Review Form 1.6

Journal Name:	**Journal of Pharmaceutical Research International**
Manuscript Number:	**Ms_JPRI_77180**
Title of the Manuscript:	**Possible mechanisms of drugs used in the treatment of COVID-19: A Pharmacological perspective**
Type of the Article	**Review Article**

General guideline for Peer Review process:

This journal's peer review policy states that **NO** manuscript should be rejected only on the basis of '**lack of Novelty'**, provided the manuscript is scientifically robust and technically sound.
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PART 1: Review Comments

	Reviewer's comment	**Author's comment** *(if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)*
Compulsory REVISION comments	The review focus on the mechanism of action of elected pharmacological agents in a non-systematic, narrative approach. The main mechanisms of action are well described. The quality of the article can be further improved by - Reorganizing the introduction with key elements highlighted below. - Giving priority to FDA approved drugs and those highlighted in latest international guidelines. - Drugs that are not discussed in the present review should be stated at the end of introduction with the reason, to justify for potential bias. - Discussing the drugs under subheadings based on mechanism would make the article more systematic. Authors should verify the copyrights of the figures used or cite/acknowledge appropriately. The article will be well received by the readers if these issues can be fixed. Comment 1 The introduction to this review should ideally contain the following four components. 1. Brief introduction to the COVID-19 including the virus involved, pathogenic mechanism in brief, clinical features. I feel this can be compressed into a single paragraph a this has been reviewed extensively in other literature. The present review should focus mainly on pharmacological agents. 2. Intervention in COVID-19 (overview of pharmacological and non-pharmacological treatments. Recommendations of international guidelines related to these agents as readers are interested if these drugs are at still being studied or in clinical practice. 3. Introduction to Rationale/Mechanism of actions of the pharmacological interventions – you may link this with the pathogenic mechanisms of COVID-9 4. State the drugs you discuss in this review and why. Justify/State why you do not discuss other treatments (many systematic reviews provide evidence on use of Vitamin D, methyelene blue, convalescent plasma, dipeptidyl peptidase-4 inhibitors, Lianhuaqingwen, Prophylactic anticoagulants (heprarin), Colchicine etc.). Fan Z, Guo G, Che X, Yang Y, Liu Y, Li L, et al. Efficacy and safety of Lianhuaqingwen for mild or moderate coronavirus disease 2019: A meta-analysis of randomized controlled trials. Medicine. 2021;100(21):e26059. Golpour M, Mousavi T, Alimohammadi M, Mosayebian A, Shiran M, Alizadeh Navaei R, et al. The effectiveness of Colchicine as an anti-inflammatory drug in the treatment of coronavirus disease 2019: Meta-analysis. International journal of immunopathology and pharmacology. 2021;35:20587384211031763. You may omit extensive review of literature on history of COVID-19, extensive details on the virus, and diagnostic methods as they are not directly related to the present review. Please state in the introduction which of the drug under discussion are FDA approved, and outline the recommendations of international guidelines (last update). (e.g. WHO or NIH). Make sure that the most updated guidelines are cited (late 2021). Comment 2	

	Please see the following recommendations in the guidelines, you may cite the guidelines where necessary and include in the reference list. Please see if your review contain all the drugs highlighted in the aforementioned guidelines, other drugs are likely to be till at research level and should be given less priority if you feel you should discuss them in the present review. 1. World Health Organization. Therapeutics and COVID-19: living guideline, 24 September 2021. World Health Organization; 2021. The WHO Therapeutics and COVID-19: living guideline currently includes a: • ** NEW ** conditional recommendation to use a combination of neutralizing monoclonal antibodies (casirivimab and imdevimab) in non-severe COVID-19 patients at the highest risk of severe disease (published 24 September 2021); • ** NEW ** conditional recommendation to use a combination of neutralizing monoclonal antibodies (casirivimab and imdevimab) in severe and critically ill COVID-19 patients with seronegative status (published 24 September 2021); • strong recommendation to use IL-6 receptor blockers (tocilizumab or sarilumab) in patients with severe or critical COVID-19 (published 6 July 2021); • recommendation not to use ivermectin in patients with COVID-19 except in the context of a clinical trial (published 31 March 2021); • strong recommendation against hydroxychloroquine in patients with COVID-19 of any severity (published 17 December 2020); • strong recommendation against lopinavir/ritonavir in patients with COVID-19 of any severity (published 17 December 2020); • conditional recommendation against remdesivir in hospitalized patients with COVID-19 (published 20 November 2020); • strong recommendation for systemic corticosteroids in patients with severe and critical COVID-19 (published 2 September 2020); • conditional recommendation against systemic corticosteroids in patients with non-severe COVID-19 (published 2 September 2020). 2. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed [insert date]. • There is insufficient evidence to recommend either for or against the routine use of remdesivir in these patients for the treatment of COVID-19, but use may be appropriate in patients at high risk of disease progression. • Two combination anti-SARS-CoV-2 monoclonal antibody (mAb) products (bamlanivimab plus etesevimab and casirivimab plus imdevimab) and a single mAb (sotrovimab) have been shown to reduce the risk of hospitalization and death in the outpatient setting in those with mild to moderate COVID-19 symptoms and certain risk factors for disease progression. • If dexamethasone is not available, an alternative corticosteroid such as prednisone, methylprednisolone, or hydrocortisone can be used • For recently hospitalized patients (i.e., those within 3 days of hospital admission) who have rapidly increasing oxygen needs, require high-flow oxygen or noninvasive ventilation, and have increased markers of inflammation, add baricitinib (BIIa) or tocilizumab (BIIa) (drugs are listed alphabetically and not in order of preference) to one of the two options above. • The Panel recommends tofacitinib as an alternative to baricitinib only when baricitinib is not available or not feasible to use (BIIa) because the evidence for the effectiveness of tofacitinib is less extensive than that for baricitinib. • Even though the REMAP-CAP trial supports that sarilumab and tocilizumab have	

	similar efficacy in the treatment of hospitalized patients with COVID-19, the Panel recommends sarilumab only when tocilizumab is not available or is not feasible to use (BIIa). Comment 3 The name as well as the route of administration should be specified for each and very drugs discussed in the review (intravenous/oral/inhalation). Comment 4 I feel authors should discuss in detail the significance of the systemic inflammatory response/cytokine storm that may lead to multiple organ dysfunction syndrome, and relate to the mechanism of steroid. And the fat the other steroids (prednisolone, methylprednisolone, hydrocortisone can also be used (in equivalent doses) as alternatives as the guidelines highlight) Consult the following paper; Soy M, Keser G, Atagündüz P, Tabak F, Atagündüz I, Kayhan S. Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. Clinical rheumatology. 2020 Jul;39:2085-94. **Comment 5** Remdesivir Authors state “Remdesivir appears to be the most promising treatment” and “Remdesivir (RDV) has been shown to be the most effective treatment” I feel this could be contradictory as the WHO Guideline Development Group (GDG) panel found a lack of evidence that remdesivir improved outcomes that matter to patients such as reduced mortality, need for mechanical ventilation, time to clinical improvement and others.	

Minor REVISION comments	Comment 6 Dexamethasone inhibits the formation of “mediators” ?? shouldn’t it be “inflammatory mediators? Comment 7 When you state “panel recommends” in several occasions in the text, please specify which panel you are referring to as there are a plenty of guideline development groups (GDGs) involved both local and international level. E.g. WHO Guideline Development Group (GDG) panel Comment 8 Figures Are figures originally created by the author? I could find exactly similar images on search. Please conider the copyright issues. If this is from another source you will have to obtain permission or cite the primary source. Comment 9 Use of abbreviations When an abbreviation is introduced use it consistently in the ensuing text. e.g. after Remdesivir (RDV) authors have used Remdesivir instead of RDV. Screen for all the abbreviations and fix. Comment 10 Author have mentioned Chloroquine and Hydroxychloroquine in several occasions both in abstract and body, but do not describe the mechanism of action.	
Optional/General comments	Comment 11 Other treatments; Rather than discussing one by one, its good and meaningful to discuss under different subheadings as many drugs sshare the common mechanism. e.g. You may discus bamlanivimab, etesevimab, casirivimab, imdevimab sotrovimab, etc under the heading of Anti-SARS-CoV-2 Monoclonal Antibodies Likewise respective agents under the heading of systemic steroids (dexamethasone, predinisolone, hydrocortisone etc) IL-6 receptor blockers (tocilizumab or sarilumab) and Interleukin-1 Inhibitors and Kinase Inhibitors: Janus Kinase Inhibitors and Bruton’s Tyrosine Kinase Inhibitors can be discussed.	

PART 2:

	Reviewer’s comment	**Author’s comment** *(if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)*
Are there ethical issues in this manuscript?	*(If yes, Kindly please write down the ethical issues here in details*	
If plagiarism is suspected, please provide related proofs or web links.	I have concern regarding the images. Please inquire regarding the copyrights. If no such issues ask authors to acknowledge/give credit to the person who created the graphical illustrations.	

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