Rifampicin for COVID-19

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Abstract

Vaccinations for coronavirus disease-2019 (COVID-19) have begun more than a year before, yet without specific treatments available. Rifampicin, critically important for human medicine (World Health Organization’s list of essential medicines), may prove pharmacologically effective for treatment and chemoprophylaxis of healthcare personnel and those at higher risk. It has been known since 1969 that rifampicin has a direct selective antiviral effect on viruses which have their own RNA polymerase (severe acute respiratory syndrome coronavirus 2), like the main mechanism of action of remdesivir. This involves inhibition of late viral protein synthesis, the virion assembly, and the viral polymerase itself. This antiviral effect is dependent on the administration route, with local application resulting in higher drug concentrations at the site of viral replication. This would suggest also trying lung administration of rifampicin by nebulization to increase the drug’s concentration at infection sites while minimizing systemic side effects. Recent in silico studies with a computer-aided approach, found rifampicin among the most promising existing drugs that could be repurposed for the treatment of COVID-19.

Key Words: COVID-19; SARS-CoV-2; Rifampicin; Antiviral activity; RNA polymerase
Core Tip: Rifampicin may prove pharmacologically effective, supplying a possible and cost-effective solution to the global battle against severe acute respiratory syndrome coronavirus 2, not only for treatment but also for chemoprophylaxis of those at higher risk. It is also possible to administer rifampicin by nebulization. The publications describing the in vitro mechanisms and providing proof of clinical efficacy of rifampicin against RNA viruses with their own RNA polymerase have emerged since 1969-1971. Recent in silico studies using a computer-aided approach, found rifampicin among the most promising existing drugs that can be repurposed for the treatment of coronavirus disease-2019.

Introduction

The coronavirus disease-2019 (COVID-19) pandemic presents a puzzling challenge without specific treatment yet[1], and while vaccinations have been initiated more than a year before[2], there is still a long way to go before herd immunity can be achieved, even in the developed countries[3]. In the critically ill patients, plasma transfusions from recovered patients have been tried[4] and specific severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) memory T cells could also treat moderate/severe cases of COVID-19[5]. When and with which pharmacological cocktail to intervene is under rigorous investigation worldwide[6]. Chemoprophylaxis of exposed healthcare personnel[7], along with those at higher risk for severe illness, is also equally exigent, at least until sizable worldwide immunization will be achieved[8]. And even if vaccination campaigns do make progress in the Western world, this process may take much longer in the developing countries. Even then, the possible emergence of SARS-CoV-2 new mutated strains could substantially impact the protection of currently available vaccines or the physical immunity acquired from previous illness from the previous SARS-CoV-2 variants[9] (https://theconversation.com/the-lambda-variant-is-it-more-infectious-and-can-it-escape-vaccines-a-virologist-explains-164156).

Rifampicin, discovered in 1965, was marketed in Italy in 1968, and approved in the United States in 1971. It is on the World Health Organization’s (WHO) list of essential medicines, classified by the WHO as critically important for human medicine. Made by the soil bacterium Amycolatopsis rifamycinica, rifampicin is widely available as a generic medication with an extremely low cost compared to any other modern antiviral medication. It belongs to the Rifamycins, characterized as antiviral drugs which inhibit transformation of cells by viruses[10]. While in the fourth wave of this pandemic, without specific medications available yet, along with the ongoing computational analysis of potential drugs[11], it becomes clearer that - at least for now and beyond active immunization - we still need to rely on one hand on the enhancement of our immune system and on the other hand on the known anti-inflammatory and immunomodulatory effects of some antibacterials and the emerging antiviral effects of old but precious drugs, such as rifampicin. For the first task, which is to strengthen our immunity, adding zinc sulphate increased patients’ discharges, decreasing the need for ventilation, intensive care unit admissions, and mortality[12]. Increased intracellular zinc concentrations seem to inhibit RNA-dependent polymerases, helping to support robust immune responses and modulating immune cell activity. For that task, researchers have tried high doses of vitamin C[13]. And last but not least, proper supplementation[14,15] or even adjunctive therapy with vitamin-D[16], to capitalize on its extra-skeletal immunomodulatory properties, may also prove valuable, playing a crucial role in enhancing and coordinating the immune system’s response to SARS-CoV-2 infection[17,19]. For that purpose, personalized immunotherapy approaches with agents/monoclonal antibodies that block receptors for interleukin-1/6 have been initiated, aiming to control the macrophage activation syndrome which has been suggested as a major mechanism of lung impairment in COVID-19[19]. Monoclonal antibodies have shown promising results, with prompt administration though being a key issue to exert their benefit[20]. Bamlanivimab, a neutralizing monoclonal antibody against SARS-CoV-2, reduced the incidence of COVID-19[21].

Herein, we discuss the possibility of repurposing rifampicin for COVID-19, and we call for immediate coordinated - international if possible - collaboration[22] in in vitro studies, open-label pilot trials, and definitive phase 3 clinical trials.

Antiviral Properties of Rifampicin: Mechanisms and Facts

Careful analysis of the COVID-19 clinical characteristics and computed tomography scans indicates that the pulmonary nontuberculous mycobacterial disease, in which azithromycin and rifampicin are among...
first line treatment options, seems to share a striking analogy with SARS-CoV-2 pneumonia\cite{23}. Going back to 1969, a conventional antibacterial of proved pharmacological acceptability in man, rifampicin (or rifampin: https://www.accessdata.fda.gov/drugsatfda_docs/Label/2018/050420s077,050627s020 Lbl.pdf), was found to have a direct antiviral effect in some mammalian viruses as poxviruses including the causative agent of smallpox and mainly on viruses which have their own RNA polymerase\cite{24}, which is the case for SARS-CoV-2 and the main mechanism of action of remdesivir. Initially developed against Ebola, remdesivir raised hope, as it incorporates into nascent viral RNA chains and results in premature termination of viral replication. Remdesivir showed higher recovery and hospital discharge rates, but no significant reduction in mean time to clinical improvement or mortality\cite{25}.

Regarding large DNA viruses, the antiviral activity of rifampicin arises from its binding to the F-ring, highly conserved across mammalian poxviruses, which cannot mutate in response to rifampicin inhibition and thus provide a potential base for the development of broad-spectrum inhibitors against infectious poxviruses species in animals and humans\cite{26}. However, the efficacy of rifampicin against viruses with their own RNA polymerase shares the same mechanism with its antibacterial activity against microbial RNA polymerases. The inhibitory mechanism of rifampicin on the RNA polymerases is a simple steric block of transcription elongation due to its ability to bind tightly to non-conserved parts of the structure, disrupting a critical RNA polymerase function\cite{27}. The rifampicin molecule is a condensation product of 3-formyl rifamycin SV and 1-amino 4-methyl piperazine with the antiviral activity existing in the rifamycin part of the molecule. Its antiviral effect is reversible as removal of the drug late in the virus cycle leads to a mature and infectious virus even within 1 h. This would mean that careful monitoring of rifampicin levels may assure effectiveness. The selective antiviral effect of rifampicin involves inhibition of late viral protein synthesis\cite{28}, virion assembly\cite{29}, and the viral polymerase itself\cite{30}.

Table 1 summarizes the studies on the possible antiviral properties of rifampicin against SARS-CoV-2 presenting their main findings.

**ADMINISTRATION ROUTE AND POTENTIALS**

Studies in volunteers have also shown a dependence of rifampicin’s antiviral effect on administration route, with local application resulting in higher concentrations of the drug at the site of viral replication\cite{31}. This would suggest trying lung administration of rifampicin by nebulization\cite{32}, increasing the drug’s concentration at infection sites while minimizing systemic side effects. This approach, using aerosolized rifampicin-loaded polymeric microspheres, reduced most measures of tuberculosis infection in experimental animals\cite{33}. However, since the major cell entry receptor for SARS-CoV-2 is the metallocarboxyl peptidase angiotensin receptor 2\cite{34}, whose expression is very low in the lung, the approach of lung administration may not exhibit the expected systemic antiviral effects of rifampicin and requires further investigation.

An effective intracellular concentration of rifampicin without serious toxicity seems possible and probable, given its pharmacokinetic profile, suitable also for chemophrophylaxis (https://pubchem.ncbi.nlm.nih.gov/compound/Rifampicin#section=Drug-Classes). Current studies have evaluated intravenous rifampicin 20 mg/kg for 2 wk followed by high dose oral formulation (35 mg/kg for 6-8 wk) for improved survival from adult tuberculous meningitis\cite{35}. Data concerning intracellular rifampicin concentrations to exhibit effective antiviral activity against influenza virus A\cite{36}, African swine fever virus\cite{37}, and cytomegalovirus\cite{38} have been already available.

**IN SILICO STUDIES INDICATE POSSIBLE EFFECTIVENESS OF RIFAMPICIN**

The above finding may have just been verified by a recent in silico study using a computer-aided drug designing approach: Rifampicin was the most promising existing drug that could be repurposed for the treatment of COVID-19\cite{39}. Moreover, using a comprehensive drug repurposing and molecular docking approach, prediction of potential inhibitors for RNA-dependent RNA polymerase of SARS-CoV-2 revealed that rifabutin could be an effective drug for COVID-19, having the lowest binding energy compared to the positive control remdesivir\cite{40}. Rifabutin, however, belongs to the rifamycins (rifampicin, rifapentine, and rifabutin), but with rifampicin being the most used\cite{41}. In silico virtual screening within the United States Food and Drug Administration (FDA)-approved drugs targeting the RNA-dependent RNA polymerase, which is the critical enzyme for coronavirus replication, also placed rifampicin among the five most potent potential anti-SARS-CoV-2 therapeutics\cite{42}. Virtual screening of FDA-approved drugs targeting not only the main protease of SARS-CoV-2 but also TNF-α, IL-6, and IL-1β, which are the key molecules involved in the 'cytokine storm' occurring in COVID-19, indicated rifampicin as one of the most promising drugs for the treatment of COVID-19, together with letermovir\cite{43}. These were systematic docking studies, further confirmed by molecular dynamics simulations and molecular calculations; however, such studies are prone to the high probability of artifacts needing experimental verification.
The SARS-CoV-2 RNA-dependent RNA polymerase (nsp12) catalyzes the replication of RNA from RNA templates. Changes in the virus life cycle are exhibited by the fixation of specific ligands in the active site of this crucial enzyme. A recent study found the highly conserved nsp12 motifs (A-G), and discovered the interactions with rifabutin and rifampicin, among other ligands. Both of them interacted with at least two nsp12 motifs, indicating that they could be both used as inhibitors of SARS-CoV-2 nsp12 protein[44]. Another in silico docking approach also found that rifampicin has good binding affinity with the COVID-19 protease[45], proposing its use as therapeutic treatment as well as prophylaxis.

Of course, all the above findings require further validation by in vitro studies and clinical trials. Table 2 summarizes the in silico studies indicating effectiveness of rifampicin against SARS-CoV-2.

### SAFETY AND ADVANTAGES OF RIFAMPICIN

Rifampicin is not the only antibiotic that could be repurposed for COVID-19. Quinupristin, for example, is an antibiotic in clinical use for two decades now with minor side effects and has also proven in silico...
Using a computer-aided drug designing approach, rifampicin was the most promising existing drug that could be repurposed for the treatment of COVID-19. The SARS-CoV-2 RNA dependent RNA polymerase (nsp12) catalyzes the replication of RNA from RNA templates. Changes in the virus life cycle are exhibited by the fixation of specific ligands in the active site of this crucial enzyme. A recent study found the highly conserved nsp12 motifs, and discovered the interactions with rifabutin and rifampicin, concluding that both could function as inhibitors of the SARS-CoV-2 nsp12 protein.

RIFAMPICIN IN COVID-19 IN CLINICAL PRACTICE

A recent case report described the favorable outcome under treatment with chloroquine and rifampin of an unusual association of COVID-19, pulmonary tuberculosis, and human immunodeficiency virus infection[58], attributed either to rifampicin inhibiting the formation of mRNA of SARS-CoV-2 and/or the possible synergistic effect of chloroquine and rifampin, despite that anti-tubercular drugs such as rifampicin are powerful enzyme inducers that can reduce the effectiveness of chloroquine. Up to now, there are no clinical studies available on the treatment of COVID-19 patients with rifampicin. Anecdotally, experienced pediatricians have also successfully treated neonates and infants[59] found positive for SARS-CoV-2 with rifampicin, clearly aiming for their protection with their parents suffering overt COVID-19 with an eventful clinical course.

CONCLUSION

Timely administration, though, is important for all current regimens on trial: It must not be too late when treatment starts. Specifically, rifampicin interferes with the viral replication, and thus, early administration after diagnosis of COVID-19 could make a significant difference to its presumed effectiveness against SARS-CoV-2 infection. Similarly, for rifampicin’s use for postexposure prophylaxis to people exposed to index cases of invasive meningococcal infection, pre-exposure together with post-exposure prophylaxis could also be a potential strategy, at least for unvaccinated people[60]. The WHO proposed a similar approach for people at elevated risk for infection, before or after exposure, during the influenza pandemic.

Call for studies

Facing this unprecedented global emergency and given the experience, safety, and knowledge behind rifampicin, we call for international collaboration proposing in vitro studies, open-label pilot trials, and definite phase 3 clinical trials for testing treatment and chemoprophylaxis efficacy of rifampicin against COVID-19. With all the above compelling evidence, rifampicin merits evaluation against COVID-19.
FOOTNOTES

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Conflict-of-interest statement: George D Panayiotakopoulos serves as Vice President of The National Public Health Organization of Greece; Dimitrios T Papadimitriou has no conflict of interests to declare.

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REFERENCES

1 Pagliano P, Scarpati G, Sellitto C, Conti V, Spera AM, Ascione T, Piazza O, Filippelli A. Experimental Pharmacotherapy for COVID-19: The Latest Advances. J Exp Pharmacol 2021; 13: 1-13 [PMID: 33442304 DOI: 10.2147/JEP.S255209]  
2 Williams J, Degeling C, McVernon J, Dawson A. How should we conduct pandemic vaccination? Vaccine 2021; 39: 994-999 [PMID: 33423839 DOI: 10.1016/j.vaccine.2020.12.059]  
3 Ghaafari A, Meurant R, Ardakani A. COVID-19 Point-of-Care Diagnostics That Satisfy Global Target Product Profiles. Diagnostics (Basel) 2021; 11 [PMID: 33457277 DOI: 10.3390/diagnostics11010115]  
4 Mandel M, Gurevich M, Mandelboim M, Amital H, Azéryn A. Convalescent Whole Blood Donors Screening Strategies for Providing Efficient and Safe COVID-19 Survivors' Plasma and Other Blood Components. J Med Assoc J 2021; 23: 7-10 [PMID: 33443334]  
5 Ferreras C, Pascual-Miguel B, Mestre-Durán C, Navarro-Zapata A, Clares-Villa L, Aparicio J, De Paz R, Marcos A, Vicario JL, Balas A, García-Sánchez F, Eguizabal C, Solano C, Mora-Rillo M, Soria B, Pérez-Martínez A. SARS-CoV-2-Specific Memory T Lymphocytes From COVID-19 Convalescent Donors: Identification, Biobanking, and Large-Scale Production for Adoptive Cell Therapy. Front Cell Dev Biol 2021; 9: 620730 [PMID: 33718360 DOI: 10.3389/fcell.2021.620730]  
6 Singh A, Gupta V. SARS-CoV-2 therapeutics: how far do we stand from a remedy? Pharmaco Rep 2021; 73: 750-768 [PMID: 33389724 DOI: 10.1007/s43440-020-00204-0]  
7 Tahiri Joutei Hassani R, Bennis A. Hydroxychloroquine as antiviral prophylaxis for exposed caregivers to Covid-19: An urgent appraisal is needed. J Infect Public Health 2020; 13: 865-867 [PMID: 32451259 DOI: 10.1016/j.jiph.2020.05.005]  
8 Neagu M, Fildes S, Marcus D. The bumpy road to achieve herd immunity in COVID-19. J Immunassay Immunochem 2020; 41: 928-945 [PMID: 33086932 DOI: 10.1080/15251819.2020.1833919]  
9 Shim E. Projecting the Impact of SARS-CoV-2 Variants and the Vaccination Program on the Fourth Wave of the COVID-19 Pandemic in South Korea. Int J Environ Res Public Health 2021; 18 [PMID: 34300029 DOI: 10.3390/ijerph18147578]  
10 Becker Y. Antiviral Drugs which Inhibit Transformation of Cells by Viruses. Monogr Virol 1976; 11 [DOI: 10.1159/000398678]  
11 Murugan NA, Kumar S, Jayakanthan J, Srivastava V. Searching for target-specific and multi-targeting organics for Covid-19 in the Drugbank database with a double scoring approach. Sci Rep 2020; 10: 19125 [PMID: 33154404 DOI: 10.1038/s41598-020-7575-7]  
12 Carlucci PM, Ahuja T, Pettit C, Rajagopalan H, Jones S, Rahimian J. Zinc sulfate in combination with a zinc ionophore may improve outcomes in hospitalized COVID-19 patients. J Med Microbiol 2020; 69: 1228-1234 [PMID: 32903657 DOI: 10.1099/jmm.0.001250]  
13 Zhang J, Ruo X, Li Y, Zha Y, Liu F, Guo G, Luo M, Meng Z, De Backer D, Xiang H, Peng Z. Pilot trial of high-dose vitamin C in critically ill COVID-19 patients. Ann Intensive Care 2021; 11 [PMID: 33420963 DOI: 10.1186/s13613-020-00792-3]  
14 Papadimitriou DT, Vassaras AK, Holick MF. Association between population vitamin D status and SARS-CoV-2 related serious-critical illness and deaths: An ecological integrative approach. World J Virol 2021; 10: 111-129 [PMID: 34079693 DOI: 10.2147/WJVirol.S255209]  
15 Papadimitriou DT. The Big Vitamin D Mistake. J Prev Med Public Health 2017; 50: 278-281 [PMID: 28768407 DOI: 10.5961/jpmph.16.111]  
16 Lakkireddy M, Gadiga SG, Malathi RD, Karra ML, Raju ISSVPM, Ragin, Chinapaka S, Baba KSSS, Kandakatla M. Impact of daily high dose oral vitamin D therapy on the inflammatory markers in patients with COVID 19 disease. Sci Rep 2021; 11: 10641 [PMID: 34017029 DOI: 10.1038/s41598-021-90189-4]  
17 Morabia A, Costanza MC. Vitamin D as in different. Prev Med 2010; 51: 195-196 [PMID: 20837203 DOI: 10.1016/j.ypmed.2010.08.007]
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18 Maghbooli Z, Sahraian MA, Ebrahimim M, Pazoki M, Kafsan S, Tabriz HM, Hadadi A, Montazeri M, Nasiri M, Shirvani A, Holick MF. Vitamin D sufficiency, a serum 25-hydroxyvitamin D at least 30 ng/mL reduced risk for adverse clinical outcomes in patients with COVID-19 infection. PLoS One 2020; 15: e0239799 [PMID: 32976513 DOI: 10.1371/journal.pone.0239799]

19 Iqbal H, Hood F, Najmi AK, Haque SE. Macrophage Activation and Cytokine Release Syndrome in COVID-19: Current Updates and Analysis of Repurposed and Investigational Anti-Cytokine Drugs. Drug Res (Stuttg) 2021; 71: 173-179 [PMID: 33434935 DOI: 10.1055/a-1291-7692]

20 Tuccori M, Ferraro S, Convertino I, Cappello E, Valdissiera G, Blandizzi C, Maggi F, Focosi D. Anti-SARS-CoV-2 neutralizing monoclonal antibodies: clinical pipeline. Mabs 2020; 12: 1854149 [PMID: 33319640 DOI: 10.1080/19420862.2020.1854149]

21 Bowen AC, Tong SY, Davis JS. Australia needs a prioritised national research strategy for clinical trials in a pandemic: lessons learned from COVID-19. Med J Aust 2021; 215: 56-58.e1 [PMID: 34145568 DOI: 10.5694/mja2.51143]

22 Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, Wang B, Xiang H, Cheng Z, Xiong Y, Zhao Y, Li Y, Wang X, Peng Z. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA 2020; 323: 1061-1069 [PMID: 32031570 DOI: 10.1001/jama.2020.1585]

23 Rifampicin and viruses. Br Med J 1969; 2: 588-589 [PMID: 5798465]

24 Abdouli A, Baziati A, Kazmi A, Fasham OE, Khan SU, Zhao D, Antar AAR, Michos ED. Rendesivir for the treatment of COVID-19: A systematic review and meta-analysis of randomized controlled trials. Contemp Clin Trials 2021; 101: 106272 [PMID: 33422642 DOI: 10.1016/j.cct.2021.106272]

25 Garriga D, Headey S, Accurso C, Gunzburg M, Scanlon M, Coulbily F. Structural basis for the inhibition of poxvirus assembly by the antibiotic rifampicin. Proc Natl Acad Sci U S A 2018; 115: 8424-8429 [PMID: 30068608 DOI: 10.1073/pnas.1810398115]

26 Campbell EA, Korzheva N, Mustaev A, Murakami K, Nair S, Goldfarb A, Darst SA. Structural mechanism for rifampicin inhibition of bacterial rna polymerase. Cell 2001; 104: 901-912 [PMID: 11920327 DOI: 10.1016/S0092-8674(01)00286-0]

27 Ben-Ishaï H, Heller E, Goldblum N, Becker Y. Rifampicin and poxvirus replication. Nature 1969; 224: 29-32 [PMID: 5822902 DOI: 10.1038/224290a0]

28 Moss B, Rosenblum EN, Katz E, Grimley PM. Rifampicin: a specific inhibitor of vaccinia virus assembly. Nature 1969; 224: 1280-1284 [PMID: 5359293 DOI: 10.1038/2241280a0]

29 Mcauslan BR. Rifampicin inhibition of vaccinia replication. Biochem Biophys Res Commun 1969; 37: 289-295 [PMID: 4989697 DOI: 10.1016/0006-291X(69)90733-5]

30 Moshkowitz A, Goldblum N, Heller E. Studies on the antiviral effect of rifampicin in volunteers. Nature 1971; 229: 422-424 [PMID: 4323457 DOI: 10.1038/229422a0]

31 Tewes F, Brillault J, Couet W, Olivier JC. Formulation of rifampicin-cyclodextrin complexes for lung nebulization. J Control Release 2008; 129: 93-99 [PMID: 18514353 DOI: 10.1016/j.jconrel.2008.04.007]

32 García-Contreras L, Sethuranam V, Kazantseva M, Godfrey V, Hickey AJ. Evaluation of dosing regimen of respirable rifampicin biomembrane microspheres in the treatment of tuberculosis in the guinea pig. J Antimicrob Chemother 2006; 58: 990-996 [PMID: 16714160 DOI: 10.1093/jac/dkl369]

33 Scalia F, Daniele A, Amato F, Pastore L, Materia MG, Cazzola M, Castaldo G, Bianco A. ACE2: The Major Cell Entry Receptor for SARS-CoV-2. Lung 2020; 198: 867-877 [PMID: 31703170 DOI: 10.1007/s40408-020-00408-4]

34 Cresswell FV, Ssebambulidde K, Grunt D, Te Brake L, Mushaire A, Atherton RR, Tugume L, Muzoora C, Lukande R, Lomarde M, Aarnoutse R, Meya D, Boulware DR, Elliott AM. High dose oral and intravenous rifampicin for improved survival from adult tuberculosis meningitis: a phase II open-label randomised controlled trial (the RifIT study). Wellcome Open Rep 2018; 3: 8 [PMID: 30175245 DOI: 10.12688/wellcomeopenres.14691.1]

35 Hamzehi M, Ledinko N. Inhibition of influenza A virus replication by rifampicin and selenocystamine. J Med Virol 1980; 6: 169-174 [PMID: 7241092 DOI: 10.1002/jmv.1890060210]

36 Dardiri AH, Bachrach HL, Heller E. Inhibition by rifampin of African swine fever virus replication in tissue culture. Infect Immun 1971; 4: 34-36 [PMID: 5158475 DOI: 10.1128/iai.4.1.34-36.1971]

37 Halsted CC, Minniford AB, Litman PS. Inhibition of cytomegalovirus by rifampin. J Infect Dis 1972; 125: 552-555 [PMID: 4336860 DOI: 10.1093/infdis/125.5.552]

38 Kumar A, Mishra DC, Angadi UB, Yadav R, Rai A, Kumar D. Inhibition Potencies of Phytochemicals Derived from Sesame Against SARS-CoV-2 Main Protease: A Molecular Docking and Simulation Study. Front Chem 2021; 9: 744376 [PMID: 34692642 DOI: 10.3389/fchem.2021.744376]

39 Parvez MSA, Karim MA, Hasan M, Jaman J, Karim Z, Tahsin T, Hasan MN, Hosen MJ. Prediction of potential inhibitors for RNA polymerase of SARS-CoV-2 using comprehensive drug repurposing and molecular docking approach. Int J Biol Macromol 2020; 152: 1787-1797 [PMID: 32950529 DOI: 10.1016/j.ijbiomac.2020.09.099]

40 Forrest GN, Tamura K. Rifampin combination therapy for nonmycobacterial infections. Clin Microbiol Rev 2010; 23: 14-34 [PMID: 20065324 DOI: 10.1128/CMR.00034-09]

41 Pokhrel R, Chapagain P, Silberg-Liberles J. Potential RNA-dependent RNA polymerase inhibitors as prospective therapeutics against SARS-CoV-2. J Med Microbiol 2020; 69: 864-873 [PMID: 32469301 DOI: 10.1099/jmm.0.001203]

42 Pathak V, Mishra A, Choudhur G, Kumar A, Tripathi V. Rifampicin and Letermovir as potential repurposed drug candidate for COVID-19 treatment: insights from an in-silico study. Pharmacol Rep 2021; 73: 926-938 [PMID: 33970450 DOI: 10.1007/s44400-021-00228-0]

43 Elkahhat Z, Charoute H, Elkahhatli L, Barakat A, Rouba H. Potential inhibitors of SARS-cov-2 RNA dependent RNA
polymerase protein: molecular docking, molecular dynamics simulations and MM-PBSA analyses. J Biomol Struct Dyn 2022; 40: 361-374 [PMID: 32873176 DOI: 10.1080/07391102.2020.1813628]

45 Soni H, Gautam D, Sharma S, Malik J. Rifampicin as potent inhibitor of COVID-19 main protease: in-silico docking approach. Saudi Journal of Medical and Pharmaceutical Sciences 2020; 588 [DOI: 10.36348/sjmps.2020.v06i09.001]

46 Semvuu HI, Kibiki GS, Kisanga ER, Boeree MJ, Burger DM, Aarnoutse R. Pharmacological interactions between rifampicin and antiretroviral drugs: challenges and research priorities for resource-limited settings. Ther Drug Monit 2015; 37: 22-32 [PMID: 24943062 DOI: 10.1097/FTD.000000000000108]

47 Hanafy AS, Abd-Elsamam S. Challenges in COVID-19 drug treatment in patients with advanced liver diseases: A hepatology perspective. World J Gastroenterol 2020; 26: 7272-7286 [PMID: 33362383 DOI: 10.3748/wjg.v26.i46.7272]

48 Chen J, Raymond K. Roles of rifampicin in drug-drug interactions: underlying molecular mechanisms involving the nuclear pregnane X receptor. Ann Clin Microbiol Antimicrob 2006; 5: 3 [PMID: 16480505 DOI: 10.1186/1476-0711-5-3]

49 Li T, Chiang JY. Rifampicin induction of CYP3A4 requirespregnane X receptor cross talk with hepatocyte nuclear factor 4alpha and coactivators, and suppression of small heterodimer partner gene expression. Drug Metab Dispos 2006; 34: 756-764 [PMID: 16455805 DOI: 10.1124/dmd.107.007575]

50 Hahn J, Choi JH, Chang MJ. Pharmacokinetic changes of antibiotic, antiviral, antituberculosis and antifungal agents during extracorporeal membrane oxygenation in critically ill adult patients. J Clin Pharmacol Ther 2017; 42: 661-671 [PMID: 28946652 DOI: 10.1111/jcpt.12636]

51 Sadeer NB, Mahomoodally MF. Antibiotic Potentiation of Natural Products: A Promising Target to Fight Pathogenic Bacteria. Curr Drug Targets 2021; 22: 557-560 [PMID: 32972338 DOI: 10.2174/1389450121666200924113740]

52 Ata F, Shafer Moussa Hussein M, Mismer AY, Sharma R, Bozom IAM, Alsiddig Ali Ibrahim Z, Ibrahim WH. Rifampicin-Induced Pneumonitis Mimicking Severe COVID-19 Pneumonia Infection. Am J Case Rep 2020; 21: e927586 [PMID: 32480240 DOI: 10.12659/AJCR.927586]

53 Sadanashv M, George AA, Mishra AK, Kuriakose CK. Rifampicin-induced immune allergic reaction. Trop Doct 2018; 48: 156-159 [PMID: 28764592 DOI: 10.1177/0049755117224689]

54 Cron RQ, Caricchio R, Chatham WW. Calming the cytokine storm in COVID-19. Nat Med 2021; 27: 1674-1675 [PMID: 34480126 DOI: 10.1038/s41591-021-01500-9]

55 Kyriazopoulo E, Poulakou G, Milionis H, Metallidis S, Adamsis G, Tsiakos K, Fragkou A, Rapti A, Damoulari C, Fantoni M, Kalomenidis I, Chrysos G, Anagnostopoulos C, Castelli F, Serino FS, Tsilika M, Chiang JY. Rifampicin induction of CYP3A4 requires pregnane X receptor cross talk with hepatocyte nuclear factor 4alpha and coactivators, and suppression of small heterodimer partner gene expression. Drug Metab Dispos 2006; 34: 756-764 [PMID: 16455805 DOI: 10.1124/dmd.107.007575]

56 Smith PB, Cotten CM, Hudak ML, Sullivan JE, Poindexter BB, Cohen-Wolkowiez M, Boakye-Agyeman F, Lewandowski JB, Cotten CM, Hudak ML, Sullivan JE, Poindexter BB, Cohen-Wolkowiez M, Boakye-Agyeman F, Lewandowski JB, Poulakou G, Milionis H, Metallidis S, Adamis G, Tsiakos K, Chiang JY. Rifampicin induction of CYP3A4 requires pregnane X receptor cross talk with hepatocyte nuclear factor 4alpha and coactivators, and suppression of small heterodimer partner gene expression. Drug Metab Dispos 2006; 34: 756-764 [PMID: 16455805 DOI: 10.1124/dmd.107.007575]

57 Bothamley G, Anand R, Benjamin DK Jr, Laughon MM; Best Pharmaceuticals for Children Act—Pediatric Trials Network Steering Committee. Rifampin Pharmacokinetics and Safety in Preterm and Term Infants. Antimicrob Agents Chemother 2019; 63 [PMID: 30910891 DOI: 10.1128/AAC.00284-19]

58 Bouaré F, Laghmari M, Etouche FN, Arjald B, Saïd I, Hajhouji F, Ghanimane H, Amro L, Tassi N, Benali SA. Unusual association of COVID-19, pulmonary tuberculosis and human immunodeficiency virus, having progressed favorably under treatment with chloroquine and rifampicin. Pan Afr Med J 2020; 35: 110 [PMID: 33282065 DOI: 10.11604/pamj.supp.2020.35.2.24952]

59 Zimmermann P, Curtis N. COVID-19 in Children, Pregnancy and Neonates: A Review of Epidemiologic and Clinical Features. Pediatr Infect Dis J 2020; 39: 469-477 [PMID: 32398569 DOI: 10.1097/INF.0000000000002700]

60 Mitjá O, Clotet B. Use of antiviral drugs to reduce COVID-19 transmission. Lancet Glob Health 2020; 8: e639-e640 [PMID: 32199468 DOI: 10.1016/S2214-109X(20)30114-5]
