

Article

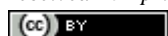
Network pharmacology of medicinal attributes and functions of Chinese herbal medicines: (IV) Classification and network analysis of medicinal functions of Chinese herbal medicines

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Abstract

In present study I used the data from CHM-DATA, the interactive database of 1127 Chinese herbal medicines with 78 medicinal functions (attributes). The relational network for medicinal functions of Chinese herbal medicines was constructed using my earlier data and methods. Results of network analysis showed that the network is a scale-free complex network at the significance level of $\alpha=0.01$. It was demonstrated that Clear away heat, Detoxification, Remove lung-heat or nourish lung, Promote secretion of saliva or body, Relieve pain, Regulate or enhance energy flow (Qi), Nourish or warm spleen / stomach / Qi, and Dispel endogenous wind, are the most influential medicinal functions. Seven main modules, corresponding links and module functions were identified and three of them were (Clear away heat, Detoxification, Relieve pain, Regulate or enhance energy flow (Qi)), (Loosen the bowels, Moisten dryness, Tonify blood, Nourish essential fluid (Yin), Inhibit or break energy flow (Qi)), and (Relieve external syndrome, Induce perspiration, Relieve muscular spasm, Expose exanthema or promote eruption). PCA of 78 medicinal functions demonstrated that the medicinal functions 1~50 accounted for 79% of the total variance. There were not absolutely significant components and medicinal functions. The 78 components from PCA were substantially 78 independent and comprehensive medicinal functions. Major medicinal functions for every component can be simply determined by their importance and contribution coefficients in the component. New medicinal definition for some the most important principal components were given. Category characteristics of medicinal functions were described. At a certain level, for example, the medicinal functions -Consolidate or warm kidney, -Whet the appetite or reinforce stomach, Cool blood, -Regulate or enhance energy flow (Qi), -Nourish or warm spleen / stomach / Qi, Clear away heat, Detoxification, and Dispel endogenous cold, are the major attributes of the principal component F_1 . Of which the medicinal functions with the same sign (+ or -) have the same direction of medicinal action. Results of system cluster analysis demonstrated that (Consolidate or warm kidney, Invigorate male impotence (Yang) or strengthen male essence), (Relieve constipation, Loosen the bowels), and (Clear away heat, Detoxification) were classified into a class respectively at the earliest stage. They were the most similar medicinal functions from each other. Finally, some principles for incorporation and generation of medicinal functions were discussed and Matlab codes for PCA and system cluster analysis were given.

Keywords Chinese herbal medicine; medicinal function; PCA; system cluster analysis; network analysis.

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1 Introduction

The theory of Traditional Chinese Medicine has developed slowly in the past thousands of years (Zhang, 2017a, b, c), which greatly retards the development and practice of the theory of Chinese herbal medicines. For this reason, Zhang (2017a) collected 1127 Chinese herbal medicines, mainly with recorded chemical composition, and analyzed the basic statistics of medicinal attributes and functions, e.g., totals, frequencies or probabilities, percentages, etc., on the basis of total population of medicines and families. Thereafter, some relational networks, i.e., the networks for medicinal attributes and functions, for chemical composition and meridians and collaterals, for meridians and collaterals and medicinal functions, and for meridians and collaterals were constructed based on the significant point correlations (Zhang, 2017b). Network analysis indicated that the former three ones are scale-free complex networks and node degrees of these networks followed power-law distribution. Furthermore, Zhang (2017c) developed canonical correlation functions for taste attribute class (7 taste attributes), medicinal property class (5 medicinal properties), chemical composition class (22 chemical composition categories), meridians and collaterals class (12 meridians and collaterals), and medicinal function class (77 medicinal functions). Linear eigenmodels were also developed for Chinese herbal medicines in this study.

However, according to my earlier discussion (Zhang, 2017b), the medicinal properties, taste attributes and chemical composition categories have relatively higher reliability. Although various meridians and collaterals are abstract, it is a conclusive result from countless experiences, which can reflect the characteristics of biological network to a certain extent. Medicinal functions still need a lot of empirical test.

Based on the previous studies (Zhang, 2017a, b, c), this study will further analyze medicinal functions by classification and network analysis in order to lay a foundation for understanding the correlations between medicinal functions and their categorical characteristics.

2 Material and Methods

2.1 Methods

2.1.1 Network analysis

Centrality measures were used to calculate the centrality values of medicinal functions in the network (i.e., medicinal attributes) (Freeman, 1978; Opsahl et al., 2010; Zhang and Zhan, 2011; Huang and Zhang, 2012; Li and Zhang, 2013; Khansari et al., 2016; Zhang, 2016b; Zhang and Feng, 2017). Degree centrality is a local centrality based on neighbourhood. It reflects the node influence on its neighbourhoods. A node degree centrality is the sum of the weights of the links attached to that node. Closeness centrality is a distance-based and global centrality which represents the independence of a node in the network. Closeness centrality is defined as reciprocal of the sum of the node's geodesic distances to all other nodes (the distances of the shortest paths) in the network. Betweenness centrality is a distance-based measure. It represents the node's ability to control the data flow in the network. This measure is the proportion of number of geodesic paths that pass through the given node to total number of geodesic paths between any pair of nodes in the network.

Some methods proposed earlier were used to detect network types (Zhang, 2012b, 2017b; Zhang and Zhan, 2011), and identify potential sub-networks / modules (Zhang, 2016a).

2.1.2 Principal Component Analysis

Principal Component Analysis (PCA) was used to classify and order medicinal functions (Zhang and Fang, 1982; Qi, 2003; Zhang, 2010; Vieira, 2012). Suppose there are n medicines, and m medicinal functions. Known $m \times n$ matrix, (z_{ij}) . First, construct normalized matrix (x_{ij}) , i.e., let $x_{ij} = (z_{ij} - z_{bar\ i}) / s_i$, where

$$z_{bar\ i} = \sum_{j=1}^n z_{ij} / n$$

$$s_i = \left(\sum_{j=1}^n (z_{ij} - z_{bar\ i})^2 / (n-1) \right)^{0.5}$$

$$i=1, 2, \dots, m$$

Calculate correlation matrix, $R=(r_{ij})$

$$r_{ij} = \sum_{k=1}^n (x_{ik} x_{jk}) / (n-1) \quad i, j=1, 2, \dots, m$$

Based on $|pI-R|=0$, determine eigenvalues p_1, p_2, \dots, p_m , and the corresponding eigenvectors u_1, u_2, \dots, u_m . I is the unit matrix. Assume $p_1 > p_2 > \dots > p_m$, and let $A=(a_{ij})=(u_1(p_1)^{0.5} \ u_2(p_2)^{0.5} \ \dots \ u_m(p_m)^{0.5})$. The i -th component of medicine j ($j=1, 2, \dots, n$) is

$$F_i = \sum_{k=1}^m (a_{ki} z_{kj}) \quad i=1, 2, \dots, m$$

Let

$$a_{bar\ i} = \sum_{k=1}^m |a_{ki}| / m$$

$$std_i = \left(\sum_{k=1}^m (|a_{ki}| - a_{bar\ i})^2 / (m-1) \right)^{0.5}$$

$$i=1, 2, \dots, m$$

For i -th component F_i , if $a_{ki} > a_{bar\ i} + t * std_i$, then a_{ki} is the principal attribute of the component F_i , $k=1, 2, \dots, m$. Here, t is a value, e.g., $t=1.5$.

The following is the Matlab program, PCA.m, of PCA

```
clear
t=input('Input threshold t of variable significance beyond the (mean+t*std) (1-2): ');
file=input('Input the excel file name of data, e.g., pca.xls. Columns are indices and rows are samples: ');
raw=xlsread(file);
z=raw';
m=size(z,1); n=size(z,2);
zbar=mean(z);
s=std(z');
for i=1:m
for j=1:n
x(i,j)=(z(i,j)-zbar(i))/s(i);
end; end
for i=1:m
for j=1:m
r(i,j)=0;
for k=1:n;
r(i,j)=r(i,j)+x(i,k)*x(j,k)/(n-1);
end; end; end
[u,p]=eig(r);
sums=sum(sum(p));
for i=1:m
p2(i)=i;
end
for i=1:m-1
```

```

k=i;
for j=i:m-1
if (p(j+1,j+1)>p(k,k)) k=j+1; end
end
i2=p2(i); p2(i)=p2(k); p2(k)=i2;
l=p(i,i); p(i,i)=p(k,k); p(k,k)=l;
end
iss="";
iss=strcat(iss,'Eigenvalues, contribution percentages, and eigenvectors for principal components\n');
for i=1:m
thr=i;
iss=strcat(iss,num2str(p(i,i)),', '(',num2str(p(i,i)/sums*100),'% ','\n');
for j=1:m
iss=strcat(iss,num2str(u(j,p2(i))),',');
end
iss=strcat(iss,'\n');
end
iss=strcat(iss,'\n');
for j=1:m
for i=1:m a(i,j)=sqrt(p(j,j))*u(i,p2(j));
end; end
iss=strcat(iss,'Principal Components\n');
for j=1:m
iss=strcat(iss,'F',num2str(j),'=');
for i=1:m
e1=num2str(i);
if (a(i,j)>0) e2=num2str(a(i,j));
elseif (a(i,j)<0) e2=num2str(abs(a(i,j)));
end
if ((a(i,j)>0) & (i~=1)) iss=strcat(iss,+',e2, 'x',e1);
elseif ((a(i,j)>0) & (i==1)) iss=strcat(iss,e2, 'x',e1);
elseif (a(i,j)<0) iss=strcat(iss, '-',e2, 'x',e1);
end
end
end
iss=strcat(iss,'\n');
end
iss=strcat(iss,'\n');
mea=mean(abs(a));
stds=std(abs(a));
thr=mea+t*stds;
for j=1:m
for i=1:m
if (abs(a(i,j))>=thr(j)) sig(j,i)=sign(a(i,j));
else sig(j,i)=0;
end

```

```

end; end
for i=1:m
iss=strcat(iss,'Significant variables of principal component-',num2str(i),'\n');
for j=1:m
if (sig(i,j)~=0)
if (sig(i,j)<0) iss=strcat(iss,'-x',num2str(j),');
else iss=strcat(iss,'x',num2str(j),');
end
end
end
iss=strcat(iss,'\n');
end
fprintf(iss)

```

2.1.3 System cluster analysis

It is called hierarchical cluster analysis also. Assume there are n medicinal functions (attributes), and m medicines. Known $m \times n$ matrix, (x_{ij}) . The following one of the two methods can be used to construct normalized matrix (a_{ij}) . Standard deviation method is

$$a_{ij} = (x_{ij} - x_{bar\ i}) / s_i$$

$$i=1, 2, \dots, m; j=1, 2, \dots, n$$

where

$$x_{bar\ i} = \sum_{j=1}^n x_{ij} / n$$

$$s_i = (\sum_{j=1}^n (x_{ij} - x_{bar\ i})^2 / (n-1))^{0.5}$$

$$i=1, 2, \dots, m$$

And max-min method is

$$a_{ij} = (x_{ij} - \min x_{ik}) / (\max x_{ik} - \min x_{ik})$$

$$i=1, 2, \dots, m; j=1, 2, \dots, n$$

where $\max x_{ik} = \max (x_{i1}, x_{i2}, \dots, x_{in})$, $\min x_{ik} = \min (x_{i1}, x_{i2}, \dots, x_{in})$.

Distance measures used in the method include Euclidean distance, Pearson correlation (1-r), point correlation (1-r), Jaccard coefficient (1-r). Their definition can be found in Zhang (2011a-b, 2012b, 2015, 2017b). There are three between-class methods (Zhang and Fang, 1982; Zhang, 2007), i.e., the shortest distance, the longest distance, and class averaging methods. Suppose there are two classes A and B . For the shortest distance, the longest distance, and class averaging methods, the distances between A and B are

$$d_{AB} = \min d_{ij} \quad i \in A, j \in B$$

$$d_{AB} = \max d_{ij} \quad i \in A, j \in B$$

$$d_{AB} = ((\sum_i \sum_j d_{ij}^2) / (n_A n_B))^{0.5}$$

$$i \in A, j \in B$$

respectively, where n_A and n_B are the number of medicinal functions in A and B .

Choose two clusters, A and B , with the minimum d_{AB} to combine into a new cluster. Repeat the cluster procedure, until all of medicinal functions are eventually classified into a cluster.

The following is the Matlab program, SystemCluster.m, of system cluster analysis

```
clear
cluster=input('Choose cluster method (1: The shortest distance; 2: The longest distance; 3: Cluster averaging): ');
sele=input('Choose between sample distance or correlation (1: Euclidean distance; 2: Pearson correlation; 3: Point correlation; 4: Jaccard coefficient): ');
sel=input('Choose data standardization method (1: Standard deviation; 2: Max-min): ');
file=input('Input the excel file name of data, e.g., cluster.xls. Columns are indices and rows are samples to be clustered: ','s');
x=xlsread(file);
m=size(x,2); n=size(x,1);
xbar=mean(x); st=std(x); maxx=max(x); minn=min(x);
for i=1:m
for j=1:n
if (sel==1) a(i,j)=(x(j,i)-xbar(i))/st(i);
elseif (sel==2) a(i,j)=(x(j,i)-minn(i))/(maxx(i)-minn(i));
end
end; end
for i=1:n-1
for j=i+1:n
if (sele==1)
r(i,j)=sqrt(sum((a(:,i)-a(:,j)).^2))/m;
elseif (sele==2)
r(i,j)=1-corr(a(:,i),a(:,j));
elseif (sele==3)
aa=sum((a(:,i)==0) & (a(:,j)==0));
bb=sum((a(:,i)==0) & (a(:,j)~=0));
cc=sum((a(:,i)~=0) & (a(:,j)==0));
dd=sum((a(:,i)~=0) & (a(:,j)~=0));
r(i,j)=1-(aa*dd-bb*cc)/sqrt((aa+bb)*(cc+dd)*(aa+cc)*(bb+dd));
elseif (sele==4)
bb=sum((a(:,i)==0) & (a(:,j)~=0));
cc=sum((a(:,i)~=0) & (a(:,j)==0));
dd=sum((a(:,i)~=0) & (a(:,j)~=0));
r(i,j)=1-(dd-(cc+bb))/(dd+cc+bb);
end
r(j,i)=r(i,j);
end; end
for j=1:n r(j,j)=0; end
r1=r;
bb1=1;
u(bb1)=0;
nu(bb1)=n;
```

```

for i=1:nu(bb1) x(bb1,i)=i; end
for i=1:nu(bb1) y(bb1,i)=1; end
while (nu(bb1)>1)
aa=1e+10;
for i=1:nu(bb1)-1
for j=i+1:nu(bb1)
if (r(i,j)<=aa) aa=r(i,j); end
end; end
aa1=0;
for i=1:nu(bb1)-1
for j=i+1:nu(bb1)
if (abs(r(i,j)-aa)<=1e-06)
aa1=aa1+1; v(aa1)=i; w(aa1)=j;
end; end; end
for i=1:nu(bb1) s(i)=0; end
nn1=0;
for i=1:aa1
if ((v(i)~=0) & (w(i)~=0))
nn1=nn1+1;
for j=1:aa1
if ((v(j)==v(i)) | (v(j)==w(i)) | (w(j)==w(i)) | (w(j)==v(i)))
s(v(j))=nn1; s(w(j))=nn1;
if (j~=i) v(j)=0; w(j)=0; end; end
end
v(i)=0; w(i)=0;
end; end
for i=1:nn1
y(bb1+1,i)=0;
for j=1:nu(bb1)
if (s(j)==i)
for k=1:n
if (x(bb1,k)==j) x(bb1+1,k)=i; end
end
y(bb1+1,i)=y(bb1+1,i)+y(bb1,j);
end; end; end
for i=1:nu(bb1)
if (s(i)==0)
nn1=nn1+1;
for k=1:n
if (x(bb1,k)==i) x(bb1+1,k)=nn1; end
end
y(bb1+1,nn1)=y(bb1,i); end
end;
bb1=bb1+1;
u(bb1)=aa;

```

```

nu(bb1)=nn1;
for i=1:nu(bb1)-1
for j=i+1:nu(bb1)
if (cluster==1) r(i,j)=1e+10;
elseif (cluster==2) r(i,j)=-1e+10;
elseif (cluster==3) r(i,j)=0;
end
nk=0;
for k=1:n
if (x(bb1,k)==i)
nk=nk+1;
nkk=0;
for kk=1:n
if (x(bb1,kk)==j)
nkk=nkk+1;
if (cluster==1)
if (r1(k,kk)<r(i,j)) r(i,j)=r1(k,kk); end
elseif (cluster==2)
if (r1(k,kk)>r(i,j)) r(i,j)=r1(k,kk); end
elseif (cluster==3)
r(i,j)=r(i,j)+r1(k,kk)^2;
end
end; end; end; end
if (cluster==3)
r(i,j)=sqrt(r(i,j)/(nk*nkk));
end
r(j,i)=r(i,j);
end; end; end;
for k=1:n
y(bb1,k)=1; end
for i=bb1-1:-1:1
rr=0;
for j=1:nu(i+1)
ww=0;
for k=1:n
if (y(i+1,k)==j) ww=ww+1; v(ww)=k; end
end
vv=0;
for ii=1:ww
ee=0;
for jj=ii-1:-1:1
if (x(i,v(ii))==x(i,v(jj))) y(i,v(ii))=y(i,v(jj)); break; end
ee=ee+1;
end
if (ee==ii-1) vv=vv+1; y(i,v(ii))=rr+vv; end

```



```

end
rr=rr+vv;
end; end
for k=1:bb1
rs(k)=1-u(k);
end;
s=1; i=0;
while (n>0)
ss=1;
for j=s+1:bb1
if (rs(j)==rs(s)) ss=ss+1; end;
end
s=s+ss;
i=i+1;
la(i)=s-1;
if (s>=bb1) break; end
end
bb1=i;
yy=zeros(n);
for k=1:bb1
for i=1:nu(la(k))
for j=1:n
if (y(la(k),j)==i) yy(k,j)=i; end;
end; end; end
for k=1:bb1
rss(k)=rs(la(k)); uu(k)=u(la(k)); nuu(k)=nu(la(k));
end
iss="";
for k=1:bb1
iss=strcat(iss,'\n','r=',num2str(rss(k)),'\n');
for i=1:nuu(k)
iss=strcat(iss,');
for j=1:n
if (yy(k,j)==i) iss=strcat(iss,num2str(j),','); end
end
iss=strcat(iss,');
end; end
fprintf(iss)

```

2.2 Data source

In present study I used the interactive database of eight tables, CHM-DATA Version 1.0 (Zhang, 2017a, b), with 1127 Chinese herbal medicines, of which 210 families and approximately 2000 species of medicinal plants and fungi were involved, which account for approximately 1/5 of medicinal plants and fungi in China. Among them, medicinal plants accounted for 98.94%, and medicinal fungi accounted for 1.06%. The list

included the most commonly used or important Chinese herbal medicines. Finally, 78 medicinal functions (Gong Xiao) and 1127 Chinese herbal medicines (Table 1) were used for further analysis. In the following, ‘/’ represents ‘or’ or ‘and’.

Table 1 Medicinal functions (Zhang, 2017c).

Function	Clean liver, relax liver, consolidate liver, bright eyes or eliminate eye screens	Breed or blacked hair	Benefit gallbladder or cure jaundice	Reduce aminotransferase	Consolidate or warm kidney	Induce diuresis or treat strangury
功效	清肝/补肝/舒肝/明目/退翳	生发/乌发	利胆/退黄	降转氨酶	补肾/温肾	利尿/通淋
<i>x</i>	x_1	x_2	x_3	x_4	x_5	x_6
Function	Activate water metabolism or excrete water	Invigorate male impotence (Yang) or strengthen male essence	Strengthen bones and muscles	Promote granulation	Remove lung-heat or nourish lung	Eliminate or relieve phlegm
功效	利水/行水	壮阳/温阳/益精	强筋骨	生肌	清肺/润肺	祛痰/化痰
<i>x</i>	x_7	x_8	x_9	x_{10}	x_{11}	x_{12}
Function	Anti-asthma	Eliminate or relieve cough	Eliminate or relieve stuffy nose	Eliminate or relieve tuberculosis	Whet the appetite or reinforce stomach	Strengthen and reinforce spleen
功效	平喘/定喘	止咳	通鼻窍	祛肺结核	开胃/益胃	健脾/补脾
<i>x</i>	x_{13}	x_{14}	x_{15}	x_{16}	x_{17}	x_{18}
Function	Improve digestion	Promote secretion of saliva or body	Relieve sore throat	Resolve food stagnation	Repel foulness	Prevent or arrest vomiting
功效	消食/化食	生津	利咽	消积/消滞	辟秽	止呕
<i>x</i>	x_{19}	x_{20}	x_{21}	x_{22}	x_{23}	x_{24}
Function	Strengthen heart or clean heart-fire	Relieve restlessness, calm the nerves, alleviate mental depression, or arrest convulsion	Arrest epilepsy	Relieve constipation	Loosen the bowels	Moisten dryness
功效	强心/清心	除烦/安神/解郁/定惊	定痫	通便	润肠	润燥
<i>x</i>	x_{25}	x_{26}	x_{27}	x_{28}	x_{29}	x_{30}
Function	Astringe intestine	Soften hardness or dissolve masses	Antidiarrheal	Stop diarrheal	Cool blood	Stop bleeding
功效	涩肠	散结/软坚	止痢	止泻	凉血	止血
<i>x</i>	x_{31}	x_{32}	x_{33}	x_{34}	x_{35}	x_{36}
Function	Tonify blood	Invigorate blood circulation	Absorb clots, eliminate stasis, resolve carbuncle or promote wound healing	Reduce swelling	Antidiabetics	Antiatherosclerosis
功效	养血/补血	活血	化瘀/消痈/敛疮	消肿	降糖	降血脂
<i>x</i>	x_{37}	x_{38}	x_{39}	x_{40}	x_{41}	x_{42}
Function	Antihypertension	Nourish essential fluid (Yin)	Regulate menstruation or promote blood flow	Prevent miscarriage or abortion	Promote lactation or stimulate milk secretion	Regulate or enhance energy flow (Qi)
功效	降压	滋阴	调经/通淋	安胎	通乳/下乳	理气/养气
<i>x</i>	x_{43}	x_{44}	x_{45}	x_{46}	x_{47}	x_{48}
Function	Inhibit or break energy flow (Qi)	Anti-aging	Remove obstruction in meridians and collaterals, or relax the muscles and joints	Nourish, warm spleen, stomach or Qi	Relieve pain	Anticancer
功效	下气/破气	抗衰老	通络/活络/舒筋	温中/和中/补中	止痛	抗癌
<i>y</i>	y_{49}	y_{50}	y_{51}	y_{52}	y_{53}	y_{54}
Function	Clear away heat	Eliminate dampness	Detoxification	Decrease internal heat	Quench ones thirst	Relieve summer-heat

功效	清热	利湿	解毒	降火	止渴	解暑/消暑
<i>x</i>	<i>x</i> ₅₅	<i>x</i> ₅₆	<i>x</i> ₅₇	<i>x</i> ₅₈	<i>x</i> ₅₉	<i>x</i> ₆₀
Function	Dispel endogenous cold	Dispel endogenous damp	Dispel endogenous wind	Relieve rheumatism or lubricate the joints	Dry dampness	Suppress perspiration
功效	祛寒	祛湿	祛风	祛风湿/利关节	燥湿	止汗
<i>x</i>	<i>x</i> ₆₁	<i>x</i> ₆₂	<i>x</i> ₆₃	<i>x</i> ₆₄	<i>x</i> ₆₅	<i>x</i> ₆₆
Function	Induce perspiration	Relieve external syndrome	Promote astringent function	Discharge pus, diminish inflammation or anti-infection	Relieve itching	Kill or expel parasites
功效	发汗	解表/发表	收敛	排脓/消炎/抗感染	止痒	杀虫/驱虫
<i>x</i>	<i>x</i> ₆₇	<i>x</i> ₆₈	<i>x</i> ₆₉	<i>x</i> ₇₀	<i>x</i> ₇₁	<i>x</i> ₇₂
Function	Anti-malaria	Relieve muscular spasm	Expose exanthema or promote eruption	Dispel evil spirit	Anesthesia	Eliminate impediment
功效	抗疟/截疟	解痉	透疹	逐邪	麻醉	除痹
<i>x</i>	<i>x</i> ₇₃	<i>x</i> ₇₄	<i>x</i> ₇₅	<i>x</i> ₇₆	<i>x</i> ₇₇	<i>x</i> ₇₈

3 Results and Analysis

3.1 Network analysis

According to my earlier data and methods (Zhang, 2017b), I construct the relational network of medicinal functions ($\alpha=0.01$), as indicated in Fig. 1. Centrality values of all medicinal functions are shown in Table 2. It is demonstrated that Clear away heat, Detoxification, Remove lung-heat or nourish lung, Promote secretion of saliva or body, Relieve pain, Regulate or enhance energy flow (Qi), Nourish or warm spleen / stomach / Qi, and Dispel endogenous wind, are the most influential medicinal functions.

Skewness of degree distribution of the network is 0.2956, aggregation index is 1.2591, variation coefficient is 2.3496, and entropy is 6.9513; so the network is identified as a complex network. Binomial distribution of degree $p=0.2854$, $\chi^2=12.7229$, and thus it is identified as a random network. Poisson distribution of degree $\lambda=5.1507$, $\chi^2=657.8589$, and so it is identified as a non-random network. Exponential distribution of degree $\lambda=0.1942$, $\chi^2=27.6564$, thus it is identified as a non exponential distribution. Power-law distribution of degree $\alpha=3.7878$, $x_{\min}=6$, and its Kolmogorov-Smirnov fitting goodness $D=0.1667$. Therefore node degree follows power-law distribution, and the density function is $p(x)=x^{-3.7878}$, $x \geq 6$. Overall, at the significance level of $\alpha=0.01$, the network is a scale-free complex network.

Table 2 Centrality values of medicinal functions.

Function	Degree	Function	Closeness	Function	Betweenness
Clear away heat	20	Clear away heat	0.0068	Clear away heat	0.2344
Detoxification	15	Relieve pain	0.0062	Detoxification	0.1853
Remove lung-heat or nourish lung	12	Detoxification	0.0062	Relieve pain	0.1062
Whet the appetite or reinforce stomach	11	Remove lung-heat or nourish lung	0.0061	Dispel endogenous wind	0.1062
Promote secretion of saliva or body	11	Whet the appetite or reinforce stomach	0.0061	Promote secretion of saliva or body	0.1043
Relieve pain	11	Promote secretion of saliva or body	0.006	Nourish, warm spleen, stomach or Qi	0.1043
Regulate or enhance energy flow (Qi)	10	Regulate or enhance energy flow (Qi)	0.006	Relieve external syndrome	0.0887
Nourish, warm spleen, stomach or Qi	10	Dispel endogenous wind	0.0059	Anti-asthma	0.0879
Dispel endogenous wind	10	Nourish, warm spleen, stomach or Qi	0.0058	Relieve summer-heat	0.0864
Invigorate blood circulation	9	Invigorate blood circulation	0.0057	Prevent miscarriage or abortion	0.086

Dispel endogenous cold	9	Consolidate or warm kidney	0.0056	Stop diarrheal	0.0856
Consolidate or warm kidney	8	Dispel endogenous cold	0.0056	Remove lung-heat or nourish lung	0.0826
Reduce swelling	8	Reduce swelling	0.0056	Dispel endogenous damp	0.0822
Prevent miscarriage or abortion	8	Strengthen bones and muscles	0.0055	Dispel endogenous cold	0.0807
Invigorate male impotence (Yang) or strengthen male essence	7	Cool blood	0.0055	Invigorate male impotence (Yang) or strengthen male essence	0.0803
Strengthen bones and muscles	7	Dispel endogenous damp	0.0053	Reduce swelling	0.0769
Stop diarrheal	7	Anti-asthma	0.0053	Regulate or enhance energy flow (Qi)	0.0753
Tonify blood	7	Improve digestion	0.0053	Kill or expel parasites	0.0715
Dispel endogenous damp	7	Stop diarrheal	0.0053	Stop bleeding	0.0677
Eliminate or relieve phlegm	6	Invigorate male impotence (Yang) or strengthen male essence	0.0052	Invigorate blood circulation	0.0674
Anti-asthma	6	Tonify blood	0.0052	Anticancer	0.0635
Eliminate or relieve cough	6	Inhibit or break energy flow (Qi)	0.0052	Promote astringent function	0.0632
Strengthen and reinforce spleen	6	Absorb clots, eliminate stasis, resolve carbuncle or promote wound healing	0.0052	Relieve restlessness, calm the nerves, alleviate mental depression, or arrest convulsion	0.0624
Relieve restlessness, calm the nerves, alleviate mental depression, or arrest convulsion	6	Remove obstruction in meridians and collaterals, or relax the muscles and joints	0.0052	Tonify blood	0.0616
Clean liver, relax liver, consolidate liver, bright eyes or eliminate eye screens	5	Clean liver, relax liver, consolidate liver, bright eyes or eliminate eye screens	0.0051	Dry dampness	0.0613
Improve digestion	5	Strengthen and reinforce spleen	0.0051	Antidiarrheal	0.0594
Loosen the bowels	5	Induce diuresis or treat strangurt	0.005	Discharge pus, diminish inflammation or anti-infection	0.059
Moisten dryness	5	Astringe intestine	0.005	Relieve rheumatism or lubricate the joints	0.0586
Cool blood	5	Eliminate dampness	0.005	Whet the appetite or reinforce stomach	0.051
Stop bleeding	5	Relieve restlessness, calm the nerves, alleviate mental depression, or arrest convulsion	0.005	Relieve constipation	0.0498
Absorb clots, eliminate stasis, resolve carbuncle or promote wound healing	5	Stop bleeding	0.005	Eliminate or relieve cough	0.0483
Remove obstruction in meridians and collaterals, or relax the muscles and joints	5	Relieve rheumatism or lubricate the joints	0.005	Strengthen heart or clean heart-fire	0.0445
Relieve rheumatism or lubricate the joints	5	Eliminate or relieve cough	0.0049	Resolve food stagnation	0.0438
Relieve external syndrome	5	Loosen the bowels	0.0049	Moisten dryness	0.0434
Kill or expel parasites	5	Prevent miscarriage or abortion	0.0048	Antihypertension	0.0426
Induce diuresis or treat strangurt	4	Relieve sore throat	0.0048	Eliminate or relieve phlegm	0.04
Eliminate or relieve tuberculosis	4	Moisten dryness	0.0048	Nourish essential fluid (Yin)	0.0396
Strengthen heart or clean heart-fire	4	Nourish essential fluid (Yin)	0.0048	Inhibit or break energy flow (Qi)	0.0396
Relieve constipation	4	Eliminate or relieve phlegm	0.0047	Activate water metabolism or excrete water	0.0392
Antiatherosclerosis	4	Relieve summer-heat	0.0047	Induce diuresis or treat strangurt	0.0384
Nourish essential fluid (Yin)	4	Relieve constipation	0.0047	Suppress perspiration	0.0381
Inhibit or break energy flow (Qi)	4	Dispel evil spirit	0.0047	Loosen the bowels	0.0373
Anticancer	4	Activate water metabolism or excrete water	0.0046	Improve digestion	0.0369
Relieve summer-heat	4	Strengthen heart or clean heart-fire	0.0045	Strengthen bones and muscles	0.0361
Dry dampness	4	Kill or expel parasites	0.0045	Strengthen and reinforce spleen	0.0361

Activate water metabolism or excrete water	3	Eliminate or relieve tuberculosis	0.0045	Absorb clots, eliminate stasis, resolve carbuncle or promote wound healing	0.0346
Resolve food stagnation	3	Anti-aging	0.0045	Decrease internal heat	0.0339
Prevent or arrest vomiting	3	Quench ones thirst	0.0045	Antiatherosclerosis	0.0327
Astringe intestine	3	Repel foulness	0.0045	Dispel evil spirit	0.0327
Soften hardness or dissolve masses	3	Anticancer	0.0045	Eliminate dampness	0.0323
Antidiarrheal	3	Discharge pus, diminish inflammation or anti-infection	0.0045	Astringe intestine	0.032
Anti-aging	3	Prevent or arrest vomiting	0.0044	Consolidate or warm kidney	0.0308
Eliminate dampness	3	Soften hardness or dissolve masses	0.0044	Eliminate or relieve tuberculosis	0.0308
Quench ones thirst	3	Antiatherosclerosis	0.0044	Cool blood	0.0308
Suppress perspiration	3	Suppress perspiration	0.0044	Quench ones thirst	0.0304
Promote astringent function	3	Resolve food stagnation	0.0043	Soften hardness or dissolve masses	0.0293
Discharge pus, diminish inflammation or anti-infection	3	Dry dampness	0.0042	Anti-aging	0.0293
Dispel evil spirit	3	Relieve external syndrome	0.0041	Antidiabetics	0.0289
Breed or blacked hair	2	Relieve itching	0.0041	Clean liver, relax liver, consolidate liver, bright eyes or eliminate eye screens	0.0274
Relieve sore throat	2	Promote astringent function	0.0041	Breed or blacked hair	0.0274
Repel foulness	2	Antidiabetics	0.004	Promote granulation	0.0274
Antidiabetics	2	Regulate menstruation or promote blood flow	0.004	Eliminate or relieve stuffy nose	0.0274
Antihypertension	2	Eliminate or relieve stuffy nose	0.004	Relieve sore throat	0.0274
Decrease internal heat	2	Expose exanthema or promote eruption	0.0039	Repel foulness	0.0274
Induce perspiration	2	Breed or blacked hair	0.0039	Prevent or arrest vomiting	0.0274
Relieve itching	2	Eliminate impediment	0.0038	Regulate menstruation or promote blood flow	0.0274
Relieve muscular spasm	2	Antihypertension	0.0038	Remove obstruction in meridians and collaterals, or relax the muscles and joints	0.0274
Expose exanthema or promote eruption	2	Decrease internal heat	0.0038	Induce perspiration	0.0274
Promote granulation	1	Antidiarrheal	0.0037	Relieve itching	0.0274
Eliminate or relieve stuffy nose	1	Promote granulation	0.0034	Anti-malaria	0.0274
Regulate menstruation or promote blood flow	1	Induce perspiration	0.0032	Relieve muscular spasm	0.0274
Anti-malaria	1	Relieve muscular spasm	0.0032	Expose exanthema or promote eruption	0.0274
Eliminate impediment	1	Anti-malaria	0.0029	Eliminate impediment	0.0274
Benefit gallbladder or cure jaundice	0	Benefit gallbladder or cure jaundice	0	Benefit gallbladder or cure jaundice	0
Reduce aminotransferase	0	Reduce aminotransferase	0	Reduce aminotransferase	0
Arrest epilepsy	0	Arrest epilepsy	0	Arrest epilepsy	0
Promote lactation or stimulate milk secretion	0	Promote lactation or stimulate milk secretion	0	Promote lactation or stimulate milk secretion	0
Anesthesia	0	Anesthesia	0	Anesthesia	0

Seven main modules and the corresponding links are identified as the follows

Module 1

(Regulate or enhance energy flow (Qi), Relieve pain) (Regulate or enhance energy flow (Qi), Clear away heat) (Regulate or enhance energy flow (Qi), Detoxification) (Relieve pain, Clear away heat) (Relieve pain, Detoxification)

Module function: Clear away heat-Detoxification-Regulate or enhance energy flow (Qi)

Module 2

(Loosen the bowels, Moisten dryness) (Loosen the bowels, Tonify blood) (Loosen the bowels, Inhibit or break energy flow (Qi)) (Moisten dryness, Tonify blood) (Moisten dryness, Nourish essential fluid (Yin))

Module function: Loosen the bowels-Moisten dryness-Nourish essential fluid (Yin)

Module 3

(Induce perspiration, Relieve external syndrome) (Induce perspiration, Relieve muscular spasm) (Relieve external syndrome, Relieve muscular spasm) (Relieve external syndrome, Expose exanthema or promote eruption)

Module function: Relieve external syndrome-Induce perspiration- Relieve muscular spasm

Module 4

(Anti-asthma, Antiatherosclerosis) (Anti-asthma, Anticancer) (Eliminate or relieve cough, Antiatherosclerosis) (Eliminate or relieve cough, Anticancer)

Module function: Anti-asthma-Eliminate or relieve cough

Module 5

(Eliminate or relieve tuberculosis, Soften hardness or dissolve masses) (Eliminate or relieve tuberculosis, Reduce swelling) (Soften hardness or dissolve masses, Reduce swelling)

Module function: Soften hardness or dissolve masses-Reduce swelling-

Module 6

(Whet the appetite or reinforce stomach, Prevent or arrest vomiting) (Prevent or arrest vomiting, Nourish or warm spleen / stomach / Qi) (Prevent or arrest vomiting, Dispel endogenous cold)

Module function: Nourish spleen-Whet the appetite or reinforce stomach

Module 7

(Clean liver / relax liver / consolidate liver / bright eyes / eliminate eye screens, Invigorate male impotence (Yang) or strengthen male essence) (Consolidate or warm kidney, Invigorate male impotence (Yang) or strengthen male essence) (Invigorate male impotence (Yang) or strengthen male essence, Stop diarrheal)

Module function: Consolidate liver-Consolidate kidney

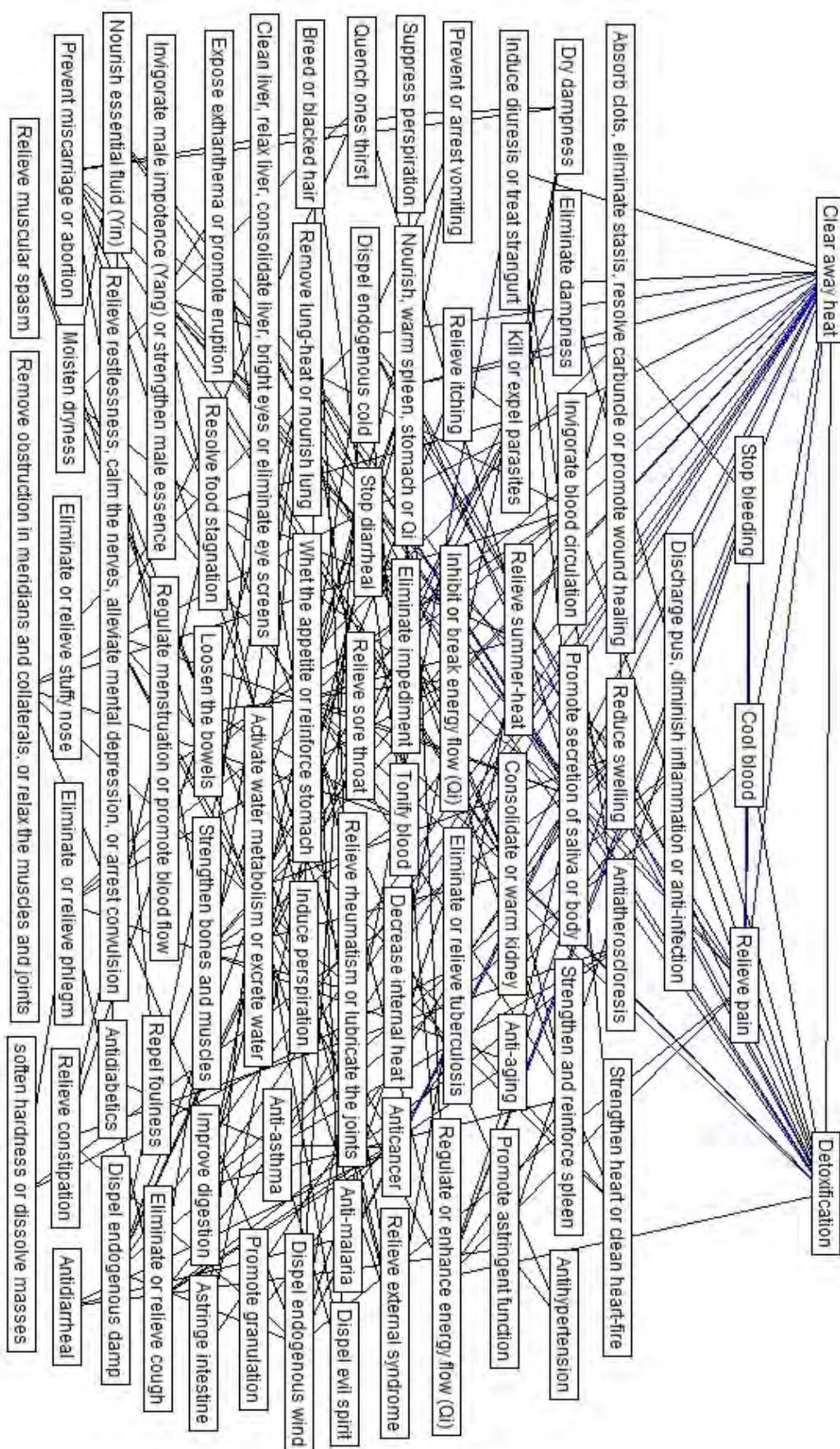


Fig. 1 Relational network for medicinal functions of Chinese herbal medicines (Zhang, 2012a). Black links represent positive point correlation and blue for negative point correlation. Isolated nodes are included.

3.2 PCA

PCA of 78 medicinal functions indicates that the medicinal functions $x_1 \sim x_{15}$ account for 33% of the total variance, $x_1 \sim x_{50}$ account for 79%, and $x_1 \sim x_{60}$ account for 88% (Table 3). Therefore, there are not absolutely significant components and medicinal functions.

The 78 components from PCA are substantially 78 independent and comprehensive medicinal functions (see supplementary material for detailed results). Major medicinal functions for every component can be simply determined by their importance and contribution coefficients in the component.

Given different t value, the new definition of medicinal functions for some of the principal components can be overallly given as follows

- F_1 : Clear away heat - Detoxification function
- F_2 : Dispel endogenous damp - Dispel endogenous wind- Relieve pain function
- F_3 : Consolidate or warm kidney - Invigorate male impotence (Yang) or strengthen male essence function
- F_4 : Relieve constipation - Loosen the bowels function
- F_5 : Kill or expel parasites - Relieve itching function
- F_6 : Relieve external syndrome function
- ...

At a certain level, for example, the medicinal functions -Consolidate or warm kidney, -Whet the appetite or reinforce stomach, Cool blood, -Regulate or enhance energy flow (Qi), -Nourish or warm spleen / stomach / Qi, Clear away heat, Detoxification, and Dispel endogenous cold, are the major attributes of the principal component F_1 . Of which the medicinal functions with the same sign (+ or -) have the same direction of medicinal action (Table 4).

Table 3 Component composition from 78 medicinal functions (the first 15 are listed only).

	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9	F_{10}	F_{11}	F_{12}	F_{13}	F_{14}	F_{15}
Eigenvalues	2.7571	2.3739	2.1204	1.8337	1.7209	1.6407	1.6256	1.6178	1.5005	1.4296	1.4045	1.3683	1.3393	1.3252	1.3002
Contribution (%)	3.5348	3.0435	2.7185	2.3509	2.2063	2.1035	2.0841	2.074	1.9237	1.8329	1.8006	1.7542	1.717	1.699	1.6669
x_1	-0.1693	0.1789	0.3681	-0.0574	0.0282	-0.1052	-0.0042	0.2013	-0.1289	-0.1338	0.0063	-0.0503	0.0823	0.1918	0.2121
x_2	-0.0272	0.0555	0.1389	-0.0338	-0.0315	-0.0394	-0.0559	0.0022	0.0552	-0.0378	-0.004	-0.0274	0.1508	0.1494	0.0335
x_3	0.0401	0.0355	0.0227	0.0558	-0.0251	-0.0413	0.0118	0.0163	-0.1702	-0.1067	-0.1143	-0.1444	-0.1003	0.0737	0.1985
x_4	0.0391	0.0123	0.0006	0.0225	0.019	-0.0131	0.0064	0.0011	-0.0227	-0.0154	0.0348	-0.0292	-0.0043	0.0173	0.0226
x_5	-0.3515	0.2398	0.5695	-0.0442	-0.0392	-0.1643	0.1865	0.0786	0.0543	0.1167	0.0657	0.0232	-0.0677	0.0726	0.0584
x_6	0.1279	0.1516	0.0507	-0.005	-0.063	-0.0053	0.0436	0.0895	-0.3745	0.1033	-0.1528	-0.1463	-0.2109	-0.0205	-0.1618
x_7	0.0522	-0.0412	-0.0629	-0.1828	0.1094	0.3182	0.1227	0.0513	-0.0403	0.1724	0.0493	0.2705	-0.0593	-0.1856	0.1746
x_8	-0.2843	0.2224	0.4342	0.0165	0.1387	-0.2561	0.2082	-0.0149	-0.044	0.1574	0.0862	0.131	-0.1807	-0.0931	-0.145
x_9	-0.1715	-0.0437	0.4293	-0.0848	-0.1627	-0.0592	-0.0539	0.1214	0.0545	0.1026	0.0838	0.0323	0.1443	0.1776	0.069
x_{10}	0.0958	-0.0105	0.0746	0.0857	-0.1105	-0.026	0.0547	-0.0841	0.1824	0.024	-0.1423	0.1404	0.219	-0.0978	-0.2375
x_{11}	-0.1366	0.3316	-0.2734	-0.2605	0.0048	-0.1736	-0.1308	-0.0416	0.2662	0.1011	0.0625	-0.0043	-0.2178	0.0047	0.1282
x_{12}	-0.0978	0.0285	-0.4061	-0.2711	0.0353	-0.0656	0.1444	0.2145	0.0827	0.0126	-0.2158	0.0766	-0.0273	0.3555	-0.0981
x_{13}	-0.0742	0.0261	-0.2953	-0.3666	-0.1404	-0.2958	0.1322	0.1292	-0.0978	-0.0318	0.0235	-0.0477	0.1287	-0.2879	0.1685
x_{14}	-0.0317	0.0398	-0.4005	-0.3894	-0.159	-0.3815	0.1136	0.151	0.1221	0.016	-0.1466	-0.0817	0.0097	-0.0159	0.1247
x_{15}	-0.0603	-0.0379	-0.0576	-0.0404	0.0243	-0.0753	-0.0406	0.0266	0.071	-0.0376	0.02	-0.0808	-0.0737	0.0762	-0.0325
x_{16}	0.0081	0.0236	-0.07	0.013	-0.0719	0.113	0.1541	0.0594	-0.1049	0.1983	0.1357	0.0992	0.0407	0.1906	-0.2141
x_{17}	-0.3771	0.1847	-0.2177	0.2997	-0.1111	0.146	0.2021	-0.105	0.0258	0.1473	0.1437	-0.0523	0.0399	0.208	0.0942
x_{18}	-0.3044	0.2325	0.0142	0.2184	-0.0587	0.0922	0.2403	-0.1277	0.0074	0.0956	-0.0349	-0.028	-0.0888	0.0372	0.2661
x_{19}	-0.2247	0.1042	-0.1928	0.2088	-0.131	0.1911	0.2144	-0.1713	-0.0663	0.1779	0.1429	0.0093	0.1292	0.1512	-0.0452
x_{20}	-0.143	0.4428	-0.2235	0.1312	-0.1112	0.0635	-0.4509	-0.0641	0.0665	0.184	0.0863	0.095	0.0619	-0.0651	-0.056
x_{21}	0.0412	0.1353	-0.0997	-0.1083	0.0396	-0.0862	-0.0732	-0.0142	-0.0187	0.0674	0.016	-0.1202	-0.1941	0.0029	-0.1041
x_{22}	-0.0139	-0.0009	-0.0217	-0.0634	0.2377	0.2596	0.1001	-0.2142	0.0505	0.0468	-0.1432	0.0342	0.1396	0.0173	0.1878
x_{23}	-0.0962	-0.0541	-0.0535	0.1059	-0.0171	0.0392	-0.0343	-0.0467	-0.1368	-0.1431	-0.2613	-0.0853	0.0178	-0.0563	-0.0531
x_{24}	-0.1566	0.0284	-0.1591	0.1184	0.1102	0.0069	0.2046	0.0841	0.0754	-0.1229	0.1044	-0.0467	0.0189	0.0702	-0.2129
x_{25}	-0.115	0.2153	-0.0086	0.1227	-0.1387	0.1421	0.0178	0.0606	-0.3516	-0.0347	-0.3945	-0.0281	-0.203	-0.0541	0.0464
x_{26}	-0.1274	0.2129	-0.1041	0.1265	-0.2083	0.091	-0.1156	-0.0101	-0.3935	-0.0945	-0.2715	-0.0149	0.0182	-0.0672	-0.0312
x_{27}	-0.0131	-0.0188	-0.0004	-0.004	-0.0236	0.0125	-0.0102	-0.0051	0.0034	-0.028	-0.0018	-0.0128	-0.0017	-0.0125	-0.0295
x_{28}	0.0089	0.1835	0.1261	-0.4368	0.3147	0.1178	0.1109	-0.3428	-0.1499	-0.1744	0.0221	-0.1868	0.0407	-0.0555	-0.1682
x_{29}	-0.0939	0.2233	0.1453	-0.4871	0.3035	0.0768	0.0767	-0.3748	-0.0257	-0.1972	0.0238	-0.069	0.0287	-0.0004	-0.1747

x_{30}	-0.062	0.2285	-0.0302	-0.0735	0.1287	0.1302	-0.374	-0.1395	0.0264	-0.0287	0.1416	0.0823	0.1452	-0.0553	-0.0757
x_{31}	-0.0812	0.123	-0.0566	0.023	0.0141	-0.0676	-0.0364	0.0387	0.174	0.1953	-0.0637	-0.1378	-0.1813	-0.352	-0.2613
x_{32}	0.091	-0.0081	-0.099	-0.1073	0.0237	0.1381	0.1471	0.2457	-0.1446	0.0901	0.0131	0.2248	-0.0936	0.1447	-0.2751
x_{33}	0.0488	0.0763	0.0312	0.0283	-0.0672	-0.0312	0.0158	0.0837	0.1881	-0.1133	-0.2665	0.1859	0.1021	-0.0728	0.0108
x_{34}	-0.1994	0.0865	0.152	0.1447	0.0135	-0.1721	0.1839	0.0809	0.1754	0.1736	-0.0285	-0.1266	-0.1824	-0.3956	-0.2097
x_{35}	0.3545	0.1121	0.0358	0.1504	0.002	-0.1943	-0.0498	-0.0613	0.1903	-0.045	-0.0214	-0.1176	0.0457	0.1741	-0.0658
x_{36}	0.3226	0.0202	0.1398	0.1293	-0.0896	-0.1355	-0.0163	-0.1527	0.3665	0.0539	-0.2049	0.0037	0.0482	-0.0016	-0.2104
x_{37}	-0.1533	0.1895	0.202	-0.1381	0.0044	0.099	-0.2006	-0.1782	-0.0763	-0.2359	0.0554	0.1561	0.0377	0.0055	0.0206
x_{38}	-0.0015	-0.3231	0.1392	-0.1483	-0.3094	0.1882	-0.0882	-0.1468	0.0251	-0.092	0.0953	0.1165	-0.0791	-0.094	-0.0491
x_{39}	0.1828	-0.1959	0.0974	-0.0753	-0.1496	0.1805	0.001	-0.1648	0.1	0.0561	0.0062	0.1517	-0.1291	0.0499	-0.0115
x_{40}	0.3104	-0.2044	-0.0495	-0.1411	-0.2332	0.1141	0.1557	0.0225	-0.0457	0.1654	0.264	0.228	-0.1147	-0.0144	-0.0293
x_{41}	0.058	0.0585	-0.0703	-0.0537	-0.05	-0.1077	-0.0359	0.0348	-0.0622	0.0178	0.1175	-0.0572	-0.0469	-0.1004	0.1634
x_{42}	0.0144	0.0077	0.0046	-0.1627	-0.0773	-0.0528	0.053	0.0648	-0.1784	-0.0246	0.1091	-0.1814	0.3637	-0.1765	-0.0423
x_{43}	-0.034	0.0691	0.0505	-0.0069	-0.1103	0.0072	-0.0566	0.2067	-0.1155	-0.0286	-0.1301	-0.0043	0.2303	0.0644	-0.08
x_{44}	-0.0688	0.338	-0.1324	0.0322	-0.0788	-0.0194	-0.4167	-0.0817	0.1157	0.0226	0.2143	0.0258	-0.0529	-0.0289	0.1659
x_{45}	0.0052	-0.0634	0.1878	-0.0945	-0.18	0.1241	-0.0093	-0.0873	0.0575	-0.1063	-0.2224	0.1656	-0.1738	-0.1308	0.0695
x_{46}	-0.149	0.0887	0.2435	0.0493	-0.0447	0.0362	0.0642	0.3511	0.1398	-0.1784	0.1044	0.0638	0.015	-0.0687	0.1011
x_{47}	0.0753	0.0055	0.0674	0.0387	-0.0823	0.141	0.0774	0.0648	0.0014	-0.0618	0.0295	0.0643	-0.0222	-0.138	0.1216
x_{48}	-0.3885	-0.0443	-0.1671	0.1599	-0.1775	0.102	0.077	-0.1369	0.0644	-0.2944	0.1399	-0.0278	-0.1115	-0.1372	0.0896
x_{49}	-0.0895	0.0868	-0.1637	-0.1793	0.1886	0.0886	0.1577	-0.0697	0.1751	0.089	-0.146	0.1328	0.0892	0.2489	0.0745
x_{50}	-0.0267	0.0642	-0.1008	-0.0516	-0.0378	-0.0451	-0.0853	0.043	0.0632	0.0827	-0.0685	0.0357	0.0462	0.0762	-0.0334
x_{51}	-0.1168	-0.2783	0.0355	-0.1407	-0.0166	0.0201	-0.203	-0.0229	-0.0429	0.0152	0.0565	-0.1265	0.031	0.0116	-0.117
x_{52}	-0.3433	-0.1138	-0.2162	0.2256	0.1114	0.0074	0.2017	-0.0745	0.0837	-0.2521	0.0822	-0.0924	0.1057	-0.0944	-0.129
x_{53}	-0.1782	-0.4668	-0.0429	-0.0314	-0.2837	0.0618	-0.0491	-0.0702	0.0148	-0.1952	0.0872	-0.0325	-0.1064	-0.0923	-0.0805
x_{54}	0.0034	-0.0069	-0.0975	-0.0637	-0.1424	-0.0827	0.1002	0.101	-0.2163	-0.0981	0.0751	-0.0324	0.3897	-0.1851	-0.0449
x_{55}	0.6484	0.1534	-0.0138	0.2437	0.1308	-0.1465	0.0238	-0.0084	-0.1064	-0.1442	0.0983	-0.1266	-0.0738	0.0401	0.101
x_{56}	0.292	0.0315	-0.0201	0.1483	-0.0377	-0.1389	0.1559	-0.1929	0.1032	-0.1998	0.0456	-0.0789	-0.0227	-0.0041	0.2794
x_{57}	0.646	0.0014	-0.018	0.0813	0.04	-0.0497	0.0891	-0.0104	-0.0894	0.0047	0.2456	-0.0104	-0.0646	0.0108	0.0603
x_{58}	0.091	0.2033	-0.0384	0.0708	0.1464	0.1254	-0.2039	0.3712	0.0156	-0.2429	0.0531	0.0278	-0.0902	-0.0285	-0.1411
x_{59}	-0.04	0.2101	-0.1362	0.0642	-0.1284	0.064	-0.275	-0.0562	-0.1109	0.1667	0.0106	-0.0011	0.1252	-0.0096	-0.1286
x_{60}	-0.0313	-0.0422	-0.0297	0.248	0.1496	-0.1047	0.0484	-0.179	0.0083	-0.0191	-0.0423	0.0702	0.2164	-0.0285	0.088
x_{61}	-0.3711	-0.2702	-0.1774	0.0538	0.0239	-0.0606	0.0663	0.0389	0.0819	-0.2135	0.1758	-0.1062	-0.0887	0.0825	-0.1433
x_{62}	-0.2145	-0.4672	0.044	0.0799	0.1392	-0.063	-0.2521	-0.0129	-0.0336	0.1864	-0.1813	-0.1136	-0.083	0.0801	0.0716
x_{63}	-0.2026	-0.5501	0.0103	-0.0019	0.1901	-0.128	-0.32	0.0176	-0.0504	0.0741	-0.0466	-0.043	-0.092	0.0887	0.0273
x_{64}	-0.096	-0.093	0.263	-0.1467	-0.1965	0.0001	-0.1033	0.1807	0.0566	0.1669	0.0675	-0.2013	0.2701	0.0943	0.0765
x_{65}	-0.0136	0.0724	-0.0364	0.1065	0.332	0.1731	-0.0418	0.4672	0.1067	-0.2376	0.1359	0.0416	-0.0471	0.0332	-0.1074
x_{66}	-0.067	0.1057	0.0291	-0.0298	0.0028	0.1199	-0.1198	0.2447	0.1753	-0.3054	-0.0081	0.2807	-0.0339	-0.0892	0.0854
x_{67}	-0.1137	-0.1097	-0.0635	0.0274	0.1399	-0.2247	-0.0191	-0.083	-0.1093	0.0664	-0.058	0.3884	0.0668	-0.0746	0.0664
x_{68}	-0.1465	-0.1613	-0.0835	0.186	0.2594	-0.4408	-0.0145	-0.1322	-0.2117	-0.0388	0.0902	0.3913	0.1084	-0.0921	0.0024
x_{69}	0.09	0.0554	0.0626	0.1206	-0.0991	-0.0516	0.0434	-0.0809	0.2483	-0.0843	-0.365	0.1349	0.2442	-0.0761	-0.1079
x_{70}	0.1305	0.0321	0.0072	0.0542	-0.0961	0.1137	0.0763	0.1002	-0.0086	0.1246	0.2145	-0.0142	0.2811	-0.1582	-0.1094
x_{71}	-0.0057	-0.1497	-0.0225	0.1554	0.3988	0.0865	-0.0578	0.1353	0.0274	0.1083	-0.0517	-0.1496	0.1229	-0.1529	0.1613
x_{72}	0.0044	-0.1103	0.0008	-0.004	0.4319	0.3091	0.0022	0.133	0.0812	0.2985	-0.0821	-0.114	0.0854	-0.2247	0.1309
x_{73}	0.0472	0.0106	-0.0523	0.0036	0.0614	0.1736	0.09	0.1107	-0.0737	0.0397	-0.1615	0.1103	0.0296	-0.0866	0.0748
x_{74}	-0.0443	-0.0774	-0.0513	-0.0319	0.0987	-0.1673	-0.0352	0.0776	-0.1091	-0.0065	-0.0257	0.3087	0.0456	0.0198	-0.0054
x_{75}	-0.0308	0.0407	0.0569	0.1399	0.1264	-0.2814	-0.0956	-0.082	-0.2849	0.0762	0.1247	0.1989	-0.0616	0.0135	-0.1054
x_{76}	-0.0052	0.0231	-0.0809	-0.1522	-0.0299	-0.0229	0.0483	0.0421	0.0176	0.1034	0.0757	0.1148	-0.0453	-0.2127	0.2031
x_{77}	-0.0407	-0.0889	0.0391	-0.0223	-0.0279	-0.0111	-0.109	0.0393	0.007	0.0816	-0.0246	-0.1312	0.0766	0.0734	0.0367
x_{78}	-0.0334	-0.0434	0.0329	0.0177	0.0097	0.0485	0.0061	0.029	0.0413	0.1418	0.0138	-0.131	0.0472	-0.176	0.0591

See Table 1 for Medicinal functions x_{1} - x_{78} .

Table 4 Major medicinal functions of the first principal components.

	$t=1.5$	$t=2$	$t=2.5$
F_1	-Consolidate or warm kidney, -Whet the appetite or reinforce stomach, Cool blood, -Regulate or enhance energy flow (Qi), -Nourish or warm spleen / stomach / Qi, Clear away heat, Detoxification, -Dispel endogenous cold	Clear away heat, Detoxification	Clear away heat, Detoxification
F_2	Remove lung-heat or nourish lung, Promote secretion of saliva or body, -Invigorate blood circulation, Nourish essential fluid (Yin), -Relieve pain, -Dispel endogenous damp, -Dispel endogenous wind	Promote secretion of saliva or body, -Relieve pain, -Dispel endogenous damp, -Dispel endogenous wind	Promote secretion of saliva or body, -Relieve pain, -Dispel endogenous damp, -Dispel endogenous wind
F_3	Clean liver / relax liver / consolidate liver / bright eyes / eliminate eye screens, Consolidate or warm kidney, Invigorate male impotence (Yang) or strengthen male essence, Strengthen bones and muscles, -Anti-asthma, -Eliminate or relieve phlegm, -Eliminate or relieve cough	Clean liver / relax liver / consolidate liver / bright eyes / eliminate eye screens, Consolidate or warm kidney, Invigorate male impotence (Yang) or strengthen male essence, Strengthen bones and muscles, -Eliminate or relieve phlegm, -Eliminate or relieve cough	Consolidate or warm kidney, Invigorate male impotence (Yang) or strengthen male essence, Strengthen bones and muscles

F_4	-Eliminate or relieve phlegm, -Anti-asthma, -Eliminate or relieve cough, Whet the appetite or reinforce stomach, -Relieve constipation, -Loosen the bowels	-Anti-asthma, -Eliminate or relieve cough, -Relieve constipation, -Loosen the bowels	-Eliminate or relieve cough, -Relieve constipation, -Loosen the bowels
F_5	Relieve constipation, Loosen the bowels, -Invigorate blood circulation, -Relieve pain, Dry dampness, Relieve external syndrome, Relieve itching, Kill or expel parasites	Relieve constipation, -Invigorate blood circulation, Dry dampness, Relieve itching, Kill or expel parasites	Relieve itching, Kill or expel parasites
F_6	Activate water metabolism or excrete water, -Invigorate male impotence (Yang) or strengthen male essence, -Eliminate or relieve phlegm, -Eliminate or relieve cough, Resolve food stagnation, -Relieve external syndrome, Kill or expel parasites, -Expose exanthema or promote eruption	Activate water metabolism or excrete water, -Eliminate or relieve phlegm, -Eliminate or relieve cough, -Relieve external syndrome, Kill or expel parasites	-Eliminate or relieve cough, -Relieve external syndrome
F_7	-Promote secretion of saliva or body, -Moisten dryness, -Nourish essential fluid (Yin), -Quench one's thirst, -Dispel endogenous wind	-Promote secretion of saliva or body, -Moisten dryness, -Nourish essential fluid (Yin), -Dispel endogenous wind	-Promote secretion of saliva or body, -Moisten dryness, -Nourish essential fluid (Yin)
F_8	-Relieve constipation, -Loosen the bowels, Prevent miscarriage or abortion, Decrease internal heat, Dry dampness	-Relieve constipation, -Loosen the bowels, Prevent miscarriage or abortion, Decrease internal heat, Dry dampness	-Loosen the bowels, Prevent miscarriage or abortion, Decrease internal heat, Dry dampness
F_9	-Induce diuresis or treat strangury, Remove lung-heat or nourish lung, -Strengthen heart or clean heart-fire, -Relieve restlessness, calm the nerves, alleviate mental depression / arrest convulsion, Stop bleeding, Promote astringent function, -Expose exanthema or promote eruption	-Induce diuresis or treat strangury, -Strengthen heart or clean heart-fire, -Relieve restlessness, calm the nerves, alleviate mental depression / arrest convulsion, Stop bleeding	-Induce diuresis or treat strangury, -Strengthen heart or clean heart-fire, -Relieve restlessness, calm the nerves, alleviate mental depression / arrest convulsion, Stop bleeding
F_{10}	-Tonify blood, -Regulate or enhance energy flow (Qi), -Nourish or warm spleen / stomach / Qi, -Decrease internal heat, -Dry dampness, -Suppress perspiration, Kill or expel parasites	-Regulate or enhance energy flow (Qi), -Suppress perspiration, Kill or expel parasites	-Suppress perspiration
F_{11}	-Repel foulness, -Strengthen heart or clean heart-fire, -Relieve restlessness, calm the nerves, alleviate mental depression, or arrest convulsion, -Antidiarrheal, Reduce swelling, Detoxification, -Promote astringent function	-Strengthen heart or clean heart-fire, -Promote astringent function	-Strengthen heart or clean heart-fire, -Promote astringent function
F_{12}	Activate water metabolism or excrete water, Suppress perspiration, Induce perspiration, Relieve external syndrome, Relieve muscular spasm	Suppress perspiration, Induce perspiration, Relieve external syndrome, Relieve muscular spasm	Induce perspiration, Relieve external syndrome
F_{13}	Antiatherosclerosis, Antihypertension, Anticancer, Relieve rheumatism or lubricate the joints, Promote astringent function, Discharge pus, diminish inflammation or anti-infection	Antiatherosclerosis, Anticancer, Relieve rheumatism or lubricate the joints, Discharge pus, diminish inflammation or anti-infection	Antiatherosclerosis, Anticancer
F_{14}	Eliminate or relieve phlegm, -Anti-asthma, -Astringe intestine, -Stop diarrheal, Inhibit or break energy flow (Qi)	Eliminate or relieve phlegm, -Anti-asthma, -Astringe intestine, -Stop diarrheal	Eliminate or relieve phlegm, -Astringe intestine, -Stop diarrheal
F_{15}	-Promote granulation, Strengthen and reinforce spleen, -Astringe intestine, -soften hardness or dissolve masses, Eliminate dampness	Strengthen and reinforce spleen, -Astringe intestine, -soften hardness or dissolve masses, Eliminate dampness	NaN

-: Negative action.

3.3 System cluster analysis

Choose distance measure as point correlation (1-r), use max-min normalization and class averaging method. The cluster tree of medicinal functions is indicated in Fig. 2. We can determine belonged class of any medicinal function at different hierarchy (see supplementary material for detailed results). The following are some of the results

$r=-0.00025741$ (8 classes)

(x1, x2, x5, x8, x9, x33, x37, x46, x58, x64, x65, x66, x73)
(x3, x6, x23, x25, x26, x41)
(x11, x12, x13, x14, x20, x21, x22, x28, x29, x30, x44, x49, x50, x59)
(x15, x17, x18, x19, x24, x27, x31, x34, x48, x52, x53, x61, x78)
(x51, x62, x63, x67, x68, x71, x72, x74, x75, x77)
(x4, x10, x35, x36, x55, x56, x57, x60, x69)
(x7, x16, x32, x40, x42, x43, x54, x70, x76)
(x38, x39, x45, x47)

$r=-0.0011981$ (7 classes)

(x1, x2, x5, x8, x9, x33, x37, x46, x58, x64, x65, x66, x73)
(x3, x6, x23, x25, x26, x41)
(x11, x12, x13, x14, x20, x21, x22, x28, x29, x30, x44, x49, x50, x59)
(x15, x17, x18, x19, x24, x27, x31, x34, x48, x51, x52, x53, x61, x62, x63, x67, x68, x71, x72, x74, x75, x77, x78)
(x4, x10, x35, x36, x55, x56, x57, x60, x69)
(x7, x16, x32, x40, x42, x43, x54, x70, x76)
(x38, x39, x45, x47)

$r=-0.0015333$ (6 classes)

(x1, x2, x5, x8, x9, x33, x37, x46, x58, x64, x65, x66, x73)
(x3, x6, x23, x25, x26, x41)
(x11, x12, x13, x14, x20, x21, x22, x28, x29, x30, x44, x49, x50, x59)
(x15, x17, x18, x19, x24, x27, x31, x34, x48, x51, x52, x53, x61, x62, x63, x67, x68, x71, x72, x74, x75, x77, x78)
(x4, x10, x35, x36, x55, x56, x57, x60, x69)
(x7, x16, x32, x38, x39, x40, x42, x43, x45, x47, x54, x70, x76)

$r=-0.0029599$ (5 classes)

(x1, x2, x5, x8, x9, x33, x37, x46, x58, x64, x65, x66, x73)
(x3, x6, x11, x12, x13, x14, x20, x21, x22, x23, x25, x26, x28, x29, x30, x41, x44, x49, x50, x59)
(x15, x17, x18, x19, x24, x27, x31, x34, x48, x51, x52, x53, x61, x62, x63, x67, x68, x71, x72, x74, x75, x77, x78)
(x4, x10, x35, x36, x55, x56, x57, x60, x69)
(x7, x16, x32, x38, x39, x40, x42, x43, x45, x47, x54, x70, x76)

$r=-0.0073534$ (4 classes)

(x1, x2, x3, x5, x6, x8, x9, x11, x12, x13, x14, x20, x21, x22, x23, x25, x26, x28, x29, x30, x33, x37, x41, x44, x46, x49, x50, x58, x59, x64, x65, x66, x73)
(x15, x17, x18, x19, x24, x27, x31, x34, x48, x51, x52, x53, x61, x62, x63, x67, x68, x71, x72, x74, x75, x77, x78)
(x4, x10, x35, x36, x55, x56, x57, x60, x69)
(x7, x16, x32, x38, x39, x40, x42, x43, x45, x47, x54, x70, x76)

Results of system cluster analysis indicate that (Consolidate or warm kidney, Invigorate male impotence (Yang) or strengthen male essence), (Relieve constipation, Loosen the bowels), and (Clear away heat, Detoxification) are classified into a class respectively at the earliest stage. They are the most similar medicinal functions from each other.

At a certain level, e.g., $r=-0.00025741$, 78 medicinal functions can be classified as the following 8 classes

Category 1:

Clean liver / relax liver / consolidate liver / bright eyes / eliminate eye screens, Breed or blacked hair, Consolidate or warm kidney, Invigorate male impotence (Yang) / strengthen male essence, Strengthen bones and muscles, Antidiarrheal, Tonify blood, Prevent miscarriage or abortion, Decrease internal heat, Relieve rheumatism or lubricate the joints, Dry dampness, Suppress perspiration, Anti-malaria;

Category 2:

Benefit gallbladder / cure jaundice, Induce diuresis / treat strangury, Repel foulness, Strengthen heart or clean heart-fire, Relieve restlessness / calm the nerves / alleviate mental depression or arrest convulsion, Antidiabetics;

Category 3:

Remove lung-heat / nourish lung, Eliminate or relieve phlegm, Anti-asthma, Eliminate or relieve cough, Promote secretion of saliva or body, Relieve sore throat, Resolve food stagnation, Relieve constipation, Loosen the bowels, Moisten dryness, Nourish essential fluid (Yin), Inhibit or break energy flow (Qi), Anti-aging, Quench one's thirst;

Category 4:

Eliminate or relieve stuffy nose, Whet the appetite / reinforce stomach, Strengthen and reinforce spleen, Improve digestion, Prevent or arrest vomiting, Arrest epilepsy, Astringe intestine, Stop diarrheal, Regulate or enhance energy flow (Qi), Nourish or warm spleen / stomach / Qi, Relieve pain, Dispel endogenous cold, Eliminate impediment;

Category 5:

Remove obstruction in meridians and collaterals / relax the muscles and joints, Dispel endogenous damp, Dispel endogenous wind, Induce perspiration, Relieve external syndrome, Relieve itching, Kill or expel parasites, Relieve muscular spasm, Expose exanthema / promote eruption, Anesthesia;

Category 6:

Reduce aminotransferase, Promote granulation, Cool blood, Stop bleeding, Clear away heat, Eliminate dampness, Detoxification, Relieve summer-heat, Promote astringent function;

Category 7:

Activate water metabolism or excrete water, Eliminate or relieve tuberculosis / soften hardness or dissolve masses, Reduce swelling, Antiatherosclerosis, Antihypertension, Anticancer, Discharge pus / diminish inflammation / anti-infection, Dispel evil spirit;

Category 8:

Invigorate blood circulation, Absorb clots / eliminate stasis / resolve carbuncle / promote wound healing, Regulate menstruation / promote blood flow, Promote lactation / stimulate milk secretion.

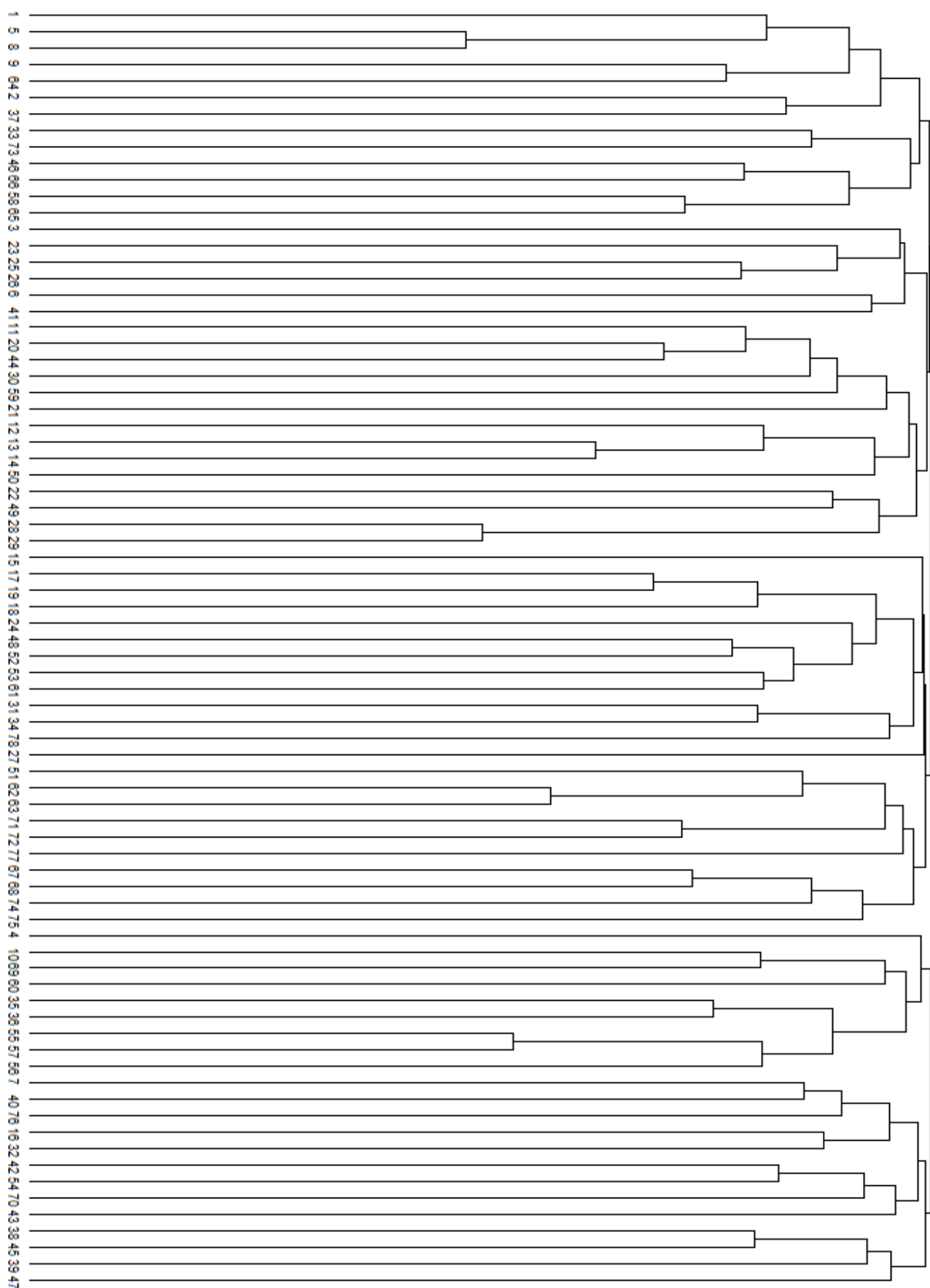


Fig. 2 System cluster tree of medicinal functions. See Table 1 for $x_1 \sim x_{78}$.

4 Discussion

Strictly speaking, any medicinal functions have direct or indirect correlation. The changes of a medicinal function may finally affect other medicinal functions through various paths in the relational network (Zhang, 2017b). Thus, the class division of medicinal functions is a continuum, as shown in Fig. 2 and supplementary material.

Suppose the two medicinal functions, x_i and x_j , belong to the same class. The possible causes for the classification are likely thus: (1) x_i and x_j are completely different medicinal functions, but the correlation between them is strong. They highly interact with each other directly or indirectly. For example, the function, Clear away heat, will result in the function, Detoxification. For these cases, two medicinal functions can be considered to be incorporated as a new function. (2) x_i and x_j overlap in the functionality but they have separate independency. (3) x_i and x_j have different names but the difference between their natural meaning is very small, i.e., they have basically the same functionality. For example, the medicinal function pairs, (Consolidate or warm kidney, Invigorate male impotence (Yang) or strengthen male essence), and (Relieve constipation, Loosen the bowels), etc. In these situations, the two functions can be considered to be incorporated as a new function also.

In general, the sub-networks / modules identified by the sub-networks /modules identification method are expected to be the most natural and their functionalities are generally the most clear. Results of system cluster analysis also have better interpretability. For PCA, the medicinal functionalities of principal components are not so clear and should be explored in the future. Generation of modules / sub-networks / attribute classes is attributed to meridians and collaterals. A Chinese herbal medicine acts on some of the meridians and collaterals and further produces different groups of medicinal functions (Zhang, 2017a, b). Furthermore, because there are certain interactions between various meridians and collaterals (Zhang, 2017b), the resulted groups of medicinal functions are not only the results of additive effects of different meridians and collaterals but new medicinal attributes may be generated. In the sense of mathematical mapping, suppose x is the Chinese herbal medicine, y is chemicals, z is meridians and collaterals, and w is medicinal functions. For a given Chinese herbal medicine, its medicinal functions are assumed to be deterministic. We have

$$y=f(x), z=g(y), w=h(z)$$

and thus

$$w=(h \circ g \circ f)(x)$$

Our studies are just aiming to determine such relationships.

In the future, some works should be done in respect to medicinal functions: (1) incorporation and generation of medicinal functions, and normalization and clarification of their names, and (2) stricter scientific definition of medicinal functions, including the specific organs and systems the medicinal function acts on, basic pharmacology and measurable indicators of the medicinal function, etc. Among them, we need to categorize medicinal functions into human body systems: motivation system, nervous system, endocrine system, circulation system, respiratory system, digestive system, urinary system, reproductive system, or some of their combinations. In this study, the choice and pre-classification of medicinal functions in the database CHM-DATA 1.0 had considered such requirements (Zhang, 2017a, 2017b, 2017c) by categorizing medicinal functions based on their belonged meridians and collaterals. With above classification of medicinal functions, this study gives a preliminary scheme and foundation for their possible categorization in body systems or organs.

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