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Prediction of the targets of the main components in blood after oral administration of *Xanthii Fructus*: a network pharmacology study[†]

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Xanthii Fructus (XF), a famous traditional Chinese medicine (TCM), has been widely used in the treatment of rhinitis and other diseases. However, the targets of the main XF components found in the blood after oral administration of XF extract are still unclear. In the current study, a feasible systems pharmacology method was developed to predict these targets. In accordance with our previous research, XF components were selected including cleomiscosin A, myristic acid, succinic acid, xanthosine, sitostenone, emodin, apigenin, and chrysophanol. Three components, namely emodin, apigenin, and chrysophanol, failed to be detected with target proteins, thus the other five components, namely cleomiscosin A, myristic acid, succinic acid, xanthosine and sitostenone, were eventually chosen for further systematic analysis. Ninety-nine target proteins and fifty-two pathways were found after a series of analyses. The frequency of some target proteins was much higher than that of others; high frequencies were obtained for P15086, P07360, P07195, MAOM_HUMAN (P23368), P35558, P35520, ACE_HUMAN (P12821), C1S_HUMAN (P09871), PH4H_HUMAN (P00439), FPPS_HUMAN (P14324), P50613, P12724, IMPA1_HUMAN (P29218), HXK1_HUMAN (P19367), P14061, and MCR_HUMAN (P08235). The frequency of eight pathways was also high, including Generic Transcription Pathway, RNA Polymerase II Transcription, Metabolism, Metabolism of steroids, Gene expression (Transcription), Cellular responses to stress, Platelet activation, signaling and aggregation, Signaling by Receptor Tyrosine Kinases, and Cellular Senescence. This study identified a common pathway - the Metabolism pathway - for all five XF components. We successfully developed a network pharmacology method to predict the potential targets of the main XF components absorbed in serum after oral administration of XF extract.

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1. Introduction

Over thousands of years, abundant clinical experience has accumulated in the use of traditional Chinese medicine (TCM). TCM has exerted synergistic effects in the treatment of complex diseases with its multi-component properties and multi-target functioning, creating a difficult challenge for its modernization. Recently, network pharmacology has risen rapidly in the research field. It explores drug targets by finding the overall correlation between drugs and diseases when combined with systems biology, multidirectional pharmacology and multidisciplinary technology, such as in network analysis, computational biology and disease-gene–drug network construction. It could therefore provide a new approach for overcoming barricades in the way of TCM modernization.

Network pharmacology, based on the network of "diseasegene-target-drug" interactions, is a way of revealing the synergistic effects of complex drugs on the human system and finding efficient and low toxicity multi-target new drugs at the network level by observing the intervention of drugs and their impact on disease. With information databases such as gene network libraries, protein network libraries, disease network libraries, and drug network libraries, and systematic spectrogram data analysis, network pharmacology is able to reveal mysterious disease–disease, disease phenotype-target protein, target protein–drug and drug–drug linkages.^{1–7}

Uncovering the material basis of TCM is the key and precondition for TCM quality control, which puts it at the core

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Paper

of TCM modernization. In a network pharmacology study, drug–drug networks can be constructed based on the similarities in the structures and efficacies of different drugs. In the process of TCM modernization, some researchers have achieved good initial results in exploring the essential properties of TCMs and revealing their comprehensive overall effects on multi-pathways, multi-targets and multi-components *via* the research ideas of network pharmacology.⁸⁻¹¹

Xanthii Fructus (XF) is the ripe fruit of *Xanthium sibiricum Patr.* XF is used for the treatment of cramping, numbness of the limbs, ulcers, sinusitis, catarrhs, and pruritus, for its function in smoothing nasal orifices and eliminating wind-dampness.¹² In modern clinic application, XF is commonly used for the treatment of rhinitis. Particularly when combined with *Magnoliae flos*, mint and other Chinese medicines, XF has enhanced effects in curing chronic rhinitis, allergic rhinitis and other rhinitis.¹³

2. Materials and methods

2.1 Screening active ingredients

In our previous study (unpublished), components such as myristic acid, succinic acid, xanthosine, emodin, apigenin, and

chrysophanol were identified from serum samples after oral administration of XF extracts. Components such as cleomiscosin A and sitostenone were filtered using the traditional Chinese medicine systems pharmacology (TcmSPTM) database, and the parameters were set as follows: oral bioavailability (OB) \geq 30%, drug-likeness (DL) \geq 0.18. The structures of the components mentioned above are shown in Fig. 1.

2.2 Prediction of active component targets

Firstly, the MDL SD (*.sdf) type files of the above active ingredients were searched using the PubMed database. Secondly, targets, including information like the target name, matching value, target protein abbreviation, function, disease and applicable results related to the modified compound, could be predicted by importing each component file in *sdf format into the PharmMapper database. The top 20 high-matching targets, by value, were used as the TCM target proteins related to the components. The targets were then searched for in the UniProt database to identify human-related target codes.

2.3 Pathway comments and analysis

The retrieved target protein information was analyzed using the Reactome database to obtain the result of the related pathway



"pathwayIdexByPathway_kegg". A pathway was selected as reliable when its *P* value was less than 0.01.

2.4 Drug-target-pathway relationship

The predicted targets of five chemical components of XF, namely cleomiscosin A, myristic acid, succinic acid, xanthosine and sitostenone, were recorded in excel tables titled as 'component-protein' and 'protein-pathway'. The tables were imported into Cytoscape software to construct the main effect components of the XF-target-pathway network. The network was mainly composed of three types of nodes: effect component, protein and pathway. The effect components and their related target proteins, and the proteins and their related pathways were all side-linked. When the target protein of the effect component was the same as the target protein of the pathway, the effect component was side-linked to the pathway. A complete network diagram was built by the establishment of connections including effect component-protein-pathway, effect component-protein-effect component, pathway-proteinpathway, protein-effect component-protein and other four kinds of connection. The whole framework, based on the active component strategy of system pharmacology, is shown in Fig. 2.

3. Results

3.1 Potential target information for five components in XF

Eight components in XF were initially selected to uncover potential target proteins. Of these, five components, namely cleomiscosin A, myristic acid, succinic acid, xanthosine, and sitostenone, were successfully analyzed. A total of 99 target proteins were related to these five XF components as shown in Table 1. The frequency of some target proteins was much higher than that of others; high frequencies were obtained for P15086, P07360, P07195, MAOM_HUMAN (P23368), P35558, P35520, ACE_HUMAN (P12821), C1S_HUMAN (P09871), PH4H_HUMAN (P00439), FPPS_HUMAN (P14324), P50613, P12724, IMPA1_HUMAN (P29218), HXK1_HUMAN (P19367), P14061, and MCR_HUMAN (P08235).

3.2 Pathway analysis of potential target proteins

The potential pathway information for the five effect components in XF is shown in Table 2.

3.3 Main effect component-target protein-pathway network construction for XF

An effect component-target-pathway network model was established using Cytoscape software, and the relationship between the 5 components, 99 targets and 52 pathways is shown in Fig. 3. There were complex network relationships between the effect components of XF and their targets, as well as the targets and pathways.

Cleomiscosin A was related to the following pathways: nuclear receptor transcription pathway (Pw1), activation of the AP-1 family of transcription factors (Pw2), MAPK targets/nuclear events mediated by MAP kinases (Pw3), p38MAPK events (Pw4), Generic Transcription Pathway (Pw5), Transcriptional regulation by RUNX2 (Pw6), Signalling to RAS (Pw7), RNA Polymerase II Transcription (Pw8), Regulation of TP53 Activity through Phosphorylation (Pw9), Metabolism (Pw10), Nuclear Events (kinase and transcription factor activation) (Pw11), MAP kinase



Fig. 2 The whole framework of system pharmacology

Table 1 (Contd.)

No.CompoundProtein codeProtein nameFrequencyNo.CompoundProtein code1Cleomiscosin AP06276CHLE_HUMAN365XanthosineP005332Cleomiscosin AP23141EST1_HUMAN366XanthosineP249413Cleomiscosin AP62937P62937367XanthosineP00734314Cleomiscosin AP00918CAH2_HUMAN368XanthosineP009155Cleomiscosin AP24941P24941369XanthosineQ128846Cleomiscosin AP07339CATD_HUMAN370XanthosineQ147577Cleomiscosin AP03372ESR1_HUMAN371XanthosineQ053158Cleomiscosin AQ15078CD5R1_HUMAN372XanthosineP047459Cleomiscosin AP00915CAH1_HUMAN373XanthosineP18075	Protein name EGFR_HUMAN P24941	Frequency
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	BMP7_HUMAN	4
10 Cleomiscosin A P04062 GLCM_HUMAN 3 74 Xanthosine P03950	ANGI_HUMAN	4
11 Cleomiscosin A P11309 PIM1_HUMAN 3 75 Xanthosine P00491	PNPH_HUMAN	4
12 Cleomiscosin A P00491 PNPH_HUMAN 3 76 Xanthosine P29218	IMPA1_HUMAN	5
13 Cleomiscosin A Q9NP99 Q9NP99 3 77 Xanthosine Q99933	BAG1_HUMAN	4
14 Cleomiscosin A 014965 STK6_HUMAN 3 78 Xanthosine P19367	HXK1_HUMAN	5
15 Cleomiscosin A Qib539 Qib539 4 79 Xanthosine P17707	DCAM_HUMAN	4
16 Cleomiscosin A Q92/31 ESR2_HUMAN 3 80 Sitostenone P52895 A	AK1C2_HUMAN	3
17 Cleonniscosin A QU/345 PDE4B_HUMAN 4 81 Sitostenone P49137	P49137	3
18 Cleomiscosin A 014/57 CHKI_HUMAN 4 82 Sitostenone P55210	CASP7_HUMAN	3
19 Cleomiscosin A P45983 MK08_HUMAN 4 83 Sitostenone P12643	BMP2_HUMAN	3
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5Myristic acidP08842STS_HUMAN399SitostenoneP027666Myristic acidP02766TTHY_HUMAN37Myristic acidQ14994NR113_HUMAN38Myristic acidP37231PPARG_HUMAN39Myristic acidP30044PRDX5_HUMAN39Myristic acidP09012P0901231Succinic acidP02743P0274342Succinic acidP12931SRC_HUMAN43Succinic acidP150824signaling (Pw19), Gene and protein3Succinic acidP15086P1508654Succinic acidP07360P0736055Succinic acidP02788TRFL_HUMAN4Succinic acidP03950ANGI_HUMAN5Succinic acidP03950ANGI_HUMAN6Succinic acidP03950ANGI_HUMAN7Succinic acidP03950ANGI_HUMAN8Succinic acidP03368MAOM_HUMAN9Succinic acidP23368MAOM_HUMAN9Succinic acidP23368MAOM_HUMAN9Succinic acidP3558P35586(Pw29), Toll Like Receptor 5 (TLR57Succinic acidP35578P355786Succinic acidP35578P355787Succinic acidP35578P355788Succinic acidP35578P355789Succinic acid </td <td>cythrocytes take Signalling to EF (Pw18), Int n expression by nulation (Pw21 via TRKA from ration of carbo ocytes (Pw25), e se oxygen (Pw2 ascade initiated ptor 10 (TLR16 5) Cascade (Pw2</td> <td>up oxygen Ks (Pw17), erleukin-17 JAK-STAT), DSCAM the plasma on dioxide rythrocytes 6), cellular on plasma)) Cascade 30), TRAF6</td>	cythrocytes take Signalling to EF (Pw18), Int n expression by nulation (Pw21 via TRKA from ration of carbo ocytes (Pw25), e se oxygen (Pw2 ascade initiated ptor 10 (TLR16 5) Cascade (Pw2	up oxygen Ks (Pw17), erleukin-17 JAK-STAT), DSCAM the plasma on dioxide rythrocytes 6), cellular on plasma)) Cascade 30), TRAF6
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5Myristic acidP08842STS_HUMAN399SitostenoneP027666Myristic acidP02766TTHY_HUMAN37Myristic acidQ14994NR113_HUMAN38Myristic acidP37231PPARG_HUMAN39Myristic acidP30044PRDX5_HUMAN30Succinic acidP09012P090123and release carbon dioxide (Pw15), S1Succinic acidP12931SRC_HUMAN4Geneexpression (Transcription)3Succinic acid015382O153824signaling after Interleukin-12 stin5Succinic acidP15086P150865interactions (Pw22), NGF signalling after6Succinic acidP07360P073605membrane (Pw23), Reversible hydr7Succinic acidP0795P071955take up carbon dioxide and release8Succinic acidP07195P071955take up carbon dioxide and release9Succinic acidP07350P355207membrane (Pw28), Toll Like Receptor 5 (TLR59Succinic acidP35520P355207mediated induction of NFkB and MAI5Succinic acidP0871C1S_HUMAN6activation (Pw31), platelet activation,6Succinic acidP0871C1S_HUMAN6activation (Pw32), oxidative stress induced se7Succinic acidP0871C1S_HUMAN8dependent cascade initiated on end	ythrocytes take Signalling to EF (Pw18), Int n expression by nulation (Pw21 via TRKA from ration of carb- ocytes (Pw25), e e oxygen (Pw2 ascade initiated ptor 10 (TLR16 5) Cascade (Pw3 bignaling and a enescence (Pw34)	up oxygen Ks (Pw17), erleukin-17 JAK-STAT), DSCAM the plasma on dioxide rythrocytes 6), cellular on plasma 0) Cascade 30), TRAF6 FLR7/8 or 9 ggregation 3), MyD88 , Toll Like
5Myristic acidP08842STS_HUMAN399SitostenoneP027666Myristic acidP02766TTHY_HUMAN37Myristic acidQ14994NR113_HUMAN38Myristic acidP37231PPARG_HUMAN39Myristic acidP30044PRDX5_HUMAN39Succinic acidP09012P0901231Succinic acidP02743P0274342Succinic acidP12931SRC_HUMAN43Succinic acidP15086P1508655Succinic acidP07360P0736056Succinic acidP0795P0719556Succinic acidP07195P0719557Succinic acidP0795P0719558Succinic acidP35528P355589Succinic acidP35520P355209Succinic acidP12821ACE_HUMAN4Succinic acidP0871C1S_HUMAN5Succinic acidP0871C1S_HUMAN6Succinic acidP0739P355207Succinic acidP35520P355208Succinic acidP0871C1S_HUMAN4Succinic acidP09871C1S_HUMAN5Succinic acidP0478PH4H_HUMAN6Succinic acidP14324FPPS_HUMAN7Succinic acidP14324FPPS_HUMAN8Genedent cascade initiat	ythrocytes take Signalling to EF (Pw18), Int n expression by nulation (Pw21 <i>via</i> TRKA from ration of carb- ocytes (Pw25), e e oxygen (Pw2 ascade initiated ptor 10 (TLR16 5) Cascade (Pw3 signaling and a enescence (Pw34) v35), MyD88:M	up oxygen Ks (Pw17), erleukin-17 / JAK-STAT), DSCAM the plasma on dioxide rythrocytes 6), cellular on plasma 0) Cascade 30), TRAF6 FLR7/8 or 9 ggregation 3), MyD88 , Toll Like al cascade
5Myristic acidP08842STS_HUMAN399SitostenoneP027666Myristic acidP02766TTHY_HUMAN37Myristic acidP17231PPARG_HUMAN39Myristic acidP37231PPARG_HUMAN39Myristic acidP37231PPARG_HUMAN39Myristic acidP0012P0901231Succinic acidP02743P0274342Succinic acidP12931SRC_HUMAN43Succinic acidP18031PTN1_HUMAN43Succinic acidP15086115Succinic acidP07360P0736056Succinic acidP07360P0736057Succinic acidP03950ANGL_HUMAN48Succinic acidP073955take up carbon dioxide and releas9Succinic acidP07350P071955take up carbon dioxide and releas9Succinic acidP03950ANGL_HUMAN4membrane (Pw28), Toll Like Receptor 5 (TLR53Succinic acidP35520P355207mediated induction of NFkB and MAI5Succinic acidP09871C1S_HUMAN6activation (Pw31), platelet activation,6Succinic acidP09871C1S_HUMAN6activation (Pw31), platelet activation,7Succinic acidP09871C1S_HUMAN6activation (Pw31), platelet activation,6Succin	ythrocytes take Signalling to EF (Pw18), Int n expression by nulation (Pw21 via TRKA from ration of carb- ocytes (Pw25), e e oxygen (Pw2 ascade initiated ptor 10 (TLR16 5) Cascade (Pw3 enescence (Pw3 dosome (Pw34) v35), MyD88:M	up oxygen Ks (Pw17), erleukin-17 JAK-STAT), DSCAM the plasma on dioxide rythrocytes 6), cellular on plasma 0) Cascade 30), TRAF6 FLR7/8 or 9 ggregation 3), MyD88 , Toll Like al cascade 2 Receptor
5 Myristic acid P08842 STS_HUMAN 3 99 Sitostenone P02766 6 Myristic acid P02766 TTHY_HUMAN 3	ythrocytes take Signalling to EF (Pw18), Int n expression by nulation (Pw21 <i>via</i> TRKA from ration of carbo cytes (Pw25), e e oxygen (Pw2 ascade initiated ptor 10 (TLR16 5) Cascade (Pw3 b) Cascade (Pw3 cascade (Pw3 dosome (Pw34) v35), MyD88:M w36), Toll Lik signaling (Pw20	up oxygen Ks (Pw17), erleukin-17 JAK-STAT), DSCAM the plasma on dioxide rythrocytes 5), cellular on plasma 0) Cascade 30), TRAF6 FLR7/8 or 9 ggregation 3), MyD88 , Toll Like al cascade 2 Receptor
5Myristic acidP08842STS_HUMAN399SitostenoneP027666Myristic acidP02766TTHY_HUMAN37Myristic acidQ14994NR113_HUMAN37Myristic acidP37231PPARG_HUMAN39Myristic acidP30044PRDX5_HUMAN39Myristic acidP09012031Succinic acidP02743P0274342Succinic acidP12931SRC_HUMAN43Succinic acidP1538243Succinic acidP160861538244Succinic acidP16086P1508655Succinic acidP07360P07360membrane (Pw23), Reversible hydr7Succinic acidP02795Take up carbon dioxide and release8Succinic acidP07195P07195take up carbon dioxide and release9Succinic acidP03558P3555869Succinic acidP355207mediated induction of NFkB and MAI5Succinic acidP03971C1S_HUMAN66Succinic acidP03971C1S_HUMAN67Succinic acidP09871C1S_HUMAN78Succinic acidP0399P44H_HUMAN77Succinic acidP0399P144L_HUMAN68Succinic acidP0613P5061388Succinic acidP12724P60138<	ythrocytes take Signalling to EF (Pw18), Int n expression by nulation (Pw21 <i>via</i> TRKA from ration of carbo cytes (Pw25), e e oxygen (Pw2 ascade initiated ptor 10 (TLR16 5) Cascade (Pw3 P kinases upon ' signaling and a enescence (Pw3 dosome (Pw34) w35), MyD88:M w36), Toll Lik signaling (Pw32	up oxygen Ks (Pw17), erleukin-17 7 JAK-STAT), DSCAM the plasma on dioxide rythrocytes 6), cellular on plasma 0) Cascade 30), TRAF6 FLR7/8 or 9 ggregation 3), MyD88 , Toll Like al cascade 2 Receptor 1), Toll Like
Myristic acidP08842STS_HUMAN399SitostenoneP02766Myristic acidP02766TTHY_HUMAN3Myristic acidP37231PPARG_HUMAN3Myristic acidP30044PRDX5_HUMAN3Myristic acidP09012P090123Succinic acidP02743P027434Succinic acidP02743SRC_HUMAN4Succinic acidP12931SRC_HUMAN4Succinic acidP13081PTN1_HUMAN4Succinic acidP15086interactions (Pw22), NGF signalling fSuccinic acidP0350ANGL_HUMAN4Succinic acidP0350ANGL_HUMAN4Succinic acidP0350ANGL_HUMAN4Succinic acidP0350ANGL_HUMAN4Succinic acidP0350ANGL_HUMAN4Succinic acidP03558P35586Succinic acidP35520P355207Succinic acidP35520P355207Succinic acidP0399P44H_HUMAN6Succinic acidP0399P44H_HUMAN6Succinic acidP14324FPPS_HUMAN8Succinic acidP14324FPPS_HUMAN8Succinic acidP14324FPPS_HUMAN8Succinic acidP14324FPPS_HUMAN8Succinic acidP14324FPPS_HUMAN8Succinic acidP14324FPPS_HUMAN8Succinic acidP14324FPPS_HUMA	ythrocytes take Signalling to EF (Pw18), Int n expression by nulation (Pw21 <i>via</i> TRKA from ration of carbo cytes (Pw25), e e oxygen (Pw2 ascade initiated ptor 10 (TLR16 5) Cascade (Pw3 dosome (Pw34) v35), MyD88:M w36), Toll Like signaling (Pw35 coll Like Recept	up oxygen Ks (Pw17), erleukin-17 / JAK-STAT), DSCAM the plasma on dioxide rythrocytes 6), cellular on plasma 0) Cascade 30), TRAF6 FLR7/8 or 9 ggregation 3), MyD88 , Toll Like al cascade e Receptor 1), Toll Like or 3 (TLR3)
Myristic acidP08842STS_HUMAN399SitostenoneP02766Myristic acidP02766TTHY_HUMAN3Myristic acidP37231PPARG_HUMAN3Myristic acidP37231PPARG_HUMAN3Myristic acidP30044PRDX5_HUMAN3Myristic acidP090129090123Succinic acidP02743P027434Succinic acidP12931SRC_HUMAN4Succinic acidP1382O153824Succinic acidP18031PTN1_HUMAN4Succinic acidP15086F15086Succinic acidP07360F07360Succinic acidP03950ANGL_HUMANSuccinic acidP03950ANG_HUMAN4Succinic acidP03950ANG_HUMAN4Succinic acidP03950ANG_HUMAN4Succinic acidP03558P3558P3558OSuccinic acidP09871C15_HUMANSuccinic acidP03871C15_HUMAN6Succinic acidP03871C15_HUMAN6Succinic acidP03613P04051P50613Succinic acidP12724P12724P12724P3P12724P3Succinic acidP30613Receptor 7/8 (TLR7/8) Cascade (PwP3Succinic acidP13723P50613P3Succinic acidP1324P12724P3 </td <td>ythrocytes take Signalling to EF (Pw18), Int n expression by nulation (Pw21 <i>via</i> TRKA from ration of carb- ocytes (Pw25), e e oxygen (Pw2 ascade initiated ptor 10 (TLR16 5) Cascade (Pw3 b) Cascade (Pw3 cascade (Pw3 dosome (Pw34) v35), MyD88:M w36), Toll Like signaling (Pw35 coll Like Recept LR1:TLR2 Casc</td> <td>up oxygen Ks (Pw17), erleukin-17 7 JAK-STAT), DSCAM the plasma on dioxide rythrocytes 6), cellular on plasma 0) Cascade 30), TRAF6 FLR7/8 or 9 ggregation 3), MyD88 , Toll Like al cascade e Receptor 1), Toll Like or 3 (TLR3) ude (Pw42),</td>	ythrocytes take Signalling to EF (Pw18), Int n expression by nulation (Pw21 <i>via</i> TRKA from ration of carb- ocytes (Pw25), e e oxygen (Pw2 ascade initiated ptor 10 (TLR16 5) Cascade (Pw3 b) Cascade (Pw3 cascade (Pw3 dosome (Pw34) v35), MyD88:M w36), Toll Like signaling (Pw35 coll Like Recept LR1:TLR2 Casc	up oxygen Ks (Pw17), erleukin-17 7 JAK-STAT), DSCAM the plasma on dioxide rythrocytes 6), cellular on plasma 0) Cascade 30), TRAF6 FLR7/8 or 9 ggregation 3), MyD88 , Toll Like al cascade e Receptor 1), Toll Like or 3 (TLR3) ude (Pw42),

No. of pathway	Pathway name	Frequency
Pw1	Nuclear receptor transcription pathway	1
Pw2	Activation of the AP-1 family of transcription factors	3
Pw3	MAPK targets/nuclear events mediated by MAP kinases	10
Pw4	p38MAPK events	3
Pw5	Generic Transcription Pathway	42
Pw6	Transcriptional regulation by RUNX2	10
Pw7	Signalling to RAS	3
Pw8	RNA polymerase II transcription	73
Pw9	Regulation of TP53 Activity through phosphorylation	5
Pw10	Metabolism	68
Pw11	Nuclear events (kinase and transcription factor activation)	7
Pw12	RUNX2 regulates osteoblast differentiation	5
Pw13	Metabolism of steroids	23
Pw14	MAP kinase activation in TLR cascade	15
Pw15	Erythrocytes take up oxygen and release carbon dioxide	1
Pw16	RUNX2 regulates bone development	5
Pw17	Signalling to ERKs	3
Pw18	Gene expression (transcription)	80
Pw19	Interleukin-17 signaling	15
Pw20	Digestion of dietary carbohydrate	2
Pw21	Gene and protein expression by JAK-STAT signaling after Interleukin-12 stimulation	3
Pw22	DSCAM interactions	2
Pw23	NGF signalling via TRKA from the plasma membrane	10
Pw24	Reversible hydration of carbon dioxide	2
Pw25	O_2/CO_2 exchange in erythrocytes	2
Pw26	Erythrocytes take up carbon dioxide and release oxygen	1
Pw27	Cellular responses to stress	27
Pw28	MyD88 cascade initiated on plasma membrane	15
Pw29	Toll like receptor 10 (TLR10) cascade	15
Pw30	Toll like receptor 5 (TLR5) cascade	15
Pw31	TRAF6 mediated induction of NFkB and MAP kinases upon TLR7/8 or 9 activation	15
Pw32	Platelet activation, signaling and aggregation	32
Pw33	Oxidative stress induced senescence	12
Pw34	MyD88 dependent cascade initiated on endosome	15
Pw35	Toll like receptor 7/8 (TLR7/8) cascade	15
Pw36	MyD88:Mal cascade initiated on plasma membrane	15
Pw37	Toll like receptor TLR6:TLR2 cascade	15
Pw38	Spry regulation of FGF signaling	2
Pw39	Netrin-1 signaling	12
Pw40	Toll like receptor 9 (TLR9) cascade	15
Pw41	Toll like receptor 3 (TLR3) cascade	15
Pw42	Toll like receptor TLR1:TLR2 cascade	15
Pw43	Toll like receptor 2 (TLR2) cascade	15
Pw44	TRIF(TICAM1)-mediated TLR4 signaling	15
Pw45	MyD88-independent TLR4 cascade	15
Pw46	Defective HK1 causes hexokinase deficiency (HK deficiency)	1
Pw47	Metabolism of angiotensinogen to angiotensins	4
Pw48	Regulation of TP53 Activity	6
Pw49	Signaling by receptor tyrosine kinases	81
Pw50	Cellular senescence	21
Pw51	HSP90 chaperone cycle for steroid hormone receptors (SHR)	3
Pw52	Interleukin-12 family signaling	3

mediated TLR4 signaling (Pw44), MyD88-independent TLR4 cascade (Pw45), Regulation of TP53 Activity (Pw48), Signaling by Receptor Tyrosine Kinases (Pw49), Cellular Senescence (Pw50) and Interleukin-12 family signaling (Pw52).

Myristic acid was related to the following pathways: nuclear receptor transcription pathway (Pw1), Activation of the AP-1 family of transcription factors (Pw2), MAPK targets/nuclear events mediated by MAP kinases (Pw3), p38MAPK events (Pw4), Generic Transcription Pathway (Pw5), Transcriptional regulation by RUNX2 (Pw6), Signalling to RAS (Pw7), RNA Polymerase II Transcription (Pw8), Metabolism (Pw10), Nuclear Events (kinase and transcription factor activation) (Pw11), RUNX2 regulates osteoblast differentiation (Pw12), Metabolism of steroids (Pw13), MAP kinase activation in TLR cascade (Pw14), RUNX2 regulates bone development (Pw16), Signalling to ERKs (Pw17), Gene expression (Transcription) (Pw18),





Interleukin-17 signaling (Pw19), NGF signalling via TRKA from the plasma membrane (Pw23), Cellular responses to stress (Pw27), MyD88 cascade initiated on plasma membrane (Pw28), Toll Like Receptor 10 (TLR10) Cascade (Pw29), Toll Like Receptor 5 (TLR5) Cascade (Pw30), TRAF6 mediated induction of NFkB and MAP kinases upon TLR7/8 or 9 activation (Pw31), Platelet activation, signaling and aggregation (Pw32), Oxidative Stress Induced Senescence (Pw33), MyD88 dependent cascade initiated on endosome (Pw34), Toll Like Receptor 7/8 (TLR7/8) Cascade (Pw35), MyD88:Mal cascade initiated on plasma membrane (Pw36), Toll Like Receptor TLR6:TLR2 Cascade (Pw37), Spry regulation of FGF signaling (Pw38), Toll Like Receptor 9 (TLR9) Cascade (Pw40), Toll Like Receptor 3 (TLR3) Cascade (Pw41), Toll Like Receptor TLR1:TLR2 Cascade (Pw42), Toll Like Receptor 2 (TLR2) Cascade (Pw43), TRIF(TICAM1)mediated TLR4 signaling (Pw44), MyD88-independent TLR4 cascade (Pw45), Signaling by Receptor Tyrosine Kinases (Pw49) and Cellular Senescence (Pw50).

Succinic acid was related to the following pathways: p38MAPK events (Pw4), Generic Transcription Pathway (Pw5), Transcriptional regulation by RUNX2 (Pw6), Signalling to RAS (Pw7), RNA Polymerase II Transcription (Pw8), Metabolism (Pw10), RUNX2 regulates osteoblast differentiation (Pw12), Metabolism of steroids (Pw13), RUNX2 regulates bone development (Pw16), Signalling to ERKs (Pw17), Gene expression (Transcription) (Pw18), NGF signalling *via* TRKA from the plasma membrane (Pw23), Platelet activation, signaling and aggregation (Pw32), Spry regulation of FGF signaling (Pw38), Netrin-1 signaling (Pw39), Metabolism of Angiotensinogen to Angiotensins (Pw47) and Signaling by Receptor Tyrosine Kinases (Pw49).

Xanthosine was related to the following pathways: Metabolism (Pw10), Gene and protein expression by JAK-STAT signaling after Interleukin-12 stimulation (Pw21), Defective HK1 causes hexokinase deficiency (HK deficiency) (Pw46) and Interleukin-12 family signaling (Pw52).

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Sitostenone was related to the following pathways: nuclear receptor transcription pathway (Pw1), Generic Transcription Pathway (Pw5), transcriptional regulation by RUNX2 (Pw6), Signalling to RAS (Pw7), RNA Polymerase II Transcription (Pw8), Metabolism (Pw10), Nuclear Events (kinase and transcription factor activation) (Pw11), RUNX2 regulates osteoblast differentiation (Pw12), Metabolism of steroids (Pw13), RUNX2 regulates bone development (Pw16), Gene expression (Transcription) (Pw18), Interleukin-17 signaling (Pw19), Cellular responses to stress (Pw27), Signaling by Receptor Tyrosine Kinases (Pw49) and HSP90 chaperone cycle for steroid hormone receptors (SHR) (Pw51).

We were surprised to find that the five components have one common pathway – the Metabolism pathway (Pw10). Nine other pathways occurred frequently including Generic Transcription Pathway (Pw5), RNA Polymerase II Transcription (Pw8), Metabolism (Pw10), Metabolism of steroids (Pw13), Gene expression (Transcription) (Pw18), Cellular responses to stress (Pw27), Platelet activation, signaling and aggregation (Pw32), Signaling by Receptor Tyrosine Kinases (Pw49) and Cellular Senescence (Pw50).

4. Discussion

The PharmMapper database can be used to search for potential targets based on small active molecules. This database uses a pharmacophore matching method to obtain drug point information by rapidly searching four major databases. This database is based on 7000 pharmacophore models and can cover most clinical indications.

According to the network pharmacological prediction of the five components in XF, all five components can be connected with the same pathway *via* the same target, and also can be connected with the same pathways with different targets. Different components can produce the same effect through different ways, and also can offer multi-target synergy.

Interestingly, this predicted common pathway is consistent with the result we got from the metabolic pathway analysis experiment (unpublished), which indicates that this result is reliable although it still requires further verification.

5. Conclusion

In this paper, a network pharmacology method has been successfully developed to predict the potential targets of the main components absorbed in serum after oral administration of XF extract. When considered alongside our previous antiallergic rhinitis metabolomics study, the predicted potential targets and the role of the pathways were considered to have a certain degree of accuracy. This article has established a "multi component-multi target-multi pathway" network model for TCM research, and started to unravel the multidimensional regulatory action of XF, which may provide a reference and basis for studying the molecular mechanism of XF.

Conflicts of interest

The authors have declared no conflicts of interest.

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