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The Mechanism of Ginkgo Biloba Extract in Treating Glioma

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Abstract: *Objective:* To explore the active components of ginkgo biloba and the possible targets and pathways for treating glioma. *Methods*: The chemical components and corresponding targets of Ginkgo biloba were searched by TCMSP, and the "component-target" network map was constructed by Cytoscape. The GenCards database, OMIM database and Disgenet database were used to search for glioma-related genes. Ginkgo biloba targets and glioma gene intersections were extracted using R software, and Veen maps were drawn to obtain key targets. PPI network construction and GO and KEGG enrichment analysis were performed by key targets. *Results:* A total of 27 active ingredients in Ginkgo biloba leaves and 5770 glioma target genes were collected, and 48 key targets were obtained. PPI analysis showed that the core targets were IL6, ESR1, EGFR, PPARG, VEGFA, CYP3A4, AHR, AR, PGR, etc. GO enrichment analysis is mainly concentrated in nuclear receptor activity, neurotransmitter receptor activity, fatty acid metabolic processes, response to foreign stimuli, etc. KEGG enrichment pathways are mainly manifested in: cholinergic synapses, resistance to EGFR tyrosine kinase inhibitors, tumor necrosis factor signaling pathway PI3K-Akt signaling pathway, etc. *Conclusion*: Ginkgo biloba can treat glioma through multi-target and multi-pathway, which is in line with the characteristics of holistic treatment of diseases in traditional Chinese medicine.

Keywords: Ginkgo Biloba, Glioma, Network Pharmacology

1. Background

Glioma is a malignant tumor that originates from glial cells [1], Currently, the main treatment is a combination of radiation and chemotherapy with surgical resection [2], However, due to the special location of glioma and the existence of blood-brain barrier, the efficiency of glioma treatment is low, and the recurrence and death rates are extremely high. With the application of molecular targeted drugs and immunotherapy, people began to explore the mechanism of molecular therapy in glioma, but there is no better therapeutic efficacy, so it is especially important to explore effective treatment methods to prolong the disease-free survival and overall survival of patients with glioma.

Ginkgo is a species native to China [3], The main bioactive components are the terpene trilactones (TTL) and the flavonoids of GBE [4], Numerous studies have shown that ginkgo has anti-inflammatory [5, 6] Lipid reduction [7] and neuroprotective effects [8], And Ginkgo biloba extract can reduce blood viscosity by [9], Improves transmitter release and reduces oxygen free radicals [10, 11], To achieve the purpose of treating tumors. In numerous studies, ginkgo has been shown to have anti-inflammatory [5, 6] Lipid reduction [7] and neuroprotective effects of hepatocellular carcinoma, Ginkgo biloba extract was found to inhibit the proliferation of HepG2 and Hep3B cells through, Delay the proliferation and migration of hepatocellular carcinoma and slow down the process of hepatocellular carcinoma [12]. It has been shown that after oral administration of flavonoid glycosides, a large amount of terpene triglycerides and ginkgo flavonoids can cross the blood-brain barrier and enter the central nervous system of rats [13], Achieve the effect of treatment. Therefore, this paper explores the active ingredients of Ginkgo biloba, the potential targets and pathways

of Ginkgo biloba for the treatment of glioma through a network pharmacology approach to provide a scientific basis for future glioma treatment.

2. Data Sources and Methods

2.1. Screening and Network Construction of Active Components and Targets of Ginkgo Biloba

The chemical components related to Ginkgo biloba were queried by the TCMSP (Traditional Chinese Medicine Systematic Pharmacology Analysis Platform), and based on the oral utilization (OB) and drug-like properties (Drug-likeness, DL) [14] To screen the active ingredients of Ginkgo biloba, OB ≥ 30% and DL ≥ 0.18 were generally used as screening criteria, and the corresponding targets were collected and annotated.

Cytoscape software (version 3.7.0) was used to construct the "component-target" network diagram. The centrality of the network nodes was analyzed, and the Degree value was used as the filtering condition. The higher the Degree value, the more targets were associated with the component, and the core components in Ginkgo biloba were identified.

2.2. Collection of Target Genes Associated with Glioma Disease

Genes related to glioma were searched through GenCards database, OMIM database, and Disgenet database, and downloaded and organized.

2.3. Acquisition of Key Targets

Ginkgo biloba action targets and glioma gene intersections were extracted using R (version 3.5.3) software, and Veen plots were drawn to obtain key targets.

2.4. Construction of PPI Network

Key targets were imported into the String database, and the study species was selected as human.

2.5. GO and KEGG Enrichment Analysis

GO and KEGG enrichment analysis of the targets was performed using R software. Import key targets into R software and perform enrichment analysis using cluster Profiler.

2.6. Statistical Processing

Considered statistically significant at $P<0.05$.

3. Results

3.1. Collection of Chemical Components and Targets in Ginkgo Biloba and Analysis of "Component-Target-Network Diagram

A total of 307 active ingredients in Ginkgo biloba were collected through the TCMSP database, and after screening with OB ≥ 30% and DL ≥ 0.18, a total of 27 active ingredients (Table 1) and 228 compound targets were obtained. 58 targets were collected by analyzing specific targets and removing duplicate targets. The 27 components and 58 targets were imported into Cytoscape software for network construction and visualization, and the images were saved (Figure 1).

Table 1. *The 27 active ingredients in Ginkgo biloba.*

Molecule ID	Molecule name	DL	OB (%)
MOL011578	Bilobalide	0.36	84.42
MOL002680	Flavoxanthin	0.56	60.41
MOL011586	ginkgolide B	0.73	44.38
MOL011587	ginkgolide C	0.73	48.33
MOL011588	ginkgolide J	0.74	44.84
MOL011589	Ginkgolide M	0.75	49.09
MOL011594	Isogoycyrol	0.83	40.36
MOL011597	Luteolin-4′-glucoside	0.79	41.97
MOL011604	Syringetin	0.37	36.82
MOL001490	bis [(2S)-2-ethylhexyl] benzene-1,2-dicarboxylate	0.35	43.59
MOL001494	Mandenol	0.19	42
MOL001558	sesamin	0.83	56.55
MOL002881	Diosmetin	0.27	31.14
MOL003044	Chryseriol	0.27	35.85
MOL000354	isorhamnetin	0.31	49.6
MOL000358	beta-sitosterol	0.75	36.91
MOL000422	kaempferol	0.24	41.88
MOL000449	Stigmasterol	0.76	43.83
MOL000492	(+)-catechin	0.24	54.83
MOL005573	Genkwanin	0.24	37.13
MOL000006	luteolin	0.25	36.16
MOL007179	Linolenic acid ethyl ester	0.2	46.1
MOL009278	Laricitrin	0.34	35.38
MOL000096	(-)-catechin	0.24	49.68
MOL000098	quercetin	0.28	46.43
MOL002883	Ethyl oleate (NF)	0.19	32.4
MOL005043	campest-5-en-3beta-ol	0.71	37.58

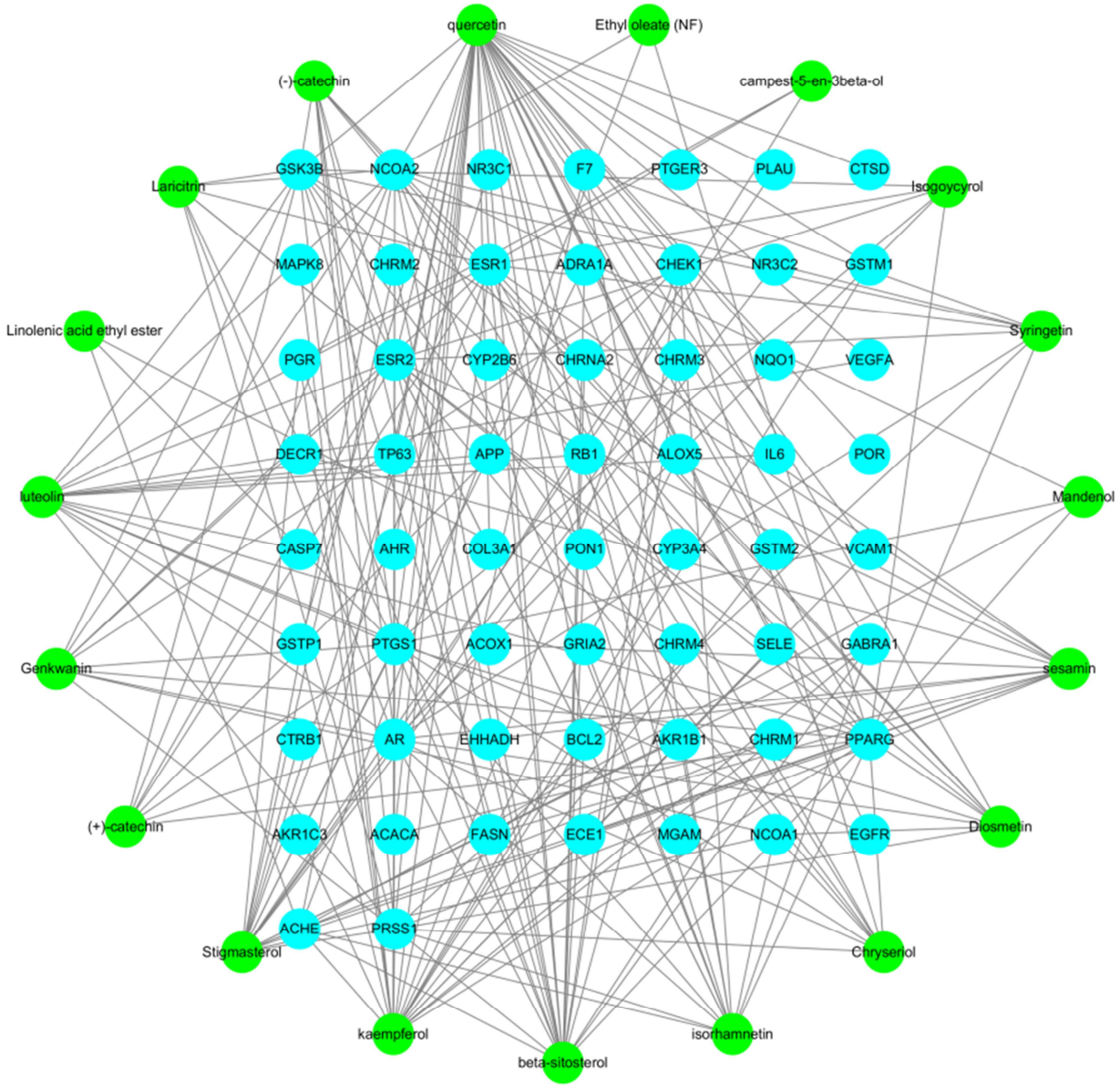


Figure 1. *Composition and target map of Ginkgo biloba.*

3.2. Target Collection and Venny Mapping in Glioma

A total of 8574 glioma-associated target genes were screened by GenCards database, OMIM database, and Disgenet database, and a total of 5770 target genes remained after removing duplicate genes. The venny diagram of ginkgo biloba and glioma-related target genes was plotted by R (version 3.5.3) software (Figure 2), and a total of 48 key targets were derived.

3.3. PPI Network Construction and Selection of Core Targets

In order to explore the interrelationship of key targets and probe the core targets of Ginkgo biloba acting on glioma, this study conducted PPI network analysis of the above screened key targets by String database (Figure 3) and mapped the network topological properties of the top ranked targets of Degree (Figure 4). The top 9 core targets were IL6, ESR1, EGFR, PPARG, VEGFA, CYP3A4, AHR, AR, PGR.

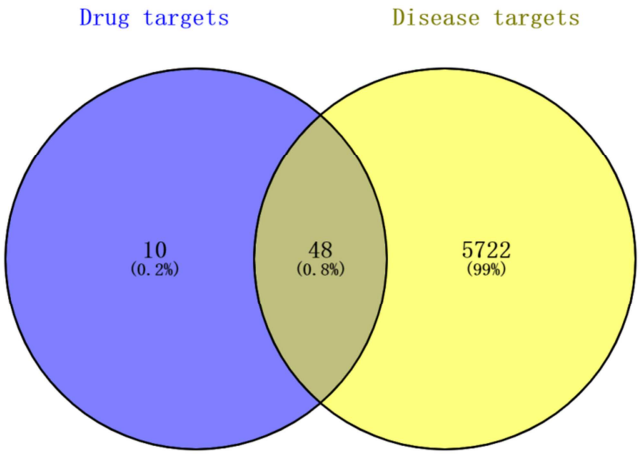


Figure 2. *Ginkgo biloba shares target genes with glioma.*

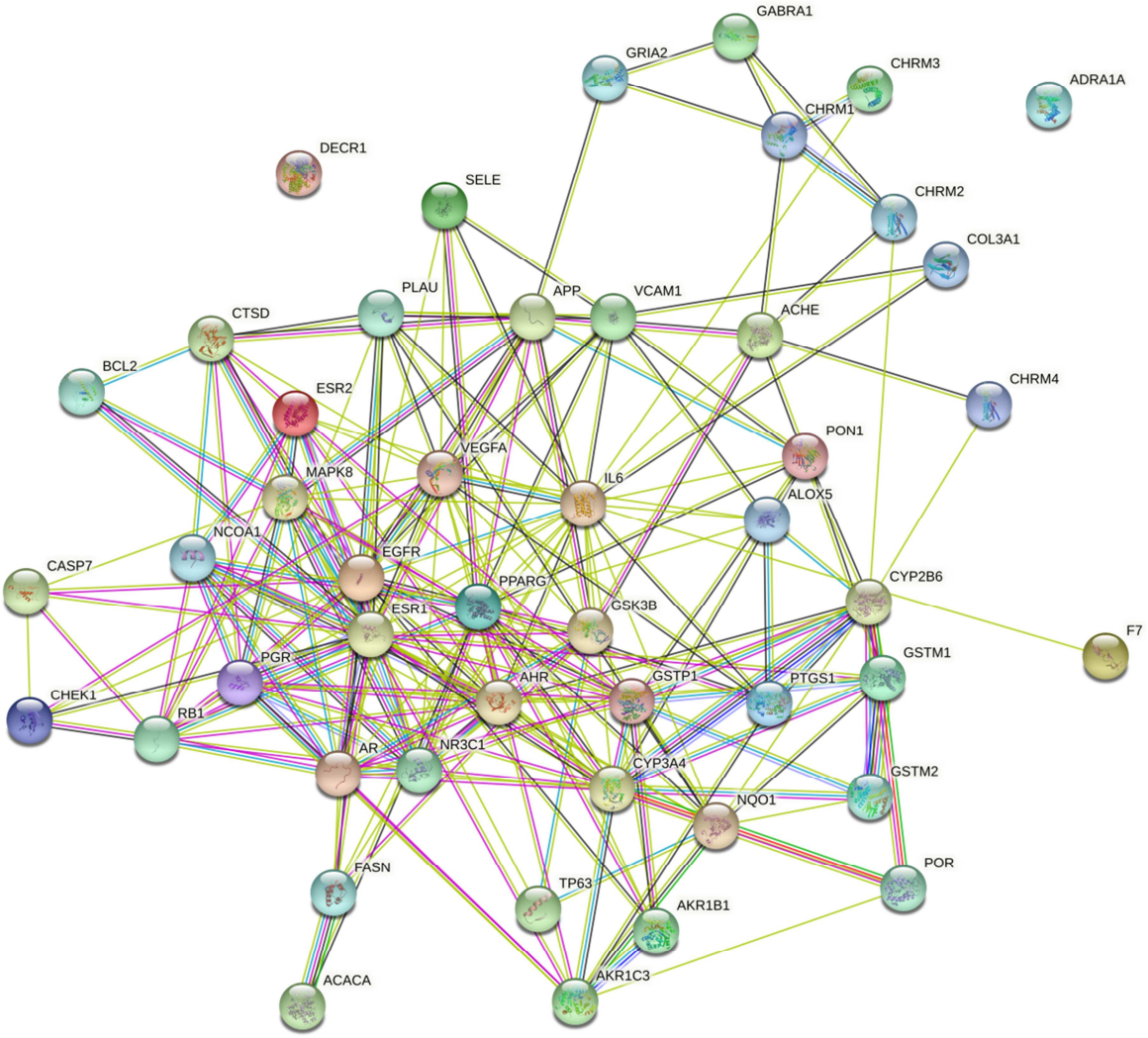


Figure 3. *PPI network analysis of key targets.*

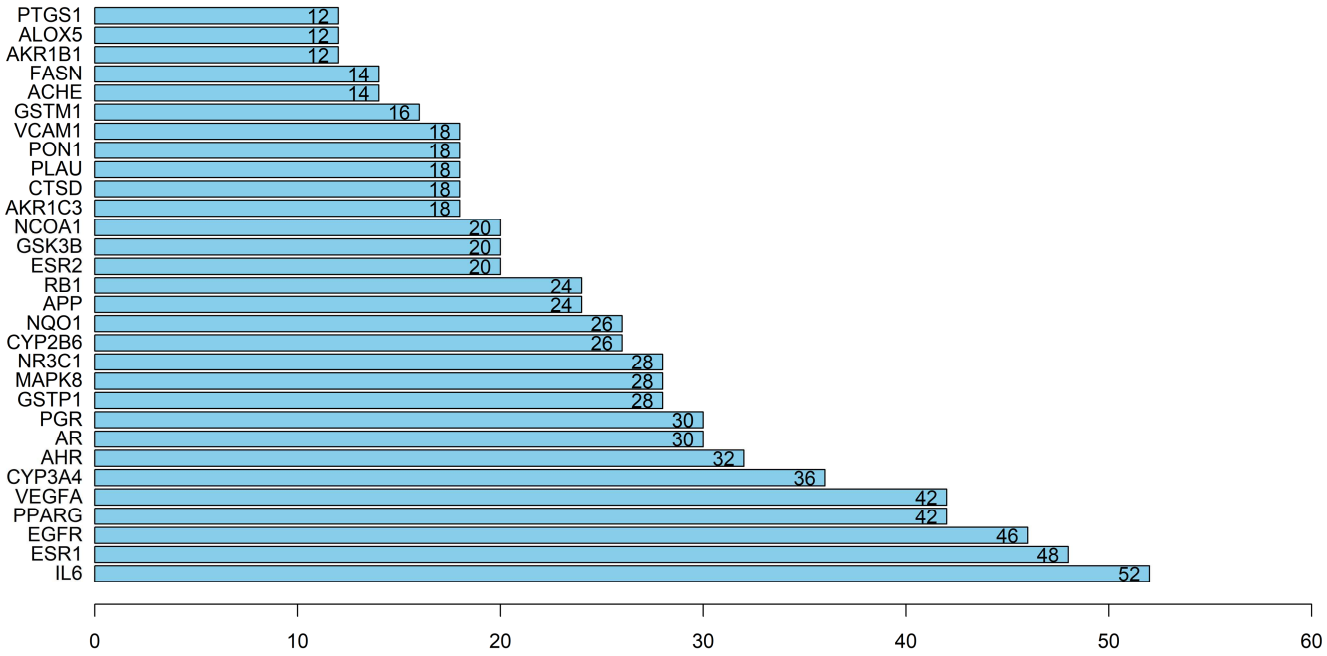
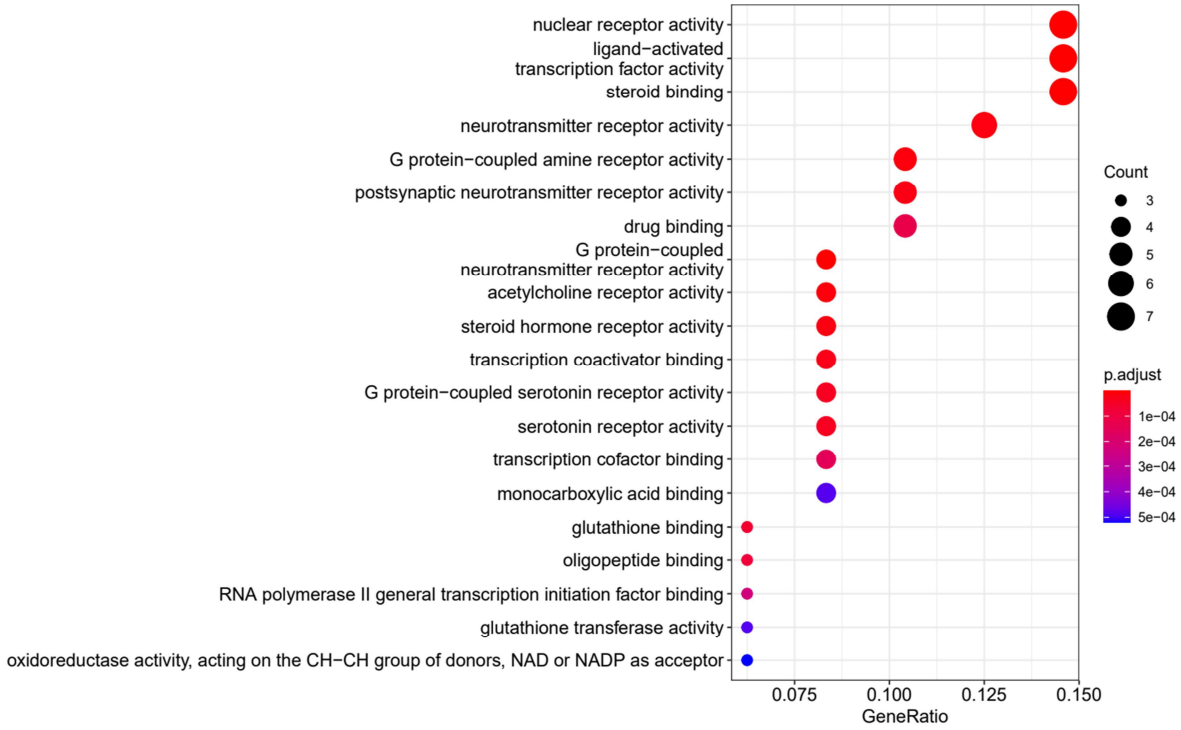
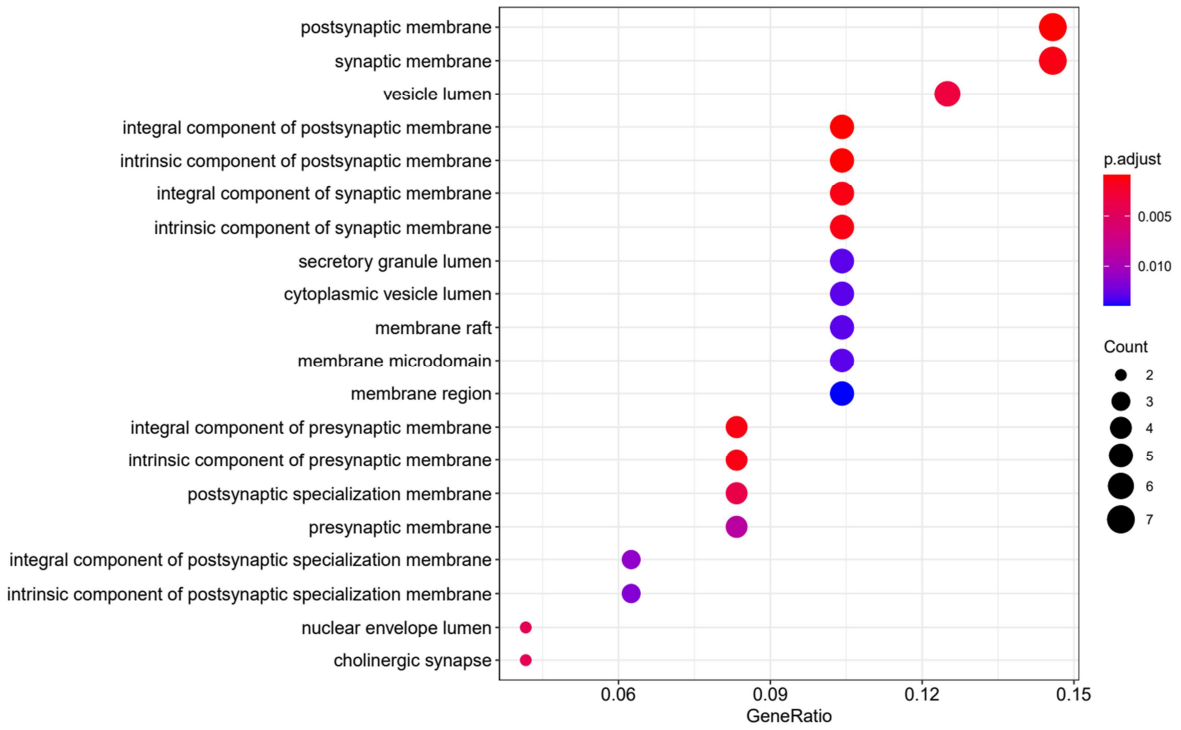


Figure 4. *Network topology property diagram.*

3.4. GO and KEGG Enrichment Analysis

The above screened key targets were imported into R software and GO enrichment analysis was performed for Biological Process (BP), Cellular Component (CC) and Molecular Function (MF), the results of which are shown in Figure 5, Figure 6. The molecular functions of Ginkgo biloba for the treatment of glioma are mainly enriched in nuclear receptor activity, ligand-activated transcription factor activity, steroid-binding proteins, neurotransmitter receptor activity, and G protein-coupled amine receptor activity. Cellular components are enriched to the postsynaptic membrane, synaptic membrane, vesicle, components of the postsynaptic membrane, intrinsic components of the postsynaptic membrane, etc. Biological processes enriched to fatty acid metabolic processes, steroid hormone responses, nutrient level responses, cellular responses to foreign stimuli, responses to foreign stimuli, etc.





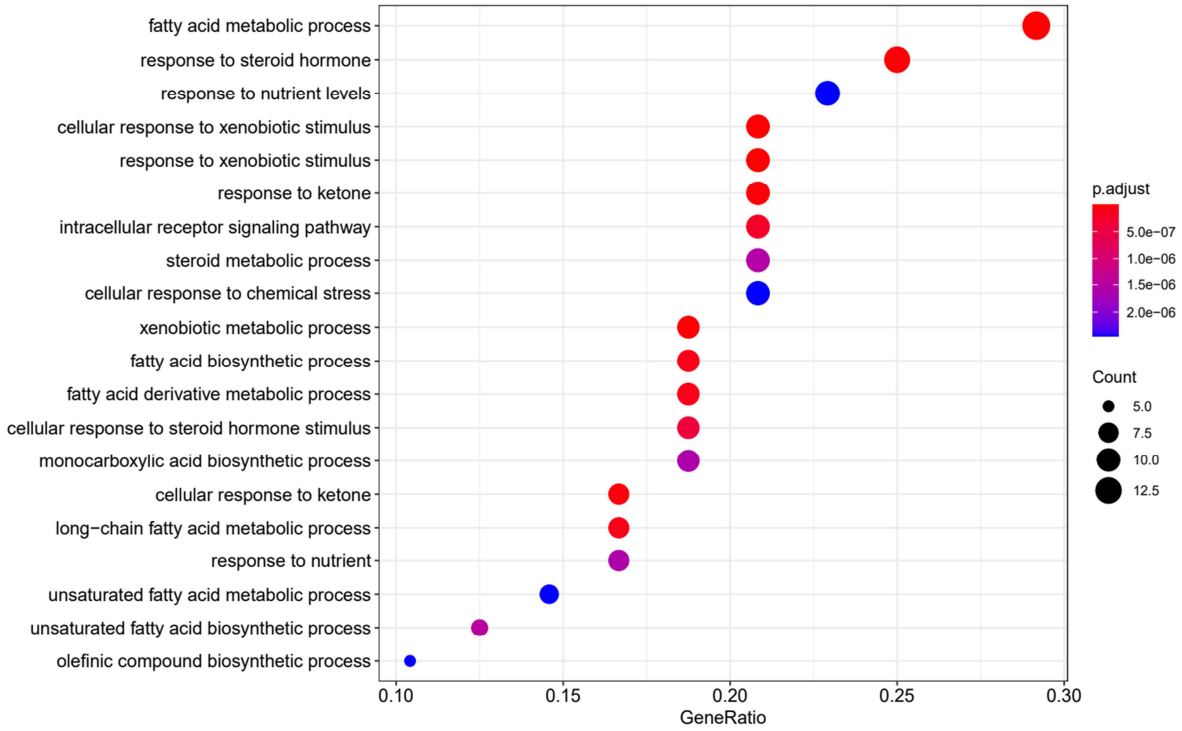
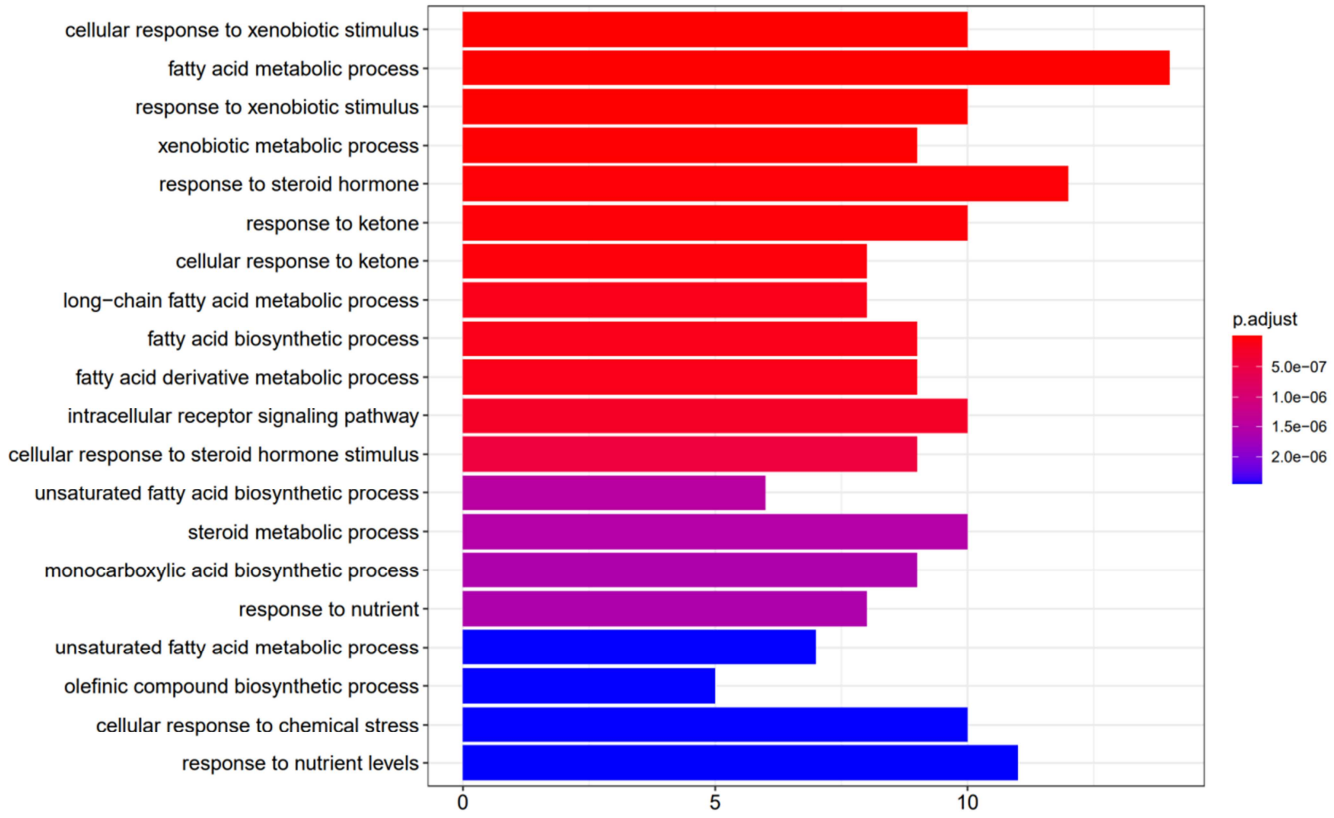


Figure 5. *Bubble diagram of GO enrichment analysis.*

Importing key targets into the R software, the KEGG enrichment pathway results (Figure 6) showed mainly: fluid shear stress and interaction in atherosclerosis, lipids and atherosclerosis, stimulation of neural tissue, prostate cancer, AGE-RAGE signaling pathway in diabetic complications, estrogen signaling pathway, breast cancer, hepatocellular carcinoma, resistance to endocrine, cholinergic synapses, drug metabolism-cytosolic Chromogranin P450, metabolism of exogenous drugs by cytochrome P450, resistance to EGFR tyrosine kinase inhibitors, tumor necrosis factor signaling pathway, calcium signaling pathway, PI3K-Akt signaling pathway.



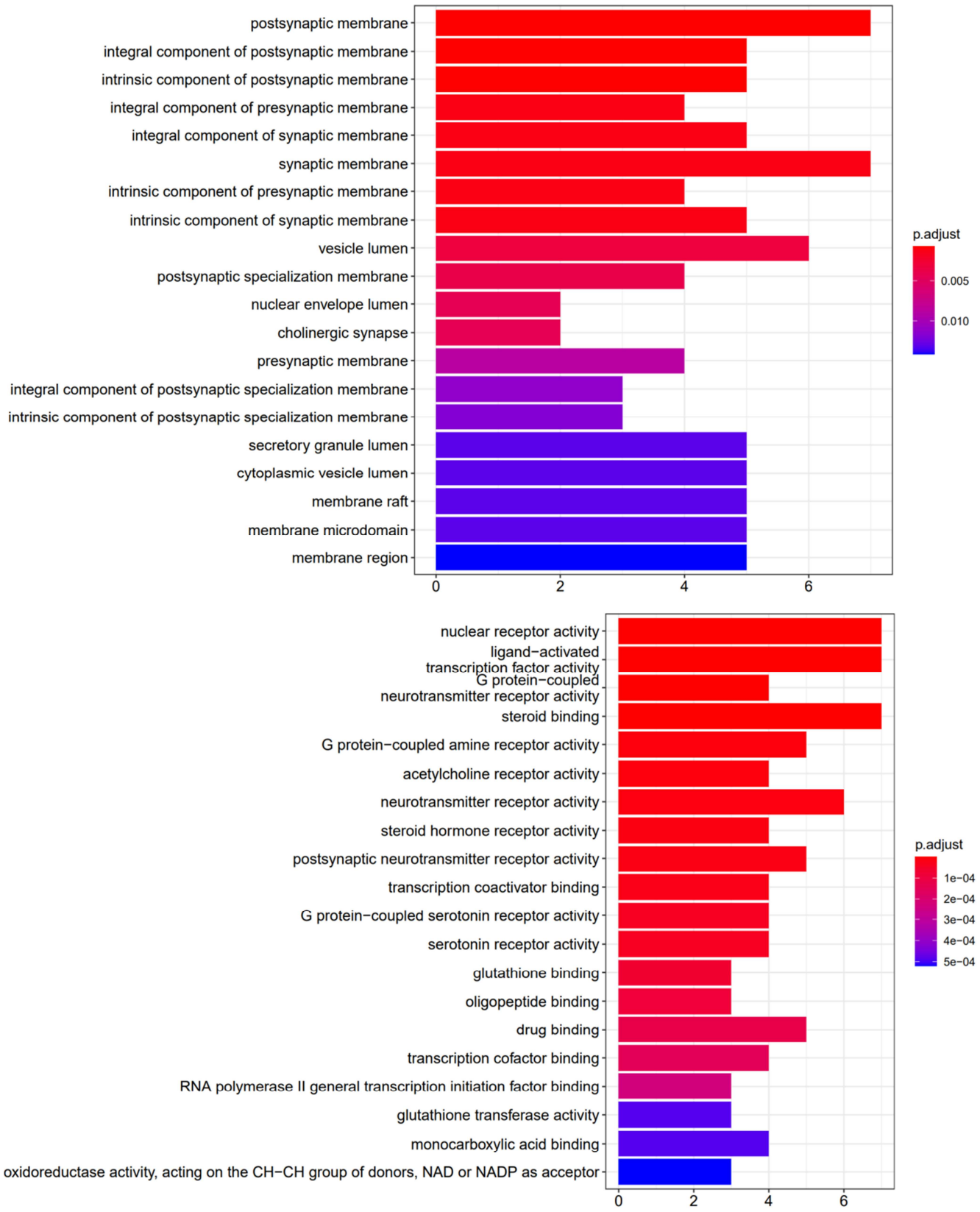


Figure 6. *Histogram of GO enrichment analysis.*

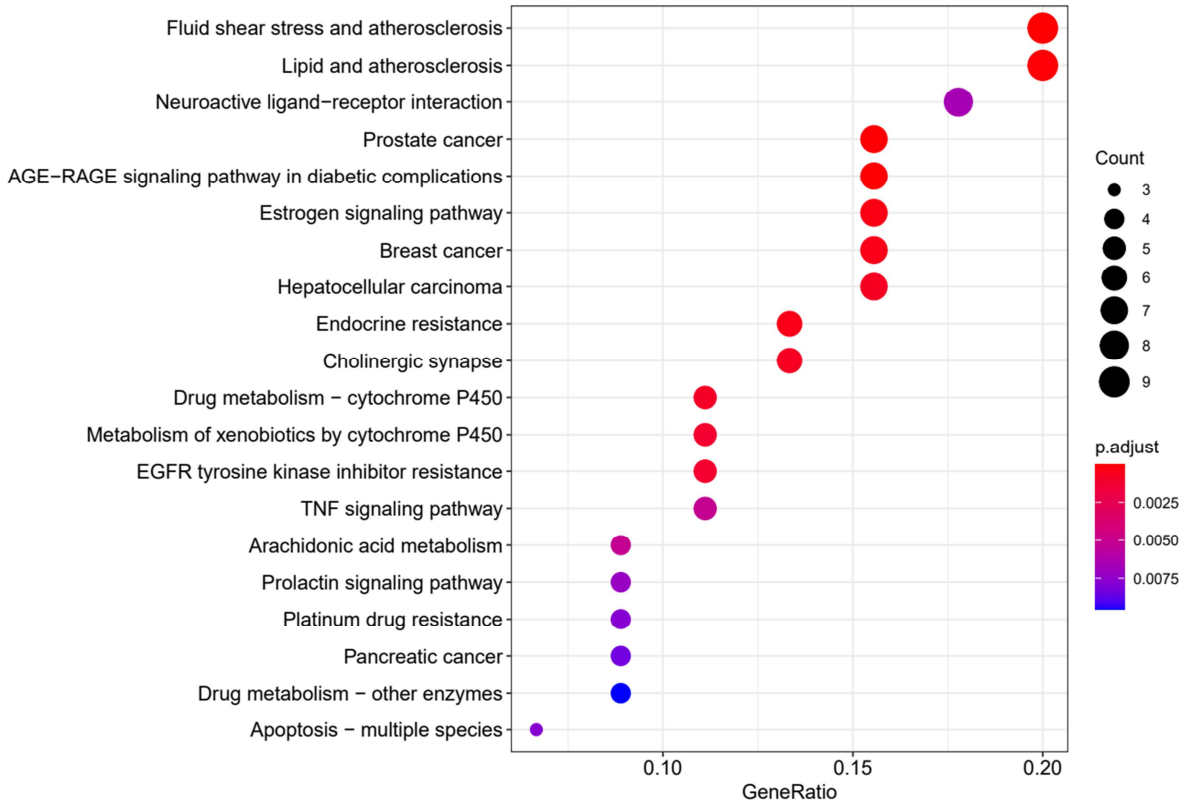


Figure 7. *Bubble diagram of KEGG enrichment analysis.*

4. Discussion

In the PPI network analysis, we found that the core targets are EGFR, VEGFA, etc. The resistance pathway of EGFR tyrosine kinase inhibitors was also found in the KEGG enrichment pathway. epidermal growth factor receptor (EGFR) is a membrane receptor with tyrosine protein kinase activity, and the EGFR-related signaling pathway is involved in the regulation of various biological functions [15, 16], and is involved in the development of a variety of tumors, showing overexpression in tumor cells [17], And EGFR overexpression is also found in gliomas [18, 19]. Excessive activation of EGFR signaling pathway can promote proliferation of glioma cells [20], Invasion, recurrence [21, 22], Transfers [23]. High EGFR expression over activates phosphatidylinositol-3-kinase-protein kinase B (PI3K-AKT) [24], The over-activation of EGFR can also induce the overexpression of CDK4 and CDK6, which can promote the over-proliferation of glioma cells [25]. Jiao Baohua et al. also concluded in their experiments that VEGF expression in tumors of rats treated with Ginkgo biloba was lower than in the control group [26]. In 2009, the FDA recommended bevacizumab for patients with recurrent GBM with VEGFR gene mutations [27]. Therefore, inhibition of the biological activity of EGFR can have a therapeutic effect on glioma [28]. Regarding whether Ginkgo biloba controls tumor cell growth through anti-angiogenesis, these need to be sexually verified in subsequent cellular and clinical experiments.

IL-6 is the most central inflammatory factor in inflammation and tumor [29], There is now a proven association with tumors [30], High IL-6 expression has a poor prognosis [31]. Increased IL-6 levels lead to conversion of normal cells to tumor cells [32], IL-6 is classified as a tumor-promoting factor [33], Ginkgo inhibits NO release, thereby reducing the expression of the inflammatory factor IL-6 mRNA and the cellular chemokine RAN TES mRNA [34], IL-6 binds to IL-6R and then binds 2 molecules of gp130, which activates the phosphatidylinositol 3-kinase (PI3K) pathway [35], Zhang Shen [36] et al. verified by PCR and western that Ginkgo biloba extract could regulate NO production in glioma cells through NF-κB signaling pathway, thus inhibiting the growth of tumor cells. We also verified the presence of IL-6 targets and PI3K pathway in PPI network analysis and KEGG enrichment analysis. Chinese medicine believes that chronic inflammation over time leads to the accumulation of phlegm and blood stasis, and then the six evil spirits take advantage of the opportunity to enter and form tumors [37].

The molecular function of Ginkgo biloba for the treatment of glioma is mainly enriched in the activity of neurotransmitter receptors. Cellular components are enriched to the postsynaptic membrane, synaptic membrane, vesicle, components of the postsynaptic membrane, and intrinsic components of the postsynaptic membrane, etc. Some studies have confirmed that ginkgolide B reduces ATPase activity [38]. This affects the level of cellular metabolism, thus providing new ideas for the treatment of glioma with Ginkgo biloba. In addition, a large number of experiments have shown that Ginkgo biloba extract can effectively inhibit the

proliferation and invasion of glioma cells and promote apoptosis [39-42].

5. Conclusion

Based on the network pharmacology, this paper investigates the active ingredients of Ginkgo biloba and their possible targets and pathways acting on glioma. 27 active ingredients of Ginkgo biloba were derived from the compositional analysis, and the top 9 core targets were IL6, ESR1, EGFR, PPARG, VEGFA, CYP3A4, AHR, AR, PGR after PPI network construction, and the possible targets and corresponding pathways were inferred by GO and KEGG analysis was used to speculate the possible targets and corresponding pathways, which led to the conclusion that Ginkgo biloba achieves therapeutic effects on glioma through multiple targets and pathways, which is in line with the characteristics of holistic treatment of diseases in Chinese medicine. However, more cellular experiments and clinical trials are needed for validation.

Data Availability

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

Conflicts of Interest

The authors declare that they have no competing interests.

Authors' Contributions

Shihua Liu and Aixia Sui wrote the article and designed the study. Shihua and Sen Yang were responsible for data collection and analysis. Sen Yang and Xiaohui Han were responsible for data analysis. Shihua Liu and Aixia Sui revised and critically reviewed the article. All authors have agreed on the journal to which the article has been submitted, agreed to be accountable for all aspects of the work criteria and made a significant contribution to the work reported.

References

[1] Kohler Betsy A, Ward Elizabeth, McCarthy Bridget J, et al. Annual report to the nation on the status of cancer, 1975-2007, featuring tumors of the brain and other nervous system. [J]. Journal of the National Cancer Institute, 2011, 103 (9).

[2] Tian Yunhong, Xie Qiang, He Jie, et al. Radioactive (125) I seeds inhibit cell growth and epithelial-mesenchymal transition in human glioblastoma multiforme via a ROS-mediated signaling pathway. [J]. BMC cancer, 2015, 15.

[3] Meng Jie, Wang Bo, He Guo, et al. Metabolomics Integrated with Transcriptomics Reveals Redirection of the Phenylpropanoids Metabolic Flux in Ginkgo biloba. [J]. Journal of agricultural and food chemistry, 2019.

[4] Bikram Singh, Pushpinder Kaur, Gopichand, R. D, et al. Biology and chemistry of Ginkgo biloba [J]. Fitoterapia, 2008, 79 (6).

[5] Tingfu Liang, Takuya Miyakawa, Jinwei Yang, et al. Quantification of terpene trilactones in Ginkgo biloba with a 1 H NMR method [J]. Journal of Natural Medicines, 2018, 72 (3).

[6] Kaur Sukhwinder, Sharma Neha, Nehru Bimla. Anti-inflammatory effects of Ginkgo biloba extract against trimethyltin-induced hippocampal neuronal injury. [J]. Inflammopharmacology, 2018, 26 (1).

[7] Fan Yu, Jin Xin, Man Changfeng, et al. Does Adjuvant Treatment With Ginkgo Biloba to Statins Have Additional Benefits in Patients With Dyslipidemia? [J]. Frontiers in pharmacology, 2018, 9.

[8] Li XiuXiu, Liu ShiHui, Zhuang SuJing, et al. Effects of oxiracetam combined with ginkgo biloba extract in the treatment of acute intracerebral hemorrhage: A clinical study. [J]. Brain and behavior, 2020, 10 (8).

[9] Evans Jennifer R. Ginkgo biloba extract for age-related macular degeneration. [J]. The Cochrane database of systematic reviews, 2013, (1).

[10] Kuller LH, Ives DG, Fitzpatrick AL, et al. Does Ginkgo biloba reduce the risk of cardiovascular events? [J]. Circ Cardiovasc Qual Outcomes. 2010, 3 (1): 41-7.

[11] Cao Shuqin, Gao Mei, Wang Ningli, et al. Prevention of Selenite-Induced Cataratogenesis by Ginkgo biloba Extract (Egb761) in Wistar Rats. [J]. Current eye research, 2015, 40 (10).

[12] Chao Jane C J, Chu Chia Chou. Effects of Ginkgo biloba extract on cell proliferation and cytotoxicity in human hepatocellular carcinoma cells. [J]. World journal of gastroenterology, 2004, 10 (1).

[13] Christian Ude, Manfred Schubert-Zsilavecz, Mario Wurglics. Ginkgo biloba Extracts: A Review of the Pharmacokinetics of the Active Ingredients [J]. Clinical Pharmacokinetics, 2013, 52 (9).

[14] Yu, Y; Yang, F; Liu, H; Biosci Rep. Network pharmacology evaluation of the active ingredients and potential targets of XiaoLuoWan for application to uterine fibroids. 2020 12 23; 40 (12).

[15] Guillem Ramis, Elena Thomàs-Moyà, Silvia Fernández de Mattos, et al. EGFR inhibition in glioma cells modulates Rho signaling to inhibit cell motility and invasion and cooperates with temozolomide to reduce cell growth. [J]. PLoS ONE, 2017, 7 (6).

[16] Karrie Mei-Yee Kiang, Xiao-Qin Zhang, Grace Pingde Zhang, et al. CRNDE Expression Positively Correlates with EGFR Activation and Modulates Glioma Cell Growth [J]. Targeted Oncology, 2017, 12 (3).

[17] Jiao KePing, Bao LiJuan, Chen HengSan, et al. Epidermal growth factor receptor gene silencing regulates the apoptosis of glioma cells via janus kinase/signal transducer and activators of transcription signaling pathway [J]. Chinese Journal of Experimental Surgery, 2021, 38 (09): 1654-1658.

[18] Fei-yi-fan Wang, Chun-Sheng Kang, Si-yi Wang-gou, et al. EGFL7 is an intercellular EGFR signal messenger that plays an oncogenic role in glioma [J]. Cancer Letters, 2017, 384.

[19] Karpel-Massler G, Westhoff M-A, Kast R E, et al. Simultaneous Interference with HER1/EGFR and RAC1 Signaling Drives Cytostasis and Suppression of Survivin in Human Glioma Cells in Vitro. [J]. Neurochemical research, 2017, 42 (5).

[20] Mao Jiani, Ran Danni, Xie Cao, et al. EGFR/EGFRvIII Dual-Targeting Peptide-Mediated Drug Delivery for Enhanced Glioma Therapy. [J]. ACS applied materials & interfaces, 2017, 9 (29).

[21] Lv Yifan, Luo Junran, Jing Guojie, et al. Differences of biological property between glioma stem cells and glioma non-stem cells [J]. Chinese Journal of Neuromedicine, 2019, (03): 225-232.

[22] Li Yanyan, Chen Xionghui, Sun Ting, et al. The anti-cancer effect of ZR30 protein via targeting extracellular signal proteins of different cell subpopulations of glioma [J]. Chinese Journal of Oncology, 2018, 40 (11): 812-817.

[23] Paul Indranil, Bhattacharya Seemana, Chatterjee Anirban, et al. Current Understanding on EGFR and Wnt/β-Catenin Signaling in Glioma and Their Possible Crosstalk. [J]. Genes & cancer, 2013, 4 (11-12).

[24] Lai K, Killingsworth M C, Lee C S. Gene of the month: PIK3CA. [J]. Journal of clinical pathology, 2015, 68 (4).

[25] Jonathan T. Elliott, Kayla Marra, et al. Simultaneous In Vivo Fluorescent Markers for Perfusion, Protoporphyrin Metabolism, and EGFR Expression for Optically Guided Identification of Orthotopic Glioma [J]. Clinical Cancer Research, 2017, 23 (9).

[26] Jiao Baohua, Zhang Xiaowei, Liang Zhaohui. ANTICANCER EFFECTS OF GINKGO BILOBA EXTRACT ON BRAIN GLIOMA IN RATS [J]. Journal of Hebei Medical University, 2011, 32 (01): 19-22+125.

[27] Wang L, Sun L, Liu F R, et al. Clinical Value of Next Generation Sequencing in Gliomas [J]. China Cancer, 2021, 30 (08): 627-634.

[28] Wang W, Zhang LY, Zhao ZL, et al. The inhibitory effect of calycosin on the proliferation of glioma cells [J]. Journal of Shenyang Pharmaceutical University, 2020, 37 (08): 725-729+755.

[29] Koji Taniguchi, Michael Karin. IL-6 and related cytokines as the critical lynchpins between inflammation and cancer [J]. Seminars in Immunology, 2014, 26 (1).

[30] McDougall Jean A, Banegas Matthew P, Wiggins Charles L, et al. Rural Disparities in Treatment-Related Financial Hardship and Adherence to Surveillance Colonoscopy in Diverse Colorectal Cancer Survivors. [J]. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology, 2018, 27 (11).

[31] Qiu M. H., Kong C. C., Chen W. M., et al. Effect of curcumin on inflammatory colorectal cancer based on IL-6/STAT3 signaling pathway [J]. Chinese Journal of Immunology, 2021, 37 (17): 2093-2098.

[32] Shen Zhengjie, Cheng Haibo, Shen Satellite, et al. Correlation between tumor inflammatory microenvironment and "cancerous toxin" pathogenesis [J]. Journal of Beijing University of Traditional Chinese Medicine, 2015, 38 (01): 14-17.

[33] Mihara Masahiko, Hashizume Misato, Yoshida Hiroto, et al. IL-6/IL-6 receptor system and its role in physiological and pathological conditions. [J]. Clinical science (London, England: 1979), 2012, 122 (4).

[34] Pang, Shan-Ying, Liao, Wen-Hui, Nie, Precious, et al. Effect of ginkgolide B on the production of NO, IL-6 and RANTES from astrocytes [J]. Acta Pharmaceutica Sinica, 2010, 45 (09): 1103-1108.

[35] Prystaz Katja, Kaiser Kathrin, Kovtun Anna, et al. Distinct Effects of IL-6 Classic and Trans-Signaling in Bone Fracture Healing. [J]. The American journal of pathology, 2018, 188 (2).

[36] ZHANG Shen, LI Xiaoyang, WEI Tao-tao. Regulatory Effect of Ginkgo Biboba Extract on the Expression of NF-κB and Nitroxide Production in Glioma Cells [J]. Cancer Research on Prevention and Treatment, 2006, (06): 397-400+476.

[37] Gao S. Overview of research on immune mechanism of Fu Zheng Chinese medicine in the treatment of malignant tumors [J]. Hunan Journal of Traditional Chinese Medicine, 2014, 30 (11): 171-173.

[38] Pretner Ewald, Amri Hakima, Li Wenping, et al. Cancer-related overexpression of the peripheral-type benzodiazepine receptor and cytostatic anticancer effects of Ginkgo biloba extract (EGb 761). [J]. Anticancer research, 2006, 26 (1A).

[39] Chen JL, Shan GJ, Sun CX, et al. Ginkgo Biloba Extract Inhibits Proliferation and Invasion of Glioblastoma U87 Cells Through Regulating NF-κB Signaling Pathway [J]. Journal of Chinese Oncology. 2020, 26 (01): 26-30.

[40] Li Xiaodong, Wang Bao, Wang Jianfang, et al. Pro-apoptotic effect of Ginkgo biloba extract on U251 glioma cells [J]. Contemporary Medicine, 2013, 19 (14): 1-2.

[41] Liu Yantong, Cheng Fan, Fu Hui, et al. Effect of EGB761 to apoptosis of brain glioma U87 cell in vitro [J]. Modern medical oncology, 2014, (10): 2270-2272.

[42] Hui Qingshan, Wu Zhizhi, Cheng Lin. The effect of Ginkgo Biloba Extracts combined with cisplatin on proliferation and apoptosis of human glioblastoma U251 cells [J]. Contemporary Medicine, 2017, 23 (28): 10-13.