天然药物抗呼吸道病毒活性成分及其作用机制研究进展

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摘要: 人类病毒性呼吸道疾病是一类广泛流行的传染性疾病, 呼吸道病毒感染的发病率在全球居民发病率总体结构中占据主要地位, 是导致人类急性和致死性疾病的主要病因之一。天然产物结构多样、作用机制新颖, 具有调节机体免疫与抗呼吸道病毒的作用, 在治疗呼吸道病毒疾病方面具有独特的优势。本文综合目前天然药物防治呼吸道病毒的研究进展, 以天然药物抗呼吸道病毒活性成分的作用机制进行分类, 以期为未来的呼吸道疾病的临床治疗与药物发现提供参考依据。

关键词: 天然药物; 活性成分; 新型冠状病毒; 呼吸道病毒感染; 抗病毒作用机制

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Progress of active ingredients of natural drugs and their mechanism of antiviral actions

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Abstract: Human viral respiratory disease is a kind of widely prevalent infectious disease. The incidence rate of respiratory virus infection occupies a major position in the overall structure of global incidence rate of residents, and is one of the main causes of acute and fatal human diseases. Natural products have diverse structures and novel mechanisms of action, which can regulate body immunity and resist respiratory viruses, and have unique advantages in the treatment of respiratory viral diseases. This article summarizes the current research progress of natural drugs in the prevention and treatment of respiratory viruses, classifies the action mechanism of the active components of natural drugs against respiratory viruses, to provide reference basis for clinical treatment and drug discovery of respiratory diseases in the future.

Key words: natural drug; active ingredient; SARS-CoV-2; respiratory virus infection; mechanism of antiviral action

呼吸道病毒以空气传播 (呼吸道飞沫传播) 为主, 传染性较强, 极易引起大规模流行性疾病。新型冠状病毒肺炎 (corona virus disease 2019, COVID-19) 疫情暴发以来, 传播迅速, 据 WHO 统计, 截至 2023 年 8 月 17 日, 全球累计确诊 COVID-19 病例超过 7.69 亿, 死亡人数逾 695 万[1], 对全球社会经济造成冲击, 在全球引发了社会动乱并对人体产生不可忽视的后遗症。呼吸道病毒感染是导致人类急性和致死性疾病的主要病因之一, 是全球卫生安全的重要威胁, 现虽然已研发出针对原始株的疫苗, 但潜在变异株的威胁仍不容小觑。

目前抗呼吸道病毒药物以西药为主, 主要有洛匹那韦、金刚烷胺、金刚乙胺奥司他韦等, 但若使用不当

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会引起急性肾衰竭等不良反应。目前广泛使用的广谱抗病毒药物利巴韦林的药效仍存在争议, 其不良反应也令人担忧。鉴于上述现状, 开发高效、低毒、使用便捷的呼吸道病毒药物具有重要意义, 而从天然药物中筛选活性成分已经成为开发各类治疗药物的有效途径与手段。

Liu等[2]从清金化痰汤的活性成分入手, 利用超高效液相色谱−四极杆飞行时间质谱 (UPLC-Q-TOF/MS) 技术分析了其中的抗病毒天然药物活性成分的组成, 对甲型流感病毒 (influenza A virus, IAV) 感染后的差异表达基因进行了RNA-seq筛选, 揭示了清金化痰汤治疗IAV肺炎的机制。天然药物活性成分抗病毒机制是什么? 根据中医理论, 天然药物抗病毒主要有两种策略, 为“祛邪”和“扶正”。“祛邪”对应于直接抑制病毒的活性, “扶正”对应于宿主的免疫调节、炎症控制和预防病毒[3]。天然药物是重要的药物开发资源, 与化学合成药物相比, 天然药物具有结构多样性、毒性低、作用机制新颖、能够调节机体免疫功能等优点, 因此从植物、微生物中寻找药物先导化合物具有极好的潜力。本文将近几年天然药物的活性成分进行归纳并阐明其抗呼吸道病毒的作用机制, 以期为未来的人类病毒性呼吸道疾病的临床治疗与药物发现提供一些有益的参考。

1 直接作用于病毒

1.1 抑制病毒的吸附 血管紧张素转化酶2 (angiotensin-converting enzyme 2, ACE2) 是存在于宿主细胞上的一种受体, 新型冠状病毒表面的刺突蛋白可以协助病毒找到宿主细胞上的ACE2受体并诱导病毒与受体细胞相结合, 吸附宿主细胞, 在酶的反应下病毒的包膜与宿主细胞融合进而入侵宿主细胞。Sehailia等[4]研究发现青蒿素及其衍生物可以缠绕新冠病毒刺突蛋白的Lys353和Lys31结合位点, 从而影响其与人体ACE2受体蛋白的融合, 从而阻止病毒吸附宿主细胞。Chen等[5]使用高分辨质谱 (high resolution mass spectrum, HRMS) 和非靶向数据挖掘方法的组合, 检测到连花清瘟中132种成分或衍生物, 通过ACE2生物色谱法筛选的数据, 确定了大黄酸、连翘苷A、连翘苷I、新绿原酸及其异构体对ACE2表现出高度抑制作用。Maurya等[6]研究表明姜黄素、醉茄素A、胡椒碱、芒果苷、蒂巴因、小檗碱、穿心莲内酯和印楝素对SARS-CoV-2的刺突蛋白和ACE2受体均具有显著的结合亲和力, 可以阻断刺突蛋白与ACE2受体的结合抑制病毒吸附宿主细胞。Yang等[7]发现中药丹参水溶性单体成分丹酚酸通过阻止刺突蛋白六螺旋束结构形成, 有效抑制新型冠状病毒的吸附。

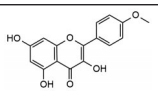
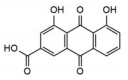
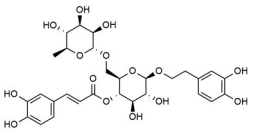
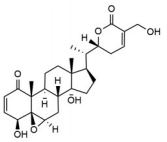
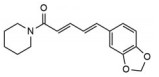
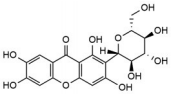
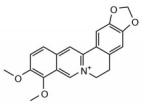
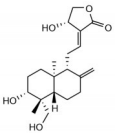
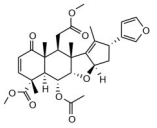
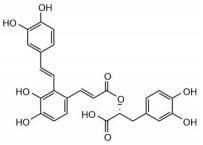
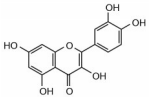
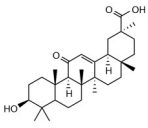
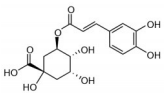
流感病毒 (influenza virus, IV) 表面的糖蛋白血凝素 (HA) 与宿主细胞的唾液酸受体结合, 引起病毒包膜与宿主细胞膜融合, 病毒以胞吞的形式入侵宿主细胞。Wu等[8]发现槲皮素可通过与流感病毒血凝素蛋白结合, 竞争性抑制流感病毒血凝素与宿主细胞的唾液酸结合, 抑制病毒包膜与宿主细胞膜融合, 抑制病毒以胞吞形式入侵宿主细胞。

人呼吸道合胞病毒 (human respiratory syncytial virus, HRSV) 含有三种膜结合蛋白: 附着蛋白 (G)、融合蛋白 (F)、病毒孔蛋白 (SH)。蛋白G可与宿主细胞结合, 蛋白F可以融合病毒和细胞膜, 使病毒核糖核蛋白能够到达细胞质。三种糖蛋白相互作用使病毒入侵宿主细胞[9]。Yeh等[10]研究发现甘草通过抑制病毒附着、内化减少HRSV感染。18β-甘草次酸可能是影响甘草抗HRSV活性的活性成分之一。通过抑制病毒吸附的抗呼吸道病毒的天然药物活性成分见表1[4-8,10-25]。

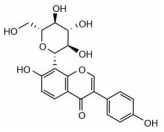
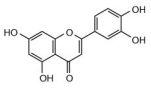
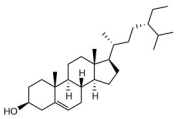
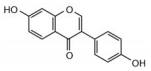
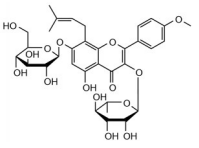
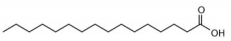
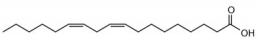
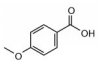
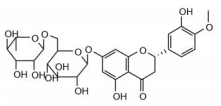
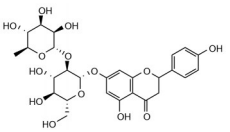
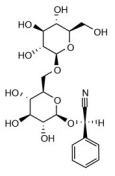
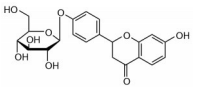
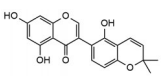
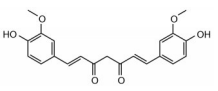
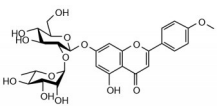
1.2 抑制病毒的增殖 病毒感染特定的活细胞后, 可以在病毒核酸的控制下, 利用宿主细胞的能量系统、核糖体等合成病毒核酸和蛋白质, 最后组装成结构完整、具有感染力的成熟病毒颗粒。冠状病毒3C样蛋白酶 (3C-like protease, 3CL^{pro}) 与木瓜蛋白酶样蛋白酶 (papain-like protease, PL^{pro}) 在病毒增殖过程能够将多肽链切割分解成病毒复制需要的片段[26]。通过研究发现, 木犀草素、β-谷甾醇、芒柄花黄素、紫檀素、蒙花苷、金丝桃苷等通过与3CL^{pro}特异性结合, 阻止3CL^{pro}发挥作用[13,14,17,20]。Chen等[27]研究发现萝卜硫素 (SFN) 是一种缓慢结合的抑制剂, SFN与3CL^{pro}能够发生共价反应, 形成了SFN-3CL^{pro}复合物, 从而阻断3CL^{pro}的作用。Su等[28]研究发现杨梅素可以与3CL^{pro}共价结合, 阻止3CL^{pro}发挥作用, 从而抑制病毒的增殖; Zhang等[29]研究发现冬凌草甲素不仅能够抑制3CL^{pro}的活性, 而且在高浓度下可以阻止PL^{pro}主导的反应活动, 从而阻止病毒的增殖。新橙皮苷、蛇床子素等与PL^{pro}结合, 阻止PL^{pro}发挥作用, 从而抑制病毒增殖[30]。Xu等[31]研究发现西北甘草异黄酮和甘草异黄酮A可以与RNA依赖的RNA聚合酶 (RNA-dependent RNA polymerase, RdRp) 结合形成复合物, 阻止RdRp发挥作用, 从而抑制病毒的增殖。

核因子-κB (nuclear factor-κB, NF-κB) 信号通路可以调节流感病毒RNA合成, 在病毒的复制过程中发挥重要作用[32]。葡萄红素B能够抑制H1N1病毒在MDCK和A549细胞中的复制, 并通过IκB激酶 (IκB kinase, IKK) 去磷酸化抑制NF-κB转入细胞核, 从而降低了病毒诱导的活性氧 (reactive oxygen species, ROS) 的生成[33]。细胞周期蛋白依赖性激酶抑制剂p21可以

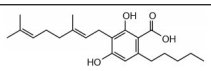
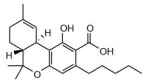
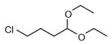
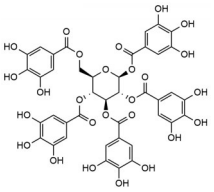
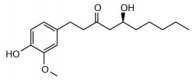
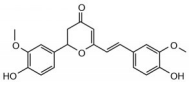
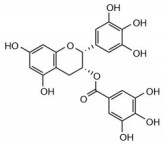
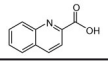
Table 1　Active ingredients of natural products against respiratory viruses by preventing viral adsorption

No.	Compound	Antiviral species	Compound structure	Mechanism of action	Ref.
1	Artemisinin	SARS-CoV-2		Artemisinin derivatives in preventing the interaction between the virus' SProtein and hACE2 receptor *via* selectively interacting with the Lys353 binding hotspot of SProtein	[4]
2	Rhein	SARS-CoV-2		Exhibited high inhibitory effect on ACE2	[5]
3	Forsythoside A	SARS-CoV-2			
4	Withaferin A	SARS-CoV-2		Significant binding affinity towards spike glycoprotein of SARS-CoV-2 and ACE2 receptor and may be useful as a therapeutic and/or prophylactic agent for restricting viral attachment to the host cells	[6]
5	Piperine	SARS-CoV-2			
6	Mangiferin	SARS-CoV-2			
7	Thebaine	SARS-CoV-2			
8	Berberine	SARS-CoV-2			
9	Andrographolide	SARS-CoV-2			
10	Nimbin	SARS-CoV-2			
11	Salvianolic acid	SARS-CoV-2		Salvianolic acid C potently inhibit SARS-CoV-2 infection by blocking the formation of six-helix bundle core of spike protein	[7]
12	Quercetin	IAV		Quercetin showed interaction with the HA2 subunit	[8]
13	18β-Glycyrrhetinic acid	HRSV		Decreased HRSV infection largely by inhibiting viral attachment, internalization, and by stimulating IFN secretion	[10]
14	Chlorogenic acid	SARS-CoV-2		Chlorogenic acid could stably combine with Gln325 and Gln42/Asp38 in ACE2, respectively, which hindered the combination between S-protein and ACE2	[11]

Continued

No.	Compound	Antiviral species	Compound structure	Mechanism of action	Ref.
15	Puerarin	SARS-CoV-2		Puerarin had good binding activity with ACE2 and hydrolase of SARS-CoV-2	[12]
16	Luteolin	SARS-CoV-2		Embrace satisfactory binding to ACE2, and also had good binding to core targets	[13-15]
17	*β*-Sitosterol	SARS-CoV-2			
18	Formononetin	SARS-CoV-2			
19	Icariine	SARS-CoV-2			
20	Palmitic acid	SARS-CoV-2		These volatile oil components had good binding activity with ACE2	[16]
21	Linoleic acid	SARS-CoV-2			
22	Anisic acid	SARS-CoV-2			
23	Hesperidin	SARS-CoV-2		They had good affinity with the core target ACE2 of SARS-CoV-2	[17]
24	Naringin	SARS-CoV-2			
25	Amygdalin	SARS-CoV-2			
26	Liquiritin	SARS-CoV-2			
27	Licoisoflavone	SARS-CoV-2			
28	Curcumin	SARS-CoV-2		A good binding energy, drug likeness and efficient pharmacokinetic parameters suggest the potential of curcumin as SARS-CoV-2 spike protein inhibitors	[18,19]
29	Fortunellin	SARS-CoV-2		It could be well embedded into the active pocket of ACE2-SARS-CoV-2 S protein	[20]

Continued

No.	Compound	Antiviral species	Compound structure	Mechanism of action	Ref.
30	Cannabigerolic acid	SARS-CoV-2		Prevent infection of human epithelial cells by a pseudovirus expressing the SARS-CoV-2 spike protein and prevented entry of live SARS-CoV-2 into cells	[21]
31	Tetrahydrocannabinolic acid	SARS-CoV-2			
32	Cannabidiolic acid	SARS-CoV-2			
33	1,2,3,4,6-Vegalacyl glucose	SARS-CoV-2		A safe and potential antiviral agent against the COVID-19 by blockade the fusion of SARS-CoV-2 spike-RBD to hACE2 receptors	[22]
34	Gingerol	SARS-CoV-2		Inhibited the viral protein of both wild-type and mutated S-protein of SARS-CoV-2	[23]
35	Thymol	SARS-CoV-2			
36	Thymohydroquinone	SARS-CoV-2			
37	Cyclocurcumin	SARS-CoV-2			
38	Epigallocatechin gallate	SARS-CoV-2		The inhibitor blocked binding to S-protein in a dose-dependent manner	[24]
39	Quinoline-2-carboxylic acids	SARS-CoV-2		Blocked the interaction between SARS-CoV-2 RBD and ACE2 in a dose-dependent manner	[25]

直接与病毒聚合酶酸性蛋白结合, 并通过破坏核糖核蛋白复合物的形成来限制IAV聚合酶活性, 从而阻止病毒增殖[34]。通过抑制病毒增殖抗呼吸道病毒的天然药物活性成分见表2[13,14,17,20,27-31,33,35-40]。

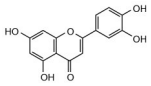
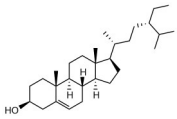
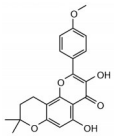
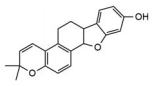
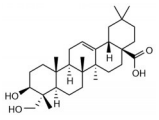
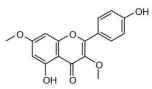
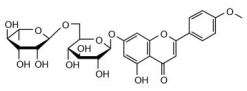
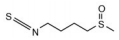
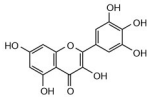
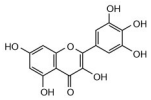
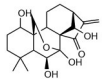
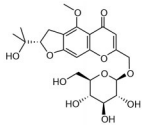
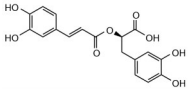
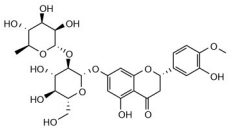
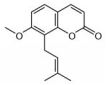
1.3　阻止病毒释放　在流感病毒中, 神经氨酸酶(NA)、血凝素 (HA) 和病毒M2蛋白被输出到质膜上, 与病毒核糖核蛋白 (viral ribonucleoprotein, vRNP) 组装产生子代IAV粒子。在NA催化下, 新组装的病毒从宿主细胞释放传播[41-43]。NA是流感病毒中重要的包膜糖蛋白之一, 在成熟的病毒细胞从宿主细胞分离时, 病毒表面的血凝素通过唾液酸与宿主细胞相连, 神经氨酸酶具有水解唾液酸的功能, 使病毒繁殖释放。Li等[44]研究发现安石榴苷抑制流感病毒的神经氨酸酶, 阻止唾液酸的分解, 阻断病毒释放。诃子酸和诃子林鞣酸可以抑制病毒NA蛋白的活性, 破坏病毒与宿主细胞上唾液酸的结合, 在感染的细胞中阻止病毒释放[45]。通过阻止病毒释放抗呼吸道病毒的天然药物活性成分见表3[44-46]。

2　免疫调节

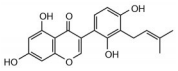
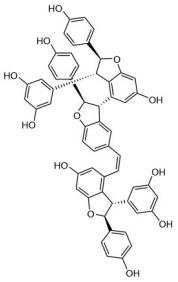
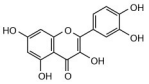
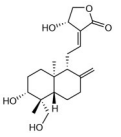
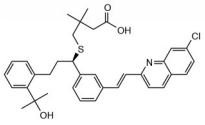
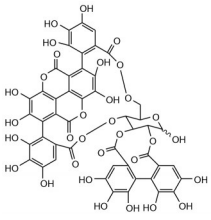
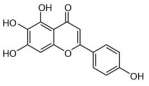
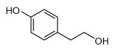
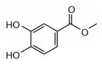
在病毒感染后, 细胞通过释放细胞因子、趋化因子等信号, 激活巨噬细胞、自然杀伤细胞 (NK) 和其他免疫细胞, 以杀死和消除被感染的细胞。一旦调节失去平衡, 就会导致过度的免疫反应和组织损伤[47]。研究表明, 细胞周期蛋白依赖性激酶抑制剂p21可以直接调节巨噬细胞分化和活性来调节免疫反应[48]。

干扰素 (interferon, IFN) 是一种广谱抗病毒糖蛋白, 作为免疫系统的触发、调节和效应器, 参与病毒感染的许多生理反应, 是最重要的细胞因子[49]。Luo等[50]研究发现表告依春降低了线粒体融合蛋白2 (mitofusin 2, MFN2) 的表达, 从而提高了线粒体抗病毒信号蛋白 (mitochondrial antiviral signaling protein, MAVS)的表达, 进而增加了干扰素β (IFN-β) 和干扰素诱导的跨膜蛋白3 (interferon-induced transmembrane protein 3, IFITM3) 的产生。研究发现黄芩苷能明显增加呼吸道合胞病毒 (respiratory syncytial virus, RSV) 感染小鼠的干扰素α (IFN-α)、IFN-β及干扰素γ (IFN-γ)

Table 2 Active ingredients of natural products against respiratory viruses by inhibiting of viral replication

No.	Compound	Antiviral species	Compound structure	Mechanism of action	Ref.
40	Luteolin	SARS-CoV-2		Embrace satisfactory binding to $3CL^{pro}$, and also had good binding to core targets	[13,14]
41	*β*-Sitosterol	SARS-CoV-2			
42	Formononetin	SARS-CoV-2			
43	Anhydroicaritin	SARS-CoV-2			
44	Shinpterocarpin	SARS-CoV-2			
45	Hederagenin	SARS-CoV-2		They had good affinity with the core target $3CL^{pro}$ of SARS-CoV-2	[17]
46	Jaranol	SARS-CoV-2			
47	Linarin	SARS-CoV-2		It had strong binding with $3CL^{pro}$	[20]
48	*DL*-Sulforaphane	SARS-CoV-2		SFN inhibits $3CL^{pro}$ in a reversible, mixed-type manner. SFN is a slow-binding inhibitor, following a two-step interaction an complex forms by specific binding of SFN to the active pocket of $3CL^{pro}$, stabilizing the SFN-$3CL^{pro}$ complex	[27]
49	Myricetin	SARS-CoV-2		Myricetin is an efficient covalent binder of the SARS-CoV-2 $3CL^{pro}$	[28]
50	Oridonin	SARS-CoV-2		Oridonin not only effectively inhibited SARS-CoV-2 $3CL^{pro}$ activity, but also had some inhibitory effects on PL^{pro}	[29]
51	Prim-*O*-glucosylcimifugin	SARS-CoV-2		They had strong $3CL^{pro}$ inhibitory activities	[30]
52	Rosmarinic acid	SARS-CoV-2			
53	Neohesperidin	SARS-CoV-2			
54	Osthole	SARS-CoV-2			

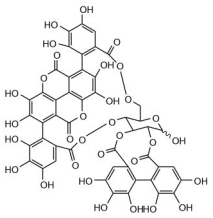
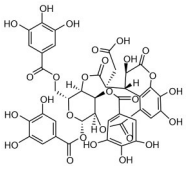
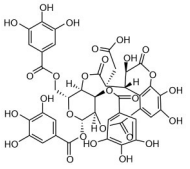
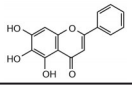
Continued

No.	Compound	Antiviral species	Compound structure	Mechanism of action	Ref.
55	Licoisoflavone A	SARS-CoV-2		Exhibited significant inhibitions against RdRp	[31]
56	Vitisin B	H1N1		Suppresses H1N1 viral replication in MDCK and A549 cells	[33]
57	Quercetin	SARS-CoV-2		Quercetin could be shown to interact with $3CL^{pro}$ using biophysical techniques and bind to the active site in molecular simulations	[35,36]
58	Andrographolide	SARS-CoV-2		Andrographolide was docked successfully in the binding site of SARS-CoV-2 $3CL^{pro}$	[37]
59	Chebulagic acid	SARS-CoV-2		By binding to SARS-CoV-2 $3CL^{pro}$ at a pocket other that substrate binding site, chebulagic acid and punicalagin act as allosteric inhibitors in reversible, noncompetitive manner	[38]
60	Punicalagin	SARS-CoV-2			
61	Scutellarein	SARS-CoV-2		Scutellarein was characterized as a potent $3CL^{pro}$ inhibitor	[39]
62	4-(2-Hydroxyethyl) phenol	SARS-CoV-2		Inhibit PL^{pro} by binding at an allosteric S2 site, an interaction and binding region for the Interferon-stimulated gene 15 molecule	[40]
63	4-Hydroxybenzaldehyde	SARS-CoV-2			
64	Methyl 3,4-dihydroxybenzoate	SARS-CoV-2			

的表达来发挥抗RSV的作用[51,52]。连翘苷E、连翘苷、马鞭草苷和大黄素, 通过调节1型IFN、NF-κB与丝裂原活化蛋白激酶 (mitogen-activated protein kinase, MAPK) 等信号通路, 改善病毒感染小鼠的症状[53-56]。

天然活性成分还可以通过调节炎症因子的释放, 来避免炎症风暴。大量研究发现连翘苷E、连翘苷、马鞭草苷、大黄素、橙皮苷与新绿原酸等可以调节免疫反应控制细胞因子的释放, 抑制炎症与细胞因子风暴, 改善细胞机体免疫调节的失衡[17,57,58]。蓟黄素可以通过体外抑制JNK MAPK和P38 MAPK的激活, 下调促炎细胞因子肿瘤坏死因子-α (TNF-α)、白细胞介素1β (IL-1β)、白细胞介素-8 (IL-8) 和白细胞介素-10 (IL-10) 和炎症相关蛋白环氧化酶2 (cyclooxygenase 2, COX-2) 的表达水平从而有效治愈IAV感染[59]。Xu等[31]研究发现甘草查尔酮B、西北甘草异黄酮和刺甘草查尔酮具有较好抗炎活性抑制严重急性呼吸综合征冠状病毒2 (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2) 所致炎症因子的释放, 且与剂量有依赖性。Zhao等[60]研究发现虎杖苷、异甘草苷、麻黄碱、山柰酚、苍术内酯I和毛蕊花苷等成分可以抑制巨噬细胞

Table 3 Active ingredients of natural products against respiratory viruses by stopping virus release

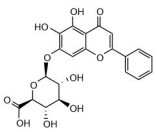
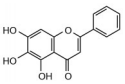
No.	Compound	Antiviral species	Compound structure	Mechanism of action	Ref.
65	Punicalagin	IAV		Punicalgin blocks viral release from the infected cells by inhibiting NA activity	[44]
66	Chebulinic acid	IAV		Exert their inhibitory effect on the NA-mediated viral release	[45]
67	Chebulagic acid	IAV			
68	Baicalein	H5N1		Baicalein interfered with the viral NA activity	[46]

的活化, 减轻炎症症状。研究发现, 槲皮素、木犀草素和芹菜素等核心成分靶向与白细胞介素-6 (IL-6) 结合下调 IL-6 的水平, 能有效阻断炎症风暴[61]。谷氨酰胺酶抑制剂 JHU-083 通过调节 l-谷氨酰胺代谢, 从而缓解病毒刺激诱导的铁死亡, 减轻炎症的严重程度, 减轻 H1N1 病毒对机体的损伤[62]。通过免疫调节抗呼吸道病毒的天然药物活性成分见表 4[17,50-61,63-73]。

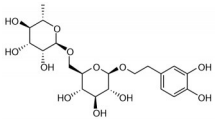
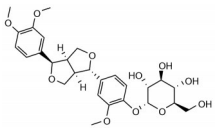
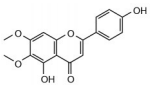
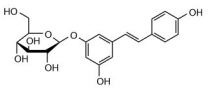
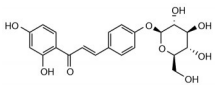
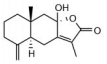
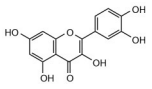
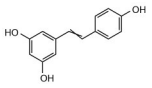
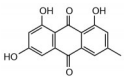
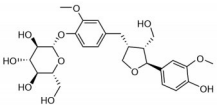
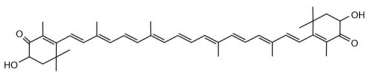
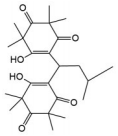
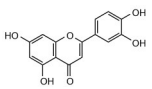
3 小结与展望

SARS-CoV-2 大流行给全人类带来了严重危害, 新冠病毒反复感染仍在持续, 如何有效减轻相关疾病负担是当下的重要课题。研究发现, 新冠病毒表现出明显的免疫学逃逸和解剖学逃逸特征[74]: 一方面, 层出不穷的变异株可以逃逸既往自然感染或疫苗诱导产生的保护性抗体; 另一方面, 人体上呼吸道的抗体水平比外周血中的抗体水平低数百倍[75], 导致新冠病毒在感染和复制的第一站, 即鼻腔中发生解剖学逃逸。因此, 新冠病毒、流感病毒等非系统性感染类呼吸道病毒易反复感染。呼吸道病毒对公众健康和经济稳定构成持

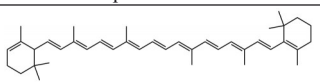
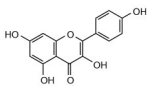
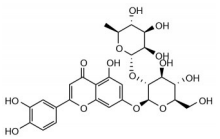
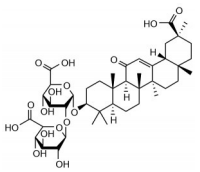
Table 4 Active ingredients of natural products against respiratory viruses by indirect immune regulation

No.	Compound	Antiviral species	Compound structure	Mechanism of action	Ref.
69	Epigoitrin	H1N1		Epigoitrin reduced the protein expression of MFN2, which elevated MAVS protein expression and subsequently increased the production of IFN-β and interferon inducible IFITM3	[50]
70	Baicalin	H1N1		Directly induce IFN-γ production in human $CD4^+$ and $CD8^+$ T cells and NK cells, and activate JAK/STAT-1 signaling pathway	[51]
		RSV		The IFN-α and IFN-β in the BALB/c mouse infected by RSV could be evaluated significantly by baicalin	[52]
		RSV		The expression of I-IFN in RSV infection rats could be down-regulated by baicalin. The expression of SOCS1/3 might be inhibited by reducing the expression IL-6 and IL-12 by baicalin	[53]
		IAV		Baicalin exerts its anti-IVA effect by downregulating miR-146a to subsequently facilitate the type I IFN response	[54]
71	Baicalein	SARS-CoV-2		Baicalein improved the respiratory function, inhibited inflammatory cell infiltration in the lung, and decreased the levels of IL-1β and TNF-α in serum	[55]

Continued

No.	Compound	Antiviral species	Compound structure	Mechanism of action	Ref.
72	Forsythoside	H1N1		TBK1, IRF3, MAPKp38, and NF-κB p65 in the forsythoside E-treated group were significantly downregulated	[56]
73	Phyllyrin	SARS-CoV-2		Regulation of NF-κB and MAPK signaling pathway and ERK pathways to improve immunity	[17,57,58]
74	Cirsimaritin	IAV		Suppress the activation of JNK MAPK and P38 MAPK *in vitro*, the expression levels of proinflammatory cytokines (TNF-α, IL-1β, IL-8, and IL-10) and the inflammation-related protein COX-2 were downregulated	[59]
75	Polydatin	SARS-CoV-2		Inhibit macrophage activation *in vitro*	[60]
76	Isoliquiritin	SARS-CoV-2			
77	Ephedrine	SARS-CoV-2			
78	Atractylenolide III	SARS-CoV-2			
79	Quercetin	RSV		Decreased the levels of TNF-α, IL-6, and IL-1α	[61]
		SARS-CoV-2		Quercetin could inhibit cytokines release, alleviate excessive immune responses and eliminate inflammation, through NF-κB, IL-17 and Toll-like receptor signaling pathway	[63]
80	Resveratrol	RSV		Resveratrol decreased TRIF expression and prevented the RSV-mediated reduction of SARM expression	[64]
81	Emodin	SARS-CoV-2		It had good binding ability with the core target of AKT1, IL-6, TP53, JUN, TNF	[65]
82	Lariciresinol-4-*O*-β-*D*-glucopyranoside	IAV		Inhibition of NF-κB pathway in influenza A virus-infected alveolar epithelial cells, decrease proinflammatory cytokine expression	[66]
83	Astaxanthin	SARS-CoV-2		Astaxanthin is shown to exert protective effect by regulating the expression of pro-inflammatory factors IL-1β, IL-6, IL-8 and TNF-α	[67]
84	Watsonianone A	RSV		Watsonianone A inhibited NF-κB activation by suppressing IκBα phosphorylation	[68]
85	Luteolin	H1N1		Reduce the expression levels of the inflammatory cytokines TNF-α, IFN-γ, IL-1 and IL-10, thus reducing the pathological damage	[69]
86	Berbamine	H1N1		Induced activation of the type I interferon pathway	[70]

Continued

No.	Compound	Antiviral species	Compound structure	Mechanism of action	Ref.
87	Carotene	SARS-CoV-2		Enter the active pocket of Akt1, prevent lung injury, lung fibrogenesis and virus infection	[71]
88	Kaempferol	SARS-CoV-2			
89	Lonicerin	SARS-CoV-2		Inhibition of the arachidonic acid metabolism pathway and preventing the release of inflammatory factors can prevent the cytokine storm	[72]
90	Glycyrrhizic acid	SARS-CoV-2		Heightened release of proinflammatory cytokines IL-1β, IL-6 and IL-8 was attenuated by glycyrrhizin	[73]

续威胁, 为传统抗病毒药物的研发带来巨大挑战。

天然产物结构丰富多变, 很多分子具有很好的药理活性。大量研究表明, 自然界中的天然药物含有大量活性物质具有调节机体免疫与抗呼吸道病毒的作用, 随着研究的深入开展, 天然药物及其活性物质在作为抵抗呼吸道病毒侵害、促进人体免疫和治疗疾病的候选药物方面展现出良好的应用前景。近几年来, 研究人员不仅从微生物、植物及海洋生物中分离出许多具有生理活性且结构新颖的天然化合物, 也发现了一些已知化合物具有较好的抗呼吸道病毒活性, 且更深入地开展了构效关系的研究, 为这些天然产物用作抗呼吸道病毒药物的相关研究提供了更多的参考信息。

病毒带来的危害让人们意识到开发抗病毒药物和治疗方案的迫切需求, 目前的抗病毒策略集中于抗体、疫苗、小分子药物等传统技术手段, 而RNA包膜病毒的高频突变特性往往会促使原有技术方法的失效。研究发现, 针对亚细胞结构稳态可能是一种有前途的抗病毒策略[76]。天然药物在抗呼吸道病毒中有很大潜力, 其相关作用机制仍需研究者们继续探索。

作者贡献: 王剑和张萍萍负责文献检索及论文撰写; 王京龙和崔清华负责相关资料的收集和文章选题; 王剑、张萍萍和于健负责文章的修改和校对文章。

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References

[1] World Health Organization. Coronavirus disease (COVID-19) [DB/OL]. 2023 [2023-8-17]. https://www. who. int/emergencies/diseases/novel-coronavirus-2019.

[2] Liu M, Zhao F, Xu J, et al. Qingjin Huatan decoction protects mice against influenza a virus pneumonia *via* the chemokine signaling pathways [J]. J Ethnopharmacol, 2023, 317: 116745.

[3] Li BH, Li ZY, Liu MM, et al. Progress in traditional Chinese medicine against respiratory viruses: a review [J]. Front Pharmacol, 2021, 12: 43623.

[4] Sehailia M, Chemat S. Antimalarial-agent artemisinin and derivatives portray more potent binding to Lys353 and Lys31-binding hotspots of SARS-CoV-2 spike protein than hydroxychloroquine: potential repurposing of artenimol for COVID-19 [J]. J Biomol Struct Dyn, 2021, 39: 6184-6194.

[5] Chen X, Wu Y, Chen C, et al. Identifying potential anti-COVID-19 pharmacological components of traditional Chinese medicine Lian hua qing wen capsule based on human exposure and ACE2 biochromatography screening [J]. Acta Pharm Sin B, 2021, 11: 222-236.

[6] Maurya VK, Kumar S, Prasad AK, et al. Structure-based drug designing for potential antiviral activity of selected natural products from Ayurveda against SARS-CoV-2 spike glycoprotein and its cellular receptor [J]. Virusdisease, 2020, 31: 179-193.

[7] Yang C, Pan X, Xu X, et al. Salvianolic acid C potently inhibits SARS-CoV-2 infection by blocking the formation of six-helix bundle core of spike protein [J]. Signal Transduct Target Ther, 2020, 5: 220.

[8] Wu W, Li R, Li X, et al. Quercetin as an antiviral agent inhibits influenza A virus (IAV) entry [J]. Viruses, 2016, 8: 6.

[9] Melero JA, Mas V, McLellan JS. Structural, antigenic and immunogenic features of respiratory syncytial virus glycoproteins relevant for vaccine development [J]. Vaccine, 2017, 35: 461-468.

[10] Yeh CF, Wang KC, Chiang LC, et al. Water extract of licorice had anti-viral activity against human respiratory syncytial virus in human respiratory tract cell lines [J]. J Ethnopharmacol, 2013, 148: 466-473.

[11] Yu J, Wang L, Bao L. Exploring the active compounds of tradi-

tional Mongolian medicine in intervention of novel coronavirus (COVID-19) based on molecular docking method [J]. J Funct Foods, 2020, 71: 104016.

[12] Zong Y, Ding ML, Ma ST, et al. Investigation of potential Chinese materia medica and its monomers in treatment of coronavirus disease 2019 (COVID-19) based on angiotensin converting enzyme II (ACE2) receptor [J]. Chin Tradit Herb Drugs (中草药), 2020, 51: 1123-1129.

[13] Wang H, Song HX, Wang DF, et al. Potential mechanism of Xuanfei Baidu Formula in treating new coronavirus pneumonia based on network pharmacology and molecular docking [J]. J Hainan Med Univ (海南医学院学报), 2020, 26: 1361-1372.

[14] Gong PY, Guo YJ, Li XP, et al. Exploring active compounds of Jinhua Qinggan Granules for prevention of COVID-19 based on network pharmacology and molecular docking [J]. Chin Tradit Herb Drugs (中草药), 2020, 51: 1685-1693.

[15] Junior AG, Tolouei SEL, dos Reis Livero FA, et al. Natural agents modulating ACE-2: a review of compounds with potential against SARS-CoV-2 infections [J]. Curr Pharm Des, 2021, 27: 1588-1596.

[16] Luo J, Yin N, Huang XY, et al. Study on the mechanism of aromatic traditional Chinese medicine compound on prevention and treatment of new coronavirus pneumonia [J]. J Jiangxi Univ Tradit Chin Med (江西中医药大学学报), 2020, 32: 66-73.

[17] Zeng YC, Liang SY, Jiang QQ, et al. Study on the molecular mechanism of classic prescription Huagai San against new coronavirus pneumonia (COVID-19) by network pharmacoloy [J]. Tradit Chin Drug Res Clin Pharmacol (中药新药与临床药理), 2021, 32: 484-491.

[18] Nag A, Banerjee R, Paul S, et al. Curcumin inhibits spike protein of new SARS-CoV-2 variant of concern (VOC) omicron, an *in silico* study [J]. Comput Biol Med, 2022, 146: 105552.

[19] Patel A, Rajendran M, Shah A, et al. Virtual screening of curcumin and its analogs against the spike surface glycoprotein of SARS-CoV-2 and SARS-CoV [J]. J Biomol Struct Dyn, 2022, 40: 5138-5146.

[20] Pan DB, Jang DW, Li XQ, et al. Discussion on mechanism of TCM compounds for prevention and treatment of COVID-19 based on network pharmacology and molecular docking [J]. Chin J Libr Inf Sci Tradit Chin Med (中国中医药图书情报杂志), 2022, 46: 9-16.

[21] van Breemen RB, Muchiri RN, Bates TA, et al. Cannabinoids block cellular entry of SARS-CoV-2 and the emerging variants [J]. J Nat Prod, 2022, 85: 176-184.

[22] Chen RH, Yang LJ, Hamdoun S, et al. 1, 2, 3, 4, 6-Pentagalloyl glucose, a RBD-ACE2 binding inhibitor to prevent SARS-CoV-2 infection [J]. Front Pharmacol, 2021, 12: 634176.

[23] Rajamanickam K, Rathinavel T, Periyannan V, et al. Molecular insight of phytocompounds from Indian spices and its hyaluronic acid conjugates to block SARS-CoV-2 viral entry [J]. J Biomol Struct Dyn, 2022, 41: 7386-7405.

[24] Wang X, Lin S, Tang RWL, et al. Polygoni Multiflori Radix extracts inhibit SARS-CoV-2 pseudovirus entry in HEK293T cells and zebrafish larvae [J]. Phytomedicine, 2022, 102: 154154.

[25] Mei J, Zhou Y, Yang X, et al. Active components in *Ephedra sinica* Stapf disrupt the interaction between ACE2 and SARS-CoV-2 RBD: potent COVID-19 therapeutic agents [J]. J Ethnopharmacol, 2021, 278: 114303.

[26] Aray B, Wang JQ, Zhu N, et al. Research progress on the potential mechanism of favipiravir against SARS-CoV-2 [J]. Her Med (医药导报), 2022, 41: 1651-1659.

[27] Chen ZN, Du R, Cooper L, et al. Sulforaphane is a reversible covalent inhibitor of 3-chymotrypsin-like protease of SARS-CoV-2 [J]. J Med Virol, 2023, 95: e28609.

[28] Su H, Yao S, Zhao W, et al. Identification of pyrogallol as a warhead in design of covalent inhibitors for the SARS-CoV-2 3CL protease [J]. Nat Commun, 2021, 12: 3623.

[29] Zhang RZ, Zhang HQ, Zhang YN, et al. Oridonin inhibits SARS-CoV-2 replication by targeting viral proteinase and polymerase [J]. Virol Sin, 2023, 38: 470-479.

[30] Shang ZP, Yi Y, Yu R, et al. Bioactive compounds of Jingfang Granules against SARS-CoV-2 virus proteases $3CL^{pro}$ and PL^{pro} [J]. J Peking Univ Health Sci (北京大学学报 医学版), 2022, 54: 907-919.

[31] Xu H, Li S, Liu J, et al. Bioactive compounds from Huashi Baidu decoction possess both antiviral and anti-inflammatory effects against COVID-19 [J]. Proc Natl Acad Sci U S A, 2023, 120: e2301775120.

[32] Kumar N, Xin Z, Liang Y, et al. NF-κB signaling differentially regulates influenza virus RNA synthesis [J]. J Virol, 2008, 82: 9880-9889.

[33] Kwon EB, Li W, Kim YS, et al. Vitisin B inhibits influenza A virus replication by multi-targeting neuraminidase and virus-induced oxidative stress [J]. Acta Pharm Sin B, 2023, 13: 174-191.

[34] Ma C, Li Y, Zong Y, et al. p21 restricts influenza A virus by perturbing the viral polymerase complex and upregulating type I interferon signaling [J]. PLoS Pathogens, 2022, 18: e1010295.

[35] Abian O, Ortega-Alarcon D, Jimenez-Alesanco A, et al. Structural stability of SARS-CoV-2 3CLpro and identification of quercetin as an inhibitor by experimental screening [J]. Int J Biol Macromol, 2020, 164: 1693-1703.

[36] Gu YY, Zhang M, Cen H, et al. Quercetin as a potential treatment for COVID-19-induced acute kidney injury: based on network pharmacology and molecular docking study [J]. PLoS One, 2021, 16: e0245209.

[37] Enmozhi SK, Raja K, Sebastine I, et al. Andrographolide as a potential inhibitor of SARS-CoV-2 main protease: an *in silico* approach [J]. J Biomol Struct Dyn, 2021, 39: 3092-3098.

[38] Du R, Cooper L, Chen Z, et al. Discovery of chebulagic acid and

punicalagin as novel allosteric inhibitors of SARS-CoV-2 $3CL^{pro}$ [J]. Antiviral Res, 2021, 190: 105075.

[39] Wu Q, Yan S, Wang Y, et al. Discovery of 4′-*O*-methylscutellarein as a potent SARS-CoV-2 main protease inhibitor [J]. Biochem Biophys Res Commun, 2022, 604: 76-82.

[40] Srinivasan V, Brognaro H, Prabhu PR, et al. Antiviral activity of natural phenolic compounds in complex at an allosteric site of SARS-CoV-2 papain-like protease [J]. Commun Biol, 2022, 5: 805.

[41] Battles MB, McLellan JS. Respiratory syncytial virus entry and how to block it [J]. Nat Rev Microbiol, 2019, 17: 233-245.

[42] Blockus S, Sake SM, Wetzke M, et al. Labyrinthopeptins as virolytic inhibitors of respiratory syncytial virus cell entry [J]. Antiviral Res, 2020, 177: 104774.

[43] Umeoguaju FU, Ephraim-Emmanuel BC, Patrick-Iwuanyanwu KC, et al. Plant-derived food grade substances (PDFGS) active against respiratory viruses: a systematic review of non-clinical studies [J]. Front Nutr, 2021, 8: 606782.

[44] Li P, Du R, Chen Z, et al. Punicalagin is a neuraminidase inhibitor of influenza viruses [J]. J Med Virol, 2021, 93: 3465-3472.

[45] Li P, Du R, Wang Y, et al. Identification of chebulinic acid and chebulagic acid as novel influenza viral neuraminidase inhibitors [J]. Front Microbiol, 2020, 11: 182.

[46] Sithisarn P, Michaelis M, Schubert-Zsilavecz M, et al. Differential antiviral and anti-inflammatory mechanisms of the flavonoids biochanin A and baicalein in H5N1 influenza A virus-infected cells [J]. Antiviral Res, 2013, 97: 41-48.

[47] Dai YJ, Wan SY, Gong SS, et al. Recent advances of traditional Chinese medicine on the prevention and treatment of COVID-19 [J]. Chin J Nat Med, 2020, 18: 881-889.

[48] Laphanuwat P, Jirawatnotai S. Immunomodulatory roles of cell cycle regulators [J]. Front Cell Dev Biol, 2019, 7: 23.

[49] Richard SA. Exploring the pivotal immunomodulatory and anti-inflammatory potentials of glycyrrhizic and glycyrrhetinic acids [J]. Mediators Inflamm, 2021, 2021: 6699560.

[50] Luo Z, Liu LF, Wang XH, et al. Epigoitrin, an alkaloid from Isatis indigotica, reduces H1N1 infection in stress-induced susceptible model *in vivo* and *in vitro* [J]. Front Pharmacol, 2019, 10: 78.

[51] Chu M, Xu L, Zhang M, et al. Role of Baicalin in anti-influenza virus A as a potent inducer of IFN-gamma [J]. BioMed Res Int, 2015, 2015: 263630.

[52] Zhan YC, Qin S, Chen F. Study on effect and mechanism of baicalin on antiviral effects about respiratory syncytial virus [J]. Int J Lab Med (国际检验医学杂志), 2017, 38: 1907-1909.

[53] Zhang P, Peng HJ, Gao CL, et al. Effects of baicalin on the expression of I -IFN and SOCS1/3 in RSV infected rats [J]. China J Tradit Chin Med Pharm (中华中医药杂志), 2018, 33: 328-332.

[54] Li R, Wang L. Baicalin inhibits influenza virus A replication *via* activation of type I IFN signaling by reducing miR-146a [J]. Mol Med Rep, 2019, 20: 5041-5049.

[55] Song J, Zhang L, Xu Y, et al. The comprehensive study on the therapeutic effects of baicalein for the treatment of COVID-19 *in vivo* and *in vitro* [J]. Biochem Pharmacol, 2021, 183: 114302.

[56] Tao Z, Chen J, Su J, et al. Quantitative proteomics analysis of systemic responses and biological mechanisms of Shu Feng Jie Du capsule using H1N1-infected RAW264. 7 cells [J]. ACS Omega, 2020, 5: 15417-15423.

[57] Li Y, Chang N, Han Y, et al. Anti-inflammatory effects of Shufeng Jiedu capsule for upper respiratory infection *via* the ERK pathway [J]. Biomed Pharmacother, 2017, 94: 758-766.

[58] Ma Q, Li R, Pan W, et al. Phillyrin (KD-1) exerts anti-viral and anti-inflammatory activities against novel coronavirus (SARS-CoV-2) and human coronavirus 229E (HCoV-229E) by suppressing the nuclear factor kappa B (NF-κB) signaling pathway [J]. Phytomedicine, 2020, 78: 153296.

[59] Yan H, Wang H, Ma L, et al. Cirsimaritin inhibits influenza A virus replication by downregulating the NF-κB signal transduction pathway [J]. Virol J, 2018, 15: 88.

[60] Zhao L, Liu H, Wang Y, et al. Multimodal identification by transcriptomics and multiscale bioassays of active components in Xuanfei Baidu formula to suppress macrophage-mediated immune response [J]. Engineering, 2021, 20: 63-76.

[61] Zhang QX, Chen JK, Wu LL. Quercetin inhibits the apoptosis and inflammatory response of respiratory syncytial virus-infected bronchial epithelial cells by up-regulating miR-140-5p [J]. J Immunol (免疫学杂志), 2022, 38: 883-889.

[62] Liu C, Wu X, Bing X, et al. H1N1 influenza virus infection through NRF2-KEAP1-GCLC pathway induces ferroptosis in nasal mucosal epithelial cells [J]. Free Radic Biol Med, 2023, 204: 226-242.

[63] Zheng W, Wu H, Wang T, et al. Quercetin for COVID-19 and DENGUE co-infection: a potential therapeutic strategy of targeting critical host signal pathways triggered by SARS-CoV-2 and DENV [J]. Brief Bioinform, 2021, 22: bbab199.

[64] Liu T, Zang N, Zhou N, et al. Resveratrol inhibits the TRIF-dependent pathway by upregulating sterile alpha and armadillo motif protein, contributing to anti-inflammatory effects after respiratory syncytial virus infection [J]. J Virol, 2014, 88: 4229-4236.

[65] Wang HJ, Han YJ, Zhang XX, et al. Study on the mechanism of Lianhua Qingwen capsule absorbed components in prevention and treatment of COVID-19 by intervening on cytokines storm based on network pharmacology and molecular docking [J]. Nat Prod Res Dev (天然产物研究与开发), 2021, 33: 1957-1968.

[66] Li J, Zhou B, Li C, et al. Lariciresinol-4-*O*-β-*D*-glucopyranoside from the root of *Isatis indigotica* inhibits influenza A virus-induced pro-inflammatory response [J]. J Ethnopharmacol, 2015, 174: 379-386.

[67] Talukdar J, Bhadra B, Dattaroy T, et al. Potential of natural astaxanthin in alleviating the risk of cytokine storm in COVID-19 [J]. Biomed Pharmacother, 2020, 132: 110886.

[68] Zhuang L, Chen LF, Zhang YB, et al. Watsonianone A from Rhodomyrtus tomentosa fruit attenuates respiratory-syncytial-virus-induced inflammation *in vitro* [J]. J Agric Food Chem, 2017, 65: 3481-3489.

[69] Deng DY. Study on the Effect and Immunomodulatory Mechanism of Luteolin on Influenza Virus H1N1 Infected A549 Cells (木犀草素对流感病毒H1N1感染A549细胞的作用及免疫调节机制的研究) [D]. Beijing: Beijing University of Chinese Medicine, 2017.

[70] Wang HJ, Li S, Lian R, et al. Antiviral effect *in vitro* and mechanism study based on type I interferon pathway of berbamine [J]. Drug Eval Res (药物评价研究), 2023, 46: 1185-1192.

[71] Xia QD, Xun Y, Lu JL, et al. Network pharmacology and molecular docking analyses on Lianhua Qingwen capsule indicate Akt1 is a potential target to treat and prevent COVID-19 [J]. Cell Prolif, 2020, 53: e12949.

[72] Ren Y, Yao MC, Huo XQ, et al. Study on treatment of "cytokine storm" by anti-2019-nCoV prescriptions based on arachidonic acid metabolic pathway [J]. China J Chin Mater Med (中国中药杂志), 2020, 45: 1225-1231.

[73] Gowda P, Patrick S, Joshi S D, et al. Glycyrrhizin prevents SARS-CoV-2 S1 and Orf3a induced high mobility group box 1 (HMGB1) release and inhibits viral replication [J]. Cytokine, 2021, 142: 155496.

[74] Wang P, Jin L, Zhang M, et al. Blood-brain barrier injury and neuroinflammation induced by SARS-CoV-2 in a lung-brain microphysiological system [J]. Nat Biomed Eng, 2023. DOI: 10.1038/s41551-023-01054-w.

[75] Russell MW, Mestecky J. Mucosal immunity: the missing link in comprehending SARS-CoV-2 infection and transmission [J]. Front Immunol, 2022, 13: 957107.

[76] Li F, Huang Q, Zhou Z, et al. Gold nanoparticles combat enveloped RNA virus by affecting organelle dynamics [J]. Signal Transduct Target Ther, 2023, 8: 285.