Analysis of Oxoglaucine in the Treatment of Breast Cancer Based on Network Pharmacology and Bioinformatics

Ting Chen¹, Haiyu Chen¹, Liang Zhang¹, Bin Zhou², Chao Yang², Xulong Huang¹, Bin Huang¹*

¹School of Pharmaceutical Sciences, Hunan University of Medicine, Huaihua 418000, China
²Department of Pharmacy, Guizhou Health Vocational College, Tongren 554301, China

Abstract. To explore the potential molecular mechanism of Oxoglaucine(OG) in the treatment of Breast Cancer(BC) based on network pharmacology and bioinformatics. TCMSP and SwissTargetPrediction databases search for OG Related targets, and GeneCards database finds all BC-related targets. Take the intersection of OG and BC as all potential targets that inhibit BC. All potential targets are topologically analyzed by Cytoscape 3.7.1 software, and finally the core target is obtained. The start analysisi function in the DAVID database performs bioinformatics analysis on all core targets, and further visualizes them with the help of R language tools. As a result, 104 potential targets were obtained, of which SRC, PIK3CA, EGFR, MTOR, ESR1, MAPK1, PTGS2, AR, and NOS3 were the main core targets. OG inhibits the occurrence of BC through Pathways in cancer, PI3K-Akt signaling pathway, Proteoglycans in cancer, ErbB signaling pathway, HIF-1 signaling pathway related pathways, mainly involving signal transduction, protein phosphorylation, negative regulation of apoptotic process, positive regulation of transcription from RNA polymerase II promoter, phosphatidylinositol-mediated signaling biological processes. This study initially reveals the molecular mechanism of OG inhibiting BC, which provides a reference for further research.

1 Introduction

Breast Cancer(BC) is a common and multiple malignant tumor all over the world, which seriously endangers the life and health of women[1]. BC originates from the malignant transformation of breast ductal epithelium or breast acinar epithelial cells, distant metastasis is one of the main causes of death[2-3]. The conventional treatment of BC is mainly based on radiotherapy and chemotherapy. Some patients will also cooperate with other drugs to improve their immune function after surgery[4-5]. The 2019 BC Diagnosis and Treatment Guidelines propose that preoperative neoadjuvant drugs (anthracyclines, taxanes) treatment can be selected according to the situation[6], so the development of new natural medicines is of great significance for the adjuvant treatment of BC.

Oxoglaucine(OG) is an alkaloid component isolated from the traditional Chinese medicine Corydalis yanhusuo[7]. OG has strong pharmacological activity. Modern research shows that OG has antiviral, antibacterial, anti-inflammatory, immune repair and other activities[8-11], but its anti-tumor effects are rarely reported, and the mechanism of action is still unclear.

This study mainly used the methods of network pharmacology and bioinformatics to predict the molecular mechanism of OG inhibiting BC, and provide reference for the in-depth study of OG anti-tumor.

2 Materials and methods

2.1 OG-related targets

We obtain all the active targets of OG from TCMSP and SwissTargetPrediction(http://www.swisstargetprediction.ch/) database, and establish a data set.

2.2 BC-related targets

We obtained BC-related targets in the GeneCards database (https://www.genecards.org/), searched for the keyword "breast cancer", and established a disease target data set.

2.3 Network construction

Potential targets for inhibiting BC are obtained by taking the intersection of disease and drug target data sets. The String database (https://string-db.org/) is used to construct the PPI network of potential targets, PPI network is analyzed using cytoscape 3.7.1 software to calculate the "Degree", "Betweenness centrality" and "Closeness centrality", Obtain all core targets, and use greater than the median as the screening condition.
2.4 Bioinformatic analysis

The core targets are entered in DAVID (https://david.ncifcrf.gov/tools.jsp) for Genetic ontology (GO) enrichment analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis. Using R language tools to visually analyze the core targets, P ≤ 0.05 as the screening criterion.

2.5 Pathway mapper construction

KEGG (https://www.genome.jp/kegg/) Mapper function will map core targets to different pathways.

3 Results

3.1 Target prediction

In the TCMSP and Swiss Target Prediction databases, 112 targets corresponding to OG were obtained, and 15207 BC targets were obtained in the GeneCards database. The disease and drug data sets were intersected to obtain 104 potential targets. The results are shown in Figure 1.

![Fig. 1. Drug-disease intersection target Venn diagram](image)

3.2 Screening of core targets

We use Cytoscape 3.7.1 software to visually analyze potential targets, the core target must be greater than the median of the three topological parameters at the same time. The median values of the three topological parameters are 10 (Degree), 0.0029 (Betweenness centrality), 0.4525 (Closeness centrality). The results are shown in Table 1 and Figure 3.

3.3 Drug-disease-core target network construction

We use Cytoscape 3.7.1 software to build a "drug-disease-core target" network, and the results are shown in Figure 2.

![Fig. 2. Drugs-diseases-core targets network](image)

3.4 GO Biological process enrichment analysis

Enrichment analysis was performed on 171 biological processes, and the top 10 biological processes, cell composition and molecular functions were selected. The results are shown in Figure 4. The results preliminary reveals that OG may inhibit BC through a variety of biological processes such as signal transduction, protein phosphorylation, negative regulation of apoptotic process, positive regulation of transcription from RNA polymerase II promoter, phosphatidylinositol-mediated signaling.

![Table 1. Related topological parameters of the core target](image)
| P11511 | CYP19A1 | Cytochrome P450 Family 19 Subfamily A Member 1 | 15 | 0.5051 | 0.0315 |
| P49841 | GSK3B | Glycogen Synthase Kinase 3 Beta | 26 | 0.5405 | 0.0276 |
| P11802 | CDK4 | Cyclin Dependent Kinase 4 | 26 | 0.5291 | 0.0259 |
| P17252 | PRKCA | Protein Kinase C Alpha | 21 | 0.5208 | 0.0252 |
| Q13255 | GRM1 | Glutamate Metabotropic Receptor 1 | 12 | 0.4566 | 0.0236 |
| Q92793 | CREBBP | CREB Binding Protein | 22 | 0.5208 | 0.0208 |
| P45983 | MAPK8 | Mitogen-Activated Protein Kinase 8 | 30 | 0.5495 | 0.0198 |
| O00329 | PIK3CD | Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Delta | 26 | 0.5051 | 0.0191 |
| P24941 | CDK2 | Cyclin Dependent Kinase 2 | 21 | 0.5051 | 0.0144 |
| Q05513 | PRKCZ | Protein Kinase C Zeta | 25 | 0.5376 | 0.0133 |
| P19793 | RXRA | Retinoic X Receptor Alpha | 13 | 0.4717 | 0.0128 |
| P42338 | PIK3CB | Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Beta | 26 | 0.5102 | 0.0107 |
| P23443 | RPS6KB1 | Ribosomal Protein S6 Kinase B1 | 27 | 0.5525 | 0.0102 |
| P04626 | ERBB2 | Erb-B2 Receptor Tyrosine Kinase 2 | 26 | 0.5405 | 0.0095 |
| P78527 | PRKDC | Protein Kinase, DNA-Activated, Catalytic Subunit | 15 | 0.4831 | 0.0092 |
| O14965 | AURKA | Aurora Kinase A | 17 | 0.4926 | 0.0088 |
| Q02750 | MAP2K1 | Mitogen-Activated Protein Kinase Kinase 1 | 26 | 0.5376 | 0.0086 |
| Q05397 | PTK2 | Protein Tyrosine Kinase 2 | 22 | 0.5181 | 0.0073 |
| Q15379 | HDAC3 | Histone Deacetylase 3 | 12 | 0.4808 | 0.0071 |
| P11388 | TOP2A | DNA Topoisomerase II Alpha | 15 | 0.4926 | 0.0057 |
| Q15759 | MAPK11 | Mitogen-Activated Protein Kinase 11 | 18 | 0.4926 | 0.0053 |
| P08069 | IGF1R | Insulin Like Growth Factor 1 Receptor | 25 | 0.5376 | 0.0050 |
| P35228 | NOS2 | Nitric Oxide Synthase 2 | 11 | 0.4695 | 0.0048 |
| P10721 | KIT | KIT Proto-Oncogene, Receptor Tyrosine Kinase | 15 | 0.4926 | 0.0031 |

Fig. 3. The protein interaction network of drug-disease intersection target
3.5 KEGG Pathway enrichment analysis

KEGG pathway analysis was performed on core targets, and 18 important pathways were presented, the results are shown in Figure 5. The main signaling pathways include Pathways in cancer, PI3K-Akt signaling pathway, Proteoglycans in cancer, ErbB signaling pathway, HIF-1 signaling pathway related pathways.

3.6 Pathway annotation diagram of OG's anti-BC effect

We enter the core target into the KEGG database, KEGG mapping function will map the target into each pathway and mark the number of targets. 21 target proteins are involved in the Pathways in cancer.

4 Discussion

The analysis results of network pharmacology and bioinformatics show that SRC, PIK3CA, EGFR, MTOR and ESR1 may be the core targets of OG to inhibit BC. Src is an important anti-tumor drug target, and it is expressed at a high level in various tumors such as lung cancer, breast cancer, rectal cancer and pancreatic cancer [12]. Abnormally activated Src can be involved in the occurrence and development of tumors, such as apoptosis, proliferation, cell adhesion, migration, invasion, blood vessel formation and metastasis[13]. PIK3CA is a proto-oncogene, and mutations in the PIK3CA gene are associated with breast cancer hormone receptor expression and tumor progression[14].

GO biological process enrichment analysis reveals that the main biological process of OG's anti-BC effect may include signal transduction, protein phosphorylation, negative regulation of apoptotic process, positive regulation of transcription from RNA polymerase II promoter.

KEGG pathway enrichment analysis shows that OG anti-BC effects through regulating Pathways in cancer, PI3K-Akt signaling pathway, Proteoglycans in cancer, ErbB signaling pathway, HIF-1 signaling pathway related pathways. The occurrence of BC is related to a variety of factors, Studies have suggested that PI3K/AKT signaling pathway gene mutations often occur in BC[15].

5 Conclusions

A total of 104 potential targets were obtained, 33 of which are core targets for OG inhibit BC. GO biological process enrichment analysis and KEGG pathway enrichment analysis revealed 10 biological processes, cell composition, molecular functions and 18 pathways are closely related to the occurrence and development of inhibiting BC, mainly involving Pathways in cancer, PI3K-Akt signaling pathway, Proteoglycans in cancer, ErbB signaling pathway, HIF-1 signaling pathway. In this study, we used the methods of network pharmacology and bioinformatics to preliminarily predict the molecular mechanism of OG inhibiting BC, and provide a reference for the in-depth development of OG anti-tumor.
Acknowledgments

The authors would like to thank the financial support from the Scientific Research Foundation of Hunan Provincial Education Department (20B415), the Technology Project Foundation of Tongren ([2018]48), the Technology Project Foundation of Tongren ([2019]55).

References

1. M. Ghoncheh, Z. Pournamdar, H. Salehiniya, *Asian Pac J Cancer Prev*, 17(S3), 43-46 (2016).
2. C. E. DeSantis, J. M. Ma, S. A. Goding, *CA Cancer J Clin*, 67(6), 439-448 (2017).
3. C. S. Benson, S. D. Babu, S. Radhakrishna, *Dis Markers*, 34(6), 395-405 (2013).
4. P. Xglv, R. Blt, M. A. Joore, *Breast Cancer Res Treat*, 165, 485-498 (2017).
5. P. Fox, A. Darley, E. Furlong, *Eur J Oncol Nurs*, 26, 63-82 (2017).
6. Chinese Society of Clinical Oncology (CSCO) Breast Cancer Diagnosis and Treatment Guidelines, *People's Medical Publishing House*, 24 (2017).
7. X. L. Zhang, Review on research progress of chemical constituents of *Corydalis yanhusuo* W. T. Wang[D], Shenyang, Shenyang Pharmaceutical University (2008).
8. N. G. Lubomira, Adelina S. Anna, Metodieva, S. Angel, Galabov, *Antiviral Research*, 90(2), A61, (2011).
9. N. Ivanovska, M. Hristova, S. Philipov, *Pharmacol Res*, 41(1), 99-105, (2000).
10. M. Remichkova, P. Dimitrova, S. Philipov, N. Ivanovska, *Fitoterapia*, 80(7), 411-4 (2009).
11. N. Ivanovska, S. Philipov, *Methods Find Exp Clin Pharmacol*, 19(9), 79-83 (1997).
12. Q. Wang, L. Liu, Y. Le, L. J. Yan, *Chin J Med Chem*, 31(04), 312-319 (2021).
13. D. L. Wheeler, M. Iida, E. F. Dunn, *Oncologist*, 14(7), 67-78 (2009).
14. Y. M. Deng, Y. J. Xu, *Int J Lab Med*, 37(15), 2110-2111+2114 (2016).
15. I. A. Mayer, C. L. Arteaga, *J Clin Oncol*, 32(27), 2932-4 (2014).