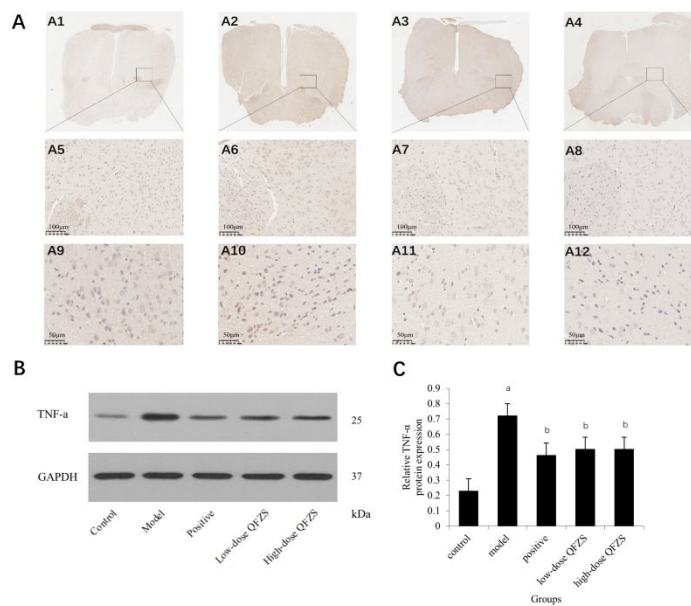


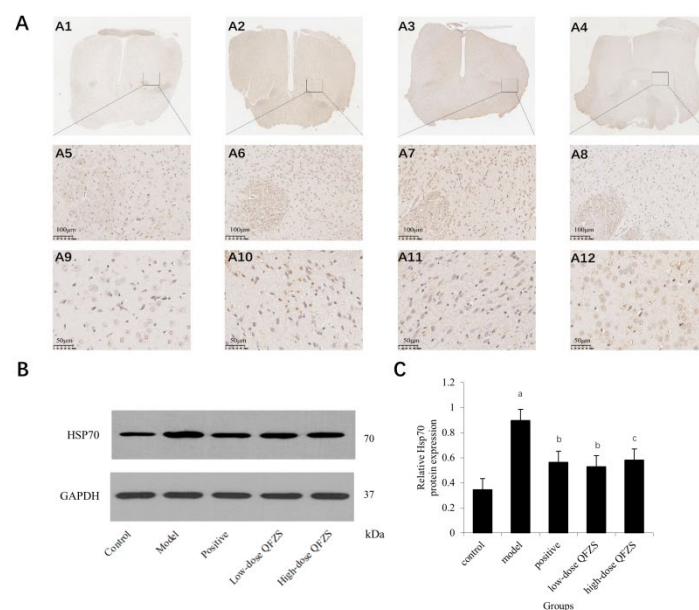
Supplementary Figure 1 High-performance liquid chromatography high-resolution mass spectrometry of standard substances and Qingfei Zhisou oral liquid

A: represent standard substances, B: represent Qingfei Zhisou oral liquid respectively. Seven identified compounds, including columbin (peak 1), aloeemodin (peak 2), rhein (peak 3), indirubin (peak 4), emodin (peak 5), chrysophanol (peak 6) and physcion (peak 7). C: Structures of these components.



Supplementary Figure 2 Effect of QFZS on TNF- α expression

A: the immunohistochemistry staining of TNF- α . A1-A4: images of control (A1), model (A2), Lose-dose QFZS (A3), High-dose QFZS (A4) ($\times 1$); A5-A8: images of control (A5), model (A6), Lose-dose QFZS (A7), High-dose QFZS (A8) ($\times 200$, bar = 100 μm); A9-A12: images of control (A9), model (A10), Lose-dose QFZS (A11), High-dose QFZS (A12) ($\times 400$, bar = 50 μm). B: Western blotting representative images of TNF- α respective quantification in the hypothalamus. C: protein expression levels of TNF- α . Control group: sham operated; Model group: Yeast-induced fever model without treatment; Positive group: Yeast-induced fever model with Aspirin (100 mg/kg); Lose-dose QFZS group: Yeast-induced fever model with low-dose QFZS (2.82 g/kg); High-dose QFZS group: Yeast-induced fever model with high-dose QFZS (5.64 g/kg). TNF- α : tumor necrosis factor- α ; GAPDH: glyceraldehyde-3-phosphate dehydrogenase; QFZS: Qingfei Zhisou oral liquid. Data represent the mean \pm standard deviation using one-way analysis of variance ($n = 5$). Compared with the sham group, ^a $P < 0.05$; compared with the model group, ^b $P < 0.05$.



Supplementary Figure 3 Effects of QFZS on HSP70 expression

A: the immunohistochemistry staining of HSP70, A1-A4: images of control (A1), model (A2), Lose-dose QFZS (A3), High-dose QFZS(A4) ($\times 1$); A5-A8: images of control (A5), model (A6), Lose-dose QFZS (A7), High-dose QFZS(A8) ($\times 200$, bar = 100 μm); A9-A12: images of control (A9), model (A10), Lose-dose QFZS (A11), High-dose QFZS (A12) ($\times 400$, bar = 50 μm). B: Western blotting representative images of HSP70 respective quantification in the hypothalamus. C: protein expression levels of HSP70. Control group: sham operated; Model group: Yeast-induced fever model without treatment; Positive group: Yeast-induced fever model with Aspirin (100 mg/kg); Lose-dose QFZS group: Yeast-induced fever model with low-dose QFZS (2.82 g/kg); High-dose QFZS group: Yeast-induced fever model with high-dose QFZS (5.64 g/kg). HSP70: heat shock protein 70; GAPDH: glyceraldehyde-3-phosphate dehydrogenase; QFZS: Qingfei Zhisou oral liquid. Data represent the mean \pm standard deviation using one-way analysis of variance ($n = 5$). Compared with the sham group, $^aP < 0.05$; compared with the model group, $^bP < 0.01$, $^cP < 0.05$.

Supplementary Table 1 Differentially produced metabolites between model and low-dose QFZS groups

No.	m/z	VIP	Adducts	Formula	Metabolites
1	758.5691	34.8501	M+H	C42H80NO8P	PC (16:1(9Z)/18:1(11Z))
2	502.2928	3.0538	M+H, M+Na	C32H39NO4	Fexofenadine
3	204.1230	2.6858	M+H	C9H17NO4	L-Acetylcarnitine
4	590.3215	1.9528	M+Na, M+K	C30H50NO7P	LysoPC (22:6(4Z,7Z,10Z,13Z,16Z,19Z))
5	303.2317	1.9487	M+H-H2O, M+H	C20H30O2	Eicosapentaenoic acid

6	319.2276	2.0959	M-H, 2M-H, M-H2O-H	C20H32O3	20-Hydroxyeicosatetraenoic acid
7	494.3242	8.1627	M+H, M+Na, M+K	C24H48NO7P	LysoPC (16:1(9Z)/0:0)
8	796.5848	14.9298	M+Na	C43H84NO8P	PE (14:0/24:1(15Z))
9	510.3920	2.1719	M+H	C26H56NO6P	LysoPC (O-18:0)
10	578.4182	2.4225	M+H	C30H60NO7P	LysoPC (22:1(13Z))
11	552.4024	4.2425	M+H	C28H58NO7P	LysoPC (20:0/0:0)
12	482.3242	6.4707	M+H, M+Na	C23H48NO7P	LysoPC (15:0)
13	570.3554	6.8526	M+H, M+K, M+Na	C30H52NO7P	LysoPC (22:5(4Z,7Z,10Z,13Z,16Z))
14	249.1556	2.5709	M+NH4	C9H17N3O4	AsparaginyI-Valine
15	554.3462	4.2484	M+FA-H	C25H52NO7P	LysoPC (17:0)
16	274.2740	9.4643	M+NH4	C16H32O2	Palmitic acid
17	550.3866	6.6137	M+H, M+Na	C28H56NO7P	LysoPC (20:1(11Z))
18	562.3150	2.2039	M+FA-H	C26H48NO7P	LysoPC (18:3(6Z,9Z,12Z))
19	318.3001	2.8399	M+NH4	C18H36O3	2-Hydroxystearic acid
20	542.3244	3.0525	M+H, M+K, M+Na	C28H48NO7P	LysoPC (20:5(5Z,8Z,11Z,14Z,17Z))
21	496.3398	31.2168	M+H, M+Na, M+H-H2O	C24H50NO7P	LysoPC (16:0)
22	566.3216	2.6563	M+Na, M+K, M+H-H2O	C28H50NO7P	LysoPC (20:4(8Z,11Z,14Z,17Z))
23	508.3764	6.2428	M+H, M+Na	C26H54NO6P	LysoPC (P-18:0)
24	548.3710	9.0515	M+H, M+K	C28H54NO7P	LysoPC (20:2(11Z,14Z))
25	594.3778	2.2844	M+FA-H	C28H56NO7P	PC (18:1(9Z)e/2:0)
26	619.2888	3.4525	2M-H	C19H19FN2O	N-Desmethylcitalopram
27	471.3470	4.1121	M+H	C30H46O4	Glycyrrhetic acid

28	570.3555	8.7700	M+Na, M+K, M+H	C30H52NO7P	LysoPC (22:5(7Z,10Z,13Z,16Z,19Z))
29	572.3710	6.6701	M+H, M+K, M+Na	C30H54NO7P	LysoPC (22:4(7Z,10Z,13Z,16Z))
30	522.3555	27.5272	M+H, M+K	C26H52NO7P	LysoPC (18:1(11Z))
31	431.0981	2.1655	M-H2O-H	C21H22O11	Phloretin 2'-O-glucuronide

Notes: QFZS: Qingfei Zhisou oral liquid; VIP: variable importance in the projection.

Supplementary Table 2 Differentially produced metabolites between model and high-dose QFZS

groups

No.	m/z	VIP	Adducts	Formula	Metabolites
1	496.3398	35.9193	M+H, M+Na, M+H-H ₂ O	C ₂₄ H ₅₀ NO ₇ P	LysoPC (16:0)
2	522.3555	25.0782	M+H, M+K	C ₂₆ H ₅₂ NO ₇ P	LysoPC (18:1(11Z))
3	274.2740	10.6796	M+NH ₄	C ₁₆ H ₃₂ O ₂	Palmitic acid
4	548.3710	9.5197	M+H, M+K	C ₂₈ H ₅₄ NO ₇ P	LysoPC (20:2(11Z,14Z))
5	570.3555	9.2218	M+Na, M+K, M+H	C ₃₀ H ₅₂ NO ₇ P	LysoPC (22:5(7Z,10Z,13Z,16Z,19Z))
6	550.3866	7.9413	M+H, M+Na	C ₂₈ H ₅₆ NO ₇ P	LysoPC (20:1(11Z))
7	572.3710	6.8614	M+H, M+K, M+Na	C ₃₀ H ₅₄ NO ₇ P	LysoPC (22:4(7Z,10Z,13Z,16Z))
8	482.3242	6.7538	M+H, M+Na	C ₂₃ H ₄₈ NO ₇ P	LysoPC (15:0)
9	508.3764	6.5666	M+H, M+Na	C ₂₆ H ₅₄ NO ₆ P	LysoPC (P-18:0)
10	570.3554	6.1066	M+H, M+K, M+Na	C ₃₀ H ₅₂ NO ₇ P	LysoPC (22:5(4Z,7Z,10Z,13Z,16Z))
11	552.4024	4.8576	M+H	C ₂₈ H ₅₈ NO ₇ P	LysoPC (20:0/0:0)
12	471.3470	4.4941	M+H	C ₃₀ H ₄₆ O ₄	Glycyrrhetic acid
13	554.3462	4.4401	M+FA-H	C ₂₅ H ₅₂ NO ₇ P	LysoPC (17:0)
14	619.2888	3.3593	2M-H	C ₁₉ H ₁₉ FN ₂ O	N-Desmethylcitalopram
15	318.3001	3.3362	M+NH ₄	C ₁₈ H ₃₆ O ₃	2-Hydroxystearic acid
16	431.0981	3.2746	M-H ₂ O-H	C ₂₁ H ₂₂ O ₁₁	Pjlorelin 2'-O-glucuronide
17	267.0719	2.9820	M+FA-H	C ₈ H ₁₄ O ₇	Ethyl glucuronide
18	380.2559	2.9799	M+H, M+Na, M+H-H ₂ O	C ₁₈ H ₃₈ NO ₅ P	Sphingosine 1-phosphate

19	533.3258	2.9616	M+H, M+K, M+NH4, M+Na, M+H-H2O	C26H45NO7S	Tauro-b-muricholic acid
20	204.1230	2.7523	M+H	C9H17NO4	L-Acetylcarnitine
21	594.3778	2.6987	M+FA-H	C28H56NO7P	PC (18:1(9Z)e/2:0)
22	578.4182	2.5765	M+H	C30H60NO7P	LysoPC (22:1(13Z))
23	510.3920	2.4826	M+H	C26H56NO6P	LysoPC (O-18:0)
24	162.1124	2.3336	M+H	C7H15NO3	L-Carnitine
25	350.1486	2.3064	M+H-H2O	C20H21N3O4	Tryptophyl-Tyrosine
26	566.3216	2.2909	M+Na, M+K, M+H-H2O	C28H50NO7P	LysoPC (20:4(8Z,11Z,14Z,17Z))
27	316.3209	2.1261	M+NH4	C19H38O2	Nonadecanoic acid
28	195.0500	1.8008	M-H	C6H12O7	Galactonic acid
29	212.0014	1.7431	M-H	C8H7NO4S	Indoxyl sulfate
30	206.1387	1.7092	M+H, M+Na	C9H19NO4	Pantothenol

Notes: QFZS: Qingfei Zhisou oral liquid; VIP: variable importance in the projection.