Supplemental Content 1

1. **The action mechanism of XueBiJing**
2. **The chemical composition of XueBiJing**

The action mechanism of XueBiJing

XueBiJing, an intravenous preparation approved by the China Food and Drug Administration (China FDA) in 2004, has been incorporated into routine sepsis care in China. XueBiJing is prepared from a combination of Carthamustinctorius flowers (Honghua in Chinese), Paeonialactiflora roots (Chishao), Ligusticum chuanxiong rhizomes (Chuanxiong), Angelica sinensis roots (Danggui), and Salvia miltiorrhiza roots (Danshen).

Pharmacological studies have shown that XueBiJing has an antagonistic effect on endotoxin, and an inhibitory effect on the uncontrolled release of endogenous inflammatory mediators produced by endotoxin-stimulated monocytes/macrophages. XueBiJing also can improve the coagulation disorder in DIC, increase the activity of superoxide dismutase, regulate hypersensitive or hyposensitive immune response, and prevent the development of organ dysfunction in acute insults. The main pharmacological effects of XueBiJing might be summarized as follows: (1) antagonizing endotoxin; (2) inhibiting inflammatory cytokines; (3) regulating immune function; (4) improving the balance of coagulation; and (5) protecting organ damage.

XueBiJing has pharmacological effects on antagonizing endotoxin, inhibiting inflammatory mediators, improving coagulation function, protecting endothelial cells, improving microcirculation, and regulating immune response. XueBiJing can obviously protect vascular endothelial cells by inhibiting the expression of early/late inflammatory cytokines, attenuate the interaction between inflammation system and coagulation system, and prevent the development of multiple organ dysfunction. Meanwhile, it markedly improves the hyperactive state of the natural immune response during the early stage of sepsis and alleviates the gradually aggravated immunosuppressive state, thereby comprehensively modulating systemic inflammation, coagulopathy and immune dissonance in the development of sepsis. Taken together, these results might suggest the integrated regulation of traditional

Chinese medicine on multi-components, multi-pathways, and multi-targets.

Markedly down-regulating synthesis and release of high mobility group box-1 protein (HMGB1), attenuating multi-organ pathological damage, and reducing the mortality rates of experimental animals [1]. Significantly promoting M2 polarization of macrophages, preventing the occurrence and development of MODS, and improving the survival rates of septic mice [2]. Enhancing the apoptosis of regulatory T cells and down-regulating inhibitory function of regulatory T cells on effector T cells [3]. Inhibiting the expression of PAR-1, decreasing the secretion of inflammatory cytokines, and improving coagulation dysfunction in sepsis [4]. Blocking the IRE1α-XBP1 signaling pathway, down-regulating the expression of PDI, and further affecting tissue factor procoagulation activity of endothelial cells [5].

References

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The chemical composition of XueBiJing

ID	Compound	Molecular Mass	Molecular Formula	Average content level
		Da		*μmol/L*
Constituents originating from the component herbs Chuanxiong/Danggui only				
1	Senkyunolide I	224.1049	$C_{12}H_{16}O_4$	293.1±28.1
2	Senkyunolide H	224.1049	$C_{12}H_{16}O_4$	64.8±6.3
3	Senkyunolide G	208.1099	$C_{12}H_{16}O_3$	44.5±3.1
4	Senkyunolide N	226.1205	$C_{12}H_{18}O_4$	40.8±5.2
5	3-Hydroxy-3-*n*-butylphthalide	206.0943	$C_{12}H_{14}O_3$	37.6±4.8
6	*Z*-6,7-Epoxyligustilide	206.0943	$C_{12}H_{14}O_3$	12.7±0.5
7	6,7-Dihydroxyligustilide	224.1049	$C_{12}H_{16}O_4$	10.9±1.1
8	Senkyunolide A	192.1150	$C_{12}H_{16}O_2$	4.8±2.6
9	Senkyunolide J	226.1205	$C_{12}H_{18}O_4$	3.4±0.4
10	4-Hydroxy-3-*n*-butylphthalide	206.0943	$C_{12}H_{14}O_3$	2.4±0.3
Constituents originating from the component herb Chishao only				
11	Mudanpioside F	344.1471	$C_{16}H_{24}O_8$	5.8±1.0
12	1-*O*-β-D-Glucopyranosyl-Paeonisuffrone	360.1420.	$C_{16}H_{24}O_9$	1.6±0.5
13	Desbenzoylpaeoniflorin	376.1369	$C_{16}H_{24}O_{10}$	22.1±13.7
14	Albiflorin	480.1632	$C_{23}H_{28}O_{11}$	102.4±27.6
15	Paeoniflorin	480.1632	$C_{23}H_{28}O_{11}$	2470±142.8
16	Oxypaeoniflorin	496.1581	$C_{23}H_{28}O_{12}$	112.9±7.6
17	Oxypaeoniflorin isomer	496.1581	$C_{23}H_{28}O_{12}$	4.0±0.8
18	Ortho-oxypaeoniflorin	496.1581	$C_{23}H_{28}O_{12}$	4.3±0.7
19	Mudanpioside E	526.1686	$C_{24}H_{30}O_{13}$	11.3±1.1
20	6'-*O*-Galloyl-desbenzoylpaeoniflorin	528.1479	$C_{23}H_{28}O_{14}$	1.3±0.5
21	Benzoylpaeoniflorin	584.1894	$C_{30}H_{32}O_{12}$	58.3±6.8

22	Benzoyloxypaeoniflorin	600.1843	$C_{30}H_{32}O_{13}$	1.9±0.2
23	Mudanpioside C	600.1843	$C_{30}H_{32}O_{13}$	1.6±0.4
24	Mudanpioside J	630.1949	$C_{31}H_{34}O_{14}$	2.0±0.3
25	Galloylpaeoniflorin	632.1741	$C_{30}H_{32}O_{15}$	56.0±13.7
26	Isomer of galloylpaeoniflorin or galloylalbiflorin	632.1741	$C_{30}H_{32}O_{15}$	7.2±1.5
27	Isomer of galloylpaeoniflorin or galloylalbiflorin	632.1741	$C_{30}H_{32}O_{15}$	2.0±0.6
28	Galloyloxypaeoniflorin	648.1690	$C_{30}H_{32}O_{16}$	2.4±0.4
Constituents originating from the component herb Danshen only				
29	Protocatechuic aldehyde	138.0	$C_7H_6O_3$	139.3±28.7
30	Protocatechuic acid	154.0	$C_7H_6O_4$	14.4±1.8
31	Tanshinol	198.1	$C_9H_{10}O_5$	66.4±15.5
32	Salvianolic acid G	340.1	$C_{18}H_{12}O_7$	0.1±0.0
33	Rosmarinic acid	360.1	$C_{18}H_{16}O_8$	40.4±6.3
34	Salvianic acid C	378.1	$C_{18}H_{18}O_9$	0.3±0.0
35	Salvianic acid C isomer	378.1	$C_{18}H_{18}O_9$	0.3±0.0
36	Salvianolic acid D	418.1	$C_{20}H_{18}O_{10}$	0.8±0.3
37	Isosalvianolic acid C	492.1	$C_{26}H_{20}O_{10}$	36.0±6.2
38	Salvianolic acid C	492.1	$C_{26}H_{20}O_{10}$	3.7±0.9
39	Salvianolic acid A	494.1	$C_{26}H_{22}O_{10}$	2.7±0.4
40	Salviaflaside	522.1	$C_{24}H_{26}O_{13}$	0.8±0.1
41	Lithospermic acid	538.1	$C_{27}H_{22}O_{12}$	1.2±0.2
42	Salvianolic acid J	538.1	$C_{27}H_{22}O_{12}$	1.9±0.3
43	Salvianolic acid B	718.1	$C_{36}H_{30}O_{16}$	23.9±3.1
44	Salvianolic acid E	718.1	$C_{36}H_{30}O_{16}$	1.3±0.3
45	4-Methoxylsalvianolic acid B	732.2	$C_{37}H_{32}O_{16}$	0.1±0.0
Constituents originating from the component herb Honghua only				
46	Saffloquinoside D	612.169	$C_{27}H_{32}O_{16}$	36.7±3.2

47	Saffloquinoside C	612.169	$C_{27}H_{32}O_{16}$	30.0±2.7
48	Hydroxysafflor yellow A	612.169	$C_{27}H_{32}O_{16}$	751.2±39.5
49	Safflomin C	614.1636	$C_{30}H_{30}O_{14}$	11.3±1.5
50	Saffloquinoside E	614.1636	$C_{30}H_{30}O_{14}$	6.7±1.1
51	Carthamin	910.2168	$C_{43}H_{42}O_{22}$	0.1±0.0
52	Anhydrosafflor yellow B	1044.2747	$C_{48}H_{52}O_{26}$	3.6±1.2
53	Kaempferol	286.0477	$C_{15}H_{10}O_6$	1.0±0.2
54	Kaempferol 3-glucoside	448.1006	$C_{21}H_{20}O_{11}$	9.0±1.3
55	Kaempferol 3-rha-(1-6)-glucoside	594.1585	$C_{27}H_{30}O_{15}$	45.6±15.4
56	Kaempferol 3-glc-(1-2)-glucoside	610.1534	$C_{27}H_{30}O_{16}$	14.9±2.5
57	3-Glc-kaempferol 7-glucuronide or 6-Glc-6-hydroxyapigenin 7-glucuronide	624.1326	$C_{27}H_{28}O_{17}$	12.2±5.6
58	6-Hydroxykaempferol 7-glucoside	464.0955	$C_{21}H_{20}O_{12}$	11.2±6.5
59	6-Hydroxykaempferol 3-glucoside	464.0955	$C_{21}H_{20}O_{12}$	0.3±0.1
60	6-Hydroxykaempferol 3-rha-(1-6)-glucoside	610.1534	$C_{27}H_{30}O_{16}$	3.6±2.0
61	6-Hydroxykaempferol 3,6-diglucoside	626.1483	$C_{27}H_{30}O_{17}$	2.2±1.1
62	6-Hydroxykaempferol 6,7-diglucoside	626.1483	$C_{27}H_{30}O_{17}$	0.9±0.1
63	6-Glc-6-Hydroxykaempferol 3-rha-(1-6)-glucoside	772.2062	$C_{33}H_{40}O_{21}$	9.0±4.2
64	6-Hydroxykaempferol 7-(3,6-diglc)-glucoside	788.2011	$C_{33}H_{40}O_{22}$	7.0±2.2
65	6-Hydroxykaempferol 7-(3,6-diglc)-glucuronide	802.1804	$C_{33}H_{38}O_{23}$	1.5±0.6
66	Quercetin	302.0427	$C_{15}H_{10}O_7$	0.7±0.1
67	Quercetin 3-glucoside	464.0955	$C_{21}H_{20}O_{12}$	5.6±1.3
68	Quercetin 3-rha-(1-6)-glucoside	610.1534	$C_{27}H_{30}O_{16}$	10.0±3.3
69	3-Rha-quercetin 7-glucuronide	624.1326	$C_{27}H_{28}O_{17}$	0.7±0.3
70	Quercetin 3,7-diglucoside	626.1483	$C_{27}H_{30}O_{17}$	22.5±7.5
71	Eriodictyol	288.0634	$C_{15}H_{12}O_6$	0.8±0.1

72	Neocarthamin	450.1162	$C_{21}H_{22}O_{11}$	10.6±2.1
73	Neocarthamin isomer	450.1162	$C_{21}H_{22}O_{11}$	13.8±2.2
74	5,6,7,4'-Tetrahydroxyflavone 6,7-diglucoside	612.169	$C_{27}H_{32}O_{16}$	47.3±11.5
75	Apigenin	270.0528	$C_{15}H_{10}O_5$	0.4±0.1
76	6-Hydroxyapigenin	286.0477	$C_{15}H_{10}O_6$	0.7±0.2
77	Luteolin	286.0477	$C_{15}H_{10}O_6$	0.3±0.0
78	Luteolin 7-glucoside	448.1006	$C_{21}H_{20}O_{11}$	0.9±0.2
79	Scutellarin	462.0798	$C_{21}H_{18}O_{12}$	2.5±1.5
80	Safflochalconeside	432.1056	$C_{21}H_{20}O_{10}$	0.1±0.0
Constituents originating from multiple component herbs of XueBiJing				
81	p-Coumaric acid	164.0473	$C_9H_8O_3$	69.0±23.1
82	4-Glucosyloxybenzoic acid	300.0845	$C_{13}H_{16}O_8$	20.9±2.3
83	p-Hydroxybenzoic acid	138.0317	$C_7H_6O_3$	52.1±7.0
84	Chlorogenic acid	354.0951	$C_{16}H_{18}O_9$	13.5±2.3
85	Caffeic acid	180.0423	$C_9H_8O_4$	43.2±11.8
86	Butanedioc acid	118.0266	$C_4H_6O_4$	118.3±34.0
87	Phenylalanine	165.0790	$C_9H_{11}NO_2$	256.5±28.6
88	Uridine	244.0695	$C_9H_{12}N_2O_6$	87.3±13.6
89	Cytidine	243.0855	$C_9H_{13}N_3O_5$	1.1±0.1
90	Adenosine	267.0968	$C_{10}H_{13}N_5O_4$	35.5±17.1
91	Guanosine	283.0917	$C_{10}H_{13}N_5O_5$	58.5±10.3
92	Adenine	135.0545	$C_5H_5N_5$	23.6±4.6
93	Thymine	126.0429	$C_5H_6N_2O_2$	3.3±1.4
94	Uracil	112.0273	$C_4H_4N_2O_2$	48.6±9.8
95	benzoic acid	122.0368	$C_7H_6O_2$	767.0±133.9
96	gallic acid	170.0215	$C_7H_6O_5$	41.1±15.8
97	1'-*O*-benzoylsucrose	446.1424	$C_{19}H_{26}O_{12}$	53.0±24.1
98	1'-*O*-galloylsucrose	494.1272	$C_{19}H_{26}O_{15}$	3.2±1.6

99	6'-*O*-galloylsucrose	494.1272	$C_{19}H_{26}O_{15}$	3.0±1.6
100	Trigalloyl glucose	636.0963	$C_{27}H_{24}O_{18}$	42±17.2
101	tetragalloyl glucose	788.1072	$C_{34}H_{28}O_{22}$	8.3±5.1
102	tetragalloyl glucose isomer	788.1072	$C_{34}H_{28}O_{22}$	2.5±0.8
103	(+)-catechin	290.0790	$C_{15}H_{14}O_6$	1.9±2.1
104	Ferulic acid	194.0579	$C_{10}H_{10}O_4$	117.0±24.4

XueBiJing, an intravenous preparation approved by the China Food and Drug Administration (China FDA) in 2004, has been incorporated into routine sepsis care in China. XueBiJing is prepared from a combination of *Carthamus tinctorius* flowers (Honghua in Chinese), *Paeonia lactiflora* roots (Chishao), *Ligusticum chuanxiong* rhizomes (Chuanxiong), *Angelica sinensis* roots (Danggui), and *Salvia miltiorrhiza* roots (Danshen).

Analysis of chemical composition of XueBiJing was based on liquid chromatography-mass spectrometry by Professor Chuan Li's laboratory at Shanghai Institute of Materia Medica, Chinese Academy of Sciences (Shanghai, China). A part of these results has been published, while details of the others are pending publication elsewhere.

References

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