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Review Article

Research Progress of Chinese Medicine against Neo-Coronavirus

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ABSTRACT

Background: A review was conducted on the anti-SARS-CoV-2 virus (SARS-CoV-2) resistance of Chinese herbal medicine monomers or active ingredients to provide a basis for elucidating the anti-SARS-CoV-2 virus mechanism of Chinese medicine from the perspective of material basis.

Method: Literature research was used to summarize the application of herbal monomers or active ingredients in the antagonism of the SARS-CoV-2 virus and analyze the problems.

Discussion: A variety of herbal monomers or active ingredients were found to have antagonistic effects against the SARS-CoV-2 virus, and on this basis, a strategy for the discovery of active compounds against the SARS-CoV-2 virus was proposed.

Conclusion: Effective drugs against the SARS-CoV-2 virus were discovered from different perspectives, providing a reference for the discovery of effective substances against the SARS-CoV-2 virus from traditional Chinese medicine.

Keywords: SARS-CoV-2; COVID-19; New crown pneumonia; Herbal medicine; Active ingredient

INTRODUCTION

New coronary pneumonia (COVID-19) has spread worldwide, seriously endangering human health, and interfering with the normal life of people around the world. The treatment of COVID-19 still has no specific drugs and is mainly symptomatic. Chinese medicine has played an outstanding role in the fight against COVID-19 in the world. By analyzing the monomers and active components of these drugs and elucidating the targets and mechanisms of action of Traditional Chinese Medicine (TCM) prescriptions involved in the treatment of COVID-19, we can help develop more drugs and targets to inhibit the development and spread of COVID-19. In this paper, we discuss the mechanisms of action of several effective herbal monomers and active ingredients, and on this basis, we propose a strategy for the discovery of anti-SARS-CoV-2 active compounds as a way to discuss the positive implications of TCM for the treatment of COVID-19.

LITERATURE REVIEW

Overview of coronavirus

Coronaviruses are RNA viruses with a capsid and a linear single-stranded positive-stranded genome. Four structural proteins are required for the assembly of viral particles and infection of

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Coronaviruses: The stinging glycoprotein (S protein), which is the key and main antigenic site for viral adhesion to host receptors; the small envelope glycoprotein (E protein), which is involved in the assembly and release of viruses and is required for pathogenesis; and the membrane glycoprotein (M protein), which is responsible for the transport of nutrients across the membrane, the release of nascent viral outgrowth and the formation of the viral outer envelope. Protein: Contains 2 structural domains, both of which bind to the viral RNA genome by different mechanisms and package the wrapped genome into viral particles [1]. The N protein is also an antagonist of the Viral-Encoded Suppressor (VSR) of interferon and RNA interference (RNAi), which facilitates viral replication [2]. In addition to these four major structural proteins, different Corona viruses encode specific structural and accessory proteins, such as HE protein, 3a/b protein, and 4a/b protein [3]. The process of coronavirus infection of host cells includes the adsorption invasion, gene synthesis, mature virus packaging and virus release, of which the most important way is the receptor-mediated membrane fusion pathway [4], and different types of Coronaviruses bind to different functional receptors with some species specificity [5]. The receptor for SARS-CoV and SARSCoV-2, which belongs to the same β coronavirus genus, is Angiotensin-Converting Enzyme II (ACE2), and the gene sequence homology of the Receptor Structural Domain (RDB) of the two viruses is high [6]. SARS-CoV and SARS-CoV-2 enter the host cell, translate the 3C-Like protease (3CLpro) required for viral replication, and rely on the virus' own RNA-dependent RNA polymerase (RdRp) for the replication process, thus 3CLpro and RdRp play a key role in the viral infection process [7]. The study of anti-coronavirus drugs can be divided into nucleic acid synthesis agents, protease inhibitors, RNA polymerase inhibitors, membrane fusion inhibitors, and complex inhibitors [8].

Mechanism of Chinese medicine interfering with the normal physiological function of neo-coronavirus and inhibiting viral replication and transcription

A new coronavirus is a single-stranded RNA virus, which belongs to the coronavirus family, and its replication and transcription require the joint participation of several active enzymes. Among them, 3CLpro, a cysteine protease, is highly conserved in neo-coronaviruses and has no human homologue, making it a very promising drug target for Coronaviruses [9]. In most of the currently known Coronaviruses, 3CLpro hydrolytie cleavage is a key step in viral replication and, therefore, it is referred to as the main protease. By interacting with the two catalytic residues of 3CLpro (the critical S1/S2 subsite and the oxygen anion ring), baicalein contained in *Scutellaria baicalensis* can bind to 3CLpro to inhibit viral replication [10]. *Glycyrrhiza glabra*, an herb included in most remedies, has been found to inhibit virus replication *in vitro* in the treatment of influenza viruses [11]. The plant protein glycyrrhizin A, derived from glycyrrhizin, can play an important role in inhibiting viral replication inside the cell after the new coronavirus enters the host cell [12]. The active ingredients in Jinhua Qingxian Granules and Xuanlung Defeat Toxin Formula, such as lenoside, ephedrine, and lignan, can bind to 3CLpro to inhibit the replication and transcription of neo-coronavirus, while lenoside can reduce the cytokines (IL-6, IL-1β, etc.,) released by host cells during immune activity, thus having antiviral activity, and both together are used in the clinical treatment of neo-coronavirus pneumonia [13]. New Coronaviruses have four structural proteins, including small envelope glycoprotein (envelope, E), spike protein (spike, S), nucleocapsid protein (nucleocapsid, N), and membrane glycoprotein (membrane, M)[9]. Inhibition of the binding of these proteins to ACE2 prevents coronavirus from entering the host cell and, therefore, becomes a research direction for the treatment of neo-coronavirus pneumonia. Modern medical studies have demonstrated that loss of ACE2 function is associated with acute lung injury; therefore, virus-induced down regulation of ACE2 expression may be important for disease pathology, and ephedrine can effectively prevent the binding of S proteins on neo-coronavirus to ACE2 and reduce viral damage to the body [14]. Also, glycyrrhizin in licorice interferes with the binding of the virus and ACE2 protein receptor [11]. Network pharmacological analysis has shown that quercetin, kaempferol, lignan, flavonoids, and phytosterol, the active ingredients contained in chemistry dampness and toxicity granules and Xuanlung defeat formula, are able to bind to ACE2, thus acting as a treatment for new coronavirus pneumonia [15]. New Corona viruses need to attach to the surface receptors of the target cells before they can fuse with the host membrane to complete the infection. In order to attach to the corresponding surface receptor, the S protein of the neo-coronavirus needs at least one corresponding receptor binding domain to ensure that it can bind to the receptor on the surface of the host cell. For cell membrane fusion after attachment, at least one host cell-derived protease is required to facilitate the fusion of the viral capsid protein with the host cell membrane by helping to solubilize the neo-coronavirus S protein into the corresponding S1 and S2 subunits [16]. Studies have shown that when TMPRSS2 is expressed in host cells, it activates the receptor binding domain of S protein and helps neo-coronavirus to successfully attach to host cell surface receptors, while 18β-glycyrrhetinic acid, the main component in licorice, can effectively inhibit the expression of TMPRSS2 in host cells, reduce the virus attached to the surface of target cells and decrease the probability of virus invasion into the target cells [17].

Mechanisms by which herbal medicine attenuates infection and inflammation-related processes

Studies have demonstrated that in neo-coronavirus-infected airway epithelial tissue cells, the virus can bind to TLR and activate the MAPK pathway. The activation of this pathway causes a high degree of strengthening of the body's immune system, which produces various inflammatory mediators in response to the invading virus, a process known as a "cytokine storm" [18]. The "cytokine storm" is characterized by the release of high levels of cytokines such as IL-6, IL-1β, and TNF-α, and is one of the main pathological features of patients with severe neo coronary pneumonia [19]. The high expression of IL-6 in the serum of patients with neo coronary pneumonia also exacerbates

inflammation and tissue damage, leading to clinical responses such as acute respiratory distress syndrome and multi-organ failure, which becomes an important factor in the high mortality rate of neo coronary pneumonia and complications of related diseases. Studies have shown that hemophilic acid injection can regulate the arachidonic acid metabolic pathway and reduce inflammatory cytokine secretion. In addition, glycyrrhizin in Mahjang Shigang Tang acts on the NOD-like signaling pathway and TLR signaling pathway to regulate the immune response and inhibit IL-6 and TNF expression to prevent cytokine storm [20]. Another herbal medicine, Liushen capsule, can reduce the mRNA expression of TNF-α, IL-6, and IL-1β, thus resisting the effect of "cytokine storm" and effectively reducing the occurrence of malignant clinical reactions and mortality in patients with neo colitis [21]. The data show that the immune response is relatively delayed in patients with neo colitis, so the recovery process is longer. Neutrophil and monocyte dysfunction often cause the production of the anti-inflammatory cytokine IL-10. The production of large amounts of anti-inflammatory cytokines interferes with the normal rejection function of the immune system and prevents the body from exerting an immune effect against invading microorganisms, a process known as immune paralysis, which greatly increases the mortality rate of patients [22]. On the other hand, overexpression of IL-6 and IL-1β can similarly lead to problems in the immune aspect of the body [23]. Chinese herbs can modulate the immune system and effectively alleviate the development of immune abnormal diseases. Glycyrrhizic acid in licorice can regulate the activation and balance of T cells and modulate immune responses; many water-soluble polysaccharides in Clear Lung Detox Soup have various immunomodulatory biological activities, such as licorice polysaccharides that promote the maturation, differentiation, and multiplication of lymphocytes, macrophages, and immune cells [24]. The herb, *Glycyrrhiza glabra*, contains a variety of potent bioactive components that not only interferes with neo-coronavirus infection and replication by binding to ACE2 and 3CLpro, but also modulate the immune system so that it exhibits efficient anti-neo-coronavirus activity [25]. The active ingredient of the Chinese herb lithospermum, has the ability to inhibit the migration of RNP from the nucleus to the cytoplasm of the SARS-CoV-2 virus; prevent the extension of viral polyprotein during migration; inhibit TNF-α production; and inhibit the replication of viral RNA [26].

The active ingredients of the Chinese herb rooibos, lisinopine [27], and the active ingredients of the Chinese herbs by Wu, et al. [28], N-cis-ferulic acid acyl tyramine, have antagonistic effects against SARS-CoV-2 virus. Lignan, the active ingredient of the Chinese herbal medicine's honeysuckle, chrysanthemum, and thornbush, has the ability to inhibit SARS-CoV-2 virus replication by regulating 3CL protease [29]. Quercetin, the active ingredient of the Chinese herbs *Glycyrrhiza glabra*, Chai Hu, *Morus alba*, *Rhizoma spinosae*, and *Fritillariae*, has the ability to inhibit SARS-CoV-2 virus replication by regulating 3CL protease [30]. The active constituents of the Chinese herbs honeysuckle, *Zanthoxylum*, kanga, and *Forsythia* have the ability to inhibit SARS-CoV-2 virus replication by regulating the 3CL protease [30]. Glycyrrhizic acid, the active ingredient in the Chinese herb licorice, may indirectly inhibit SARS-CoV-2 virus replication by inducing cellular synthesis of nitric oxide [31].

DISCUSSION

Strategies for the recovery of active substances in anti-SARS-CoV-2 virus herbal medicines

SARS-CoV-2 virus is a novel pathogenic β-coronavirus with the largest known viral RNA genome and high genetic sequence similarity to six previously discovered human pathogenic Corona viruses, with 80% similarity to SARS-CoV-2 coronavirus in 2002 and about 50% similarity to MERS-CoV [32], and Zhou, et al. [33], studies have shown that the receptor for SARS-CoV-2 entry into cells is Angiotensin-Converting Enzyme 2 (ACE2) like SARS-CoV-2. Therefore, we can draw reference from the experience of drug development for SARS-CoV-2, MERs-CoV, and screen the active ingredients from the existing anti-MERS or SARS activities on the one hand, and screen the new active ingredients or components of anti-SARS-CoV-2 Chinese medicine according to the pathway and mechanism of virus inhibition on the other hand.

Screening study of active compounds that inhibit virus entry into host cells

Studies have shown that spike-protein (spike protein) is a key protein for coronavirus to bind to ACE2 receptors on the host cell surface and thus mediates viral invasion into host cells [34], and is an important target for antibody and drug development. *In vitro* studies have shown that the spike glycoprotein of ACE2 is closely related to its activity, and when spike protein expression is reduced, ACE2 activity is significantly reduced, and it is speculated from the currently available laboratory data that ACE2 expression/activity levels may be positively correlated with the risk of coronavirus infection and negatively correlated with the degree of lung injury after coronavirus infection, and therefore regulation of the RAS system is also important screening pathway. Astragaloside, ginsenoside Rg3, and betaine have been reported to have RAS-modulating effects [35-37].

Screening study of active compounds to inhibit SARS-CoV-2 virus replication

During the process of coronavirus infestation of host cells, the viral polypeptide is cleaved by enzymatic cleavage into nonstructural components capable of forming new viruses. SARS-CoV-2 virus, in addition to the stinging protein, four other nonstructural proteins: 3-trypsin-like protease, papain-like protease, decamping enzyme, and RNA-dependent RNA polymerase play critical roles in virus proliferation and are important targets for the development of antiviral drugs to control viral replication and proliferation [38]. It has also been shown that the cellular protease TMPRSS2 is used for SARS-CoV-2 initiation and TMPRSS2 inhibitors block entry and may be a choice for therapeutic agents [39].

Screening of compounds with indirect anti-SARS-CoV-2 viral effects such as anti-inflammatory immunomodulation

Since viruses often stimulate the production of various inflammatory mediators and reduce human immunity after the invasion, they can play an indirect antiviral role by inhibiting the release of inflammatory mediators, regulating the overall immune function, and preventing cytopathic lesions caused by viral infections. The current clinical investigation of COVID-19 has shown that the severity of pneumonia correlates with the intensity of the viral and organismal inflammatory response, and that an excessive inflammatory response in patients, i.e., a "cytokine storm", may lead to serious consequences or even death [40]. Therefore, in addition to direct antiviral effects, modulation of immune function and inhibition of inflammatory factor release are also important indicators for the screening of anti-SARS-CoV-2 active ingredients.

CONCLUSION

In summary, most of the active ingredients of traditional Chinese medicine have broad-spectrum antiviral effects, and their antiviral mechanisms include both direct antiviral effects such as preventing viruses from entering cells and disrupting viral replication, and indirect antiviral effects through modulating the immune capacity of the body or blocking signal transduction pathways closely related to viral infection. The research and development of new anti-SARS-CoV-2 viral drugs or lead compounds from traditional Chinese medicine have a broad prospect. With the in-depth understanding of SARS-CoV-2 virus properties and host-virus interactions, more viral and host proteins can be identified as drug targets, and virtual screening can be performed by computer-aided drug design to establish high-throughput screening methods for these new drug targets to screen the active ingredients or components of anti-SARS-CoV-2 Chinese medicine, and multiple monomers can be selected according to the pathways and mechanisms of virus inhibition. It is also possible to select multiple monomers or components for orderly combination according to the different pathways and mechanisms of viral inhibition, and integrate them into multi-effective combinations, providing a basis and reference for the development of anti-SARS-CoV-2 specific drugs.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1. Fehr AR, Perlman S. Coronaviruses: An overview of their replication and pathogenesis. Methods Mol Biol. 2015;1282:1-23.
2. Cui L, Wang H, Ji Y, Yang J, Xu S, Huang X, et al. The nucleocapsid protein of coronaviruses acts as a viral suppressor of RNA silencing in mammalian cells. J Virol. 2015;89(17):9029-9043.
3. Chen Y, Liu Q, Guo D. Emerging coronaviruses: Genome structure, replication, and pathogenesis. J Med Virol. 2020;92(4):418-423.
4. Papagerakis S, Said R, Ketabat F, Mahmood R, Pundir M, Lobanova L, et al. When the clock ticks wrong with COVID-19. Clin Transl Med. 2022;12(11):e949.
5. Yi J, Miao J, Zuo Q, Owusu F, Dong Q, Lin P, et al. COVID-19 pandemic: A multidisciplinary perspective on the pathogenesis of a novel coronavirus from infection, immunity and pathological responses. Front Immunol. 2022;13:4779.
6. Cascella M, Rajnik M, Aleem A, Dulebohn SC, Di Napoli R. Features, evaluation, and treatment of coronavirus (COVID-19). Statpearls. 2022.
7. Rahmah L, Abarikwu SO, Arero AG, Essouma M, Jibril AT, Fal A, et al. Oral antiviral treatments for COVID-19: Opportunities and challenges. Pharmacol Rep. 2022;74(6):1255-1278.
8. Kumari M, Lu RM, Li MC, Huang JL, Hsu FF, Ko SH, et al. A critical overview of current progress for COVID-19: Development of vaccines, antiviral drugs, and therapeutic antibodies. J Biomed Sci. 2022;29(1):68.
9. Li L, Wu Y, Wang J, Yan H, Lu J, Wang Y, et al. Potential treatment of COVID-19 with traditional chinese medicine: What herbs can help win the battle with SARS-CoV-2?. Engineering. 2021;19:139-152.
10. Su HX, Yao S, Zhao WF, Li MJ, Liu J, Shang WJ, et al. Anti-SARS-CoV-2 activities *in vitro* of Shuanghuanglian preparations and bioactive ingredients. Acta Pharmacol Sin. 2020;41(9):1167-1177.
11. Michaelis M, Geiler J, Naczk P, Sithisarn P, Ogbomo H, Altenbrandt B, et al. Glycyrrhizin inhibits highly pathogenic H5N1 influenza A virus-induced pro-inflammatory cytokine and chemokine expression in human macrophages. Med Microbiol Immunol. 2010;199:291-297.
12. Hoever G, Baltina L, Michaelis M, Kondratenko R, Baltina L, Tolstikov GA, et al. Antiviral activity of glycyrrhizic acid derivatives against SARS−coronavirus. J Med Chem. 2005;48(4):1256-1259.
13. Zhang ZJ, Wu WY, Hou JJ, Zhang LL, Li FF, Gao L, et al. Active constituents and mechanisms of respiratory detox shot, a traditional Chinese medicine prescription, for COVID-19 control and prevention: Network-molecular docking-LC-MSE analysis. J Integr Med. 2020;18(3):229-241.
14. Lv Y, Wang S, Liang P, Wang Y, Zhang X, Jia Q, et al. Screening and evaluation of anti-SARS-CoV-2 components from Ephedra sinica by ACE2/CMC-HPLC-IT-TOF-MS approach. Anal Bioanal Chem. 2021;413:2995-3004.
15. Zheng S, Baak JP, Li S, Xiao W, Ren H, Yang H, et al. Network pharmacology analysis of the therapeutic mechanisms of the traditional Chinese herbal formula Lian Hua Qing Wen in Corona Virus Disease 2019 (COVID-19), gives fundamental support to the clinical use of LHQW. Phytomedicine. 2020;79:153336.
16. Saghazadeh A, Rezaei N. Towards treatment planning of COVID-19: Rationale and hypothesis for the use of multiple immunosuppressive agents: Anti-antibodies, immunoglobulins, and corticosteroids. Int Immunopharmacol. 2020;84:106560.
17. Sun Y, Jiang M, Park PH, Song K. Transcriptional suppression of androgen receptor by 18β-glycyrrhetinic acid in LNCaP human prostate cancer cells. Arch Pharm Res. 2020;43:433-448.
18. An X, Zhang Y, Duan L, Jin D, Zhao S, Zhou R, et al. The direct evidence and mechanism of traditional Chinese medicine treatment of COVID-19. Biomed Pharmacother. 2021;137:111267.
19. Turnquist C, Ryan BM, Horikawa I, Harris BT, Harris CC. Cytokine storms in cancer and COVID-19. Cancer Cell. 2020;38(5):598-601.
20. Li Y, Chu F, Li P, Johnson N, Li T, Wang Y, et al. Potential effect of Maxing Shigan decoction against Coronavirus Disease 2019 (COVID-19) revealed by network pharmacology and experimental verification. J Ethnopharmacol. 2021;271:113854.

21. Ma Q, Pan W, Li R, Liu B, Li C, Xie Y, et al. Liu Shen capsule shows antiviral and anti-inflammatory abilities against novel coronavirus SARS-CoV-2 *via* suppression of NF-κB signaling pathway. Pharmacol Res. 2020;158:104850.
22. Shang J, Wan Y, Luo C, Ye G, Geng Q, Auerbach A, et al. Cell entry mechanisms of SARS-CoV-2. Proc Natl Acad Sci. 2020;117(21):11727-11734.
23. Giamarellos-Bourboulis EJ, Netea MG, Rovina N, Akinosoglou K, Antoniadou A, Antonakos N, et al. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. Cell Host Microbe. 2020;27(6):992-1000.
24. Cao P, Wu S, Wu T, Deng Y, Zhang Q, Wang K, et al. The important role of polysaccharides from a traditional Chinese medicine-Lung cleansing and detoxifying decoction against the COVID-19 pandemic. Carbohydr Polym. 2020;240:116346.
25. Ren X, Shao XX, Li XX, Jia XH, Song T, Zhou WY, et al. Identifying potential treatments of COVID-19 from Traditional Chinese Medicine (TCM) by using a data-driven approach. J Ethnopharmacol. 2020;258:112932.
26. Li SY, Chen C, Zhang HQ, Guo HY, Wang H, Wang L, et al. Identification of natural compounds with antiviral activities against SARS-associated coronavirus. Antiviral Res. 2005;67(1):18-23.
27. Liu J, Yang Y, Xu Y, Ma C, Qin C, Zhang L. Lycorine reduces mortality of human enterovirus 71-infected mice by inhibiting virus replication. Virol J. 2011;8(1):1-9.
28. Wu CY, Jan JT, Ma SH, Kuo CJ, Juan HF, Cheng YS, et al. Small molecules targeting severe acute respiratory syndrome human coronavirus. Proc Natl Acad Sci. 2004;101(27):10012-10017.
29. Pillaiyar T, Manickam M, Namasivayam V, Hayashi Y, Jung SH. An Overview Of Severe Acute Respiratory Syndrome–Coronavirus (SARS-CoV) 3CL protease inhibitors: Peptidomimetics and small molecule chemotherapy. J Med Chem. 2016;59(14):6595-6628.
30. Chen L, Li J, Luo C, Liu H, Xu W, Chen G, et al. Binding interaction of quercetin-3-β-galactoside and its synthetic derivatives with SARS-CoV 3CLpro: Structure-activity relationship studies reveal salient pharmacophore features. Bioorg Med Chem. 2006;14(24):8295-8306.
31. Cinatl J, Morgenstern B, Bauer G, Chandra P, Rabenau H, Doerr H. Glycyrrhizin, an active component of liquorice roots, and replication of SARS-associated coronavirus. Lancet. 2003;361(9374):2045-2046.
32. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: Implications for virus origins and receptor binding. Lancet. 2020;395(10224):565-574.
33. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270-273.
34. Xu X, Chen P, Wang J, Feng J, Zhou H, Li X, et al. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. Sci China Life Sci. 2020;63:457-460.
35. Perkins GD, Ji C, Connolly BA, Couper K, Lall R, Baillie JK, et al. Effect of noninvasive respiratory strategies on intubation or mortality among patients with acute hypoxemic respiratory failure and COVID-19: The RECOVERY-RS randomized clinical trial. JAMA. 2022;327(6):546-558.
36. Matsuishi Y, Mathis BJ, Shimojo N, Subrina J, Okubo N, Inoue Y. Severe COVID-19 infection associated with endothelial dysfunction induces multiple organ dysfunction: A review of therapeutic interventions. Biomedicines. 2021;9(3):279.
37. Tian ZH, Weng JT, Shih LJ, Siao AC, Chan TY, Tsuei YW, et al. Arecoline inhibits the growth of 3T3-L1 preadipocytes *via* AMP-activated protein kinase and reactive oxygen species pathways. PLoS One. 2018;13(7):e0200508.
38. Li G, Hilgenfeld R, Whitley R, de Clercq E. Therapeutic strategies for COVID-19: Progress and lessons learned. Nat Rev Drug Discov. 2023;22(6):1-27.
39. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181(2):271-280.
40. Zhou H, Fang Y, Xu T, Ni WJ, Shen AZ, Meng XM. Potential therapeutic targets and promising drugs for combating SARS-CoV-2. Br J Pharmacol. 2020;177(14):3147-3161.