Targeting SARS-COV2 Main Protease Using HTVS and Simulation Analysis: A Drug Repurposing Approach against COVID-19

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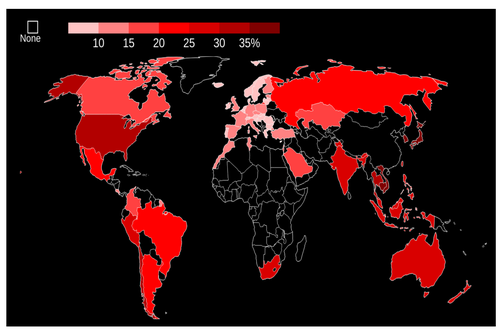
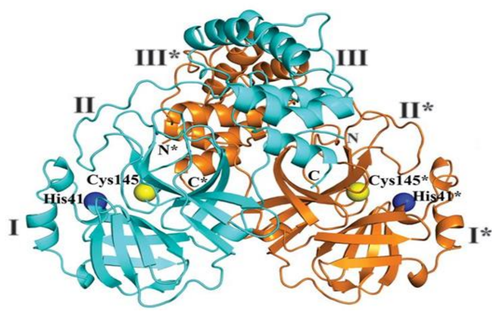
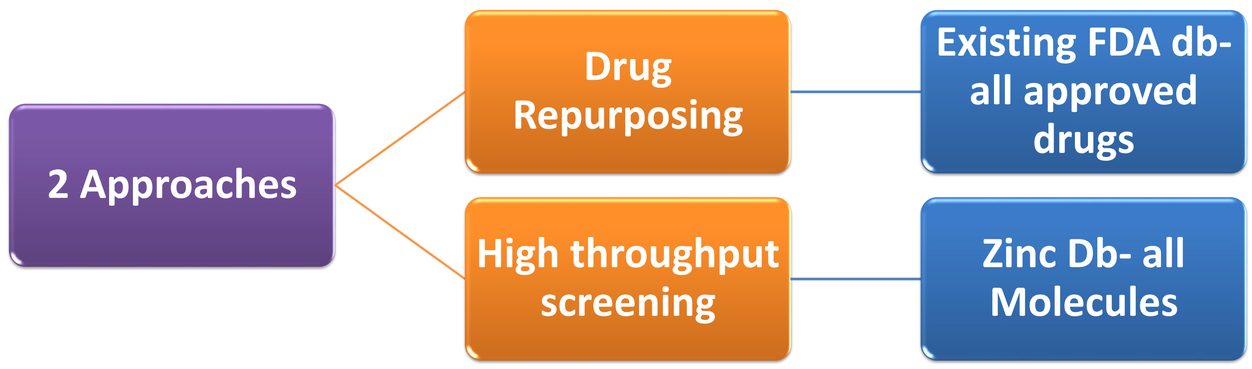
Abstract:

Coronavirus pandemic COVID 19 has caused a wide range of harm worldwide with its inception in December 2019 in Wuhan, China. To date there is no promising drug identified for the treatment of disease. In the view of this, scientists have elucidated X-ray structures of the proteins in **SARS-COV2** virus. These can act as probable drug targets for the designing of drugs what is urgent need. One of the main proteins of the virus is its main protease M^{pro} which is responsible for producing polyproteins of the virus. In this study we have used main protease as the target for drug design and repurposing for COVID-19. Two approaches were applied in order to develop a fast and effective treatment against the virus. The first approach was drug repurposing through *in-silico* docking analysis of existing FDA approved drugs and the second approach was high throughput screening of molecules from the ZINC database against main protease. Two docking protocols- a fast docking algorithm to screen the hits or lead molecules and simulation based molecular dynamics docking procedure to optimize the obtained hits were utilized. We could observe a definite scaffold based binding affinity against the main protease. These scaffolds were lutein, steroids, morphine and quinolone, CPT. Thiotepa was identified as the best docked molecule with highest binding affinity. Unique molecules like lutein, beta carotene, Buprenorphine etc were identified as promising hits which can be used as repurposed drugs against **SARS-COV2**. Also these scaffolds show unique pharmacophores that can be utilized to design potential novel leads against Sars-Cov 2 for future treatment.

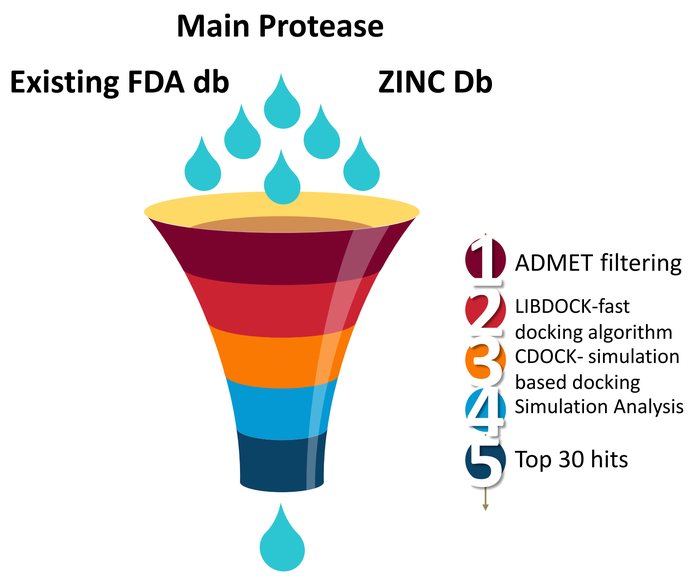


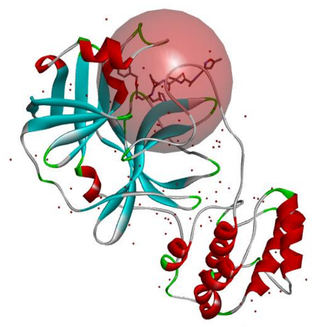


Crystal structure of Main Protease with the catalytic dyad of His41 and Cys145



Methodology

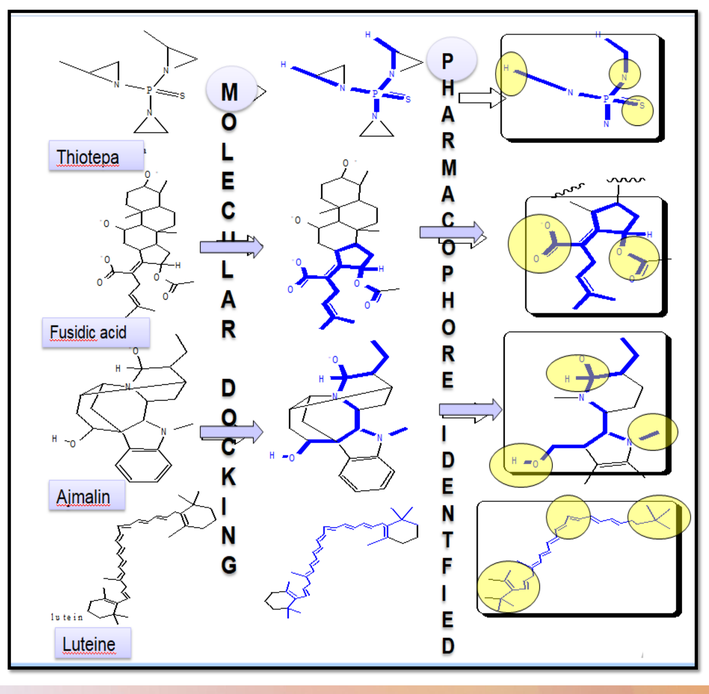




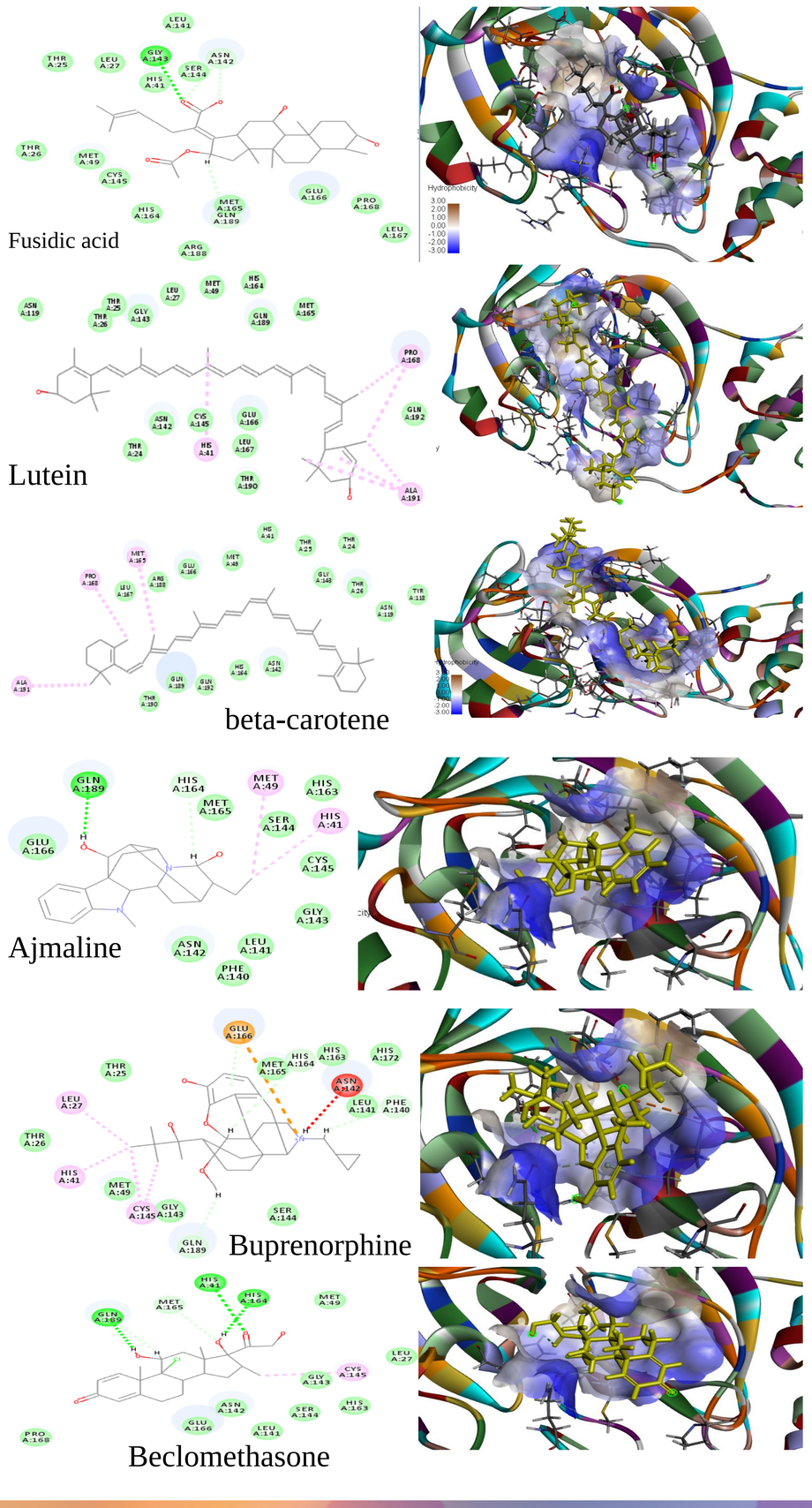
The active site was identified around the existing inhibitor. sphere radius of 13.807549 and XYZ coordinates were -10.7118, 12.4113 and 68.8312 respectively.

The active site residues include aminoacids from 24-26, 41, 49, and 54, 140-145 and 163-192.

Active site sphere of Main Protease



Results



Molecule Name	Cdocker Score	Libdock Score
Thiotepa	-245.519	69.4739
Fusidic acid	-91.3714	122.439
Lutein	-84.3549	113.997
Ajmaline	-77.8805	100.21
Beta-Carotene	-76.6497	106.593
Topotecan	-69.8488	145.016
Buprenorphine	-67.4387	121.502
Nalbuphine	-62.0371	116.755
Cyproterone	-56.5033	110.924
Isocodeine HCl	-55.6457	98.2887
Calcipotriolhydrate	-54.7226	135.549
B-sitosterol	-52.4574	126.077
Desogestrel	-51.8337	102.095
Cefotetan	-51.4352	112.046
Norethynodrel	-49.2817	112.084
5-androstenediol	-49.1489	94.279
Methylprednisolone acetate	-49.0357	115.474
Drospirenone	-48.2456	115.429
Beclomethasone	-46.9818	105.501
Gatifloxacin	-46.9551	117.005
Vecuronium	-46.5503	118.917
Amcinonide	-46.4805	118.309
Grepafloxacin	-45.6419	125.04
Paramethasone	-45.5	105.835
Betamethasone	-44.7844	109.953
Gestodene	-44.543	106.403

Conclusion

Thus molecules like the Thiotepa, Lutein, Buprenorphine, Gatifloxacin, Beclomethasone Ajmaline and Topothecan can act as potential drugs against Sars-Cov 2 with main protease as their target. These results can be taken up for further in vitro and in vivo trials.Recently it has been proved that dexamethasone can be used as an Anti Sars Cov2 drug. This validates our research findings that corticosteroids can be used and maybe are potential drugs that can act against Sars Cov2.

References

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