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The mechanism of *Bai He Gu Jin Tang* against non-small cell lung cancer revealed by network pharmacology and molecular docking

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Abstract

Background: Non-small cell lung cancer (NSCLC) is a leading cause of cancer-related burden and deaths, thus effective treatment strategies with lower side effects for NSCLC are urgently needed. To systematically analyze the mechanism of Bai He Gu Jin Tang (BHGJT) against NSCLC by network pharmacology and molecular docking.

Methods: The active compounds of BHGJT were obtained by searching the Bioinformatics Analysis Tool for Molecular Mechanism of Traditional Chinese Medicine and Encyclopaedia of Traditional Chinese Medicine. Search tool for interactions of chemicals was used for acquiring the targets of BHGJT. The component-target network was mapped by Cytoscape. NSCLC-related genes were obtained by searching Genecards, DrugBank and Therapeutic Target Database. The protein-protein interaction network of intersection targets was established based on Search Tool for Recurring Instances of Neighboring Genes (STRING), and further, the therapeutic core targets were selected by topological parameters. The hub targets were transmitted to Database for Annotation, Visualization and Integrated Discovery for gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) analysis. Finally, AutoDock Vina and MglTools were employed for molecular docking validation.

Results: Two hundred fifty-six compounds and 237 putative targets of BHGJT-related active compounds as well as 1721potential targets of NSCLC were retrieved. Network analysis showed that 8 active compounds of BHGJT including kaempferol, quercetin, luteolin, isorhamnetin, beta-sitosterol, stigmasterol, mairin and liquiritigenin as well as 15 hub targets such as AKR1B10 and AKR1C2 contribute to the treatment of BHGJT against NSCLC. GO functional enrichment analysis shows that BHGJT could regulate many biological processes, such as apoptotic process. Three modules of the endocrine related pathways including the inflammation, hypoxia related pathways as well as the other cancer related pathways based on Kyoto Encyclopedia of Genes and Genomes pathway enrichment analysis might explain the biological mechanisms of BHGJT in treating BHGJT. The results of molecular docking verified that AKR1B10 and AKR1C2 had the strongest binding activity with the 8 key compounds of NSCLC.

Conclusion: Our study reveals the mechanism of BHGJT in treating NSCLC involving multiple components, multiple targets and multiple pathways. The present study laid an initial foundation for the subsequent research and clinical application of BHGJT and its active compounds against NSCLC.

Abbreviations: BHGJT = Bai He Gu Jin Tang, GO = gene ontology, KEGG = Kyoto encyclopedia of genes and genomes, NSCLC = non-small cell lung cancer, PPI = protein-protein interaction, STRING = search tool for recurring instances of neighboring genes.

Keywords: Bai He Gu Jin Tang, network pharmacology, non-small cell lung cancer, target prediction

1. Introduction

As one of the most frequently diagnosed malignancies, lung cancer caused an estimated 1.8 million deaths in 2020, whereas non-small cell lung cancer (NSCLC) accounts for 85% of the cases remains the most common subtype.[1,2] There are only a few limited and ineffective therapeutic options left for a majority of NSCLC patients diagnosed at late stages. The available treatments for NSCLC patients also could not get them rid of tumor relapse or develop drug resistance, highlighting the necessity for

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novel alternative approaches.[3] Therefore, effective treatment strategies with lower side effects for NSCLC are urgently needed in order to improve the quality of life of those patients.

Chinese medicine has shown its superior efficacy and reduced toxicity compared to conventional therapy in the treatment of NSCLC.[4] In this context, Bai He Gu Jin Tang (BHGJT) is one of the most commonly applied formulas for the treatment of lung cancer.[5,6] BHGJT is composed of 10 Chinese medicinal herbs: Radix Rehmanniae Praeparata (Shu Di Huang), Radix Rehmanniae (Sheng Di Huang), Radix Angelicae Sinensis (Dang Gui), Radix Paeoniae Alba (Bai Shao), Radix et Rhizoma Glycyrrhizae (Gan Cao), Radix Platycodonis (Jie Geng), Radix Scrophulariae (Xuan Shen), Bulbus Fritillariae Thunbergii (Beimu), Radix Ophiopogonis (Maidong), and Bulbus Lilii (Bai He). BHGJT is a representative formula for cough patients with Yin deficiency syndrome, characterized by cough with little sputum, hemoptysis, lean body, dry mouth, dry stool, a red tongue with a little coating and thin pulse. In the meanwhile, Yin deficiency syndrome was identified as the main syndrome in NSCLC patients through integrative proteomics and lipidomics analysis.[7] However, the molecular mechanisms involved in the NSCLC treatment with BHGJT are still elusive due to the complicated compounds of Chinese herbal medicines.

Network pharmacology is in accordance with the holistic concept of Chinese medicine theory, which could elucidate the multi-target, multi-faceted and comprehensive interactions between disease-associated genes and small ingredients in the formula. Molecular docking is a structure-based method that helps the prediction of the interaction between the chemical compounds and core targets.[8] In this work, we tried to explore the molecular mechanisms of BHGJT in the treatment of NSCLC. We used the method of network pharmacology and the verification of molecular docking to provide a certain theoretical basis for future cellular experiments.

2. Materials and methods

2.1. Screening of active compounds and prediction of targets in BHGJT

The names of the 10 Chinese herbal medicines in BHGJT were entered to acquire the corresponding compounds from the databases of Bioinformatics Analysis Tool for Molecular Mechanism of Traditional Chinese Medicine (http://bionet.ncpsb.org/batman-tcm/) and Encyclopaedia of Traditional Chinese Medicine (http://www.tcmip.cn/ETCM/index.php/Home/Index/). Based on the database of Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP) (https://old.tcmsp-e.com/index.php), the compounds that corresponded to the parameters including oral bioavailability ≥ 30% and drug likeness ≥ 0.18 were selected and considered as active compounds of BHGJT. Following the filtration, a part of the relative targets was confirmed by the valid SMILE number in the Pubchem database (https://pubchem.ncbi.nlm.nih.gov/). Those targets with the same chemical abstracts service number were deduplicated. The rest targets of BHGJT were normalized in the UniProt protein database (https://www.uniprot.org) for specification. The databases of Swiss Target Prediction (http://www.swisstargetprediction.ch/index.php) and search tool for interactions of chemicals (http://stitch.embl.de) were subsequently applied for screening out those targets closely associated with the active compounds of BHGJT.

2.2. Collection of known NSCLC targets

NSCLC-related genes were obtained by searching the keyword "NSCLC" in the databases of Genecards (http://www.genecards.org),[9] DrugBank (https://go.drugbank.com/)[10] and Therapeutic Target Database (http://db.idrblab.net/ttd/).[11] The duplicated and invalid data were deleted after relative genes were merged. The ethical approval was not necessary since all the data were acquired from public databases.

2.3. Construction of component-target network

The component-target network was mapped by Cytoscape 3.7.1 software to visualize the intricate relationships between compounds and targets.[12] The "Network Analyze" plugin was used to get access to the features of the network including degree value to obtain the main active compounds.

2.4. Establishment of protein-protein interaction (PPI) network and mining of hub targets

The intersection genes of NSCLC-related targets and BHGJT-related targets were imported to the Search Tool for Recurring Instances of Neighboring Genes (STRING) platform (https://string-db.org)[13] with the species limited to "Homo sapiens" and a confidence score > 0.4 to acquire PPI relationships. The hub targets of PPI network were screened out by ranking the confidence score and the PPI network was visualized by Cytoscape 3.7.1 software.

2.5. Enrichment analysis of gene ontology (GO) and Kyoto encyclopedia of genes and genomes pathway (KEGG)

The candidate targets were transmitted to the Database for Annotation, Visualization and Integrated Discovery database (https://david.ncifcrf.gov).[14] GO enrichment and KEGG pathway annotations were performed to identify the core biological processes and key signaling pathways involved in BHGJT in treating NSCLC. An adjusted P value of <.05 was considered to identify the enriched GO terms and KEGG pathways.

2.6. Molecular docking

The hub targets were imported to the The Research Collaboratory for Structural Bioinformatics Protein Data Bank (RSCB PDB) (https://www.omicshare.com) database to download protein compositions in PDB format. Crystals of proteins were forwarded to Autodock Vina (version 1.2.0) and MglTools (version 1.5.6) software to conduct the molecular docking. The high-quality 3D structures of small molecules and proteins were exhibited by LIGPLOT + (version 2.2) software and PyMOL (version 2.5). Molecular docking scores obtained from Proteins Plus (https://proteins.plus/) were introduced to evaluate the docking activity between receptors and ligands. The receptors and ligands are docked to verify their binding activity, which can be evaluated by molecular docking score. It is generally acknowledged that binding energy which is less than –4.25 kcal/mol, –5.0 kcal/mol, or –7.0 kcal/mol, respectively, indicates a certain, good or strong binding activity between the ligand and the receptors.[15]

3. Results

3.1. Compounds of BHGJT targets

A total of 256 compounds in BHGJT were retrieved through the Bioinformatics Analysis Tool for Molecular Mechanism of Traditional Chinese Medicine and Encyclopaedia of Traditional Chinese Medicine. Forty-eight active compounds were further screened out according to the filter criteria of oral bioavailability ≥ 30% and drug likeness ≥ 0.18 in TCMSP database, as shown in Table 1. The BHGJT targets comprised 20 for Radix Rehmanniae, 26 for Bulbus Lilii, 21 for Radix Ophiopogonis,

Table 1

Active compounds in Bai He Gu Jin Tang (BHGJT).

Pubchem ID	Compound	OB%	DL	Chinese medicinal herbs
5280794	stigmasterol	43.83	0.76	Radix Ophiopogonis, Radix Rehmanniae, Bulbus Lilii, Radix Angelicae Sinensis
5372945	p-coumaroyltyramine	112.9	0.20	Radix Ophiopogonis
222284	beta-sitosterol	36.91	0.75	Radix Rehmanniae, Bulbus Lilii, Radix Paeoniae Alba, Radix Angelicae Sinensis, Bulbus Fritillariae Thunbergii, Radix et Rhizoma Glycyrrhizae, Radix Scrophulariae
5742590	daucosterol	2.72	0.60	Radix Rehmanniae
442048	isopimaric acid	36.2	0.28	Bulbus Lilii
299664	3-demethylcolchicine	39.34	0.57	Bulbus Lilii
9064	catechin	54.83	0.24	Radix Paeoniae Alba
442534	paeoniflorin	53.87	0.79	Radix Paeoniae Alba
64971	mairin	55.38	0.78	Radix Paeoniae Alba, Radix et Rhizoma Glycyrrhizae
5280863	kaempferol	41.88	0.24	Radix Paeoniae Alba, Radix et Rhizoma Glycyrrhizae
68081	isoimperatorin	15.73	0.22	Radix Angelicae Sinensis
440832	pelargonidin	37.99	0.21	Bulbus Fritillariae Thunbergii
72435	picropodophyllin	51.77	0.86	Bulbus Fritillariae Thunbergii
68071	pinocembrin	64.72	0.18	Radix et Rhizoma Glycyrrhizae
5280378	formononetin	69.67	0.21	Radix et Rhizoma Glycyrrhizae
5319013	licoricone	63.58	0.47	Radix et Rhizoma Glycyrrhizae
72301	tetrahydropalmatine	73.94	0.64	Radix et Rhizoma Glycyrrhizae
5318869	kumatakenin	50.83	0.29	Radix et Rhizoma Glycyrrhizae
5281628	hispidulin	30.97	0.27	Radix et Rhizoma Glycyrrhizae
336327	medicarpin	49.22	0.34	Radix et Rhizoma Glycyrrhizae
5281654	isorhamnetin	49.60	0.31	Radix et Rhizoma Glycyrrhizae
5280448	calycosin	47.75	0.24	Radix et Rhizoma Glycyrrhizae
124052	glabridin	53.25	0.47	Radix et Rhizoma Glycyrrhizae
480774	glabrene	46.27	0.44	Radix et Rhizoma Glycyrrhizae
5280343	quercetin	46.43	0.28	Radix et Rhizoma Glycyrrhizae
5317480	lupiwighteone	51.64	0.37	Radix et Rhizoma Glycyrrhizae
5316900	quercetin der.	46.45	0.33	Radix et Rhizoma Glycyrrhizae
5317478	gancaonin A	51.08	0.40	Radix et Rhizoma Glycyrrhizae
90479675	glabrolide	17.46	0.61	Radix et Rhizoma Glycyrrhizae
5318585	isolicoflavonol	45.17	0.42	Radix et Rhizoma Glycyrrhizae
5281789	licoisoflavone	41.61	0.42	Radix et Rhizoma Glycyrrhizae
114829	liquiritigenin	32.76	0.18	Radix et Rhizoma Glycyrrhizae
73205	sigmoidin B	34.88	0.41	Radix et Rhizoma Glycyrrhizae
480784	glyasperin B	65.22	0.44	Radix et Rhizoma Glycyrrhizae
480859	glyasperin C	45.56	0.40	Radix et Rhizoma Glycyrrhizae
5281619	glepidotin A	44.72	0.35	Radix et Rhizoma Glycyrrhizae
5317768	glypallichalcone	61.60	0.19	Radix et Rhizoma Glycyrrhizae
5318999	licochalcone B	76.76	0.19	Radix et Rhizoma Glycyrrhizae
10336244	shinpterocarpin	80.30	0.73	Radix et Rhizoma Glycyrrhizae
124049	glabranin	52.90	0.31	Radix et Rhizoma Glycyrrhizae
5460988	gadelaidic acid	30.70	0.20	Radix et Rhizoma Glycyrrhizae
177149	vestitol	74.66	0.21	Radix et Rhizoma Glycyrrhizae
480780	gancaonin G	60.44	0.39	Radix et Rhizoma Glycyrrhizae
5481949	gancaonin H	50.10	0.78	Radix et Rhizoma Glycyrrhizae
5281331	spinasterol	42.98	0.76	Radix Platycodonis
5280442	acacetin	34.97	0.24	Radix Platycodonis
5280445	luteolin	36.16	0.25	Radix Platycodonis
457801	γ-sitosterol	36.91	0.75	Radix Scrophulariae

DL = drug likeness, OB = oral bioavailability.

130 for Radix Paeoniae Alba, 24 for Radix Angelicae Sinensis, 22 for Bulbus Fritillariae Thunbergii, 105 for Radix Platycodonis, 25 for Radix Scrophulariae and 438 for Radix et Rhizoma Glycyrrhizae. After merging and deleting duplicate values, 237 putative targets corresponding to active compounds were collated.

3.2. Herb-compound-target network of BHGJT's treatment against NSCLC

A total of 1721 NSCLC-related targets were gained from Genecards, DrugBank and Therapeutic Target Database databases. Herb-compound-target network was constructed with 163 nodes and 384 edges, using the Cytoscape software to illustrate the relationship, as shown in Figure 1. The key compounds, which are defined as the nodes with a degree greater than twice the median,[16] are kaempferol (degree = 58), quercetin (degree = 56), luteolin (degree = 47), isorhamnetin (degree = 41), beta-sitosterol (degree = 14), stigmasterol (degree = 12), mairin (degree = 11), and liquiritigenin (degree = 10).

3.3. Establishment of PPI network and mining of the hub targets of BHGJT in the treatment of NSCLC

The PPI network was established by inputting the potential targets of BHGJT to the STRING database. There were 2308 interactions in the overlapped targets of BHGJT and NSCLC. The visualization of the PPI network was displayed by Cytoscape, as shown in Figure 2.

The hub targets of BHGJT in the treatment of NSCLC were screened out by ranking the combined score according

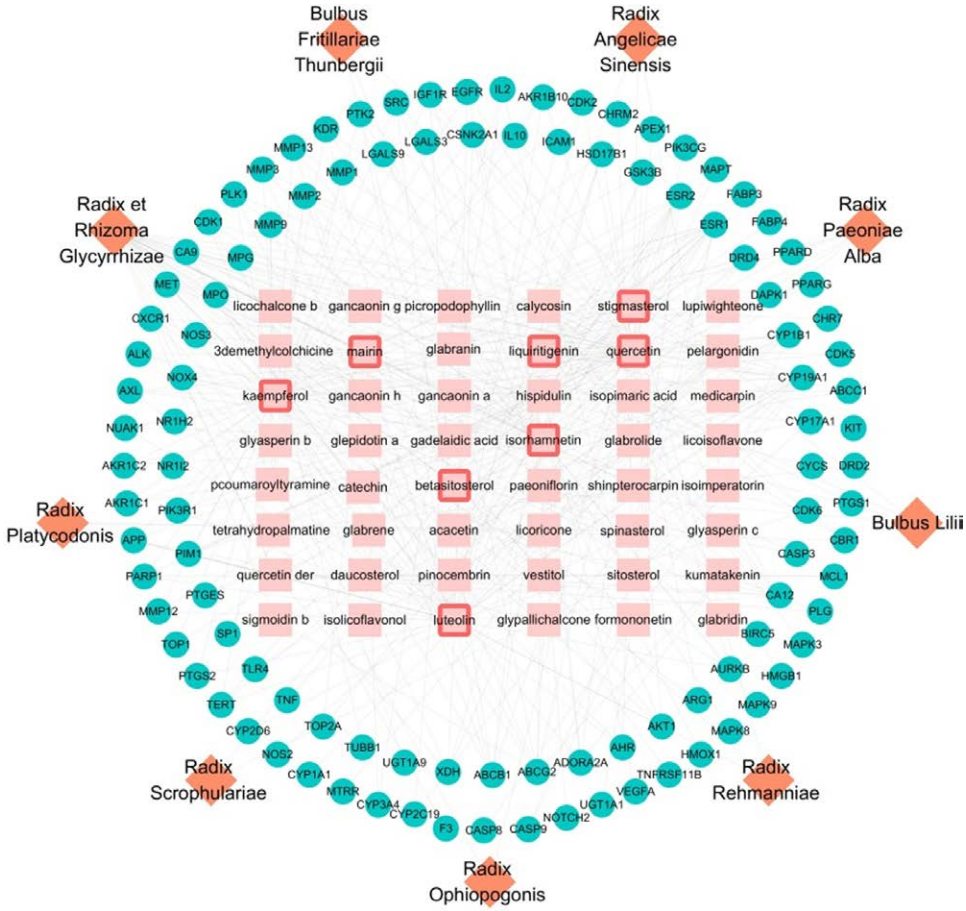

Figure 1. Herb-compound-target network of BHGJT against non-small cell lung cancer (NSCLC). BHGJT = Bai He Gu Jin Tang.

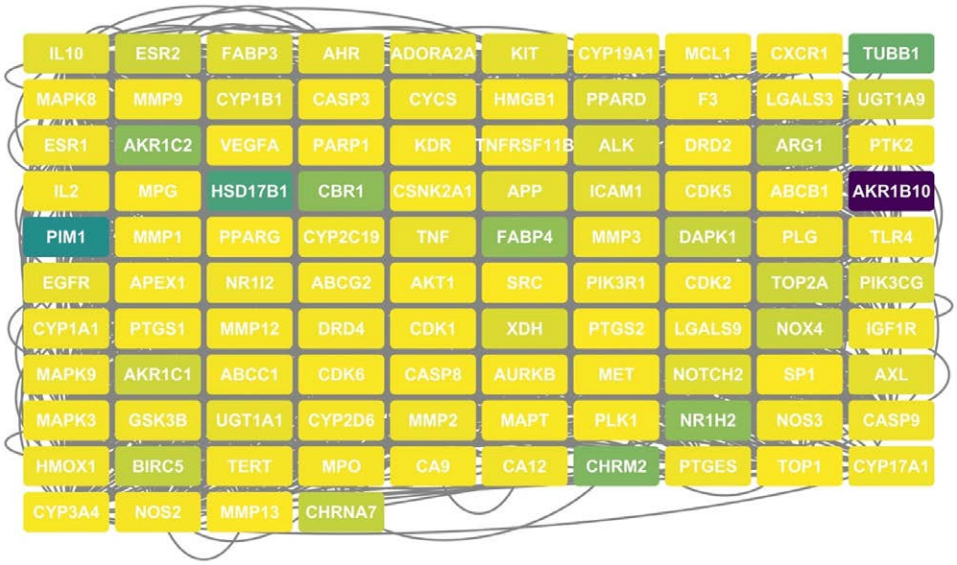

Figure 2. PPI network of the overlapped targets of BHGJT and NSCLC. BHGJT = Bai He Gu Jin Tang, NSCLC = non-small cell lung cancer.

to the platform of the STRING database. The top 15 targets in the PPI network were considered as the hub targets, which are AKR1B10 (0.91), PIM1 (0.663), HSD17B1 (0.608), TUBB1 (0.572), CHRM2 (0.545), AKR1C2 (0.532), CBR1 (0.529), NR1H2 (0.528), FABP4 (0.523), BIRC5 (0.466), ARG1 (0.465), DAPK1 (0.459), NOX4 (0.457), ESR2 (0.454), and TOP2A (0.454). The Sankey diagram was presented by describing the relationship between the hub targets, the compounds and the herbs of BHGJT clearly, as shown in Figure 3.

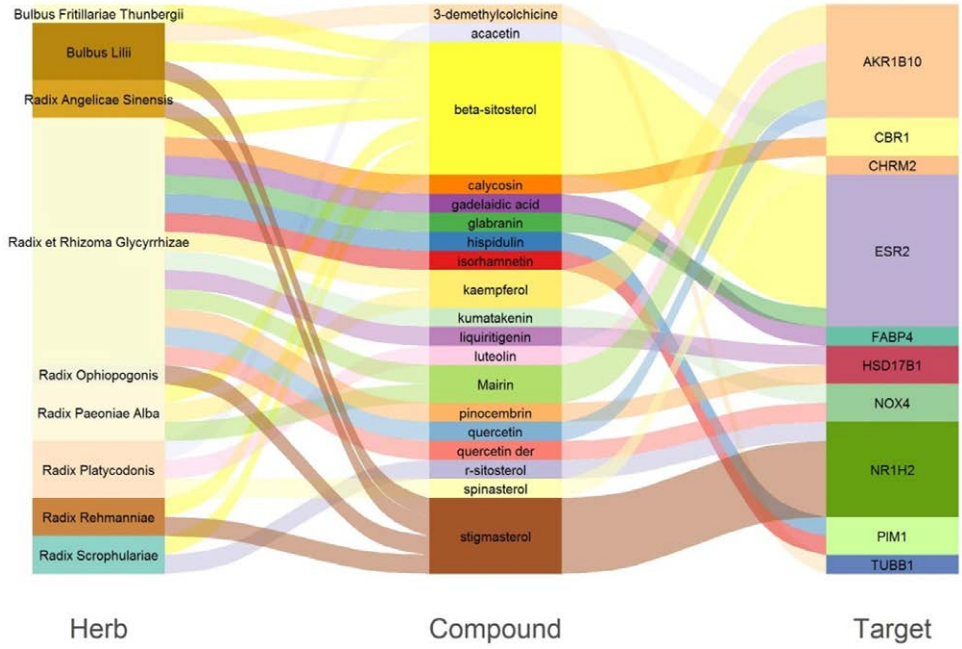

Figure 3. The relationship between the hub targets, compounds and herbs of BHGJT. BHGJT = Bai He Gu Jin Tang.

3.4. GO and KEGG pathway enrichment analysis

A series of GO and KEGG pathway enrichment analysis were performed to illuminate the biological mechanisms of BHGJT against NSCLC by importing the 106 potential targets to the Database for Annotation, Visualization and Integrated Discovery database. According to the adjusted *P* value, the top 10 GO terms of biological process were a negative regulation of apoptotic process, cytokine-mediated signaling pathway, response to xenobiotic stimulus, response to drug, positive regulation of protein kinase B signaling, positive regulation of apoptotic process, steroid metabolic process, rhythmic process, positive regulation of ERK1 and ERK2 cascade, and protein phosphorylation. The top 10 GO terms of molecular function were protein serine/threonine/tyrosine kinase activity, enzyme binding, heme binding, ATP binding, oxidoreductase activity, protein serine/threonine kinase activity, identical protein binding, RNA polymerase II transcription factor activity, ligand-activated sequence-specific DNA binding, protein kinase activity and protein homodimerization activity. The top 10 GO terms of cellular component were receptor complex, nucleus, nucleoplasm, cytoplasm, membrane raft, macromolecular complex, cell surface, plasma membrane, extracellular space and mitochondrion. Figure 4 illustrates the main GO terms, mentioned above.

Modularity is one of the critical measurements for the network analysis.[17] Nodes closely interconnected within a network usually take part in the same biological modules. According to functional distribution, the interaction network of the top 15 significant signaling pathways and corresponding

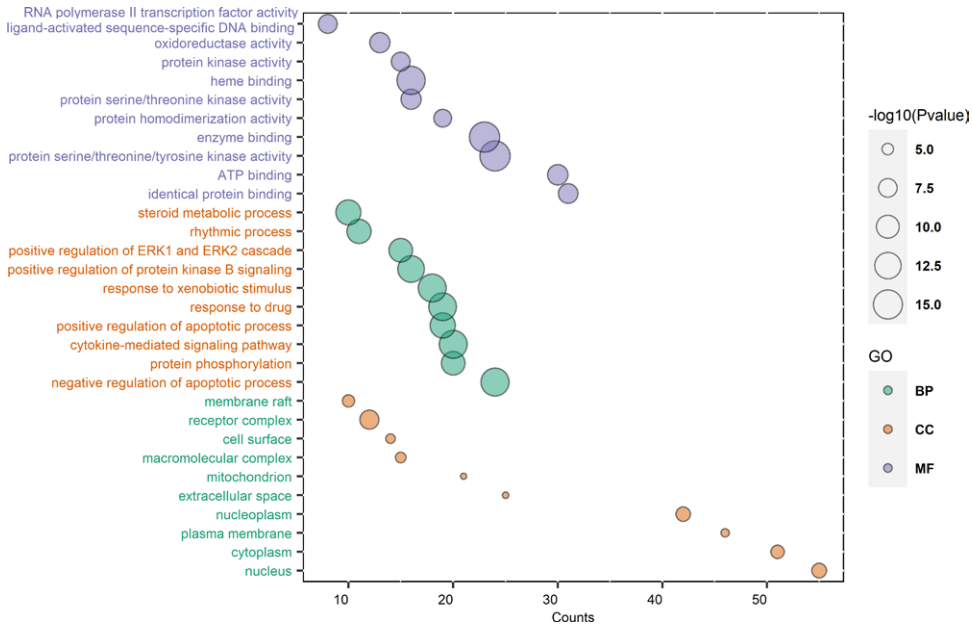

Figure 4. The top 10 GO terms of biological process, molecular function and cellular component. GO = gene ontology.

targets was categorized into 3 modules, as shown in Figure 5. The minimum module was mainly associated with endocrine, including Prolactin signaling pathway, Estrogen signaling pathway, Relaxin signaling pathway and Endocrine resistance. The medium module was mostly related with inflammation and hypoxia, including IL-17 signaling pathway, TNF signaling pathway, HIF-1 signaling pathway, C-type lectin receptor signaling pathway and Chemical carcinogenesis-reactive oxygen species. The maximum module comprised the pathways of cancer generation and treatment, including VEGF signaling pathway, EGFR tyrosine kinase inhibitor resistance, PI3K-Akt signaling pathway, apoptosis, Platinum drug resistance and pathways in cancer.

3.5. Molecular docking

The molecular docking between 8 key compounds (kaempferol, quercetin, luteolin, isorhamnetin, beta-sitosterol, stigmasterol, mairin, liquiritigenin) and 15 hub targets (AKR1B10, PIM1, HSD17B1, TUBB1, CHRM2, AKR1C2, CBR1, NR1H2, FABP4, BIRC5, ARG1, DAPK1, NOX4, ESR2 and TOP2A) was carried out to obtain docking scores, as shown in Figure 6.

The targets of AKR1B10 and AKR1C2 had the strongest binding activity with the key compounds of BHGJT. The best docking affinity of 4 couples was selected for visualization, as shown in Figures 7–10.

4. Discussion

NSCLC is a leading cause of cancer-related burden and deaths. Some Chinese herbal medicines in BHGJT including Bulbus Lilii and Radix Ophiopogonis have shown significant effects in the substantial improvement of NSCLC patients' life quality.[18] Our work has revealed the key compounds of BHGJT in the treatment of NSCLC and their potential molecular mechanisms.

The analysis of the herb-compound-target network obtained 8 key compounds in BHGJT including kaempferol, quercetin, luteolin, isorhamnetin, beta-sitosterol, stigmasterol, mairin and liquiritigenin. Most of the key compounds in BHGJT, mentioned above including kaempferol, quercetin, luteolin, isorhamnetin

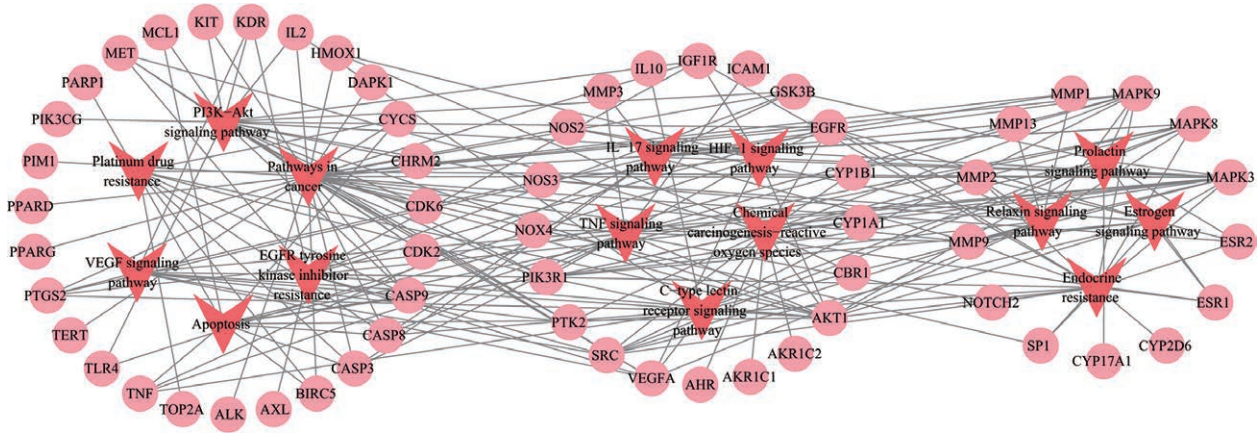

Figure 5. KEGG pathway enrichment of BHGJT's treatment in NSCLC. BHGJT = Bai He Gu Jin Tang, NSCLC = non-small cell lung cancer.

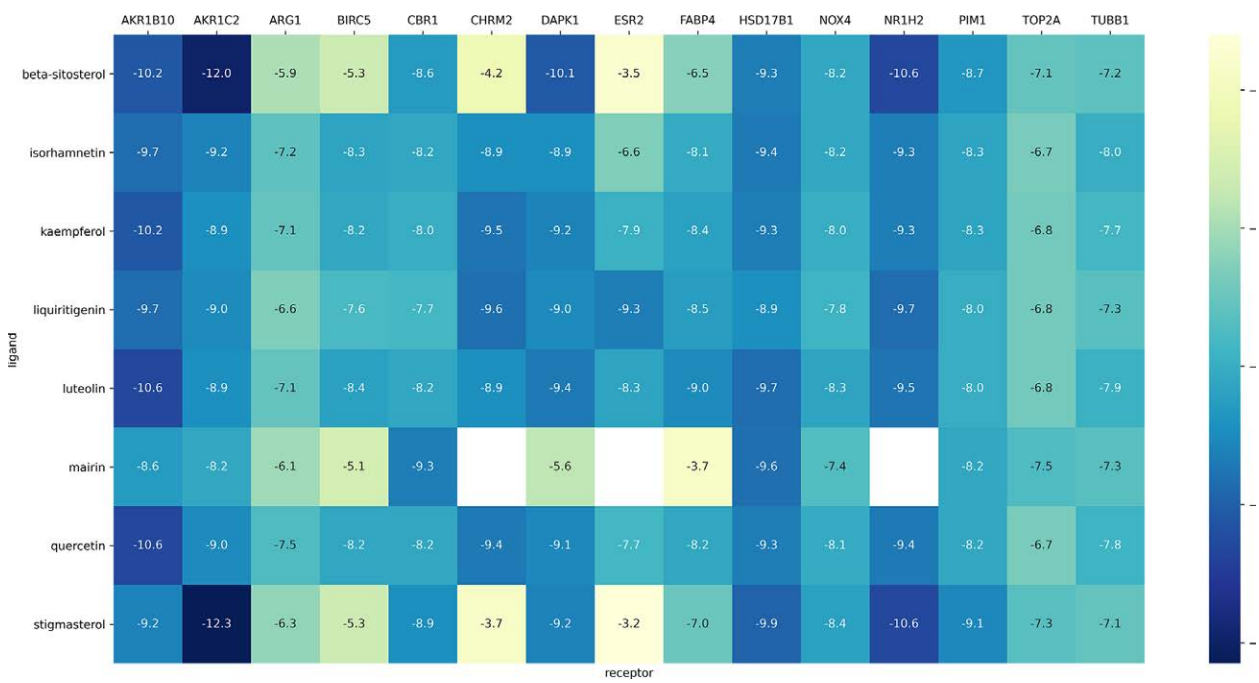

Figure 6. Molecular docking between the key compounds and the hub targets in BHGJT. BHGJT = Bai He Gu Jin Tang.

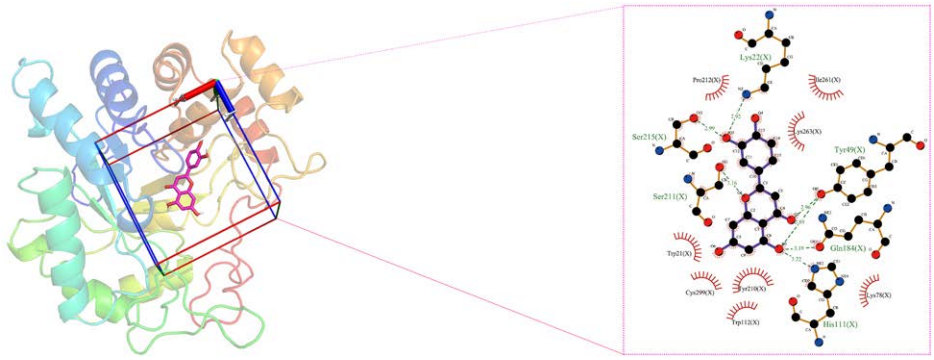

Figure 7. Docking of luteolin and AKR1B10.

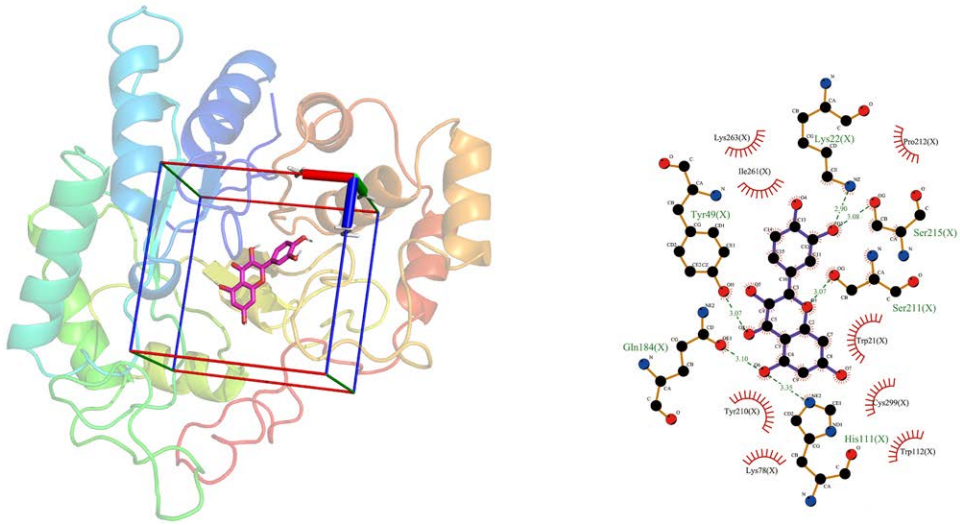

Figure 8. Docking of AKR1B10 and quercetin.

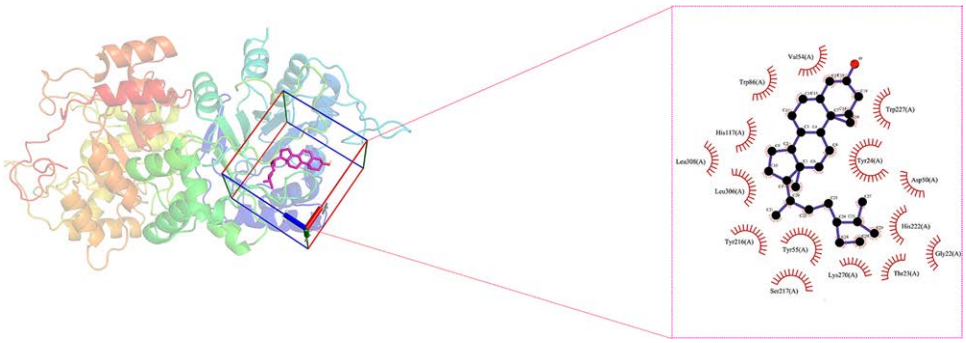

Figure 9. Docking of AKR1C2 and beta-sitosterol.

and liquiritigenin, belong to flavonoid compounds. Flavonoids are natural products with the significant effects of reversing the tumor-immunosuppressive microenvironment.[19] Kaempferol has anti-cancer potentials in a broad spectrum including apoptosis, metastasis, inflammation, and angiogenesis.[20] It has been reported that kaempferol could induce the apoptosis of NSCLC cells via down-regulation of Nrf2 mRNA to suppress the proliferation of cancer cells.[21] Additionally, kaempferol also plays a key role in the inhibition of TGF-β1-induced epithelial-to-mesenchymal transition, migration and invasion of NSCLC cells to slow down the progression of cancer.[22] Quercetin displayed its significant cytotoxicity on the viability and growth of human NSCLC cells.[23] Studies have shown that quercetin exerted its therapeutic effect on NSCLC cells by inhibition of proliferation, suppression of migration and the enhancement of apoptosis.[24,25] It has also been reported that quercetin delivered superior anticancer activity in NSCLC-bearing mice model by biotinylated mixed micelles.[26] Studies have further unveiled that luteolin could inhibit the viability, migration, angiogenesis and invasion of NSCLC,[27,28] and alleviate the inflammatory conditions in NSCLC cells via down-regulation of the AIM2 expression.[29] Isorhamnetin has the ability to inhibit the migration and invasiveness in NSCLC cells,[30] while enhancing the radiosensitivity of NSCLC cells.[31] Beta-sitosterol and

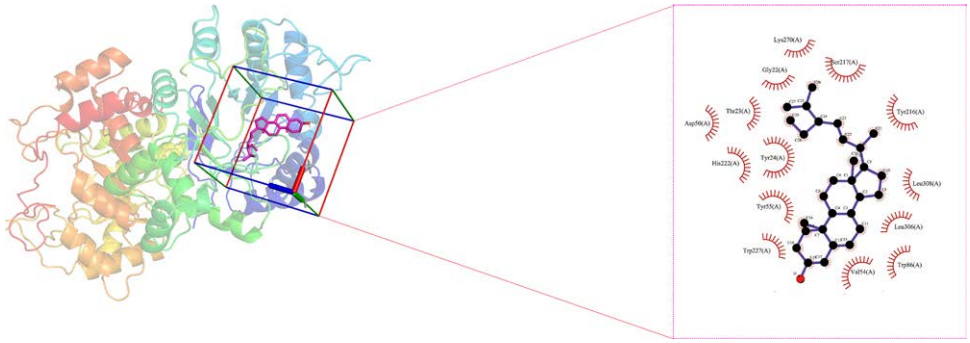

Figure 10. Docking of AKR1C2 and stigmasterol.

stigmasterol pertain to phytosterol, which has shown the preventive effect against various tumors including NSCLC.[32] Beta-sitosterol could interfere with multiple cell signaling pathways, including cell cycle, apoptosis, proliferation, survival, invasion, angiogenesis, metastasis and inflammation to exert its anti-cancer effects on lung cancer.[33] Stigmasterol could inhibit the proliferation and promote the apoptosis of NSCLC cells.[34] Liquiritigenin was reported as a promising candidate for the treatment of breast cancer,[35] and its suppression function also contributes to the migration of NSCLC via down-regulation of PI3K/Akt signaling pathway.[36]

The top GO-biological process term of BHGJT's treatment in NSCLC cells was negative regulation of the apoptotic process, while BHGJT has shown an inhibitory effect on the growth of NSCLC cells by inducing cell apoptosis via the AKT/GSK3β/β-catenin signaling pathways.[6] Interestingly, most of the key compounds in BHGJT such as kaempferol, quercetin, beta-sitosterol and stigmasterol could also trigger the apoptosis of NSCLC. The top 15 KEGG pathways were mostly enriched in the endocrine-related pathways, the inflammation and hypoxia-related pathways as well as other cancer-related pathways. Endocrine, especially hormone matters to the pathological mechanism of NSCLC. Estrogen and prolactin could contribute to the development and progression of NSCLC.[16,37] Studies have shown that flavonoid compounds, which share structural similarities with human estrogens, could bind to the estrogen receptors to alter the endocrine responses,[38–40] and might exert antagonizing effects on the endocrine resistance in NSCLC. As a typical inflammation-associated cancer, NSCLC could use the Systemic Immune Inflammatory Index as a promising prognostic biomarker.[41] NSCLC patients had significant up-regulated levels of TNFα, which is also in correlation with the occurrence and prognosis of cancer pain in patients.[42] IL-17 and chondrolectin were reported to promote the proliferation and growth of NSCLC.[43,44] In the meanwhile, the key compounds in BHGJT including quercetin, isorhamnetin and kaempferol derivates have shown great potential in the anti-inflammatory activities.[45] Hypoxia has been considered as a critical factor in the poor survival of NSCLC, and targeting hypoxia could improve NSCLC outcomes.[46] As a key compound in BHGJT, kaempferol has shown an inhibitory effect on hypoxia.[47,48] It has been demonstrated that kaempferol also has angioprevention effects by inhibiting VEGF expression,[49] inhibitory effect against tumor glycolysis targeting EGFR signaling pathway[50] and induction of ROS-dependent apoptosis via Akt/mTOR signaling pathway.[51]

In this study, we found that AKR1B10 and AKR1C2 have a high affinity for the key compounds of BHGJT. As human members of the AKR superfamily, AKR1B10 and AKR1C2 are up-regulated in NSCLC cells.[52] AKR1B10 is a biomarker for epithelial tumors including NSCLC.[53] It has been reported that AKR1B10 could promote the extravasation of NSCLC cells through the blood-brain barrier structure.[54] The inhibitors of AKR1B10 could suppress the proliferation, metastasis, and cisplatin resistance of NSCLC.[54] Overexpression of AKR1C2 is associated with drug resistance in NSCLC.[55] The down-regulation of AKR1C2 could sensitize keap1-mutant NSCLC cells to chemotherapy.[56]

5. Conclusions

In summary, kaempferol, quercetin, luteolin, isorhamnetin, beta-sitosterol, stigmasterol, mairin and liquiritigenin and other active compounds in BHGJT may exert anti-cancer effects via AKR1B10, AKR1C2 and other targets. This is mainly through the endocrine related pathways, the inflammation and hypoxia related pathways as well as the other cancer related pathways in treating NSCLC. However, further experimental researches are needed to determine whether the above compounds can be applied in the treatment of NSCLC.

Author contributions

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