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Research on the mechanism and pharmacological effects of Sophora alopecuroides L based on the Network and Data Mining

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Abstract

In order to investigate the preliminary mechanism and pharmacological effects of the *Sophora alopecuroides* L, the data mining and network pharmacology were applied. The regularation of *Sophora alopecuroides* L by the Ancient and Modern Medical Records Cloud Platform, the molecular and structural of activity ingredient in Sophora alopecuroides L were gained by herb and the Internet of chemical, the targets of mouse were recevied by the analyze of BATMAN-TCA, Uniprot, Metascape. The data mining manifest demonstrated it was effective for both skin sores and diarrhea, the targets of the two diseases were exported from the disease database such as Genecards, String, Uniprot and Metascape. The relationship between the diseases and medicine were gained by importing the gating targets in veen Bioinformatics and Cytoscape Networks. The results showed that the therapeutic activity of Sophora alopecuroides L Centered on 11 active components such as oxymatrine, matrine, aloperine operated on key targets including $TP_{53}COR_1$, IL-6, TNF-α. There were respectively 21 and 30 common targets between the skin sores, diarrhea and Sophora alopecuroides L. The results indicated that the Sophora alopecuroides L can cure the skin sores and diarrhea through PI3K-Akt, JAK-STAT and the action of phosphorylation in protein by the activity compounds of oxymatrine, matrine, aloperine alkaloid.

Keywords: *Sophora alopecuroides* L; network pharmacology; data mining; skin sores; diarrhea; activity ingredients

1.Introduction

The traditional Chinese medicine *Sophora alopecuroides* L were bitter in tastes and cold in pharmacological properties. The main pharmacological effects were Qingre Jiedu, Anti-bacterial and anti-inflammatory, anti-parasitic and Zhitong. The effects of healing dysentery and eczema in clinical[1]. For the toxicity of the medicine, the main methods to avoid the acute toxicity were to changing the method of administration and the preparations[2]. The related preparation could be applied to control the ulcerative colitis in oral administration and to cure the skin injured[3~4]. The prescription of the medicine were mainly applied to skin sores and diarrhea based on the summary of Data Mining. The mechanism of the pharmacological effects were not clear for the widespread pharmacological activity.

The main symptoms of diarrhea were the abnormal morphology and number of feces, which could be cured in application of the granules of Kushen Zhili[5]. There were many injury model in skin sores, these could be relieved through the powders of Ruyi Jinhuang[6]. Traditional Chinese medicine had the benefits of minimal side effects and no recurrence, despite the fact that several chemical medications were used to treat skin ulcers and diarrhea.

The mechanism of traditional Chinese medicine could be conjectured through the network pharmacology, which could be provided a reference for the application in clinical. The medication *Clerodendrum japonicum* could be applied to relieve the cow mastitis by many active ingredients to act on many targets to control the inflammatory response[7]. The medicine *Echinacea purpurea* could be used to improve immunity through P13K-Akt and AMPK signaling pathway[8]. There were many activity components in the medication, such as the aloperine, matrine, oxymatrine. The activity components aloperine can act as an anti-apoptotic to enhance apoptosis through acting as a potential Bcl2 inhibitor in human glioma cells[9]. The oxymatrine could improve steatosis and reveal hepatic proteomic changes through Sirt1/AMPK signaling activation[10]. The matrine can cure simultaneous intervention of COVID-19 combined with liver injury through multi-dimensional pharmacological mechanism, which could be predicted through the network pharmacology[11]. There were no related researches on curing the skin sores and diarrhea on the medicine.Therefore, this research based on the activity of the medicine, the data mining, the target and signaling pathway of the diseases, then the key targets for diseases treatment and network construction were constructed. All of these were to provide a new drug and target trial in theoretical basis.

2.Material and methods

2.1 The sources and screening of the prescription

All the prescription of the medicine were collected from many books, such as the Xinjiang Zhongcaoyao Shouce, Inner Mongolia Zhongcaoyao, Shouyibencao Buyi. These related prescriptions were extracted and collated, then imported in Gujin Yi’an Yunpingtai(https://www.yiankb.com/home). The database of these medical were standardized processing through the related rules in platform to correct all the name of traditional Chinese medications. Then the data mining were added and carried out in the analysis pool. The analysis modules were applied to the drug rules, frequencies, properties, clustering and association rules of the medications and prescriptions.

2.2 The target of activity components

The activity components were retrieved through the network pharmacology platform of herb(http://herb.ac.cn/). The target genes and pharmacological effects were received. The related diseases and targets were screened through the conditions of $P < 0.00001$ and FDR-BH$<$0.001, then, these conditions were imported in CAS(https://www.chemsrc.com/). The main activity ingredients of the medication were clear for the molecular formula, structure, pharmacological effects of the components and pathways.

2.3 The identification of target and enrichment analysis of components

The activity components were received by 2.2, these components were imported into the BATMAN-TCA database(https://bionet.ncpsb.org/batman-tcm). The different *P*-values and scores were designed to constructed the relationship between the medication-compounds-pathways and targets. The related genes were imported into Uniprot(https://www.uniprot.org/) and the Metascape(https://metascape.org/gp/) . The species were chosen M. musculus, then the related pathways and targets were analysised through the Go(Gene Ontology. GO) and KEGG(kyoto encyclopedia of genes and genomes. KEGG).

2.4 The identification of target and enrichment analysis of diseases

The medication were applied to the skin sores and diarrhea, the key words of “skin sores” and “diarrhea” were selected to constructed and screened the targets. The related pathways and targets of these diseases were received through the database of genecards (https://www.genecards.org/), string(https://cn.string-db.org/), Cyto NCA Network Analysis and Cyto NCA. The related targets on M. musculus were preserved to construct the core network. These targets were imported the metascape to get the diseases of the skin sores and diarrhea -targets in the same way of 2.3.

2.5 The obtained of key targets and construction of internet

The targets of the activity components and diseases were taken the intersection through the Venn database(http://bioinformatics.psb.ugent.be/webtools/Venn/). The key targets were received of the diseases and medication, then these targets were imported into the cytoscape. The network figures were constructed of the Chinese medicine-compounds-pathways-targets-targets(diseases)-pathways-diseases.

3.Results

3.1 The analysis of the prescription

There were 17 prescriptions which collected from the above classical book, 7 prescriptions related to the diarrhea and 8 prescriptions related to the skin sores. The property analysis of the Chinese medicine *Sophora alopecuroides* L indicated the frequencies of usage were 21, 14.09%, the four Qi was warm, 40.33%, the five Wei was pungent, 53.44%. The main diseases in Chinese were Zenghan Zhuangre, Liji, Wenyi. The distribution and radar map of the properties of the medication were in Figure 1. The results of club analysis indicated that the highest related medicine were *Rheum rhaponticum* L. and Glycyrrhiza uralensis Fisch.

The prescriptions analysis indicated that the pharmacological effects of the prescriptions were Qingre Zaoshi(60), Jiedu(48), Lishui Shenshi(48), the ratios were 9.15%, 7.32% and 7.32% respectively. The properties were in spleen(356, 54.27%), the four Qi was in warm(186, 28.35%), the five Wei was in bitter(279, 42.53%). Therefore, the medication and related prescriptions were to cure the acute-bacterial-dysentery, diarrhea, inflammation of bacterial through oral administration. The distribution and radar map of the properties of the prescriptions were in Figure 2. The related prescriptions were to cure the dermatitis, itching, eczema, wounds, skin sores through external administration.

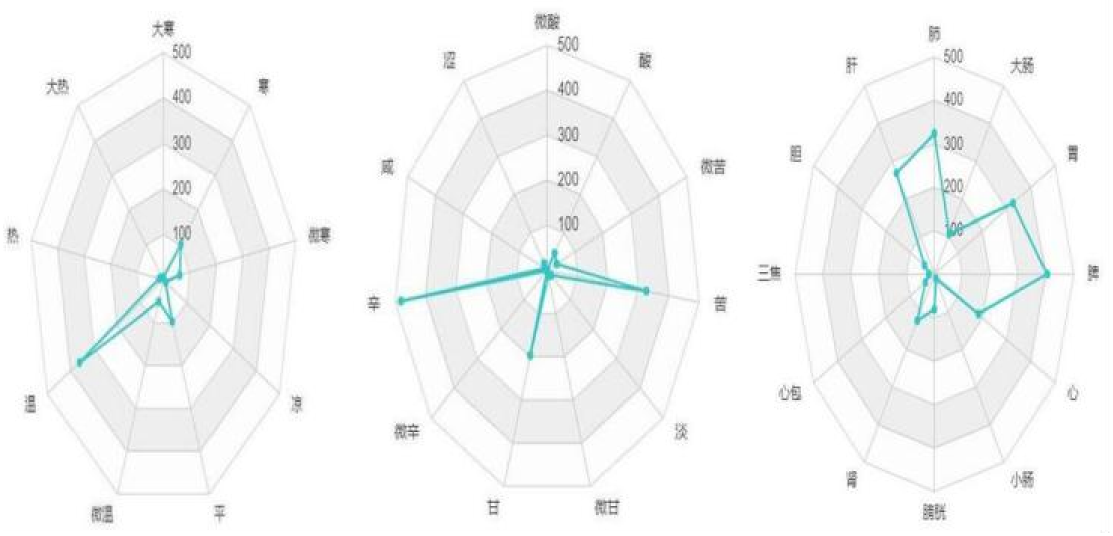


Fig.1 Distribution and radar map of the properties of traditional chinese medicine in Sophora alopecuroides L four Qi, five flavors and meridian trosim

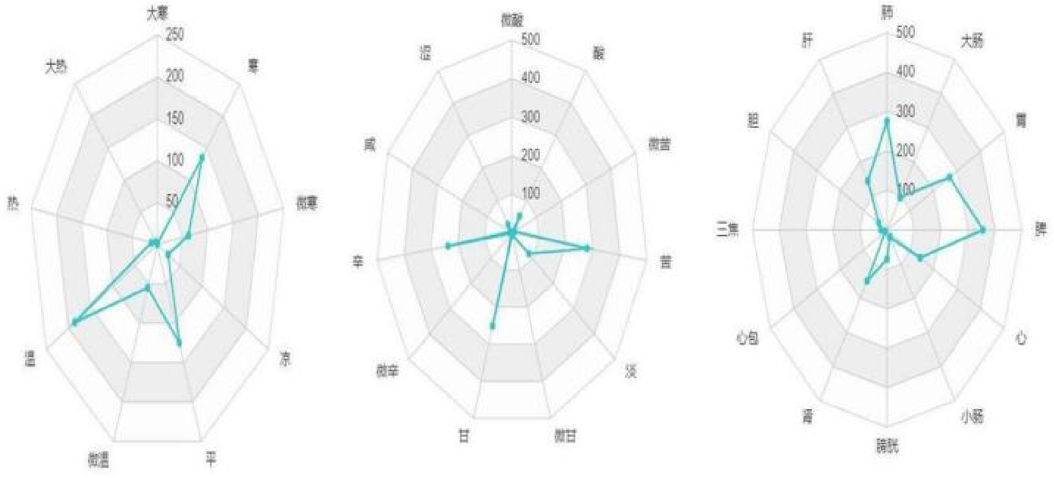


Fig.2 Distribution and radar map of the properties of prescription in Sophora alopecuroides L four Qi, five flavors and meridian trosim

3.2 The activity components of the medicine

There were 26 activity components in the medication according to the herb. The compounds were 11 according to the internet(https: //www.chemsrc.com/) which were in clearly of the pharmacological effects, pathways, conformations and targets. The compounds were in Table 1. There were 6 targets in $P<0.00001$，which were CD_{44}、$TP_{53}COR_1$、$CHRNA_7$、ADTRP、IL-6、TNF-α, FDR＜0.001 were 15, the related diseases were in Table 2.

Table1. The activity substances of the compounds, conformations and molecular fomulation

Components identification	compounds	Isomer and variety of comformations	molecular formula
HBIN015319	Aloperine	2/14	$C_{15}H_{24}N_2$
HBIN022522	Cytisine	7/95	$C_{15}H_{12}O_5$ /$C_{21}H_{22}O_{10}$
HBIN034558	12,13-lehmannine	1/2	$C_{15}H_{22}N_2O$
HBIN034559	Matrine	22/150	$C_{15}H_{24}N_2O$
HBIN037080	N-methylcytisine	5/76	$C_{12}H_{16}N_2O$
HBIN038488	Oxymatrine	7/85	$C_{15}H_{24}N_2O_2$
HBIN038489	Oxysophocarpine	1/6	$C_{22}H_{25}NO_8$
HBIN044342	Sophocarpine	7/123	$C_{15}H_{22}N_2O$
HBIN044381	Sophoramine	1/36	$C_{15}H_{20}N_2O$
HBIN044346	Oxysophocarpine	3/7	$C_{22}H_{22}O_{10}$
HBIN044394	Sophoridine	6/91	$C_{15}H_{24}N_2O$

Table 2. The P-value and FDR of Sophora alopecuroides L

Diseases identification	Name of diseases	P-value	FDR-BH
HBDIS001806	Lymphocytic Choriomeningitis	9.37e-05	0.00082
HBDIS000246	Arthritis, Infectious	8.92e-05	0.00078
HBDIS001642	Lacrimal Duct Obstruction	8.50e-05	0.00075
HBDIS003463	Chronic mastitis	8.50e-05	0.00075
HBDIS004999	Chest discomfort	8.50e-05	0.00075
HBDIS007802	Simple pneumoconiosis	8.50e-05	0.00075
HBDIS011787	fluid retention in lung	8.50e-05	0.00075
HBDIS002449	Post-kala-azar dermal leishmaniasis	7.60e-05	0.00069
HBDIS006978	Inflammatory Breast Carcinoma	7.15e-05	0.00065
HBDIS014611	Tendinopathy	5.69e-05	0.00054
HBDIS003747	Non-arthropod borne lymphocytic choriomeningitis	5.25e-05	0.00050
HBDIS003635	Disorder of tendon	4.86e-05	0.00047
HBDIS008651	Neurosarcoidosis	4.19e-05	0.00048
HBDIS026846	Polyarticular juvenile idiopathic arthritis	4.19e-05	0.00042
HBDIS006531	Inflammatory neuropathy	1.17e-05	0.00014

3.3 The targets and enrichment analysis of the medicine

The relationship of the compounds-pathways-targets were to design the different scores and *P*-value were exported from the database of bata database. The relationships were in Figure 3. All the pathways were collected on the 11 components, which obtained 32 common pathways. The pathways on M. musculus were preserved, then which were applied to enrichment analysis. There were 75 pathways and 2558 targets were summarized which the Z-scores were beyond 20.

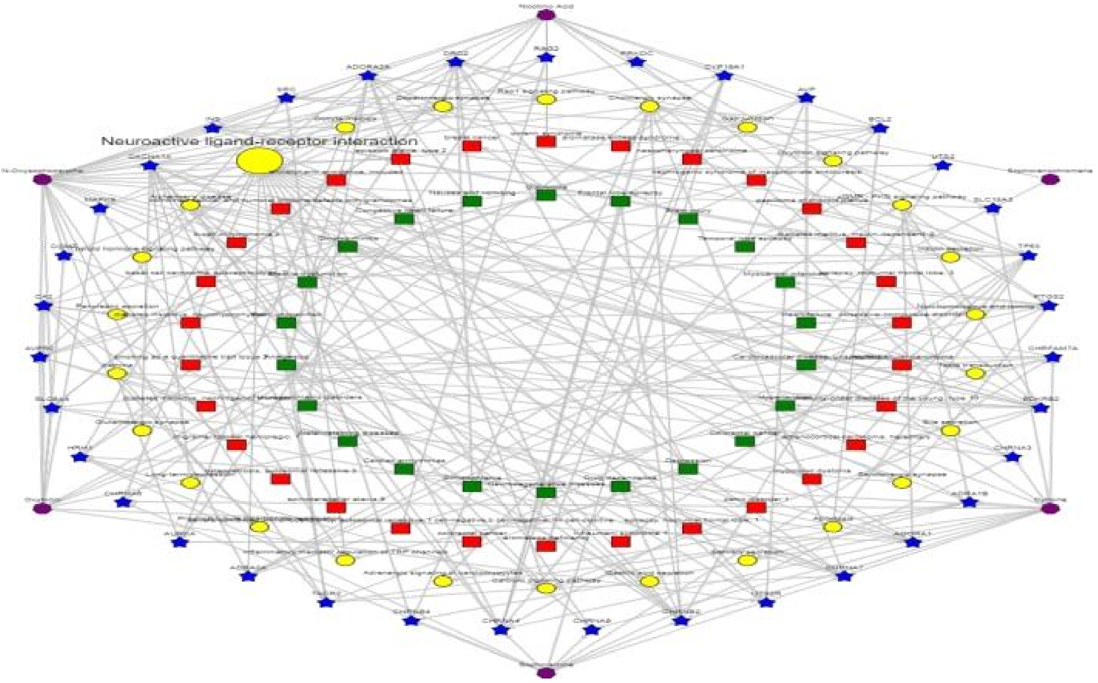
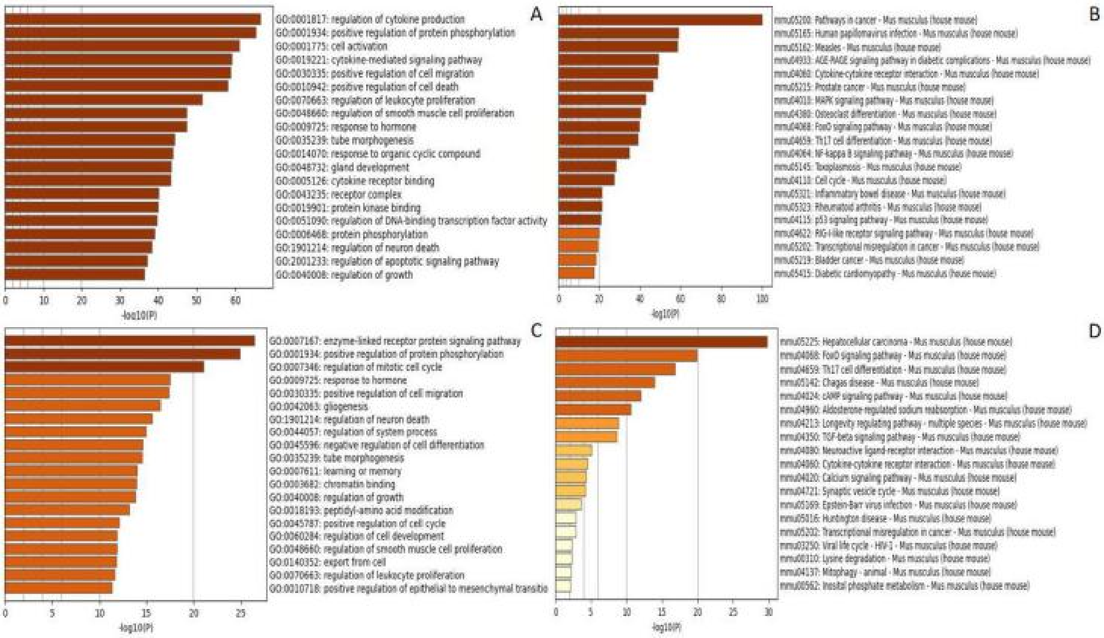


Fig.3 The network of “ traditional Chinese medicine-compounds-targets”, score=20, P=0.1

3.4 The targets and enrichment analysis of the diseases

The targets of skin sores and diarrhea were exported from the genecards database. The related scores were in 0.999, and the targets were imported into the string database. The targets of skin sores and diarrhea were 888 and 208 respectively. The KEGG and GO analysis were in Figure 4. The targets of the components and diseases were calculated through the character parameter values of the average shortest path length, clustering coefficient, eccentricity, correlated protein linkages. Therefore, there were 48 and 82 pathways, 477 and 505 targets in Z-scores>20。



A: GO in skin sores; B: KEGG in skin sores; C: GO in diarrhea; D: KEGG in diarrhea

Fig.4 GO and KEGG enrichment analysis of “skin sores” and “diarrhea”.

3.5 The internet construction of the diseases and medicine

The common key targets of the medicine and the skin sores and diarrhea were 21 and 30 respectively. The targets were 12 and 2 respectively in scores which were beyond 0.99. The main pathways were MAPK and PI3K/AKT, respectively. The Internet map of the medicine and diseases were exported form the Cytoscape Networks of the medicine, components, targets. The relationship were in Figure 5 and Figure 6.

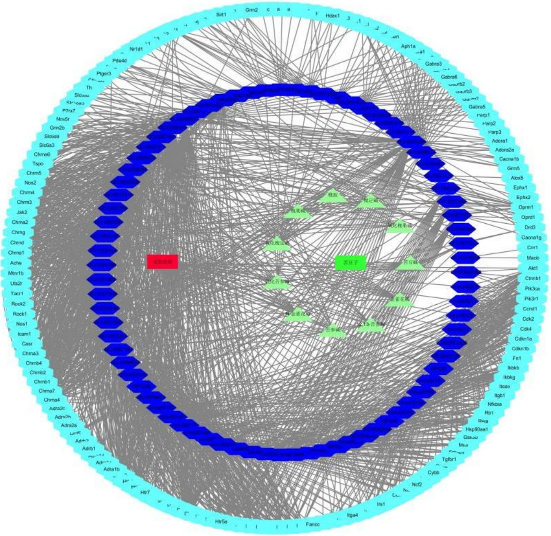


Fig.5 The network map of *Sophora alopecuroides* L—activity compounds—pathways—targets—disease targets—pathways—skin sores

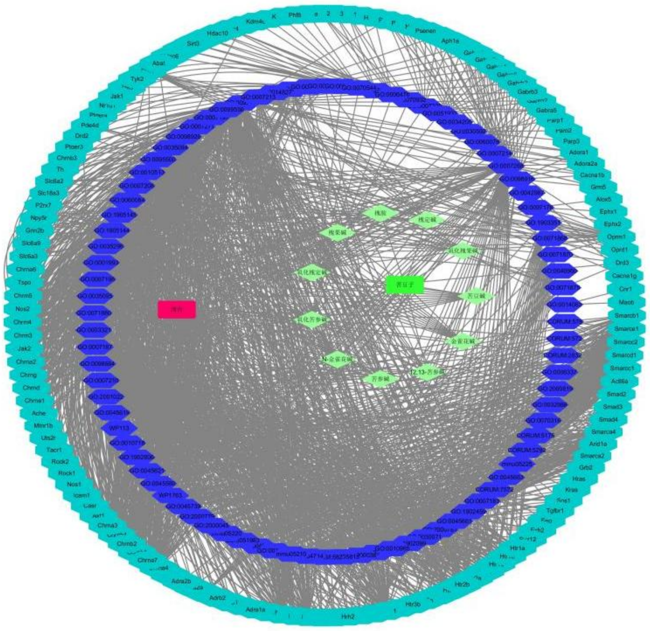


Fig.6 The network map of *Sophora alopecuroides* L—activity compounds—pathways—targets—disease targets—pathways—diarrhea

4.Discussion

The traditional Chinese medicine *Sophora alopecuroides* L were widely applied and documented in several classical books. The primary pharmacological effects were to Qingre Zaoshi, Zhitong Shachong and the application were to treat the diarrhea and skin sores. In clinical settings, the medication belonged to the toxicity drug, which could change the administration in external application or altering the dosages, preparations, extracting methods to avoid the toxicity[12~13]. The diseases of diarrhea could be caused through the bacterial of Escherichia coli and sodium chondroitin sulfate[14~15]. The skin could be injured through the Staphylococcus epidermidis, mechanical injury, Aedes albopictus[16~18]. All the related diseases could be cured through the medication.

There were 11 activity components in the medicine according to the herb. Numerous studies indicated that the monomer alkaloid of the medication were sophocarpine, oxysophocarpine, oxymatrine, matrine, lehmannine, sophoridine and cytisine, which were similar to the herb database[19~20]. The total alkaloids, monermer alkaloid of oxymatrine, matrine and aloperine were effective for the skin sores, which could be prepared for the gels, then applied to the skin sores and ulcers[17]. The oxymatrine had the pharmacological effects of antipruritic in skin through the pathways of MAPK and p-38 and reduced human scar fibroblast viability through the mechanism of inhibition of fibroblast autophagy[21~22]. The matrine could inhibit itching through the inhibiting of the calcium channel activity[23]. The aloperine could relieve the allergic contact dermatitis through the reducing of TNF-α、IFN-γ and IL-6 and cure psoriasis through the attenuating of Th17 caused by the ameliorates[24~25]. As a result, the components of the medicine had the pharmacological effects of the variety of skin sores and dermatitis, the pathways of JAK-STAT were different from the researches while the PI3K-Akt were similar.

The components of the medication also could treat the diarrhea. The total alkaloids could control the gut microbiota which caused by the infestation of Escherichia coli and sodium chondroitin sulfate[15]. The total alkaloids also could cure the diarrhea through the inhibition of multidrug resistant Escherichia coli isolates through the AcrAB-ToLC Efflux Pump[26]. The compound alkaloids also had the similar pharmacological effects, such as the oxymatrine, matrine, aloperine. The oxymatrine could inhibit the acute intestinal inflammation through the pathways of RhoA/ROCK[27]. The matrine could alleviate lipopolysaccharide-induced intestinal inflammation by decreasing the inflammatory factors through the pathways of CCR-7 and PPAR-α[28~29]. The related diseases on aloperine of the pathways were the PI3K/Akt/mTOR[30]. Consequently, the pathways in anti-diarrhea were similar to the related researches, including the MAPK and PI3K/AKT. The construction of the medicine and diseases indicated that the results of the internet pharmacological could verify the data mining.

5.Conclusion

The traditional Chinese medicine were effective for the skin sores and diarrhea through the data mining. Then the activity components medication could cure these disease through variety pathways and targets in internet pharmacological. All of which could provide a references for the development of the preparations.

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Competing interests

The authors declare that they have no competing interests.

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