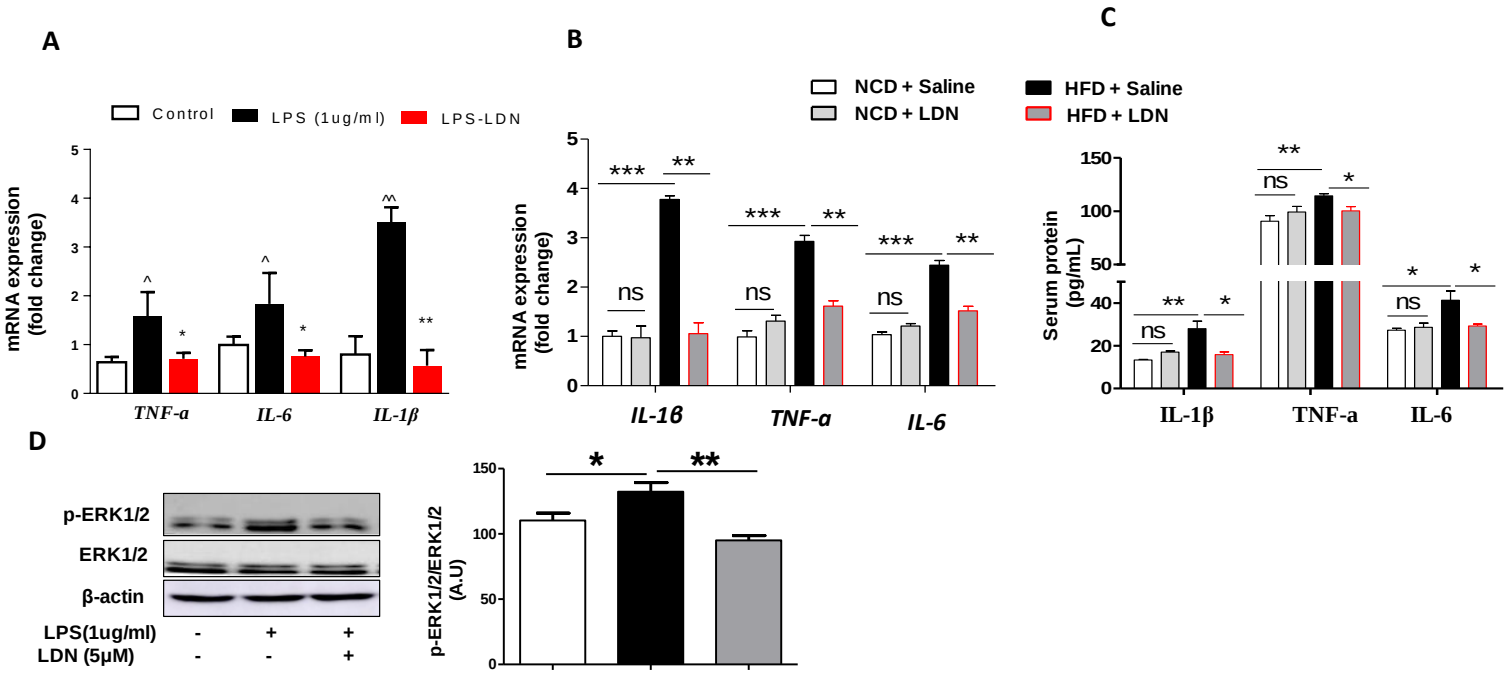

Figure 1: (A) LDN prevents LPS induced proinflammatory cytokines expression and release Quantitative mRNA expression of indicated genes (tnf-α, il-6 and Il1b) in murine macrophage cells. (B) Quantitative mRNA expression of il-1β, tnf-α and il-6 in purified ATMs from all group mice. (C) ELISA of proinflammatory proteins (IL-1β, TNF-α and IL-6) in serum from all experimental group mice. Values are expressed as mean ± SEM (n=3) from three independent sets of repeats (mean ± SEM ***p<0.001, **p<0.01 *p<0.05.) (D) LDN acts as EKR1 inhibitor and improved insulin sensitivity in LPS treated macrophage cells. ERK1/2 (Immunoblot) in RAW cells treated with LPS (1ug/ml) in presence and absence of LDN.

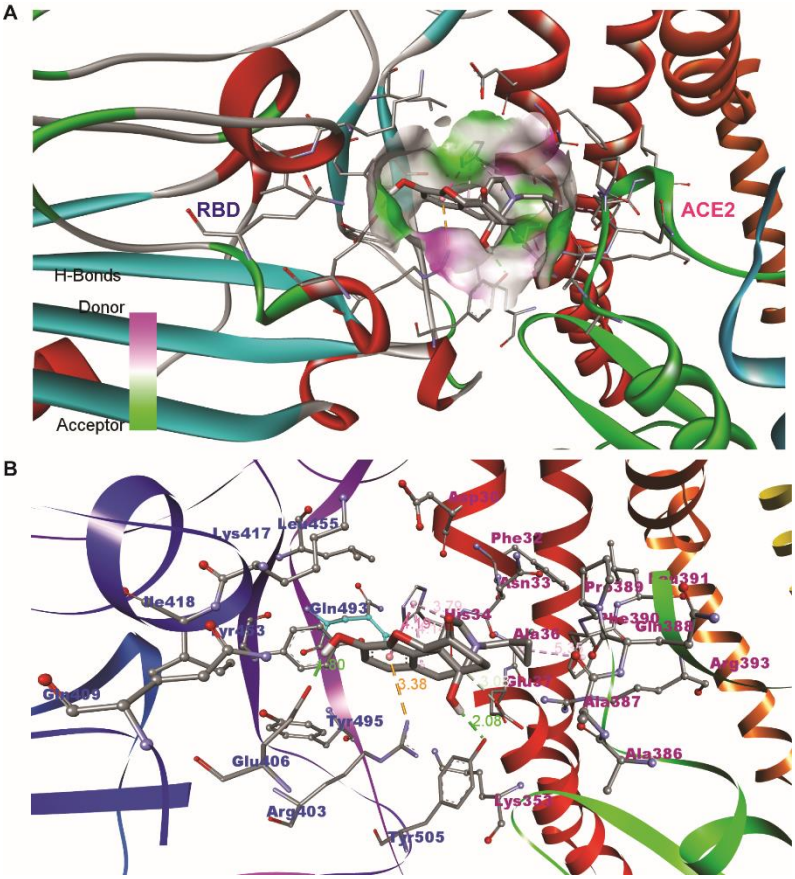

Figure 2. The docked conformation of naltrexone at the binding interface of RBD-ACE2 complex obtained from AutoDock (**A**) and interface amino acid residues involved in non-bonded contacts are labelled (**B**). The residues labelled in blue represent RBD and in pink are ACE2.

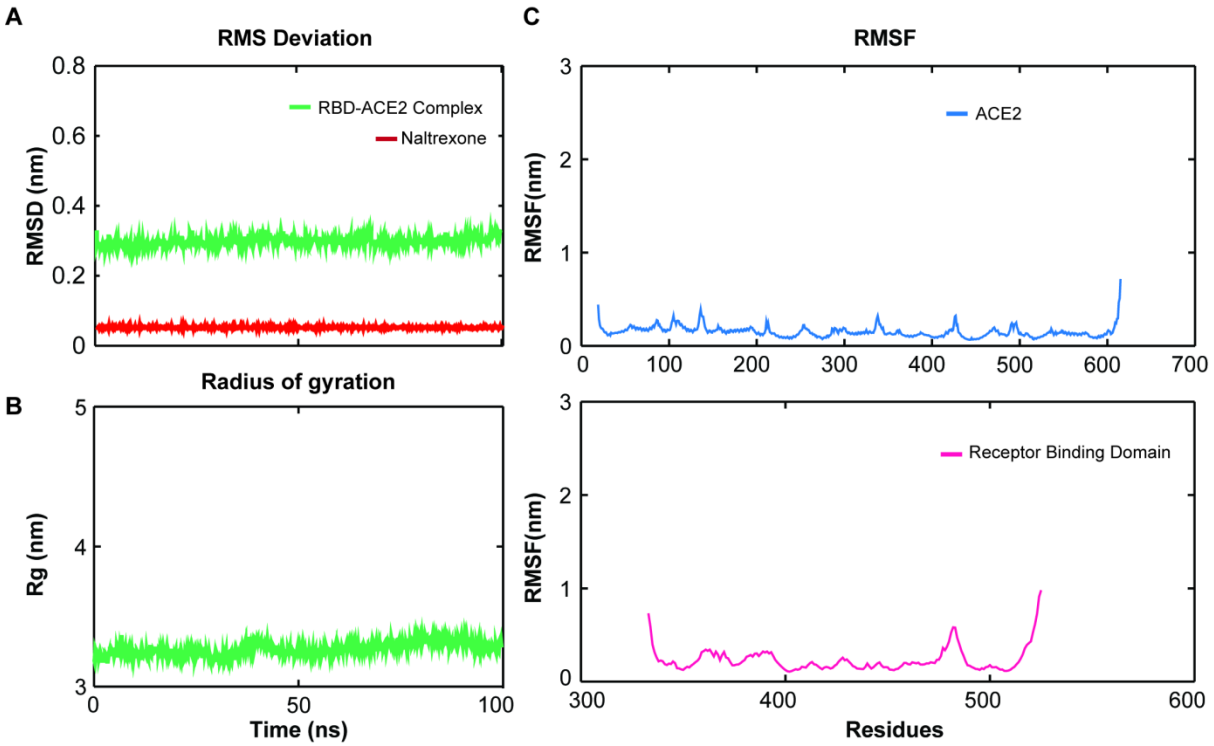

Figure 3. Dynamics stability of RBD-ACE2-Naltrexone complex during 100 ns molecular dynamics simulation. (**A**) The root-mean square deviation (RMSD) of RBD-ACE2-Naltrexone complex during 100 ns MD in aqueous solution. (**B**) The compactness of the measured by the radius of gyration profile of complex with respect to time (**C**) The Cα-root mean squared fluctuation profile of the ACE2 and RBD during MD.

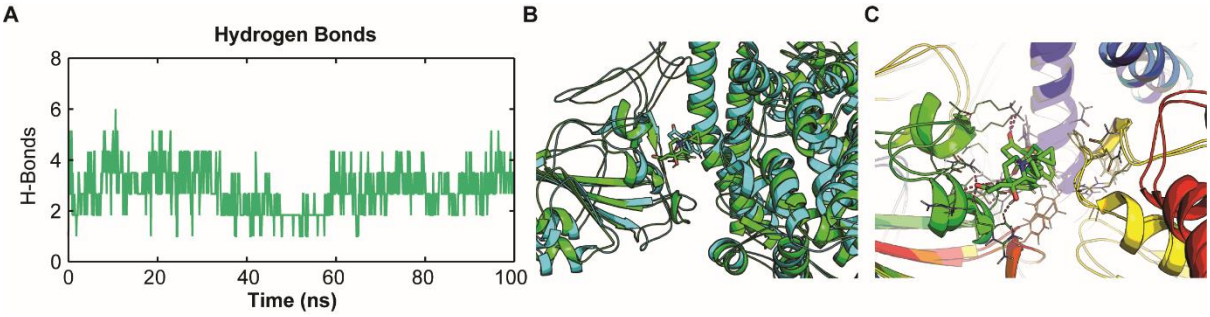

Figure 4: Inter-molecular hydrogen bond dynamics and structural superposition of the initial complex with the simulated RBD-ACE2-naltrexone complex during 100 ns MD. (**A**) Dynamics stability of RBD-ACE2-naltrexone complex with respect to inter-molecular hydrogen bonds along the 100 ns time scale. (**B**) Structural superimposed view of the starting complex used for MD (green) and the snapshot obtained from clustering analysis (cyan) of MD trajectory during the last 50 ns. (**C**) Inter-molecular contacts of the docked complex and MD simulated complex.