Covid-19: Current updates on drugs and their impact on liver

Project report submitted in partial fullfilment of the award of the degree

BACHELOR OF PHARMACY

Submitted By:

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(17SMAS102002)

IN

BACHELOR OF PHARMACY

SCHOOL OF MEDICAL AND ALLIED SCIENCES

Under the supervision of

MR. RAKESH SAHU

MAY, 2021

CERTIFICATE

This is to certified that the work contained in this project on Sources of **COVID-19 CURRENT UPDATES ON DRUGS AND THEIR IMPACT ON LIVER** Submitted in partial fulfillment for the academic requirement in the degree of Bachelor of Pharmacy is the original work carries out by **SOBIT KUMAR TIWARI** during the academic year 2020-21, under the guidance of **MR. RAKESH SAHU** (Assistant Professor) the work is completed and the ready for evaluation in partial fulfillment for the award of bachelor of pharmacy under Galgotias university greater Noida during the academic year 2020-21.

Date:
Place:

Prof**. PRAMOD KUMAR SHARMA**
DEAN SCHOOL OF MEDICAL
AND
ALLIED SCIENCE

CERTIFICATE

This to certify that the project work entitled **"COVID-19 CURRENT UPDATES ON DRUGS AND THEIR IMPACT ON LIVER"** by **"SOBIT KUMAR TIWARI"** for the award of **"Bachelor of Pharmacy"** degree, comprises of the bonafide research work done by him/her at Department of Pharmacy, School of Medical & Allied Sciences, Galgotias University, Greater Noida under my guidance and supervision and to my full satisfaction.

MR. RAKESH SAHU
Associate Professor
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DECLARATION

The project report **COVID-19 CURRENT UPDATES ON DRUGS AND THEIR IMPACT ON LIVER,** entitled is the compilation work of **SOBIT KUMAR TIWARI** under supervision of **MR.RAKESH SAHU** (Assistant Professor) **Department of Pharmacy**, **GALGOTIAS UNIVERSITY Greater Noida U.P. India**. All structures, tables and information used in project are taken from various sources are true and best of my knowledge.

Name and signature of candidate
(SOBIT KUMAR TIWARI)
ENROLLMENT No. 1712102091

DEDICATION

I dedicate this to my guider teacher **MR.RAKESH SAHU** (Assistant Professor) who taught me everything about this project and taught me the basics rules of life that are very useful and important for a person to live a healthy life. Sir taught that never too late to start a thing and achieve your goals. Sir you and your thoughts really motivates me in my life and my carrier so sir thank you for guiding me.

I also dedicate this thesis to my parents, Thank you for supporting me.

ACKNOWLEDGEMENT

First and foremost, I would like to thank god for giving me the knowledge, strength, opportunity and ability to undergo this study of research, and to persevere and complete it satisfactorily. This attainment would not have been possible without his blessings.

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I would like to thank **Mr. RAKESH SAHU,** Assistant Professor, School of Medical and Allied Science, Galgotias University, Greater Noida for his continuous guidance on the project.

Lastly, I wish to express my gratitude to my colleagues and friends for encouragement and support.

SOBIT KUMAR TIWARI

Approval Sheet

This thesis/dissertation/report entitled "**Covid-19: Current updates on drugs and their impact on liver**" by SOBIT KUMAR TIWARI is approved for the degree of Bachelors Of Pharmacy

Examiners

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Supervisor (s)

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Chairman

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Date:_____

Place:_____

Statement of Project Report Preparation

1. Thesis title: Covid-19: Current updates on drugs and their impact on liver
2. Degree for which the report is submitted: BACHELORS OF PHARMACY
3. Project Supervisor was referred to for preparing the report.
4. Specifications regarding thesis format have been closely followed.
5. The contents of the thesis have been organized based on the guidelines.
6. The report has been prepared without resorting to plagiarism.
7. All sources used have been cited appropriately.
8 The report has not been submitted elsewhere for a degree.

Signature of Student:

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ABSTRACT

In this article we have discussed about how different drug used in covid-19 have impact on liver. Coronavirus disease is a newly discovered virus that causes an infectious disease. It enters in the body by nose or by the help of mouth and various problems in the body such as difficulty in breathing, fever, loss of smell and taste etc. most common symptoms of covid are dry cough, fever and tiredness. The corona virus is of four types alphacoronavirus, betacoronavirus, gammacoronavirus and deltacoronavirus. In this article we have discussed about impact of sars-cov on liver injury, impact of mers-cov on liver injury and sars-cov-2 i.e corona virus on liver injury among these three sars-cov -2 is most dangerous and fatal. The main aim of this article is to discuss the effects of drugs on liver such as remdesivir is the most potent drug used in treatment of covid-19 it is an antiviral drug so it works by decrease in viral RNA production and its effect on liver is that it induces hepatotoxicity and causes hepatic enzymes elevation. We have written others information related to the drug such as its composition, outcome in covid, drug category and its chemical structure. We have also discussed about the several drugs are currently being developed for the treatment of covid-19 and the vaccines under development for COVID-19.

LIST OF TABLES

LIST OF ABBREVIATIONS

1. COVID- Corona virus disease
2. WHO- world health organization
3. SARS-cov-2- severe acute respiratory syndrome corona virus 2
4. Mers-cov- middle east respiratory syndrome corona virus
5. RNA- ribose nucleic acid
6. ARDS- acute respiratory distress syndrome
7. MOF- multiple organ failure
8. ACE- angiotensin-converting enzyme
9. RT-PCR- reverse transcriptase polymerase chain reaction
10. HBV- hepatitis B
11. HCV- Hepatitis C
12. DPP-4- Dipeptidyl Peptidase-4
13. IFN- Interferons
14. TNF- Tumour necrosis factor
15. IL-15- Interleukin-15
16. IL-17- Interleukin-17
17. AST- aspartate aminotransferase
18. ALT- alanine aminotransferase

Covid-19: Current updates on drugs and their impact on liver

1. INTRODUCTION

Coronavirus disease (COVID19) is a newly discovered coronavirus that causes an infectious disease. The majority of people infected with the covid-19 virus will have mild to moderate respiratory symptoms and will recover without needing any special care. People over the age of 65, as well as those with underlying medical conditions such as cardiovascular disease, diabetes, chronic respiratory disease, and cancer, are at a higher risk of developing serious illness. When an infected individual coughs or sneezes, the COVID-19 virus spreads mainly by saliva droplets or nasal discharge[1].

According to WHO Globally,As of 3:44 p.m. CET on March 19, 2021, WHO had received reports of 121,464,666 confirmed cases of COVID-19, with 2,684,093 deaths. A total of 364,184,603 vaccine doses had been distributed as of March 18, 2021.[2]

The coronavirus that causes severe acute respiratory syndrome 2 (SARS-cov-2) has become a major concern to global public health.[3,4] While the virus appears to be only partially related to the coronaviruses that cause extreme acute respiratory syndrome and Middle East respiratory syndrome, both of these viruses cause severe and potentially fatal acute respiratory syndromes in humans. [5] Unfortunately, no specific/targeted medications or vaccines are available at this time, and the number of SARS-cov-2-positive patients is increasing in many parts of the world. [6] COVID-19 (coronavirus disease) is a highly infectious disease. In certain cases, it can quickly progress to acute respiratory distress syndrome (ARDS), which can lead to multiorgan dysfunction or death. [7,8] Coronavirus (covs) is a coronavirus family virus with the largest genome of any known RNA virus. It is present in humans, mice, pigs, cats, dogs, and other species. Human disease is caused by seven coronavirus types, four of which (hcov-NL63, hcov-229E, hcov-OC43, and hcov-HKU1) cause respiratory infections in immunocompromised people, children, and the elderly[9]. The extreme acute respiratory syndrome coronavirus (SARS-cov), the Middle East respiratory syndrome coronavirus (MERS-cov), and the 2019 new coronavirus are the other three extremely pathogenic human coronaviruses (SARS-cov-2). These three viruses may cause respiratory, intestinal, hepatic, and neuronal diseas

es, as well as ARDS, multiple organ failure (MOF), and even death in extreme cases. [10-12]. Patients infected with SARS-cov, MERS-cov, and SARS-cov-2 have been shown to have varying degrees of liver damage, according to studies. Coronaviruses are enveloped, single-stranded large RNA viruses that infect humans and a variety of animals. Coronaviruses are divided into four subgroups: alpha, beta, gamma, and delta. SARS-cov-2, like SARS-cov, belongs to the beta subgroup of the coronavirus family, which caused a worldwide outbreak in 2003. [13,14].According to the World Health Organization, the disease caused by SARS-cov-2 is now known as COVID-19. SARS-cov-2, like SARS-cov, primarily targets the respiratory system. Medical symptoms of the disease in symptomatic patients include fever, cough, exhaustion, and other signs of respiratory tract infections. [15,16]. Individuals with severe acute respiratory distress syndrome, acute cardiac injury, kidney failure, and death develop signs of pneumonia, which are associated with complications such as severe acute respiratory distress syndrome, acute cardiac injury, kidney failure, and death. Even if it is not a prominent feature of the disease, liver dysfunction has been identified as a typical clinical manifestation in patients with SARS-cov infection. [17,18]. It's also uncertain how serious the liver damage is in the new SARS-cov-2 outbreak.

The first cases of Coronavirus disease (COVID-19) were discovered in December 2019 in Wuhan, Hubei Province, China, with cases of viral pneumonia. [19]. Since then, the disease has spread worldwide, and the World Health Organization has declared it a global pandemic (WHO). The illness, which is caused by the extreme acute respiratory syndrome coronavirus 2 (SARS-cov-2), has resulted in a significant number of hospital admissions and deaths, putting a strain on health-care services. With time, knowledge of the disease has grown, and it has become clear that it affects not only the lungs, but also the gastrointestinal system, the heart, and the liver[20]. The hepatic involvement in two recent pathogenic coronaviruses, SARS-COV and Middle East Respiratory Syndrome Coronavirus, has been well reported (MERS-COV). These two viruses have striking genetic similarities (especially SARS-

COV) to the novel coronavirus, SARS-cov-
2, and thus hepatic involvement is not surprising.Indeed, several studies have indicat ed that SARS-cov-
2 infection causes an increase in liver transaminases Hepatology International1 3. Th e purported mechanisms include the virus's direct effect on hepatocytes or the biliary epithelium, liver injury due to an accentuated immune response (cytokine storm) and immune mediated damage, drug toxicity (due to drugs like acetaminophen, antivirals, and hydroxychloroquine), and ischemic hepatitis, which can occur in patients with m ultiorgan dysfunction, including hemorrhagic hepatitis.[21]. The angiotensin-converting enzyme (ACE-2) receptor, which is the recognised binding site of SARS-cov-
2, is expressed in the biliary epithelium, while it is likely much lower in hepatocytes. However, in animal models of liver damage, the receptor expression was found to be upregulated. [22].

1.1 Classification of corona virus

TABLE NO. 01: THE DETAILED CLASSIFICATION OF CORONA VIRUS

Class	Types	Family (sub family)	Virulent Ability in humans	Derived from	Reference
On the bases of genera	Alphacoronavirus	Coronaviridae(Orthocoronavirinae)	Very high	Bat gene pool	[23-29]
	Betacoronavirus	Coronaviridae(Orthocoronavirinae)	Very High	Bat gene pool	[23-29]
	Gammacoronavirus	Coronaviridae(Orthocoronavirinae)	High	Avian and pig gene pools.	[23-29]
	Deltacoronavirus	Coronaviridae(Orthocoronavirinae)	High	Avian and pig	[23-29]

				gene pools.	
On basis of virus infecting humans	Hcov-NL63 (alphacoronavirus)	Coronaviridae(Orthocoronavirinae)	Very high	Bat gene pool	[23-29]
	Hcov229e (alphacoronavirus)	Coronaviridae(Orthocoronavirinae)	Very high	Bat gene pool	[23-29]
	Hcov-OC43 (betacoronavirus)	Coronaviridae(Orthocoronavirinae)	Very high	Bat gene pool	[23-29]
	Hcovhku1 (betacoronavirus)	Coronaviridae(Orthocoronavirinae)	Very high	Bat gene pool	[23-29]

2. General impact of covid on liver

2.1 Sarscov on liver injury

The mechanism of liver damage caused by SARS-cov has been investigated in depth. Large numbers of virus particles were present in the parenchymal cells and vascular endothelium of other organs, including the liver, during autopsies of SARS patients. RT-PCR was used to detect the SARS-cov genome in hepatocytes [30,31].During the early stages of SARS-cov infection, abnormal serum levels of cytokines and chemokines were discovered in patients. [32] According to Duan et al., serum IL-1, IL-6, and IL-10 levels were higher in patients with abnormal liver function than in patients with normal liver function, implying a connection between liver damage and the inflammatory responses induced by SARS-cov infection. Furthermore, SARS patients infected with HBV/HCV were more likely to experience liver damage and serious hepatitis, which is likely due to increased hepatitis virus replication during SARS-covinfection[33]. It's worth noting that antibiotics (macrolides, quinolones), antivirals (ribavirin), steroids, and other medications used to treat SARS patients can cause liver damage as well[34,35].

2.2 Merscov on liver injury

MERS-
cov and hepatitis The majority of Middle East respiratory syndrome (MERS) cases w ere first reported in Saudi Arabia in 2012, and were caused by MERS-
cov infection. Since then, the virus has spread throughout Europe, Asia, Africa, and North America [36]. Fever, cough, and shortness of breath are symptoms of MERS-cov infection in patients. Patients with severe MERS developed respiratory and kidne y failure rapidly [37]. Furthermore, patients with MERS had elevated liver enzymes a nd bilirubin levels, as well as lower albumin levels, according to a number of retrosp ective studies[38-
42]. Saad et al. have also shown this. The severity of the decrease in albumin levels was a predictor of disease severity [38]. Mild portal tract and lobular lymphocytic inf lammation, as well as mild cellular hydropic degeneration in the hepatic parenchyma, are pathological manifestations of liver damage in MERS patients, similar to what h as been observed in SARS patients[43,44].

MERS-cov, unlike SARS-cov, was discovered to use Dipeptidyl Peptidase-4 (DPP-4) as its functional receptor for infecting cells [45]. The liver has a high level of DPP -4 expression, indicating that it may be a possible MERS-cov target organ.[46].

In the acute phase of MERS-cov infection, strong pro-
inflammatory cytokine responses were observed in patients, with serum IFN-, TNF- , IL-15, and IL-
17 concentrations significantly increased [47]. However, there are still no studies on t he connection between pro-
inflammatory cytokine responses and liver injury. It's still unclear if the liver damage seen during MERS-cov infection is the result of direct viral infection, inflammation-mediated pathogenesis, or the use of liver-damaging drugs during treatment[48].

2.3 SARS-cov-2 on liver injury

Fever, weakness, dry cough, vomit, and diarrhoea were all signs of COVID-
19 in mild cases. Respiratory distress and/or hypoxemia occurred one week after the onset of the disease in serious cases, and then progressed to ARDS, septic shock, met abolic acidosis, and death. [49].

In a COVID-
19 patient who died recently, postmortem biopsies revealed moderate microvasculars teatosis and mild lobular and portal activity, suggesting that the injury may have bee

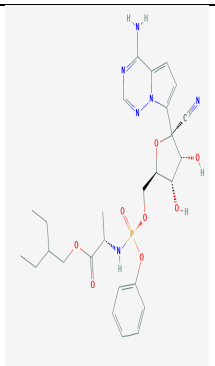
n caused by either SARS-cov-2 infection or drug-
induced liver injury[50]. Antibiotics, antivirals, and steroids are commonly used to tr eat COVID-
19, similar to how they were used to treat SARS [51]. Both of these drugs have the p otential to cause liver damage during COVID-
19, but no evidence of this has yet been found [52]. In reality, lopinavir/litonavir, whi ch are antivirals used to treat SARS-cov-
2 infection, may be to blame for the liver injury seen in COVID-
19 patients, according to a recent review[53].
The viral infection of liver cells can directly cause liver damage in patients with coro navirus infections. Approximately 2–10% of COVID-
19 patients have diarrhoea, and SARS-cov-
2 RNA has been found in stool and blood samples[54]. This evidence suggests that t he liver may have been exposed to a virus. Both SARS-cov-2 and SARS-
cov bind to the ACE2 receptor to reach the target cell, where the virus replicates and infects other cells in the upper respiratory tract and lung tissue, resulting in clinical si gns and manifestations.Pathological tests in SARS patients confirmed the virus's exis tence in liver tissue, though the viral titre was poor due to the absence of viral inclusi ons[56]. The presence of viral particles in the liver tissue of MERS patients was not detected[57]. disease as well as infectious diseases, with direct clinical and research e xperience in the area. As a result, authors are encouraged to submit high-
quality research papers about COVID-
19.It will take less than a week to complete the project. We The diagnostic biomarker for cholangiocyte injury, gamma-
glutamyltransferase (GGT), has not been documented in existing COVID-
19 case studies; however, we discovered that it was elevated in 30 (54%) of 56 patie nts with COVID-
19 during hospitalisation in our centre (unpublished). During hospitalisation, we also discovered that one (18%) of 56 patients with COVID-
19 had elevated alkaline phosphatase levels. SARS-cov-2 can directly bind to ACE2-
positive cholangiocytes to dysregulate liver function, according to a preliminary stud y (albeit not peer-
reviewed) that suggested ACE2 receptor expression is enriched in cholangiocytes[58]

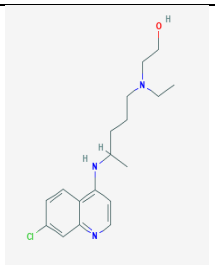
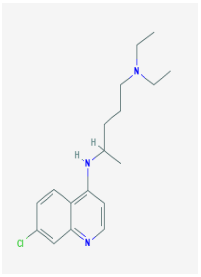
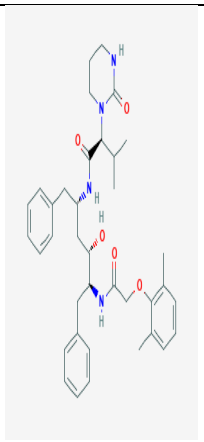
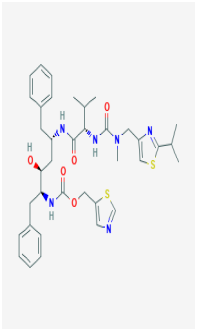
.Despite this, pathological examination of liver tissue from a COVID-
19 patient who died revealed no viral inclusions in the liver[59].

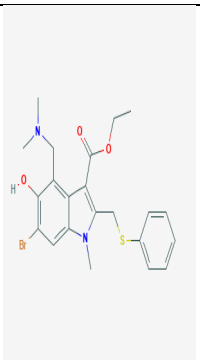
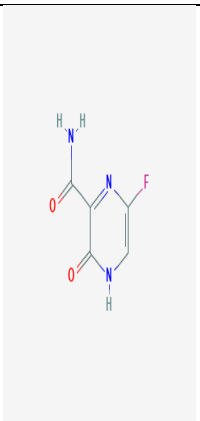
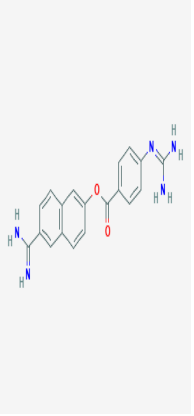
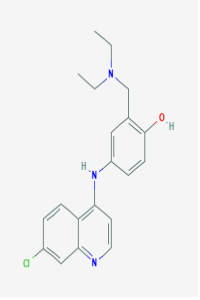
3.Drugs approved for the treatment of the corona virus and their effects on the liver, as well as many ongoing drugs and vaccines being developed for the treatment of the covid-19 virus

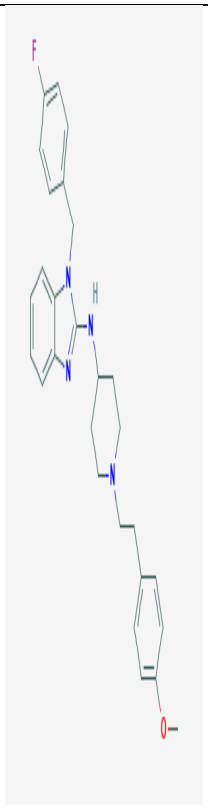
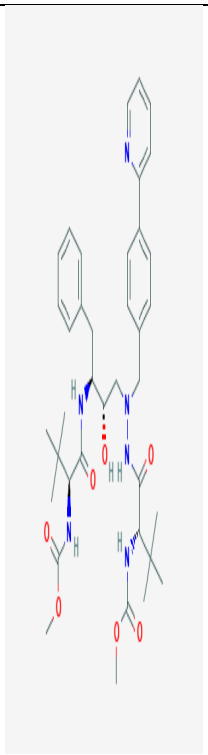
Early diagnosis, prompt reporting, isolation, and supportive treatments are critical lines of defence against COVID-
19 infections in the absence of conclusive and specific treatment regimens. Current social activities, such as timely dissemination of disease knowledge and the preservation of social order, as well as personal practises like enhancing personal hygiene, wearing face coverings or masks, getting enough rest, and keeping rooms well ventilated, are among the first lines of defence against the COVID-
19 pandemic.Patients with SARS-cov-
2 infection are currently treated mostly by repurposing available therapeutic medications and based on symptomatic conditions. Antibiotics, antiviral therapy, systemic corticosteroids, and anti-inflammatory medications (including anti-
arthritis drugs) are often used in the treatment of ARDS, which is often accompanied by secondary infections. In addition to antiviral interferers and antibiotics, COVID-
19 has been treated with neuraminidase inhibitors, RNA synthesis inhibitors, convalescent plasma, and conventional herbal medicines [60-63].

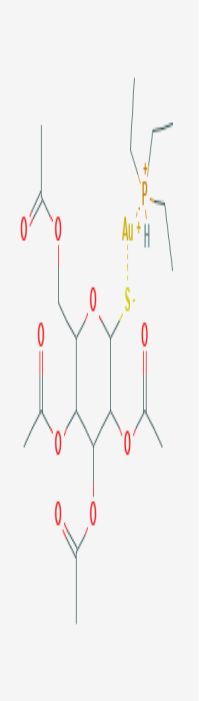
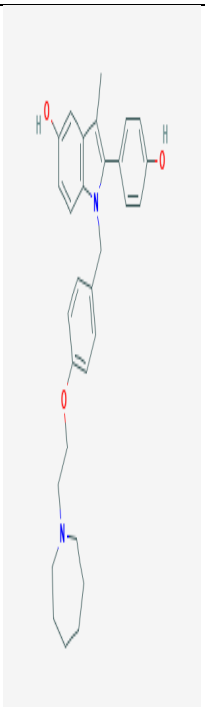
3.1 Table no. 02 Approved drugs used for treatment of covid-19

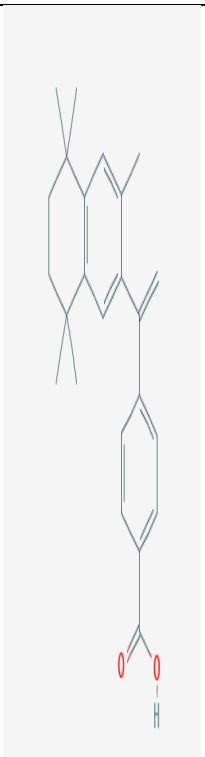
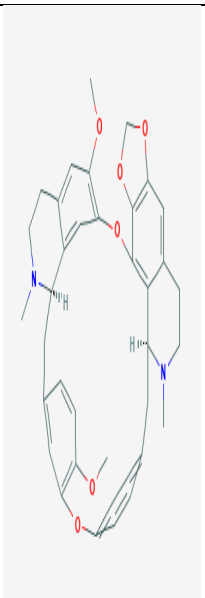
Serial no.	Name of drug	Composition	Outcome	Drug category	Impact on liver	Chemical Structure	Refrences
1.	Remdesivir	Phosphoramidate prodrug of an adenosine C-nucleoside	Decrease in viral RNA production	Anti-viral	Hepatotoxicity, Hepatic enzymes elevation		[64-69]

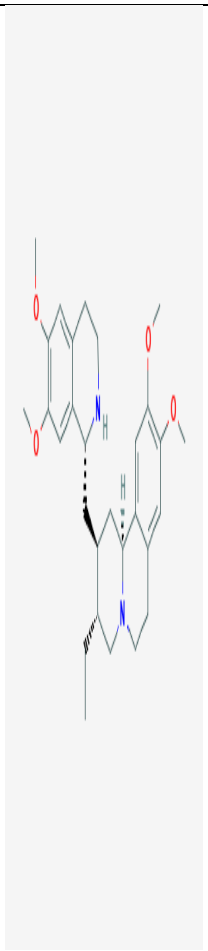
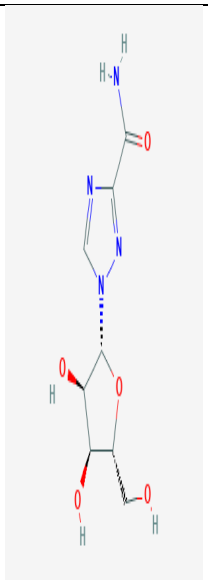
2.	Hydroxychloroquine and Chloroquine	4-aminoquinoline	Substantial lower EC50 for hydroxychloroquine vs chloroquine in inhibiting covid-19	Anti-malarial	Very rare chances of liver injury	 	[70-74]
3.	Lopinavir-Ritonavir	Peptidomimetic molecule, containing a hydroxyethylene scaffold	Improved clinical symptoms. Inconclusive whether the antiviral therapy was effective.	Antiviral	Hepatotoxicity/increased AST and ALT etc	 	[75-79]

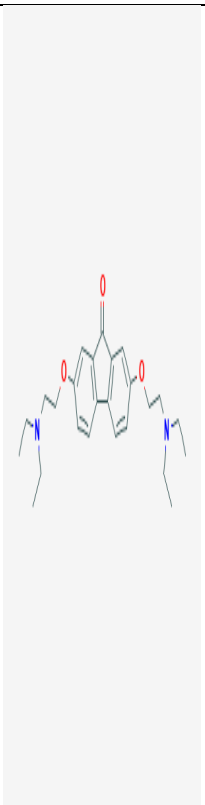
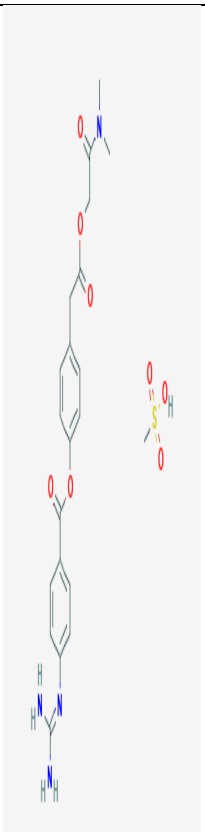
4.	Umifenovir (Arbidol)	A derivative of indole carboxylic acids	Inhibits the fusion of the viral envelope with host cell membrane	Antiviral	Transaminase elevation		[80-84]
5.	Favipiravir (Avigan)	Guanine analogue with pyrazinecarboxamide structure	Interrupting the nucleotide incorporation process during viral RNA replication	Anti-viral	Moderate-to-severe elevations in serum aminotransferase levels		[85-87]
7.	Nafamostat	Synthetic serine protease inhibitor	Inhibited SARS-cov-2 infection by blockade of Viral entry	Anticoagulant, anti-inflammatory	Liver dysfunction , peptic ulcer		[91-93]
8.	Amodiaquine	4-aminoquinoline derivative	Substantial lower EC50	Anti-parasitic	Aminotransferase elevations, acute liver injury		[94-96]

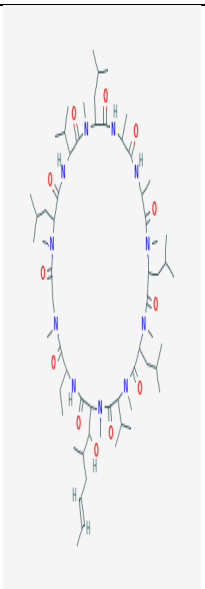
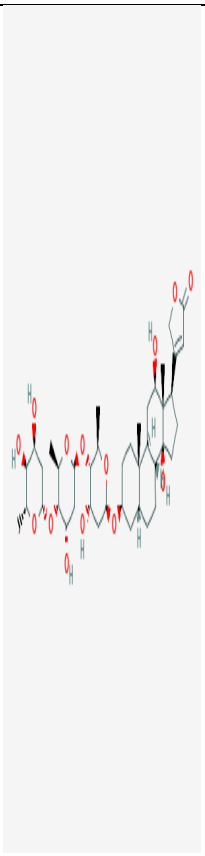
9.	Astemizole	Piperidine compound having a 2-(4-methoxyphenyl)ethyl group at the 1-position and an N-[(4-fluorobenzyl)benzimidazol-2-yl]amino group at the 4-position	Inhibited the replication of SARS-cov-2 with an EC_{50} of *ca* .1 μm	Anti-allergic	Low chances of Liver injury		[97-99]
10.	Atazanavir	Aza-dipeptide analogue with a bis-aryl substituent on the (hydroxethyl)hydrazine moiety	Effective against the germ that causes COVID-19 in the laboratory will be tested in patients diagnosed with moderate to severe COVID-	Anti-viral	Transient serum enzyme elevations, indirect hyperbilirubinemia, idiosyncratic acute liver injury, serum aminotransferase elevations		[100-102]

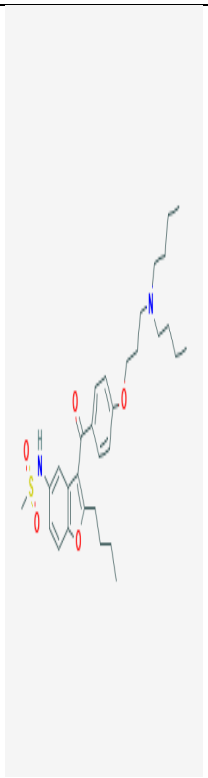
			19				
11.	Auranofin	Gold-based compounds	Inhibits SARS-COV-2 replication in human cells at low micro molar concentration.	Anti-inflammatory	No effect on liver		[103-105]
12.	Bazedoxifene	Indole derivative	Inhibit IL-6 signaling at therapeutic doses, suggesting they have the potential to prevent the cytokine storm, ARDS and mortality	Anti-osteoporosis	Rare cause of liver injury		[106-108]

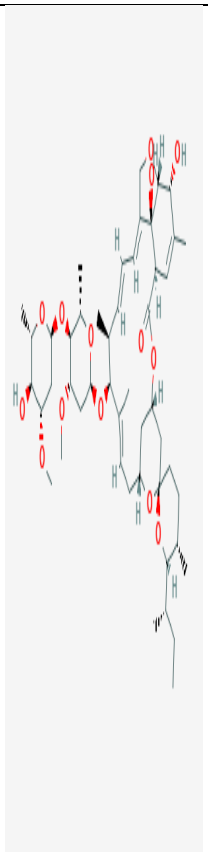
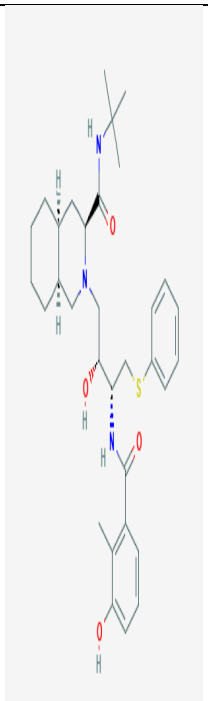
			in severe COVID-19 patients				
13.	Bexarotene	Retinoid analogue	Has broad-spectrum anti-coronaviral activity and a higher Cmax to EC_{50} ratio than most other reported potential anti-SARS-cov-2 agents.	Anti-tumor	Serum aminotransferase elevations, liver injury with jaundice		[109-111]
14.	Cepharanthine	Bisbenzyl isoquinoline alkaloid	Inhibits viral entry and replication	Anti-inflammatory	Whether it affects the activity of human liver cytochrome P450 (CYP) enzymes remains unclear.		[112-117]

15.	Emetine	Pyridoisoquinoline comprising emetam having methoxy substituents at the 6'-, 7'-, 10- and 11-positions.	Higher potency against the coronavirus, minimise or eliminate any significant cardiac toxicity and nausea while maintaining antiviral effectiveness	Anti-protozoal	Very rare chances of liver injury		[118-120]
16.	Ribavirin	1-ribosyltriazole that is the 1-ribofuranosyl derivative of 1,2,4-triazole-3-carboxamide.	Broad-spectrum antiviral drug against infections of different RNA viruses	Antiviral	Serum aminotransferase elevations, cirrhosis		[121-123]

17.	Tiloro ne	9H-fluoren-9-one which is substituted by a 2-(diethylam ino)ethoxy group at positions 2 and 7.	Inhibits rna replication	Anti-viral	Losses of hepatic microsom al ethylmorp hine N-demethyla se, benzo(a)p yrene hydroxyla se and aniline hydroxyla se activities		[124-126]
18.	Camo stat	4-(4-guanidino benzoylox yl)phenyl acetic acid	Reduced mortality following SARS-cov infection from 100% to 30-35%.	Anti-pancreatiti s	Increase in hepatic plasmin and TGF-b levels, HSC activation, and hepatic fibrosis without apparent systemic or local side effects		[127-130]

19.	Cyclosporine A	Natural cyclic polypeptide immunosuppressant isolated from the fungus Beauveria nivea	Improve outcomes and reduce mortality, mainly in those with moderate to severe disease	Immunosuppressive	Mild elevations in serum bilirubin levels, cholestatic liver injury.		[131-134]
20.	Digoxin	Cardenolide glycoside that is digitoxin beta-hydroxylated at C-12	Significant inhibition of severe acute respiratory syndrome coronavirus	Cardiac glycosides	That there is no evidence that the cardiac glycosides cause liver injury even at high doses, and that the major concern would be the possibility of increased risk of cardiac complicati		[135-138]

					ons of glycosides in patients with advanced liver disease		
21.	Dronedarone	Derivative of amiodarone	Prevent SARS-cov-2 infection	Antiarrhythmic	Hepatic injury arises after 1 to 6 months of therapy presenting with jaundice and fatigue, usually with a hepatocellular pattern of enzyme elevations		[139,140]

22.	Iverm ectin	Macrocycl ic lactone derived from Streptomy ces avermitilis	The random effect model revealed that adding ivermectin led to significant clinical improvem ent compared to usual therapy	Anti-parasitic	Low rate of serum aminotran sferase elevations(possible rare cause of clinically apparent liver injury)		[141-143]
23.	Nelfin avir	Aryl sulfide	Inhibited the cytopathic effect induced by SARS-cov infection	Anti-viral	Some degree of serum aminotran sferase elevation, possible rare cause of clinically apparent liver injury		[144,145]

3.2 Table no. 03 Several drugs are currently being developed for the treatment of covid-19

Serial	Study title	Drug name	Sponsor	Clinical stage	Referenc

no.					es
1.	Efficacy and Safety of Direct Anti HCV Drugs in the Treatment of SARS-COV-2 (COVID-19)	Sofosbuvir 400 MG plus Daclatasvir 200mg NCT04535869	Mansoura University	Phase 3	[146]
2.	Efficacy and Safety of Drug Combi nation Therapy of Isotretinoin and Some Antifungal Dru gs as A Potential Aerosol Therapy for COVID-19 : An Innovative Therapeutic Approach COV ID-19	Isotretinoin(Aerosoli zed 13 cis retinoic acid) plus Aerosolized Itraconazole NCT04577378	Kafrelsheikh University	Phase 2	[146]
3.	Multi-Arm Therapeutic Study in Pre-icu Patients Admitted With Covid-19 - Experimental D rugs and	EDP1815 NCT04393246	Cambridge University Hospitals NHS Foundation Trust	Phase 2	[146]

	Mechanisms				
4.	Multi-Arm Therapeutic Study in Pre-icu Patients Admitted With Covid-19 - Experimental Drugs and Mechanisms	Dapagliflozin NCT04393246	Cambridge University Hospitals NHS Foundation Trust	Phase 3	[146]
5.	Multi-Arm Therapeutic Study in Pre-icu Patients Admitted With Covid-19 - Repurposed Drugs (TACTIC-R)	Ravulizumab Baricitinib NCT04390464	Cambridge University Hospitals NHS Foundation Trust	Phase 4	[146]
6.	New Antiviral Drugs for Treatment of COVID-19	Combination of Nitazoxanide, Ribavirin and Ivermectin NCT04392427	Mansoura University	Phase 3	[146]
7.	Rapid Experimental Medicine for COVID-19 (DEFINE)	Nafamostat Mesilate NCT04473053	University of Edinburgh	Phase 2	[146]

8.	Rapid Experimental Medicine for COVID-19 (DEFINE)	TD139 NCT04473053	University of Edinburgh	Phase 3	[146]
9.	An Experiment to Evaluate the Safety of agent-797 in COVID-19 Patients With Severe Difficulty Breathing.	Agent-797 NCT04582201	Agentus Therapeutics, Inc.	Phase 1	[146]
10.	Hydroxychloroquine and Nitazoxanide Combination Therapy for COVID-19	Hydroxychloroquine plus Nitazoxanide NCT04361318	Tanta University	Phase 2	[146]
11.	Silymarin in COVID-19 Patients Admitted to Hospital With Elevated Liver Enzymes (SILCOVINT-21)	Silymarin NCT04816682	F.D. Roosevelt Teaching Hospital with Policlinic Banska Bystrica	Phase 4	[146]
12.	COVID-19 Treatment in	Artesunate-amodiaquine	Shin Poong Pharmace	Phase 2	[146]

	South Africa	Pyronaridine-artesunate Favipiravir plus Nitazoxanide Sofosbuvir/daclatasvir	utical Co. Ltd.		
13.	Sarilumab Treatment In cytokine Storm Caused by Infection With COVID-19 (STRIKESARS)	Sarilumab NCT04661527	Clinica Universidad de Navarra, Universidad de Navarra	Phase 2	[146]
14.	Silymarin in COVID-19 Patients Admitted to Hospital With Elevated Liver Enzymes (SILCOVINT-21)	Silymarin NCT04816682	F.D. Roosevelt Teaching Hospital with Policlinic Banska Bystrica	Phase 4	[146]
15.	Combination Therapies to Reduce Carriage of SARS-Cov-2 and Improve Outcome of COVID-	Lopinavir/Ritonavir 200 MG-50 MG Oral Tablet NCT04466241	ANRS, Emerging Infectious Diseases	Phase 2	[146]

	19 in Ivory Coast: a Phase Randomized iib Trial (INTENSE-COV)				
16.	Combination Therapies to Reduce Carriage of SARS-Cov-2 and Improve Outcome of COVID-19 in Ivory Coast: a Phase Randomized iib Trial (INTENSE-COV)	Telmisartan 40Mg Oral Tablet NCT04466241	ANRS, Emerging Infectious Diseases	Phase 3	[146]
17.	Trial Evaluating Efficacy and Safety of Anticoagulation in Patients With COVID-19 Infection, Nested in the Corimmuno-19 Cohort	Tinzaparin or unfractionated heparin NCT04344756	Assistance Publique - Hôpitaux de Paris	Phase 2	[146]

	(CORIMMUNO-COAG)				
18.	Study of Efficacy and Safety of DV890 in Patients With COVID-19 Pneumonia	DFV890 NCT04382053	Novartis Pharmaceuticals	Phase 2	[146]
19.	Chloroquine Phosphate Prophylactic Use in Health Personnel Exposed to COVID-19 Patients	Chloroquine phosphate NCT04443270	CMN "20 de Noviembre"	Phase 1	[146]
20.	Evaluation of Efficacy of Levamisole and Formoterol+Budesonide in Treatment of COVID-19	Levamisole Pill + Budesonide+Formoterol inhaler NCT04331470	Fasa University of Medical Sciences	Phase 2	[146]
21.	Evaluation of Efficacy of Levamisole and Formoterol+Bu	Lopinavir/Ritonavir + hydoxychloroquine	Fasa University of Medical Sciences	Phase 3	[146]

	desonide in Treatment of COVID-19				

3.3 Table no. 04 Vaccines under development for COVID-19

Serial no.	Title	Vaccine name	Sponsor	Clinical stage	References
1.	Use of BCG Vaccine as a Preventive Measure for COVID-19 in Health Care Workers	BCG vaccine NCT04659941	Universidade Federal do Rio de Janeiro	Phase 2	[146]
2.	Safety and Immunogenicity of Two Different Strengths of the Inactivated COVID-19 Vaccine ERUCOV-VAC (ERUCOV-VAC)	ERUCOV-VAC NCT04691947	Health Institutes of Turkey	Phase 1	[146]
3.	Study of the Safety, Reactogenicity and Immunogenicity of "epivaccorona" Vaccine for the Prevention of COVID-19 (epivaccorona)	Epivaccorona NCT04527575	Federal Budgetary Research Institution State Research Center of Virology and Biotechnology "Vector"	Phase 1	[146]
4.	A Study to Evaluate MVC-COV1901 Vaccine Against COVID-19 in Elderly Adults	MVC-COV1901 NCT04822025	Medigen Vaccine Biologics Corp.	Phase 2	[146]
5.	The Phase I Clinical Trial of Booster Vaccination of Adenovirus Type-5 Vectored COVID-19 Vaccine	Adenovirus Type-5 Vectored COVID-	Jiangsu Province Centers for Disease Control and Prevention	Phase 1	[146]

		19 Vaccine NCT04568811			
6.	COVID-19 Supplemental Vaccine Boost to Enhance T Cell Protection in Those Who Have Already Received EUA S-Based Vaccines	Had5-S-Fusion+N-ETSD vaccine NCT04843722	Immunitybio, Inc.	Phase 1Phase 2	[146]
7.	Safety, Tolerability, and Immunogenicity of the COVID-19 Vaccine Candidate (VBI-2902a)	VBI-2902a NCT04773665	VBI Vaccines Inc.	Phase 1	[146]
8.	A Controlled Phase 2/3 Study of Adjuvanted Recombinant SARS-cov-2 Trimeric S-protein Vaccine (SCB-2019) for the Prevention of COVID-19 (SCB-2019)	Cpg 1018/Alum-adjuvanted SCB-2019 vaccine NCT04672395	Clover Biopharmaceuticals AUS Pty Ltd	Phase 2	[146]
9.	PTX-COVID19-B, an mrna Humoral Vaccine, is Intended for Prevention of COVID-19 in a General Population. This Study is Designed to Evaluate Safety, Tolerability, and Immunogenicity of PTX-COVID19-B Vaccine in Healthy Seronegative Adults Aged 18-64	PTX-COVID19-B NCT04765436	Providence Therapeutics Holdings Inc.	Phase 1	[146]
10.	Clinical Trial of the	Gam-	Gamaleya	Phase 3	[146]

	Immunogenicity, Safety, and Efficacy of the Gam-COVID-Vac Vaccine Against COVID-19 in Venezuela (VENEZUELA)	COVID-Vac NCT04642339	Research Institute of Epidemiology and Microbiology, Health Ministry of the Russian Federation		
11.	GLS-5310 Vaccine for the Prevention of SARS-cov-2 (COVID-19)	GLS-5310 NCT04673149	Geneone Life Science, Inc.	Phase 1	[146]
12.	Vaccination of Ex-acute COVID-19 Patients With Fibrosing Lung Syndrome at Discharge (COVINVAC)	IN01 vaccine NCT04537130	Instituto Oncológico Dr Rosell	Phase 1	[146]
13.	Safety and Immunogenicity Trial of an Oral SARS-cov-2 Vaccine (VXA-cov2-1) for Prevention of COVID-19 in Healthy Adults	VXA-cov2-1 NCT04563702	Vaxart	Phase 1	[146]
14.	Safety and Immunogenicity Study of GX-19N, a COVID-19 Preventive DNA Vaccine in Healthy Adults	GX-19N NCT04715997	Genexine, Inc.	Phase 1Phase 2	[146]
15.	A Study to Evaluate the Safety and Immunogenicity of COVID-19 (adimrsc-2f) Vaccine	Adimrsc-2f NCT04522089	Adimmune Corporation	Phase 1	[146]
16.	Dose Finding Study to Evaluate Safety, Tolerability and Immunogenicity of an	VLA2001 NCT04671017	Valneva Austria gmbh	Phase 1Phase 2	[146]

	Inactiviated Adjuvanted Sars-Cov-2 Virus Vaccine Candidate Against Covid-19 in Healthy Adults				
17.	COVID-19: SARS Vaccination (SARS)	Moderna COVID-19 Vaccine NCT04761822	National Institute of Allergy and Infectious Diseases (NIAID)	Phase 2	[146]
18.	A Study to Evaluate UB-612 COVID-19 Vaccine in Adolescent, Younger and Elderly Adult Volunteers	UB-612 NCT04773067	United Biomedical Inc., Asia	Phase 2	[146]
19.	Safety and Immunogenicity Study of adcld-cov19: A COVID-19 Preventive Vaccine in Healthy Volunteers	Adcld-cov19 NCT04666012	Cellid Co., Ltd.	Phase 1Phase 2	[146]
20.	Clinical Trial to Evaluate the Efficacy of RUTI® Against SARS-COV-2 Infection (COVID-19) in Healthcare Workers	RUTI® vaccine NCT04453488	Fundació Institut Germans Trias i Pujol	Phase 3	[146]

Conclusion

Coronavirusidiseaseihasibeenidiscussediinithisiarticlei(COVID-19).iIt'sianiinfectiousidiseaseicausedibyiairecentlyidiscoveredicoronavirusivirusithatispreadsimainlyibyisalivaidropletsiorinasalidischargeiwhenianiinfectediindividualicoughsiorisneezes.iCOVID-

19i(coronavirusidisease)iisiaihighlyiinfectiousidisease.iInicertainicases,iiticaniquickly iprogressitoiacuteirespiratoryidistressisyndromei(ARDS),iwhichicanileaditoimultiorg anidysfunctioniorideath.iCoronavirusesiareienveloped,isingle-strandedilargeiRNAivirusesithatiinfectihumansiandiaivarietyiofianimals.Coronaviruse siareidividediintoifourisubgroups:ialpha,ibeta,igamma,iandidelta.iSARS-cov-2ibelongsitoitheicoronavirusifamily'sibetaisubgroup.iInithisiarticle,iweiclassifiedicoro navirusesibasedionitheirigeneraiandiwhetheriorinotitheyiinfectihumans.iWe'veiwritte niaboutitheieffectsioficovidionitheiliver,iwhichiareiclassifiediasiSARS-covioniliveriinjury,iMerscovioniliveriinjury,iandiSARS-cov-2ioniliveriinjury.iWe'veialsoiwritteniaboutiapprovedidrugsiforicoronaivirusitreatment ianditheirieffectsionitheiliver,iasiwelliasimanyiongoingidrugsiandivaccinesibeingidev elopediforicovid-19itreatment.Weihaveicategoriseditheiapprovedidrugsiaccordingitoitheiriname,icomp osition,ioutcome,idrugicategory,iliverieffect,iandichemicalistructure.iWeihaveiclassifi editheiongoingidrugsithatihaveibeenidevelopediforiCOVID-19itreatmentiintoiStudyititle,iDruginame,iNCTinumber,iSponsor,iandiclinicalistage,ia ndiweihaveialsoiclassifieditheiVaccinesiunderidevelopmentiforiCOVID-19iintoiTitle,iVaccineiname,iSponsor,iandiclinicalistage.Theimainigoaliofithisiarticlei isitoidescribeitheidifferentieffectsiofidrugsiusediinitheitreatmentioficoronaivirusidisea seionitheiliver,iandiweihaveicomeitoitheiconclusionithatidrugsiusediinitheitreatmenti oficovid-19ihaveiaisignificantiimpactionitheiliver.iSinceiseveralimedicationsiareiuseditoitreati covid-19,iweicaniinferithatisomeidrugsihaveiaisignificantieffectionitheiliver,iwhileiothersih aveiaimildiimpact,iandistilliothersihaveiainegligibleiorinoiimpactionitheiliver.iHepato toxicity,ihepaticienzymeielevation,ielevatediASTiandiALTilevels,iandiotherieffectsio nitheiliveriareiallipossible.

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