of systems biology, genomics, proteomics, and other disciplines to reveal the network relationship of drug-gene-target-disease interactions and predict the mechanism of action of drugs through the network relationship [10, 11]. In the modernization process of TCM, some researchers have made good preliminary results in exploring the essential properties of TCM by referring to the research ideas of network pharmacology and revealing the comprehensive overall effects of TCM with multiple pathways, multiple targets, and multiple components [12, 13]. In this study, network pharmacology was adopted to study the antioxidant multitarget and multipathway action characteristics of bitter almond and to explore the active substance basis and action mechanism of antioxidant action of bitter almond, so as to provide theoretical basis for further research on bitter almond.

2. Methods of Analysis

2.1. Screening of Bitter Almond for Active Ingredients and Targets of Action. The TCMSP database platform [14] (https://tcmsp-e.com/) was used to retrieve data related to the active ingredients in bitter almond, and important parameters affecting the absorption, distribution, metabolism, and excretion processes, such as oral bioavailability (OB) and drug-like properties (DL), were used as screening conditions. Set oral bioavailability (OB) ≥ 30% and drug-like properties (DL) ≥ 0.18 to obtain active ingredients with the required parameter specifications [15]. The active ingredients that met the requirements were entered into the TCMSP database platform and their properties were set to "*homosapiens*" to obtain the corresponding targets of each active ingredient.

2.2. Screening for Antioxidant Targets. Disease targets related to oxidation and antioxidant were searched through the Genecards database platform [16] (https://www.genecards.org/), duplicate genes were removed and targets with a correlation coefficient >1 were screened from them. Bitter almond antioxidant disease targets were retrieved by entering the genes acting in bitter almond in the STRING (https://string-db.org) database. Using the Venny platform (https://bioinfogp.cnb.csic.es/tools.venny/), the intersection of bitter almond active ingredient targets and antioxidant-related targets was used to obtain a Venn diagram of the intersection of bitter almond antioxidant targets.

2.3. Bitter Almond-Component-Target-Antioxidant Network Construction. The bitter almond-component-target-antioxidant network was constructed by Cytoscape 3.9.0 software based on the main active ingredients of bitter almond and the intersection targets of oxidation and antioxidation as nodes [17]. Network topology analysis was constructed to show that the active ingredient and most of the targets have more interactions in the effect map to visualize the relationship between drug ingredients and disease targets.

2.4. Protein Interaction (PPI) Network Construction. The potential targets of bitter almond antioxidant were entered in STRING (https://string-db.org), and the condition "minimum required interaction score = 0.4" was set to obtain the protein interaction information, and the PPI was plotted using Cytoscape 3.9.0 software. The core targets were selected according to the node degree value [18].

2.5. Target Enrichment Analysis and Visualisation. The intersection targets of bitter almond and antioxidant were entered in Metascape (https://metascape.org), to do GO analysis and KEGG analysis, to understand the biological processes and pathways related to antioxidant, and carry out visual analysis [19].

2.6. Molecular Docking. The key active ingredient of bitter almond was used as ligand in PubChem database (https://pubchem.ncbi.nlm.nih.gov/) and the target protein with the top degree value in the protein interaction network was identified as receptor by RDB database (https://www.rcsb.org/) and SailVina software was used for Molecular docking [20].

3. Results and Analysis

3.1. Main Active Ingredients of Bitter Almonds. The TCMSP database was searched for 113 active ingredients of bitter almond, and the screening conditions of oral bioavailability (OB) ≥ 30% and drug-like properties (DL) ≥ 0.18 were used to obtain 19 active ingredients that met the conditions, and the results are shown in Table 1.

3.2. Bitter Almond-Antioxidant Intersectional Target Acquisition. A search of the Genecards database using "oxidation/antioxidant" as a keyword identified 3553 potential targets [21]. Using the Venny platform (https://bioinfogp.cnb.csic.es/tools.venny/), a total of 53 common

Table 1: Table of the main active ingredients of bitter almonds.

No	ID	Active ingredient	OB (%)	DL (%)
1	MOL010921	Estrone	53.56	0.32
2	MOL010922	Diisooctyl succinate	31.62	0.23
3	MOL002211	11,14-Eicosadienoic acid	39.99	0.2
4	MOL002372	(6Z,10E,14E,18E)-2,6,10,15,19,23-hexamethyltetracosa-2,6,10,14,18,22-hexaene	33.55	0.42
5	MOL000359	Sitosterol	36.91	0.75
6	MOL000449	Stigmasterol	43.83	0.76
7	MOL005030	Gondoic acid	30.7	0.2
8	MOL000953	CLR	37.87	0.68
9	MOL000211	Mairin	55.38	0.78
10	MOL000492	(+)-catechin	54.83	0.24
11	MOL002311	Glycyrol	90.78	0.67
12	MOL003410	Ziziphin_qt	66.95	0.62
13	MOL004355	Spinasterol	42.98	0.76
14	MOL004841	Licochalcone B	76.76	0.19
15	MOL004903	Liquiritin	65.69	0.74
16	MOL004908	Glabridin	53.25	0.47
17	MOL005017	Phaseol	78.77	0.58
18	MOL007207	Machiline	79.64	0.24
19	MOL012922	l-SPD	87.35	0.54

targets were obtained by mapping Venn diagrams based on drug active ingredient targets and antioxidant targets; that is, a potential target for antioxidant intervention by bitter almonds. The results are shown in Figure 1.

3.3. Bitter Almond-Component-Target-Antioxidant Network Construction. The main active ingredients and potential targets for antioxidant intervention obtained from bitter almond screening were imported into Cytoscape 3.9.0 software. The composition-target-antioxidant network map of bitter almond was constructed. The results are shown in Figure 2. The bitter almond-component-target-antioxidant network was constructed by Cytoscape 3.9.0 software. The results of network topology analysis showed that the active ingredients and most of the targets had more interactions, among which the top 5 active ingredients in terms of Degree were MOL000449, MOL002311, MOL010921, MOL000492, and MOL004841, reflecting that these ingredients were the main active ingredients in the antioxidant effect of bitter almond. The top five targets were NR3C2, NCOA2, MAOA, ADRA2A, and CHRM1, indicating that bitter almond exerts antioxidant effects through a multicomponent, multitarget, and multipathway synergistic mechanism [22].

3.4. PPI Network Construction and Topology Analysis. The 53 common targets obtained from bitter almond and antioxidant were imported into the STRING data platform to construct a protein interaction PPI network model, and then the obtained PPI network result information was imported into Cytoscape 3.9.0 software for visual analysis, and the results are shown in Figure 3. Note: the node size and colour shade reflect the degree value, the darker the colour indicates that the number of proteins a protein has interaction with is higher [23]. The top ten key target proteins were filtered according to the degree value, and the results are shown in Table 2.

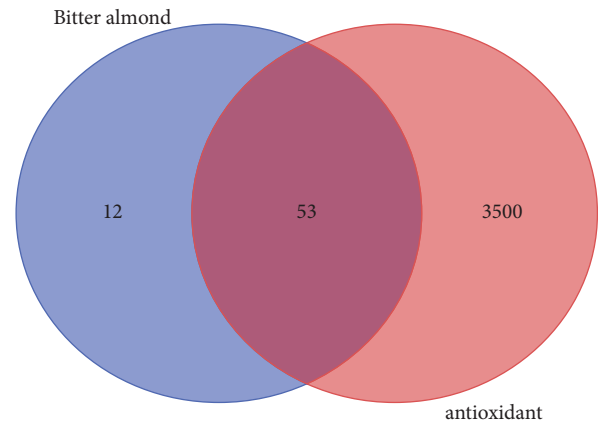


Figure 1: Venn diagram of bitter almond and antioxidant targets.

3.5. GO Enrichment Analysis Results. After importing 53 potential targets of bitter almond intervention against antioxidants into the Metoscape database, GO (Geneontology) functional analysis was performed using the Microlife Letter platform, and GO analysis showed that 53 drug-disease intersection targets yielded 3616 entries. 20 biological processes, 15 molecular functions and 11 cellular compositions were affected. The 10 most significant data from each of the three were selected to plot the GO functional analysis (see Figure 4) [24]. Biological processes include mainly: cellular response to organic cyclic compound, blood circulation, response to hormone, regulation of system process, regulation of ion transport, and so on. From the cell composition it can be assumed that these targets are mainly concentrated in integral component of presynaptic membrane, membrane raft, receptor complex, transcription regulatorcomplex, and so on. Molecular functions are mainly focused on protein domain specific binding, G protein-coupled amine receptor activity, neurotransmitter receptor activity, oxidoreductase activity,

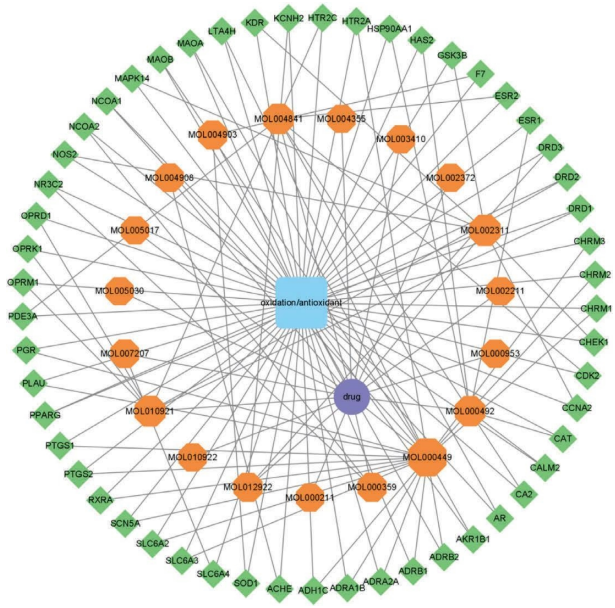


Figure 2: Network of active ingredients and potential targets for antioxidant intervention in bitter almonds. Note: blue indicates disease; purple indicates drug; orange indicates bitter almond active ingredient; and green indicates predicted target.

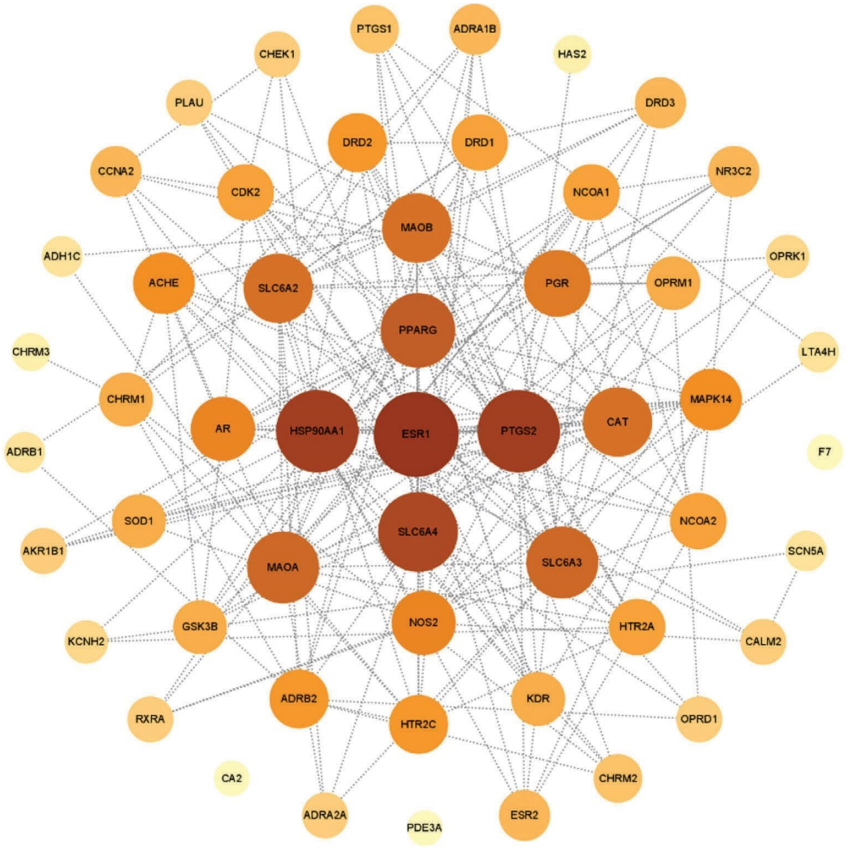


Figure 3: Bitter almond antioxidant intersectional target interaction network.

and so on. Thus, bitter almonds may intervene as antioxidants by acting as inhibitors of oxidation through cellular responses to organic cyclic compounds, blood circulation, and responses to hormones. The top GO entries were listed according to count value size and the results are shown in Figure 4 and Table 3.

Table 2: Key targets of the bitter almond antioxidant PPI network.

NO	Target	Degree
1	ESR1	19
2	HSP90AA1	18
3	PTGS2	18
4	SLC6A4	17
5	PPARG	15
6	MAOA	14
7	SLC6A3	14
8	MAOB	13
9	CAT	13
10	SLC6A2	13

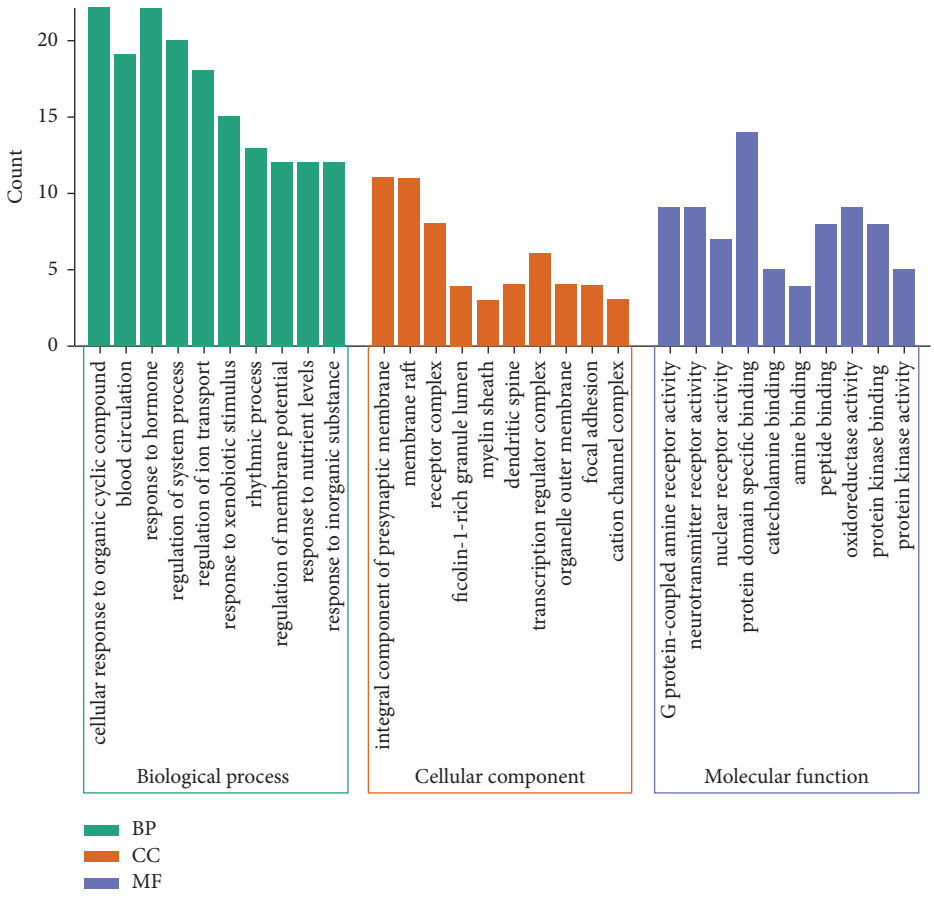


Figure 4: GO enrichment analysis graph.

3.6. KEGG Enrichment Analysis. KEGG pathway analysis yielded 184 pathways ($p < 0.05$) by entering drug-disease intersection targets into the Metoscape database, and 15 pathways were filtered from smallest to largest p value. The visual analysis was carried out using the Microlife Letter platform as shown in Figure 5 [25]. Based on the results of the enrichment analysis, the main pathways are Pathways in cancer, cAMP signaling pathway, Pathyways of neurodegeneration, and Prolactin signaling pathwayare closely related to the antioxidant mechanism of bitter almond.

3.7. Molecular Docking. The PDB database was used to find the antioxidant active ingredients of bitter almond MOL000359 (Stigmasterol), MOL002311 (Glycyrol), MOL010921 (estrone), and MOL000492 ((+)-catechin) and the target proteins NR3C2, NCOA2, MAOA, and the three-dimensional structures of the interactions of (1) Stigmasterol-NR3C2, (2) Glycyrol-NCOA2, (3) estrone-MAOA, and (4) (+)-catechin-ADRA2A. The MOL structural formulae of the compounds were downloaded and imported separately into SailVina software for molecular docking, OpenBabel software was used for conformational

Table 3: Information on GO enrichment analysis data.

GO	Subgroup	Count
Cellular response to organic cyclic compound	Biological processes	22
Blood circulation	Biological processes	19
Response to hormone	Biological processes	22
Regulation of system process	Biological processes	20
Regulation of ion transport	Biological processes	18
Response to xenobiotic stimulus	Biological processes	15
Rhythmic process	Biological processes	13
Regulation of membrane potential	Biological processes	12
Response to nutrient levels	Biological processes	12
Response to inorganic substance	Biological processes	12
Integral component of presynaptic membrane	Cellular components	11
Membrane raft	Cellular components	11
Receptor complex	Cellular components	8
Ficolin-1-rich granule lumen	Cellular components	4
Myelin sheath	Cellular components	3
Dendritic spine	Cellular components	4
Transcription regulator complex	Cellular components	6
Organelle outer membrane	Cellular components	4
Focal adhesion	Cellular components	4
Cation channel complex	Cellular components	3
G protein-coupled amine receptor activity	Molecular functions	9
Neurotransmitter receptor activity	Molecular functions	9
Nuclear receptor activity	Molecular functions	7
Protein domain specific binding	Molecular functions	14
Catecholamine binding	Molecular functions	5
Amine binding	Molecular functions	4
Peptide binding	Molecular functions	8
Oxidoreductase activity	Molecular functions	9
Protein kinase binding	Molecular functions	8
Protein kinase activity	Molecular functions	5

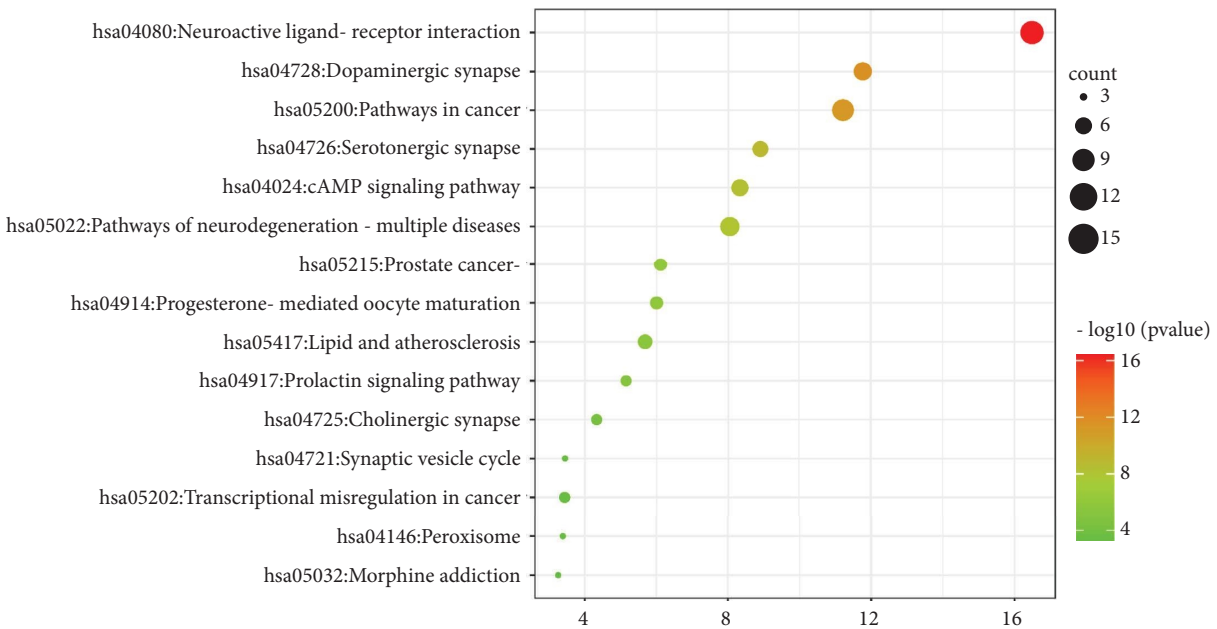
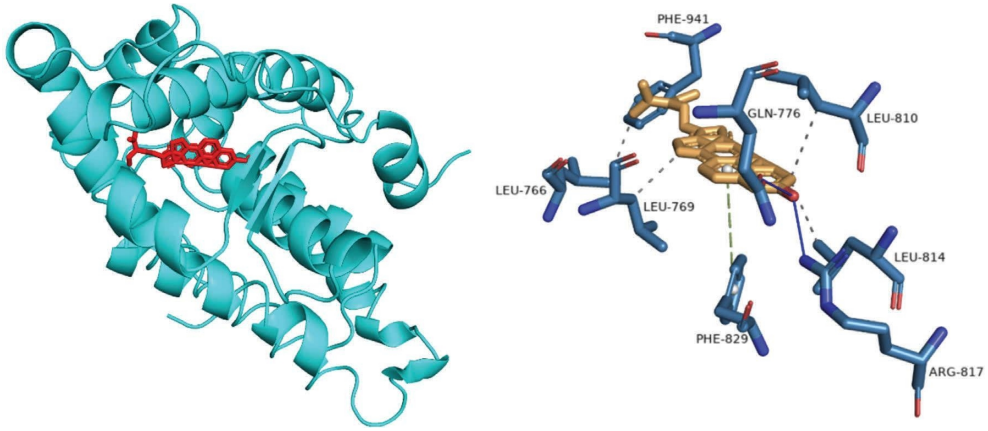


Figure 5: KEGG enrichment analysis graph.

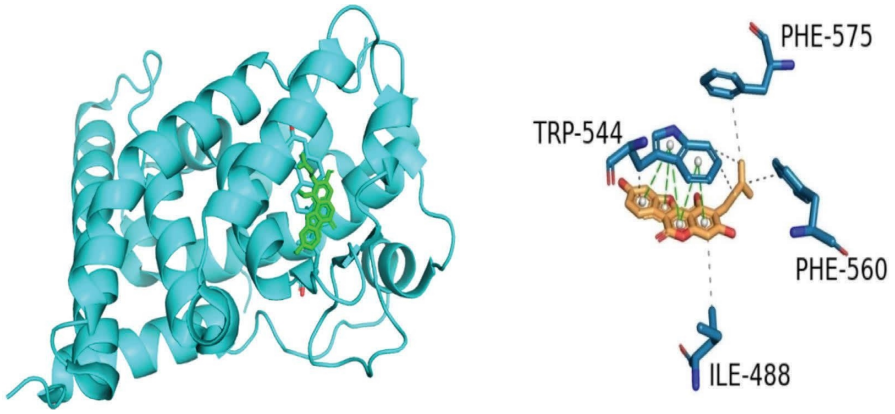
optimisation and PYMOL was used to process the small molecule files for virtual docking. The binding energy is less than 0 indicating that spontaneous binding between receptor and ligand is possible. The binding of the four key active ingredients of bitter almond to the target proteins was relatively stable. The results are shown in Table 4, the docking graphs and specific docking positions are shown in Figure 6.

Table 4: Molecular docking information.

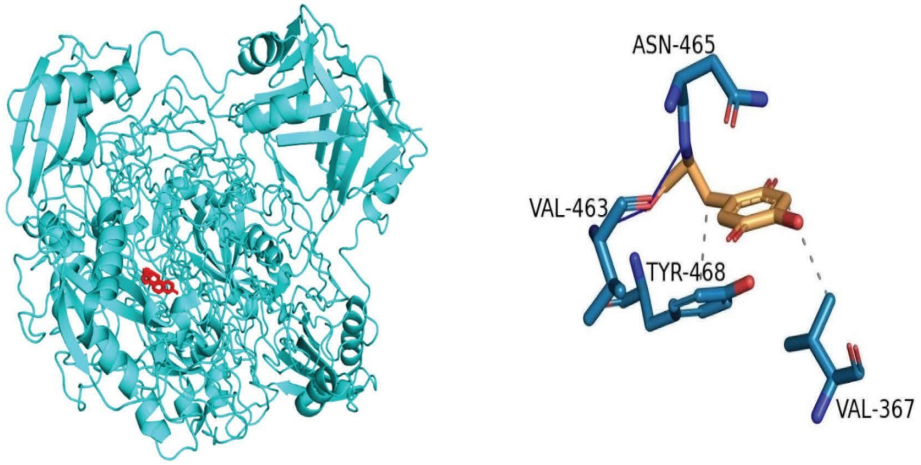
Target proteins	Chemical composition	Binding energy (kcal/mol)
NR3C2	Stigmasterol	−12
NCOA2	Glycyrol	−11.4
MAOA	Estrone	−11.2
ADRA2A	(+)-Catechin	−9.2



(a)

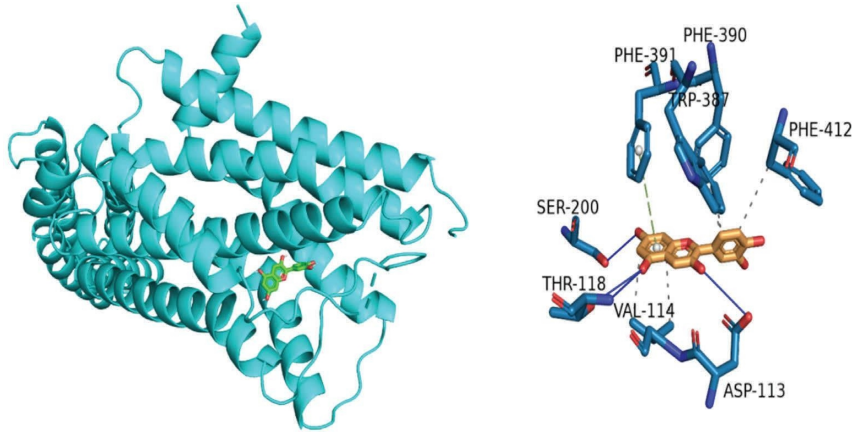


(b)



(c)

Figure 6: Continued.



(d)

Figure 6: Molecular docking results. (a) Stigmasterol-NR3C2. (b) Glycyol-NCOA2. (c) Estrone-MAOA. (d) (+)-Catechin-ADRA2A.

4. Result

A total of 19 kinds of antioxidant active components were obtained through data mining, mainly stigmasterols, glycyrrhizol, estrone, and so on. There were 53 overlapping targets of oxidation targets regulated by main active ingredients, and the key targets involved NR3C2, NCOA2, MAOA, ADRA2A, and CHRM1. GO analysis yielded 3616 GO pathways, including 2821 biological processes (BP), 316 cell components (CC), 479 molecular functions (MF), and 184 KEGG pathways. The results of molecular docking showed that the key target had good binding with the main active ingredients. These results indicated that stigmasterol, glycyrrhizol, and estrone had good antioxidant activity in bitter almond.

5. Discussion

Antioxidant refers to the abbreviation of antioxidant-free radicals. Free radicals are constantly produced in the human body due to continuous contact with the outside world, including respiration (oxidation reaction), external pollution, radiation exposure, and other factors. Scientific studies have shown that excess free radical production is associated with cancer, aging, and other diseases. This study investigated the antioxidant mechanism of action of bitter almond by means of network pharmacology. From the "bitter almond-component-target-antioxidant" network diagram, it can be seen that compounds such as Stigmasterol, Glycyrol, estrone, (+)-catechin, and LicochalconeB are important nodes in the network, and it is assumed that these compounds may be the antioxidant substance base. The PPI network of bitter almond and antioxidant crossover targets showed that NR3C2, NCOA2, MAOA, ADRA2A, and CHRM1 interacted with several compounds with high degree values and played key roles in the network diagram, suggesting that they may be key targets for antioxidants. Significantly enriched according to the GO enrichment analysis function in cellular response to organic cyclic compound, blood circulation, response to hormone, regulation of system process, and other biological processes. The results of KEGG pathway enrichment analysis showed better binding in Pathways in cancer. Molecular docking results showed that Stigmasterol-NR3C2, Glycyrol-NCOA2, estrone-MAOA, and (+)-catechin-ADRA2A bound better, providing a strong basis for the reliability of network pharmacology to predict targets. Liu et al. [26] studied the difference of antioxidant capacity of almond and almond peel polyphenols by using four antioxidant capacities of reducing power, OH, DPPH, and ABTS free radical scavenging and found that different varieties of bitter almond had different degrees of antioxidant capacity. Wang et al. [27] extracted bitter almond oil with bitter almond as raw material and studied the antioxidant effect of bitter almond with total phenolic content, DPPH free radical scavenging ability and reducing ability as factors. The results showed that bitter almond oil had certain antioxidant effect. Li [28] investigated the antioxidant activity of almond extract from prunus chinensis with DPPH, ABTS scavenging capacity, and total reducing capacity, and the results showed that almond extract from Prunus chinensis had antioxidant capacity. Chen [29] obtained through T-AOC experiment that glycyrrhizin A not only has antioxidant activity in vitro, but also has strong antioxidant capacity in cells. Therefore, the study showed that the extract of bitter almond had better antioxidant effect.

In this study, the active constituents of bitter almond and its multitarget and multipathway properties in the antioxidant process were investigated on the basis of network pharmacology, and the mechanism of antioxidant action of bitter almond was initially explained to provide reference for further in vitro and in vivo experimental validation of the antioxidant activity of bitter almond and the screening and evaluation of antioxidant drugs.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

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