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In silico study of the drugs for the management of SARS-CoV-2

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ABSTRACT:-

Background: Coronavirus disease (COVID-19) is an infectious disease caused by newly discovered coronavirus SARS-CoV-2 (Severe acute respiratory syndrome coronavirus-2). *Ardraka* (*Zingiber officinale)* and *Pippali* (*Piper longum)* are two medicinal plants used in the Indian system of medicines for respiratory disorders.

Objective: The objective of the present study was to discover whether the phytoconstituents present in *Ardraka* and *Pippali* have potential against SARS-CoV-2 through structure-based in-silico study.

Materials and Methods: The structure of the target protein SARS-CoV-2 retrieved from the Protein databank and all the phytoconstituents present in both the plants are screened for Lipinski rule of five through SWISS ADME filter. After that, protein-ligand docking was performed using Pyrx AutoDock wizard with MGL tools 1.5.6 by using a genetic algorithm, and visualization is done using UCSF chimera.

Results: All the molecules have shown binding energy ranges from -3.30 kcal/mol to -6.20 kcal/mol in *Ardraka* and -4.80kcal/mol to -6.90kcal/mol in *Pippali*. Smaller binding energy value shows stronger interaction.

Conclusion: It can be concluded that bioactive present in *Ardraka* and *Pippali* could be an effective inhibitor against the SARS-CoV-2

KEYWORDS

Zingiber officinale. Piper longum, Docking, Lipinski, Swiss Target.

INTRODUCTION

Coronaviruses are a large family of viruses that may cause disease in animals or humans. They usually cause a respiratory infection ranging from the common cold to more severe diseases such as Severe Acute Respiratory Syndrome (SARS). A novel coronavirus, designated as 2019-nCoV, emerged in Wuhan, China, at the end of 2019. Coronaviruses are a group of enveloped viruses with nonsegmented, single-stranded, and positive-sense RNA genomes. Apart from infecting a variety of economically important vertebrates (such as pigs and chickens), six coronaviruses have been known to infect human hosts and cause respiratory diseases[1]. Generally, the coronavirus was spread via airborne zoonotic droplets. The virus was replicated in the ciliated epithelium that caused cellular damage and infection at the infection site. According to a study published in 2019, Coronavirus causes respiratory infection including pneumonia, cold, sneezing, and coughing while in the animal it causes diarrhea and upper respiratory diseases. Coronavirus transmitted human to human or human to animal via airborne droplets[2,3].

Ardraka (*Zingiber officinale)* and *Pippali* (*Piper longum)* are two medicinal plants belongs to the family *Zingiberaceae* and *Piperaceae* used in the Indian system of medicines for respiratory disorders. In Ayurveda literature Adaraka is mostly recommended for enhancement of appetite (Deepani), alleviate constipation (Bhedini), appetizer (Ruchya), clear the tongue and throat (jihwa kanta vishodhanam), balancing circulation (Anulomana), cardio-protective (Hrudya), enhance digestion (Pachana), and dissolve calculi (Ashmadoshahara) etc[4]. Whereas Pippali has been used against various Rejuvenator (Rasayan), CNS stimulant (Medhya), enhancement of appetite (Dipan), Digestive (Pachana), Anti-pyretic (Jvaraghana), Respiratory disorders (Kasaghana) etc[5].

Given the spread of the new coronavirus and its impacts on human health, an attempt was made to study whether the phytoconstituents present in ***Ardraka*** (*Zingiber officinale)* and ***Pippali*** **(***Piper longum)* have potential against SARS-CoV-2 through structure-based in-silico study.

MATERIALS AND METHOD

Proteins/Macromolecules

COVID-19 3clpro/Mpro (PDB ID: 6LU7) structures was obtained from PDB (https://www.rcsb.org/), in pdb format. PDB is an archive for the crystal structures of biological macromolecules, worldwide. The 6LU7 protein contains two chains, A and B, which form a homodimer. Chain A was used for macromolecule preparation. The native ligand for 6LU7 is n-[(5-methylisoxazol-3yl)carbonyl]alanyl-l-valyl-n~1~-((1r,2z)-4-(benzyloxy)-4-oxo-1-{[(3r)-2-oxopyrrolidin-3yl]methyl}but-2-enyl)-l-leucinamide[6].

Ligand and Drug Scan

The 3-dimensional (3D) structures of the chemical constituents present in ***Ardraka*** (*Zingiber officinale)* and ***Pippali*** **(***Piper longum)* were retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/), and Dr. Duke's Phytochemical and Ethnobotanical Databases (https://phytochem.nal.usda.gov/phytochem/search/list) in sdf format[7].

Swiss ADME

Drug-like properties (Lipinski's rule of five) were calculated using Swiss ADME filter, which proposes that molecules with poor permeation and oral absorption have molecular weights > 500, C logP > 5, not more than 5 hydrogen-bond donors, and not more than 10 acceptor groups. (http://www.swissadme.ch/).[8,9,10]

Molecular Docking

All the ligands are converted to pdb format from sdf format and docked against the protein and the interactions were analyzed by using by pyrx 0.8. For the docking of ligands into protein active site and to estimate the binding affinities of docked compounds, an advanced molecular docking program AutoDock Vina (4) was used in this study. All computational studies were carried out using pyrx AutoDock wizard with MGL tools 1.5.6 installed in a Pentium ®Dual–Core CPU T4200 machine running on a 2.0 GHz Intel core processor with 2GB RAM by using the Lamarckian algorithm. The scoring function gives the score based on the best-docked ligand complex is picked out.

Swiss Target Prediction

SwissTargetPrediction is based on the observation that similar bioactive molecules are more likely to share similar targets. Therefore, the targets of a molecule can be predicted by identifying proteins with known ligands that are highly similar to the query molecule. The active site of a protein was determined using the SWISS TARGET PREDICTION. It gives the active site bind to the molecule. (http://www.swisstargetprediction.ch/)[11]

RESULTS

Swiss ADME

Lipinski's Rule of Five is important for drug pharmacokinetic in the human body including their ADME. The selected drug that confirms to the RO 5 tends to have lower attrition rates during clinical trials and hence have an increased chance of reaching the market. For the drugs mentioned in the protocol, Lipinski's rule was applied. The results are shown in table no.1

Table No.1:- Pharmacokinetic of phytoconstituents present in *Ardraka* (*Zingiber officinale)* and ***Pippali* (***Piper longum)*

Sr No.	Chemical Compound	Formula	MW	#H-bond acceptors	#H-bond donors	iLOGP	Lipinski #violations
Ardraka (*Zingiber officinale)*							
1	6gingesulphonic acid	C17H26O6S	358.45	6	2	2.48	0
2	6 dehydrogingerdione	C17H22O4	290.35	4	2	3.02	0
3	Alpha curcumin	C27H28O12	544.5	12	5	1.88	2
4	10 gingerdione	C21H32O4	348.48	4	1	3.84	0
5	Gingerol	C17H26O4	294.39	4	2	3.48	0
6	1 dehydrogingerdione	C17H22O4	290.35	4	2	3.02	0
7	6 gingerdione	C17H24O4	292.37	4	1	3.14	0
8	Cysteine	C3H7NO2S	121.16	3	2	0.37	0
9	Arginine	C6H14N4O2	174.2	4	4	0.04	0
Pippali* (Piper longum)*							
1	Bisdemethoxycurcumin	C19H16O4	308.33	4	2	1.75	0
2	Coumaperine	C16H19NO2	257.33	2	1	2.84	0
3	2 ethyl 1 pentanoylpiperidine	C12H23NO	197.32	1	0	3	0
4	3 methylxanthine	C10H14N4O2	222.24	3	1	1.74	0

Molecular docking

Protein-Ligand interaction plays a significant role in structural based designing. The protein molecule used for the study is 6lu7. As hydroxychloroquine and quinine is being used at present for the treatment of covid

19. Thus, we are comparing the efficacy of the following drugs with hydroxychloroquine and quinine. Molecular docking of selected drugs was shown in table no.2

Table No.2:- Output of molecular docking score of SARS-CoV-2 and ***Ardraka*** (*Zingiber officinale)* and ***Pippali* (***Piper longum)* with respect to the minimum binding energy

Ardraka* (Zingiber officinale)*		
1	6gingesulphonic acid	-6.20 kcal/mol
2	6 dehydrogingeridione	-5.50 kcal/mol
3	Alphacurcumin	-5.50 kcal/mol
4	10 gingerdione	-5.40 kcal/mol
5	Gingerol	-5.30 kcal/mol
6	1 dehydrogingerdione	-5.20 kcal/mol
7	6 gingerdione	-5.20 kcal/mol
8	Cysteine	-3.47 kcal/mol
9	Arginine	-3.30 kcal/mol
Pippali* (Piper longum)*		
1	Bisdemethoxycurcumin	-6.90 kcal/mol
2	Coumaperine	-6.30 kcal/mol
3	2 ehtyl 1 pentanoylpiperidine	-4.90 kcal/mol
4	3 methylxanthine	-4.80 kcal/mol

Swiss Target Prediction

Target prediction was done on the selected molecule, SARS COV2, antiviral and humoral immunity were selected as the target for the selected molecule. The results are as shown in table no.3

Table No.3:- Swiss target prediction of selected phytoconstituents present in ***Ardraka*** (*Zingiber officinale)* and ***Pippali* (***Piper longum)*

Sr No.	Chemical Constituents	Target Name
Ardraka *(Zingiber officinale)*		
1	6gingesulphonic acid	Interferon-induced, double-stranded RNA-activated protein kinase
2	6gingesulphonic acid	Angiotensin-converting enzyme
3	6gingesulphonic acid	Tyrosine-protein kinase LCK-

4	6gingesulphonic acid	Tyrosine-protein kinase HCK
5	6 Dehydrogingerdione	Glycogen synthase kinase-3 beta
6	6 dehydrogingerdione	Toll-like receptor (TLR7/TLR9)
7	6 dehydrogingerdione	Toll-like receptor 4
8	6 dehydrogingerdione	Tyrosine-protein kinase ABL
9	6 dehydrogingerdione	Tyrosine-protein kinase ABL
10	10 gingerdione	Tyrosine-protein kinase JAK3
11	10 gingerdione	Tyrosine-protein kinase JAK1
12	Gingerol	Interleukin-8 receptor B
13	Gingerol	Tyrosine-protein kinase JAK1
14	1 dehydrogingerdione	Toll-like receptor (TLR7/TLR9)
15	1 dihydrogingerdione	Toll-like receptor 4
16	1 dehydrogingerdione	Toll-like receptor 4
Pippali (*Piper longum)*		
1	Bisdemethoxycurcumin	Glycogen synthase kinase-3 beta
2	Bisdemethoxycurcumin	Inhibitor of NFkappa-B kinase (IKK)
3	Bidemethoxycurcumin	Macrophage colony stimulating factor receptor
4	Coumaperine	Inhibitor of nuclear factor kappa B kinase epsilon subunit
5	Coumaperine	Tyrosine-protein kinase JAK2
6	Piperine	Tyrosine-protein kinase LCK
7	Piperine	Tyrosine-protein kinase JAK3
8	Piperine	Tyrosine-protein kinase JAK2
9	Piperine	Interleukin-1 receptorassociated kinase 4
10	2 ethyl 1pentanoylpiperidine	Indoleamine 2,3dioxygenase
11	2 ethyl 1 pentanoylpiperidine	Nuclear receptor ROR-ara
12	2 epentanoylpuperdine	Tyrosine-protein kinase JAK2
13	2 epentanoylpuperdine	Tyrosine-protein kinase JAK3
14	2 epentanoylpuperdine	Tyrosine-protein kinase JAK1
15	3 methylxanthine	Tyrosine-protein kinase TYK2
16	3 methylxanthine	Indoleamine 2,3dioxygenase

DISCUSSION

Lipinski screening has shown that all the molecules present in *Ardraka* (*Zingiber officinale)* and *Pippali* **(***Piper longum)* have passed the rule except Alpha curcumin. It has a higher molecular weight and number of H bond acceptor which affects the solubility and permeability of the molecule. A molecular docking study reveals that all the molecules present in both the plants have shown inhibition against SARS-CoV-2. The lowest binding energy is shown by 6 gingesulphonic acid from *Ardraka* (*Zingiber officinale),* Coumaperine from *Pippali* (*Piper longum).* Swiss target prediction has predicted a total of 16 targets for both the plants against SARS COV2, antiviral and humoral immunity.

CONCLUSION

Coronavirus causes respiratory infection including pneumonia, cold, sneezing, and coughing while in the animal it causes diarrhea and upper respiratory diseases. Coronavirus is transmitted human to human or human to animal via airborne droplets. There is a new world health crisis threatening the public with the spread of COVID-19 (Coronavirus Disease-2019). The World Health Organization has declared it a Public Health Emergency of International Concern. Based on the results obtained from the docking study in the present study all the compounds may be suggested as the potential therapeutic drug for the treatment. Further in-vitro and in-vivo experimental work is required for validation of our in-silico results and to generate more efficacy.

REFERENCES

1. Unhale SS, Ansar QB, Sanap S, Thakhre S, Wadatkar S, Bairagi R et al. A review on coronavirus. World J Pharma Life Sci. 2020;6(4):109-115
2. Woo PC, Lau SK, Huang Y, Yuen KY. Coronavirus diversity, phylogeny, and interspecies jumping. Exp Biol Med (Maywood). 2009;234:1117–27
3. De Souza Luna LK, Heiser V, Regamey N, Panning M, Drexler JF, Mulangu S, et al. Generic detection of coronaviruses and differentiation at the prototype strain level by reverse transcription–PCR and nonfluorescent low-density microarray. J Clin Microbiol. 2007;45:1049–52.
4. Bhavaprakasha. Mishra S. Bhavaprakasha Nighantu Vidyodhini hindi commentary. 10th edi. Varanasi: Chaukhamba orientalia; 2002. p.15.
5. Pandey Gyanendra,2012. Bhavaprakash Nighantu, Haritakyadi Varga: 62-63, Varansi:Chaukhamba
6. Berman HM, Battistuz T, Bhat TN, Bluhm WF, Bourne PE. 9/04 15: 13) VCH/G J-1158 Hartmann PMU: WSL (W) 07/09/2004 ScalaLF&SansLF (0). 3.04. 05 (170Â240mm) pp. 560–576 III-34_P (p. 573) K. Burkhardt, Z. Feng, GL Gilliland, L. Iype, S. Jain et al. Acta Crystallogr. D. 2002;58:899-907
7. https://phytochem.nal.usda.gov/phytochem/search/list

8. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Advan drug del rev. 1997 Jan 15;23(1-3):3-25.

9. Gimenez BG, Santos MS, Ferrarini M, Fernandes JP. Evaluation of blockbuster drugs under the rule-of-five. Die Pharmazie. Intern J Pharma Sci. 2010 Feb 1;65(2):148-52.

10. Daina A, Michielin O, Zoete V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Scient rep. 2017 Mar 3;7:42717

11. Gfeller D, Grosdidier A, Wirth M, Daina A, Michielin O, Zoete V. SwissTargetPrediction: a web server for target prediction of bioactive small molecules. Nuc acid res. 2014 Jul 1;42(W1):W32-8