Available online on 15.08.2020 at http://ajprd.com

Asian Journal of Pharmaceutical Research and Development

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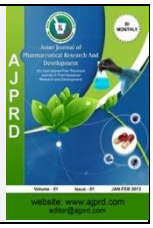

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Review Article

Anti-COVID-19 natural products are spotlights for drug discovery and development

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ABSTRACT

Traditional plants and marine natural products have plausible medicinal compounds of anti-COVID-19 potential. They became spotlights for the development and discovery of new marketable antivirals. The global COVID-19 pandemic invigorated medicinal chemists to evolve new feasible ideas for the non-toxic medications.

Keywords: Covid-19, Natural product, Phytochemical and CL^{pro} inhibitor.

ARTICLE INFO: Received 14 May 2020; Review Completed 18 July 2020; Accepted 05 August 2020; Available online 15 August 2020

Cite this article as:

Pawar RS, Dimri M, Maithani A, Kush L, Anti-COVID-19 natural products are spotlights for drug discovery and development, Asian Journal of Pharmaceutical Research and Development. 2020; 8(4):88-90.

DOI: http://dx.doi.org/10.22270/ajprd.v8i4.785

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INTRODUCTION

COVID-19[1,2]virus is responsible for the alarming threat to public health. Natural products[3-5]spotlighted the optimistic future to combat COVID-19. They are reservoir for discovery and development of new antivirals.

The phytochemicals[5] of antibiotics terrestrial herbs and marine natural products[6] have recently screened through databases chemical libraries to search anti-COVID compounds. Modern techniques-virtual screening, homology modeling and molecular docking were applied to select potential drugs in precision medicine.

Theoretical methodology

The corona virus disease 2019[7] is worldwide fast spreading infection. Unfortunately, so far no well-proven allopathic medicines of viral specificity are known, therefore natural products offeran alternative strategy for discovery of antivirals.[8,9]COVID-19 virus is an enveloped positive sense single-stranded RNA virus, made of 29,903 nucleotides and untranslated sequences 254 and 229 nucleotides at 5′ and 3′ ends. SARS-CoV-2 enters the human cells via binding of viral spike protein.

The biological targets for drug discovery and development are spike glycoprotein, an envelope membrane glycoprotein a nucleocapsid phosphoprotein and replicase complex. The interactions of the natural products with these targets[10-16] attributed to their antiviral actions. The various inhibitory approaches[5,9] classify them as follows.

- Viral spike protein inhibitors
- Human ACE-2 receptor inhibitors
- $3CL^{pro}$ inhibitors
- PL^{pro} inhibitors
- Viral growth inhibitors
- Helicase inhibitors
- Cellular entry inhibitors

We selected $3CL^{pro}$ inhibitors[10,18] (Table one) of diverse phytochemicals. The top ranked phytochemicals against COVID-19 are given in table-two with their docking scores and binding affinities. The reported data of both the table one and two was interpreted with different view point.

Table: 1 Potential phytochemicals with $3CL^{pro}$ inhibitory activity [5]

S.no	Phytochemicals	Inhibitory concentrations(µM)	References
1	Betulinic acid	8.2±0.7	13
2	Betulonic acid	20	13
3	Chalcones	11.4-129.8	14
4	Curcumin	40	13
5	Celastrol	10.3	15
6	Hesperetin	8.3	12
7	Hinokinin	>100	13
8	Iguesterin	9.9	15
9	3-isotheaflavin-3-gallate	7	9
10	Pristimerin	5.5	15
11	Savinin	25	13
12	Savirin	9.1±2.4	13
13	Sinigrin	217	12
14	Tannic acid	3	9
15	Tingenone	9.9	15

Table: 2 The top ranked phytochemicals against SARS-CoV-2 $3CL^{pro}$ receptors[8,20]

Phytochemicals	Docking score	Binding affinity (kcal\mole)
5,7,3′,4′- tetrahydroxy-2′-(3,3-dimethylallyl)isoflavone	-16.35	-29.57
Myricitrin	-15.64	-22.13
Methyl rosmarinate	-15.44	-20.62
3,5,7,3′,4′,5′-hexahydroxyflavanone 3-O-beta-D- glucopyranoside	-14.42	-19.10
(2S)-Eriodictyol 7-O-(6″-O-galloyl)-beta-D-glucopyranoside	-14.41	-19.47
Calceotarioside B	-14.36	-19.87
Myricetin-3-O-beta-D- glucopyranoside	-13.70	-18.42
Licoleafol	-13.63	-19.64
Amaranthin	-12.67	-18.14
Nelfinavir	-12.20	-17.31
Prulifloxacin	-11.32	-15.40
Colistin	-13.73	-18.57

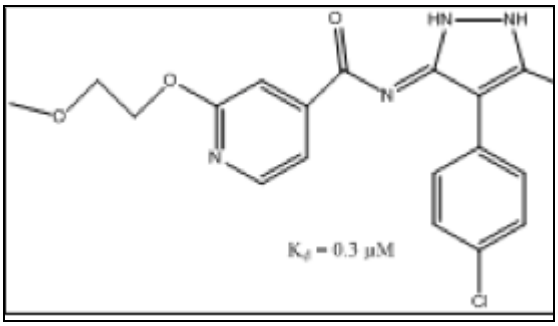
DISCUSSION AND RESULT

$3CL^{30}$ is C-30 endopeptidase[19] which cleaves the polyprotein at two self-cleavage sites. This cysteine protease replicates polyprotein processing and potential drug-target for coronavirus infectivity. To discover and develop functionally effective inhibitors, templates of natural products were searched by computational techniques (Virtual screening, molecular dynamics stimulations, molecular docking and modeling). The ideal structure of one such compound is The $3CL^{pro}$ inhibitors[7] of drug able properties should have structural features and shape to match mutual complementariness at site of action. $3CL^{pro}$ inhibitors target cysteine protease. They irreversibly alkylate the active site of cysteine residue via 1, 4 conjugate addition with the participation of Michael acceptor.[21]

The inhibitory actions of fifteen phytochemicals (Table-one) revealed that tannic acid (polyphenol) has aromatic system with phenolic strength, thus appeared to be most potent. Curcumin has Bis-4 hydroxy -3 methoxy phenolic groups and diketones to form stable enols (keto-enol tautomers). Despite this phenolic contribution is far off from tannic acid. Similarly sinigrin is allyl glucosinolate

lacks phenolic structural strength. Therefore it led to conclude that the structural strength of aromatic system with phenolic hydroxys is important for the inhibitory potency.

The top ranked twelve phytochemicals (Table-two) suggested that compound 1 has highest score and binding affinity whereas compound 11 ranked lowest. The binding affinity and docking scores are interrelated. They depend on the numbers of bond formations at the available binding sites or their extension. It improves HITS or leads discovery for drug design and development. The ranking of phytochemicals reflected that they have drugable potentials through molecular modifications.



CONCLUSION

Natural products spotlighted anti-COVID-19 phytochemicals. The synergy of virtual screening docking and modeling is indispensable for exploiting chemical diversity of natural products. The molecular modifications of natural products through Michael acceptor groups may be new strategy for $3CL^{pro}$ inhibitors.

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