Cardiovascular protection in the pandemic and post-COVID-19 era

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Abstract

This article introduces briefly current status of the Covid-19 pandemic and discusses "antidotes" of coronavirus (SARS-CoV-2 and its variants), that is, "ISISI" barriers from locals, nations or regions to the globe, namely, [Isolation with Masks, Unit protective clothing, Stay at "home", and Travel restriction (MUST); Screening and testing; Individual immunity by healthy E(e)SEEDi lifestyle, bio-agents (chemical agents, convalescent plasma, neutralizing antibody, and Chinese medicine), and vaccination; Social and medical supports; International cooperation and information sharing]. Since there are several major coronavirus variants with more infectious, such as Delta and Omicron, many more cases with cardiac injury and cardiac arrest need better cardiovascular prevention and protection. With further understanding of the pathogenesis of Covid-19 and development of novel mRNA vaccines and discovery of new antiviral drugs, such as Molnupiravir and Paxlovid, people will do better in fighting against SARS-CoV-2 and its variants and cardiovascular protection in the pandemic and post-Covid-19 era.

Review

Cardiovascular protection in the pandemic and post-COVID-19 era

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Abstract

This article introduces briefly current status of the Covid-19 pandemic and discusses "antidotes" of coronavirus (SARS-CoV-2 and its variants), that is, "ISISI" barriers from locals, nations or regions to the globe, namely, [Isolation with Masks, Unit protective clothing, Stay at "home", and Travel restriction (MUST); Screening and testing; Individual immunity by healthy E(e)SEEDi lifestyle, bio-agents (chemical agents, convalescent plasma, neutralizing antibody, and Chinese medicine), and vaccination; Social and medical supports; International cooperation and information sharing]. Since there are several major coronavirus variants with more infectious, such as Delta and Omicron, many more cases with cardiac injury and cardiac arrest need better cardiovascular prevention and protection. With further understanding of the pathogenesis of Covid-19 and development of novel mRNA vaccines and discovery of new antiviral drugs, such as Molnupiravir and Paxlovid, people will do better in fighting against SARS-CoV-2 and its variants and cardiovascular protection in the pandemic and post-Covid-19 era.

Keywords:

cardiovascular protection | Covid-19 | E(e)SEEDi | "ISISI" | post-Covid-19 era

1 | INTRODUCTION

Since the World Health Organization (WHO) declared the Covid-19 pandemic, it has spread rapidly in more than 200 countries. The Covid-19 pandemic in the globe was far more severe than the 2003 SARS in China due to transmission in multiple ways. So far (April 5, 2022), there were more than 489.77 million confirmed cases and over 6.15 million deaths in countries worldwide. And these data are still climbing since there are more emerging coronavirus variants (Table 1), which include Delta and Omicron with more transmissible, infectious, and severe. Hence, the SARS-CoV-2 and its variants are the strong "enemy" of humankind. It can be said that "active Covid-19, painful world". Then, how to effectively fight against coronavirus and Covid-19? Are there some reliable "antidotes"? How to do better cardiovascular protection and prevention during the pandemic and post-Covid-19 era?

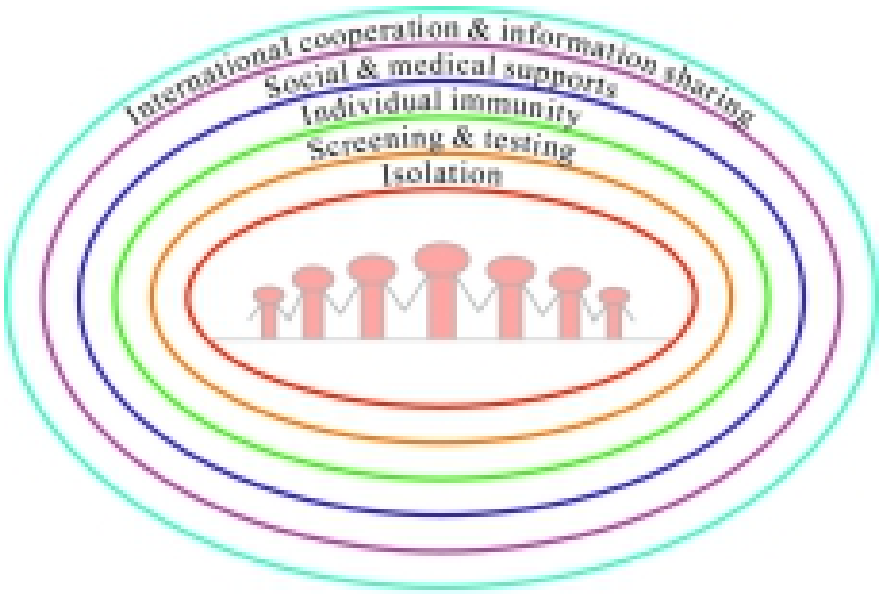

Figure 1 "ISISI" Barriers for Fighting Against Coronavirus (SARS-CoV-2 and Its Variants) and Covid-19. As solid barriers, the "ISISI" strategies should be conducted positively from locals, nations or regions to the globe so as to combat better the Covid-19 pandemic.

2 | "ISISI" BARRIERS AS "ANTIDOTES" FOR THE COVID-19 PANDEMIC

"ISISI" as solid barriers (Fig. 1.), namely, [Isolation with Masks, Unit protective clothing, Stay at "home", and Travel restriction (MUST); Screening and testing; Individual immunity by a healthy lifestyle, for example, a magic and novel "polypill"—"environment-sleep-emotion-exercise-diet" intervention [E(e)SEEDi] (1), bio-agents (chemical agents, convalescent plasma, neutralizing antibody, and Chinese medicine), and vaccination; Social and medical supports; International cooperation and information sharing]. From locals, nations or regions to the globe, these solid barriers are very suitable for not only major virus communicable diseases, which include Avian influenza, Covid-19, Dengue fever, Ebola, Middle East respiratory syndrome (MERS), and Zika fever, but also major bacteria communicable diseases. It's also termed "antidotes" for the Covid-19 pandemic. Hence, during the pandemic, these barriers should be strengthen so as to combat SARS-CoV-2 and its variants.

Remdesivir and chloroquine as chemical agents were confirmed by basic and clinical studies for antiviral therapy (2, 3). A clinical trial showed that Baricitinib plus Remdesivir for hospitalized adults with Covid-19 have better clinical outcomes and fewer serious adverse events (4). And use of dexamethasone may also lower mortality in hospitalized Covid-19 cases (5). Some chemical agents which have the antiviral role of SARS-CoV-2 are discovered (6). Particularly, new antiviral drugs Merck's Molnupiravir and Pfizer protease inhibitor Paxlovid can cut Covid-19 hospitalizations and could change the course of the pandemic (7, 8). Traditional Chinese medicine (TCM) for Covid-19, such as Lianhua Qingwen (9), and TCM hot pot consisting of "bark-flower-fruit-grass-leaf-nucleolus-root (BFFGLNR)", and others, are also effective but need to more clinical evidences. Hence, integration of TCM with western medicine will be better.

Since there are acute antibody responses to SARS-CoV-2, serological testing for IgG and IgM is helpful to the diagnosis of suspected and asymptomatic cases (10). A highly effective neutralizing antibody (NA) found by Chinese scientists (11) is a specific "antidote" of SARS-CoV-2. It acts like a powerful firefighting force and can put out the "raging fire" in human body. Covid-19 convalescent plasma (CCP) treatment is beneficial to patients (12, 13), particularly, it is effective for severe Covid-19 cases (14), it confirms the role of NA for SARS-CoV-2. However, the NA for Covid-19 still needs clinical trials for its reliable efficacy.

Prevention is the best cure. So far, a number of novel Covid-19 vaccines have been developed, clinical trials as well vaccination are being accelerated to do so as to fight against this major viral disease. A study found that circulating SARS-CoV-2-specific CD8+ and CD4+ T cells were identified in 70% and 100% of Covid-19 convalescent cases (15), respectively, this adaptive immunity to SARS-CoV-2 supports current vaccine development in the globe.

Animal experiments have also showed DNA vaccine protection against SARS-CoV-2 in nonhuman primates due to elicited NA (16), and confirmed infection with SARS-CoV-2 can result in protective humoral and cellular immune responses against re-exposure (17). Clinical trials confirmed the safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored Covid-19 vaccine developed by Chinese scientists (18, 19). The reported inactivated vaccines, "universal vaccines" (20), and novel mRNA vaccines for SARS-CoV-2 and its variants will offer a new hope for humankind to combat the Covid-19 pandemic (21). In short, "more vaccines, more hope".

3 | NOT ONLY FIGHTING AGAINST COVID-19, BUT ALSO LOWERING CARDIOVASCULAR RISK

According to a new report on cardiovascular diseases (CVD) in China (22), there are 290 million patients with CVD and the prevalence and death rate are still on the rise, and CVD remains the No. 1 "killer" of global residents. Thus, it's time to strengthen the prevention and treatment of CVD, diabetes, and cancer during fighting against and after combating Covid-19. At the same time, it's very important to speed up the development, clinical trials, and application of antiviral drugs and Covid-19 vaccines.

Not only fighting against Covid-19 but also effectively lowering cardiovascular risk should be done better, because there are obviously weight gain and abnormal indicators among CVD patients during the Covid-19

pandemic lockdown and restrictions. If not enough preventive measures, many individuals preexisting CVD may die not of Covid-19 but major adverse cardiocerebrovascular events (MACCE), such as cardiac injury, cardiac arrest, acute coronary syndrome, heart failure, stroke, and other unexpected events.

There are myocardial inflammation (23) in patients with COVID-19 due to an immune-mediated myopathy by SARS-CoV-2 infection (24). Actually, there is myocarditis among 33.3% of Covid-19 confirmed cases (25). Herein, SARS-CoV-2-induced myocarditis, endothelial injury, and microvascular/macrovascular thrombosis are common pathophysiological features (26, 27). There is also acute myocardial injury including both epicardial vessel thrombosis and microvascular thrombosis identified by cardiovascular magnetic resonance (CMR) imaging in Covid-19 cases (28).

In some cases, post-vaccination myocarditis may occur (29, 30), but it remains unceitain (31), hence, long follow-up is needed. There were also slight cardiac abnormalities (imaging features of pericardial inflammation) in college student athletes (32). Some cases may suffer from cardiac arrest (33). There are also common atrial arrhythmias (atrial fibrillation or atrial flutter, AF/AFL) due to the systemic inflammation of severe viral illnesses (34), even postural orthostatic tachycardia syndrome (35). Covid-19 cases treated with hydroxychloroquine and azithromycin (HCQ/AZM) had an increase in corrected QT (QTc) prolongation (36). These problems on cardiovascular health are direct or indirect consequences related to infection of the SARS-CoV-2 and its variants (37). Thus, during the Covid-19 pandemic, there was an increase in deaths in the US due to CVD including ischemic heart disease and hypertension (38).

4 | CARDIOVASCULAR PROTECTION IN THE COVID-19 PANDEMIC

During the Covid-19 pandemic and post-Covid-19 era (39), it is very important to do better cardiovascular protection and prevention for not only confirmed, suspected and recovered cases with CVD but also healthy individuals. The latter should pay attention to unexpected events. Since there is a high prevalence of established CVD among hospitalized cases, and it may easily lead to complications in preexisting cases and an increased risk of adverse outcomes, and/or myocardial injury due to pulmonary infection and injury as well as other cardiovascular hazards (Table 2) (40), and increases the uncertainty of medical workers due to changes in the work mode during the Covid-19 pandemic (41). For example, patients hospitalized for Covid-19 with history of heart failure have higher risk of complications and mortality (42, 43).

On angiotensin converting enzyme inhibitors or angiotensin receptor blockers (ACEI/ARB) in Covid-19 infections, American College of Cardiology (ACC), Heart Failure Society of American (HFSA), American Heart Association (AHA), and European Society of Cardiology (ESC) Hypertension Council had rejected several hypotheses. Obviously, their positive effects are major and beneficial. RAAS inhibitors do not increase the risk of Covid-19 (44). But myocardial injury in COVID-19 cases is prevalent and is associated with an adverse prognosis and increased mortality (45). So far, the Covid-19 pandemic has deeply changed humankind lifestyle, everyone needs to protect cardiovascular system due to its acute and long-term complications.

Moreover, during the lockdown and restrictions in the Covid-19 pandemic era, since these pre-existing CVD (hypertension, arrhythmia, cardiomyopathy and coronary heart disease) and SARS-CoV-2 infection-related cardiovascular complications or events (myocardial injury, myocarditis, acute arrhythmia and heart failure) among confirmed and suspected cases with Covid-19 may together result in myocardial injury, which is one of the important pathogenic features of Covid-19 (46), herein, it's very important to cardiovascular protection and prevention. And there are obvious changes in cardiometabolic medicine in the Covid-19 era (Table 3) (47-77) due to the isolation policies (lockdown and restrictions) in different countries.

Since some AMI patients cannot receive timely and effective treatment with percutaneous coronary intervention (PCI) due to the Covid-19 pandemic, and the more delay, the higher the adverse events and cardiovascular mortality in Covid-19 cases (78, 79), pre-existing oral anticoagulants is very helpful to cardiovascular protection in these patients (80). In addition, Chinese herbal medicine combined with conventional therapy may be effective and safe among mild to moderate cases with Covid-19 (81). In fact, Covid-19 cases with acute coronary syndrome (ACS) or STEMI had increased in-hospital mortality and other worse outcomes due to cardiogenic shock (82). Primary PCI for these cases with STEMI is feasible and remains

the predominant reperfusion strategy (83). And antithrombotic strategies are also necessary (27).

5 | FUTURE PERSPECTIVES

With the further understanding of its etiology and potential mechanisms, epidemiology, risk factors, clinical features, diagnosis, treatment, care and rehabilitation (84-86), cardiovascular protection will be done better during the Covid-19 pandemic (87-90) and the post-Covid-19 era. Although sedentary behaviors may increase cardiovascular risk, isolation for confirmed or suspected cases is still necessary. New models and recommendations are worthy of conducting for better prevention and treatment of MACCE (1, 91). Because viral RNAaemia is highly associated with clinical prognosis of severe Covid-19, it provides a basis for the early identification and management of critically ill patients (92).

A new clinical trial showed that a single immunization with the Ad26.COV2.S vaccine in humans can induce rapid binding and NA responses as well as cellular immune responses (93), but its safety and efficacy need to be confirmed by further clinical trials. Currently, more novel vaccines including mRNA vaccines (94-97) are being developed, but we should also carefully evaluate their safety and efficacy before emergency use authorization or licensing of SARS-CoV-2 vaccines, and whether they are still effective for those variants of SARS-CoV-2. Hence, due to the ability to escape natural or vaccine-induced immunity, new variants may add the risk of combating the Covid-19 pandemic (98). However, several novel vaccines developed in China had already been highly recommended by the WHO for emergency use and wide coverage in the globe (99).

Since there are some cases with depression and stress (100), and related C-type hypertension and MACCE (101, 102), to screen positively asymptomatic cases (103), and identify high-risk cardiovascular individuals early according to visual and measured clinical phenotypes (104), psychological prevention (105), vitamin D supplementation (106), and a tiered model of care learned from lessons in London (107), will be very helpful to their recovery. In addition, a living WHO guideline on drugs to prevent Covid-19 is also recommended (108). As a vital preventative strategy for reducing the risk of the cytokine storm (109), healthy E(e)SEEDi lifestyle is highly recommended because of improvement of human immunity (86), particularly in the pandemic and post-Covid-19 era, because there are high risk of MACCE and adverse cardiovascular outcomes (110).

Currently, there are a number of asymptomatic carriers of SARS-CoV-2 in the pandemic or post-Covid-19 era (111), these cases have the risk of developing future CVD (fCVD). Novel strategies of rehabilitation and public health are needed to reduce overall morbidity and improve and prevent long-term adverse outcomes of Covid-19 (112). As a good choice, the remote cardiac rehabilitation will help to protect individuals from SARS-CoV-2 infection and improve the short-term prognosis of CVD (113). And a novel clinical assay by a quantitative ELISA to detect anti-SARS-CoV-2 spike antibodies is applicable and reliable (114).

In the pandemic and post-Covid-19 era, more precise and rapid test will help to improve the diagnosis of SARS-CoV-2 infection and CVD outcomes, such as extensive usage of point-of-care cardiac ultrasound (115). And digital health (telemedicine services, robotic telemedicine carts, use of artificial intelligence and machine learning, use of digital gadgets like smartwatches and web-based applications) is a safe alternative for the management of CVD (116, 117). In addition, due to the anti-viral, anti-inflammatory, cardioprotective and anti-coagulatory activity, bromelain, a biomolecule, is suitable for protection of cardiovascular health (118), but its potential needs to be confirmed by further studies.

All in all, these novel strategies will lead to a paradigm shift (119) in cardiac care delivery in the pandemic and post-Covid-19 era. And it's believed that we will finally combat Covid-19 for protection of human cardiovascular health by these comprehensive "ISISI" strategies (120), which include effective antiviral candidates or agents for Covid-19 and SARS-CoV-2 infection (Table 4) as well as vaccines and clinical trials. Whatever, "Healthy, Opening, Peaceful, and Excellent innovation and clinical studies will bring us more benefits".

6 | CONCLUSIONS

The Covid-19 pandemic is still continuing. The "ISISI" barriers including healthy E(e)SEEDi lifestyle are worthy of conducting from locals, nations or regions to the globe for control of the pandemic. Since cases with Covid-19 are easy to suffer from cardiac injury, cardiac arrest, and other MACCEs in the pandemic and

post-Covid-19 era, it's very important to do better cardiovascular prevention and protection for confirmed, suspected and recovered cases as well as healthy individuals. Moreover, people should positively develop new antiviral drug and novel vaccines for combating Covid-19 in the future since the SARS-CoV-2 and its variants are high risk factors to human cardiovascular system.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

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Table 1

Emerging SARS-CoV-2 variants (a variety of critical mutations) and their features.

Specific variants of SARS-CoV-2	Sites of SARS-CoV-2 mutant & mechanisms	Features (transmissible, infectious, and severe)	Notes
Omicron variant	**B.1.1.529** The S1-RBD/S2 mutation/deletion (the alterations of SARS-CoV-2 S RNA sequences) lead to escape immune surveillance. The 3.0 Å cryo-EM structure of the omicron spike protein shows extensive mutations in RBD regions. Key mechanisms: binding of the RBD of the viral spike protein with the ACE2 receptor in the host-cells, improved host-cell entry and the replication of the virus.	+++ More infectious sites of SARS-CoV-2 and more than existed deadly Delta variants Spread globally, increased hospitalization, exhibited more severity for the young generation, invaded defense mechanism of natural immunity; Not responsive to the available vaccines, and significant resistance to current antibody therapies. Extraordinary potency in immune escape compared to the other variants	On Nov 26th 2021, WHO designated the new SARS-CoV-2 strain – named Omicron, from letter "όμικρον" in the Greek alphabet – as a variant of concern (B.1.1529 variant) RBD: the receptor-binding domain; ACE2: the angiotensin-converting enzyme 2.
Delta variant	**B.1.617.2** Arginine-203-methionine (R203M) mutations; Delta T478K substitution plays a vital role in stabilizing and reshaping the RBM loop$^{473\text{-}490}$.	++	A
Beta and Kappa variants	**B.1.351** Efficiently interact with ACE2 receptor	+	
Alpha variant	**B.1.1.7** Tthe S1-RBD/S2 mutation/deletion	+	
Others new variants (recombinant variant)	XE Omicron (BA.1-BA.2) XD Delta-Omicron (BA.1) XF Delta-Omicron (BA.1)		637 cases in UK 49 cases in France or globe 38 cases in UK
wild-type (WT)	The progenitor variant S (D614G) or G614 spikes (wt-S^{614G})	+/-	

Table 2

Covid-19 related cardiovascular comorbidities and complications in systemic, inside and outside of the heart.

Systemic
ARDS Coagulation abnormalities or dysfunction Endothelial dysfunction Hyperinflammatory cardiogenic shock SCD Venou

Notes : ACS: acute coronary syndrome; AF: atrial fibrillation; AMI: acute myocardial infarction; ARDS: acute respiratory distress syndrome; ECMO: extracorporeal membrane oxygenation; NSTEMI: non-ST elevated myocardial infarction; PE: pulmonary embolism; SCD: sudden cardiac death; STEMI: ST elevated myocardial infarction.

Table 3

Changes in cardiometabolic medicine in the Covid-19 pandemic.

Items	Before Isolation (Non-Lockdown)	During Isolation (Lockdown)	After Isolation (Reopening)	Countries
Incidences of CVD CVD (32) MI (33) Arrhythmias/ICDs (34)		—— — – (not impact)		France Italy
HA for CVD ACS (35) AMI (36-38) New-onset Af (39) HF (40) Acute CV events (41) STEMI (42) Diabetics & hypertension with STEMI (42) AHF (43) ADHF admissions (44)	——	— —— — —(not uniform) —47% —— — —31% —11.5% & 9.38% ——	—	New Zealand France France India Italy Danish South India South India London, UK South India
Diabetes Glycaemic control (45)		—		
To ICCU Overall & CVD causes (46) All causes ACS (47)		—— ——35% ——49% ——49% Women —28% Men ——61% NSTEMI ——33% STEMI	—	
Medical Treatment Prescription rates of CVD & Diabetes (48) Pharmacy purchases of CV drugs (49)		—— ——		Germany Germany
PCI procedures PCI for NSTEMI (50) Primary PCI for STEMI (51) Reperfusion of STEMI (52)		—— — a significant lag		England England

Items	Before Isolation (Non-Lockdown)	During Isolation (Lockdown)	After Isolation (Reopening)	Countries
Cardiac Surgery Adult cardiac surgery (53) CABG (54) Life-threatening aortic surgery (55)		˜˜˜ (volatility) — – (maintained)		Brazil UK
CVD Care Acute and chronic CVD care (56) QOL in T2D (57) Heart rate (58) Quality of care for AMI (59)		—— — — —		India Australia China England & Wales
Mortality Rates of CVD Non-Covid-19 related diseases (60) CABG (54)		— —		Non-Wuhan, China Brazil

Notes: It's a double-edged sword with both benefits and downsides during the COVID-19 pandemic lockdown and restrictions (61). Totally, levels of physical activity were reduced and social support increased, but there were increased risk of negative psychosocial or behavioural changes and negative changes in the CV outcome variables (62). Here are abbreviations. ACS: acute coronary syndrome; ADHF: acute decompensated heart failure; Af: atrial fibrillation; AHF: acute heart failure; AMI: acute myocardial infarction; CABG: coronary artery bypass graft; CVD: cardiovascular disease; HF: heart failure; ICCU: intensive cardiac care unit; ICDs: implantable cardioverter-defibrillators; MI: myocardial infarction; NSTEMI: non-ST-segment-elevation myocardial infarction; PCI: percutaneous coronary intervention; QOL: quality of life; STEMI: ST-segment-elevation myocardial infarction.

Table 4 Effective antiviral agents for Covid-19 and SARS-CoV-2 infection.

Types of Specific Inhibitors	Agents	Therapeutic targets & Mechanisms	Notes
Specific M^{pro} ($3CL^{pro}$ or NSP5) inhibitors PLpro inhibitors Exonuclease inhibitors (EI) Nucleotide inhibitors (NI) (selective RdRp inhibitors) 4'-modified nucleoside drug candidates	Small molecular compound PAXLOVID= Nirmatrelvir (PF-07321332, NMV) + Ritonavir (as a pharmacokinetic enhancer) 9,10-dihydrophenanthrenes peptidomimetic YH-53 (compounds) GC376, bocepre-vir, calpain inhibitors II, and XII, Chloroquine (CQ) & Hydroxychloroquine (HCQ), peptide inhibitors and GRL0617 Pibrentasvir & Ombitasvir Remdesivir, Sofosbuvir, Lopinavir, Favipiravir, Molnupiravir & AT-527 FNC (azvudine) islatravir balapiravir	Inhibit the viral target Mpro, an orally administrated inhibition of viral replication and its survival in the host cell, a potent and selective inhibitor of the SARS-CoV-2 main protease (M^{pro}), lack of genetic toxicity. Inhibit the viral target PLpro, regulate viral replication; dysregulates host immune sensing by viral polypeptide cleavage, de-ISGlyation and immune suppression. Inhibit the viral target RdRp. Oct 2020, the US FDA approved remdesivir as the first drug for the treatment of Covid-19 better therapeutic efficacy than remdesivir.	main protease (3C-Like protease), covalent inhibitors of $3CL^{pro}$, a better selectivity index than remdesivir, no clinically relevant risks associated with PAXLOVID administration. Papain-like protease broad-spectrum prodrugs Due to CV adverse drug reactions (CV-ADRs), need adequate CV monitoring
Specific inhibitors of RdRp and Nsp15/EndoU, and others	Alectinib Naldemedine & Ergotamine Stapled peptides	for RdRp for NSP15 mimic Helix 1 of the human ACE2 receptor other several kinases including CMGC, CK2, CDK, PKC, PIKFYVE, and EIF2AK2	Various signaling pathways including MAPK, GFR signaling, TGF-β, autophagy, and AKT.
Specific anti- hepatitis C virus (HCV) drugs Anti-HIV drugs	neoechinulin B (1a) N3G, a mimetic of the HIV-1 gp41 HR1 trimer anti-HIV-drug-vitamin c derivatives cocktails	inactivating the liver X receptors (LXRs), antiviral activities against HCV & SARS-CoV-2 Inhibit infection of HIV-1 & human β-coronaviruses by blocking the hexameric structure formation	a prenylated indole diketopiperazine alkaloid β-coronaviruses (MERS-CoV, HCoV-OC43 & SARS-CoV-2)

Types of Specific Inhibitors	Agents	Therapeutic targets & Mechanisms	Notes
Antimalarial drugs	Mefloquine chloroquine (CQ)/ hydroxychloroquine (HCQ)	inhibit SARS-CoV-2 replication & reduce SARS-CoV-2 entry against SARS-CoV-2 PLpro	An orally available host-acting agent
Adjunctive treatment	Melatonin (a low dose), 9 mg daily, orally for 14 days. Methylprednisolone (MP) Chitosan and its derivatives	its anti-oxidation, anti-inflammation by inflammasome activation, and improvements of immune and clinical symptoms. reduce inflammation reaction and tissue damage direct antiviral activity as vaccine adjuvants	reduce the levels of TNF-α, IL-1β cytokines, MDA, and NO levels, and significantly increase SOD level. bradycardia on the premise of the long-term use of arbidol
Nanotechnology (Nanomaterials)	personal protective equipment anti-viral nano-coats, nano-based vaccines nanomaterial-based point-of-care devices agents carriers gene editing agents therapeutic agents ZnO nanoparticles	based on modifiable engineering materials and useful physicochemical properties, nanobubble ozonated hyaluronic acid-decorated liposomal (NOHAL) solution	possible unintended immunotoxicity, through the nose and/or oral cavity. ZnONPs
Botanical Drugs or medicinal plants	plant chemicals: Artemisia annua L. Angeloylgomisin O Schisandrin B *Vitex negundo* L. (VNL) Kabasura kudineer Nilavembu kudineer	phytomedicine-based therapies, effectively inhibit SARS-CoV-2 entry adjuvant therapeutic agent & a single source of a cocktail of Mpro inhibitors the two most widely approved formulations to treat COVID-19.	Lower side effects, combination with remdesivir
MNPs	Gallinamide A Seaweed's bioactive compounds Microalgal metabolites (carotenoids and lipids)	directly interacted with cathepsin L in cells can inhibit the omicron variant anti-inflammatory properties	broad-spectrum target inhibition by marine natural products

Types of Specific Inhibitors	Agents	Therapeutic targets & Mechanisms	Notes
TCM or Herbal medicine	Jinzhen granule (JZ) (gallic acid 1.97 mg/g, baicalin 20.69 mg/g, glycyrrhizic acid 4.92 mg/g, hyodeoxycholic acid 4.86 mg/g, cholic acid 4.07 mg/g) A combination of Huoxiang Zhengqi Oral Liquid and Jinhao Jiere Granules Baidu Jieduan granules Bufei Huoxue (BFHX) Jinhua Qinggan granule (JHQG) Keguan-1 Lianhua Qingwen (LHQW) Maxingshigan-Weijing decoction (MWD) Reduning injection Reyanning mixture Shenhuang granule Shufeng Jiedu capsule (SFJDC)* Xiyanping (XYP) injection Plant secondary metabolites or herbal bioactives (e.g., Green tea extract)	antiviral activity by inhibition of main protease and endoribonuclease (NSP15), regulating the NF-κB/MAPK pathway and the mitochondria-mediated apoptotic pathway. antiviral, anti-inflammatory, and immunoregulatory activities in acute lung injury, reduce the use of antibiotics and glucocorticoids, improve LPS-induced ALI by reducing inflammation and pulmonary vascular endothelial injury, safe and effective for patients with mild to moderate COVID-19, especially when combined with conventional western medicine.	An alternative treatment Huoxiang Zhengqi Oral Liquid: oral before meals, 10 mL/time, 2 times/day, a course of 5 days. Jinhao Jiere Granules: dissolve in boiling water and take after meals, 8 g/time, 2 times/day, a course of 5 days, followed up for 14 days, respectively. *A patented herbal drug composed of eight medicinal plants.
Macrolide antimicrobial agents	Clarithromycin Azithromycin	An immunomodulating drug and suppresses cytokine storms in viral respiratory diseases (including influenza)	Monotherapy or combination, but may induce QT long and malignant arrhythmias
Others: Multi-targeted anti-viral drugs	three alkaloids (lycorine, emetine, and cephaeline)	inhibitors of viral entry	target N-terminal domain (NTD) of nucleocapsid protein (NPro) to inhibit the replication
Combinations in Covid-19 management	Such as iota carrageenan nasal spray, ermectin oral drops, omega-3 supplementation, and a quadruple treatment of zinc, quercetin, bromelain, and vitamin C.	The comprehensive effects of logical combinations with different mechanisms of action.	

Notes: FDA approved drugs include chloroquine, remdesivir, favipiravir, nefamostate mesylate, penciclovir, nitazoxanide, ribavirin, etc. Combination antiviral therapies by protease inhibitor drugs include atazanavir/ritonavir (ATV/r) plus hydroxychloroquine or lopinavir/ritonavir (LPV/r) plus hydroxychloro-

quine, but hyperbilirubinemia and arrhythmia were significantly.