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Possible agent for COVID 19 treatment; Rifampicin

Dear Editor,

Thank you for giving us the opportunity to submit a revised draft of the manuscript. We appreciate the time and effort that you and the reviewers dedicated to providing feedback on our manuscript and are grateful for the insightful comments on and valuable improvements to our paper. We have incorporated most of the suggestions made by the reviewers. Please see below for a point-by-point response to the reviewers' comments and concerns.

Reviewer #1:
Scientific Quality: Grade D (Fair)
Language Quality: Grade B (Minor language polishing)
Conclusion: Minor Revision
Specific Comments to Authors: The letter to editor covers an interesting topic for role of rifampicin in COVID-19. The original article by Panayiotakopoulos et al published in 2021 is based on in-silico studies from 2020 and 2021 with no further support from lab or clinical trials thereafter. So, it will be interesting to know if there is any further development on this subject in the last 1 year. Furthermore, you have mentioned about interaction of rifampicin with Favipiravir which is not a drug utilized widely for COVID-19 and is not FDA approved yet. Is there any information about interaction with more commonly used drug like Remdesivir? How about interaction with DOACs like apixaban which is metabolized via CYP 3A4 pathway as well.
Response: We have added the following information in line with your comments: "In a study in which 20 FDA-approved drugs were screened by molecular docking method in possible drug design for COVID-19, rifampicin showed in silico binding to more than one target protein of SARS-COV2. Other macrocyclic antibiotics showing binding are polymyxin B and bafilomycin A(4).In another in silico studyof FDA-approved drugs to treat COVID 19 infection, rifampicin has a stronger binding affinity for COVID-19 main protease Mpro(5). " "Remdesivir is widely used in COVID-19 treatment which is metabolized through hydrolysis reaction to itstriphosphate active form via by carboxylesterase1 (CES1) (80%), cathepsin A (10%), and CYP3A (10%). Since Rifampicin is a potential inductor of CYP3A4, concomitant administration might increase the metabolism of Remdesivir (9). "

"Apixaban and other direct oral anticoagulants can also be utilised. Rifampicin coadministration significantly increased apixaban plasma concentrations. When used orally, approximately 15% of apixaban is metabolised by CYP3A and roughly 6% by CYP1A2 and CYP2J2. The balance (50%) is eliminated unaltered in the form of faeces and urine. A single dose of rifampicin decreased apixaban clearance by 25%. Rifampicin largely influenced apixaban absorption (and/or distribution), which could be attributed to an impairment of intestinal P-glycoprotein(13). "

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: The primary aim of this letter to the Editor is the describe the utility of rifampicin in potentially serving as a treatment for COVID. Therefore, going into the detail regarding the available evidence of this efficacy (of rifampicin in treating COVID) should have been the utmost priority. However, the manuscript has gone into very little detail for this, and is a clear weak point of the article. For the manuscript to be publishable, considering the overall purpose of this letter, the authors need to revise the manuscript greatly to include a lot more detail about the potential efficacy of rifampicin based on prior studies. Looking for additional studies, aside from the review that the paper is focusing on, will make this letter stronger. The authors also go into a lot of detail about other drugs such as chloroquine and corticosteroids - it is hard to see the purpose of this in this letter, and how it contributes to the central points. Making this section more concise, and more to the point about positives and negatives of rifampicin as potential COVID treatment, is necessary. There are numerous grammatical issues. Extensive proofreading is recommended.

Response: We have added the following information in line with your comments: "In a study in which 20 FDA-approved drugs were screened by molecular docking method in possible drug design for COVID-19, rifampicin showed in silico binding to more than one target protein of SARS-COV2. Other macrocyclic antibiotics showing binding are polymyxin B and bafilomycin A(4).In another in silico studyof FDA-approved drugs to treat COVID 19 infection, rifampicin has a stronger binding affinity for COVID-19 main protease Mpro(5). " According to your and the other reviewer’s recommendations, we have modified and summarized the following sections: "However, due to the properties of rifampicin, various drug interactions may occur during its possible use. Rifampicin promotes the expression of

CYP 3A4 in the small intestine and liver, as noted in the review. Additionally to the work by Panayiotakopoulos et al., an essential feature of Rifampicin is that it activates proteins such as the P glycoprotein drug transporter and CYP2C-mediated metabolism(6).There are possible drug interactions with drugs used for the treatment of COVID-19 and for additional diseases. "

"Remdesivir is widely used in COVID-19 treatment which is metabolized through hydrolysis reaction to itstriphosphate active form via by carboxylesterase1 (CES1) (80%), cathepsin A (10%), and CYP3A (10%). Since Rifampicin is a potential inductor of CYP3A4, concomitant administration might increase the metabolism of Remdesivir (9). Dexamethasone has a strong anti-inflammatory impact and is typically used as an adjunctive treatment for COVID-19 pneumonia. Rifampin may increase corticosteroid hepatic metabolism, hence diminishing their therapeutic impact. Corticosteroids' half-life of elimination has been demonstrated to be shortened by up to 45% when coadministered with rifampin(10, 11). "

"Apixaban and other direct oral anticoagulants can also be utilised. Rifampicin coadministration significantly increased apixaban plasma concentrations. When used orally, approximately 15% of apixaban is metabolised by CYP3A and roughly 6% by CYP1A2 and CYP2J2. The balance (50%) is eliminated unaltered in the form of faeces and urine. A single dose of rifampicin decreased apixaban clearance by 25%. Rifampicin largely influenced apixaban absorption (and/or distribution), which could be attributed to an impairment of intestinal P-glycoprotein(13). "