Analysis on Therapeutic Potential and Action Mechanism of Folium Pyrrosiae Based on Biolabel Pattern

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Abstract [**Objectives**] The therapeutic potential and action mechanism of Folium Pyrrosiae were analyzed based on the biolabel pattern. [**Methods**] The chemical components of Folium Pyrrosiae were analyzed by liquid chromatography-mass spectrometry (LC-MS). Ten databases, including Pubchem, CTD, BindingDB, HERB, TCMIP, ETCM, SwissTargetPrediction, SuperPred webserver, TargetNet and SEA, were used in turn to retrieve the targets of related components, and key components were obtained according to the enrichment degree of targets. The obtained targets were imported into the STRING database to obtain PPI information and screen out core targets. The DAVID database was employed to analyze KEGG pathways of core targets and obtain key pathways. A key component-core target-key pathway network of Folium Pyrrosiae was constructed by Cytoscape3.10.1 software. The obtained KEGG pathways were input into the CTD database to predict corresponding diseases, and discussion and analysis were carried out. [**Results**] Ten key components, 30 potential targets and 10 key pathways were screened out, and they participated in many diseases, of which five diseases were mainly analyzed. [**Conclusions**] Folium Pyrrosiae had the characteristic of multi-component, multi-target and multi-pathway synergistic effect in the treatment of lung cancer, type 2 diabetes, atherosclerosis, liver cancer, prostate cancer and other diseases, and the therapeutic potential and action mechanism of Folium Pyrrosiae were analyzed through the biolabel pattern. This study provides a research basis for further developing new functions of Folium Pyrrosiae.

Key words Biolabel pattern; Folium Pyrrosiae; Target; Pathway; Therapeutic potential; Material basis

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Folium Pyrrosiae refers to dried leaves of *Pyrrosia shearera* (Bak.) Ching, *Pyrrosia lingua* (Thunb.) Farwell or *Pyrrosia petiolosa* (Christ) Ching plants in Polypodiaceae. It was first recorded in *Shen Nong's Herbal Classic* and listed as a medium grade. It is sweet and bitter in taste, slightly cold in nature, and attributive to the lung and bladder meridians. Folium Pyrrosiae is a Chinese herb that has the effects of inducing diuresis for treating strangurtia, removing heat from the lung to relieve cough, and cooling blood and hemostasis[1]. Folium Pyrrosiae is a commonly used herb in Guizhou, and it is also used by Han, Miao, Bouyei (Buyi) and Shui nationalities in Guizhou. Guizhou has abundant resources, and Folium Pyrrosiae is an important diuretic and stranguria-relieving herb for Guizhou ethnic minorities. It is often used to treat stranguria, edema, dysuria, phlegm-heat cough and asthma, hemoptysis and hematemesis[2]. There are few reports on the chemical composition of Folium Pyrrosiae, mainly including flavonoids, triterpenes, phenolic acids, steroids, and volatile oils[3]. For the study of multi-component Chinese herbs, treating complex disease mechanisms relying solely on a single component is clearly not convincing. Therefore, exploring the synergistic effects between multiple effective components is crucial. In this study, the therapeutic potential, material basis and action mechanism of Folium Pyrrosiae were explored using the biolabel research pattern, providing a certain basis for further research on Folium Pyrrosiae[4].

The current research direction of traditional Chinese medicine is the synergistic effects among individual components of traditional Chinese medicine. The rising and falling of the four qi and five flavors of traditional Chinese medicine correspond to the intricacies of diseases, which makes it particularly difficult to study the pharmacological mechanism of multi-functional Chinese herbs in depth. Based on the development of big data, bioinformatics and chemoinformatics have gradually improved. Exploring the complex components of Chinese herbs with the biolabel research pattern provides a shortcut for us to explore the pharmacological mechanism in depth, and the biolabel-led research pattern is especially suitable for the research of traditional Chinese medicine. In previous studies[5-9], the biolabel-led research pattern has been used to locate the functions and mechanisms of various Chinese herbs. The expression of biolabels reflects the combined effect of effective components in Chinese herbs in the internal environment. In traditional research patterns, pathological models are usually used to explore drugs' action mechanisms. Under pathological conditions, we usually tend to pay attention to the influence of drugs on a single target of a specific disease, while ignoring the possibility of their intervention in other targets. However, the role of these targets may be related to the pathogenesis of other diseases. Under physiological conditions, we can avoid the influence of other factors and focus on the potential of drugs to interfere with any target. Therefore, we can understand the general situation of drug-target interaction more comprehensively and screen out drug-sensitive targets (biolabels). We can correlate these targets with the pathogenesis of diseases by analyzing the biological effects and related pathways of these targets. Consequently, we can explore the

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therapeutic potential of drugs for treating multiple diseases at the same target at the same time, thus expounding the mechanism of these drugs. Biolabels are unique information groups, which are used to locate the action and mechanism of drugs through endogenous targets and are associated with biomarkers of diseases. With the continuous development of drug biolabels and disease biomarkers, their network association will be established. Based on these biolabels, scholars may have a comprehensive understanding of the relationship between drugs and diseases. This research pattern can guide follow-up studies, reduce the input of manpower and material resources, and thus shorten the drug development cycle.

It has certain significance for exploring the potential of Folium Pyrrosiae in treating various diseases and developing new drugs[10]. Complex diseases are often controlled by multiple targets. Although a single target can characterize the action mechanism of traditional Chinese medicine, it causes some errors in the accuracy of in-depth study of diseases. In this study, a "herb-component-target-pathway" network of Folium Pyrrosiae was constructed based on the biolabel research pattern, and the action targets and related pathways of the main effective components in Folium Pyrrosiae were predicted to explore its therapeutic potential, aiming to reveal the multi-component and multi-target therapeutic mechanism of Folium Pyrrosiae.

Materials and Methods

LC-MS analysis of water extract from Folium Pyrrosiae

Through SCIEX Exit LC™ AC liquid chromatograph of AB Company combined with SCIEX 5600 + Q-TOF mass spectrometer and Waters QI software (v2.4) were used to analyze the chemical components of Folium Pyrrosiae.

Prediction of targets of components from Folium Pyrrosiae and screening of key components

The targets of the chemical components contained in Folium Pyrrosiae were predicted using ten databases, including the Pubchem database (https://pubchem.ncbi.nlm.nih.gov/), CTD database (http://ctdbase.org/), BindingDB database (http://www.bindingdb.org/rwd/bind/), HERB database (http://herb.ac.cn/search/), TCMIP database (http://www.tcmip.cn/tcmip/index.php/home/index/index.html), ETCM database (http://www.tcmip.cn/etcm/index.php/home/index/index.html), SwissTargetPrediction database (http://www.swisstargetprediction.ch/index.php), SuperPred webserver database (https://prediction.charite.de/index.php), TargetNet database (http://targetnet.scbdd.com/home/index/), and SEA database (https://sea.bkslab.org/). The obtained targets were finally merged and reduced by removing duplicates.

The chemical components were ranked according to the degree of target enrichment, and the top 10 components were selected as key components for analysis.

Construction of protein-protein interaction (PPI) network and core target analysis

The integrated target information was imported into the STRING 10 database, with the species limited to "*homo sapiens*", to obtain PPI information. The file was imported into Cytoscape 3.10.1 software to draw a PPI network. Network topology parameters were analyzed to filter out core targets.

Analysis of KEGG signal pathways

The KEGG pathways of the core targets mentioned above were analyzed using the DAVID database (https://david.ncifcrf.gov/home.jsp). Pathways with FDR values less than 0.05 were selected as critical pathways with humans (Homo sapiens) as the research species.

Construction of key component-core target-key pathway network diagram

A network of key components, core targets and key pathways of Folium Pyrrosiae was constructed using Cytoscape 3.10.1 software.

Disease prediction

The KEGG signal pathways obtained in "Analysis of KEGG signal pathways" were input into the CTD database (http://ctdbase.org/) to predict corresponding diseases.

Results and Analysis

Chemical composition of Folium Pyrrosiae

Fifty four chemical components in Folium Pyrrosiae were identified by liquid chromatography-mass spectrometry (LC-MS), as shown in Table 1.

Table 1 Fifty four chemical components in Folium Pyrrosiae

No.	CAS No.	Compound name
1	693-23-2	Dodecanedioic acid
2	6915-15-7	DL-Malic acid
3	5746-55-4	3-O-p-Coumaroylquinic acid
4	5428-46-6	2-Amino-4-chloro-3,5-dimethylphenol
5	531-75-9	Esculin
6	52187-80-1	Luteolin-7,3'-di-O-glucoside
7	520-18-3	Kaempferol
8	516-05-2	Methylmalonic acid
9	506-13-8	16-Hydroxyhexadecanoic acid
10	505-95-3	12-Hydroxydodecanoic acid
11	484-12-8	Osthole
12	482-39-3	Afzelin
13	4049-38-1	Eriodictyol
14	37942-07-7	3,5-Di-tert-butyl-2-hydroxybenzaldehyde
15	327-97-9	Chlorogenic acid
16	27661-51-4	Leucoside
17	24579-14-4	4'-Hydroxywarfarin
18	22688-79-5	Miquelianin
19	22688-78-4	Kaempferol 3-glucuronoside
20	1852-04-6	Undecanedioic acid
21	149697-30-3	4-O-Methylpinosylvic acid
22	14917-41-0	3,4,2',4',6'-Pentahydroxychalcone
23	14534-61-3	Isochlorogenic acid b
24	139-85-5	3,4-Dihydroxybenzaldehyde
25	137-00-8	5-(2-Hydroxyethyl)-4-methylthiazole

(Continued)

(Table 1)

No.	CAS No.	Compound name
26	102-32-9	3,4-Dihydroxyphenylacetic acid
27	120-80-9	Pyrocatechol
28	99-50-3	3,4-Dihydroxybenzoic acid
29	906-33-2	Neochlorogenic acid
30	89576-29-4	1-Oleoyl-sn-glycero-3-phosphoethanolamine
31	87099-71-6	3-O-Coumaroylquinic acid
32	82073-91-4	8,11-Eicosadiynoic acid
33	77-92-9	Citric acid
34	7665-99-8	Guanosine 3',5'-cyclic monophosphate
35	73-22-3	L-Tryptophan
36	57-50-1	Sucrose
37	3682-3-9	Hemiphloin
38	331-39-5	Caffeic acid
39	19895-95-5	3-O-Feruloylquinic acid
40	16290-07-6	Loniceroside
41	15664-29-6	Pheophorbide a
42	14091-08-8	D-p-Chlorophenylalanine
43	885177-37-7	Sonchifolignan A
44	524034-30-8	N-Allyl-5-chloro-2-nitroaniline
45	1219370-00-9	1, 5-Anhydro-1-(2-(3, 4-dihydroxyphenyl)-5, 7-dihydroxy-4-oxo-3,4-dihydro-2H-chromen-6-yl)hexitol
46	31564-49-5	2-Glucosyloxy-4-methoxycinnamic acid
47	125535-06-0	Eriodictyol 7-O-glucuronide
48	1217866-47-1	(9Z)-5,8,11-Trihydroxyoctadec-9-enoic acid
49	599-54-2	Pantothenic acid
50	53862-35-4	1-Palmitoyl-2-hydroxy-sn-glycero-3-phosphoethanolamine
51	488-30-2	D-Arabinonic acid
52	263399-34-4	9,10-Dihydroxy-12Z-octadecenoic acid
53	17278-74-9	14-Hydroxymyristic acid
54	158196-35-1	Naringenin-4'-O-. beta. -D-glucuronide

Prediction of targets of components from Folium Pyrrosiae and screening of key components

A total of 2 438 target components were retrieved from 10 databases including Pubchem, CTD, BindingDB, HERB, TCMIP, ETCM, SwissTargetPrediction, SuperPred webserver, TargetNet, SEA, *etc.*

According to the degree of target enrichment, 10 key components were obtained, as shown in Table 2.

Table 2 Key components of Folium Pyrrosiae

No.	Compound name	Count
1	Caffeic acid	599
2	Kaempferol	538
3	3,4-Dihydroxybenzoic acid	498
4	Citric acid	497
5	Pyrocatechol	472
6	Osthole	457
7	3,4-Dihydroxyphenylacetic acid	429
8	3,4-Dihydroxybenzaldehyde	428
9	DL-Malic acid	409
10	Eriodictyol	395

Analysis on PPI network for key targets of components in Folium Pyrrosiae

The PPI network involved a total of 2 046 nodes and 36 607 edges, and the average degree was 35.7. With node degree value as the evaluation parameter, nodes with higher degree values were more important in the PPI network and might play an important role in exerting biological functions. The targets with degree values ranking in the top 30 were core targets, as shown in Table 3.

Table 3 Core targets of Folium Pyrrosiae

No.	Gene	Degree centrality
1	GAPDH	438
2	TP53	420
3	AKT1	414
4	TNF	384
5	ALB	359
6	IL6	354
7	INS	336
8	MYC	328
9	IL1B	326
10	EGFR	318
11	SRC	318
12	CXCL8	311
13	STAT3	300
14	CTNNB1	300
15	JUN	290
16	HIF1A	289
17	CASP3	285
18	NFKB1	283
19	HSP90AA1	279
20	BCL2	278
21	ESR1	270
22	MAPK3	264
23	HSP90AB1	258
24	PTEN	254
25	IFNG	253
26	PPARG	241
27	FOS	240
28	CCND1	232
29	MMP9	231
30	TGFB1	227

KEGG pathway analysis

136 KEGG signal pathways were obtained through the DAVID database by analyzing 30 core targets. The obtained pathways were sorted based on FDR < 0.05 and number of target hits, and the top 10 pathways were analyzed, as shown in Table 4.

Construction results of key component-core target-key pathway network diagram

The network consisted of 50 nodes and 167 edges, including 10 key components, 30 core targets and 10 key pathways, as shown in Fig. 1 (where rectangles represent key components, diamonds represent key pathways, circles represent core targets, and connecting lines represent interaction).

Table 4 Key pathways of Folium Pyrrosiae

Term	Pathway name	Count	FDR
hsa05200	Pathways in cancer	24	2.25×10^{-21}
hsa05417	Lipid and atherosclerosis	18	4.23×10^{-19}
hsa05161	Hepatitis B	16	9.79×10^{-18}
hsa04657	IL-17 signaling pathway	13	1.08×10^{-15}
hsa05215	Prostate cancer	13	1.28×10^{-15}
hsa05418	Fluid shear stress and atherosclerosis	14	1.54×10^{-15}
hsa04933	AGE-RAGE signaling pathway in diabetic complications	13	1.54×10^{-15}
hsa05132	Salmonella infection	16	2.41×10^{-15}
hsa05167	Kaposi sarcoma-associated herpesvirus infection	15	2.41×10^{-15}
hsa05205	Proteoglycans in cancer	15	4.72×10^{-15}

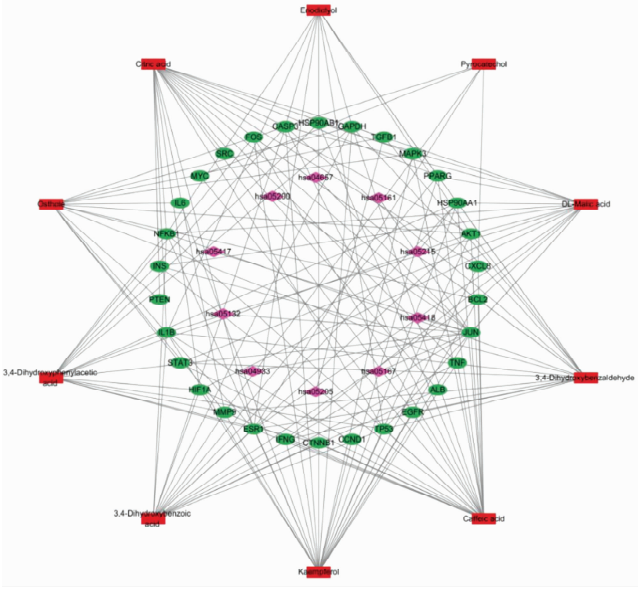

Fig. 1 "Key component-core target-key pathway" network of Folium Pyrrosiae

Prediction of diseases

Ten key pathways were imported into the CTD disease database. The diseases involved in the 10 pathways were summarized and analyzed, which mainly involved lung cancer in respiratory system, atherosclerosis in cardiovascular system, prostate tumor in urogenital system, type 2 diabetes in endocrine system, liver cancer in digestive system and other diseases.

These results are highly correlated to the pharmacological mechanism of Folium Pyrrosiae reported by previous studies, indicating the reliability of active component screening and network analysis. It provides some ideas and research basis for the further study of Folium Pyrrosiae.

Discussion

In this study, through the biolabel research pattern, the effective components and specific pharmacological functions of Folium Pyrrosiae were explored from the aspects of informatics and biochemistry, and a medicinal component-target-pathway diagram were constructed. The functional mechanism of therapeutic potential of Folium Pyrrosiae was analyzed through targets and pathways. The effective components such as caffeic acid, kaempferol, protocatechuic acid and catechol were obtained by screening. The involved diseases mainly included lung cancer, type 2 diabetes, atherosclerosis, liver cancer and prostate tumor.

Caffeic acid can affect cancer, diabetes, atherosclerosis and other diseases. Many studies have shown that caffeic acid has anti-proliferation effect on various types of cancer cells. Caffeic acid can act on cancer cells alone or in combination with anticancer drugs[11]. Caffeic acid inhibits the growth of non-small cell lung cancer cell H1299 by inducing apoptosis, and caffeic acid and paclitaxel have synergistic anticancer effect in H1299 cells[12]. Pharmacokinetic experiments in vivo and xenotransplantation experiments of lung tumors showed that the combined use of 5.4 mg/kg caffeic acid and 4.1 mg/kg adriamycin could achieve an inhibition rate of 85.6% on lung tumor and enhance the anti-tumor effect of adriamycin[13]. In hepatocellular carcinoma WCH-17A cells, higher concentration of caffeic acid (1 mM) prevented proliferation and induced apoptosis by destroying mitochondrial potential[14]. In alloxan-induced diabetic mice, caffeic acid (50 mg/kg) could reduce blood sugar level, increase hepatic glucokinase (GCK) level, normalize body weight, and reduce the level of low density lipoprotein in blood[15]. Caffeic acid (20 μM) had a significant anti-atherosclerosis effect on human umbilical vein endothelial cells: it could reduce the production of interleukin-8 (IL-8) induced by adiponectin, the expression of toll-like receptor 4 (TLR4) protein and the NF-κB signaling pathway[16]. Kaempferol is a common flavonoid, which is currently used in cancer chemotherapy. It has inhibitory effects on lung cancer, liver cancer, colon cancer, oral cancer, bladder cancer and ovarian cancer, and anti-diabetic activity[17]. Studies have shown that kaempferol can induce apoptosis of hepatocellular carcinoma HepG2 cells through endoplasmic reticulum stress CHOP signaling pathway[18]. Protocatechuic acid has been considered as an effective anti-tumor drug by inhibiting the cell proliferation of carcinogens in digestive organs[19]. A large number of accumulated studies have proved that chronic inflammation is usually related to the onset of age-related diseases, such as cardiovascular disease, diabetes and cancer[20-22]. Catechol can play an anti-inflammatory role by inhibiting the expression of inflammatory cytokines[23].

Through the analysis of core targets, GAPDH is a pleiotropic enzyme, which is overexpressed in apoptosis and various human chronic diseases[24]. The protein accumulates in mitochondria during the process of apoptosis, and induces the permeability of apoptotic mitochondrial membrane, which is the decisive event of the internal pathway of apoptosis[24]. TP53, as a tumor suppressor gene, responds to various cell stresses, including DNA damage, oncogene activation and hypoxia, by initiating cell cycle arrest, apoptosis and aging, so as to maintain the integrity of the genome[25-27]. TP53 is a common mutant gene in hepatocellular carcinoma, which occurs in more than 30% cases of hepatocellular carcinoma[28-29]. Genome analysis of human prostate cancer shows that abnormal changes of TP53 are common in advanced prostate cancer. Specifically, the change of gene TP53 is common in CRPC of castration-resistant prostate cancer[30-31]. Clinical

observation shows that TP53 gene changes occur more frequently in advanced, recurrent and metastatic prostate cancer, further indicating the key role of p53 in promoting the progress of prostate cancer[30]. Studies have found that AKT1 deletion can prevent the occurrence and progress of many tumors, including lung cancer and prostate cancer[32-33]. More and more evidences show that AKT1 may be the most important subtype in tumor occurrence and progression, and it is a potential target for therapeutic intervention of various tumor types[32]. On the other hand, it is found that the deletion of AKT1 reduces the production of EC NO and promotes the activation of EC, thus changing the balance of apoptosis of vascular cells and macrophages, thus promoting the progress of atherosclerosis[34]. AKT1 has also been proved to be expressed in insulin-sensitive tissues, such as liver, skeletal muscle and adipose tissue, indicating that AKT1 also affects the development of diabetes[35]. TNF (tumor necrosis factor) is the main mediator of cell apoptosis, inflammation and immunity, which is related to the pathogenesis of many human diseases, including diabetes, cancer and other diseases[36].

According to KEGG analysis, the key therapeutic pathways of Folium Pyrrosiae were cancer pathway, lipid and atherosclerosis, hepatitis B, IL-17 signaling pathway, prostate cancer and so on.

Cancer pathway is a universal pathway, including genes related to all aspects of tumor occurrence, such as proliferation, invasion, drug resistance and apoptosis. Several diseases are related to this pathway, including non-small cell lung cancer. For example, antiproliferation and apoptosis-promoting effects on non-small cell lung cancer can be achieved by inhibiting most genes in the cancer pathway (Flt3, IGF1R, DAPK2, PLD1 and MMP9)[37]. It has been proved that lipid metabolism is related to atherosclerosis. In atherosclerosis, endothelial dysfunction or apoptosis occurs after chronic injury, which affects the normal physiological function and integrity of intima, leading to increased lipid infiltration under intima, which is the initial link of atherosclerosis[38]. Hepatitis B infection caused by hepatitis B virus is a life-threatening cause of liver fibrosis, cirrhosis and hepatocellular carcinoma[39]. Hepatitis B virus (HBV) is a non-cytopathic hepatophilic virus, which may cause persistent infection and eventually lead to cirrhosis and hepatocellular carcinoma[40]. According to reports, IL-17 family cytokines have powerful immunomodulatory function because they can induce a variety of immune signal molecules, most notably participating in the pro-inflammatory reaction[41]. IL-17 is an important proinflammatory factor, secreted by helper T lymphocytes 17 (Th17) and innate immune cells, and plays a key role in the pathological process of various inflammatory and autoimmune diseases[41]. A large number of studies have shown that IL-17 signaling pathway is involved in atherosclerosis, diabetic nephropathy and ischemia-reperfusion injury[42]. Studies have shown that IL-17 plays a key role in inflammation and complications of type 2 diabetes[43]. Meanwhile, Folium Pyrrosiae may directly act on prostate cancer pathway to play an anti-prostate cancer role.

Conclusions

It was found that Folium Pyrrosiae has certain therapeutic significance for many diseases through the analysis of biolabel pattern. Folium Pyrrosiae could exert its therapeutic potential on lung cancer, type 2 diabetes, atherosclerosis, liver cancer, prostate cancer and other diseases through cancer pathway, lipid and atherosclerosis, hepatitis B, IL-17 signaling pathway and prostate cancer. It indicates that the therapeutic potential and action mechanism of Folium Pyrrosiae have the characteristics of multiple pathways and targets, which will provide certain ideas and foundations for the subsequent new pharmacological research and application of Folium Pyrrosiae.

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