A narrative review of COVID-19: magnesium isoglycyrrhizinate as a potential adjuvant treatment

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Abstract: Coronavirus disease 2019 (COVID-19) has become a global pandemic affecting more than 200 countries with 87 million patients worldwide as of January 7, 2021. Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) replicates in a large amount and reaches high-titer levels in a short time after the infection. COVID-19 caused by SARS-CoV-2 shows clinical symptoms mainly including fever, fatigue, dry cough, and dyspnea. In more severe COVID-19 patients, viral pneumonia characterized by bilateral ground glass or patchy opacity, may lead to acute respiratory distress syndrome (ARDS), cytokine storm, multi-organ damage, and even death. Unfortunately, there is no effective therapy for COVID-19 until now. Magnesium isoglycyrrhizinate (MgIG), a magnesium salt of 18-α glycyrrhizic acid stereoisomer, belongs to the fourth generation of glycyrrhizic acid preparation. MgIG has various pharmacological activities including anti-inflammation, anti-oxidation, anti-virus, and immunoregulation, showing the protection against the injury of the vital organs (such as kidney, heart, and lung). Clinically, MgIG injection is usually used as a hepatoprotective agent to treat liver diseases. This narrative review summarizes the research and application of MgIG, and provides the evidence supporting the recommended MgIG as supportive therapy in the "Management Standard for Mild and Common Patients of Coronavirus Disease 2019 (COVID-19) (Second Edition)", which is jointly issued by National Health Commission of People's Republic of China and National Administration of Traditional Chinese Medicine.

Keywords: Magnesium isoglycyrrhizinate (MgIG); COVID-19; cytokine storm; multiple organ damage; anti-virus

Introduction

Coronavirus disease 2019 (COVID-19) outbreak with the infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused worldwide pandemic transmission by human-to-human rapidly. As of January 7, 2021, the total number of infected people confirmed has reached more than 87 million, and global deaths have exceeded 1 million. COVID-19 carries a mortality of approximately 3.02% (WHO reported). The mortality rate of COVID-19 patients from 5 to 17 years old is about

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Table 1 Development of glycyrrhizic drugs

Generations	Medicine	Product name	Main ingredient
First	Glycyrrhizin	Potenlin	Monoammonium Glycyrrhizinate, L-Cysteine hydrochloride, Glycine
Second	Compound Glycyrrhizin	Stronger Neo-Minophagen C	Glycyrrhizin, Glycine, DL-Methionine
	Compound Ammonium Glycyrrhetate	Maineng	Monoammonium Glycyrrhizinate, Glycine, L-Cysteine hydrochloride
Third	Diammonium glycyrrhizinate	Ganlisin	Isomer mixture preparation of 18α-glycyrrhizic acid and 18β-glycyrrhizic acid
Fourth	Magnesium isoglycyrrhizinate	Tianqing Ganmei	18α-glycyrrhizic acid content above 97%

0.30%, and that of the patients over 85 years old is about 30.49%. Among patients admitted to the intensive care unit, the case fatality rate is as high as 40% in the US (1).

The SARS-CoV-2 shortly replicates in a large amount and reaches high-titer levels in the early and advanced stages of the disease (2). When the infection is out of control, cytokine storm (an uncontrolled inflammatory response) occurs. Cytokine storm is characterized by excessive activation and release of inflammatory factors and chemokines including interleukin-1β (IL-1β), IL-2, IL-6, IL-7, IL-10, monocyte chemoattractant protein-1 (MCP1), tumor necrosis factor-α (TNF-α), IL-4, interferon-γ (IFN-γ), macrophage inflammatory protein 1 alpha (MIP-1α), MIP-1β, granulocyte-colony stimulating factor (G-CSF), etc. (3,4). This cytokine storm is related to the deterioration of many infectious diseases with severe acute respiratory syndrome (SARS) (5), and Middle East respiratory syndrome (MERS) (6). Of note, in the early stage of SARS-CoV-2 infection, early inflammatory response with high serum levels of IL-1β, IL-2, and IL-7 are observed in COVID-19 patients (3,7). Patients with moderate to severe COVID-19 show a cytokine storm (2,7), which causes pathological changes of the respiratory system (8-11), and leads to extrapulmonary manifestations, mainly liver injury (12), myocardial dysfunction (13), acute kidney injury (14), hyperglycemia and ketosis (9), as well as complications of immunological, hematological, nervous and gastrointestinal systems (7,15-18). Therefore, both cytokine storm and multiple organ damage are major reasons resulting in COVID-19 patients condition deterioration and even death. Effective drugs are needed urgently for COVID-19 therapy.

Traditional Chinese herbal medicine has achieved certain effects in the treatment of COVID-19 patients in China. Gancao (*Glycyrrhizae Radix et Rhizoma*), is one of the main representative medicine (19-21). Recent studies have shown that its main active ingredient glycyrrhizic acid is a promising candidate of COVID-19 (22-27). This compound has anti-virus (28), anti-inflammation (29), anti-bacteria (30), modulation of immune function and gut microbiota (31,32), protection of liver, kidney and heart (32-35). Due to the clinical urgent need, glycyrrhizic acid preparations have undergone four generations of development, including the first-generation of glycyrrhizin preparation, the second-generation of compound glycyrrhizin and compound ammonium glycyrrhizate, the third-generation of diammonium glycyrrhizinate and diammonium glycyrrhizinate liposomes, and further modified and optimized fourth-generation of magnesium isoglycyrrhizinate (MgIG) injection (*Table 1*).

MgIG is a magnesium salt mainly composed of 18α-glycyrrhizic acid stereoisomers (*Figure 1*). Its injection is a new drug for viral hepatitis treatment independently developed in China. Clinical trials and basic researches have shown that MgIG has anti-inflammatory, antioxidant, anti-viral, immunomodulatory and hepatocyte protective effects (37-40). Meanwhile, a series of studies have shown that MgIG has good intervention effects on kidney, heart, lung and brain -related diseases, protecting the function of these organs and tissues (38-47). Therefore, MgIG injection is often used in clinical treatment of various diseases. On the other hand, MgIG as the latest preparation of glycyrrhizic acid has stable pharmacological activity and high safety, which should be considered for supportive treatment of COVID-19 patients. In this narrative review, we introduce the research progress of MgIG and provide evidence to support the use of MgIG in the treatment of COVID-19.

We present the following article in accordance with the Narrative review checklist (available at http://dx.doi.org/10.21037/apm-20-1971).
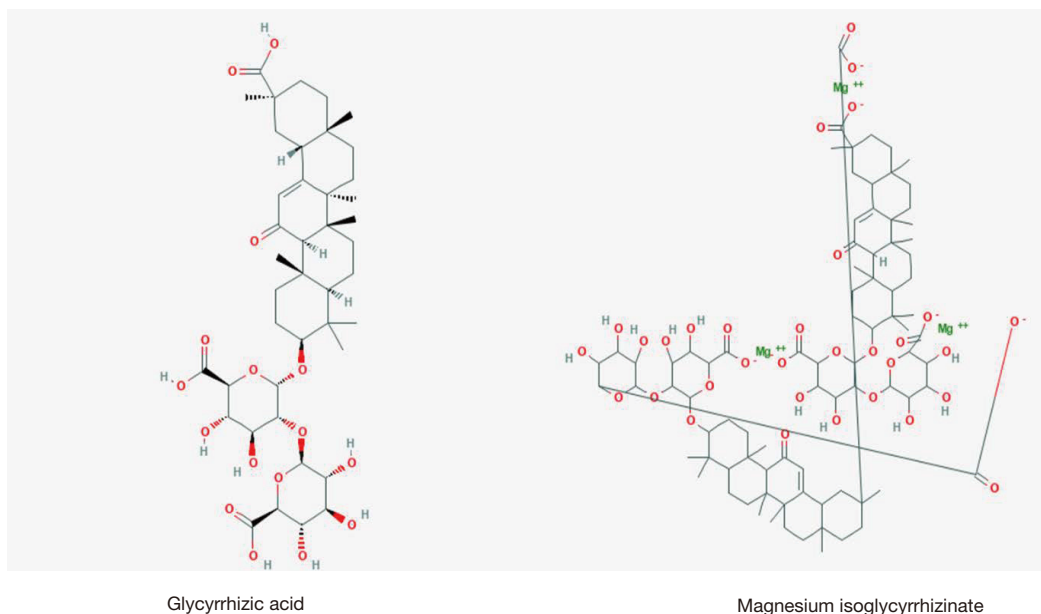
Figure 1 Structure of Glycyrrhizic acid and magnesium isoglycyrrhizinate (36).

Protecting vital organs

Liver

Clinical risk factors (virus infection, drug- or alcohol-induced hepatitis or coronavirus-induced cytokine storm, etc.) cause abnormal liver function in patients. MgIG effectively prevents and treats liver diseases such as viral hepatitis, drug hepatitis, alcoholic hepatitis, and liver fibrosis possibly through inhibiting transcription factor kappa B (NF-κB), IL-6, tyrosine protein kinase 2/signal transducer and transcription activator 3 (JAK2/STAT3) signaling pathways.

Viral hepatitis

Viral hepatitis is an infectious disease caused by hepatitis viruses. On the basis of conventional treatment, the combination of glycyrrhizic acid preparations such as compound ammonium glycyrrhizinate, diammonium glycyrrhizinate and MgIG can more effectively inhibit viral replication, improve liver function, and increase clinical effectiveness for the treatment of viral hepatitis in clinic (48-50). Especially, the fourth-generation MgIG injection can accelerate the recovery of liver function in patients (51,52). For patients with chronic hepatitis B, after 2 and 4 weeks of MgIG injection treatment, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), and γ-glutamyl transpeptidase (γ-GT) levels in serum are lower than that before treatment (53). Furthermore, combined use of MgIG injection (150 mg, iv qd) and adefovir is beneficial to inhibit virus proliferation and enhance immunity than adefovir administration group alone in patients with hepatitis B (53). MgIG also enhances the antiviral efficacy of nucleoside analogues treatment and help to improve liver function (50). Lamivudine is often used for the treatment of adult chronic hepatitis B patients with compensatory liver function accompanied by elevated ALT and viral activity replication. MgIG injection (150 mg, iv qd) in combination with lamivudine on chronic hepatitis B is beneficial to the continued decline of HBV viral load, and decreases serum ALT levels (49). Of note, studies of MgIG on viral hepatitis are mostly clinical trials, but the corresponding basic experiments are scarce. The mechanism for hepatoprotective effects of MgIG in the setting of hepatitis is worthy of further exploration.

Drug-induced hepatitis

MgIG effectively treats drug-induced hepatitis. It reduces serum ALT and AST levels, and improves liver function and prognosis of patients with drug-induced hepatitis (54). A randomized, double-blind, multi-doses, active drug controlled, multicentre phase II trial in China show that, compared with control group (Tiopronin, for early treatment of viral hepatitis, alcoholic hepatitis, drug-induced hepatitis, heavy metal toxic hepatitis, severe

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hepatitis and liver cirrhosis, as standard therapy for liver injury in China), low-dose (200 mg iv, qd) and high-dose (400 mg iv, qd) of MgIG injection produce better curative effect in the early stage as well as 4-week treatment, showing that the proportion of ALT normalization is significantly greater in 174 patients with eligible liver injury. These results clearly demonstrate that MgIG injection is used as an effective strategy for the treatment of drug-induced liver injury (55).

Basic researches initially reveal the potential mechanism of MgIG intervention in drug-induced liver injury. Methotrexate has limited clinical application due to its hepatoenteric toxicity. Prophylactic administration of MgIG (9 or 18 mg/kg ip, qd) can effectively attenuate methotrexate-induced liver fibrosis and hepatotoxicity damage in mice (56). MgIG decreases serum ALT and AST levels, down-regulates liver cyclooxygenase-2 expression, and reduces liver collagen deposition in these animals (56). MgIG (15 or 45 mg/kg ip, qd) also prevents oxaliplatin-induced liver injury. It inhibits mRNA and protein expression of liver metallothionein 1, peroxiredoxin 1, superoxide dismutase 2, IL-6 and STAT3, and suppresses mRNA and protein expression of liver von Willebrand factor, plasminogen activator inhibitor-1 in this animal model, thus showing its attention of liver injury-related oxidative stress, IL-6 pathway activation and coagulation system disturbances (57).

Consistently, in oxaliplatin-exposed L-02 cells, MgIG (40 or 100 μM) significantly attenuates the expression abnormality of metallothionein 1, peroxiredoxin 1 and superoxide dismutase 2, as well as IL-6 secretion. In addition, MgIG (13.5 mg/kg intragastric administration, qd) can upregulate mRNA and protein levels of the nuclear factor erythroid 2-related factor 2 (Nrf2), and activate Nrf2-related antioxidant pathway to reduce hepatotoxicity caused by triptolide in rats (35). Of note, MgIG also ameliorate doxorubicin-induced acute hepatotoxicity via anti-oxidant and anti-apoptotic mechanisms in mice (58). MgIG significantly increases superoxide dismutase (SOD) and glutathione peroxidase and decreases malondialdehyde (MDA) levels in serum, and down-regulates liver expression levels of apoptosis-related proteins Bax/Bcl-2, and caspase-3 in doxorubicin-treated mice (58). MgIG (25, 50, 100, and 200 mg/kg ip, qd) reduces serum ALT levels, and protects against docetaxel-induced liver injury in mice (40). Additionally, MgIG (25, and 50 mg/kg ip, qd) can reduce cyclophosphamide-induced liver injury by inhibiting NF-κB -mediated inflammation and phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) axis-mediated autophagy in mice (59).

Alcoholic liver injury

Long-term excessive alcohol drinking is the main reason for high morbidity and mortality of liver diseases worldwide. MgIG alone or in combination with other drugs can help treat alcoholic hepatitis. MgIG injection (200 mg iv, qd) is reported to significantly reduce serum AST, ALT, direct bilirubin (DBIL) and glutamyltransferase (GCT) levels in patients with alcoholic hepatitis, showing an enhanced therapeutic effect when combined with glutathione (60,61).

In mouse model of the chronic plus binge ethanol feeding, MgIG (22.5 or 45 mg/kg ip, qd) can lower serum ALT and AST levels, reduce neutrophil reactive oxygen species (ROS) production, and inhibit proinflammatory cytokine secretion, thereby preventing liver damage (62). Meanwhile, MgIG (5 mg/mL) inhibits the transduction of hedgehog signaling pathway, which is related lipometabolic genes [such as peroxide enzyme proliferators activate receptor α (PPARα) and cholesterol regulatory element binding protein 1c (SREBP-1c)] as well as oxidation-related genes (such as ROS, SOD), to prevent steatosis, oxidative stress, mitochondrial dysfunction, and apoptosis in hepatocytes (63). However, more studies are needed to explore possible molecular mechanisms by which MgIG protects from alcoholic hepatitis.

Liver fibrosis and others

In animal model of carbon tetrachloride (CCl_4)-induced liver fibrosis, MgIG (15, 30 or 45 mg/kg ip, qd) markedly prevents hepatic injury and reduces fibrotic scar formation, further results from *in vitro* experiments show that the anti-fibrosis effect of MgIG (2.5, 5, 10 mg/mL) may be associated with its regulation of hepatic stellate cell (HSC) ferroptosis via a heme oxygenase-1 (HO-1) dependent mechanism (64). Similarly, MgIG (2.5, 5 or 10 mg/mL) is reported to suppress HSCs proliferation and induce cell cycle arrest, and then stimulate endoplasmic reticulum stress-induced apoptosis in activated HSCs, which are consistent with its attenuation of CCl_4-induced liver fibrosis in mice treated with MgIG (60 mg/kg ip, qd) (65). Additionally, MgIG (15, 30 or 60 mg/kg ip, qd) alleviates CCl_4-induced liver fibrosis and inflammation in mice, possibly by reducing transforming growth factor-βR1 (TGF-βR1), platelet derived growth factor-βR (PDGF-βR), and tumor inhibitor of metalloproteinase 1 (TIMP1) expression, and increasing matrix metalloproteinase-2 expression, indicating that MgIG can regulate two key pro-fibrogenic pathways TGF-β signaling and MMP/TIMP system to inhibit liver fibrosis (66). In fact, in TGF-β1-

induced human HSCs LX2 fibrotic cell model, MgIG (1 mg/mL) reduces the production of α-smooth muscle actin (αSMA) and type I collagen, and inhibits extracellular regulated protein kinases (ERK) pathway to suppress the nuclear localization of Smad protein, resulting in decreased cell proliferation and increased senescence (66).

On the other hand, MgIG suppresses inflammation of liver fibrosis, with the down-regulation of TNF-α, IL-1β, IL-4, IL-6, IL-8, IL-10, and IL-18 levels, and the reduction of the proportion of Ly6 G positive cells, CD68 positive cells, and CD11b positive cells *in vivo* (67). Furthermore, MgIG (2.5, 5 or 10 mg/mL) not only inhibits the expression of pro-inflammatory cytokines TNF-α, IL-18, IL-8, IL-6, and IL-1β, but also promotes the activation of HSC to produce anti-inflammatory cytokines IL-10 and IL-4, possibly through inhibiting Hippo/Yes-associated protein (Hippo/Yap) signaling pathway in primary HSCs cultured with recombinant mouse platelet derived growth factor-BB (PDGF-BB) (67).

MgIG also ameliorates metabolic syndrome-associated chronic liver injury and fibrosis. In high fructose-fed rats, MgIG (10, 20, and 40 mg/kg ip, qd) mitigates the pathological characteristics of metabolic syndrome and improves hepatocyte epithelial-mesenchymal transition and liver fibrosis by increasing liver miR-375-3p expression to inhibit JAK2/STAT3 pathway and TGF-β1/Smad signaling (68). It alleviates liver inflammation and lipid accumulation induced by high fructose diet possibly through inhibiting NF-κB/NLR family pyrin domain containing 3 (NLRP3) inflammasome activation and regulating lipid metabolism-related proteins PPARα, carnitine palmitoyl transferase-1, sensor for fatty acids to control-1 (SREBP-1) and stearoyl-CoA desaturase 1 (69). In concanavalin A-induced mouse autoimmune hepatitis model, MgIG (50 or 100 mg/kg ip, qd) can reduce serum AST and ALT levels, inhibit $CD4^+CD25^-CD69^+$ subset proliferation and NLPR3 inflammasome activation to improve autoimmune hepatitis (70). In rat model with acute necrotizing pancreatitis through retrograde injection of 5% sodium taurocholate into the biliary-pancreatic duct, MgIG (30 mg/kg ig, qd) increases liver SOD levels, reduces MDA accumulation, and inhibits IL-1β, and NF-κB, showing its inhibition of oxidative stress and inflammatory response as well as attenuation of liver damage aggravation induced by high fat diet (71).

We summarized the therapeutic effects of MgIG on liver diseases and the possible mechanisms in *Figure 2*.

Heart

Cardiac hypertrophy is an independent risk factor for increasing cardiovascular disease mortality and threatens human (72,73). In isoproterenol-induced mouse model of myocardial injury, MgIG injection (25 or 50 mg/kg ip, qd) for 14 days lowers serum lactate dehydrogenase (LDH) and creatine kinase (CK) levels, and down-regulates heart expression of basic fibroblast growth factor (bFGF), pro-apoptotic gene (Bax), Toll-like receptor 4 (TLR4) and NF-κB p65, suggesting that MgIG may inhibit TLR4/NF-κB pathway to alleviate myocardial hypertrophy and fibrosis (43). Additionally, MgIG inhibits L-type Ca^{2+} currents (I_{Ca-L}) in a dose-dependent manner, and reduces the cell shortening and the peak of calcium transients at 0.3 mg/mL in rat cardiomyocytes, indicating that MgIG exerts the cardioprotective effects (74).

Kidney

The kidney is an important organ that affects blood composition, blood pressure regulation, and metabolism. Kidney diseases cause the imbalances in the body's water and electrolytes, metabolic acidosis, immune system or developmental abnormality, leading to kidney failure and death. MgIG has positive effects on patients with hemorrhagic fever with renal syndrome (HFRS) and renal ischemia-reperfusion injury. In HFRS patients, MgIG injection (100 mg iv, qd) is used as an effective method for decreasing serum ALT levels, shortening the hospitalization period and improving HFRS accompanied with liver injury (75). MgIG (30 mg/kg ip, qd) protects rats from renal ischemia-reperfusion injury through anti-inflammatory, anti-oxidation, anti-apoptosis effects. It reduces serum TNF-α and IL-1β and IL-6 levels, increases serum SOD and glutathione peroxidase (GSH-Px) activity, and inhibits serum inducible nitric oxide synthase (iNOS) activity and protein expression, suppresses renal caspase 3 activity as well as matrix metalloproteinase-2, STAT3 and intercellular adhesion molecule-1 (ICAM-1) protein expression in renal ischemia-reperfusion injury of rats (41). MgIG (10, 20 or 40 mg/kg ip, qd) is reported to significantly prevent renal dysfunction, proteinuria and podocyte apoptosis by the inhibition of miR-193a and the up-regulation of Wilms
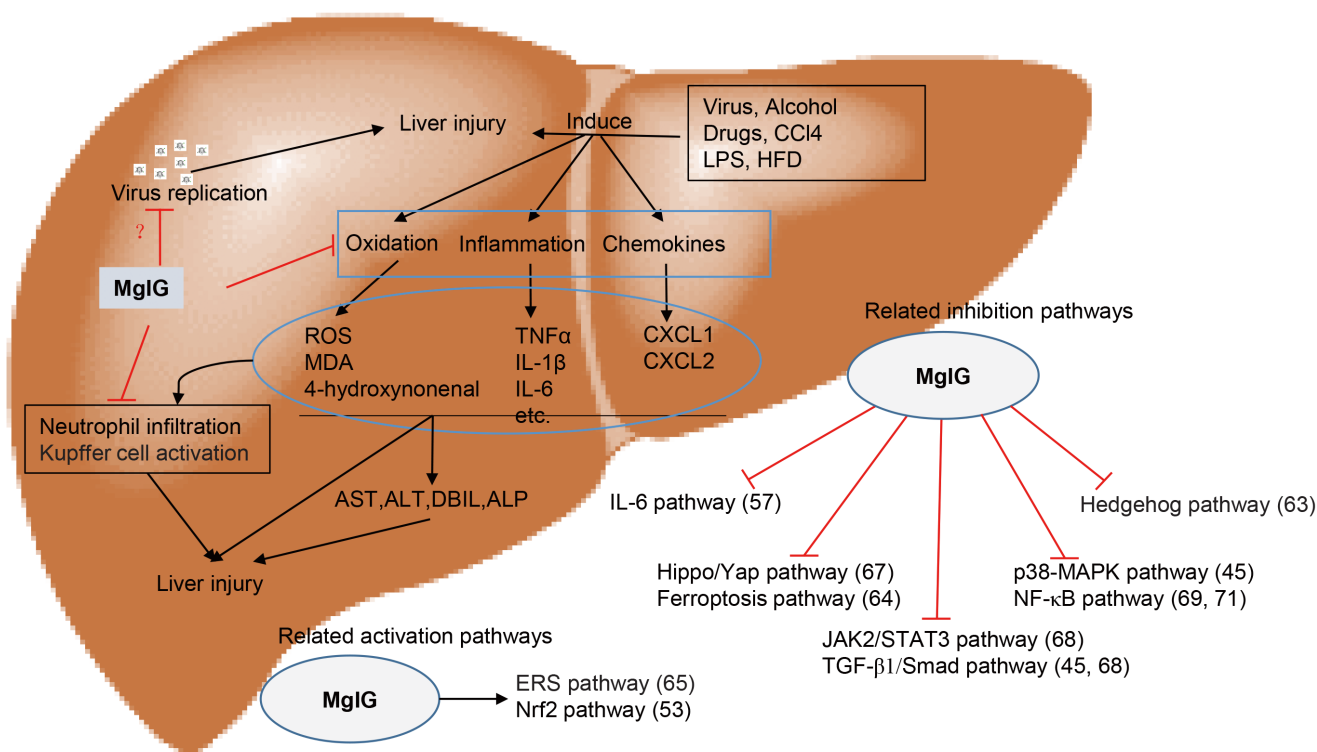
Figure 2 MgIG's effects on various liver diseases and possible mechanisms. MgIG has hepatoprotective properties mainly by inhibiting IL-6 pathway, Hippo/Yap pathway, and ferroptosis pathway, etc. (45,57,63,64,67-69,71), and activating ERS pathway and Nrf2 pathway (53,65). MgIG, magnesium isoglycyrrhizinate; CCl4, carbon tetrachloride; LPS, lipopolysaccharide; HFD, high-fat diet; ROS, reactive oxygen species; MDA, malondialdehyde; TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β; CXCL, chemokine (C-X-C motif) ligand; AST, aspartate aminotransferase; ALT, alanine aminotransferase; DBIL, direct bilirubin; ALP, alkaline phosphatase; Hippo/Yap pathway, Hippo/Yes-associated protein pathway; p38 MAPK, p38 adenosine 5'-monophosphate-activated protein kinase; NF-κB, transcription factor kappa B; JAK2, tyrosine protein kinase 2; STAT3, signal transducer and transcription activator 3; Smads, Sterile alpha motif domain-containing proteins; TGF-β1, transforming growth factor -β1; Nrf2, nuclear factor-erythroid 2-related factor-2; ERS, endoplasmic reticulum stress.

tumor protein 1 (WT1) in high fructose-fed rats (38).

Lung

The protective effect of MgIG on paraquat and radiation-induced pulmonary fibrosis is reported (44,45). MgIG (100 mg/kg ip, qd) significantly reduces pulmonary tissue collagen deposition and serum TGF-β1 levels in radiation-induced pulmonary fibrosis of mice (45). Furthermore, MgIG regulates p38 adenosine 5'-monophosphate (AMP)-activated protein kinase/protein kinase B/nicotinamide adenine dinucleotide phosphate oxidase 4 (p38 MAPK/Akt/NOX4) pathway to inhibit the differentiation of lung fibroblasts, thereby improving pulmonary fibrosis in this animal model (45). MgIG (15, 30 or 45 mg/kg ip, qd) also slow down the process of pulmonary fibrosis, with

the reduction of serum and lung ICAM-1 and MMP-9 expression in paraquat-induced lung injury of rats (44). These results provide experimental basis for the selection of MgIG for clinical treatment of lung diseases.

Cognitive ability and depression-like behavior

MgIG (25 or 50 mg/kg ip, qd) effectively alleviates the decline in spatial learning ability and memory ability in epirubicin-induced hepatic encephalopathy of mice. It reduces serum and hippocampal SOD activity, reduces MDA, TNF-α, IL-6 and IL-1β levels, down-regulates thioredoxin-interacting protein and NF-κB pathway, activates Nrf2/HO-1/Thioredoxin (TRX) axis in hippocampal region in this animal model (46). MgIG (25 or 50 mg/kg ig, qd) significantly improves the immobile

Table 2 Protective effects of magnesium isoglycyrrhizinate (MgIG) on organ and tissue injury of related diseases and its underlying mechanism

Tissue	Diseases	Protective effects	Mechanism
Liver	Viral hepatitis, drug-induced hepatitis, alcoholic hepatitis, liver fibrosis, etc.	Improve serum biochemical indicators, reduce viral replication and pro-inflammatory factor levels, inhibit oxidative stress, apoptosis and liver lipid synthesis	Inhibit TLR4/NF-κB, PI3K/AKT/mTOR, JAK2/STAT3, TGF-β1/Smads, Hippo/Yap signaling pathway, activates Nrf2, NOX4/ROS signaling, and reduces the expression of key genes for lipid synthesis
Heart	Myocardial fibrosis	Inhibit myocardial hypertrophy and fibrosis	Inhibit TLR4/NF-κB signaling pathway, inhibit I_{Ca-L} and cell shortening
Kidney	Kidney dysfunction, renal ischemia-reperfusion injury	Anti-inflammatory, antioxidant and anti-apoptotic effects	Inhibit iNOS, ICAM-1 and MMP-2 expression, inhibit JAK2/STAT3 and TGF-β1/Smads signaling pathway
Lung	Pulmonary fibrosis	Inhibit fibroblast differentiation, improve pulmonary fibrosis, reduce collagen deposition, anti-inflammatory, anti-oxidation, anti-apoptosis effects	Inhibit p38 MAPK/Akt/NOX4 signaling pathways, reduce the expression of ICAM-1 and MMP-9
Brain	Cognitive impairment, depression	Ameliorate memory ability, cognitive ability, depression-like behavior and neuroinflammation	Inhibit TXNIP/Nrf2/NF-κB and JAK/STAT/NF-κB signaling pathways

Summarize the effects of magnesium isoglycyrrhizinate in part of "protecting vital organ". The references are consistent with the text, and will not be referred here. MgIG, magnesium isoglycyrrhizinate; TLR4, toll-like receptor 4; NF-κB, transcription factor kappa B; PI3K, phosphatidylinositol 3-kinase; Akt, protein kinase B; mTOR, mammalian target of rapamycin; JAK2, tyrosine protein kinase 2; STAT3, signal transducer and transcription activator 3; TGF-β1, transforming growth factorβ; Smads, sterile alpha motif domain-containing proteins; Hippo/Yap pathway, Hippo/Yes-associated protein pathway; Nrf2, nuclear factor erythroid 2-related factor 2; NOX4, nicotinamide adenine dinucleotide phosphate oxidase 4; ROS, reactive oxygen species; I_{Ca-L}, L-type Ca^{2+} currents; iNOS, inducible nitric oxide synthase; ICAM-1, intercellular adhesion molecule-1; MMP-2, matrix metallopeptidase-2; p38 MAPK, p38 adenosine 5'-monophosphate (AMP)-activated protein kinase; TXNIP, thioredoxin-interacting protein.

time in the tail suspension test and forced swimming test in lipopolysaccharide-induced depressive-like behavior of mice (47). MgIG inhibits the rise of pro-inflammatory cytokines and oxidative stress in serum and hippocampus, mainly down-regulates p-JAK2, p-STAT3, p-NF-κB p65 and p-IκBα protein levels in hippocampus, suggesting that the inhibition of hippocampus JAK/STAT/NF-κB pathway may be related to its anti-depressant effects (47).

We summarized the protective effects of MgIG on organ and tissue injury of related diseases and its underlying mechanism (*Table 2*).

Current treatment difficulties of COVID-19

The new pneumonia COVID-19 that has recently erupted in many parts of the world is a severe acute respiratory disease caused by a novel coronavirus of the genus β. The novel coronavirus gene sequence has extremely high similarity with the SARS-CoV outbreak in 2003 and the MERS-CoV outbreak in 2012 (76). Thus, SARS-CoV-2

infects humans, and is listed as the seventh member of the coronavirus family (77).

At present, there are no specialized antiviral drugs for COVID-19 patients, and the widespread of SARS-CoV-2 causes a huge increase in the number of COVID-19 patients and the resulting deaths worldwide. Therefore, identifying effective antiviral agents to treat COVID-19 is of most urgency. The medications used for COVID-19 include remdesivir, chloroquine and hydroxychloroquine, tocilizumab, lopinavir/ritonavir, favipiravir, convalescent plasma therapy, azithromycin, vitamin C, corticosteroids, interferon and colchicine (78-86).

Drugs that are hotly discussed in the scientific research and medical community for the treatment of COVID-19 mainly include remdesivir and chloroquine, both of them may cause side effects such as organ injury. Redoxivir has a wide range of antiviral activity against Ebola virus, zoonotic coronaviruses, Nipah virus, respiratory syncytial virus, etc. (87-90). However, its adverse reactions (such as nausea, vomiting, gastrointestinal symptoms, multiple-organ-

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dysfunction syndrome, septic shock, acute kidney injury and hypotension) cannot be ignored (84,91). In the rhesus macaque model of SARS-CoV-2 infection, 12 hours after the first treatment of a 10 mg/kg intravenous injection of remdesivir, the viral load of the lower respiratory tract is reduced, while no reduction in viral shedding is observed, especially in the upper respiratory tract compared with control group. On the 7th day after infection, the viral load in the lungs of rhesus macaques in the remdesivir group is significantly reduced, and the lung tissue injury is also significantly improved. Although remdesivir has shown obvious effects in alleviating respiratory symptoms and reducing virus replication in the lung in the treatment of rhesus macaques infected with SARS-CoV-2, the viral shedding of rhesus macaques during the period of carrying the virus has not been reduced, and it is still transmissible (92).

The therapeutic effect of chloroquine and hydroxychloroquine on COVID-19 is still controversial (93,94). A prospective, observational study assesses the QT interval (calculated as the time from the start of the Q wave to the end of the T wave, and approximates to the time taken from when the cardiac ventricles start to contract to when they finish relaxing) of 211 COVID-19 patients treated with chloroquine/hydroxychloroquine. The use of chloroquine/hydroxychloroquine and azithromycin results in a significantly greater increase in the corrected QT interval when compared to monotherapy with either chloroquine or hydroxychloroquine, and a prolongation of the QT interval possibly increases the risk of Torsade de pointes and arrhythmogenic death (95). In a randomized trial which enrolled 821 participants of a post-exposure prevention study on SARS-CoV-2, hydroxychloroquine or placebo are given to subjects who have not taken appropriate protective measures but have close contact with COVID-19 patients for more than 10 min. About 12% of people in the hydroxychloroquine group have COVID-19-related symptoms, but there is no statistically significant difference compared with 14% in the placebo group (85). These data suggest hydroxychloroquine has no obvious preventive effect for symptomatic infection after SARS-CoV-2 exposure. Furthermore, on the basis of standard treatment, the use of hydroxychloroquine does not significantly improve the probability of negative conversion of mild to moderate COVID-19 patients, but causes a higher incidence of adverse reactions than in non-recipients, especially diarrhea, reported in 7/70 (10%) patients in a multicentre, open label, randomized controlled

trial of hydroxychloroquine (96).

In addition to existing drugs, clinical vaccines are also under continuous development, 30 (WHO reported) vaccines of the COVID-19 have entered clinical trials in the world, including inactivated virus vaccine, adenovirus vector vaccine, mRNA, DNA and recombinant protein vaccine (97). In the latest research, BNT162b1 developed by Pfizer is a lipid nanoparticle-formulated, nucleoside-modified, mRNA vaccine that encodes trimerized SARS-CoV-2 spike receptor binding domain (RBD). Phase 1/2 study shows that BNT162b1-induced SARS-CoV-2 neutralization titers reach 1.8- to 2.8-fold of those from sera of convalescent humans, with mild to moderate, transient, local reactions and systemic events, like fever, pain at the injection site, mild to moderate fatigue and headache (98). The vaccine mRNA-1273 developed by Moderna causes a high level of antibody responses and still shows a dose-dependent effect after two vaccinations. The geometric mean titer at the 100 µg dose is 2.1 times higher than the titer observed in control convalescent serum specimens after 57 days of vaccination, but solicited adverse events occur common, particularly after the second vaccination of the highest dose (99). More than half of the participants experience solicited systemic and local adverse events, including fatigue, chills, headache, myalgia and pain at the injection site across both vaccinations (99). The above two clinical trials confirm the good effect of the mRNA vaccine and support the further evaluation of them to be candidate vaccines for COVID-19.

In a randomized clinical trial of 103 patients with severe or life-threatening COVID-19, convalescent plasma transfusion therapy does not show statistically significant improvement in the time to clinical improvement (defined as patient discharged alive or reduction of 2 points on a 6-point disease severity scale) within 28 days, compared with the standard treatment group alone (86). And there is no significant difference in 28-day mortality and time from randomization to discharge, while the rate of viral polymerase chain reaction (PCR) results turns from positive at baseline to negative at up to 72 has been greatly improved. It is worth noting that two participants have adverse reactions within a few hours after convalescent plasma transfusion, including chills, rashes, shortness of breath, cyanosis, and severe dyspnea (86). However, several limitations cannot be ignored. Observing clinical improvement takes longer to confirm the response and recovery of severe COVID-19 patients. The quality of the convalescent plasma products, the timing of convalescent

plasma transfusion and the selection of the patients are all factors that must be considered for subsequent large-scale clinical applications.

We summarized the progress of drug discovery since the epidemic outbreak in *Figure 3*.

The possibility of the use of MgIG for the treatment of COVID-19

Antiviral Effect

SARS-CoV-2, a single-stranded RNA virus, is the third coronavirus causing severe respiratory disease in humans. The two previous coronaviruses, SARS-CoV and MERS-CoV, cause SARS (118) and MERS, respectively (119). The structural protein of SARS-CoV-2 is mainly composed of spike protein (S protein), envelope glycoprotein, membrane glycoprotein and nucleocapsid protein. When SARS-CoV-2 infects the host cell, the surface S protein is priming by transmembrane protease serines (TMPRSS2). As a common surface receptor for SARS-CoV and SARS-CoV-2, angiotensin-converting enzyme 2 (ACE2) can combine with the receptor-binding domain (RBD) of S protein to play its role as a channel for the virus to infect host cells (120). The binding affinity of SARS-CoV-2 to ACE2 is 10–20 times that of SARS-CoV (121,122), which explains the reason why SARS-Cov-2 is more contagious to a certain extent. SARS-CoV-2 and its induced cytokine storm can increase ACE2 expression in host cells, further accelerating viral infection and transmission. Thus, reducing ACE2 expression or inhibiting the bind of ACE2 to the surface spike glycoprotein of the virus may be an effective strategy for blocking viral infection (121,123).

Glycyrrhizic acid compounds with antiviral effects, have been used in the treatment of SARS as early as 2003. Glycyrrhizin is found to inhibit the process of viral replication, adhesion and infection in vero cells and lung epithelial (A549) cell (124-126), these effects may be related to its induction of NO synthase (125). In addition, glycyrrhizin effectively inhibits replication of human immunodeficiency virus (HIV) in cultures of peripheral blood mononuclear cells from HIV-seropositive patients (127). Glycyrrhizic acid also has high antiviral activity against varicella zoster virus, coxsackievirus and enterovirus and rotavirus (128-130). The statistical analysis of herbs and formulae for treating COVID-19 proposes that glycyrrhizic acid compounds have good immunoregulatory and antiviral effects (131). Glycyrrhizin

may be combined with ACE2 through molecular docking simulation technology (132). Glycyrrhizic acid metabolizes into glycyrrhetinic acid, which suppresses the expression of androgen target genes TMPRSS2 (133). Moreover, some of important antiviral drugs commonly used in China contain Glycyrrhizin ingredients, such as Lianhua Qingwen capsule, Maxing Shigan decoction and Sijikangbingdu herbal mixture (23,134-136). A case of severe COVID-19 patient with a negative PCR result but a positive antibody test recovers after receiving diammonium glycyrrhizinate and vitamin C replacement therapy (137). These observations suggest that glycyrrhizic acid compounds could be used as potential antiviral drugs by inhibiting the replication, proliferation to take control of the spread of SARS-CoV-2 (22).

As the fourth-generation preparation of glycyrrhizic acid, MgIG hydrolyzes to glycyrrhetinic acid in the body, its structure is similar to steroid hormones. MgIG is often used in the treatment of viral hepatitis. It inhibits the replication of hepatitis virus, showing its better effect than previous generations of glycyrrhizic acid preparations (48-52). ACE2 is expressed in lung, liver, kidney, heart, brain, intestine and other tissue cells, while MgIG has protective effects on these organs and tissues in various disease states. Are these effects related to the inhibition of ACE2? It is worth exploring.

Inhibition of cytokine storm and oxidative stress

Cytokine storm, also known as cytokine cascade, is an excessive inflammatory response, which often occurs under the influence of external stimuli, such as infection of viruses and bacteria (138). Cytokine storm starts the attack of the immune system on tissues and organs, further causing acute respiratory distress syndrome (ARDS) and multiple organ failure.

SARS-CoV-2 infects the human body, first characterized by increased secretion of early response cytokines such as IL-1, and TNF-α, further promoting the secretion of anti-inflammatory cytokines to adjust the degree of inflammatory response and maintain immune homeostasis (139). When the balance between pro-inflammatory and anti-inflammatory is broken, early response cytokines could further trigger a series of cytokines' excessive activation and release (such as IL-2, IL-6, IL-8, IL-12, MIP-1α and MIP-1β), ultimately causing the out of control of inflammatory response and develop into cytokine storm (140,141). In addition, redox homeostasis generally occurs during viral
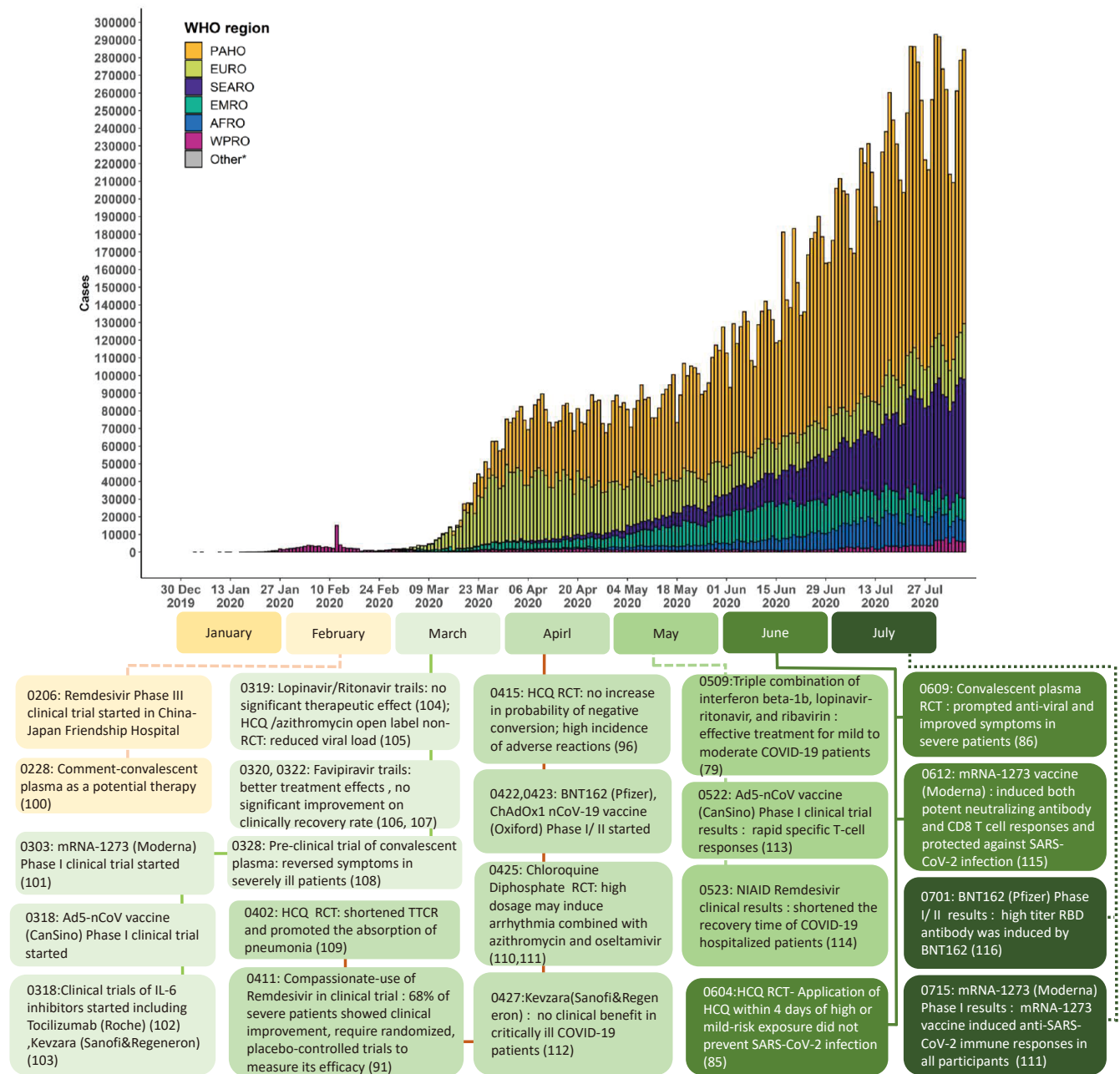
Figure 3 Progress of COVID-19 treatment drugs. As shown above, the therapy and drugs mainly include comment-convalescent plasma, Moderna, CanSino, remdesivir, chloroquine, lopinavir/ratonavir, etc. (79,85,86,91,96,100-116). The column chart above figure 3 is from the WHO report (117). PAHO, Pan American Health Organization; EURO, European Region; SEARO, South-East Asia Region; EMRO, Eastern Mediterranean Region; AFRO, African Region; WPRO, Western Pacific Region; COVID-19, coronavirus disease 2019; Ad5-nCoV, recombinant adenovirus type-5 vectored novel COVID-19; IL-6, interleukin-6; HCQ, hydroxychloroquine; RCT, randomized clinical trial; TTCR, time to clinical recovery; NIAID, national institute of allergy and infectious disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; RBD, receptor binding domain.

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infections, such as human immunodeficiency virus type-1 (HIV-1) (142), hepatitis B virus (143,144), and influenza A virus infection (145). Clinical trials show that COVID-19 patients have high levels of cytokines, also accompanied by oxidative stress in various degrees (10,146). In alveolar type II cells of elderly COVID-19 patients, the redox-active genes like SOD3, transcription factor 4 (ATF4) and metallothionein 2A (M2TA) are down-regulated significantly (147). Mitochondria dysfunction-mediated oxidative stress is indicated as a key player in COVID-19 pathogenesis and severity (148,149). Thus, the interaction of inflammation and oxidative stress will further worsen the condition of COVID-19 patients.

MgIG has shown anti-inflammatory, antioxidant, and immune-regulating effects as mentioned above. MgIG reduces the production and release of IL-1β, IL-6 and TNF-α, and inhibits the migration and activation of neutrophils, resulting in the improvement of inflammatory response and inflammatory cell infiltration of liver, kidney, lung and nervous system (39,41,46,62,69). These results indicate that MgIG may block the further development of the inflammatory response at an early stage of COVID-19. Meanwhile, MgIG significantly decreases NOX1, NOX2 and NOX4 expression (39,45), inhibits ROS and iNOS production, normalizes SOD and MDA level (39,41,45,57,71), therefore, MgIG effectively inhibits oxidative stress response in the body. In terms of mechanism, MgIG may inhibit the activation of inflammation and oxidative pathways, such as TLR4/NF-κB, TGF-β1/Smad, JAK2/STAT3 and p38 MAPK/Akt/NOX4 signaling pathways (43,45,68).

In general, MgIG may play a critical role in protecting against pro-inflammatory cytokine-induced inflammation and oxidative stress in different diseases, and it is expected to be an effective drug to ameliorate cytokine storm and restore redox balance for COVID-19.

Improvement of multiple organ damage

The clinically significant pathological features of COVID-19 patients are lung lesions by computed tomography (CT) scans, including single or multiple ground-glass opacities (GGOs) in the early stage, and then the number of lesions like pulmonary consolidation, and paving appearance is increased in the later stage (150,151). Histopathologic examination of lung biopsy tissues reveals diffuse alveolar damage and interstitial fibrosis (152), proteinaceous exudate, edema, focal reactive hyperplasia of

pneumocytes with patchy inflammatory cellular infiltration, and multinucleated giant cells (153). Glycyrrhizin as an inhibitor of high mobility group box-1(HMGB1) attenuates pulmonary hypertension (154,155) and acute lung injury (156,157). MgIG significantly inhibits inflammation response and oxidative stress, reduces collagen deposition and slows down the process of pulmonary fibrosis. Its action mechanism may be related to the regulation of TGF-β, NF-κB and MAPK pathways (43,45,158).

In addition to the damage of the respiratory system, clinical evidence shows that COVID-19 patients have a very high proportion of organ damage including liver, kidney, heart, brain or others, and the cause of this condition may have a certain relevance to ACE2 expressed widely in body (17). Among 99 COVID-19 patients, 43 patients have abnormal liver function, and 7 patients have different degrees of kidney injury (146). In the early study report of 41 patients, about 12% of patients have acute myocardial injury (7), usually with abnormal myocardial enzymes (159). Among the 52 patients with severe novel pneumonia, 12 of them suffer heart damage and 9 of them have died (160). Equally importantly, the abnormal mental behavior of COVID-19 patients cannot be ignored (161). The latest pathological results obtained from systematic autopsy (37 cases) and percutaneous multiple organ biopsy ("minimally invasive autopsy", 54 cases), show multiple organs with different extent of acute injury in lung, liver, spleen, kidney, heart, etc. Detected by PCR, immunohistochemistry and transmission electron microscopy, SARS-CoV-2 infection are found in lung, liver, heart, kidney, spleen, etc., possibly resulting in direct organ injury by inducing lymphocyte degeneration, necrosis, macrophage proliferation, and neutrophil infiltration (162). Additionally, brain hyperemia and edema, partial neuron degeneration, and ischemic changes are detected in nervous system of these patients (162). These observations make it clear that SARS-CoV-2 not only attacks the respiratory system to cause pneumonia and respiratory failure, but also drive injury and even failure of multiple organs.

As showed in *Figure 2*, MgIG improves liver injury induced by various factors, decreases oxidative stress and inflammatory response, normalizes AST, ALT and DBIL levels, and restores liver function (54-57,67-71,163). For kidney injury, MgIG stabilizes the structure of podocytes to reduce proteinuria, pro-inflammatory response and oxidative stress (38,41,75). Moreover, MgIG improves the contraction of myocardial cells, inhibits myocardial hypertrophy and fibrosis (74). MgIG also enhances

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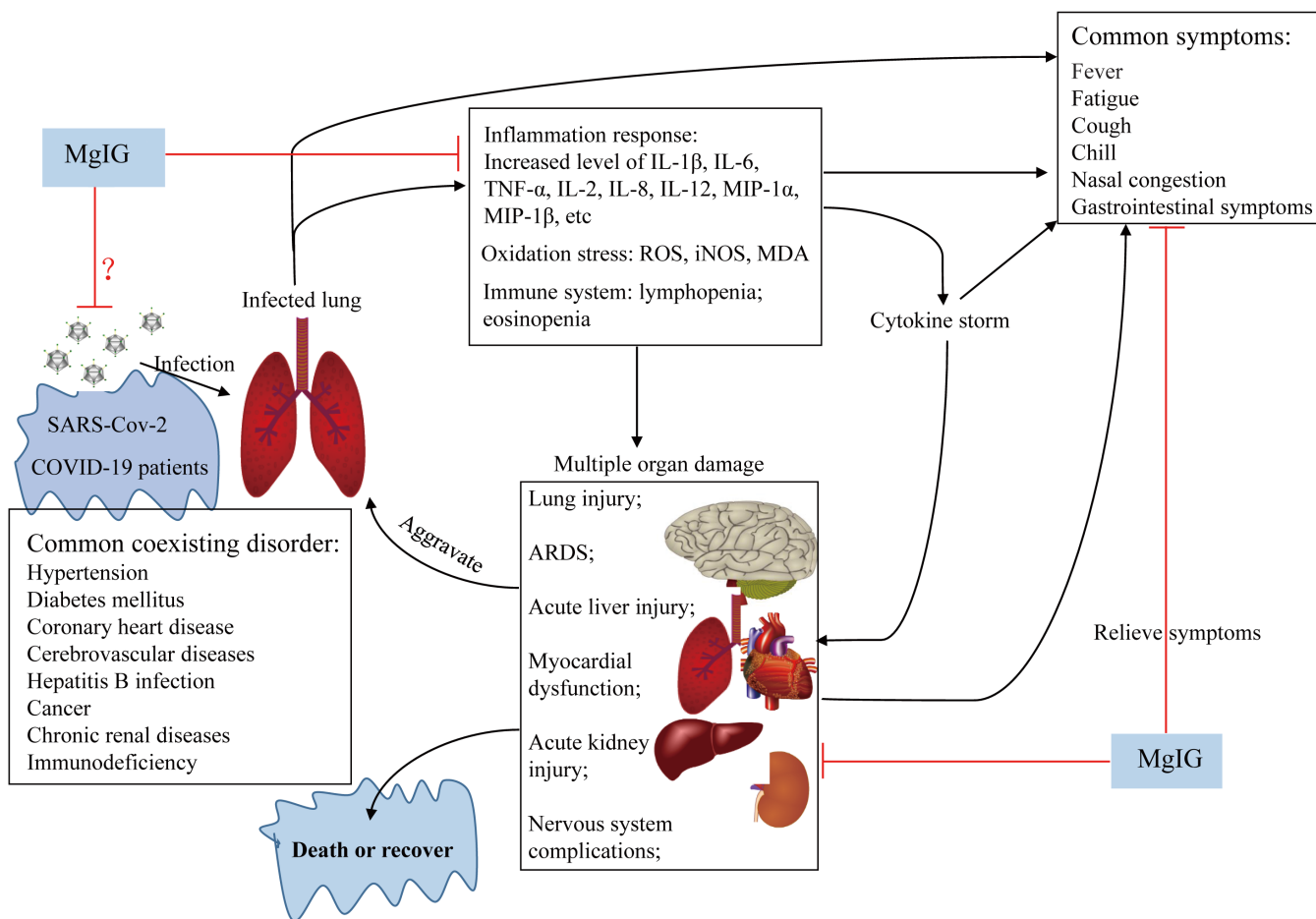
Figure 4 Summary of action modes of magnesium isoglycyrrhizinate. MgIG, magnesium isoglycyrrhizinate; SARS-CoV-2, Severe acute respiratory syndrome coronavirus -2; COVID-19, coronavirus disease 2019; IL-1β, interleukin-1β; TNF-α, tumor necrosis factor-α; ROS, reactive oxygen species; MIP-1α, macrophage inflammatory protein 1 alpha; iNOS, inducible nitric oxide synthase; MDA, malondialdehyde; ARDS, acute respiratory distress syndrome.

cognitive ability and improves depression-like behavior (46,47). Therefore, MgIG could ameliorate the multiple organ damage caused by the infection of SARS-CoV-2.

Based on the clinical efficacy and basic research results of MgIG mentioned above, the application of MgIG in this program may ameliorate cytokine storm and oxidative stress induced by the SARS-CoV-2 infection of host cells, reduce the injury of multiple organs in COVID-19 patients. Here, we summarized the full text related to action modes of MgIG shown in *Figure 4*. In the "Management Standard for Mild and Common Patients of Coronavirus Disease 2019 (COVID-19) (Second Edition)" issued by the National Health Commission of the People's Republic of China, the intravenous drip solution of MgIG is included in supportive

treatment. MgIG 150–200 mg is added to 250 mL of 5% glucose, intravenous drip, once a day, 7 to 14 days as a course of treatment.

Safety

According to the drug instructions and clinical experiences, the daily dosage of MgIG for adult patients is between 100–200 mg, generally not more than 200 mg. In elderly patients, the dosage of MgIG is also within the above range (164,165), but there is no clear clinical dosage instruction for pregnant women. MgIG (25 mg iv, qd) is often used in combination with ganciclovir for the treatment of infant cytomegalovirus hepatitis, significantly improving the

infant's liver function, reducing the viral load, and being able to improve symptom with fewer adverse reaction (166,167). In children with severe hand-foot-mouth disease and associated liver injury, MgIG injection (3–5 mg/kg·iv, qd) significantly decreases serum ALT and AST levels, and restores normal liver function (168). Moreover, MgIG injection (100 mg iv, qd) can reduce serum levels of IL-7, chemokine (C-X-C motif) ligand 8 (CXCL8) and CXCL10 in children with autoimmune hepatitis, and inhibit inflammation caused by excessive immune response (169).

In addition to the different dosages for different ages, the compatibility of MgIG with some drugs requires special attention in clinic. The mixture of 15 mg ambroxol hydrochloride injection and 100 mg MgIG injection produces white flocs (170). Similarly, after mixing 100 mL ciprofloxacin lactate sodium chloride injection and 150 mg MgIG injection, white flocs and sediments appear immediately, which do not disappear after shaking, and there is no change after 24 h (171). However, these have not been proved whether this adverse phenomenon will cause adverse reactions to the human body. In addition, when combined with injections such as ademetionine 1,4-butanedisulfonate, sodium ferulate, pazufloxacin mesylate, etc., similar phenomena also exist (163,172,173). Combination of drugs is common in clinical practice, but drug interactions are prone to occur. The flocculation produced by the combination of MgIG injection and other drugs for COVID-19 patients indicates that the compatibility between these drugs is poor. There may be a chemical reaction, which is prone to adverse reaction. In addition, these concentrations of drug combination will also be affected. When this happens, it is recommended to stop the medication (MgIG injection combined with other drugs) and adopt a separate interval administration method for COVID-19 patients.

Clinical studies have found that increased or long-term use of glycyrrhizic acid preparations may induce pseudoaldosteronism, mainly manifested as hypokalemia, increased blood pressure, sodium, fluid retention, edema, weight gain and other pseudo-aldosterone symptoms (174). The pseudoaldosteronism caused by glycyrrhizic acid preparations is mainly related to 18-β isomer. The target organ distribution of 18-α and 18-β isomers is different. The concentration of 18-α isomer is significantly higher than that of 18-β isomer in the liver, but lower than 18-β isomer in the kidney in rats (175). At the same time, 18-β isomer inhibits the activity of 11 β-hydroxysteroid dehydrogenase (11 β-OHSD) more obviously in rat kidney. As a result of hypokalemia, symptoms such as fatigue, low muscle strength and arrhythmia may occur in patients (hypertension or heart failure) (176). Therefore, it is necessary to fully observe the determination of serum potassium, and stop the administration when abnormality is detected. The18α-isomer glycyrrhizic acid can also inhibit 11 β-OHSD activity, resulting in a decrease of serum potassium ion concentration, but compared with 18β isomer, its effect is significantly weaker in guinea pigs and rats. The main adverse reaction of glycyrrhizic acid preparations is the inhibitory effect of renal 11 β-OHSD, while 18α-glycyrrhizic acid stereoisomers contained as high as 98% in MgIG has very little effect on renal 11 β-OHSD (177,178). Consistently, MgIG injection (100, 150, and 200 mg iv, qd) have no side effects of pseudoaldosteronism in the phase 2 and 3 clinical studies of viral hepatitis and acute liver injury according to the description in the drug's instructions (179).

In addition to pseudoaldosteronism, there are some other adverse reactions in clinical trials, but the incidence is low. In the phase III clinical trial of 332 cases of viral hepatitis dominated by Chia Tai Tianqing Pharmaceutical Group, there is one case each of palpitations, eyelid edema, dizziness, rash, and vomiting with the treatment of MgIG injection (100, 150 mg iv, qd) (179). In the phase III clinical trial of MgIG injection (200 mg iv, qd) on acute drug-induced liver injury, 14 out of 354 patients have adverse reactions, mainly including palpitations, allergies, hypokalemia, abnormal liver function indicators, etc. The above symptoms are mild and tolerable. A number of clinical studies have confirmed the safety of MgIG injection (180-183). The meta-analysis results of clinical trials also show that the incidence of adverse drug reactions in patients in the MgIG injection treatment group is significantly lower than that of other glycyrrhizic acid preparations (184). However, clinical trials have the limitations. Phase I clinical trial shows the safety of MgIG injection, but the supporting populations are all from China. For people from other countries, further experiments and clinical evidence are needed (185). And as mentioned above, the Phase III clinical trial of MgIG led by Chia Tai Tianqing is mainly for patients with viral hepatitis, and lacks universality for other types of hepatitis (179).

In general, MgIG is safe for clinical use. During the treatment with MgIG, blood pressure as well as serum potassium and sodium concentrations should be checked

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regularly. The combined use of MgIG with thiazides such as etanic acid and furosemide, antihypertensive diuretics such as triclosan and chlorthalidone, may increase potassium excretion, therefore, it is necessary to monitor serum potassium.

As a drug with higher effectiveness and safety in glycyrrhizic acid preparations, MgIG is widely used clinically. MgIG has a low probability of adverse reactions when used within a safe dose, but attention should be paid to the compatibility of contraindications and changes in potassium ion concentration. For COVID-19 patients, the adjuvant treatment of MgIG will improve the multiple processes from SARS-CoV-2 infection to organ injury, and slow down the disease process in all directions to restore the patient's health. MgIG has been used as a therapeutic drug in the clinical treatment of COVID-19 in China. The effective dose of MgIG, specific treatment plans and precautions need to be continuously tried and summarized in the clinic.

Conclusions

The COVID-19 epidemic is serious and has a high mortality rate. More than 87 million cases of COVID-19 and over 1 million deaths have been reported as of January 7, 2021. All countries in the world are facing great challenges. Therefore, the active implementation of effective treatment is very important. MgIG has anti-inflammatory, anti-oxidative, anti-viral, and immunomodulatory effects, protecting liver, kidney, heart, lung, brain, and other organs from damage under disease conditions. MgIG injection as a mature drug is used to treat hepatic disorders for a long time. This narrative review provides the evidence supporting the recommended MgIG as supportive therapy in the "Management Standard for Mild and Common Patients of Coronavirus Disease 2019 (COVID-19) (Second Edition)", which is jointly issued by National Health Commission of People's Republic of China and National Administration of Traditional Chinese Medicine. MgIG may help shorten the course of COVID-19 patients, effectively curb the transition from mild and common patients to severe and critical illnesses, prevent organ failure and reduce mortality. Therefore, MgIG is expected to play an active role in the clinical practice of the prevention and treatment of COVID-19.

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Footnote

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