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Identification of Doxorubicin as Repurposing Inhibitory Drug for MERS-CoV PLpro

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Abstract: The Middle East Respiratory Syndrome coronavirus (MERS-CoV), belonging to betacoronavirus genus can cause severe respiratory illnesses, accompanied by pneumonia, multi-organ failure, and ultimately death. Coronaviruses (CoVs) have the ability to transgress-species barrier and spread swiftly into new host species especially human to human transmission causing epidemic diseases. Despite the severe public health threat of MERS-CoV there are currently no vaccines or drugs available for its treatment. MERS-CoV papain-like protease (PLpro) is a key enzyme that plays an important role in its replication. In the present study, we evaluated the inhibitory activities of Doxorubicin (DOX) against the recombinant MERS-CoV PLpro by employing protease inhibition assay, the hydrolysis of fluorogeneic peptide from Z-RLRGG-AMC–peptide bond in presence of DOX showed IC_{50} value of 1.67 μM at 30 minutes. Subsequently, we confirmed the interaction between DOX and MERS-CoV PLPro by Thermal shift assay (TSA), DOX increased ΔT_m by ~20^{0}C clearly indicating a coherent interaction between the MERS-CoV PL protease and DOX. The binding site of DOX on MERS-CoV PLpro was assessed using docking techniques as well as molecular dynamic (MD) simulations. DOX bind to the thumb region of the catalytic domain of the MERS-CoV PLpro. Moreover, MD simulations results showed flexible BL2 loops as well as other potential residues such as R231, R233, and G276 of MERS-CoV PLpro. Development of drug repurposing is a remarkable opportunity to quickly examine the efficacy of different aspects of treating various diseases. Protease inhibitors have been found to be effective against MERS-CoV to date, and numerous candidates are currently undergoing clinical trials to prove this and our effort is in similar direction.

Keywords: Middle East Respiratory Syndrome coronavirus; Papain-like protease; Doxorubicin.

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Table S1. IC_{50} of MERS-CoV PLpro inhibition identified by dissociation of Z-RLRGG-AMC substrate against DOX **at different time intervals.**

	30 minutes	**60 minutes**
IC_{50} µg/mL	1.992	1.705
R^2	0.8857	0.8619