Exploring the Active Compounds of Traditional Mongolian Medicine Agsirga in Intervention of Novel Coronavirus (2019-nCoV) Based on HPLC-Q-Exactive-MS/MS and Molecular Docking Method

Jie Cheng[1, #], Yuchen Tang[1, #], Baoquan Bao[1,*], Ping Zhang[1,*]

[1] College of Pharmacy, Inner Mongolia Medical University, 010110, Hohhot, China

[*]Correspondence to: baobaoquan123@yeah.net (Baoquan Bao) ; pingzhang@vip.126.com(Ping Zhang)

[#] These authors contributed equally to this work

Objective: To screen all compounds of Agsirga based on the HPLC-Q-Exactive high-resolution mass spectrometry and find potential inhibitors that can respond to 2019-nCoV from active compounds of Agsirga by molecular docking technology.

Methods: HPLC-Q-Exactive high-resolution mass spectrometry was adopted to identify the complex components of Mongolian medicine Agsirga, and separated by the high-resolution mass spectrometry Q-Exactive detector. Then the Orbitrap detector was used in tandem high-resolution mass spectrometry, and the related molecular and structural formula were found by using the chemsipider database and related literature, combined with precise molecular formulas (errors $\leq 5 \times 10^{-6}$) , retention time, primary mass spectra, and secondary mass spectra information, The fragmentation regularities of mass spectra of these compounds were deduced. Taking ACE2 as the receptor and deduced compounds as the ligand, all of them were pretreated by discover studio, autodock and Chem3D. The molecular docking between the active ingredients and the target protein was studied by using AutoDock molecular docking software. The interaction between ligand and receptor is applied to provide a choice for screening anti-2019-nCoV drugs.

Result: Based on the fragmentation patterns of the reference compounds and consulting literature, a total of 96 major alkaloids and stilbenes were screened and identified in Agsirga by the HPLC-Q-Exactive-MS/MS method. Combining with molecular docking, a conclusion was got that there are potential active substances in Mongolian medicine Agsirga which can block the binding of ACE2 and 2019-nCoV at the molecular level.

Key words: Agsirga; 2019-nCoV; ACE2; molecular docking; HPLC- MS

Introduction:

The 2019 novel coronavirus (2019-nCoV) caused the pneumonia outbreak in Wuhan, hubei, China, in late December 2019 and has rapidly spread to more than 20 countries and regionsaround the world. The World Health Organization (WHO) has declared the 2019- nCoV epidemic a public health emergency of international concern (PHEIC). By Mar 2, 2020, more than 80174 individuals were infected and more than 2900 fatalities had been reported in China. For now, it is mainly to use the combination of traditional Chinese and Western medicine to treat In clinical[1], but there is no specific antiviral drugs for this new epidemic. Therefore, it is urgent and significant to study new effective therapeutic methods and drugs.

Mongolian medicine is an important part of traditional Chinese medicine. In the past millennium, Mongolian medicine has played a unique role in the prevention and treatment of epidemic and it has very good clinical effect in curing and preventing infectious diseases such as influenza, tuberculosis, SARS,H7N9 and H1N1. According to Mongolian medicine, the outbreak infectious diseases are called pestilence and the treatment of pestilence is an important part of Mongolian medicine.The 2019-nCoV pneumonia belongs to the category of"epidemic fever" and "sticky epidemic" in Mongolian medicine, it is a pestilence fever caused by virus infection[2]. Therefore, in the development stage of specific western medicine, the combination of Mongolian, Chinese and Western medicine may be a breakthrough.

Agsirga, the dried roots and rhizomes of *Veratrum nigrum L.*, is a traditional Mongolian medicine commonly used to treat tumor and cancer in the characteristic “Purgative therapy” of Mongolian medicine[3], and its clinical effect is obvious. There is no report on the treatment of pestilence fever caused by virus infection, but the main components of Agsirga, For instance, resveratrol, cyclophosphamide, sinafenamine, etc, have excellent curative effect on virus infection, such as DNA viruses: Herpesvirus [4-6], HBV [7,8] and RNA viruses：Enteroviruses (EV11, EV71, EV84, CVB3 and CVA10)[9,10], HIV[11,12], HCV[13,14], DFV, influenza virus, Respiratory syncytial virus[15]. There are many chemical components with complex structure and huge polar differences in Mongolian medicine Aghiriga, the traditional method of liquid phase analysis can not identify all kinds of them. We intends to screen all compounds of Agsirga with the effection of anti-2019-nCoV based on the HPLC-Q-Exactive high-resolution mass spectrometry and molecular docking

technology.

Molecular docking is a a mature technology for the direct design of chemicals by using computational tool，which is widely used for the study of protein–ligand interactions and for drug discovery and development. Its principle is to simulate the geometric structure and intermolecular force of molecules by means of chemometrics, and to find the low-energy binding mode of active sites between small molecules (or ligands) and protein with known structures. Docking is then used to calculate and predict the bound conformation and binding free energy of small molecules to the target protein, to identify new inhibitors in the target prediction of drug organisms for drug development. In this study, molecular docking screening was carried out to evaluate the binding energy between the key compounds of Agsirga and the angiotensin-converting enzyme 2（ACE2）which is one of target protein in the process of 2019-nCoV infection, and obtain active compounds for the further development of anti-2019nCoV drugs.

2. Experimental

2.1. Chemicals and reagents

HPLC-grade acetonitrile was purchased from Fisher (USA). Formic acid was purchased from Tianjin Yongsheng Fine Chemical (Tianjin, China). Deionized water (18 MΩ/cm) was purified by a water purification system from Millipore (Bedford, MA, USA).

Reference substances of(1) jervine, (2) verdine, (3) pseudojervine, (4) veratramine, (5) veratrosine, (6) 1α,3β-dihydroxy-5α-jervanin-12-en-11-one, (7) Resveratrol, (8) Oxyresveratrol, (9) piceid, (10)Peimine, (11) Peiminine, (12) imperialine, (13) 2 , 3, 5, 4' - tetrahydroxysilbene- 2- O- β- D- glucopyranoside, (14) Isoscopoletin, (15) methyljervine- N- 3'- propanoate, (16) resveratrol- 4,3' - di- O- β- D- glucopyranoside , (17) L- Pyroglutamic acid methyl ester, (18) desoxyrhaponticin, (19) α- D- Glucopyranoside, 2 - methoxy- 4- methylphenyl, (20) β- D- Glucopyranoside, 2- methoxy- 4- (2- propen- 1- yl) phenyl 6- O- β- D- glucopyranosyl, (21) β- D- Glucopyranoside, 2, 6 - dimethoxy-4-(2-propen-1-yl)phenyl-6-O-b-D-glucopyranosyl, (22) mulberroside A, (23) Mulberroside E, (24) Piceatannol 4'- O- β- D- glucopyranoside were isolated from “Agsirga” species in our laboratory .and their identities were confirmed by IR, 1H- and 13C- NMR, MS analyses. The purity of these substances was determined to be more than 98% by normalization of the peak areas detected by HPLC with ESI/MS. Stock standard solutions of 26 reference substances were prepared in methanol at a final concentration of 0.1mg/ml. These

solutions were stored at 4 ◦C for further study.

2.2 Sample preparation

Herbal materials of “Agsirga” were Collected from saihanwula national nature reserve (Inner Mongolia, China), and identified by Professor Baoquan Bao (Inner Mongolia Medical University). The voucher specimens were deposited at the Herbarium of Inner Mongolia Medical University, Hohhot, China.

steroidal alkaloids: The dried roots of “Agsirga” species were powdered to a homogeneous size, and sieved through a 32 mesh screens, followed by drying at 60 ◦C in the oven for 2 h. 1.0g of the powder of “Agsirga” were accurately weighed and pre-alkalized with 2ml ammonia solution (25%) for 1h, and immersed in 40 ml trichlormethane:methanol(4:1, v/v) mixture overnight, then refluxing for 2 h. After being filtered, the extracts (10 ml) were concentrated to dryness in vacuum at 50 ◦C. The residue was made up to exactly 2ml with initial mobile phase using a volumetric flask. The resultant solutions were centrifuged at 12,000rpm for 10 min; the supernatants were transferred to an autosampler vial for HPLC-Q-Exactive-MS/MS analysis.

Stilbene samples: 1.0g of the powder of “Agsirga” (over 32 mesh screens) were accurately weighed and extracted by refluxing with 25mL of 50% methanol for 1h. After being filtered, the extracts (10ml) were concentrated to dryness in vacuum at 50 ◦C. The residue was made up to exactly 2ml with initial mobile phase using a volumetric flask. The resultant solutions were centrifuged at 12,000 rpm for 10 min; the supernatants were transferred to an autosampler vial for HPLC-Q-Exactive-MS/MS analysis.

2.3 Instrumentation and analytical conditions

For separation, we using a Thermo ScientificTM Q ExactiveTM Quadrupole-Orbitrap Mass Spectrometer system (Thermo Fisher Scientific, Grand Island, NY, USA) and Thermo Scientific Dionex Ultimate 3000 HPLC system. The data were captured and analyzed by Xcalibur 3.0 software, which was designed by Thermo Fisher Scientific.

For steroidal alkaloids separation, the chromatographic analysis was performed with a HPLC Agilent Zorbax Extend-C18 (4.6× 150mm, 5μm). The mobile phase consisted of water containing 0.1% v/v formic acid (A) and acetonitrile(B). A gradient program was used as follows: 0–20min, 7–31% B; 20–30.01min, 31–100% B. The column temperature was set as 35 ℃. The flow rate was

kept at 0.3 mL/min. Sample injection volume was turned to 1μL.

For stilbene separation, the chromatographic analysis was performed with a HPLC Apollo C18(4.6×250mm, 5μm). The mobile phase consisted of water containing 0.1% v/v formic acid (A) and acetonitrile(B). A gradient program was used as follows: 0–5min, 5–10% B; 5–20min, 10-15% B; 20-40min, 15%-40% B; 40-45min, 40%-100% B. The column temperature was set as 35 ℃. The flow rate was kept at 1.0 mL/min. Sample injection volume was turned to 10μL.

The conditions of the ESI source were as follows: capillary temperature and aux gas heater temperature was set as 350 and 150 ℃, respectively; shealth gas flow rate was turned to 40 L/min and aux gas flow rate was 2 L/min; S-lens RF level was kept at 50; spray voltage was 3.5 KV; mass spectra were recorded across the range m/z 100–1000 with accurate mass measurement of all mass peaks. steroidal alkaloids samples were analyzed in positive mode to provide information for structural identification. stilbene samples were analyzed in negative mode to provide information for structural identification.

3. Results and discussion

3.1 Identification of Chemical composition in "Agsirga" species

In addition, the effect of adding formic acid into the mobile phase was also investigated. The retention time of alkaloids was advanced by adding formic acid and the separability and peak shape was much better; and the ionizing effect of stilbene was improved by adding formic acid. The amount of formic acid to be added was estimated and 0.1% v/v formic acid were selected as the desired separationand ionization.

The main components of Mongolian medicine Agsirga are alkaloids and stilbenes. Due to the great difference in polarity and the fact that alkaloids are easily soluble in organic solvents under alkaline conditions, different extraction methods are used for stilbenes and alkaloids in order to achieve the best extraction efficiency.

Based on the fragmentation patterns of the reference compounds and consulting literature, a total of 96 major alkaloids and stilbenes were screened and identified in Agsirga by the HPLC-Q-Exactive-MS/MS method, including 31 cevanine type alkaloids, 8 jervine type alkaloids, 10 veratramine type alkaloids, 7 secosolanidine type alkaloids and 18 stilbenes. (Supporting Information Table S1 and Table S2) . And the total ion chromatography of the alkaloids and stilbenes are listed in Supporting Information Figure S1 to Figure S2. The results of this study clearly demonstrated the potential of HPLC-Q-Exactive-MS/MS for the rapid and sensitive structural elucidation of the multi-groups of constituents in Agsirga.

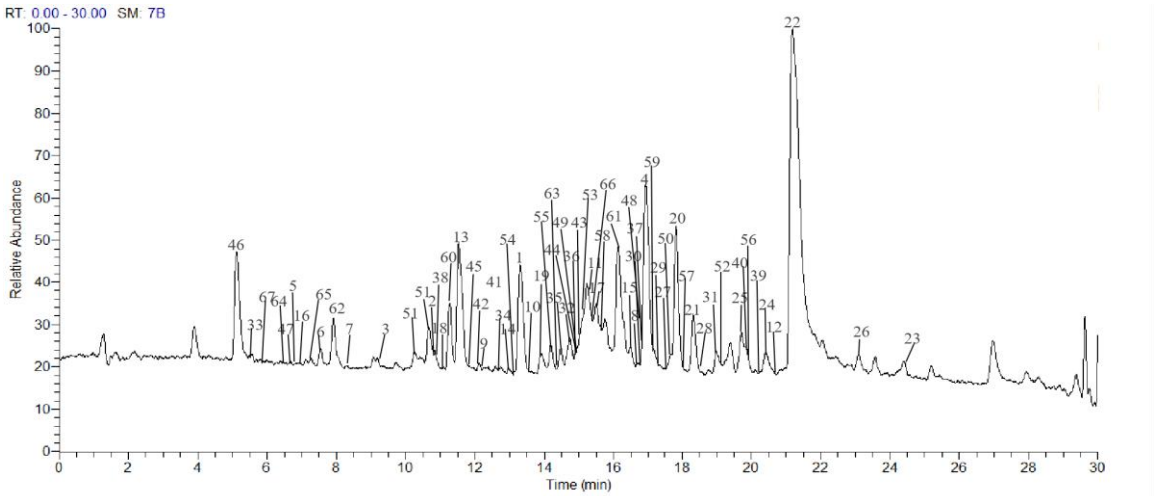

Fig. S1 total ion flow in the positive mode of Mongolian medicine Agsirga alkaloid samples

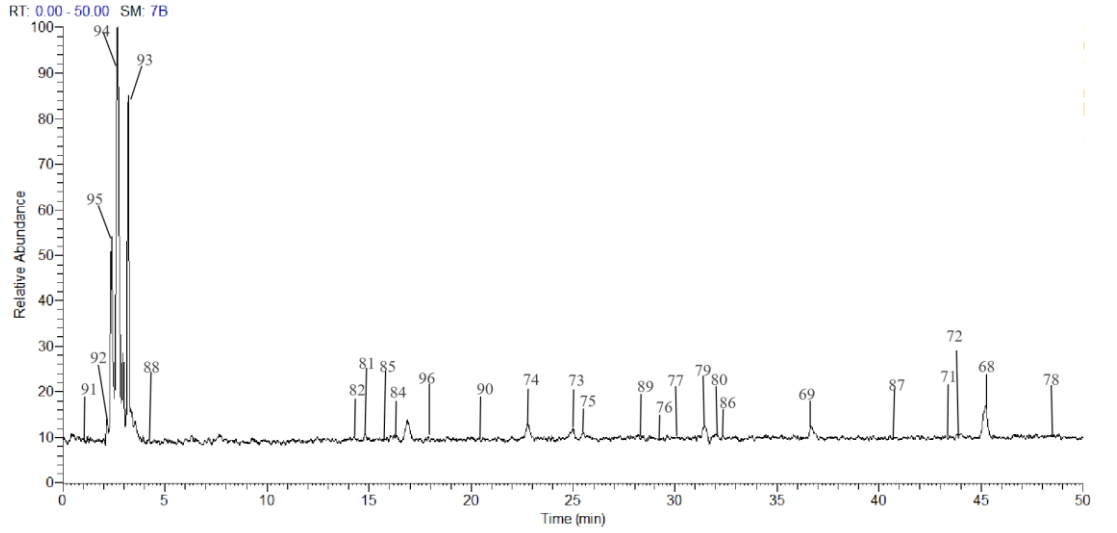

Fig. S2 total ion flow in the negative ion mode of Mongolian medicine Agsirga stilbenes samples

3.2 Screening of potential pharmacodynamic components against 2019-ncov based on molecular docking

In the following section, we will summarize these natural compounds in Traditional Mongolian Medicine Agsirga that may have therapeutic effects against 2019-nCov infection. To generate putative binding poses, we used the AutoDock Vina software package with the default scoring function (Trott O, Olson AJ, 2010). The structure of the full-length human ACE2 bound to the RBD of the 2019-nCoV Provided by Zhou Qiang team of West Lake University[19]. Use the discovery studio 2016 client software to remove the ligands and non protein molecules in the target protein and save them as PDB format files. Download the mol format file of the 2D structure of the

compound from the Scifinder database (https://scifinder.cas.org), use Chem3D software to minimize its energy and convert it to PDB format for future use. We assigned the Gasteiger atomic partial charges and converted all receptors and ligands to the PDBQT format using the AutoDockTools package[16].

We identified the receptor binding pocket based on the structures of the full-length human ACE2 bound to the RBD of the 2019-nCoV (Q24, D30, H34, Y41, Q42, M82, K353, R357)[17]. The calculation results show that the lowest binding free energy (△G) of different components combined with ACE2 is between -2.3 ~ -7.1 kcal•mol-1, the median is -6.0 kcal•mol-1, and △G < -6.0 kcal•mol^{-1} as a potential anti-2019-nCoV infection active ingredient (Supporting Information Table S3 and Figure S3).

It is generally believed that the lower the energy when the conformation of ligand binding to receptor is stable, the more likely the interaction will occur. In this study, the results of molecular docking showed that the compounds with the lowest binding energy to human ACE2 were pseudojervine binding energy of (−6.8 kcal•mol^{-1}), imperialine- 3- β- D- glucoside binding energy of (−7.1 kcal•mol-1). According to table S3, it is not difficult to see that the potential anti-2019-nCoV active components in Mongolian medicine Agsirga are mainly alkaloids, and D30 and H34 are their mainly binding sites.

As we know, The overall interface between the 2019-nCoV and ACE2 mediated mainly through polar interactions，An extended loop region of RBD spans above the arch-shaped α1 helix of ACE2 like a bridge. The α2 helix and a loop that connects the β3 and β4 antiparallel strands, referred to as Loop 3-4, of the PD also make limited contributions to the coordination of RBD. The contact can be divided to three clusters. The two ends of the “bridge” attach to the amino (N) and carboxyl (C) termini of the α1 helix as well as small areas on the α2 helix and Loop 3-4. The middle segment of α1 reinforces the interaction by engaging two polar residues.[19]

Human ACE2 is the surface receptor for SARS-CoV and 2019-nCoV to enter the host cells. It is the channel and key factor for successful infection of the virus. The University of Hong Kong [18]has first revealed that SARS-CoV, MERS-CoV and 2019-nCoV may enhance their infection and transmission ability by inducing ACE2 receptor on host cell surface. ACE2 may be used as the cell receptor of 2019-nCoV which enter the cell through ACE2 for reproduction and further transmission. Reducing the expression of ACE2 can prevent the virus from entering the cell. According to

previous studies, the main components of Mongolian medicine Agsirga are alkaloids and stilbene compounds, among which stilbene compounds have been found to bind well with 2019-nCoV 3CL hydrolase[20]; alkaloid compounds have antitumor and antibacterial activities[21]. Matrine sodium chloride injection has a significant therapeutic effect on the mice model with pneumonia caused by coronavirus, and the inhibition rate of lung index in the model group was 86.86% and 76.53%, which was related to the inhibition of virus replication, the regulation of immune function and the inhibition of the release of inflammatory factors. We wonder whether veratrum alkaloids have the similar effects with Matrine sodium chloride injection and whether they can reduce the expression of ACE2 to block the invasion of virus into cells.

The structure of the 2019-nCoV RBD (nCoV-RBD) is similar to the RBD of SARS-CoV (SARS-RBD). Despite the overall similarity, a number of sequence variations and conformational deviations are found on their respective interface with ACE2. The most significant change can be seen in the middle bridge, The most prominent alteration is the substitution of Val404 in the SARS-RBD with Lys417 in the nCoV RBD [19], This may also be the main reason for its increased affinity. Through the results of molecular docking, we found that the main binding site between alkaloids and human ACE2 protein is in the middle bridge, namely D30、H34. This also confirmed our conjecture to some extent that alkaloids and stilbenes may have synergistic effect on the anti-2019-nCoV virus.

Next, we select the two compounds with the lowest binding energy and analyze their molecular models. Molecular docking results showed that pseudojervine and D30 of human ACE2 were mainly combined in the form of hydrogen bonds and had good binding activity, which indicated that pseudojervine could hinder the binding of 2019-nCoV S-protein RBD domain and ACE2 at D30. Imperialine-3-β-D-glucoside combines with ACE2 H34 in the form of hydrogen bonds. which indicates that Imperialine-3-β-D-glucoside can hinder the binding of 2019-nCoV S-protein RBD domain and ACE2 at H34. The above results show that the combination of pseudojervine and Imperialine-3-β-D-glucoside will probably block the binding of ACE2 and S-protein. (Supporting Information Figure S4-S6).

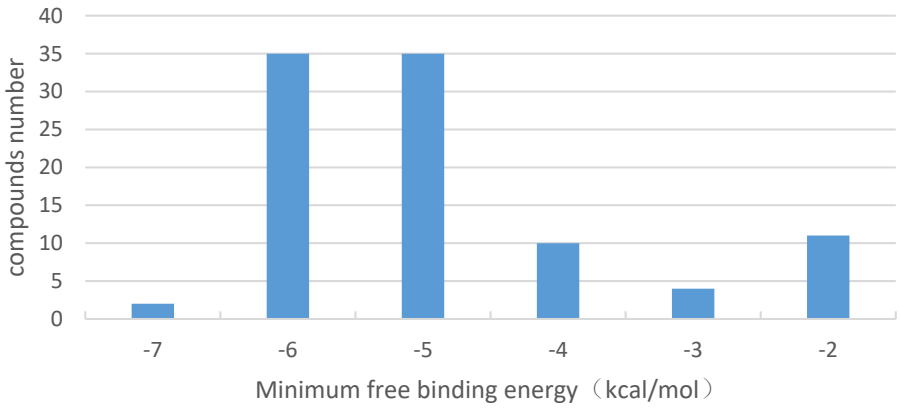

Fig. S3 Distribution of the lowest binding free energy of the candidate compounds

Table S3 Binding energy value of candidate compounds (Top 20)

Active order	compound	locus	binding energy
1	hupehemonside	H34	-7.1
2	Imperialine-3-β-D-glucoside	H34	-7.1
3	pseudojervine	D30	-6.8
4	zhebeininoside	H34	-6.8
5	Veratroylzygadenine	D30 H34	-6.8
6	Zhebeinone-3-β-D-glucoside	H34	-6.7
7	Mulberroside E	D30	-6.7
9	Hupehenisine	D30	-6.6
10	verdine	D30	-6.6
12	verticinone-3-β-D-glucoside	H34	-6.6
13	(E)-Resveratrol 3,5-O-β-diglucoside	D30	-6.6
15	peimisine	D30	-6.4
16	15-O-(2-Methylbutanoyl)-3-O-veratroylprotoverine	D30	-6.4
17	3-Acetylzygadenine	D30	-6.4
18	Polydatin IV	D30	-6.4
19	Piceatannol 3,4'-di-β-D-glucopyranoside	Q42	-6.4
20	puqietinone	H34	-6.3

Discussion

The clinical manifestations of 2019-nCoV are fever, fatigue and dry cough. Because of the

cytokine storm caused by the invasion of of 2019-nCoV and the poor tolerance of patients, the application of high doses of glucocorticoids leads to serious sequelae. Critically ill patients usually developed dyspnea, acute respiratory distress syndrome, septic shock, metabolic acidosis, hemorrhage and coagulation dysfunction gradually one week after onset, some or even dead; Patients with mild symptoms may not have fever. The 2019-nCoV was found to be the seventh coronavirus that can infect humans. It is also the third coronavirus that causes severe pandemic and severe respiratory diseases following severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) in the past 20 years. Compared with SARS, 2019-nCoV has higher infectivity and variability which can spread without symptoms.It's not only affects the lungs, but also causes damage to kidney, heart, liver and other organs that leading to systemic organ exhaustion, and there is also a phenomenon that a return to the 2019-nCoV-positive after treatment.

However, the vaccine development process usually takes months or even years. It may take a long time before its clinical application even though the vaccine research against 2019-nCoV is being carried out in various countries. Nearly 100 clinical medication trials related to 2019-nCoV had been registered in the national clinical trial registry, but there were no specific therapeutic drugs and preventive drugs with definite curative effect so far.

In this context, promoting the establishment of 2019-nCoV in vitro and in vivo models, screening anti-2019-nCoV drugs, studying on antiviral mechanism and providing laboratory data for clinical recommended drugs are of great significance to fight against the epidemic at this stage.

Computer Aided Drug Design has the characteristics of high speed and low cost, which is suitable for the screening of chemical components in large-scale production of traditional Chinese medicine. Scientists have used molecular docking technology to screen out a large number of potential pharmaceutical ingredients from traditional Chinese Medicine. Cinatl j et al [22]analyzed the coronavirus isolated from SARS patients in the clinical center of Frankfurt University in Germany, evaluated the antiviral potential of Ribavirin, 6-azauridine,Pyrazomycin, Mycophenolic acid and Glycyrrhizin, and found that glycyrrhizin was not only inhibited the replication of SARS-CoV, but also inhibited the adsorption and penetration of SARS-CoV. According to the literature reports, the extract from Isatis tinctoria and its chemical components Indigo, Sinapiside, Aloe emodin and Hesperidin[23]; Houttuyniae Herba extract[24]; two kinds of Cibotii Rhizoma extract[25]; Amentoflavone isolated from Torreya nucifera (L.) Sieb. et Zucc[26]have obvious inhibitory effect

on SARS-CoV 3CLpro. These studies provid scientific and theoretical basis for the treatment of 2019-nCoV with Chinese Medicine and reveal the feasibility of traditional Chinese medicine as an auxiliary drug of chemical drugs at the molecular level.

Mongolian medicine have the same origin as traditional Chinese medicine, but its application is less developed and utilized. The medicine used in this research institute is called Agsirga, the dried roots and rhizomes of wild Veratrum nigrum L. of Inner Mongolia, is a traditional Mongolian medicine commonly used to treat tumor and cancer in the characteristic “Purgative therapy” of Mongolian medicine. Agsirga mainly contains alkaloids, flavonoids, stilbenes, organic acids, saponins , etc, among which steroidal alkaloid is the main active components. These alkaloid can temporarily increase ca^{2+} current, prolong action potential duration, enhance myocardial contractile function, and improve the cardiac overload state in hypertension[27].

Veratrum alkaloids can lower blood pressure in rats, rabbits, cats and rats with renal hypertension in varying degrees, with fast and strong effect in a dose-dependent manner. Its hypotensive effect may be related to its central effect and direct vasodilation action[28]. Chen Shizhong et al. [29] have found that veratrum alkaloids have anti transplanted hepatoma activity in mice, and have a strong inhibitory effect on the proliferation of human breast cancer cells MCF7, MDA 468. Cyclopamine, one of the mesofenamine alkaloids, has shown good antitumor potential due to its specific blocking effect on hedgehog signaling pathway. The research on cyclopamine has become a hotspot in the field of anticancer [30] Veratrum alkaloids also have antifungal effects. Its aqueous extract (1:4) Have strong bacteriostatic action to dermatophyte in varying degrees，such as Trichophyton violaceum, Trichophyton concentric, Xanthomonas schlegeli, Microsporum audouinii, Epidermophyton inguinale　Nocardia asteroides and also Mycobacterium tuberculosis.

Based on HPLC-MS technology, the potential anti-2019-ncov chemical components in Mongolian medicine Agsirga were quickly separated and identified in this research. In combination with molecular docking technology, the identified compounds were virtual screened with $\triangle g < -6.0$ $kcal \cdot mol^{-1}$ as a potential anti-2019-ncov infection active ingredent and 37 potential effective components were screened out, which provided scientific basis for further development and utilization of Mongolian medicine Agsirga.

To sum up, the core active compounds alkaloids of Agsirga have been explored to block the binding of 2019-nCoV S-protein and ACE2 by molecular docking technology. It provides a

reference for the further development of Mongolian medicine treatment for 2019-nCoV epidemic.However, the obtained results may have deviations because of the lack of consideration of the content of chemical components, insufficient understanding of viruses and diseases, or limitations of molecular docking itself. The research should also be verified Later at multiple levels through pharmacodynamic evaluation, metabonomics, single target, etc.

Conclusions

The research combining HPLC-MS with molecular docking was conducted which got a conclusion that there are potential active substances in Mongolian medicine Agsirga which can block the binding of ACE2 at the molecular level, all of them can be used as potential inhibitors of 2019-nCoV for further research and development. The relevant research results of this experiment will provide theoretical basis for Mongolian medicine Agsirga potential active substances anti-2019-nCoV, as well as methodological reference for the study of the mechanism of antiviral active components of Mongolian medicine.

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The structure of the full-length human ACE2 bound to the RBD of the 2019-nCoV provided by Zhou Qiang team of West Lake University

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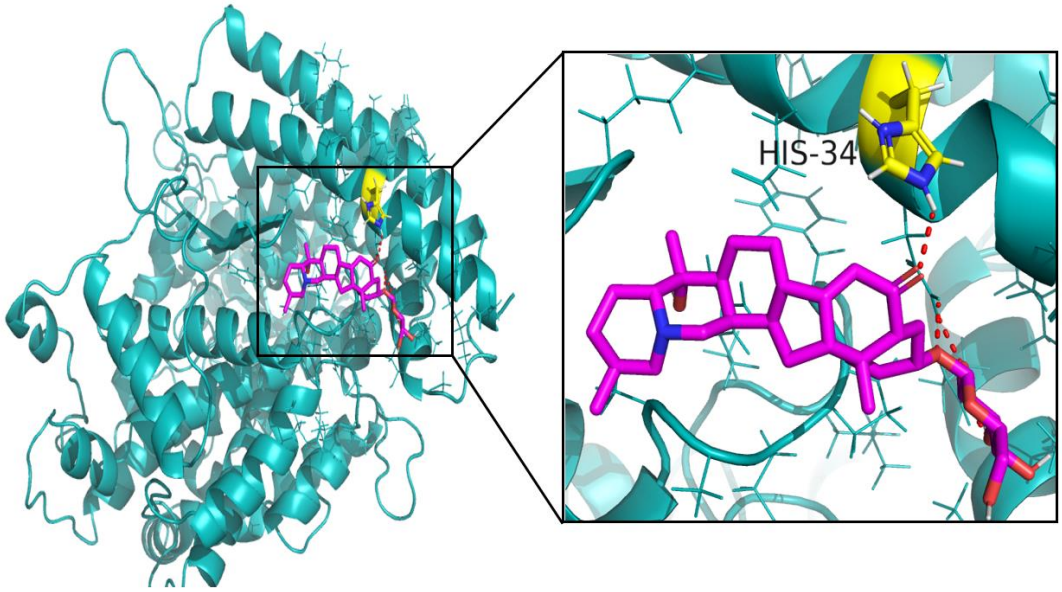

Fig S4：the molecular docking between Imperialine-3-β-D-glucoside and ACE2. Imperialine-3-β-D-glucoside and HIS-34 in ACE2 are bonded to each other through hydrogen bonds;

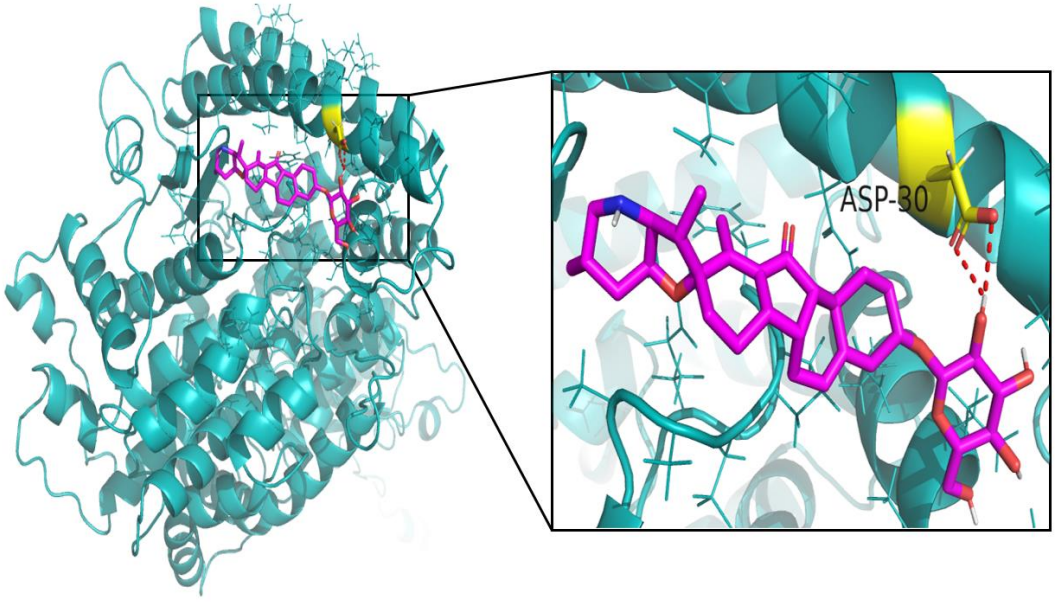

Fig S5：The binding situation of pseudojervine and ACE2, and the pseudojervine interacts with D30 in ACE2 through hydrogen bonds.

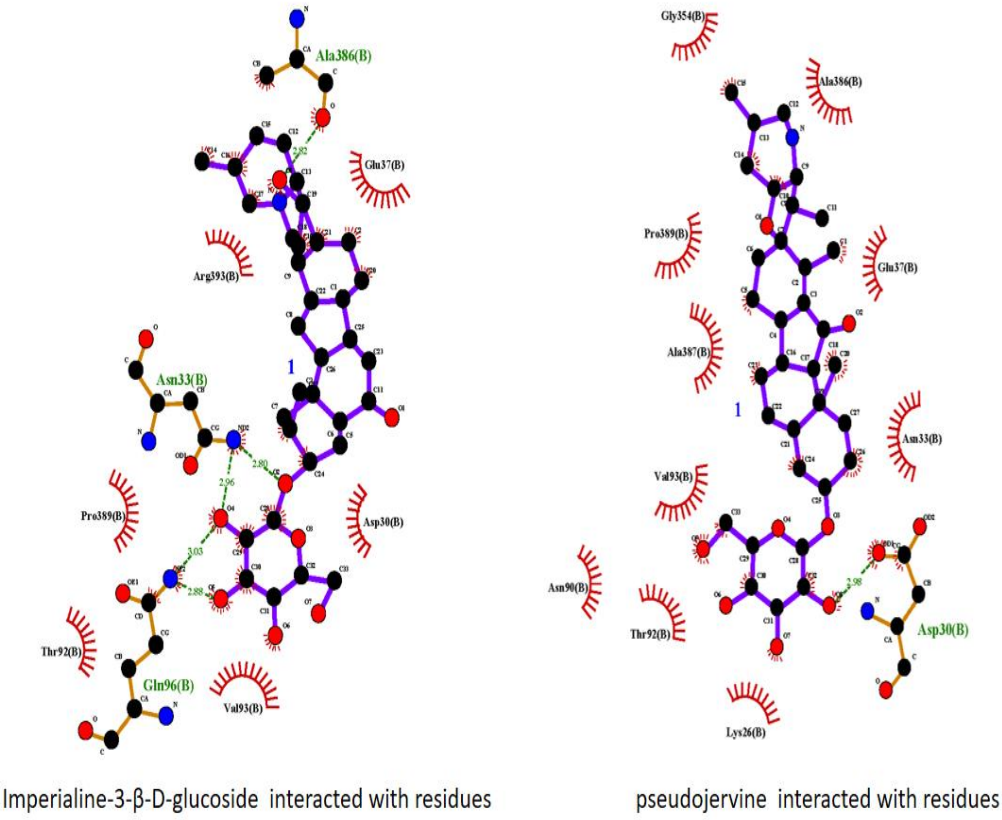

Fig S6： **Two-dimensional graph of interaction between** ACE2 **protein** Imperialine-3-β-D-glucoside **and** pseudojervine

Table S1 identification of alkaloid constituents of Mongolian medicine ageshiriga by HPLC-Q-Exactive-MS/MS analysis (positive ion mode)

No.	tR/min	Compounds	Molecular formula	[M+H]+ ion，m/z		Error	fragment ion	Ref
				theoretical	measured			
1	13.20	Resveratrol	C14H12O3	229.0859	229.0860	0.077	229.0860、211.0754、135.0444、107.0496、193.0648、165.0700、183.0809、119.0495	Standard
2	10.87	Oxyresveratrol	C14H12O4	245.0808	245.0808	-0.024	245.0809、227.0699、199.0754、203.0228、161.0597、135.0440、221.0331、181.0650、107.0495	Standard
3	9.44	piceid	C20H22O8	391.1387	391.1386	-0.001	229.0859、211.0763、183.0812、135.0443、149.0233、119.0439、107.0495、	Standard
4	17.16	veralosidine	C27H43NO2	414.3366	414.3366	0.033	414.3366、253.1948、126.1279、124.1131、396.3262、98.0958、55.0553	31
5	6.80	puqienine A	C28H47NO3	446.3628	446.3633	0.145	446.3626、428.3412、98.0966、128.1076、253.1977、81.0703、107.0865	32
6	7.54	puqienine C or puqienine D	C28H45NO4	460.3421	460.3421	0.012	460.3421、442.3266、128.1101、98.0922、424.3122	32
7	8.31	puqienine C or puqienine D	C28H45NO4	460.3421	460.3426	0.193	460.3427、128.1078、98.0946、128.1066、124.1125	32
8	16.77	veratramine	C27H39NO2	410.3053	410.3058	0.185	410.3058、114.0917、392.2953、84.0814、142.1227、295.2058、225.8624、171.1161、84.0813	Standard
9	12.35	veratrosine	C33H49NO7	572.3581	572.3594	-1.028	572.3594、457.2593、84.0814、142.1230、114.0917、	Standard
10	13.49	puqienine B	C28H45NO3	444.3472	444.3472	0.045	444.3472、105.0685、128.1101、426.3277、98.0914、93.0711、147.1168	33
11	14.61	puqietinone	C28H47NO2	430.3679	430.3675	0.156	430.3695、128.1101、412.3635、95.0855、81.0766、	35

							98.0988	
12	20.66	N-demethylpuqietinone	C27H45NO2	416.3523	416.3503	-1.419	416.3503、398.3477、131.0874、81.0766、98.0984	32
13	11.74	puqietinonoside	C34H57NO7	592.4207	592.4196	-3.114	592.4196、128.1101、430.3636、69.0855、142.1569、412.3569	32
14	13.2	peimisine	C27H41NO3	428.3159	428.3142	-0.861	428.3142、410.30577、114.0915、67.0549、84.0814、109.1025、81.0711、93.0697	33
15	16.66	Hupehenisine	C27H41NO3	428.3159	428.3140	-1.146	428.3156、410.4457、114.0965、 392.1255、84.0851、124.0977	35
16	6.97	verdine	C27H41NO5	460.3057	460.3039	-0.915	460.3057、114.0961、442.2945、95.2148、81.3569、67.6432、84.0813、109.1014、、126.1278、293.1896、241.1040	Standard
17	15.51	jervine	C27H39NO3	426.3002	426.2987	-0.52	426.2987、114.0961、408.3011、124.9520、149.0960、210.1442、266.2279、313.2155、351.2290、102.0915、126.1278、84.0812	Standard
18	11.08	pseudojervine	C33H49NO8	588.3530	588.3057	0.603	114.0961、426.3011、408.3026、124.9517、 84.0811、109.1013、570.3410、518.9392、275.1027、397.2942、163.0335、142.1365	Standard
19	14.06	veratvirine	C27H41NO4	444.3108	444.3114	1.48	114.0961、426.2964、124.1146、408.2922、84.0813、92.7212、109.1014、121.1020、126.1280、158.1519、295.2062、	Standard
20	17.55	Cyclopamine	C27H41NO2	412.3210	412.3213	0.76	114.0961、114.0911、85.0524、81.0342、109.0286、98.0969、126.1276、164.9211、396.3261、364.3001、313.1528、251.1791、	33

21	18.33	methyljervine-N-3'-propanoate	C31H45NO5	512.3370	512.3356	-2.55	512.3356、114.0961、124.9500、408.3022	36
22	21.35	solanidin	C27H43NO	398.3417	398.3408	1.058	398.3408、380.2946 、126.1276、150.3362、204.6659、213.1628	32
23	24.56	Demissidine	C27H45NO	400.3573	400.3584.	1.066	400.3584、382.3458、98.0969、150.3362、204.6653、248.1434、91.8098	34
24	20.50	Tomatidine	C27H45NO2	416.3523	416.3509.	0.769	416.3523、398.3437、99.0809、114.0549、138.0548、248.1434、91.8098、69.0705、	34
25	19.97	Solasodine,acetate	C29H45NO3	456.3472	456.3463.	1.02	456.3463、396.3253、112.0760、114.0588、138.0569、248.1434、130.0864、69.0769、	34
26	25.35	Solasodine	C27H43NO2	414.3366	414.3357	0.99	414.3357、396.3299、98.0968、114.0912、138.8181、69.0705	35
27	17.78	Rubijervin or isorubijervine	C27H43NO2	414.3366	414.3352	-0.114	414.3352、396.3269、150.1278、396.3246、204.1756、81.0698、	35
28	18.31	Rubijervine or isorubijervine	C27H43NO2	414.3366	414.3355	0.474	414.3352、396.3269、150.1278、396.3246、204.1756、81.0698、	35
29	17.41	puqietinedinone	C28H45NO2	428.3523	428.3540	-0.344	428.3540、410.3042、81.0711、69.0623、95.0896、93.0681	32
30	16.94	ebeiedinone	C27H43NO2	414.3366	414.3385	1.274	414.3385、98.0969、396.3260、95.0851、119.0851、105.0327	32
31	19.23	puqiedinone	C27H43NO2	414.3366	414.3368	0.597	414.33640、98.0968、396.3260、112.1102、95.0754、105.0327	32
32	14.79	zhebeinone	C27H43NO3	430.3315	430.3304	0.502	430.3389、98.0965、412.3259、396.3841、176.2453、110.0987、148.9963、55.7461、96.1042	32
33	5.74	pingpeimine A	C27H45NO5	464.3370	464.3361	0.955	464.3371、446.3166、98.0961、138.1266、124.1123、	32

							93.0711	
34	13.22	verticinone N-oxide	C27H43NO4	446.3264	446.3256	-1.489	446.3256、428.3162、98.0961、112.1188、410.3011、384.2977、138.1255、96.6322、82.0644、58.0655。	32
35	14.56	korsine N-oxide	C27H43NO4	446.3264	446.3249	-0.36	446.3249、428.6662、128.1088、98.0916、410.3366、95.0833	37
36	15.23	Hupehenirine or hupehenizine	C27H43NO2	414.3366	414.3354	0.3276	414.3355、98.0969、396.3247、111.1233、98.0911、140.6622	32
37	16.77	Hupehenirine or hupehenizine	C27H43NO2	414.3366	414.3352	-0.114	414.3355、98.0969、396.3247、111.1233、98.0911、140.6622	32
38	11.08	verticine N-oxide	C27H45NO4	448.3421	448.3413	1.286	448.3413、98.0969、430.3309、412.9605、138.5132、114.0916、111.1115、98.0970、82.9451	33
39	20.47	Puqiedine or ebeiedine	C27H45NO2	416.3523	416.3523	0.028	416.3523、98.0969、398.3377、107.9674、91.0538	33
40	19.88	Puqiedine or ebeiedine	C27H45NO2	416.3523	416.3524	0.366	416.3523、98.0969、398.3377、107.9674、91.0538	33
41	12.65	Zhebeinone-3-β-D-glucoside or verticinone-3-β-D-glucoside or Imperialine-3-β-D-glucoside or hupehemonside	C33H53NO8	592.3843	592.3822	-2.332	98.0969、574.3722、412.3212、112.1123	32、38

42	12.1	Zhebeinone-3-β-D-glucoside or verticinone-3-β-D-glucoside or Imperialine-3-β-D-glucoside or hupehemonside	C33H53NO8	592.3843	592.3845	2.665	98.0969、574.3722、412.3212、112.1123	32、38
43	14.55	Zhebeinone-3-β-D-glucoside or verticinone-3-β-D-glucoside or Imperialine-3-β-D-glucoside or hupehemonside	C33H53NO8	592.3843	592.3824	-3.561	98.0969、574.3722、412.3212、112.1123	32、38
44	15.04	Zhebeinone-3-β-D-glucoside or verticinone-3-β-D-glucoside or Imperialine-3-β-D-glucoside or hupehemonside	C33H53NO8	592.3843	592.3866	5.696	98.0969、574.3722、412.3212、112.1123	32、38
45	11.60	zhebeininoside	C33H55NO8	594.4	594.3967	-0.3360	594.3967、98.0969、432.2261、414.3374、396.3351	39
46	5.38	Zygadenin or its isomer	C27H43NO7	494.3112	494.3102	0.7186	494.3112、98.0979、476.3006、458.2890、440.2823、422.2692	40
47	6.78	Zygadenin or its isomer	C27H43NO7	494.3112	494.3098	-0.0220	494.3112、98.0979、476.3006、458.2890、440.2823、422.2692	40

48	16.82	15-O-(2-Methylbutanoyl)-3-O-veratroylprotoverine	C41H59NO13	774.4059	774.4030	-3.1300	774.4030、112.1135、756.3933、574.3366、472.2685、 436.2461、636.3136	41
49	14.77	verticinone	C27H43NO3	430.3315	430.3308	1.4240	412.219、430.3308、98.0965、176.5209、158.0914、112.1011、91.8113、71.4900、110.0855	Standard
50	17.87	peimine	C27H45NO3	432.3472	432.3482	2.277	414.33755、432.3482、112.1077、69.0693、176.1441、98.0969、397.14908、365.65713、158.1719、108.7695、166.3599	Standard
51	10.32	Imperialine	C27H43NO3	430.3315	430.3310	-1.1990	412.3220、430.3310、98.0965、397.1374、158.1071、176.1326、109.5145、78.5701、	Standard
52	19.20	Protoveratrine A	C41H63NO14	794.4321	794.4321	-0.0290	776.4194、658.3527、538.4126、478.3699、436.3325、112.1126	40
53	15.00	Germinalinine	C39H61NO13	752.4215	752.4201	-2.4550	752.4201、98.0969、734.4106、674.3894、572.3194、554.3129、438.2630	40
54	13.36	germbudin	C37H59NO12	710.411	710.4112	0.3660	710.4112、98.0969、692.4003、559.3448、456.2740、438.2662、420.2543、98.0970	40
55	14.46	Germidine	C34H53NO10	636.3742	636.3722	3.2260	636.3742、618.3635、600.3532、558.3420、98.0969、456.2742、438.2629、420.2521、112.1125	40
56	19.76	Verabenzoamine	C41H59NO12	758.411	758.4099	-3.5690	740.3978、758.4099、98.0959、558.3405、456.2727、438.2625、420.2517、165.0542、112.1120	40
57	18.01	Angeloylzygadenine	C32H49NO8	576.353	576.3507	0.6160	576.3507、98.0959、558.3411、540.3296、440.3671、422.2966、112.1120	40
58	15.62	Veramarine, acetate	C29H45NO4	472.3421	472.3410	0.6399	472.3410、98.0959、454.3322、430.3081、412.3196、394.3090	40
59	17.11	Veratroylzygadenine	C36 H51N	658.3585	658.3563	-2.0560	658.3563、98.0969、 622.3352、640.3457、440.2776、	42

			O10				422.3413、112.1123	
60	11.32	3-Acetylzygadenine	C29H45NO8	536.3217	536.3201	0.3105	536.3201、98.0969、518.3095、102.3998、458.2872、440.2837、422.3658	40
61	16.15	Germerin	C37H59NO11	694.416	694.4135	4.1060	694.4135、676.40302、618.3635、600.3532、558.3420、456.2742、438.2629、420.2521、112.1125	40
62	8.18	Gentiobiose	C12H22O11	365.1054	[M+Na]+365.10511	-0.1530	365.10511、203.05251、185.04225	34、35
63	14.36	cue-lure	C12H14O3	229.0835	[M+Na]+229.0859	3.589	186.9412	36
64	6.54	gentiatibetine	C9H11NO2	166.0862	166.0865	1.49	120.0812、166.0861、131.0494、107.0497、149.0594	37
65	7.09	Isoscopoletin	C10H8O4	193.0495	193.0502	3.45	193.0502、149.0600、178.0265、133.0290、122.0367、165.0550、162.0500	Standard
66	15.33	Ritalinic acid	C13H17N	188.1433	188.1433	0.0154	188.1433	39
67	5.66	α-D-Glucopyranoside, 2-methoxy-4-methylphenyl	C14H20O7	301.1081	301.1042	-1.667	301.1042	Standard

Table S4 identification of Mongolian medicine ageshiriga qi by hplc-q-exactive-ms /MS analysis (negative ion mode)

NO.	tR/min	alkaloids	Molecular formula	[M-H]- OR [M+Na]+ ion，m/z		Error	fragment ion	Ref.
				theoretical	measured			
68	45.25	Resveratrol	C14H12O3	227.0714	227.0710	3.275	227.07101、185.06097、143.04915、130.98273、102.95605	Standard
69	36.68	Oxyresveratrol	C14H12O4	243.0662	243.0662	-0.36	243.06612、201.05516、159.95518、	Standard

70	31.49	Piceid	C20H22O8	389.1241	389.1242	0.256	389.12419、227.07106、185.04292、143.29558、	Standard
71	40.37	Resveratroloside or Polydatin IV or its isomer	C20H22O8	389.1241	389.1246	0.556	389.12460、227.07094、185.04230、143.34976	43
72	43.98	Resveratroloside or Polydatin IV or its isomer	C20H22O8	389.1241	389.1246	0.145	389.12463、227.07100、185.04230、143.34976、	43、44
73	24.96	Resveratroloside or Polydatin IV or its isomer	C20H22O8	389.1241	389.1245	0.856	389.12451、227.07104、185.04230、143.34976	43、44
74	22.78	Piceatannol 4'-O-β-D-glucopyranoside	C20H22O9	405.1191	405.1195	1.266	405.11951、243.06610、201.05492、159.95598	Standard
75	25.45	3,4,3',5'-Tetrahydroxystilbene 3'-glucoside or β-D-Glucopyranoside, 4-[(1E)-2-(2,5-dihydroxyphenyl)ethenyl]-2-hydroxyphenyl or β-D-Glucopyranoside, 5-[2-(3,4-dihydroxyphenyl)ethenyl]-2-hydroxyphenyl, (E)- (9CI)	C20H22O9	405.1191	405.1197	2.663	405.11969、243.06599、201.05428、159.95560、	45
76	28.29	3,4,3',5'-Tetrahydroxystilbene 3'-glucoside or β-D-Glucopyranoside, 4-[(1E)-2-(2,5-dihydroxyphenyl)ethenyl]-2-hydroxyphenyl or β-D-Glucopyranoside, 5-[2-(3,4-dihydroxyphenyl)ethenyl]-	C20H22O9	405.1191	405.1196	1.266	405.11960、243.06602、201.05411、159.95528	45

		2-hydroxyphenyl, (E)- (9CI)						
77	30.1	3,4,3',5'-Tetrahydroxystilbene 3'-glucoside or β-D-Glucopyranoside, 4-[(1E)-2-(2,5-dihydroxyphenyl)ethenyl]-2-hydroxyphenyl or β-D-Glucopyranoside, 5-[2-(3,4-dihydroxyphenyl)ethenyl]-2-hydroxyphenyl, (E)- (9CI)	C20H22O9	405.1191	405.1197	1.369	405.11972、243.06604、201.03758、159.95453	45
78	48.81	Resveratrol 4'-methyl ether	C15H14O3	241.0870	241.0850	3.661	241.08503、199.03931、184.05263	46
79	31.31	3,3',5-Stilbenetriol, 4'-methoxy-, (E)- (8CI)	C15H14O4	257.0819	257.0827	2.748	257.08266、215.23622、200.08266	46
80	32.03	resveratrol-4,3'-di-O-β-D-glucopyranoside or its isomer	C26H32O13	551.1770	551.1715	-3.524	5551.17150、389.12570、227.07100、	49、47
81	14.87	Piceatannol 3,4'-di-β-D-glucopyranoside	C26H32O14	567.1719	567.1717	-1.231	567.17175、405.11945、243.06606、	50、48
82	14.16	Mulberroside A	C26H32O14	567.1719	567.1721	3.661	567.17212、405.11801、243.06609、	Standard
83	18.74	Mulberroside E	C26H32O13	597.1834	597.1834	0.157	597.18341、435.13327、389.12610、227.07103	Standard
84	16.29	(E)-Resveratrol 3,5-O-β-diglucoside	C26H32O13	597.1834	597.1837	-0.245	597.18372、435.13417、389.12460、227.07100	49
85	15.78	β-D-Glucopyranoside, 3-hydroxy-5-[(1E)-2-(4-hydroxyphenyl)ethenyl]phenyl 2-O-β-D-glucopyranosyl-	C26H32O13	597.1834	597.1836	-0.859	597.18362、435.13316、389.12463、227.07104	49、50

86	32.25	resveratrol-4,3'-di-O-β-D-glucopyranoside	C26H32O13	551.1770	551.1771	0.859	551.1771、209.1436	Standard
87	40.77	desoxyrhaponticin	C21H24O8	427.2663	427.2609	-3.55	427.2609、223.0467	Standard
88	4.33	L-Pyroglutamic acid methyl este	C6H9NO3	166.0475	166.04746	0.256	166.04746	Standard
89	27.41	β-D-Glucopyranoside,2-methoxy-4-(2-propen-1-yl)phenyl-6-O-β-D-glucopyranosyl	C22H32O12	489.1967	489.19665	-0.145	489.19665、	Standard
90	20.33	β-D-Glucopyranoside, 2,6-dimethoxy-4-(2-propen-1-yl)phenyl 6-O-b-D-glucopyranosyl	C23H34O13	541.1892	541.1891	-0.114	541.1891、	Standard
91	1.03	Arginine	C6H14N4O2	173.1043	173.1034	0.527	173.10339、131.08144、86.05969、73.02814、59.01230	51
92	2.36	4-Oxo-4H-pyran-2,6-dicarboxylic acid	C7H4O6	182.9935	182.9926	1.012	182.99257、139.00259、95.01260、67.01754	52
93	3.25	Citric Acid	C7H8O7	203.0197	203.0196	-0.526	191.02145、146.93759、102.94756、85.02814	53
94	2.69	Quinic acid	C7H12O6	191.0561	191.0555	-0.361	191.05547、131.03400、87.00739	54
95	2.41	Pectinose	C5H10O5	195.0503	195.0504	-1.554	195.05038、177.03941、159.02879、141.01820	55
96	16.89	2-(4-Hydroxybenzyl)malic acid	C11H12O6	239.0561	239.0558	-2.175	239.05531、195.06573、150.06341、	56