Scientific Efforts of University of Sadat City (USC) to Combat COVID-19 Outbreak

- **Projects Funded by USC (2020):**
  - Applying Drug Repurposing Approach via Utilizing Virtual Screening toward Development of SARSCoV-2 inhibitors, *Faculty of Pharmacy*.
  - PCR Based Molecular Detection and Characterization of Coronaviruses Infection and Protection Trails, *Faculty of Veterinary Medicine*.
- **Projects under Evaluation (STDF and ASRT, 2020):**
  - Targeting the pathophysiology of Acute Lung Injury and Respiratory failure in COVID-19 patients in light of a Retrospective study, ***Genetic Engineering and Biotechnology Research Institute.***
  - Implementation of Artificial Intelligence and Deep Docking techniques for Discovery of Small Molecules/Macromolecules Targeting COVID-19 and Cancer, ***Faculty of Pharmacy***
- **Published Articles:**

1- Targeting Neprilysin (NEP) pathways: A potential new hope to defeat COVID-19 ghost, **Manar Mohammed El Tabaa**, MaramMohammed El Tabaa, ***Biochemical Pharmacology***, **2020**, 178, 114057.
https://doi.org/10.1016/j.bcp.2020.114057

Abstract:

COVID-19 is an ongoing viral pandemic disease that is caused by SARS-CoV2, inducing severe pneumonia in humans. However, several classes of repurposed drugs have been recommended, no specific vaccines or effective therapeutic interventions for COVID-19 are developed till now. Viral dependence on ACE-2, as entry receptors, drove the researchers into RAS impact on COVID-19 pathogenesis. Several evidences have pointed at Neprilysin (NEP) as one of

pulmonary RAS components. Considering the protective effect of NEP against pulmonary inflammatory reactions and fibrosis, it is suggested to direct the future efforts towards its potential role in COVID-19 pathophysiology. Thus, the review aimed to shed light on the potential beneficial effects of NEP pathways as a novel target for COVID-19 therapy by summarizing its possible molecular mechanisms. Additional experimental and clinical studies explaining more the relationships between NEP and COVID-19 will greatly benefit in designing the future treatment approaches.

2- New putative insights into neprilysin (NEP)-dependent pharmaco-therapeutic role of roflumilast in treating COVID-19, **Manar Mohammed El Tabaa**, MaramMohammed El Tabaa. ***European Journal of Pharmacology***, 889, **2020**, 173615. https://doi.org/10.1016/j.ejphar.2020.173615

Abstract:

Nowadays, coronavirus disease 2019 (COVID-19) represents the most serious inflammatory respiratory disease worldwide. Despite many proposed therapies, no effective medication has yet been approved. Neutrophils appear to be the key mediator for COVID-19-associated inflammatory immunopathologic, thromboembolic and fibrotic complications. Thus, for any therapeutic agent to be effective, it should greatly block the neutrophilic component of COVID-19. One of the effective therapeutic approaches investigated to reduce neutrophil-associated inflammatory lung diseases with few adverse effects was roflumilast. Being a highly selective phosphodiesterase-4 inhibitors (PDE4i), roflumilast acts by enhancing the level of cyclic adenosine monophosphate (cAMP), that probably potentiates its anti-inflammatory action via increasing neprilysin (NEP) activity. Because activating NEP was previously reported to mitigate several airway inflammatory ailments; this review thoroughly discusses the proposed NEP-based therapeutic properties of roflumilast, which may be of great importance in curing COVID-19. However, further clinical studies are required to confirm this strategy and to evaluate its in vivo preventive and therapeutic efficacy against COVID-19

3- An *in silico* perception for newly isolated flavonoids from peach fruit as privileged avenue for a countermeasure outbreak of COVID-19, Ahmed E. Allam, Hamdy . Assaf, Heba Ali Hassan, Kuniyoshi Shimizu and **Yaseen A. M. M. Elshair**, ***RSC Adv.***, **2020**, 10, 29983. https://doi.org/10.1039/D0RA05265E

Abstract:

3′-Hydroxy-4′-methoxy-chroman-7-O-β-D-glucopyranoside 4 was first isolated from a natural source, together with three known compounds, the ferulic acid heptyl ester 1, naringenin 2, and 4,2′,4′-trihydroxy-6′-methoxychalcone-4′-O-β-D-glucopyranoside 3, which were isolated from peach [Prunus persica (L.) Batsch] fruits. These compounds were subjected to different virtual screening strategies in order to examine their activity to combat the COVID-19 outbreak. The study design composed of some major aspects: (a) docking with main protease (Mpro), (b) docking with spike protein, (c) 3D shape similarity study (Rapid Overlay Chemical Similarity-ROCS) to the clinically used drugs in COVID-19 patients, and finally, (d) the rule of five and the estimated pre-ADMT properties of the separated flavonoids. Docking study with Mpro of SARS-CoV-2 (PDB ID:6LU7, and 6Y2F) showed that compound 3, its aglycone part, and compound 4 have a strong binding mode to a protease receptor with key amino acids, especially Gln:166AA, and having a similar docking pose to co-crystalized ligands. Docking with the spike protein of SARS-CoV-2 illustrated that compounds 3 and 4 have a good binding affinity to PDB ID:6VSB through the formation of HBs with Asp:467A and Asn:422A. According to ROCS analysis, compounds 1, 3, and 4 displayed high similarities to drugs that prevent SARS-Co2 entry to the lung cells or block the inflammatory storm causing lung injury. Compounds 3 and 4 are good candidates for drug development especially because they showed predicted activity against SARS-CoV-2 through different mechanisms either by preventing genome replication or by blocking inflammatory storm that trigger lung injury. These compounds were isolated from peach fruit, and the study supports data and continues with the recommendation of peach fruits in controlling and managing COVID-19 cases.

4- FDA-Approved drugs with potent in vitro antiviral activity against Severe Acute Respiratory Syndrome Coronavirus 2, **Ahmed Mostafa, Ahmed Kandeil, Yaseen A. M. M. Elshaier, Omnia Kutkat, Yassmin Moatasim , Adel A. Rashad, Mahmoud Shehata , Mokhtar R. Gomaa, Noura Mahrous, Sara H. Mahmoud, Mohamed GabAllah, Hisham Abbas, Ahmed El Taweel, Ahmed E. Kayed, Mina Nabil Kamel, Mohamed El Sayes, Dina B. Mahmoud, Rabeh El-Shesheny, Ghazi Kayali, and Mohamed A. Ali *Pharmaceuticals*, 2020**, *13* (12), 443. https://doi.org/10.3390/ph13120443

Abstract:

(1) Background: Drug repositioning is an unconventional drug discovery approach to explore new therapeutic benefits of existing drugs. Currently, it emerges as a rapid avenue to alleviate the COVID-19 pandemic disease. (2) Methods: Herein, we tested the antiviral activity of anti-microbial and anti-inflammatory Food and Drug Administration (FDA)-approved drugs, commonly prescribed to relieve respiratory symptoms, against Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the viral causative agent of the COVID-19 pandemic. (3) Results: Of these FDA-approved antimicrobial drugs, Azithromycin, Niclosamide, and Nitazoxanide showed a promising ability to hinder the replication of a SARS-CoV-2 isolate, with IC50 of 0.32, 0.16, and 1.29 µM, respectively. We provided evidence that several antihistamine and anti-inflammatory drugs could partially reduce SARS-CoV-2 replication in vitro. Furthermore, this study showed that Azithromycin can selectively impair SARS-CoV-2 replication, but not the Middle East Respiratory Syndrome Coronavirus (MERS-CoV). A virtual screening study illustrated that Azithromycin, Niclosamide, and Nitazoxanide bind to the main protease of SARS-CoV-2 (Protein data bank (PDB) ID: 6lu7) in binding mode similar to the reported co-crystalized ligand. Also, Niclosamide displayed hydrogen bond (HB) interaction with the key peptide moiety GLN: 493A of the spike glycoprotein active site. (4) Conclusions: The results suggest that Piroxicam should be prescribed in combination with Azithromycin for COVID-19 patients

5- Efficacy and safety of remdesivir in hospitalized Covid-19 patients: Systematic review and meta-analysis including network meta-analysis, Hozaifa Khalil Elsawah Mohamed Ahmed Elsokary **Mahmoud Samy Abdallah Ahmed** Hanei ElShafie, ***Reviews in Medical Virology***, **2020**, 31, 10, https://doi.org/10.1002/rmv.2187

Abstract:

Remdesivir is an antiviral agent that has shown broad-spectrum activity, including against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clinical trials investigating the role of remdesivir in coronavirus disease 2019 (Covid-19) reported conflicting results. This study aimed to systematically review the best available evidence and synthesize the results. Several electronic databases were searched for candidate studies up to 12 October 2020. Studies eligible for meta-analysis were selected based on the inclusion criteria. Primary outcomes are the recovery and mortality rates, while secondary outcomes are the safety profile of remdesivir. The main effective measures are the rate ratio (RR) and rate difference (RD). Four clinical trials and one observational study were included. Remdesivir treatment for 10 days increased the recovery rate on day 14 by 50% among severe Covid-19 patients (RR = 1.5, 95%CI = 1.33–1.7), while on day 28 it was increased by 14% among moderate and severe Covid-19 patients (RR = 1.14, 95%CI = 1.06–1.22). Additionally, remdesivir decreased the mortality rate on day 14 by 36% among all patients (RR = 0.64, 95%CI = 0.45–0.92) but not on day 28 (RR = 1.05, 95%CI = 0.56–1.97). Nonmechanically ventilated Covid-19 patients showed better response to remdesivir in the recovery (RR = 0.3, 95%CI = 0.13–0.7) and mortality (RR = 2.33, 95%CI = 1.24–4.4) rates on day 14. Remdesivir reduced serious adverse effects by absolute 6% and no significant Grade 3 or 4 adverse effects were reported. At this early stage of the pandemic, there is evidence that remdesivir can be safely administered for hospitalized Covid-19 patients. It improves the recovery rate in both moderate and severe patients but, the optimal effect is achieved for those who are severely affected but not mechanically ventilated.