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Drug-induced organ injury in coronavirus disease 2019 pharmacotherapy: Mechanisms and challenges in differential diagnosis and potential protective strategies

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Abstract

The world is currently facing an unprecedented pandemic caused by a newly recognized and highly pathogenic coronavirus disease 2019 (COVID-19; induced by SARS-CoV-2 virus), which is a severe and ongoing threat to global public health. Since COVID-19 was officially declared a pandemic by the World Health Organization in March 2020, several drug regimens have rapidly undergone clinical trials for the management of COVID-19. However, one of the major issues is drug-induced organ injury, which is a prominent clinical challenge. Unfortunately, most drugs used against COVID-19 are associated with adverse effects in different organs, such as the kidney, heart, and liver. These side effects are dangerous and, in some cases, they can be lethal. More importantly, organ injury is also a clinical manifestation of COVID-19 infection. These adverse reactions are increasingly recognized as outcomes of COVID-19 infection. Therefore, the differential diagnosis of drug-induced adverse effects from COVID-19-induced organ injury is a clinical complication. This review highlights the importance of drug-induced organ injury, its known mechanisms, and the potential therapeutic strategies in COVID-19 pharmacotherapy. We review the potential strategies for the differential diagnosis of drug-induced organ injury. This information can facilitate the development of therapeutic strategies, not only against COVID-19 but also for future outbreaks of other emerging infectious diseases.

KEYWORDS

antiviral drug, biomarker, COVID-19, drug-induced organ injury, inflammation, oxidative stress, viral infection

1 | DRUG THERAPY OF COVID-19

COVID-19 belongs to the coronavirus superfamily; the first cases of human infection were diagnosed in Wuhan city, China.[1–3] There is a good body of evidence demonstrating that COVID-19 severely affects the respiratory system.[3,4] However, it is clearly recognized that COVID-19 infection represents a multiorgan disease that can affect almost every organ, including the brain,[5] liver,[6] gastrointestinal tract,[7] kidneys,[8,9] and cardiovascular system with the occurrence of thrombotic episodes.[10] A high mortality rate has been reported in the old population and patients with background diseases (e.g., asthma, diabetes, cardiovascular abnormalities, and immunosuppressive-related diseases).[3,11,12]

There is no specific and fully approved pharmacotherapeutic regimen for the management of COVID-19 infection to date. Therefore, different countries have treated patients with conventional drugs that were previously administered against similar outbreaks (e.g., Ebola viral disease), the severe acute respiratory syndrome coronavirus SARS-CoV, and the Middle East respiratory syndrome coronavirus (MERS-CoV).[13,14] In actual fact, many of these drugs have been repurposed for treating COVID-19.[15–17] The best known pharmacotherapeutic intervention against COVID-19 includes antimalarial agents (chloroquine [CQ] and hydroxychloroquine [HCQ]), azithromycin, favipiravir, lopinavir, ritonavir, remdesivir, ribavirin, and arbidol (Table 1).[3,16,18–20] Although not clinically investigated yet, redesigning/repurposing other antiviral agents, such as sofosbuvir, tenofovir, galidesivir, cidofovir, and brincidofovir also have been suggested as potential therapeutic strategies against COVID-19 infection.[15,17] Other therapeutic interventions, including monoclonal antibodies, antisense RNA, convalescent plasma, and mTOR inhibitor rapamycin, and calcineurin inhibitor cyclosporin A have also been tested against COVID-19.[21–27] In the following sections, the potential mechanisms of organ injury induced by these drugs are discussed.

2 | ORGAN INJURY AS A FEATURE OF DRUGS USED IN COVID-19 PHARMACOTHERAPY: THE KNOWN MECHANISMS OF TOXICITY

As previously mentioned, drug-induced organ injury can persist in COVID-19 infected patients with the current pharmacotherapy regimens (Figure 1). Any detrimental effects of drugs outside their estimated medicinal effects upon clinical uses are considered adverse drug reactions. Drug-induced heart injury and arrhythmia, hepatotoxicity, and renal failure are reported in the association of drugs administered against COVID-19. Identifying organ injury mechanisms could serve as a critical step in diagnosing and treating this complication (Figure 1). Therefore, in the next section, the potential mechanisms for drug-induced organ injury of COVID-19 pharmacotherapy are discussed.

2.1 | Drug-induced hepatotoxicity (DILI)

DILI is the most prevalent cause of drug withdrawal from the market or stopping drug administration against a specific disease.[44,45] Hence, the identification of DILI mechanisms could have a significant clinical value for managing hepatic injury and the development of therapeutic strategies against this complication.[45,46] Several intracellular mechanisms have been proposed for DILI.[47] Enhanced generation of reactive oxygen species[48] and the induction of oxidative stress is a well-known mechanism associated with DILI.[47,49,50] ROS could hit different cellular targets, such as lipids, proteins, and DNA.[47] Cellular organelles, such as mitochondria and

TABLE 1 Drugs were tested to manage patients with the newly emerged COVID-19 and their hepatotoxic effects

Drugs	Mechanism(s) of action	Reports of hepatotoxicity	Reference(s) (hepatotoxicity)	Reference(s) (administration in COVID-19)
Antimalarial agents (chloroquine and hydroxychloroquine)	Preventing virus penetration to cells	+	[28]	[29]
Azithromycin		Rare/Idiosyncratic	[30–33]	[29, 34]
Favipiravir	Selective inhibition of RNA-dependent RNA polymerase enzyme in RNA viruses	Not reported to date	-	[35,36]
Ritonavir, lopinavir	Protease inhibition in retroviruses	+	[37–39]	[19]
Remdesivir	Adenosine analog, insertion into viral RNA chains, and termination of replication	Not reported to date	-	[16,40]
Ribavirin	Guanosine analog, inhibition of RNA replication	+	[41,42]	[43]
Arbidol	Prevention of virus entry into target cells	Not reported to date	-	[20]

Note: COVID-19, coronavirus 2019.

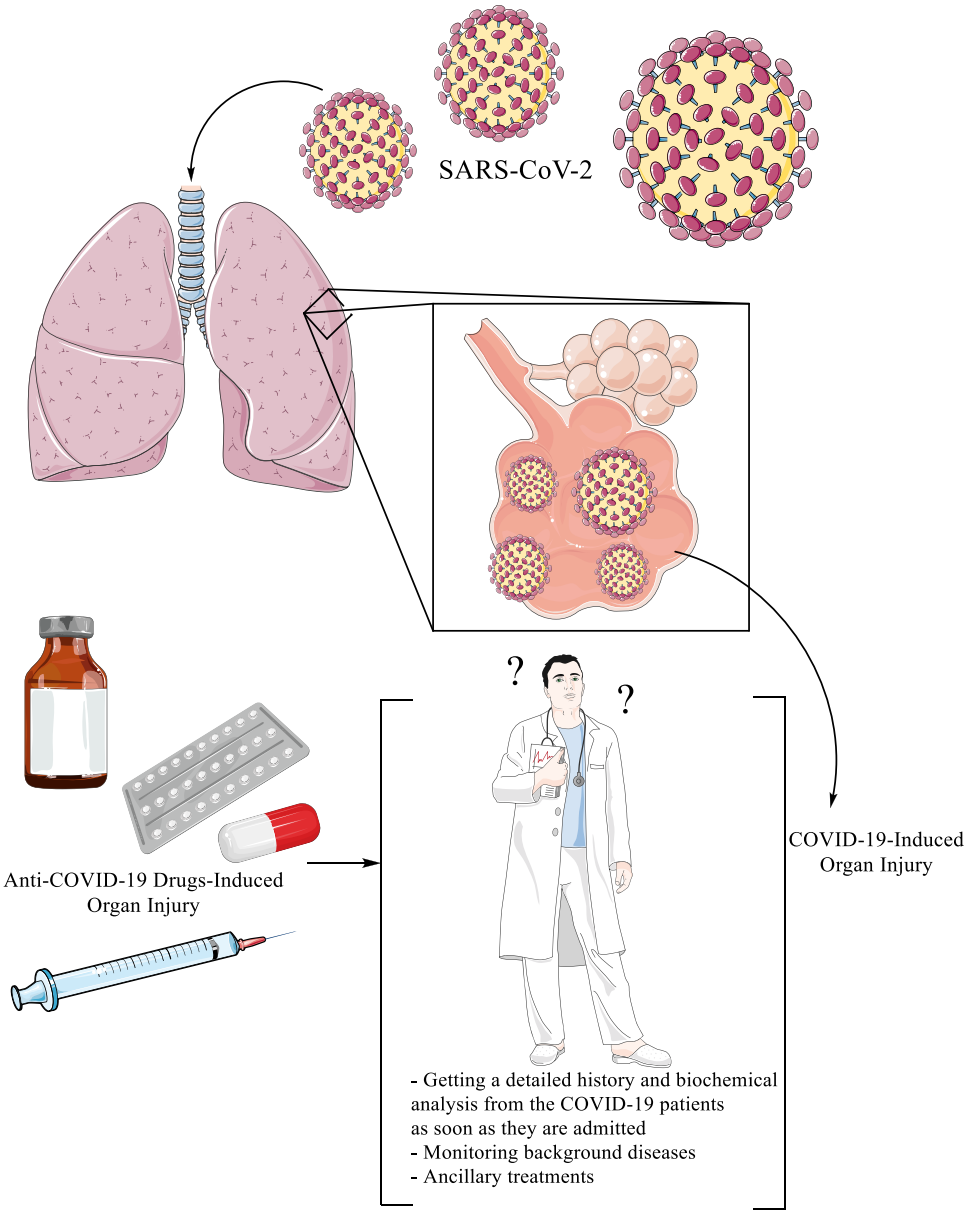

FIGURE 1 The diagnosis of COVID-19-induced organ injury from drug-induced toxicities is a major clinical challenge

endoplasmic reticulum (ER), could also be affected by ROS.[51] Oxidative stress, mitochondrial injury, and disturbances in cellular calcium ion (Ca^{2+}) homeostasis (ER stress) are mechanistically interrelated events that could finally lead to cell death through apoptosis and/or autophagy.[51–54] In the following section, the reported mechanisms of hepatotoxicity induced by anti-COVID-19 drugs are reviewed (Table 1).

Antimalarial agents, including CQ and HCQ, are among the first drugs tested to treat COVID-19 disease.[13,55] The idea came from in vitro studies and previous clinical trials that reported the effectiveness of these drugs against other virus outbreaks.[20,56] It has been suggested that CQ and/or HCQ prevent the virus membrane fusion and endocytosis to the target cells.[20] The immune-modulatory properties of these drugs might also be involved in their antiviral mechanisms.[37] Unfortunately, it is well-known that these drugs are hepatotoxic.[57–60] Several cases of antimalarial DILI have been reported.[56,61,62] Although it is a challenge to differentiate DILI from COVID-19-induced liver injury, various authors reported the hepatotoxic effects of these drugs in COVID-19 patients.[28] The hepatotoxicity induced by CQ and HCQ has been stopped after the cessation of drug administration.[28]

At the cellular level, CQ and HCQ are able to induce severe oxidative stress and mitochondrial impairment in hepatocytes.[60,63] The reactive quinone metabolite of CQ or HCQ is involved in the oxidative stress and mitochondrial impairment induced by these drugs.[64–66] Some investigations mentioned the use of antioxidants, such as lipoic acid, *N*-acetylcysteine, carnosine (CAR), taurine (Tau), or quercetin in the management of antimalarial drugs-induced

hepatotoxicity.[59,67] Based on these data, it can be strongly recommended to test a cotreatment of one high-potential antioxidant upon treatment with CQ or HCQ in patients suffering from COVID-19. Unfortunately, the hepatotoxicity induced by other anti-COVID19 drugs (e.g., azithromycin) occurs in an idiosyncratic manner. Hence, there is no specific mechanism for this form of drug-induced hepatotoxicity.

An interesting DILI mechanism, especially for idiosyncratic DILI, is the "drug-inflammation interaction" theory.[68–70] It has been found that the presence of a mild background inflammation could enhance the liver injury induced by drugs (e.g., azithromycin, CQ, diclofenac) that are not hepatotoxic at the same doses when administered to control animals.[71–73] Conversely, some studies have mentioned that the simultaneous presence of an infection in the liver (e.g., hepatitis) could enhance the hepatotoxicity induced by different drugs.[71] One of the proposed mechanisms for enhancing drug-induced hepatotoxicity during inflammation could be associated with the production of reactive drug metabolites by inflammatory cells[73] (Figure 2). Myeloperoxidase is an enzyme present in inflammatory cells, such as macrophages and neutrophils. Myeloperoxidase is able to convert some drugs to reactive cytotoxic metabolites.[74–78]

The wide-speared and severe inflammatory response is an important clinical manifestation of COVID-19.[79] Severe inflammatory cell infiltration and cytokine release have been reported in different organs and tissues of COVID-19 patients.[79,80] Therefore, the inflammation-drug interaction in these patients might be a plausible mechanism of liver (or other organs) injury. Interestingly, it has been found that the hepatotoxicity of antimalarial drugs, such as HCQ and amodiaquine, was boosted in the presence of an inflammatory response in both experimental models and clinical settings.[62,74] Falcao et al.[62] reported severe HQ-induced hepatotoxicity in a COVID-19 patient with a severe inflammatory response. Drug inflammation could also occur in organs other than the liver (e.g., kidney).[81] These data could mention the importance of anti-inflammatory therapeutic options in COVID-19. Today, anti-inflammatory and corticosteroid drugs, such as dexamethasone (DEX), have found clinical value in managing COVID-19 patients.[82] Therefore, concomitant administration of anti-inflammatory agents (e.g., DEX) not only could decrease the level of inflammation in COVID-19 patients but also might low the risk of drug-inflammation interaction and drug-induced organ injury (Figure 2).

TABLE 2 Drug-induced renal injury in COVID-19 pharmacotherapy

Drugs	Case reports of renal injury	Reference(s) (renal injury)
Antimalarial agents (chloroquine and hydroxychloroquine)	+	[8]
Azithromycin	+	[92]
Favipiravir	+	[93]
Ritonavir, Lopinavir	+	[94,95]
Remdesivir	–	[96]
Ribavirin	–	[96]
Cyclosporine A	–	[89]
Rapamycin	+	[89]
Arbidol	–	-

Note: (+) means adverse effect and (−) no adverse effect has been reported.

2.2 | Drug-induced renal injury in COVID-19 pharmacotherapy

Renal injury is another major complication induced by several anti-COVID-19 drugs (Table 2).[8,9] Renal injury can occur as a clinical

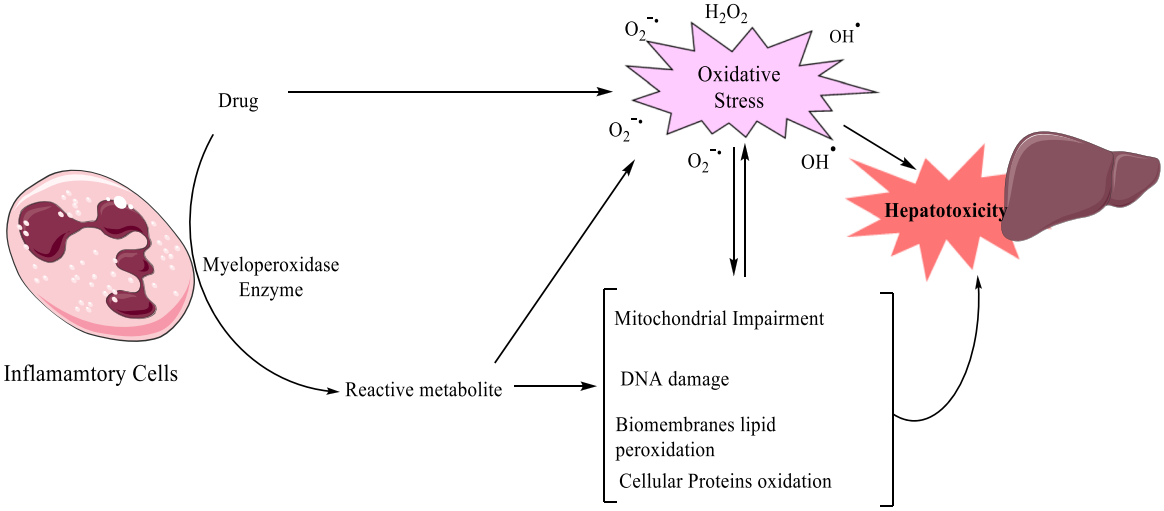

FIGURE 2 A schematic representative of inflammatory cell-mediated reactive metabolites formation. Myeloperoxidase enzyme could produce reactive metabolites, leading to oxidative stress and/or directly affect different cellular targets

manifestation of COVID-19 disease.[83,84] Anti-COVID-19 drugs, such as CQ and HCQ, are not recommended in patients with liver or renal diseases.[85,86] In this context, Risambaf and colleagues have reported that COVID-19-induced renal and hepatic failures might increase the possibility of CQ and HCQ-induced liver and renal toxicity during COVID-19 patients.[87] Many other drugs (oseltamivir, lopinavir/ritonavir, and ribavirin) are metabolized in the liver and excreted through urine.[88] Hence, the administration of these drugs might be associated with renal injury risk (Table 2). Drugs such as rapamycin (an mTOR inhibitor) and cyclosporine A (a calcinurin inhibitor) also have been proposed for use against COVID-19.[21,22] However, renal injury is a potential challenge induced by mTOR inhibitors, such as rapamycin.[22,89] Cyclosporine A seems to be well-tolerated and no significant renal injury has been reported in the association with its administration to date[89,90] (Table 2). However, the administration of cyclosporine A to patients with significant renal impairment is not recommended.[91] Based on these data, monitoring renal function in COVID-19 patients before and after drug therapy is critically important.

There is ample evidence that reported an increased incidence of acute renal injury during the COVID-19 outbreak, which might be due to the severe renal inflammation induced by the disease.[97] Therefore, any injury to these organs (liver and kidney) can induce some adverse effects on drug metabolism, metabolite excretion, dosing, and/or expected concentrations of the pharmaceutics, and enhance drug-induced organ risk injury, in COVID-19 patients. The presence of inflammation in the kidney of COVID-19 patients might also enhance the risk of drug-induced renal injury.

The risks of renal injury induced by remdesivir, a Food and Drug Administration (FDA)-approved drug against COVID-19, has been widely reviewed.[98] Adamsick et al.[98] reported that even though the mitochondrial toxicity of remdesivir is significantly low, there is apprehension regarding the potential toxicity of this anti-COVID-19 agent in patients suffering renal diseases due to both remdesivir actions and the potential accumulation of its sulfobutylether-b-cyclodextrin (SBECD) carrier. Herlitz et al.[99] have reported that renal toxicity takes place after prolonged exposure to this agent. Nevertheless, Wang et al.[1] have claimed no increased risk of renal toxicity in patients treated with remdesivir. Similar to the observations made by Wang et al., Mulangu et al. have shown no significant renal adverse events in Ebola patients treated with remdesivir.[100]

Previous studies mentioned that the cellular mechanism underlying the nephrotoxicity induced by several drugs is associated with oxidative stress and mitochondrial impairment[101] (Figure 3). Mitochondria are essential organelles in kidney tissue.[102] The proper function of renal mitochondria guarantees enough energy (ATP) for the reabsorption of essential chemicals.[102] Hence, drug-induced mitochondrial injury in the kidney could lead to serum electrolytes imbalance.[102–104] Mitochondrial impairment and oxidative stress are two firmly related events.[51] Based on these data, the administration of antioxidants or mitochondrial protecting agents could be used as an axillary treatment for preventing anti-COVID-19 drugs-induced renal injury (Figure 3).

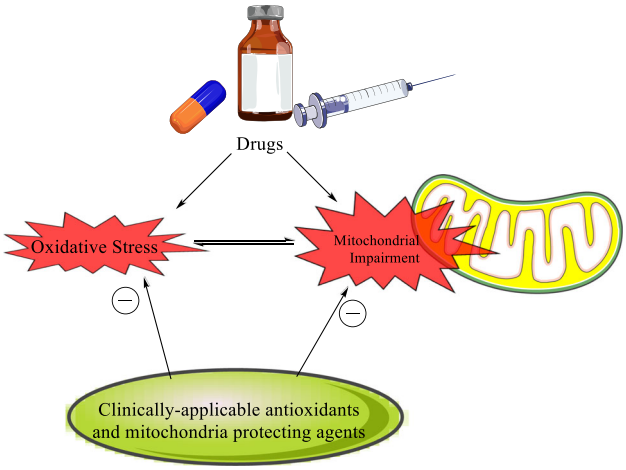

FIGURE 3 Prevent oxidative stress and protect cellular mitochondria as potential strategies to reduce/prevent drug-induced organ injury in COVID-19 pharmacotherapy

Collectively, renal injury is a major adverse event associated with COVID-19 pharmacotherapy. Therefore, close monitoring of renal function, in addition to therapeutic strategies, such as fluid therapy or administration of safe antioxidants and mitochondria-protecting agents, might help to prevent further complications associated with renal impairment in COVID-19 patients.

2.3 | Drug-Induced cardiovascular injury

Cardiovascular injury is a serious complication associated with the administration of several anti-COVID drugs[13] (Table 3). Arrhythmia is the primary manifestation of anti-COVID-19 drugs-induced cardiovascular injury[105,106] (Table 3). Unfortunately, there are no mechanistic clues concerning the cardiovascular injury induced by COVID-19 pharmacotherapy. It has been shown that background cardiovascular diseases, such as hypertension, coronary heart disease, or cardiomyopathy-prone patients to drug-induced cardiovascular events during COVID-19 management.[107] It has been reported that acute cardiac events in COVID-19 hospitalized patients (Wuhan) comprised 16.7% for arrhythmia, 8.7% for shock, and 7.2% for cardiac injury. Additionally, comprehensive investigations reported an increment in in-hospital mortality through cardiac arrhythmia on COVID-19 patients.[108] Unfortunately, the type and severity of arrhythmias associated with COVID-19 have not been precisely described to date.[109] Nevertheless, sinus bradycardia with high-grade atrioventricular block, premature atrial beats, paroxysmal atrial fibrillation, and decreased left ventricular ejection fraction have been reported in COVID-19.[109] Hence, there is a challenge for physicians who want to distinguish these indices from anti-COVID-19 agents-induced cardiovascular diseases.

QT prolongation is the most prevalent cardiac event in anti-COVID-19 drugs-treated patients (Table 3). It has been found that drugs, such as CQ, azithromycin, and ritonavir/lopinavir caused QT

TABLE 3 Drug-induced cardiovascular injury in COVID-19 pharmacotherapy

Drugs	Reports of cardiovascular events	Reference(s) (cardiovascular injury)
Antimalarial agents (chloroquine and hydroxychloroquine)	+	[105]
Azithromycin	+	[106]
Favipiravir	+	[106]
Ritonavir, lopinavir	+	[110]
Remdesivir	+	[106]
Ribavirin	+	[106]
Arbidol	−	-

Note: (+) means adverse effect and (−) no adverse effect has been reported so far.

prolongation.[13] Hence, combining more than one proarrhythmic medication, such as antimalarial agents (CQ and HCQ), azithromycin, favipiravir, ritonavir/lopinavir, remdesivir, ribavirin, sarilumab, and baricitinib, is reported to intensify the risk of QT prolongation[106] (Table 1). Therefore, antimicrobial agents, such as azithromycin and CQ should be cautiously administered in patients with cardiovascular background disease. Therefore, the regular monitoring of the patient's cardiac rhythm is advised in the clinical setting.[111]

The mechanism of drug-induced QT prolongation in cases such as azithromycin has been reported to be attributed to the inhibition of the potassium channels.[112,113] Choy et al.[114] reported successful "normalization of acquired QT prolongation in humans by intravenous potassium." Hence, potassium supplementation might play a key role in preventing, decreasing, or reversing anti-COVID-19 drugs-induced QT prolongation.[115]

Sapp *et al*. recommended three strategies to minimize the risk of drug-induced arrhythmia in COVID-19 pharmacotherapy.[111] The supposed strategies include discontinuing unnecessary medications that could also increase the QT interval, identifying outpatients who are expected to be at low risk for cardiovascular events, and finally performing baseline testing in hospitalized patients.[111] Hence, these criteria must be mentioned in admitted COVID-19 patients. Drugs with lower adverse effects on cardiac rhythm (Table 3) are recommended in COVID-19 patients with background cardiac diseases.

3 | ORGAN INJURY ASSOCIATED WITH COVID-19 INFECTION: A CHALLENGE IN DIFFERENTIAL DIAGNOSIS FROM DRUG-INDUCED TOXICITY

Several reports in the published literature have mentioned hepatic, renal, and cardio-toxicity as critical clinical manifestations of COVID-19 disease.[8,9,13,55,97] Therefore, the diagnosis of drug-induced liver, kidney, and heart injury remains a clinical challenge. Based on the aim of this section, we propose two methodologies: first, allocating the COVID-19 patients into two groups (A and B); Group A, infected patients receiving the anti-COVID-19 drugs; Group B, COVID-19 ones without the same treatment with group A. The results can then be compared. However, it should be highlighted that the proposed procedure is not in accordance with the ethical guidelines. The second clinical suggestion might be the simultaneous use of drug administration in healthy volunteers. This could be a potential strategy to differentiate drug-induced hepatotoxicity, nephrotoxicity, and cardiotoxicity from the manifestation of COVID-19-induced organ injury in clinical settings.

A critical point concerning the differential diagnosis of drug-induced organ injury and viral-infection-associated organ damage is performing comprehensive baseline testing in patients upon their hospitalization.

4 | POTENTIAL CLINICAL INTERVENTIONS TO MANAGE DRUG-INDUCED ORGAN TOXICITY IN COVID-19 PHARMACOTHERAPY

Several protective agents have been investigated against drug-induced organ injury.[116] The safety of the protective agents for critically ill patients is a crucial factor that should be considered in clinical studies. Compounds, such as N-acetylcysteine [117] and supplemental compounds (i.e., CAR and Tau), might be readily used in this grim situation, COVID-19 outbreak, because of safety and a lower rate of adverse reactions.[118,119] Interestingly, there are several reports on the effectiveness of NAC in alleviating the respiratory symptoms of COVID-19.[120–122] The possible effectiveness of NAC in COVID-19 patients could be attributed to its role in preventing oxidative stress and replenishing the cellular glutathione (GSH) as a vital antioxidant system.[120] The protective effects of NAC on mitochondrial indices also have been reported in several studies.[123–125] However, Van Hecke et al.[126] reported that there is yet limited clinical trial data to justify the use of NAC in COVID-19. Based on our previously published work on NAC's positive effects in alleviating severe oxidative stress (e.g., in cirrhosis), we recommend the use and further clinical evaluation of such agents.[52]

Oxidative stress-triggered intracellular routes related to programmed cell death (apoptosis and autophagy), and over-activation of inflammatory cells, as well as immunosuppression in some patients also might play a role in the mechanism of drug/COVID-19-induced toxicity.[127] Therefore, simultaneous administration of anti-inflammatory and high-potential antioxidant agents (e.g., NAC) might mitigate drug and/or COVID-19 adverse effects.[128,129]

As mentioned earlier, the simultaneous use of drug-treated control groups could be an essential strategy for monitoring and prevention of drug-induced adverse reactions in clinical trials under this grim pandemic situation. Importantly, this strategy could help in diagnosing adverse drug reactions from

disease (COVID-19 infection)-induced organ injury. However, as previously mentioned, the situation in virus-infected patients might be quite different (e.g., the presence of inflammation and immunosuppression). Another strategy could be using virus-infected patients as the control group. However, as already mentioned, this method raises important ethical and moral concerns, especially in relation to depriving patients of a potential therapy.

5 | PROSPECTS

In the recent COVID-19 pandemic, many antimicrobial drugs with in silico and in vitro properties against RNA viruses have also been proposed as potential candidates for testing in clinical trials. However, besides the issues associated with the extrapolation of in vitro experiments to the clinical situation, another critical factor that should be considered is adverse drug effects. Therefore, risk assessment is a critical factor for COVID-19 or other similar infectious diseases-related drug therapy.

Considering that most severely ill patients are elderly and patients with various comorbidities, such as asthma, diabetes, and cardiovascular diseases, the importance of organ injury induced by these drugs becomes clearer. Hence, more safe drugs should be considered in these patients. Drugs like arbidol and favipiravir seem to be at a lower risk of hepatotoxic events in humans. However, these drugs have been generically used in some specific regions (e.g., Japan, Russia, and China); hence the lower incidence of liver injury induced by these agents might be associated with a lower drug administration rate. It has been well reported that some of the anti-COVID-19 drugs, such as remdesivir triphosphate, are well-known as weak inhibitors of mammalian DNA and RNA polymerases; hence, it is counted to have a low potential for mitochondrial toxicity and then further organ toxicities. The simultaneous administration of adjuvant treatments (e.g., NAC supplementation) could be a way to prevent adverse drug reactions in the liver and other organs during COVID-19 pharmacotherapy. Finally, it should be mentioned that obtaining a detailed medical history and a comprehensive biochemical analysis of blood biomarkers from the COVID-19 patients as soon as they are admitted is critical for differential diagnosis of drug or disease-induced organ injury.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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