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RESEARCH ARTICLE

Bioinformatics analysis of Qingfeipaidu Decoction for 2019-nCoV by TCM-BATMAN and GSH

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Abstract: Traditional Chinese medicine Qingfeipaidu Decoction was reported effective in treatment of 2019-nCoV diseases. However, the mechanisms of the drug were still unknown. Our paper tried to discover the potential mechanism of the medicine in modern science methods. TCM-BATMAN tool were used to analyze the ingredients of QingfeiPaidu decoction. STRING were used to built the PPI network. 428 genes of Qingfeipaidu Decoction were obtained by TCM-BATMAN. The main KEGG pathways were associated with the interaction of Neuroactive ligand-receptor interaction, calcium signaling pathway, amino acid synthesis and metabolism pathway, glutathione metabolism pathway and so on. Patients of SARS and HIV were reported benefitting from applying the GSH. 2019-ncov containing HIV components and SARS sequence were report low glutathione. Anti-HIV drugs such as remdesivir and kaletra were useful for the diseases. Glutathione metabolism were regarded as an important pathway for the disease. Qingfeipaidu Decoction may be used to treat new coronavirus by glutathione metabolism pathway, and GSH may be a potential therapeutic drug for the new coronavirus.

Keywords: Qingfeipaidu Decoction, 2019-nCoV, TCM-BATMAN, GSH

1 Introduction

The novel coronavirus (2019-nCoV) from Wuhan is currently causing concern in the medical community as the virus is spreading around the world[1]. Since identification of the virus in late December 2019, the number of cases have been increased significantly all over china and some cases been found in other countries with an rising epidemiologic picture[2]. There is no effective medicine for the new outbreak of new coronavirus pneumonia. However, in the process of treating new coronavirus pneumonia, in addition to modern medicine and drugs, attempts have been made to treat traditional Chinese medicine in China[3]. According to the announcement issued by the Chinese Medicine Administration, the emergency scientific research project organized by the Bureau has made gradual progress. According to the clinical observations of the 4 provinces, the total effective rate of Qingfei Paidu Decoction for the treatment of patients with pneumonitis infected by new coronavirus can reach 90%[4]. The ingredients of Qingfei Paidu Decoction are as follows:

MA HUANG 9g, ZHI GAN CAO 6g, XING REN 9g, SHENG SHI GAO 15g, GUI ZHI 9g, ZE XIE 9g, ZHU LING 9g, BAI SHU 9g, FU LING 15g, CHAI HU 16g, HUANG CEN 6g, JIANG BAN XIA 9g, SHENG JIANG 9g, ZI WAN 9g, DONG HUA 9g, SHE GAN 9g, XI XIN 6g, SHAN YAO 12g, ZHI SHI 6g, CHEN PI 6g and HUO XIANG 9g. However, the theory of the treatment explanation is still not clear and convincible in modern scientific methods.

BATMAN-TCM (http://bionet.ncpsb.org/batman-tcm) is a Bioinformatics Analysis Tool for Molecular mechanism of Traditional Chinese Medicine[5]. It will contribute to the understanding of the "multi-component, multi-target and multi-pathway" combinational therapeutic mechanism of TCM and provide valuable clues for subsequent experimental validation, accelerating the elucidation of TCM's molecular mechanism. My article tries to use the tools to display the mechanism of Qingfeipaidu Decoction for the treatment of patients with pneumonitis infected by new coronavirus.

2 Methods

The ingredients of MA HUANG, ZHI GAN CAO, XING REN, SHENG SHI GAO, GUI ZHI, ZE XIE, ZHU LING, BAI SHU, FU LING, CHAI HU , HUANG CEN, JIANG BAN XIA, SHENG JIANG, ZI WAN, DONG

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HUA, SHE GAN, XI XIN, SHAN YAO, ZHI SHI, CHEN PI and HUO XIANG were input into the tools of TCM-BATMAN (http://bionet.ncpsb.org/batman-tcm/). As we set, predicted candidate targets (including known targets) with scores not smaller than Score cutoff = 20 for each ingredient are presented and used for further bioinformatics analyses.

Significantly enriched KEGG pathways/GO terms with adjusted P_value smaller than Adjusted P_value cutoff = 0.05 are highlighted in the results. The genes of these drugs were obtained from the analysis. The PPI network was construct by STRING (https://string-db.org/). And its KEGG pathways and gene ontology process were displayed in my article.

3 Results

There are a total of 428 genes recommended by the TCM-BATMAN tools for the Qingfei Paidu Decoction. The PPI network of these genes were showed in Figure 1. These drugs were associated with the KEGG pathways of Neuroactive ligand-receptor interaction (hsa04080), Calcium signaling pathway (hsa04020), Arginine and proline metabolism (hsa00330), Glycine, serine and threonine metabolism (hsa00260), Biosynthesis of amino acids (hsa01230), Carbon metabolism (hsa01200), Glutathione metabolism (hsa00480), Alanine, aspartate and glutamate metabolism (hsa00250), Tyrosine metabolism (hsa00350), Valine, leucine and isoleucine degradation (hsa00280), cGMP - PKG signaling pathway (hsa04022), Tryptophan metabolism (hsa00380), Metabolism of xenobiotics by cytochrome P450 (hsa00980), Cardiac muscle contraction (hsa04260), Propanoate metabolism (hsa00640) (As shown in Table 1). The gene ontology process were mainly associated with Small Molecule Metabolic Process (GO:0044281), Cell-Cell Signaling (GO:0007267), Cellular Amino Acid Metabolic Process (GO:0006520), Transmembrane Transporter Activity (GO:0022857), Transmembrane Transport (GO:0055085), Transport (GO:0006810), Homeostatic Process (GO:0042592), Response To Stress (GO:0006950), Oxidoreductase Activity (GO:0016491), Lipid Metabolic Process (GO:0006629), Cytoplasm (GO:0005737), Biosynthetic Process (GO:0009058), Cell Proliferation (GO:0008283), Anatomical Structure Development (GO:0048856), Circulatory System Process (GO:0003013) *et al*., as shown in Table 2.

4 Discussion

The 2019-nCoV causes respiratory disease and can be transmitted from person to person[6]. As with other respiratory illnesses, infection with 2019-nCoV can cause mild symptoms including a runny nose, sore throat, cough, and fever. It can be more severe for some persons and can lead to pneumonia or breathing difficulties[7]. The disease can be rarely fatal, and older people, as well as the patients with pre-existing medical conditions appear to be more vulnerable to becoming severely ill with the virus[8]. HIV protease inhibitors such as lopinavir and ritonavir were effective in patients infected with 2019-nCoV for they could effectively inhibit the 3-chymotrypsin-like and papain-like proteases of 2019-nCoV. Delivery systems of spike inhibitors for the HIV treatment should be re-evaluated for the treatment or prevention of 2019-nCoV. The Component of the 2019-nCoV is closely associated with the HIV virus, as the recently evidence shows. As mentioned above, the Chinese Medicine Administration announced that the total effective rate of Qingfei Paidu Decoction for the treatment of patients with pneumonitis infected by new coronavirus can reach 90%. However,its mechanism is still unclear. TCM-BATMAN(http://bionet.ncpsb.org/batman-tcm) is a Bioinformatics Analysis Tool for Molecular mechanism of Traditional Chinese Medicine. My article tries to use the tools to display the mechanism of Qingfei Paidu Decoction for the treatment of patients with pneumonitis infected by new coronavirus. As shown in table 1, these drugs were associated with the KEGG pathways of Neuroactive ligand-receptor interaction, Calcium signaling pathway, Arginine and proline metabolism, Glycine, serine and threonine metabolism, Glutathione metabolism and so on. Among all the pathways, the Glutathione metabolism was special and caught our attention. Glutathione (GSH), a cysteine-containing tripeptide, is essential for the viability and function of virtually all cells[9]. *In vitro* studies showing that low GSH levels both promote HIV expression and impair T cell function suggested a link between GSH depletion and HIV disease progression. GSH deficiency as a key determinant of survival in HIV disease. GSH deficient had impaired owner's mitochondrial fuel oxidation and this improved with an increase in intracellular GSH concentrations[10]. GSH was also reported applied in several pneumonia treatment with good effects[11, 12]. It may prevent the tissue of the pulmonary and other normal immune cells from peroxidation. So it is reasonable to believe that Qingfei Paidu Decoction cured the disease by Glutathione metabolism pathways, and the GSH may assistant the treatment of patients with pneumonitis infected by new coronavirus.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

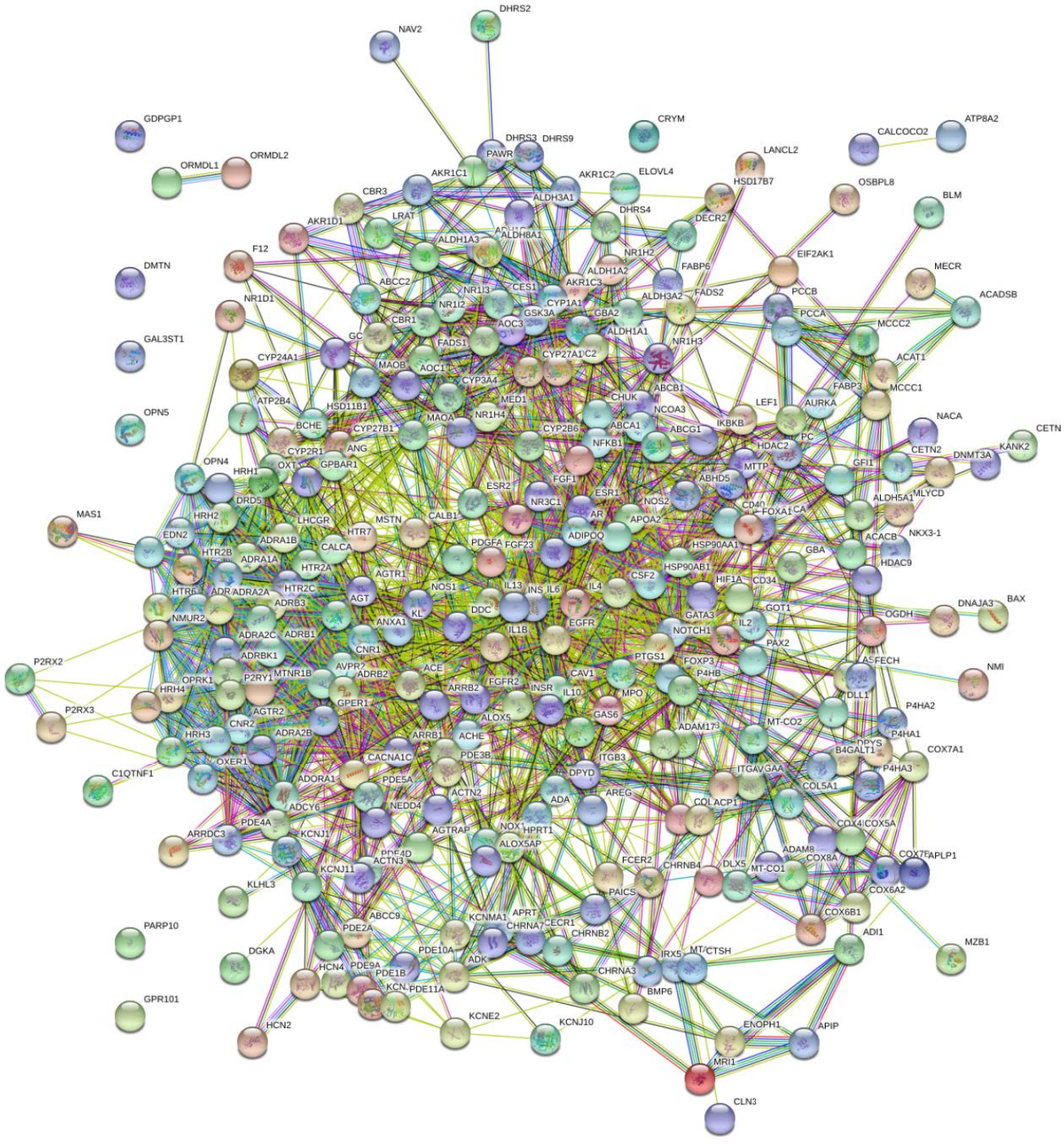

Figure 1: The PPI network of Qingfeipaidu Decoction

Table 1-1 KEGG signal pathway of Qingfeipaidu Decoction (top 15)

Annotation Term ID	Term description	Cluster 1 (p-value)	Benjamini value	gene names
hsa04080	Neuroactive ligand-receptor interaction	2.78E-33	3.32E-31	ADORA1;ADORA2A;ADORA2B;ADORA3;ADRA1A;ADRA1B;ADRA1D;ADRA2A;ADRA2B;ADRA2C;ADRB1;ADRB2;ADRB3;AGTR1;AGTR2;AVPR1A;AVPR1B;AVPR2;BDKRB2;CHRM1;CHRM2;CHRM3;CHRM4;CHRM5;CHRNA1;CHRNA10;CHRNA2;CHRNA3;CHRNA4;CHRNA5;CHRNA6;CHRNA7;CHRNA9;CHRNB1;CHRNB2;CHRNB3;CHRNB4;CHRND;CHRNE;CHRNG;CNR1;CNR2;CRHR1;CRHR2;CYSLTR1;DRD1;DRD2;DRD3;DRD4;DRD5;F2RL1;GABRA1;GABRA2;GABRA3;GABRA4;GABRA5;GABRA6;GABRB1;GABRB2;GABRB3;GABRD;GABRE;GABRG1;GABRG2;GABRG3;GABRP;GABRQ;GHR;GLRA1;GLRA2;GLRA3;GLRB;GRIA1;GRIA2;GRIA3;GRIA4;GRIK1;GRIK2;GRIK3;GRIK4;GRIK5;GRIN1;GRIN2A;GRIN2B;GRIN2C;GRIN2D;GRIN3A;GRIN3B;GRM6;GRM7;HRH1;HRH2;HRH3;HRH4;HTR1A;HTR1B;HTR1D;HTR1F;HTR2A;HTR2B;HTR2C;HTR4;HTR6;HTR7;LEP;LHCGR;MAS1;MC1R;MC2R;MC3R;MC4R;MC5R;MLNR;MTNR1B;NMUR2;NPFFR2;NPY2R;NPY5R;NR3C1;NTSR1;OPRD1;OPRK1;OPRL1;OPRM1;OXTR;P2RX2;P2RX3;P2RY1;P2RY2;PLG;PRLR;PTGER1;PTGER2;PTGER3;PTGER4;PTGFR;PTGIR;S1PR5;TAAR1;TACR2;THRA;THRB;TRPV1;TSPO;UTS2R;
hsa04020	Calcium signaling pathway	6.78E-23	4.05E-21	ADORA2A;ADORA2B;ADRA1A;ADRA1B;ADRA1D;ADRB1;ADRB2;ADRB3;AGTR1;ATP2A1;ATP2B4;AVPR1A;AVPR1B;BDKRB2;CACNA1A;CACNA1B;CACNA1C;CACNA1D;CACNA1F;CACNA1G;CACNA1H;CACNA1I;CACNA1S;CALM1;CALM2;CALM3;CAMK2A;CAMK2D;CAMK2G;CHRM1;CHRM2;CHRM3;CHRM5;CHRNA7;CYSLTR1;DRD1;DRD5;ERBB2;GNA11;GNA14;GNA15;GRIN1;GRIN2A;GRIN2C;GRIN2D;HRH1;HRH2;HTR2A;HTR2B;HTR2C;HTR4;HTR6;HTR7;ITPR1;ITPR2;ITPR3;LHCGR;MYLK2;NOS1;NOS2;NOS3;NTSR1;OXTR;P2RX2;P2RX3;PDE1A;PDE1B;PDE1C;PHKG2;PLCG2;PLN;PPIF;PPP3CA;PPP3CB;PPP3R1;PPP3R2;PTGER1;PTGER3;PTGFR;PTK2B;RYR1;RYR2;RYR3;SLC25A4;SLC25A5;SLC25A6;SLC8A1;SLC8A2;SLC8A3;STIM1;STIM2;TACR2;TNNC1;TNNC2;VDAC1;VDAC2;VDAC3;
hsa00330	Arginine and proline metabolism	1.02E-19	4.06E-18	ACY1;ALDH18A1;ALDH1B1;ALDH2;ALDH3A2;ALDH4A1;ALDH7A1;ALDH9A1;AOC1;ARG1;ARG2;ASL;ASS1;AZIN2;CKB;CKM;CKMT1A;CKMT1B;CKMT2;CPS1;DAO;GAMT;GATM;GLS;GLS2;GLUL;GOT1;GOT2;HOGA1;MAOA;MAOB;NAGS;NOS1;NOS2;NOS3;OAT;OTC;P4HA1;P4HA2;P4HA3;PRODH;PYCR1;PYCR2;PYCRL;SMOX;
hsa00260	Glycine, serine and threonine metabolism	7.68E-15	2.04E-13	AGXT;AGXT2;ALAS1;ALAS2;ALDH7A1;AMT;AOC2;AOC3;BHMT;CBS;CHDH;DAO;DLD;DMGDH;GAMT;GATM;GCAT;GCSH;GLDC;GNMT;MAOA;MAOB;PHGDH;PIPOX;PSAT1;PSPH;SDS;SDSL;SHMT1;SHMT2;SRR;
hsa01230	Biosynthesis of amino acids	1.44E-12	3.15E-11	AADAT;ACO2;ACY1;ALDH18A1;ALDH7A1;ALDOA;ALDOB;ALDOC;ARG1;ARG2;ASL;ASS1;BCAT1;BCAT2;CBS;CPS1;GLUL;GOT1;GOT2;GPT;GPT2;MTR;NAGS;OTC;PAH;PC;PFKL;PHGDH;PKLR;PKM;PRPS1;PSAT1;PSPH;PYCR1;PYCR2;PYCRL;SDS;SDSL;SHMT1;SHMT2;TALDO1;TAT;TKT;
hsa01200	Carbon metabolism	1.45E-12	3.15E-11	ACADM;ACADS;ACAT1;ACAT2;ACO2;ACSS1;ACSS2;AGXT;ALDOA;ALDOB;ALDOC;AMT;CPS1;DLD;DLST;ESD;FBP1;FH;G6PD;GLDC;GOT1;GOT2;GPT;GPT2;HADHA;MCEE;MUT;OGDH;OGDHL;PC;PCCA;PCCB;PDHB;PFKL;PGD;PGLS;PHGDH;PKLR;PKM;PRPS1;PSAT1;PSPH;SDHA;SDHB;SDHC;SDHD;SDS;SDSL;SHMT1;SHMT2;SUCLA2;SUCLG1;SUCLG2;TALDO1;TKT;

Table 1-2 KEGG signal pathway of Qingfeipaidu Decoction (top 15)

Annotation Term ID	Term description	Cluster 1 (p-value)	Benjamini value	gene names
hsa00480	Glutathione metabolism	2.17E-12	4.32E-11	ANPEP;G6PD;GGT1;GPX1;GPX2;GPX3;GPX4;GPX5;GPX6;GPX7;GPX8;GSR;GSS;GSTA1;GSTA2;GSTA3;GSTA4;GSTA5;GSTK1;GSTM1;GSTM2;GSTM3;GSTM4;GSTM5;GSTO1;GSTO2;GSTP1;GSTT1;MGST1;MGST2;MGST3;OPLAH;PGD;TXNDC12;
hsa00250	Alanıne, aspartate and glutamate metabolism	5.21E-12	9.58E-11	ABAT;ACY3;ADSL;ADSS;ADSSL1;AGXT;AGXT2;ALDH4A1;ALDH5A1;ASL;ASNS;ASPA;ASS1;CAD;CPS1;DDO;GAD1;GAD2;GLS;GLS2;GLUL;GOT1;GOT2;GPT;GPT2;NIT2;PPAT;
hsa00350	Tyrosine metabolism	1.23E-11	2.10E-10	ADH1A;ADH1B;ADH1C;ADH4;ADH7;ALDH1A3;ALDH3A1;ALDH3B1;ALDH3B2;AOC2;AOC3;COMT;DBH;DCT;DDC;FAH;FAHD1;GOT1;GOT2;GSTZ1;MAOA;MAOB;MIF;TAT;TH;TPO;TYR;TYRP1;
hsa00280	Valine, leucine and isoleucine degradation	1.84E-11	2.93E-10	ABAT;ACADM;ACADS;ACADSB;ACAT1;ACAT2;ALDH1B1;ALDH2;ALDH3A2;ALDH7A1;ALDH9A1;AUH;BCAT1;BCAT2;BCKDHA;BCKDHB;DBT;DLD;HADHA;HIBADH;HMGCL;IVD;MCCC1;MCCC2;MCEE;MUT;OXCT1;OXCT2;PCCA;PCCB;
hsa04022	cGMP - PKG signaling pathway	1.64E-10	2.45E-09	ADORA1;ADORA3;ADRA1A;ADRA1B;ADRA1D;ADRA2A;ADRA2B;ADRA2C;ADRB1;ADRB2;ADRB3;AGTR1;ATF2;ATF4;ATP1A1;ATP1A2;ATP1A3;ATP1B1;ATP2A1;ATP2B4;BAD;BDKRB2;CACNA1C;CACNA1D;CACNA1F;CACNA1S;CALM1;CALM2;CALM3;CREB1;CREB3;FXYD2;GNA11;GUCY1B3;INS;INSR;ITPR1;ITPR2;ITPR3;KCNJ8;KCNMA1;MEF2C;MYLK2;NFATC1;NOS3;NPR1;NPR2;OPRD1;PDE2A;PDE3A;PDE3B;PDE5A;PLN;PPIF;PPP1CC;PPP3CA;PPP3CB;PPP3R1;PPP3R2;RGS2;ROCK1;ROCK2;SLC25A4;SLC25A5;SLC25A6;SLC8A1;SLC8A2;SLC8A3;VDAC1;VDAC2;VDAC3;
hsa00380	Tryptophan metabolism	2.74E-10	3.64E-09	AADAT;ACAT1;ACAT2;ACMSD;AFMID;ALDH1B1;ALDH2;ALDH3A2;ALDH7A1;ALDH9A1;AOC1;CAT;CCBL1;CCBL2;CYP1A1;CYP1A2;DDC;HAAO;HADHA;IDO1;KMO;KYNU;MAOA;MAOB;OGDH;OGDHL;TDO2;
hsa00980	Metabolism of xenobiotics by cytochrome P450	1.52E-09	1.73E-08	ADH1A;ADH1B;ADH1C;ADH4;ADH7;AKR1C1;AKR1C2;ALDH1A3;ALDH3A1;ALDH3B1;ALDH3B2;CBR1;CBR3;CYP1A1;CYP1A2;CYP2B6;CYP2E1;CYP3A4;GSTA1;GSTA2;GSTA3;GSTA4;GSTA5;GSTK1;GSTM1;GSTM2;GSTM3;GSTM4;GSTM5;GSTO1;GSTO2;GSTP1;GSTT1;HSD11B1;MGST1;MGST2;MGST3;SULT2A1;UGT1A1;
hsa04260	Cardiac muscle contraction	1.64E-09	1.78E-08	ATP1A1;ATP1A2;ATP1A3;ATP1B1;CACNA1C;CACNA1D;CACNA1F;CACNA1S;CACNA2D1;CACNA2D2;CACNB1;CACNB2;CACNB4;CACNG1;CACNG2;CACNG3;CACNG4;COX1;COX2;COX3;COX4I1;COX5A;COX5B;COX6A2;COX6B1;COX6C;COX7A1;COX7B;COX7C;COX8A;FXYD2;MYL2;RYR2;SLC8A1;SLC9A1;SLC9A6;TNNC1;TNNI3;TNNT2;TPM1;
hsa00640	Propanoate metabolism	7.64E-09	7.61E-08	ABAT;ACACA;ACACB;ACADM;ACAT1;ACAT2;ACSS1;ACSS2;ALDH1B1;ALDH2;ALDH3A2;ALDH7A1;ALDH9A1;HADHA;MCEE;MLYCD;MUT;PCCA;PCCB;SUCLA2;SUCLG1;SUCLG2;

Table 2 The Gene Ontology associated with Qingfeipaidu Decoction (top 15)

GO id	Description	Pvalue	Benjamini	EnrichRatio
GO:0044281	Small Molecule Metabolic Process	1.50E-121	2.10E-119	2.1
GO:0007267	Cell-Cell Signaling	4.50E-113	3.20E-111	3.1
GO:0006520	Cellular Amino Acid Metabolic Process	1.28E-94	6.02E-93	4.4
GO:0022857	Transmembrane Transporter Activity	7.55E-79	2.66E-77	2.7
GO:0055085	Transmembrane Transport	4.33E-78	1.22E-76	2.5
GO:0006810	Transport	5.26E-76	1.24E-74	1.8
GO:0042592	Homeostatic Process	2.38E-75	4.80E-74	2.7
GO:0006950	Response To Stress	1.73E-73	3.06E-72	1.9
GO:0016491	Oxidoreductase Activity	3.98E-64	6.24E-63	2.8
GO:0006629	Lipid Metabolic Process	1.10E-56	1.55E-55	2.4
GO:0005737	Cytoplasm	4.42E-56	5.67E-55	1.3
GO:0009058	Biosynthetic Process	6.37E-54	7.48E-53	1.5
GO:0008283	Cell Proliferation	1.76E-53	1.91E-52	2.2
GO:0048856	Anatomical Structure Development	2.23E-53	2.24E-52	1.6
GO:0003013	Circulatory System Process	2.20E-50	2.07E-49	3.9

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