doi:10.3969/j.issn.1006－4931.2020.19.003

基于网络药理学探讨白花蛇舌草治疗口腔癌的作用机制*

顾 磊[1],廖 维[2],周建萍[3△]

(1. 武警重庆市消防总队医院口腔科,重庆 401120; 2. 中国人民解放军陆军军医大学第二附属医院麻醉科,重庆 400037; 3. 重庆医科大学附属口腔医院,重庆 401147)

摘要:目的 探讨白花蛇舌草治疗口腔癌的作用机制及其药用价值。**方法** 采用 HIT、中药综合资源数据库(TCMID)、PubMed、中药系统药理数据库和分析平台(TCMSP)数据库检索白花蛇舌草的化合物成分,根据毒药物动力学(ADME)参数和里宾斯基五规则筛选具有成药性的化合物成分,采用 TCMSP,TargetNet,Pharmmapper 数据库检索并筛选潜在靶点,采用 DiseaseGene Network 数据库检索口腔癌的相关靶点。采用 STRING 数据库建立蛋白质－蛋白质相互作用(PPI)关系,通过基因映射、拓扑分析与富集分析的方法,预测白花蛇舌草治疗口腔癌的核心靶点与通路,以及生物过程(BP)、细胞成分(CC)、分子功能(MF)。**结果** 共收集到 93 种白花蛇舌草的化合物成分,经 ADME 标准及里宾斯基五规则进行筛选后共获得 32 个化学结构不同的化合物成分,353 个不同的白花蛇舌草化合物的相关靶点;通过 DiseaseGene Network 数据库,共收集到 281 个口腔癌的相关靶点;通过基因映射与拓扑分析,共获得 200 个白花蛇舌草治疗口腔癌的作用靶点,75 个具有拓扑重要性的靶点;通过富集分析获得白花蛇舌草治疗口腔癌的 336 个 BP、38 个 CC、105 个 MF、25 条相关作用通路($P<0.05$ 时),51 个 BP、7 个 CC、31 个 MF、4 条核心作用通路($P<0.01$, $FDR<0.01$ 时)。**结论** 白花蛇舌草治疗口腔癌的作用机制涉及多个靶点和信号通路,其与细胞凋亡、增殖、炎性反应、氧化应激等多个生物过程相关。

关键词:白花蛇舌草;口腔癌;网络药理学;靶点;信号通路

中图分类号:R932;R285.5 **文献标识码:A** **文章编号:1006－4931(2020)19－0009－07**

Mechanism Investigation of *Hedyotis Diffusa* for Treating Oral Cancer Based on Network Pharmacology

GU Lei[1], *LIAO Wei*[2], *ZHOU Jianping*[3]

(*1. Department of Stomatology, Chongqing Fire Brigade Hospital of Armed Police, Chongqing, China 401120; 2. Department of Anesthesiology, The Second Affiliated Hospital of Army Military Medical University, Chongqing, China 400037; 3. Stomatological Hospital of Chongqing Medical University, Chongqing, China 401147*)

Abstract: Objective To investigate the mechanism and medicinal value of *Hedyotis diffusa* on oral cancer. **Methods** HIT, TCMID, PubMed, TCM System Pharmacological Database and Analysis Platform(TCMSP) database were used to search for the compound components of *Hedyotis diffusa*, and the compounds were screened with druggability according to the absorption, distribution, metabolism, excretion(ADME)

*基金项目:重庆市基础研究与前沿探索项目[cstc2018jcyjAX0220]。

第一作者:顾磊,男,大学本科,主治医师,研究方向为口腔全科医学,(电子信箱)392545634@qq.com。

△通信作者:周建萍,男,博士研究生,副主任医师,研究方向为生物力学和牙颌畸形矫治,(电子信箱)zjp@hospital.cqmu.edu.cn。

[13] 康传依,胡 建. 慢性酒精中毒脑损伤的研究进展[J]. 医学综述,2017,23(24):4895－4899.

[14] GEORGE AK, BEHERA J, KELLY KE, et al. Hydrogen sulfide, endoplasmic reticulum stress and alcohol mediated neurotoxicity[J]. Brain Res Bull, 2017, 130: 251－256.

[15] 高 平,谢宝君,李 光,等. MRI 对 Wernicke 脑病的临床诊断价值[J]. 放射学实践,2014,29(1):45－48.

[16] 中国医师协会神经内科分会脑与脊髓损害专业委员会. 慢性酒精中毒性脑病诊治中国专家共识[J]. 中华神经医学杂志,2018,17(1):2－9.

[17] LATT N, DORE G. Thiamine in the treatment of Wernicke encephalopathy in patients with alcohol use disorders[J]. Intern Med J, 2014, 44(9): 911－915.

[18] BOULANGER AS, PAQUETTE I, LETOURNEAU G, et al. Wernicke encephalopathy: Guiding thiamine prescription[J]. Encephale, 2017, 43(3): 259－267.

[19] 周露玲,曾 立,贾 薇,等. 35 例韦尼克脑病临床分析[J]. 中风与神经疾病杂志,2016,33(9):816－819.

[20] 王晶华. 酒精中毒的中枢神经表现[J]. 世界最新医学信息文摘,2017,17(54):162.

[21] PANDEY D, KUHN JL, TEJERO H, et al. Alcohol Induced Wernicke Encephalopathy with Atypical MRI Findings[J]. Cureus, 2019, 11(7): e5203.

[22] 白志红. 酒依赖致慢性酒精中毒性脑病的临床和 CT 表现[J]. 中国药物与临床,2019,19(2):240－241.

[23] SCHABELMAN E, KUO D. Glucose before thiamine for Wernicke encephalopathy: a literature review[J]. J Emerg Med, 2012, 42(4): 488－494.

[24] KOOB GF, VOLKOW ND. Neurobiology of addiction: a neurocircuitry analysis[J]. The Lancet Psychiatry, 2016, 3(8): 760－773.

(收稿日期:2020－05－28)

parameters and Ribinski's Five Rules. TCMSP, Tagnet, and Phaser database were used to search and screen potential targets, and the DiseaseGeneNetwork database was used to retrieve relevant targets for oral cancer. STRING database was used to establish protein-protein interaction(PPI) relationships, and the core targets and pathways of *Hedyotis diffusa* in the treatment of oral cancer were predicted through gene mapping, topological analysis and enrichment analysis, as well as biological processes(BP) and cells composition(CC), molecular function(MF). **Results** A total of 93 chemical components of *Hedyotis diffusa* were collected. After screening by ADME standards and the Ribinski Five Rules, a total of 32 compounds with different chemical structures and 353 related targets of *Hedyotis diffusa* were obtained. A total of 281 oral cancer-related targets were collected through the Disease GeneNetwork database; through gene mapping and topological analysis, a total of 200 *Hedyotis diffusa*'s therapeutic targets for oral cancer were obtained, and 75 targets of topological importance. Through enrichment analysis, 336 BPs, 38 CCs, 105 MFs, 25 related pathways in the treatment of oral cancer by *Hedyotis diffusa* were obtained(when $P < 0.05$), and 51 BPs, 7 CCs and 31 MF, 4 core function pathways were obtained(when $P < 0.01$, $FDR < 0.01$). **Conclusion** The mechanism of *Hedyotis diffusa* in the treatment of oral cancer involves multiple targets and signal pathways, which is related to multiple biological processes such as apoptosis, proliferation, inflammatory response, and oxidative stress.
Key words: *Hedyotis diffusa*; oral cancer; network pharmacology; target; signal pathway

口腔癌是临床常见的恶性肿瘤，也是导致患者死亡的重要原因[1]，具有高发病率、高致死率的特点[2-3]，临床多采用手术切除、放射线治疗、化学治疗、中药治疗等方式治疗。中医学认为，癌症多由热、毒、痰、瘀及体虚等因素诱发[4]，中药以其疗效确切、应用广泛、不良反应小等优点，受到临床医师和科研人员的广泛关注[5]。白花蛇舌草 *Oldenlandia diffusa* 属茜草科植物，为临床治疗癌症的常用药物之一[6]，广泛用于治疗结直肠癌[7]、白血病[8]、肝癌[9]、肺癌[10]、卵巢癌[11]、乳腺癌[12]等。TING 等[9]对台湾地区中草药处方频度进行横断面分析发现，白花蛇舌草治疗肝癌具有显著疗效。此外，白花蛇舌草具有抗增殖[13]、促凋亡[11,14-15]抗炎[16-17]、抗氧化[18]、抗血管生成[19]、调节免疫功能[16,20-23]等多种抗癌作用机制；其提取物可通过激活 p53 诱导细胞凋亡，从而抑制癌细胞的生长[13]，还可增强巨噬细胞功能，从而抑制小鼠肾癌细胞生长。鉴于白花蛇舌草在抗肿瘤治疗中的广泛应用及其良好的临床疗效，本研究中采用网络药理学方法整体、系统地阐述药物、靶点和疾病间的关系[24-25]，直观地呈现药物靶点网络[26]，探讨了白花蛇舌草治疗口腔癌的作用机制及其药用价值，为白花蛇舌草治疗口腔癌药效机制的定位和产生协同作用的潜在蛋白靶点的确定提供新的研究方法。现报道如下。

1 资料与方法

1.1 数据集构建

数据集收集：检索 HIT(http://lifecenter.biosino.org/hit/)[27]、中药综合资源数据库(TCMID, http://www.megabionet.org/tcmid/)[28]数据库，PubMed 数据库(https://pubchem.ncbi.nlm.nih.gov/)[29]和中药系统药理数据库和分析平台(TCMSP)数据库(http://lsp.nwu.edu.cn/)[30]，从生物医学文献中收集白花蛇舌草的化合物成分，构建白花蛇舌草化合物数据集。

化合物筛选：根据毒药物动力学(ADME)药物筛选标准，口服生物利用度(OB)≥30%，类药性指数(DL)≥0.18，血脑屏障(BBB)＞-0.3，可旋转键数目(RBN)≤10，分子极性表面积(PSA)≤60，对化合物进行初筛，剔除重复出现的化合物成分。进一步运用 PubChem 数据库(https://pubchem.ncbi.nlm.nih.gov/)查询获得化合物的化学结构式[31]，基于化学结构式，运用 TargetNet 数据库(http://targetnet.scbdd.com)[32]，根据里宾斯基五规则对化合物的成药性进行评分。

1.2 靶点预测

通过搜索 TCMSP 数据库中白花蛇舌草化合物的名称，获得其对应的靶蛋白信息；在基于当前化学基因组学数据构建大量的 QSAR 模型来预测化合物靶点的 TargetNet 数据库中检索，并筛选 Prob≥0.9 的靶点[32]。运用 Pharmmapper 数据库(http://lilab-ecust.edu.cn/Pharmmapper/)[33]，通过反向药效团映射方法识别小分子的潜在靶点。

1.3 靶点收集及蛋白质-蛋白质相互作用(PPI)网络建立

采用 DiseaseGene Network 数据库(http://www.disgenet.org/)[34]和 DrugBank 数据库(https://www.drugbank.ca/)[35]，搜索与“Oral Cavity Carcinoma”相关的疾病靶点，采用 GeneMANIA 数据库(http://genemania.org/)[36]建立与已获取疾病靶点关联性较强的靶点。基于收集的口腔癌相关靶点，采用 STRING 数据库(https://string-db.org/)[37]建立 PPI 网络，作为基因映射的背景网络。

1.4 预测靶点的基因映射提取及 PPI 网络建立

采用 Cytoscape 软件将白花蛇舌草化合物的靶点映射在口腔癌疾病靶点的 PPI 背景网络上，提取白花蛇舌草治疗口腔癌的预测靶点，并将其在 STRING 数据库建立 PPI 网络[37]，进一步研究具有高置信度(＞0.7)的 PPI。

1.5 拓扑分析与富集分析

拓扑分析：采用 Cytoscape 软件，对获取的上述相关

靶点，计算“Degree”“ClosenessCentrality”“Betweenness Centrality”3 个拓扑性质，选取 3 个指标均大于中位数的靶点[38]，筛选出具有拓扑重要性的 Hub 节点，将其定义为白花蛇舌草治疗口腔癌的核心靶点。

富集分析：采用 DAVID 数据库（https://david.ncifcrf.gov/）[39]对生物过程（BP）、细胞成分（CC），分子功能（MF）及作用通路进行富集分析。$P<0.05$ 为白花蛇舌草治疗口腔癌的相关作用通路；$P<0.01$ 和 $FDR<1$ 为白花蛇舌草治疗口腔癌的核心作用通路。

基于收集获得的白花蛇舌草治疗口腔癌的预测靶点，采用 KEGG 数据库（http://www.kegg.jp/）[40]搜索并建立核心通路的路线图，标注通路内的预测作用靶点。

1.6 “靶点－通路”网络建立

基于收集获得的预测靶点及富集分析核心作用通路，采用 Cytoscape 软件建立白花蛇舌草治疗口腔癌的“靶点－通路”网络。

2 结果

2.1 数据集构建及靶点预测

通过 HIT，TCMID，PubMed，TCMSP 数据库，共获得 93 种白花蛇舌草化学成分，根据 ADME 药物筛选标准及里宾斯基五规则，共筛选出 32 种具有良好成药性的化学成分。基于此，采用 3 种方法预测白花蛇舌草的靶点信息，获得 1 468 个靶点信息，删除不同化合物间的重复靶点，共获得 353 个白花蛇舌草的预测靶点。

2.2 口腔癌疾病相关靶点及 PPI 网络的建立

检索 DiseaseGene Network 和 DrugBank 数据库，共收集获得 281 个口腔癌的预测靶点，采用 STRING 数据库建立口腔癌的 PPI 网络，获得 1 个具有 281 个节点、4 096 条边的 PPI 网络。详见图 1。

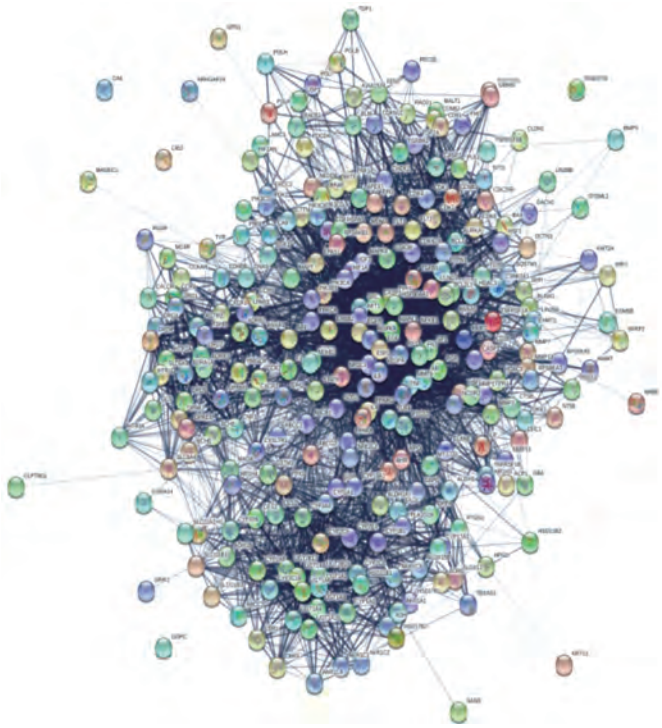

图 1 口腔癌 281 个靶点的 PPI 网络

2.3 基因映射结果与拓扑分析结果

基因映射：采用 Cytoscape 软件，将 353 个白花蛇舌草预测靶点映射在以口腔癌 PPI 网络为背景的网络上，共获得 200 个预测靶点，占口腔癌疾病靶点的 71.17%。详见图 2。

拓扑分析：白花蛇舌草治疗口腔癌的 200 个预测靶点中，“Degree”中位数为 23，“Closeness Centrality”中位数为 0.476 534 985，“Betweenness Centrality”中位数为 0.002 067 075，其中，“Degree”“ Closeness Centrality”“Betweenness Centrality 均大于中位数，且具有重要拓扑意义的节点共 75 个，即为 Hub 节点，为白花蛇舌草治疗口腔癌的核心靶点。

2.4 预测靶点的 PPI 网络建立、富集分析结果及“靶点－通路”网络建立

基于已获得的 200 个白花蛇舌草治疗口腔癌的预测靶点信息，建立 PPI 网络，得 1 个具有 200 个节点、2 604 条边的 PPI 网络，选择高置信度 PPI，得 1 个具有 200 个节点、1 204 条边的 PPI 网络，详见图 3。对预测靶

图 2 基因映射提取白花蛇舌草治疗口腔癌的预测靶点

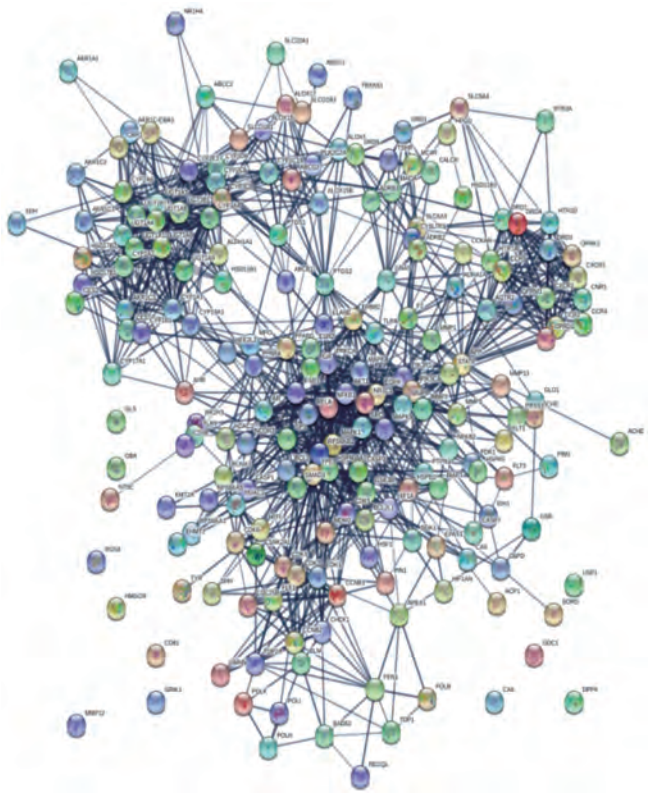

图3 白花蛇舌草治疗口腔癌的预测靶点高置信度PPI网络

点信息进行富集分析，$P < 0.05$ 时包括336个BP、38个CC、105个MF、25条相关作用通路，$P < 0.01$ 及FDR < 0.01时包括51个BP、7个CC、31个MF、4条核心作用通路。基于此，构建白花蛇舌草治疗口腔癌的“靶点－通路”网络图，详见图4。基于在KEGG建立的4个核心作用通路的可视化通路网络图，建立白花蛇舌草治疗口腔癌的可视化通路网络图，详见图5。

3 讨论

本研究中，根据里宾斯基五规则和ADME参数[30,32]筛选出白花蛇舌草中32种具有良好成药性的不同化合物成分，根据这些化合物成分，采用TCMSP，TargetNet，Pharmmapper数据库检索，收集到353个白花蛇舌草靶点，结合在DiseaseGene Network及DrugBank数据库收集的281个口腔癌相关靶点，通过基因映射获得了白花蛇舌草治疗口腔癌的200个预测靶点，由此建立了一个具有200个节点、1 204条边的高置信度PPI网络，通过拓扑分析，获得了白花蛇舌草治疗口腔癌的75个核心靶点。

富集分析结果显示，白花蛇舌草治疗口腔癌主要作用于胞浆、核质、细胞器膜、质膜、细胞核等7个细胞成分，涉及了包括凋亡、增殖、炎性反应、氧化应激等51个生物过程及31个分子功能，这与已有的体内外实验研究结果一致[13－16]，其还参与如类固醇、单萜类、杂环类等多种物质的生物代谢过程，这些代谢过程也一定程度上促进了白花蛇舌草的抗癌作用，LIEW等[41]研究发

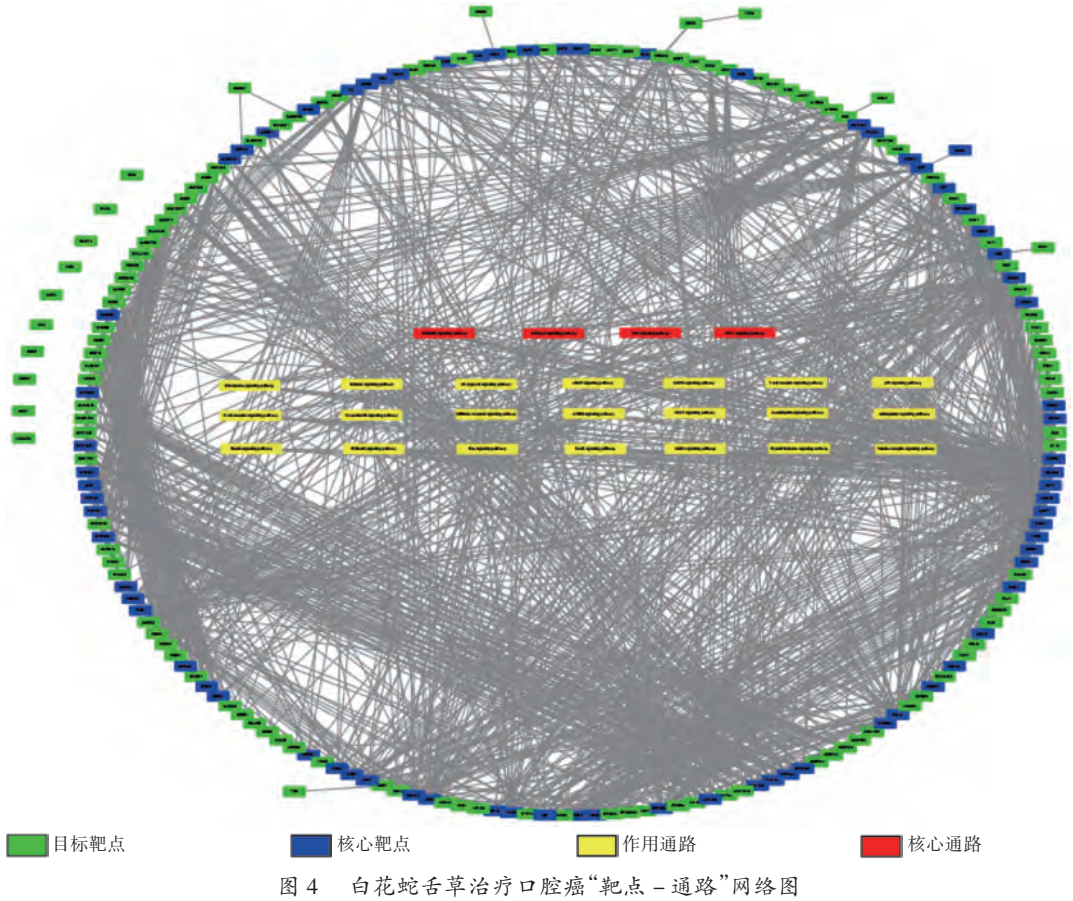

图4 白花蛇舌草治疗口腔癌“靶点－通路”网络图

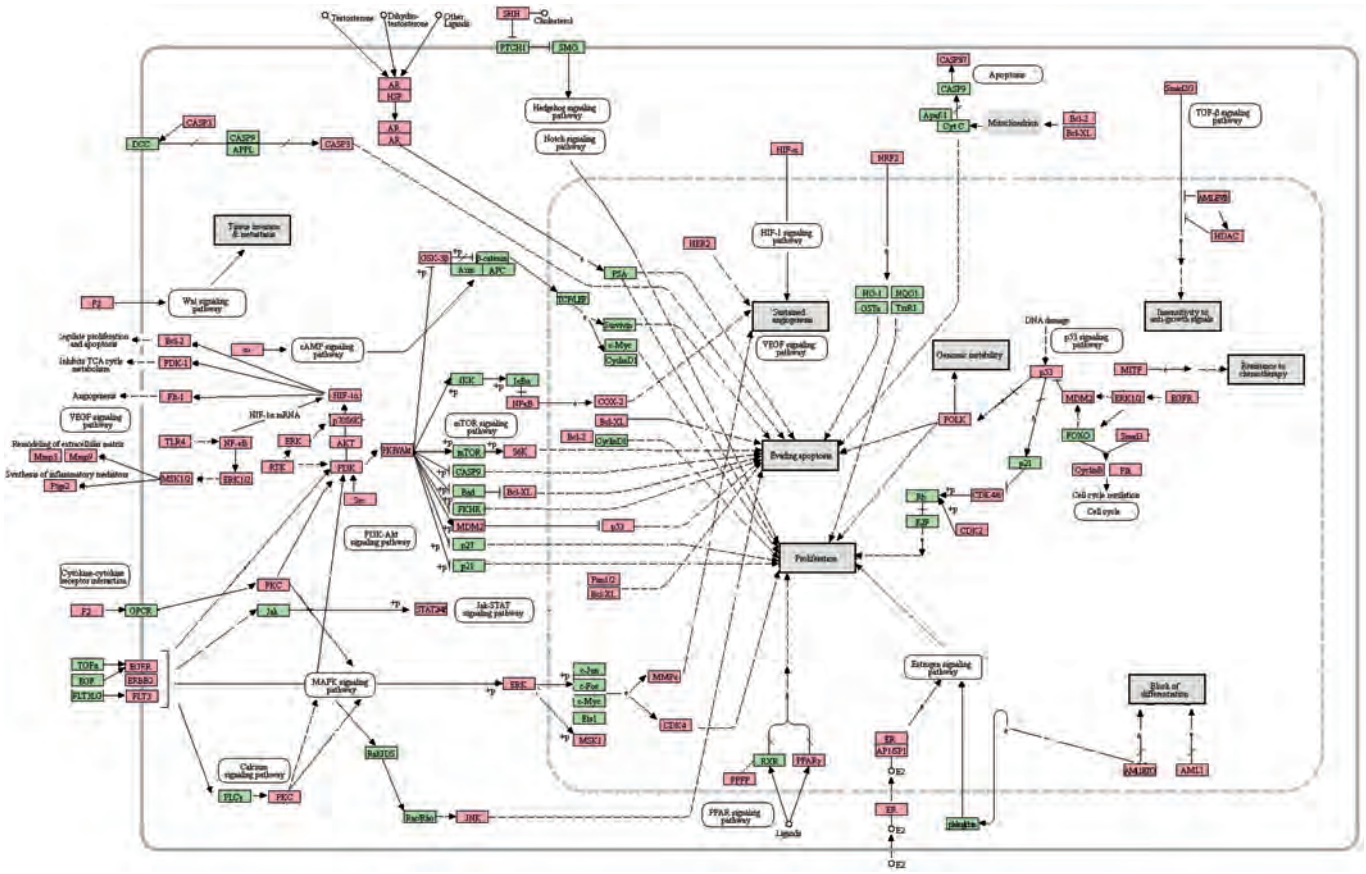

图 5 白花蛇舌草治疗口腔癌的可视化通路网络图

现，单萜吲哚生物碱具有显著的细胞生长抑制作用，且对癌细胞具有靶向选择性。通路富集分析结果表明，HIF－1 signaling pathway，Prolactin signaling pathway，Estrogen signaling pathway，TNF signaling pathway 为核心作用通路。HIF－1 signaling pathway 可通过调节细胞凋亡、炎症、氧化应激及细胞周期等发挥抗癌作用。有研究发现，HIF－1 通路的激活可诱导癌细胞线粒体解偶联从而发挥抗癌作用，核心靶点 HIF－1 被认为具有广泛前景的抗肿瘤药物靶点[42]。ALBADARI 等[43]研究认为，HIF－1/2 抑制剂及 HIFs 调节的广泛复杂性有利于开发更精确的抗癌治疗方法。Prolactin signaling pathway 及 Estrogen signaling pathway 被认为是参与乳腺癌、前列腺癌等多种恶性肿瘤的经典作用通路[44－45]。YAMAGUCHI 等[46]研究发现，阻断 Estrogen signaling pathway 可显著降低芳香化酶基因表达，从而抑制癌细胞的生长，这 2 条通路与 p53 signaling pathway，PI3K signaling pathway，MAPK signaling pathway 等多条通路间存在复杂的交互作用，从而发挥抗肿瘤作用[47－49]。TNF signaling pathway 在肿瘤相关研究中一直是被关注的焦点，ROBAYE 等[50]及 TARTAGLIA 等[51]研究发现，TNFR1 可触发肿瘤内皮细胞凋亡机制。MONTFORT 等[52]研究发现，在肿瘤细胞中输送高浓度的肿瘤坏死因子能显著提高免疫治疗效果，TNF signaling pathway 不仅是与炎症、凋亡密切相关的信号通路，与 PI3K－Akt signaling pathway 间的交叉作用还参与细胞周期调节[53]。WANG 等[54]研究发现，通过 TNF－α/NF－κB 与 PI3K/AKT signaling pathway 逆转 EMT 可抑制癌细胞的侵袭与迁移。

综上所述，本研究中通过网络药理学的方法建立了白花蛇舌草治疗口腔癌的可视化“靶点－通路”网络图及作用机制图，并明确了白花蛇舌草治疗口腔癌的多通路、多靶点的作用机制，白花蛇舌草治疗口腔癌药效机制的定位和协同作用的潜在蛋白靶点与通路。

参考文献：

[1] DIZ P，MELETI M，DINIZ－FREITAS，MÁRCIO，et al. Oral and pharyngeal cancer in Europe：Incidence，mortality and trends as presented to the Global Oral Cancer Forum[J]. Translational Research in Oral Oncology，2017，2：1－13.

[2] FERLAY J，STELIAROVA－FOUCHER E，LORTET－TIEULENT J，et al. Cancer incidence and mortality patterns in Europe：Estimates for 40 countries and 25 major cancers in 2018[J]. European Journal of Cancer，2013，49(6)：1374－1403.

[3] STURGIS EM，CINCIRIPINI PM. Trends in head and neck cancer incidence in relation to smoking prevalence[J]. Cancer，2007，110(7)：1429－1435.

[4] 吴茂林. 癌邪学说及肿瘤病机探讨[J]. 中医药导报，2016，

22(12):27 – 29.

[5] GUPTA SC, PRASAD S, SETHUMADHAVAN DR, et al. Nimbolide, a Limonoid Triterpene, Inhibits Growth of Human Colorectal Cancer Xenografts by Suppressing the Proinflammatory Microenvironment[J]. Clinical Cancer Research, 2013, 19(16): 4465 – 4476.

[6] 徐祖华. 中医论癌症的治疗[C]//中华中医药学会、中国癌症基金会. 第四届全国鲜药学术研讨会论文汇编. 中华中医药学会、中国癌症基金会:中华中医药学会,2014:98.

[7] LU PH, CHEN MB, JI C, et al. Aqueous Oldenlandia diffusa extracts inhibits colorectal cancer cells via activating AMP – activated protein kinase signalings[J]. Oncotarget, 2016, 7 (29): 45889 – 45900.

[8] WILLIMOTT S, BARKER J, JONES LA, et al. Apoptotic effect of Oldenlandia diffusa on the leukaemic cell line HL60 and human lymphocytes[J]. Journal of Ethnopharmacol, 2007, 114 (3): 290 – 299.

[9] TING CT, KUO CJ, HU HY, et al. Prescription frequency and patterns of Chinese herbal medicine for liver cancer patients in Taiwan: a cross – sectional analysis of the National Health Insurance Research Database[J]. BMC Complementary and Alternative Medicine, 2017, 17 (1): 118.

[10] SADAVA D, AHN J, ZHAN M, et al. Effects of four Chinese herbal extracts on drug – sensitive and multidrug – resistant small – cell lung carcinoma cells[J]. Cancer Chemother Pharmacol, 2002, 49 (4): 261 – 266.

[11] SONG YH, JEONG SJ, KWON HY, et al. Ursolic acid from Oldenlandia diffusa induces apoptosis via activation of caspases and phosphorylation of glycogen synthase kinase 3 beta in SK – OV – 3 ovarian cancer cells[J]. Biol Pharm Bull, 2012, 35(7): 1022 – 1028.

[12] CHUNG TW, CHOI H, LEE JM, et al. Oldenlandia diffusa suppresses metastatic potential through inhibiting matrix metalloproteinase – 9 and intercellular adhesion molecule – 1 expression via p38 and ERK1/2 MAPK pathways and induces apoptosis in human breast cancer MCF – 7 cells[J]. Journal of Ethnopharmacology, 2017, 195: 309 – 317.

[13] GU G, BARONE I, GELSOMINO L, et al. Oldenlandia diffusa extracts exert antiproliferative and apoptotic effects on human breast cancer cells through ERalpha/Sp1 – mediated p53 activation[J]. Journal of Cellular Physiology, 2012, 227 (10): 3363 – 3372.

[14] KATO H, TSUJII H, MIYAMOTO T, et al. Results of the first prospective study of carbon ion radiotherapy for hepatocellular carcinoma with liver cirrhosis[J]. International Journal of Radiation Oncology Biology Physics, 2004, 59(5): 1468 – 1476.

[15] YANG L, LIU X, LU Z, J. et al. Ursolic acid induces doxorubicin – resistant HepG2 cell death via the release of apoptosis – inducing factor[J]. Cancer Letters, 2010, 298 (1): 128 – 138.

[16] KIM SJ, CHUNG WS, KIM SS, et al. Antiinflammatory effect of Oldenlandia diffusa and its constituent, hentriacontane, through suppression of caspase – 1 activation in mouse peritoneal macrophages[J]. Phytotherapy Research, 2011, 25(10): 1537 – 1546.

[17] ZHU H, LIANG QH, XIONG XG, et al. Anti – Inflammatory Effects of the Bioactive Compound Ferulic Acid Contained in Oldenlandia diffusa on Collagen – Induced Arthritis in Rats[J]. Evidence Based Complementary and Alternative Medicine, 2014, 2014: 1 – 10.

[18] BONOFIGLIO D, GIORDANO C, AMICIS FD, et al. Natural products as promising antitumoral agents in breast Cancer: mechanisms of action and molecular targets[J]. Mini Rev Med Chem, 2016, 16 (8): 596 – 604.

[19] LIANG Z, HE M, FONG W, et al. A comparable, chemical and pharmacological analysis of the traditional Chinese medicinal herbs Oldenlandia diffusa and O. Corymbosa and a new valuation of their biological potential[J]. Phytomedicine, 2008, 15 (4): 259 – 267.

[20] WONG BY, LAU BH, JIA TY, et al. Oldenlandia diffusa and Scutellaria barbata augment macrophage oxidative burst and inhibit tumor growth[J]. Cancer Biother Radiopharm, 1996, 11(1): 51 – 56.

[21] YOSHIDA Y, WANG MQ, LIU JN, et al. Yamashita Immunomodulating activity of Chinese medicinal herbs and Oldenlandia diffusa in particular[J]. Int J Immunopharmacol, 1997, 19 (7): 359 – 370.

[22] SHAN BE, YOSHIDA Y, SUGIURA T, et al. Stimulating activity of Chinese medicinal herbs on human lymphocytes *in vitro*[J]. International Journal of Immunopharmacology, 1999, 21(3): 149 – 159.

[23] CHUNG HS, JEONG HJ, HONG SH, et al. Induction of nitric oxide synthase by Oldenlandia diffusa in mouse peritoneal macrophages[J]. Biol Pharm Bull, 2002, 25 (9): 1142 – 1146.

[24] TERSTAPPEN GC, SCHLÜPEN C, RAGGIASCHI R, et al. Target deconvolution strategies in drug discovery[J]. Nature Reviews Drug Discovery, 2007, 6(11): 891 – 903.

[25] ZHANG GB, LI QY, CHEN QL, et al. Network Pharmacology: A New Approach for Chinese Herbal Medicine Research[J]. Evidence – Based Complementary and Alternative Medicine, 2013, 2013: 1 – 9.

[26] ZENG L, YANG K. Exploring the pharmacological mechanism of Yanghe Decoction on HER2 – positive breast cancer by a network pharmacology approach[J]. Journal of Ethnopharmacology, 2017, 199: 68 – 85.

[27] MATADAMAS – MARTÍNEZ F, HERNÁNDEZ – CAMPOS A, TÉLLEZ – VALENCIA A, et al. Leishmania mexicana Trypanothione Reductase Inhibitors: Computational and Biological Studies[J]. Molecules, 2019, 24(18): 3216.

[28] WAN Y, XU L, LIU Z, et al. Utilising network pharmacology to explore the underlying mechanism of Wumei Pill in treating pancreatic neoplasms[J]. BMC Complementary and Alternative

Medicine, 2019, 19(1): 158.
[29] WANG Y, XIAO J, SUZEK TO, et al. PubChem: a public information system for analyzing bioactivities of small molecules[J]. Nucleic Acids Research, 2009, 37(2): W623 – W633.
[30] RU J, LI P, WANG J, et al. TCMSP: a database of systems pharmacology for drug discovery from herbal medicines[J]. Journal of Cheminformatics, 2014, 6(1): 13.
[31] LI Q, CHENG T, WANG Y, et al. PubChem as a public resource for drug discovery[J]. Drug Discovery Today, 2010, 15(23 – 24): 1052 – 1057.
[32] YAO ZJ, DONG J, CHE YJ, et al. TargetNet: a web service for predicting potential drug – target interaction profiling via multi – target SAR models[J]. Journal of Computer Aided Molecular Design, 2016, 30(5): 413 – 424.
[33] WANG X, SHEN Y, WANG S, et al. PharmMapper 2017 update: A web server for potential drug target identification with a comprehensive target pharmacophore database[J]. Nucleic Acids Research, 2017, 45(W1): W356 – W360.
[34] PIÑERO J, BRAVO Ú, QUERALT – ROSINACH N, et al. DisGeNET: a comprehensive platform integrating information on human disease – associated genes and variants[J]. Nucleic Acids Research, 2017, 45(D1): D833 – D839.
[35] WISHART DS, FEUNANG YD, GUO AC, et al. DrugBank 5.0: a major update to the DrugBank database for 2018[J]. Nucleic Acids Research, 2018, 46(D1): D1074 – D1082.
[36] FRANZ M, RODRIGUEZ H, LOPES C, et al. GeneMANIA update 2018[J]. Nucleic Acids Research, 2018, 46(W1): W60 – W64.
[37] SZKLARCZYK D, GABLE AL, LYON D, et al. STRING v11: protein – protein association networks with increased coverage, supporting functional discovery in genome – wide experimental datasets[J]. Nucleic Acids Research, 2019, 47(D1): D607 – D613.
[38] LIU P, DUAN JA, BAI G, et al. Network pharmacology study on major active compounds of siwu decoction analogous formulae for treating primary dysmenorrhea of gynecology blood stasis syndrome[J]. Zhongguo Zhong Yao Za zhi, 2014, 39(1): 113 – 120.
[39] DENNIS G, SHERMAN BT, HOSACK DA, et al. DAVID: Database for Annotation, Visualization, and Integrated Discovery[J]. Genome Biology, 2003, 4(9): R60.
[40] KANEHISA M, GOTO S, FURUMICHI M, et al. KEGG for representation and analysis of molecular networks involving diseases and drugs[J]. Nucleic Acids Research, 2010, 38(database issue): D355 – D360.
[41] LIEW SY, LOOI CY, PAYDAR M, et al. Subditine, a new monoterpenoid indole alkaloid from bark of Nauclea subdita (Korth.) Steud. induces apoptosis in human prostate cancer cells[J]. PLoS One, 2014, 9(2): e87286.
[42] MANDUJANO – TINOCO EA, GALLARDO – PÉREZ JC, MARÍN – HERNÁNDEZ, A, et al. Anti – mitochondrial therapy in human breast cancer multi – cellular spheroids[J]. Biochimica Et Biophysica Acta Molecular Cell Research, 2013, 1833(3): 541 – 551.
[43] ALBADARI N, DENG S, LI W. The transcriptional factors HIF – 1 and HIF – 2 and their novel inhibitors in cancer therapy[J]. Expert Opinion on Drug Discovery, 2019, 14(7): 667 – 682.
[44] DAMIANO JS, WASSERMAN E. Molecular pathways: blockade of the PRLR signaling pathway as a novel antihormonal approach for the treatment of breast and prostate cancer[J]. Clin Cancer Res, 2013, 19(7): 1644 – 1650.
[45] HUO HN, XIE KP, WANG LM, et al. Relationship between the inhibitory effect of fraxetin on breast cancer and estrogen signaling pathway[J]. Acta Physiologica Sinica, 2013, 65(3): 323 – 328.
[46] YAMAGUCHI Y, TAKEI H, SUEMASU K, et al. Tumor – stromal interaction through the estrogen – signaling pathway in human breast cancer[J]. Cancer Res, 2005, 65(11): 4653 – 4662.
[47] GÜLSEREN V, KOCAER M, ÖZDEMIR IA, et al. Do estrogen, progesterone, P53 and Ki67 receptor ratios determined from curettage materials in endometrioid – type endometrial carcinoma predict lymph node metastasis?[J]. Current Problems in Cancer, 2019, 44(1): S0147 – S0272.
[48] LIU A, ZHANG D, YANG X, et al. Estrogen receptor alpha activates MAPK signaling pathway to promote the development of endometrial cancer[J]. Journal of Cellular Biochemistry, 2019, 120(10): 17593 – 17601.
[49] CORDEIRO ER, FILETTI FM, SIMÕES MR, et al. Mercury induces nuclear estrogen receptors to act as vasoconstrictors promoting endothelial denudation via the PI3K/Akt signaling pathway[J]. Toxicol Appl Pharmacol, 2019, 381: 114710.
[50] ROBAYE B, MOSSELMANS R, FIERS W, et al. Tumor necrosis factor induces apoptosis (programmed cell death) in normal endothelial cells in vitro[J]. Am J Pathol, 1991, 138(2): 447 – 453.
[51] TARTAGLIA LA, AYRES TM, WONG GHW, et al. A novel domain within the 55 kd TNF receptor signals cell death[J]. Cell, 1993, 74(5): 845 – 853.
[52] MONTFORT A, COLACIOS C, LEVADE T, et al. The TNF Paradox in Cancer Progression and Immunotherapy[J]. Front Immunol, 2019, 10: 1818.
[53] LÜ L, TANG D, WANG L, et al. Gambogic acid inhibits TNF – α – induced invasion of human prostate cancer PC3 cells in vitro through PI3K/Akt and NF – κB signaling pathways[J]. Acta Pharmacol Sin, 2012, 33(4): 531 – 541.
[54] WANG S, YAN Y, CHENG Z, et al. Sotetsuflavone suppresses invasion and metastasis in non – small – cell lung cancer A549 cells by reversing EMT via the TNF – α/NF – κB and PI3K/AKT signaling pathway[J]. Cell Death Discovery, 2018, 4(1): 26.

(收稿日期:2020 – 02 – 15)