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RESEARCH ARTICLE

INTERACTION OF THERAPEUTIC DRUGS USED FOR TACKLING COVID-19 PATIENTS

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ABSTRACT

Coronaviruses, such as HCoV 229E and HCoV OC43, were identified in the early 1960s. This coronavirus causes the most severe acute respiratory illnesses. SARS is a coronavirus that has been connected to a respiratory illness in the Middle East (MERS). The outbreak of Novel corona virus disease (COVID-19) was initially noticed in mid December, 2019,To improve the success rate of COVID-19treatment, several pharmacological approaches are proposed, and some clinical data are reviewed in the literature. Comorbid patients require many pharmacological therapies. Multiple medication use (polypharmacy) dramatically increases pharmacological adverse effects. As a result, diagnosis and treatment of drug-drug and disease-drug interactions are critical. When prescribing new drugs to COVID-19patients, clinicians should examine the likelihood of drug-drug and disease-drug interactions. Detecting drug-drug and disease-drug interactions of the medications utilized will thus be critical in the treatment of COVID-19. This article will concentrate on the drug-drug and disease-drug interactions of COVID-19 therapeutic medicines. Variations in the expression of a transporter are well recognized to result in changes in the PK/PD of the prescribed medication; hence, prescription medicine during inflammation may be a major contributor to inter-individual variability in drug efficacy and toxicity. It also highlighted the possibility of drug-drug and disease-drug interactions of the specified medicine in the treatment of COVID-19. It will aid in lowering risk in individuals with co-morbidities and providing better therapy with fewer adverse effects.

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INTRODUCTION

Coronaviruses, such as HCoV 229E and HCoV OC43, were identified in the early 1960s and considered to be responsible for minor diseases such as the common cold. They are enclosed viruses, which have a single-stranded positive-sense RNA genome and cause sickness in humans and animals [(1)].This coronavirus causes the most severe acute respiratory illnesses. SARS is a coronavirus that has been connected to a respiratory illness in the Middle East (MERS). SARS-CoV-2 is a recently identified coronavirus that causes severe acute respiratory syndrome. COVID-19. Coronaviruses affect animals and humans' respiratory and digestive systems, including the SARS pandemic in 2002 and the MERS epidemic in 2012 [(2)]. These are zoonotic illnesses that resulted in death rates of more than 10% and 35%, respectively. Cases of pathogenic viral pneumonia caused by a SARS-like illness identified as SARS-CoV-2 in Wuhan, Hubei Province, China, have been confirmed to the World Health Organization (WHO) [(3)]. The outbreak of Novel corona virus disease (COVID-19) was initially noticed in mid December, 2019, has now spread to 215 countries worldwide.On January 30, 2020, the WHO declared this pandemic a "Public Health Emergency of International Concern" in compliance with international health laws (PHEIC). COVID-19was declared a pandemic by the World Health Organization on March 11, 2020. The average incubation time is 5.1 days (range 1–14 days). According to the findings of the study, infectivity begins two days before the onset of symptoms and rapidly decreases within the first week following symptom onset[(4)]. The most common symptoms Fever, dry cough, dyspnea, chest discomfort, tiredness, and myalgia [(5–7)]. The severity of illness can range from moderate to critical, and risk factors for severe illness include older age (65 years) and comorbidities such as diabetes mellitus, heart disease, lung disease, hypertension, and obesity. One of the problems to consider before recommending a medicine to a patient and after therapy is the drug's adverse effects.

The side effects of a medication should be evaluated both before and after treatment. Multiple medication use (polypharmacy) dramatically increases pharmacological adverse effects [8, 9]. Polypharmacy is more common in elderly people. However, studies clearly demonstrate that as the number of medications used grows, so may the number of adverse effects noticed in patients [10–12]. As a result, predicting drug-drug interactions (DDI) and adverse drug responses (ADR) for medications employed in illness therapy is crucial [9, 13]. Understanding the adverse effects and DDI of the COVID-19treatment drugs is crucial to the process's effectiveness. Changes in the expression and activity of transporters in extremely frequent acute and chronic inflammatory settings may affect the pharmacokinetics (PK) and pharmacodynamics (PD) aspects of COVID-19treatment. To improve the success rate of COVID-19treatment, several pharmacological approaches are proposed, and some clinical data are reviewed in the literature. Comorbid patients require many pharmacological therapies. Drug-drug and disease-medication interactions can have a detrimental impact on patient therapy and generate adverse drug effects, although they are avoidable. The intensity, methods, start of effect, and clinical importance of drug-drug and disease-drug interactions may differ. As a result, diagnosis and treatment of drug-drug and disease-drug interactions are critical. When prescribing new drugs to COVID-19patients, clinicians should examine the likelihood of drug-drug and disease-drug interactions. Detecting drug-drug and disease-drug interactions of the medications utilized will thus be critical in the treatment of Covid-19. This article will concentrate on the drug-drug and disease-drug interactions of COVID-19therapeutic medicines.

POTENTIAL DRUGS USED IN TREATMENT OF COVID-19

Chloroquine Phosphate: Chloroquine Phosphate is also known as chloroquine, which is approved by the U.S FDA to treat malaria and extraintestinal parasites. It's a crystalline white material with no odour that's taken orally in 150 mg and 300 mg doses [14-16]. Chloroquine excretion is delayed because only a tiny percentage of the dosage supplied is detected in stools, while the remaining is absorbed in the gastrointestinal tracts [17].

Mechanism of action: Chloroquine has the ability to inhibit particular enzymes, enabling deadly heme to accumulate within the parasite. It also inhibits nucleic acid synthesis by inhibiting DNA and RNA polymerase. It may also influence the parasite enzyme heme polymerase. It can also block viral fusion, which may result in acidification of the cell's surface [18-19].

IN COVID-19TREATMENT AND THEIR CONTRAINDICATION

Chloroquine phosphate, an experimental emergency use medication for some hospitalized COVID-19patients, remains an unapproved therapy for coronavirus illness. It is an investigational drug with little data on its safety and efficacy. The FDA has granted an emergency use authorisation (EUA) for chloroquine phosphate for COVID-19positive hospitalised patients weighing 50kgs or more [20-21]. Chloroquine phosphate has demonstrated great improvements in patients with pneumonia caused by SARS-CoV-2 infection, according to research.

Patients with renal or liver impairment, diabetes, G6PD deficiency, porphyria, allergies to chloroquine phosphate, chloroquine hydrochloride, or hydroxychloroquine sulphate, and pregnancy or breastfeeding are all suggested against using it [22-23].

DRUG INTERACTION

Chloroquine phosphate interacts with a number of medications. When taking nonsteroidal anti-inflammatory drugs (NSAID), antacids, azithromycin, insulin, amiodarone, moxifloxacin, treatments for epilepsy or seizures, vitamins, methotrexate, digoxin, tamoxifen, vitamins, or herbal items with chloroquine, there is a significant interaction [24]. Chloroquine increases the risk of a prolonged QT interval in COVID-19patients who are also taking azithromycin. Chloroquine increases the risk of hypoglycemia by enhancing the pharmacodynamic effect of oral hypoglycemic medications. Chloroquine is a moderate inhibitor of CYP2D6. Therefore, chloroquine could raise the serum concentrations of risperidone, metoprolol, aripiprazole, iloperidone, haloperidol, Tricyclic Antidepressants, fluoxetine, and paroxetine. On the contrary. Chloroquine will reduce the serum level of the prodrugs that are dependent on CYP2D6 for their activation. For instance, Tramadol and Codeine. Chloroquine is an inhibitor of the transport system P-glycoprotein (P-gp). Therefore, Chloroquine is expected to rise the serum level of the cyclosporine [25-36].

Hydroxychloroquine Sulfate: Hydroxychloroquine Sulfate is also known as hydroxychloroquine. The FDA has authorised it to treat disorders like as malaria, rheumatoid arthritis, and lupus erythematosus [37-39].

Mechanism of action: Through its interaction with DNA, hydroxychloroquine sulphate can block specific enzymes. It has the ability to suppress processes such as virus release, particle transport, viral protein glycosylation, and DNA & RNA polymerase. It has the potential to block viral fusion by acidifying the surface of cell membranes. It also prevents heme polymerization [40-42].

IN COVID-19TREATMENT AND THEIR CONTRAINDICATION: Hydroxychloroquine Sulfate is expected to be authorised for the treatment of COVID-19individuals weighing 50 kg or more in 2020. According to FDA, there is an ideal dose for individuals who test positive for COVID-19based on specific factors. However, for COVID-19positive individuals, it suggests starting with 800 mg of hydroxychloroquine sulphate base on the first day and then switching to 400 mg base for the next 4-7 days [43, 44]. The recommended dose may change depending on the outcome of current clinical research. It is also advised that patients' QT intervals, as well as renal and hepatic functions, be studied and monitored. Cardiovascular illness makes hydroxychloroquine sulphate contraindicated.

DRUG INTERACTION: QT interval prolongation is still a risk factor for persons taking antibiotics such as azithromycin and other antibacterials. Such patients' electrocardiograms should be closely examined[45.] Cimetidine, for example, inhibits the metabolism of hydroxychloroquine, resulting in a rise in hydroxychloroquine levels in the blood plasma. As a result, both medications should not be used at the same time. Similarly, hydroxychloroquine can raise serum digoxin levels, which should be continuously monitored during combination

dosage administration. Antacids can also inhibit hydroxychloroquine absorption. The FDA recommends that a gap of at least 4 hours be maintained between the two medications [46, 47]. The metabolism of beta-blockers such as carvedilol and metoprolol is slowed by hydroxychloroquine. Hydroxychloroquine is a transport system inhibitor (P-gp). As z result, the blood level of this cellular pump inhibitor's substrates rises (such as cyclosporine and digoxin). In individuals with COVID-19who are also taking Azithromycin, hydroxychloroquine increases the risk of a prolonged QT interval. Hydroxychloroquine enhances the impact of other drugs that prolong the QTc interval (e.x. Azithromycin & Domperidone). Hydroxychloroquine improves the pharmacodynamic effect of oral hypoglycemic medications and raises the risk of hypoglycemia. Hydroxychloroquine is a moderate inhibitor of CYP2D6. Therefore, chloroquine could raise the serum concentrations of risperidone, metoprolol, aripiprazole, iloperidone, haloperidol, Tricyclic Antidepressants, fluoxetine, and paroxetine. On the contrary. Chloroquine will reduce the serum level of the prodrugs that are dependent on CYP2D6 for their activation. For instance, Tramadol and Codeine. The risk of peripheral neuropathy may be increased if Hydroxychloroquine used concurrently with tocilizumab [48, 28, 30–33, 36, 49-52].

Disease-drug interaction: IL-6, a proinflammatory cytokine, stimulates CYP2B1 expression through an epigenetic mechanism. Because COVID-19infected individuals have a greater amount of IL-6 than healthy participants, it's possible that IL-6 interacts with the metabolism of HCQ. The point is especially important for drugs with a restricted therapeutic index, such as HCQ and CQ.

Remdesivir: Remdesivir has been licenced by the FDA for emergency use, however clinical trials have yet to be completed. It has been proven in animal models in vitro and in vivo to be effective against viral infections that cause Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) (SARS) [53-54].

Mechanism of action: Remdesivir is a remdesivir triphosphate prodrug (RDV-TP). Remdesivir is an RNA dependent RNA polymerase inhibitor (RdRp). It binds to viral RNA chains and competes with adenosine triphosphate. Remdesivir triphosphate (RDV-TP) does not produce chain termination immediately. [55].

IN COVID-19TREATMENT AND THEIR CONTRAINDICATION: Remdesivir has begun phase 3 clinical studies to assess the drug's safety and effectiveness. Patients from high-risk COVID-19nations were able to participate in this randomised, openlabel trial that was done internationally in several sites [56]. Remdesivir's role in COVID-19positive individuals with severe manifestations such as oxygen need, as well as people with no severe manifestations, is being studied. Remdesivir is also being examined for the treatment of COVID-19positive patients by the National Institute of Allergy and Infectious Diseases (NIAID) in the United States. Remdesivir may be contraindicated if you have renal or hepatic impairment [57].

DRUG INTERACTION: Certain drugs, such as metamizole(analgesics), may reduce Remdesivir exposure. Antibacterials such as rifabutin, rifampin, and rifapentine can drastically reduce Remdesivir exposure.

Similarly, anticonvulsants such as carbamazepine, phenobarbital, phenytoin, oxcarbazepine, primidone, rufinamide, and others can lower Remdesivir's potential exposure. Antihypertensive medications such as Bosentan can also significantly limit Remdesivir's potential [58, 59]. Remdesivir effect could be reduced by CYP3A4 inducers such as rifampicin, dexamethasone (at massive doses or with extended duration), phenytoin, carbamazepine, or phenobarbital. Chloroquine or Hydroxychloroquine can diminish Remdesivir's antiviral activity. Therefore, it is not recommended to coadminister such medicines [60, 61].

Disease-drug interaction: In vitro evidence suggests that inflammation lowers mRNA expression of various CYP450 isoenzymes and transporters, including CYP1A2, CYP2B6, CYPC9, CYP2C19, CYP2D6, and CYP3A4 [62]. As a result, inflammation may have an impact on their pharmacokinetics.

Lopinavir and Ritonavir: Lopinavir and Ritonavir are antiretroviral medicines that are classed as HIV-1 Protease Inhibitors and are prescribed for adults and children over the age of 14 days. Kaletra is the brand name for the combination of these two medications, Lopinavir and Ritonavir. Adults should take 800/200mg once or twice a day, and children should take 100/25mg as directed by their pediatrician [63].

Mechanism of action: Kaletra - Lopinavir; Ritonavir may decrease coronavirus activity by binding to one of the essential enzymes Mpro, according to clinical research. The plasma level of lopinavir is raised due to ritonavir-induced suppression of lopinavir's CYP3A-mediated metabolism[64].

IN COVID-19TREATMENT AND THEIR CONTRAINDICATION: According to animal and in-vitro investigations, this combination has significant antiviral action against SARS-CoV and MERS-CoV coronaviruses. COVID-19infected individuals are now undergoing randomised, controlled, open-label studies. Kaletra has been shown to be effective against coronaviruses in preclinical tests, although there is no difference in the length of viral shedding in COVID-19positive hospitalised patients [65]. Patients with hypersensitivity, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria, and erythema multiforme, should avoid Kaletra. Kaletra is not recommended for individuals with high serum cholesterol and triglyceride levels, as well as those with diabetes, Torsades de pointes (TdP), cardiomyopathy, and low blood oxygen levels [66].

DRUG INTERACTION: Certain medicines that are possible CYP3A inducers, such as lopinavir, can decrease Kaletra's potential plasma levels and hence limit virologic response. Furthermore, medicines that rely on CYP3A clearance might result in excessive amounts of Kaletra in the bloodstream, which can have major health implications. Alfuzosin (alpha1-adrenoceptor antagonist), which might cause hypotension with Kaletra owing to elevated alfuzosin concentration [67].is one of the medicines that is contraindicated. Antiarrhythmic medicines, such as dronedarone, can cause cardiac arrhythmias.Similarly, muscle relaxants such as propofol and sevoflurane can induce QT and TdP prolongation. Kaletra can cause an increase in analgesic concentration. Antipsychotics such as pimozide and lurasidone can produce serious life-threatening responses with life-threatening symptoms. Anti-gout medications, such as colchicine, can also induce hepatic and renal damage [68-70].

Disease-drug interaction: Hepatotoxicity is a documented side effect of lopinavir/Ritonavir. Kaletra should thus be avoided in individuals with hepatic impairment. When Lopinavir/Ritonavir is given to haemophilia patients, the risk of bleeding increases. The combination of lopinavir/ritonavir has been connected to an increase in blood sugar levels. As a result, patients with Diabetes Mellitus should exercise caution when using it. The use of ritonavir has been associated to second and third degree AV block. Individuals having a history of conduction irregularities, underlying heart disease, ischemic heart disease, or cardiomyopathies should use Kaletra with care, since they are more prone to develop cardiac conduction abnormalities [71–76]. In HIV-positive patients, CYP3A activity was roughly 50% lower than in healthy volunteers[77.] The inclusion of booster RTV, which is consistently connected with atazanavir to limit its clearance, may have reduced the effect of inflammation later in this trial. In recent publications, increased plasma concentrations of LPV were found in severe COVID-19patients, compared to those seen in HIV patients, and this was associated with inflammation. Because COVID-19patients are given protease inhibitor-based regimens, which have a higher risk of interactions than other antiretroviral medications [78, 79].

Dexamethasone: Dexamethasone is a potent anti-inflammatory adrenal corticosteroid that is synthesised. Dexamethasone inhibits NF-kB activation and apoptotic pathways in addition to binding to particular nuclear steroid receptors. Other comparable adrenal hormones have salt-retaining capabilities, but this one doesn't. It is a glucocorticoid agonist, commonly known as dexone or decadron, and belongs to the 21-hydroxysteroids class of chemical substances[80, 82].

Mechanism of action: Dexamethasone suppresses neutrophil migration and decreases lymphocyte colony growth in the body. Corticosteroids have short-term effects such as reduced vasodilation and capillary permeability, as well as decreased leukocyte migration to inflammatory areas. When vitamin A molecules in the serum rise, prostaglandins and some cytokines (interleukin-1, interleukin-12, interleukin-18, tumour necrosis factor, interferon-gamma, and granulocyte-macrophage colony-stimulating factor become inhibited. Dexamethasone has also been associated with higher surfactant levels and improved pulmonary circulation [80-85].

IN COVID-19TREATMENT AND THEIR CONTRAINDICATION: The COVID-19patient has a high level of inflammation. Because SARS-3 CoV-2's C-like proteinase prevents Histone deacetylases-2 (HDAC2) from entering the nucleus and so impairing the way it regulates inflammation and cytokine response, dexamethasone-induced histone deacetylase activation may directly counteract SARS-activity. CoV-2's Patients with systemic fungal infections, dexamethasone hypersensitivity, or cerebral malaria should not use dexamethasone [86-89]. Based on the preliminary report from the recovery trial, the COVID19 treatment guidelines Panel recommends using dexamethasone 6 mg per day for up to 10 days or until hospital discharge, whichever occurs first, for the treatment of COVID-19in mechanically ventilated hospitalised patients and in hospitalised patients who require supplementary oxygen but are not mechanically ventilated [90-93].

DRUG INTERACTION: When used with NSAIDS, dexamethasone increases the risk of peptic ulcers and bleeding, as well as gastrointestinal ulceration when combined with Nicorandil [90-96]. Dexamethasone has the potential to induce gastrointestinal bleeding and perforation. In individuals with ulcerative colitis, bowel anastomosis, or diverticulitis, Dexamethasone should be used with caution or avoided altogether. Dexamethasone impedes the immune response. Therefore, Dexamethasone should not be commenced in actively infected patients or those who develop serious infections after its administration. Dexamethasone can raise blood glucose levels by inhibiting insulin secretion and antagonising its activity, resulting in increased gluconeogenesis and decreased peripheral glucose absorption. As a result, in individuals with Diabetes Mellitus, Dexamethasone should be administered with caution. Dexamethasone is primarily processed in the liver, thus individuals with hepatic illness may have stronger pharmacological effects. Dexamethasone usage in individuals who have recently recovered from a myocardial infarction has been linked to the development of left ventricular free-wall rupture. As a result, in the case of myocardial infarction, Dexamethasone should be administered with great caution [96-106].

Disease-drug interaction: The inflammatory cytokine's potential effect on dexamethasone's PK. Because inflammatory cytokines suppress CYPs, which are principally involved in dexamethasone metabolism.

Ivermectin: Ivermectin is the most effective anti-parasite medicine. The US Food and Drug Administration licenced it for human use to treat onchocerciasis, but it also cures strongyloidiasis, ascariasis, trichuriasis, and enterobiasis. Scientists recognised its potential in a variety of viral diseases, including HIV and Dengue Virus 1-4. (DENV), Influenza Pseudorabies virus, Venezuelan Equine Encephalitis Virus (VEEV), West Nile Virus (WNV), and SARS-CoV-2 virus in the present decade due to its safety [107-113].

Mechanism of action: The specific mechanism of action is unknown, scientists have discovered a number of mechanisms that contribute to its broad-spectrum antiviral activity. Inhibition of importin/1/mediated nuclear import of viral proteins by RNA viruses [112]. Because SARS-CoV-2 is an RNA virus, the chances of it having a similar effect are increased [113].

IN COVID-19TREATMENT AND THEIR CONTRAINDICATION

Despite the lack of reliable evidence, certain Latin American nations have approved the use of Ivermectin for the treatment of COVID-19patients. An externally controlled pilot experiment was conducted to determine the efficacy of Ivermectin as a COVID-19add-on medication. A dosage of 0.2 mg/kg (single dose at once = 2 tablets of 6mg/weekly) was given to mild and moderate symptoms with a comorbidity of hypertension, diabetes, and asthma in this experiment. In a four-week period, all of the patients were effectively treated. Furthermore, between March 10th and March 30th 2020, a retrospective investigation was conducted at a hospital clinic in Barcelona, Spain. A single 200 g/kg dose of Ivermectin did not improve clinical or microbiological outcomes in individuals with severe COVID-19when compared to a similar group of patients who did not receive Ivermectin. Ivermectin should be taken with caution in individuals with severe hepatic disease due to its high hepatic metabolism. Furthermore, individuals with severe asthma should exercise caution when using

Ivermectin since systemic Ivermectin has been proven to worsen bronchial asthma [114-116].

DRUG INTERACTION

When alcohol is combined with ivermectin, the plasma concentrations of ivermectin rise. Due to the powerful inhibitory properties of specific drug transporters, orange juice lowers the AUC and Cmax of Ivermectin [117].

Disease-drug interaction: The PK of ivermectin in the elderly has not been studied. In the elderly, metabolism slows with age, resulting in greater ivermectin exposure. Exposure to inflammation may have an effect on drug metabolism and disposition [118].

Azithromycin: Azithromycin was proven to be efficacious against Ebola in vitro [119]. In addition, azithromycin is regarded to be capable of preventing severe respiratory tract infection [120]. COVID-19patients were treated with azithromycin in conjunction with HCQ [121].

Mechanism of action: Azithromycin is a macrolide antibiotic that works by attaching to the 50S ribosomal subunit to suppress protein synthesis[122]. This antibiotic is given to COVID-19patients to protect them against subsequent bacterial infections. Azithromycin may have immunomodulatory properties by raising interferon b and k expression and significantly lowering TNFa production during viral respiratory infections [123].

IN COVID-19TREATMENT AND THEIR CONTRAINDICATION

Azithromycin is a macrolide antibiotic used to prevent secondary infections when combined with COVID-19. It has a strong tissue affinity and is widely distributed throughout the body. It has a half-life in the body of 2 to 4 days.

DRUG INTERACTION

Azithromycin is a P-gp inhibitor, and when combined with a P-gp substrate (such as DigoxIn), it has been shown to raise serum levels. It also inhibits CYP3A4 [124], OATP1A2 [125], and OATP2B1 [126]. COVID-19-related mortality was reduced when this drug was used with HCQ [123]. The danger of probable interactions is pharmacodynamic, rather than pharmacokinetic. While prescribing azithromycin as a comedication, the impact on QT prolongation was demonstrated. The use of azithromycin in combination with HCQ enhanced QT prolongation, which raised the risk of heart failure and cardiovascular death [126].

Convalescent plasma: Convalescent plasma is plasma donated by patients who have recovered from an infection with the COVID-19virus. Antibodies in convalescent plasma aid in the recovery of COVID-19patients [127-128].

IN COVID-19TREATMENT AND THEIR CONTRAINDICATION

Further research into the impact of Convalescent Plasma in lowering mortality, morbidity, and length of illness in COVID-19patients is ongoing. Whether Convalescent Plasma is effective against COVID-19is yet unknown.

Convalescent Plasma has received FDA approval for use in hospitalized COVID-19positive patients [129]. It might be a risk factor for those who have had bad transfusion responses.

DRUG INTERACTION

Convalescent Plasma is usually thought to be safe for transfusion and well tolerated by patients. Through emergency experimental new medications, a licenced physician can seek the use of Convalescent Plasma for a single patient (eIND). It also means that Convalescent Plasma is not a bigger risk factor than the illness or condition [130-132].

Drug transporter pathways change in response to inflammation: Inflammation is linked to a variety of cytokine responses. This is a large class of tiny cell-signaling proteins that are responsible for immune system homeostasis. Cytokines that promote inflammation Tumor necrosis factor (TNF-α), interleukin-1 (IL-1) and interleukin-6 (IL-6). (TNF-α) are the primary cause of an acute immune response. These locally generated cytokines can circulate in the circulation and have a systemic influence during an infection by interacting with cell membrane receptors, transporters on the vascular endothelium, and parenchymal cells from a number of organs. Inflammation and immune response play essential roles in many acute and chronic illnesses, impacting medication clearance by altering the mechanism of drug transporters and the activity of drug-metabolizing enzymes. [133].

Drug metabolising enzyme activity changes in response to inflammation: As the primary contributor, CYPs are widely involved in the metabolic biotransformation of most drugs [134]. CYP regulation, like drug transporter regulation, has been associated to inflammation in a number of metabolic and infectious illnesses, including viral infection [135]. Cytokines released during the inflammation process are primarily responsible for inflammatory-induced polymorphisms in hepatic CYPs [136]. Control is crucial when considering pharmaceutical interactions since drug pharmacokinetics will eventually be altered dependent on sickness kind and released cytokines, as well as the provided dose[137,138]. Many investigations utilizing hepatocytes and in vivo in mice [139], rats [140], and humans [141] have revealed cytokine-induced CYPs activity modification. Extrahepatic CYPs were also inhibited by inflammatory mediators [142–145].The most proinflammatory cytokines include IL-1 [146–148], IL-6, TNF-, and IFN-, which have been shown to decrease CYPs production and activity [147–151]. Other cytokines, such as IL-2 and IL-10, had the similar impact [152–154]. IL-6 is the primary inflammatory substance that has been identified to have a significant inhibitory effect on the expression and activity of various CYPs. In rat hepatocytes, human recombinant IL-6 reduced phenobarbital-mediated activation of CYP2B1/2 in a concentration-dependent manner[155]. It inhibited the activity of multiple CYPs. Human recombinant IL-6 treatment dramatically lowered CYP1A1, CYP1A2, and CYP3A3 mRNA levels in human hepatoma cell lines [156]. The lowering of CYPs activity by cytokines is not fully understood. However, it is thought that a decrease in CYPs mRNA strongly indicated a transcriptional mechanism involving many transcriptional factors [157,158]. Nuclear factor Kappa B (NF-kB) and the aryl hydrocarbon receptor are regulatory transcription factors in the inflammatory and immunological response, and they impact the gene expression of various CYPs in humans, rats, and mice [157–160]. Pyrrolidine dithiocarbamate, for

example, is an NF-kB inhibitor that can prevent the inflammatory drop in CYP1A2 activity.[161,162]. The Pregnane X Receptor (PXR) is linked to a number of genes, the most prominent of which being CYP3A4. PXR is regulated by NF-kB factors, and NF-kB is regulated by inflammatory stimuli, which leads in modulation of Hepatic CYPs expression [163–165].

Conclusion

Variations in the expression of a transporter are well recognised to result in changes in the PK/PD of the prescribed medication; hence, prescription medicine during inflammation may be a major contributor to interindividual variability in drug efficacy and toxicity. It also highlighted the possibility of drug-drug and disease-drug interactions of the specified medicine in the treatment of COVID-19. It will aid in lowering risk in individuals with co-morbidities and providing better therapy with fewer adverse effects.

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