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

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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.

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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, $P \leq 0.05$ 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

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

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

UniProt CID	Gene name	Protein name	Degree	Closeness Centrality	Betweenness Centrality
P12931	SRC	SRC Proto-Oncogene, Tyrosine Kinase	50	0.6536	0.1270
P11511	PIK3CA	Phosphatidylinositol-4, 5-Bisphosphate 3-Kinase Catalytic Subunit Alpha	42	0.6173	0.0976
P00533	EGFR	Epidermal Growth Factor Receptor	42	0.6173	0.0800
P42345	MTOR	Mechanistic Target Of Rapamycin Kinase	46	0.6329	0.0783
P03372	ESR1	Estrogen Receptor 1	39	0.5988	0.0701
P28482	MAPK1	Mitogen-Activated Protein Kinase 1	39	0.5988	0.0674
P35354	PTGS2	Prostaglandin-Endoperoxide Synthase 2	30	0.5618	0.0611
P10275	AR	Androgen Receptor	33	0.5714	0.0540
P29474	NOS3	Nitric Oxide Synthase 3	24	0.5376	0.0536
P09874	PARP1	Poly(ADP-Ribose) Polymerase 1	23	0.5236	0.0392

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	Retinoid 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
O15379	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

Fig. 4. Top 10 biological process enrichment results

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.

Fig. 5. The 18 pathways enriched by major hubs

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).

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