Supplementary Information

Drug target identification using network analysis: Taking active components in *Sini* decoction as an example

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Supplementary Table S1. Metabolism of components in SND retrieving from admetSAR[3].

No.	Compounds	CYP450 1A2 inhibitor	CYP450 2C9 inhibitor	CYP450 2D6 inhibitor	CYP450 2C19 inhibitor	CYP450 3A4 inhibitor
S3	Mesaconine	No	No	No	No	No
S4	Senbusine A	No	No	No	No	No
S5	Senbusine B	No	No	No	No	No
S6	Talatizidine	No	No	No	No	No
S7	Aconine	No	No	No	No	No
S8	Hypaconine	No	No	No	No	No
S9	Fuziline	No	No	No	No	No
S10	Neoline	No	No	No	No	No
S11	Bikhaconine	No	No	No	No	No
S12	Talatisamine	No	No	No	No	No
S13	14-O-acetyl neoline	No	No	No	No	No
S15	Benzoylmesaconine	No	No	No	No	No
S16	Benzoylaco	No	No	No	No	No

	nine					
S18	Jesaconitine	No	No	No	No	No
S19	Beiwutine	No	No	No	No	No
S21	Mesaconitin e	No	No	No	No	No
S22	Aconifine	No	No	No	No	No
S30	Crassicaulin e A	No	No	No	No	No
S31	Salsolinol	No	pAC50=4.8nM	No	No	No
S32	Coryneine	No	No	No	No	No
S33	Chuanfumin e	No	No	No	No	No
S34	Karakanine	No	No	No	No	No
Z14	24-Hydroxy glycyrrhetic acid	No	No	No	No	pAC50=5nM
Z25	Methyl 3b, 24-dihygrox y olean-11,13(18)-diene 30-O ate	No	No	No	No	No
Z27	Betulic acid	No	No	No	No	No
Z28	Uralenolide	No	No	No	No	pAC50=5.4nM
H27	Licochalcon e B	pAC50=7.2n M	No	No	pAC50=6.1nM	No
H28	Echinatin	pAC50=7.2n M	No	No	pAC50=6.1nM	No
H29	Isoliquiritige nin	pAC50=5.3n M	pAC50=4.7nM	pAC50=4.8nM	pAC50=4.9nM	pAC50=5.5nM
H31	Glepidotin	pAC50=5.45n	pAC50=5.6nM	pAC50=4.85nM	pAC50=5.55nM	pAC50=5.85nM

Reference

1 Cheng, F. *et al.* admetSAR: a comprehensive source and free tool for assessment of chemical ADMET properties. *J Chem Inf Model* **52**, 3099-3105, doi:10.1021/ci300367a (2012).

Supplementary Table S2. Results of the physiochemical characteristics similarity between 196 components in herbs in SND and 105 FDA-approved oral drugs from drugbank.

Variables	Mean		Wilcoxon test	Kolmogorov-Smirnov test
	drug	herb	Significance (2-tailed)[a]	Significance (2-tailed)[a]
ALogP	2.48556	3.03900	0.034	0.006
Molecular Weight	335.153013	425.179603	0.000	0.000
Num_H_Acceptors	4.12	6.60	0.000	0.000
Num_H_Donors	1.73	2.82	0.000	0.006
Num-Rotatable Bonds	5.97	7.32	0.003	0.020
Num_AromaticRings	1.54	1.08	0.005	0.025
Molecular_Fractional/PolarSurfaceArea	0.22856	0.23206	0.095	0.001

[a] The significance level is 0.05.

Supplementary Table S3. Targets of active components in SND validated by references.

Gene symbol	Target name	Serial number	Name	Reference	Activity
ESR2	Estrogen receptor beta	**H60**	Daidzein	[1]	Ki=300 nM
ESR1	Estrogen receptor alpha	**H60**	Daidzein	[1]	Ki=1800 nM
XDH	Xanthine dehydrogenase	**H60**	Daidzein	[2]	IC_{50}= 429800nM
PPARG	Peroxisome proliferator-activated receptor gamma	**H60**	Daidzein	[3]	Fold activation=1.2
ESR2	Estrogen receptor beta	**H56**	Davidigenin	[4]	IC_{50}= 1000000 nM
ESR1	Estrogen receptor alpha	**H56**	Davidigenin	[4]	IC_{50}= 1000000 nM
PPARG	Peroxisome proliferator-activated receptor gamma	**H28**	echinatin	[5]	Activity
PPARG	Peroxisome	**H34**	formononetin	[3]	Fold activation=

	proliferator-activated receptor gamma				4.6
XDH	Xanthine dehydrogenase	**H34**	formononetin	[6]	Inhibition= 17.6%
PPARG	Peroxisome proliferator-activated receptor gamma	**H41**	Gancaonin L	[5]	Activity
PPARG	Peroxisome proliferator-activated receptor gamma	**Z29**	Glycyrrhetic acid	[7]	Activity
PPARG	Peroxisome proliferator-activated receptor gamma	**H29**	Isoliquiritigenin	[3]	Fold activation= 1.3
XDH	Xanthine dehydrogenase	**H20**	Liquiritigenin	[6]	IC_{50}= 11300 nM
ESR1	Estrogen receptor alpha	**H10**	rutin	[8]	Activity=107.97 %
XDH	Xanthine dehydrogenase	**H10**	rutin	[9]	IC_{50}= 52200 nM
PPARG	Peroxisome proliferator-activated receptor gamma	**H10**	rutin	[10]	Activity
ADRA2A	Alpha-2A adrenergic receptor	**H10**	rutin	[11]	Ki=9340 nM
ESR1	Estrogen receptor alpha	**H11**	quercetin	[8]	Activity=76.81 %
HIF1A	Hypoxia-inducible factor 1-alpha	**H11**	quercetin	[12]	IC_{50}= 10200nM
PPARG	Peroxisome proliferator-activated receptor gamma	**H11**	quercetin	[3]	Fold activation= 1.3
CA2	Carbonic anhydrase II	**H11**	quercetin	[13]	Ki= 2540nM
XDH	Xanthine dehydrogenase	**H11**	quercetin	[14]	Fold activation=170
PON1	Serum paraoxonase/arylesterase 1	**H11**	quercetin	[15]	Activity
CDK2	Cyclin-dependent kinase 2	**H11**	quercetin	[16]	IC_{50}= 40000nM
ADRB2	Beta-2 adrenergic receptor	**S39**	higenamine	[17]	EC_{50}= 126.5 ng/mL
HMOX1	Heme oxygenase 1	**S39**	higenamine	[18]	Activity
NOS2	Nitric Oxide	**S39**	higenamine	[19]	IC_{50}=

	Synthase 2, Inducible				53μM
NOS2	Nitric Oxide Synthase 2, Inducible	**J13**	1-Dehydro-[6]-gingerdione	[20]	Activity
AGTR1	Angiotensin II Receptor, Type 1	**J54**	6-Gingerol	[21]	IC_{50}= 8.173 μM
ESR2	Estrogen receptor beta	**H20**	liquiritigenin	[22]	EC_{50}= 36.5 nM

Reference

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Supplementary Table S4. The significance of every relevant pathway of high degree (20-41), middle degree (10-19) and low degree (1-9) targets.

High Degree (20-41) pathway	p-value	Middle degree (10-19) pathway	p-value	Low degree (1-9) pathway	p-value
HIF-1 signaling pathway	1.95E-07	Dilated cardiomyopathy	6.46E-04	HIF-1 signaling pathway	5.48E-08
Calcium signaling pathway	9.49E-05	TNF signaling pathway	9.35E-04	VEGF signaling pathway	1.16E-07
Insulin secretion	8.32E-04	cGMP-PKG signaling pathway	2.03E-03	Oxytocin signaling pathway	5.53E-07
Oocyte meiosis	1.39E-03	Calcium signaling pathway	2.49E-03	cGMP-PKG signaling pathway	6.69E-07
Tuberculosis	3.59E-03	Neuroactive ligand-receptor interaction	5.84E-03	Calcium signaling pathway	1.22E-06
				Adrenergic signaling in cardiomyocytes	8.89E-06

Supplementary Table S5. In vivo components in SND retrieving from our previous research[1,2].

NO	In vivo components	Origins	Formula
1	Yunganoside K2	plasma and urine	C42H62O17
2	Uralsaponin B	urine	C42H62O16
3	Talatizamine	plasma and urine	C24H39NO5
4	Songorine	plasma and urine	C22H31NO3
5	Senbusine B	urine	C23H37NO6
6	Senbusine A	plasma and urine	C23H37NO6
7	Neoline	plasma and urine	C24H39NO6
8	Mesaconine	plasma and urine	C24H39NO9
9	Liquiritin apioside	plasma and urine	C26H30O13
10	Liquiritin	plasma and urine	C21H22O9
11	Liquiritigenin-O-sulfate	urine	C15H12O7S
12	Liquiritigenin glucuronide	plasma and urine	C21H21O10
13	Liquiritigenin	plasma and urine	C15H12O4
14	licoricesaponine H2/K2 or Uralsaponin B	plasma	C42H64O15
15	Licoricesaponin A3	plasma	C48H72O21
16	Licorice saponin J2	plasma	C42H64O16
17	Licorice saponin G2	plasma and urine	C42H62O17
18	Licorice saponin C2	plasma	C42H62O15
19	Licorice saponin B2	plasma	C42H64O15
20	Licorice saponin A3	urine	C48H72O21
21	licoisoflavone B-O-sulfate	urine	C20H16O9S
22	Licoisoflavone B	urine	C20H16O6
23	Licoisoflavone	urine	C20H18O6
24	Licochalcone D-O-glucuronide	urine	C27H30O11
25	Licochalcone D	urine	C21H22O5
26	Licobenzofuran-O-glucuronide	urine	C27H30O11
27	Licobenzofuran	urine	C21H22O5
28	Karakoline	urine	C22H35NO4
29	Karakolidine	urine	C22H35NO5
30	Isotalatizidine	plasma and	C23H37NO5

		urine		
31	Isomer of licorice saponin B2	plasma		C42H64O15
32	Isoliquiritin apioside	plasma	and	C26H30O13
		urine		
33	Isoliquiritin	plasma	and	C21H22O9
		urine		
34	Isoliquiritigenin-O-sulfate	urine		C15H12O7S
35	Isoliquiritigenin glucuronide	plasma	and	C21H21O10
		urine		
36	Isoliquiritigenin	plasma	and	C15H12O4
		urine		
37	Hypaconitine	urine		C33H45NO10
38	Hypaconine	urine		C24H39NO8
39	Hetisine	urine		C20H27NO3
40	Glyzaglabrin	urine		C16H10O6
41	Glycyrrhizin	plasma	and	C42H62O16
		urine		
42	Glycyrrhisoflvanone	urine		C21H20O6
43	Glycyrrhetic acid	plasma		C30H46O4
44	Glycyroside	plasma		C27H30O13
45	Glycycoumarin	urine		C21H20O6
46	Glucoliquiritin apioside	plasma		C32H40O18
47	Gancaonin N/Gancaonin B	urine		C21H20O6
48	Gancaonin L	urine		C20H18O6
49	Gancaonin B/Gancaonin N	urine		C21H20O6
50	Fuzitine	urine		C20H24NO4
51	Fuziline	plasma	and	C24H39NO7
		urine		
52	Foromonetin-O-sulfate	urine		C16H12O7S
53	Foromonetin-O-glucuronide	urine		C22H20O10
54	Foromonetin monohydroxylate	urine		C16H12O5
55	Foromonetin monohydroxylate	urine		C16H12O5
56	Foromonetin monohydroxylate	urine		C16H12O5
57	Foromonetin monohydroxylate	urine		C16H12O5
58	Foromonetin monohydroxylate	urine		C16H12O5
59	Formononetin glucuronide	plasma		C22H20O10
60	Formononetin	plasma	and	C16H12O4
		urine		
61	Dihydroformanonetin	urine		C16H14O4
62	Demethyl-8-methoxyl-14-benzoylaconine	urine		C32H45NO10
63	Demethyl-14-acetyltalatizamine	urine		C24H35NO7
64	Demethyl-14-acetylkarakoline	urine		C23H35NO5
65	Demethyl talatizamine	urine		C23H37NO5
66	Demethyl talatizamine	urine		C23H37NO5

67	Demethyl senbusine B	urine	C22H35NO6
68	Demethyl senbusine A	urine	C22H35NO6
69	Demethyl neoline	urine	C23H37NO6
70	Demethyl neoline	urine	C23H37NO6
71	Demethyl karakolidine	urine	C21H33NO5
72	Demethyl karakolidine	urine	C21H33NO5
73	Demethyl isotalatizidine	urine	C22H35NO5
74	Demethyl hypaconitine	urine	C32H43NO10
75	Demethyl dehydrogen isotalatizidine	urine	C22H33NO5
76	Demethyl benzoylhypaconine	urine	C30H41NO9
77	Demethyl benzoyldeoxyaconine	urine	C31H43NO9
78	Demethyl benzoylaconine	urine	C31H43NO10
79	Demethyl isotalatizidine	urine	C22H35NO5
80	Dehydrogen karakolidine	urine	C22H33NO5
81	Dehydrogen chuanfunine	urine	C22H33NO5
82	Dehydrated benzoylmesaconine	plasma and urine	C31H41NO9
83	Dehydrated benzoyhypaconine	urine	C31H41NO8
84	Dehydrated 6-gingerol	urine	C17H24O3
85	Davidigenin-O-sulfate	urine	C15H14O7S
86	Davidigenin-O-sulfate	urine	C15H14O7S
87	Davidigenin-O-sulfate	urine	C15H14O7S
88	Davidigenin-O-sulfate	urine	C15H14O7S
89	Davidigenin-O-glucuronide	urine	C21H22O10
90	Davidigenin	urine	C15H14O4
91	Daidzein-O-sulfate	urine	C15H10O7S
92	Daidzein	urine	C15H10O4
93	Chuanfunine	plasma and urine	C22H35NO5
94	Benzoylmesaconine	plasma and urine	C31H43NO10
95	Benzoylhypaconine	plasma and urine	C31H43NO9
96	Benzoyldeoxyaconine	plasma and urine	C32H45NO9
97	Benzoylaconine	plasma and urine	C32H45NO10
98	Beiwudine	urine	C31H41NO8
99	Aconine	plasma and urine	C25H41NO9
100	8-methoxyl-14-benzoylaconine	urine	C33H47NO10
101	6-Gingerol glucuronide	plasma	C23H34O10
102	6-Gingerol	urine	C17H26O4
103	4',7-dihydroxyflavone	urine	C15H10O4

104	16-β-Hydroxycardiopetaline	urine	C21H33NO4
105	14-benzoy-10-OH-mesaconine	urine	C31H43NO11
106	14-benzoy-10-OH-aconine	urine	C32H45NO11
107	14-acetyltalatizamine	plasma and urine	C26H41NO6
108	14-acetylneoline	urine	C26H41NO7
109	14-acetylkarakoline	urine	C24H37NO5
110	10-OH-mesaconine	urine	C24H39NO10
111	10-OH-aconine	urine	C25H41NO10
112	10-Hydroxytalatizamine	urine	C24H39NO6

Reference

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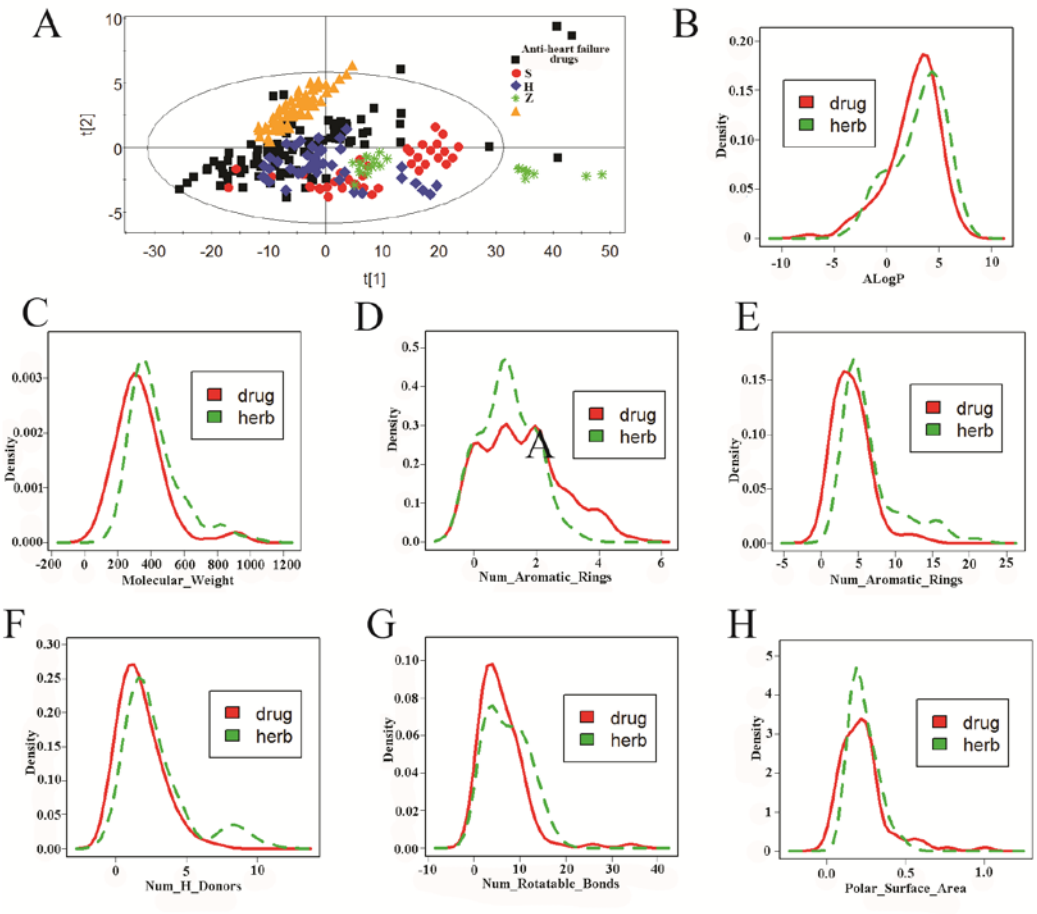
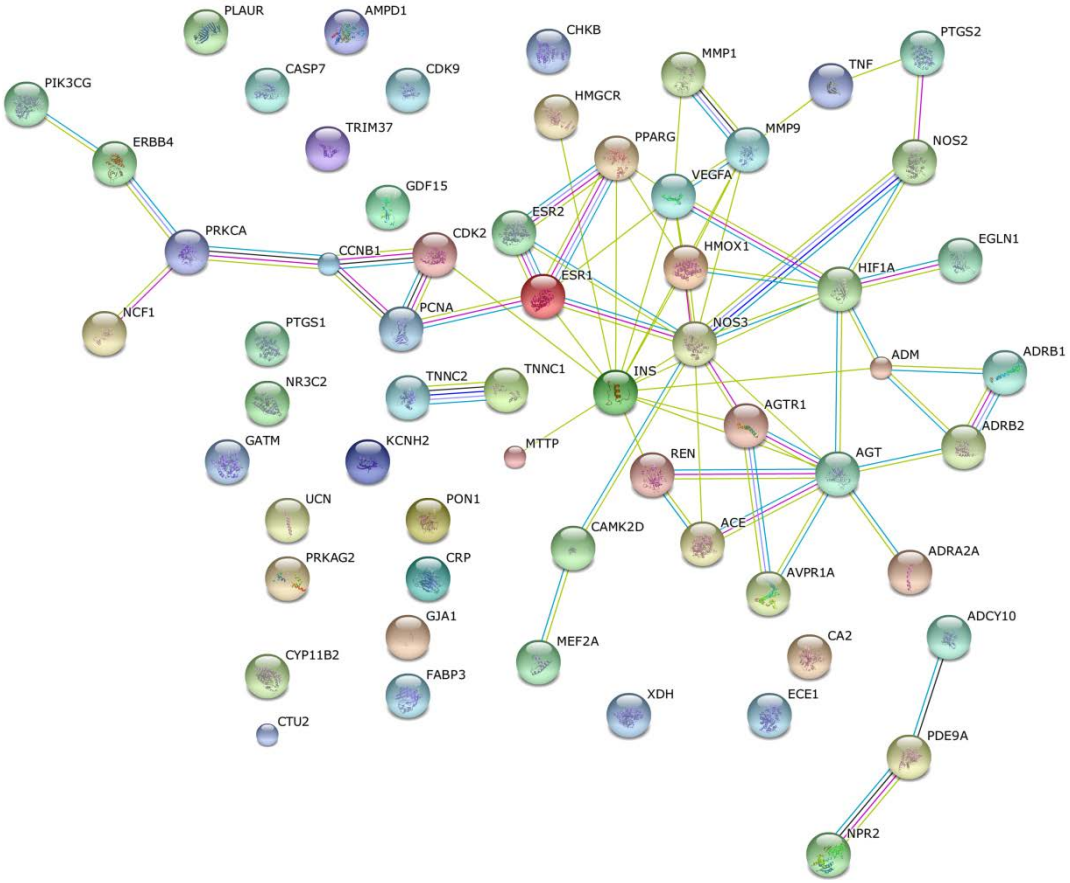
Supplementary Table S6. Quality control statistics on the performance of text mining for the term "heart failure"

Database Name	target proteins by searching	false positives	True target proteins
DrugBank database	4	0	4
OMIM	2	1	1
UniProtKB	114	94	20
TTD	28	20	8
GeneCards	72	60	12



Supplementary Figure 1. Comparing chemical characteristics of active ingredients in SND. (A) PCA of active components in SND and approved anti-heart failure drugs calculated from seven chemical characteristics. Molecular weight; Num_AromaticRings: the number of aromatic rings; Num_H_Donors: the number of hydrogen bond donors; Molecular_FractionalPolarSurfaceArea: the molecular polar surface area; Num_RotatableBonds: the number of rotatable bonds; ALogP: the octanol–water partition coefficient; Num_H_Acceptors: the number of hydrogen bond acceptors. S: Aconitum carmichaelii, G: Glycyrrhiza uralensis, J: Zingiber officinale. (B)–(H) are distributions of these seven chemical characteristics of ingredients in SND and approved oral drugs.



Supplementary Figure 2. Target protein-target protein interaction network