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The exploration of phytocompounds theoretically combats SARS-CoV-2 pandemic against virus entry, viral replication and immune evasion

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Abstract

Background: The novel coronavirus disease-2019 (COVID-19) that emerged in China, is an extremely contagious and pathogenic viral infection caused by the severe acute respiratory syndrome-corona virus-2 (SARS-CoV-2) that has sparked a global pandemic. The few and limited availability of approved therapeutic agents or vaccines is of great concern. Urgently, Remdesivir, Nirmatrelvir, Molnupiravir, and some phytochemicals including polyphenol, flavonoid, alkaloid, and triterpenoid are applied to develop as repurposing drugs against the SARS-CoV-2 invasion.

Methods: This study was conducted to perform molecular docking and absorption, distribution, metabolism, excretion and toxicity (ADMET) analysis of the potential phytocompounds and repurposing drugs against three targets of SARS-CoV-2 proteins (RNA dependent RNA polymerase, RdRp, Endoribonuclease, S-protein of ACE2-RBD).

Results: The docking data illustrated Arachidonic acid, Rutin, Quercetin, and Curcumin were highly bound with coronavirus polyprotein replicase and EbolaVirus envelope protein. Furthermore, anti-Ebolavirus molecule Remedesivir, anti-HIV molecule Chloroquine, and Darunavir were repurposed with coronavirus polyprotein replicase as well as EbolaVirus envelope protein. The strongest binding interaction of each targets are Rutin with RdRp, Endoribonuclease with Amentoflavone, and ACE2-RBD with Epigallocatechin gallate.

Conclusions: Taken altogether, these results shed a light on that phytocompounds have a therapeutic potential for the treatment of anti-SARS-CoV-2 may base on multi-target effects or cocktail formulation for blocking viral infection through invasion/activation, transcription/reproduction, and posttranslational cleavage to battle COVID-19 pandemic.

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Introduction

The recent COVID-19 outbreak caused by novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an ongoing pandemic and presents a public health crisis. Once SARS-CoV-2 infects the host particular human being by firstly binding to the ectoenzyme Angiotensin Converting Enzyme 2 (ACE2), a serine protease acting as the receptor, while another serine protease-transmembrane serine protease 2 (TMPRSS2) is indispensable for priming the viral spike protein requisite for entering the cells. Two phases of COVID-19 pathophysiology are being marked 1. increased SARS-CoV-2 virus transmission and infection rates due to the wide expression of the main infection-related ACE2, TMPRSS2 and CTSB/L human genes in tissues of the respiratory and gastrointestinal tract as well as 2. an overwhelming inflammatory response due to cytokine storm, the development of acute respiratory distress syndrome (ARDS), severe thrombotic events containing pulmonary embolism, deep vein thrombosis, and microthrombi emerged as additional symptoms, multiple organ damages, and systemic failure likely because of
imbalance ACE/ANGII/AT1R and ACE2/ANG1-7/MAVR axes signalling [12]. The virus genome would be reproduced by host cell growth, and finally virus is egoistic to prevent other virus to concurrently infect the same host cell [3]. In addition, SARS-CoV-2 has an unique machinery proofreading appliance to preserve the genome maintenance in the virus world and their transaction are complicatedly affected by multiple factors [4]. Owing to living in intermediate host and unique machinery proofreading, coronavirus could adapt the series of environmental stress subsequently to infect the human [5]. Infection with SARS-CoV-2 leads to COVID-19 pandemics, the severity of which originates from the host’s immune response, particularly the release of a storm of pro-inflammatory cytokines.

The mutation rate of SARS-CoV-2 is very fast and there have been found several major variants (i.e. variant beta, delta, omicron) that caused at least 5 surges global spread associated with 7 waves of death peaks under the global circumstance (https://COVID19.who.int/). Unfortunately, the effective drug has not been officially licensed or approved to suppress the epidemic prevalence due to non-specific treatment even vaccination currently available. Presently, several vaccines (Oxford AstraZeneca, Pfizer–BioNTech, Moderna, SINOVAC etc.) and drugs (Remdesivir, Molnupiravir, and Paxlovid) are being used for COVID-19 treatment under emergency use authorization (EUA) by approval of FDA or WHO. Even people due to non-specific treatment even vaccination currently available. Omicron, delta variant) infection WHO, but are still predisposed to new variants of SARS-CoV-2 (i.e. omicron, delta variant) infection [6–8] and some of COVID-19 patients may endure serious symptoms and lead to death [9,10]. The repurposing of drugs including antiviral agents (Chloroquine, Ivermectin, Nizatixoxonide, Hydroxychloroquine, Lopinavir, Remdesivir, Tocilizumab), supporting agents (Azithromycin, Corticosteroids, Vitamin C, Vitamin D) and favourable investigational vaccines are tried to meet this urgent demand against COVID-19 pandemic [11]. Remdesivir is an inactive form prodrg of nucleotide can be converted into its active form metabolite as an adenosine nucleoside triphosphate analog to inhibit the viral RNA polymerase activity [12]. Therefore, the emerging researches repurposed the nucleoside analogue, Remdesivir (anti-Ebola) could suppress human and zoonotic coronavirus at the cell culture level and mouse model [12,13]. Interestingly, previous anti-Ebola prodrg Remdesivir was demonstrated as a RNA-dependent RNA polymerase (RdRp) inhibitory regime in COVID-19 pandemics by co-crystallized structure of Remdesivir with CoV-2 RdRp [14]. This evidence shown not only the active metabolite from Remdesivir can act on RdRp of SARS-CoV-2 to interrupt viral replication, but this prodrg may direct bind and interact with RdRp of SARS-CoV-2 to alter enzyme activity.

In terms of transcription and replication of SARS-CoV-2, main protease (Mpro) and papain-like protease (PLpro) play a main function to cleave the polypeptide replica into non-structure protein. A previous literature elicited that Mpro could attach and cleave the C-terminus of polypeptide replicase at 11 protease digestion sites [15] to construct nsp4–nsp16 [16]; in contrast PLpro should adhere on the N-terminus of polypeptide replicase to form nsp1–nsp3 as well [17]. Subsequently, RdRp of SARS-CoV-2 consists of one catalytic subunit (nsp12) and two non-structure proteins (nsp7 and nsp8) has been illustrated in the replication of viral RNA. Taken a deep insight of COVID-19 immune evasion, uridylicate-specific endoribonuclease (nsp15) will assist the SARS-CoV-2 virus escape from the detection of host cell dsRNA sensors as well as endoribonuclease is simultaneously active during the replication of the poly(A) region of viral genomic and subgenomic RNAs to degrade the S-polyruridines of the anti-genome [18,19]. With respect to virus entry, the human ACE2 transmembrane receptor is firstly anchored by spike protein (S-protein) of SARS-CoV-2. Hereafter, the S-protein attached cells can form an endosome which will lead virus encapsulated to facilitate the virus entering the human host cell [14].

There potential phytochemical candidates include Curcumin, Cinnamaldehyde, Quercetin, Lactoferrin, Probiotics, Selenium, Zn, Vitamin D, Vitamin C, etc. [20]. Notably, according to accumulative evidence reveal that the phyto compounds have been classified into at least four categories including polyphenol, flavonoid, alkaloid, and triterpenoid [21]. The biological and pharmacological activities of medicinal phytochemicals such as anti-oxidation, anti-inflammation, anti-tumor and anti-virus have been well investigated [22]. Furthermore, numerous studies have illustrated that some natural products i.e. flavonoid could be an inhibitor to interact with SARS-CoV-2 3CL protease (3CLpro) by computational analysis [23–25]. As an alternative therapeutic strategy, flavonoids should be considered into one of potential anti-virus agents. Thereby, those phyto medi cines are evidenced to hinder SARS-CoV-2 activity via exploring the mechanisms of PLpro, 3CLpro, and NTPase/helicase [26]. Epigallocatechin gallate (EGCG) is one of polyphenols, which has been suggested to prevent and treat COVID-19 via suppressing Mpro and PLpro to interrupt viral non-structure protein reproduction [27]. In terms of alkaloid, Berberine was isolated from a plenty of traditional Chinese formulas; and moreover has been investigated to reduce virus replication and targets specific interactions between the virus and host cells [28]. As for the development of innovative drug, a major effort has been directed to the discovery of therapeutic antibodies targeting S-protein and inhibitors of 3CLpro as well as RdRp of SARS-CoV-2. In the investigations of repurposed or prodrg from natural compounds to fight COVID-19 pandemics become an urgent demand. Henceforth, this study attempted to search some phyto compounds according to their anti-viral and anti-inflammatory properties and subsequently docked according to three major aspects of SARS-CoV-2 infection such as virus-entry, viral replication, and immune evasion related proteins as targets for abrogating the virus expansion via in silico to shorten the exploration time of new phytomedicine discovery and development. Moreover, this study might provide a favourable perspective for evaluating the efficacy of a single antiviral drug candidate as well as afford an integrated on various levels of SARS-CoV-2 infection from viral infection, viral replication, and immune evasion to accomplish the COVID-19 prevention or treatment strategies.

Materials and methods

Molecule docking

Program, protein module, and chemical structure preparation

Molecular docking was performed by CCDC Gold Suite V5.3 (Cambridge Crystallographic Data Centre, Cambridge, UK) [29]. 3-D chemical structure of small molecules were retracted from PubChem (https://pubchem.ncbi.nlm.nih.gov) (Supplementary document). Replicate polyprotein of coronavirus SARS: 5N19 [30]; NL33: SHNO [30]; 229E: 2ZU2 [31]; COVID-19: 6M2Q [32], and 6WX4 [33] as well as Ebola virus envelope protein: 6G91 [34] were retrieved from PDB database of National Center for Biotechnology Information (NCBI, https://www.rcsb.org). The preparation of protein module/structure was executed by the Macromolecule preparation protocol in Discovery Studio (BIOVIA, San Diego, CA, USA). The key residues of putative binding pocket are: 229E 3CL protease (2ZU2): His41, Asn141, Ala143, Cys144, His162; SARS main protease (5N19): His41, Phe140, Gly143, Ser144, Cys145, Met165, Glu166, Pro168, Asp187, Arg188, Gin189; NL33 3CL protease (5NHO): His41, Phe139, Cys144, Gly142, Ala143, Glu166, Gly168, Asp187, Gin188, Pro189, Ser190, Leu191; COVID-19 main protease (6M2Q): Pro39, His41, Asn142, Gly146, Leu167, Pro168, Thr169, Gly170, Gin189, Thr190, Ala191; COVID-19 PL protease (6WX4): Trp106, Asn109 Cys111, Tyr112, Leu112, Gly163, Asp164, Pro247, Pro248, Tyr264, Thr268, Gin269, Cys270, Gly271, His272, Tyr273; COVID-19 RdRp (7AAP): Lys545, Arg555, Val557, Cys622, Asp623, Ser682, Thr687, Ala688, Asn691, Asp760.
Ser814; **COVID-19 Endoribonuclease (6WXC):** Ser294, Cys293, His250, Val292, Lys290, Gln245, Lys345, Tyr343; **COVID-19 ACE2-RBD (6M17):** Gln24, Thr27, Phe28, Asp30, Lys31, His34, Glu35, Glu37, Asp38, Tyr41, Gln42, Leu79, Met82, Tyr83, Gln325, Glu329, Asn330, Lys333, Gly354, Asp355, Arg357, Arg393, Lys417, Gly446, Tyr449, Tyr453, Leu455, Phe486, Ala475, Phe486, Asn487, Tyr489, Gln493, Gly496, Gln498, Thr500, Asn501, Gly502, Tyr505; **Ebola virus envelope protein (6G9I):** Leu59, Leu63, Arg64, Phe88, Lys95. Finally, the full energy minimization was carried out in the presence of bound ligand by the steepest descent (SD) method with the selection of AMBER force field.

**Docking procedure**

The setup of the docking platform was as follows: GA run 10, and GA search efficiency 200%. The binding pocket was identified by a two dimensional molecular mapping technique provided by LigPlot*(European Molecular Biology Laboratory (EMBL), the Wellcome Genome Campus, Hinxton, Cambridgeshire, CB10 1 SD, UK); furthermore, the presumed binding pockets were defined as a supplementary material. In addition, the binding score ChemPLP, which adopts ChemScore to gauge the hydrogen bonding and multiple linear potentials to model van der Waals and repulsive terms, was used. The three dimensional docking structures were analyzed by
Furthermore, the interacting amino acid residues of docking results were visualized and elucidated their interactions of 2-dimensional and 3-dimensional conformation using Discovery studio 3.5 and PyMOL (Schrödinger, New York, USA). The chemical structures calculation were executed by Online SMILES Translator and Structure File Generator website (https://cactus.nci.nih.gov/translate/) as well as bioactivity capability information of top five potential compounds were analyzed and collected from Pre AMEDT (https://preadmet.bmdrc.kr/). In terms of chemical and physical properties, the LogP value is applied for predicting the lipophilicity of chemicals as well as presuming solubility, permeability plasma binding, and adsorption of biological membrane. Furthermore, in order to collect more LogP value of a plethora of chemicals; in previous study, researcher developed an additive model (XLogP3) to predict the presumed LogP value of unknown compounds [35]. Additionally, topological molecular polar surface area (TPSA) is an essential descriptor that could indicate the transport efficiency of chemical compounds [36].
Table 1
The binding affinity of phytocompounds compared to clinical drugs docked with RNA dependent RNA polymerase.

| Target          | Clinical drug | Polyphenol          | Triterpenoid | Flavonoid | Alkaloid | Other             |
|-----------------|---------------|---------------------|--------------|-----------|----------|-------------------|
| RdRp PDB:7AAP   | 121304016     | 63064 Epigallocatechin gallate | 49.44 | 451674 Triterpenoid | 52.00 | 5280805 Rutin  | 60.07 | 10177 Indirubin | 47.14 | 5280483 Vitamin K | 65.01 |
| Remdesivir      | 155903259     | 5281647 Mangiferin   | 44.33 | 4455946 Cucurbitacin | 47.63 | 5281600 Amentoflavone | 52.79 | 245005 Aconitine | 43.18 | 14985 Vitamin E | 59.57 |
| Nirmatrelvi     | 145986610     | 1794427 Chitosan acid | 41.66 | 5281319 Cucurbitacin E | 44.56 | 165549 Sophoridine | 47.31 | 444899 Arachidonic acid | 37.43 | 5280795 Vitamin D3 | 56.47 |
| Molnupravi      | 6323266       | 1203 Catechin       | 40.28 | 21139520 Limonin | 37.73 | 5280343 Quercetin | 46.29 | 24721085 Oxytetracycline | 35.27 | 403570 Vitamin B2 | 52.04 |
| Tipiracil       | 35.72         | 370 Gallic Acid     | 33.37 | 21139520 Sapogenins | 37.42 | 5281605 Baicalen | 43.22 | 71466 Sophocarpidine | 34.98 | 440354 Vitamin A | 51.60 |
|                 |               |                     |             |           |          |                   |      | 72378 Matrine      | 33.28 | 171548 Vitamin B12 | 44.79 |
|                 |               |                     |             |           |          |                   |      | 189377 Lycorine    | 31.05 | 8955 Biotin         | 38.69 |
|                 |               |                     |             |           |          |                   |      | 29435 Alexine      | 30.81 | 3314 Syringaldehyde | 36.20 |
|                 |               |                     |             |           |          |                   |      | 42301-Deoxynojirimycin | 33.90 | 546700067 Vitamin C | 31.00 |
The intermolecular interaction between three COVID-19 infectious protein and phytomedicine.

### Results

To search potential compounds for battling certain virus, the top 10 candidates in docking potency of clinic drugs and small molecules with Ebola virus envelope protein are shown in Fig. S1. Unexpectedly, unsaturated fatty acid Arachidonic acid, Rutin, and Curcumin were highly bound with Ebola virus envelope protein as well as anti-Ebola virus molecule Remdesivir did. As evidence showed that unique amino acids of binding site for four potential molecules are unsaturated fatty acid Arachidonic acid, Rutin, and Curcumin were 10 candidates in docking potency of clinic drugs and small molecules.

Fig. S1. Unexpectedly, the intermolecular interaction between three COVID-19 infectious protein and phytomedicine. van der Waals

Table 2

| Genre       | H bond                      | van der Waals          |
|-------------|-----------------------------|------------------------|
| Clinical Drug | Ser549, Asp555, Asp760, Ser814     | Ile548, Lys551, Asp618, Asn691, Leu758, Glu811 |
| Clinical Drug | Asp618, Tyr619, Cys622, Asp623, Asp760, Asp761     | Lys621, Leu758, Ser759, Lys798, Trp800, Glu811, Cys813, Ser814 |
| Clinical Drug | Ser682, Thr687, Ala888     | Lys545, Val557, Tyr619, Asp618, Cys622, Cys683, Asp684, Leu758, Ser759, Asp760, Asp761, Cys813, Ser814 |
| Clinical Drug | Arg553, Thr556, Cys622, Asp623     | Val545, Arg555, Val557, Tyr619, Pro620, Lys621, Arg624, Ser682, Leu628, Leu758, Ser759, Asp760, Leu758, Cys798, Glu811, Cys913, Ser914, Trp617, Trp620, Leu761, Ala762, Lys798 |
| Clinical Drug | Tyr619, Asp623, Asp760     | Lys621, Ser759, Asp760, Ser761, Ser814, Glu815 |

Endoribonuclease (50VX)

| Genre       | H bond                      | van der Waals          |
|-------------|-----------------------------|------------------------|
| Clinical Drug | Gly248, Gly248, Val292     | Asp240, His250, Lys290, Cys293, Ser294, Lys345 |
| Clinical Drug | Gly248, His250, Ser294, Tyr343, Lys345 | Leu246, Gly247, Asn278, Cys293, Met331, Trp333, Thr341, Pro344, Leu346 |
| Clinical Drug | Val292, Ser294, Pro343, Pro344 | Gln245, Gly247, Gly248, Asn278, Cys293, Ser294, Ser391, Lys345 |
| Clinical Drug | Gln245, Gln248, His250     | Glu245, His250, Asn278, Lys290, Cys293, Ser294, Trp333, L345 |
| Clinical Drug | Gln245, Cys291, Val292     | His235, Leu246, Gly247, Ser294, Trp333, Cys340, Trp341, Lys345 |
| Other       | Ser244, Leu246, Gly248, Ser289, Cys293, Ser294, Cys340, Thr341, Pro344, Lys345 | Lys345 |

ACE2-RBD

| Genre       | H bond                      | van der Waals          |
|-------------|-----------------------------|------------------------|
| Clinical Drug | Gly245, Cys291, Val292     | Asp240, His250, Lys290, Cys293, Ser294, Lys345 |
| Clinical Drug | Lys31, Asp38, Gly42, Tyr449, Leu492, Gly493 | Leu39, Asn450, Tyr451, Leu452, Phe490, Leu492, Gln493, Ser494 |
| Clinical Drug | Gly42, Tyr449     | Clu35, Asp38, Asn64, Asp67, Lys68, Ala71, Gin76 |
| Clinical Drug | Gln35, Asp38, Tyr449     | His34, Leu39, Gln42, Asn450, Cys484, Leu492, Gln493, Ser494 |
| Other       | Gly354, Arg393     | Gln42, Leu452, Phe490, Leu492, Ser494 |
| Other       | Gln42, Asp38, Ser44, Ser47, Trp349, Asp350, Leu351, Gly352, Phe356, Ala386, Phe390, Asn394 | Gln354, Arg393 |

To explore the basis of binding affinity of tested chemicals docked with selected viral protein molecules, the 3D docking of clinic drug and chemical compounds at Ebola virus envelope protein and the replicase of coronavirus SARS, 229E, and NL63 are demonstrated in Fig. 1. From the results are shown, those of natural products such as Arachidonic acid, Rutin, and Curcumin had high ChemPLP docking score (SARS: Arachidonic acid 67.74, Rutin 69.62, Curcumin 64.14, Remdesivir 77.21; NL63: Arachidonic acid 67.19, Rutin 67.01, Curcumin 64.07, Remdesivir 72.90; 229E: Arachidonic acid 69.99, Rutin 73.51, Curcumin 65.56, Remdesivir 74.09, Ebola: Arachidonic acid 68.40, Rutin 61.08, Curcumin 61.05, Remdesivir 62.92) with the specifically binding site, respectively. The computer analysis (Fig. 1, Table S1) revealed that Arachidonic acid, Rutin, Curcumin, and some anti-virus molecules Remdesivir (Ebola), Tenofovir alafenamide (HIV), Darunavir (HIV), Arbidol (HIV) etc. might affect the replicase of coronavirus furthermore inhibiting viral reproduction.

Strikingly, for a better understanding the interaction of potential candidates with putative binding pocket, the binding results are shown in Fig. 2. It portrays that the binding interaction with top five potential molecules as well as the 3D conformation of each compound at the putative binding pocket with Mpro and PLpro of SARS-CoV-2. In 3D mapping, the inhibitory compounds were decorated in five different colors (Squalene/black; α-tocopheryloquinone/yellow; Darunavi/red; Vitamin E/purple; Remdesivir/green). Form the figures, there are some hydrogen bonds between ligands and Mpro as
Table 3
The binding affinity of phytocompounds compared to clinical drugs docked with endoribonuclease.

| Target            | Clinical Drug       | Polyphenol | Triterpenoid | Flavonoid | Alkaloid | Other         |
|-------------------|---------------------|------------|--------------|-----------|----------|---------------|
| Endoribonuclease PDB: 6WXC |                     | 65064      | 21139920     | 54.00     | 71.81    | 245005        |
|                   |                     | 12 121      | 57.76        | 49.17     | 65.67    | 10177         |
|                   |                     | 1794427     | 179651       | 48.62     | 55.96    | 165549        |
|                   |                     | 5281647     | 5280845      | 46.04     | 53.93    | 72728         |
|                   |                     | 1203        | 5280343      | 52.84     | 45.11    | 114850        |
|                   |                     | 370         | 5280863      | 42.45     | 45.54    | 24721085      |
|                   |                     | 44.35       | 5281605      | 52.43     | 5.11     | 189377        |
|                   |                     | 41.56       | 5281505      | 42.65     | 44.68    | 181977        |
|                   |                     | 33 1 4      | 5281505      | 42.65     | 44.68    | 181977        |
|                   |                     | 1-Deoxynojirimycin | 40.50 | 40.50 | 40.50 | 40.50 |

Remdesivir
Epigallocatechin gallate
Sapogenins
Amentoflavone
Acacetine
Vitamin K

Image: Screenshot of the table and associated text.
### Table 4

The binding affinity of phytocompounds compared to clinical drugs docked with ACE2-RBD of SARS CoV-2.

| Target   | Clinical Drug   | Polyphenol | Triterpenoid | Flavonoid | Alkaloid | Other                |
|----------|-----------------|------------|--------------|-----------|----------|----------------------|
| ACE2-RBD PDB:6M17 | 121304016 Remdesivir | 52.47 | 65064 Epigallocatechin gallate 1203 | 56.33 | 5281319 Cucurbitacin E 44559416 | 50.14 | 5281600 Amentoflavone 0490485 | 54.70 | 245005 Aconitine 0490485 | 47.46 | 111028977 Arachidonic acid 4590893 | 60.90 |
|          | 14596610 Molnupiravir | 37.86 | 1794427 Catechin 5281647 | 48.43 | 2113920 Mangiferin 370 | 43.78 | 5280863 Kaempferol 5281605 | 41.02 | Baicalein 04901085 | 32.67 | 38972117 Alpha-tocopherol 171548 | 34.67 |
|          | 155903299 Nirmatrelvir | 36.05 | 1794427 Chlorogenic acid 5281647 | 48.43 | 2113920 Mangiferin 370 | 38.18 | 5280863 Kaempferol 5281605 | 41.02 | Baicalein 04901085 | 32.67 | 38972117 Alpha-tocopherol 171548 | 34.67 |
| Tipiracil | 6323286 Gallic Acid 370 | 38.18 | 2113920 Mangiferin 370 | 38.18 | 5280863 Kaempferol 5281605 | 41.02 | Baicalein 04901085 | 32.67 | 38972117 Alpha-tocopherol 171548 | 34.67 |

Remdesivir  Epigallocatechin gallate  Cucurbitacin E  Amentoflavone  Aconitine  Arachidonic acid
well as those bonds showed in green dotted lines (Pro168/Vitamin E; Glu166/Remdesivir; Pro168 and Gln189/Darunavir). On the other hand, Gly163 of PLpro with α-tocopheroylquinone and Gly266 with Remdesivir molecules form sole one H-bond, respectively, compared to Darunavir with PLpro which composed two H-bonds at Tyr246 and Tyr268.

It is worth noting that this study provided three therapeutic strategies of anti-COVID-19 drug development via virus entry, virus proliferation, and immune evasion. The binding affinity between RdRp and natural compounds is shown in Table 1; For binding affinity of RdRp: Vitamin K > Rutin > Vitamin E > Arachidonic acid > Remdesivir > Amentoflavone > Vitamin D3 > Triterpenoid > Vitamin B2. In addition, there were only two compounds excessed 60 in the scoring function of Vitamin K and Rutin were 65.01 and 60.07, respectively. Furthermore, the scores of Vitamin E and Arachidonic acid were 59.57 and 56.47, respectively, and both of them were higher than Remdesivir was 53.47. With depicts in Table 2, the interaction group between EGCG and RdRp formed six hydrogen bonds; while four were found at Remdesivir and Rutin as well as three at Triterpenoid and Indirubin, separately, and one at Vitamin K. In Table 3, the overall scoring function of endoribonuclease was relevant higher than those of RdRp and ACE2-RBD groups. Especially, the scoring of Vitamin K and Amentoflavone approximately reached to 71.5 by contrast 64.23 of Remdesivir. There were some scores of natural products close to the score of Remdesivir such as Rutin, Vitamin E, Aconitine, and Arachidonic acid which were 65.67, 65.75, 62.34, and 61.15, respectively. The data revealed that there were five hydrogen bonds between EGCG and Endoribonuclease and four at Amentoflavone (Table 2). For the binding affinity of Endoribonuclease: Amentoflavone > Vitamin K > Vitamin E > Rutin > Remdesivir > Aconitine > Arachidonic acid > EGCG > Nirmatrelvir > Chlorogenic acid > Vitamin B2 > Luteolin > Vitamin D3 > Mangiferin > Molnupiravir > Sapogenins > Quercetin > Indirubin > Catechin > Kaempferol > Baicalein > Vitamin A. It is worth mentioned that there was a common amino acid residue Gln245 appeared at the interaction groups of Remdesivir, Indirubin, and Arachidonic acid as well. Additionally, there were three hydrogen bonds were formed in each category. With respect to virus entry, the interaction scoring between co-crystallized ACE2-RBD structure and phytochemical compounds were represented in Table 4. For binding affinity of ACE-RBD: Arachidonic acid > EGCG > Vitamin E > Vitamin B2 > Amentoflavone > Catechin > Remdesivir > Rutin > Cucurbitacin E. Of note, the scoring functions of EGCG, Catechin, Amentoflavone, Arachidonic acid, Vitamin E, Vitamin B2 were higher than Remdesivir which was 52.47. In accordance with Table 2, there was only one hydrogen bond was formed between Remdesivir and ACE2-RBD complex; in contrary to six at EGCG, three at Amentoflavone, two at Cucurbitacin E and Vitamin K, and one at Aconitine.

In terms of bioactivities, the collected ADMET information is exemplified in Table S2. All tested compounds were passed through the ADME filter. All tested compounds showed the considerable aqueous solubility and lipophilicity. Depending on molecular properties such as the molecular weight (MW), the number of hydrogen bond acceptors, donors, and partition coefficient (LogP) have been formulated. As far as chemical and physical properties is concerned, the top five hit molecules had been analysed by Lipinski’s rule of five (RO5); moreover, the methodology of RO5 is considered by MW values (MW < 500), numbers of hydrogen bond acceptors (HBA ≤10) and donors (HBD ≤5), and LogP value (LogP < 5). Based on the principle of RO5, the data are shown in Table S3, the range of MW values was from 400 to 605 g/mol as well as the TPSA values of compounds was observed to be in the range from 0 to 203.57 Å². All tested compounds obeyed RO5 and do not show any violation. Therefore, tested compounds were predicted to have a good bioavailability. In addition, the numbers of hydrogen bond acceptors and donors of Squalene, α-tocopheroylquinone, Darunavir, and Vitamin E located at a suitable range of RO5. The data exposed that those five candidate chemicals located into the appropriate range as well as illustrated the prospective for further drug discovery. Furthermore, tested compounds do not show any violations in Ghose, Veber, Egan, and Muegge filter. Besides, pharmacokinetic behaviours such as Gl absorption and blood-brain barrier (BBB) permeate were also calculated. Likewise, tested compounds showed high Gl absorption, suggesting both as better absorption quality on oral administration. It also showed that all tested compounds cannot penetrate the BBB, therefore it has less possibility to produce neurotoxicity. Regarding metabolism predictions, the program analyses if the molecules are P-glycoprotein (P-gp) substrates. P-gp substrate plays a role to protect the brain from toxic substances [37]. Fascinatingly, all tested compounds resulted “yes” for P-gp substrate. The webserver also predicts whether a compound can be capable of inhibiting 5 CYP isoenzymes or not [38]. Surprisingly, all tested compounds resulted “no” for 5 CYP isoenzymes inhibition. That means all tested compounds will not produce any toxic or not all possible adverse effects of such compounds. This online server also allows us to identify potentially problematic fragments such as PAINS (Panassay interference compounds) that are responsible for the false positive results in high-throughput screens [39]. All tested compounds did not contain any type of problematic fragments. That means proposed compound did not tend to non-specifically react with numerous biological targets rather than specifically affecting one desired target. Thus, considering all ADMET parameters together, we can conclude that all selected compounds would be useful for discovery and development of new purpose or repurpose drug in further study.

Discussion

Molecule docking is a primary medicinal screening approach based on bioinformatics and drug design assistance for exploring potential candidate drugs. The mainstream purpose of molecule docking is to envisage the interaction of small molecules with the known three dimensional (3D) structure of target proteins. In the computer analysis, the molecule docking simulation could be applied to virtually screen the binding affinity of chemical ligands interacted with template proteins, rank the binding score, and assume the inhibition efficacy of small molecules with target proteins [40]. In previous literature, the virtual screening of small molecules selected some natural products like flavonoids have been reported to find the inhibitors of SARS-CoV Mpro [41] for restraining coronavirus reproduction [23]. At present, there are several agents such as Remdesivir, Nirmatrelvir, and Molnupiravir are now used for the treatment of SARS-CoV-2 infection, however effective treatment options remain very limited.

Apparently, this study presented that some natural compounds i.e. polyphenol and flavonoid are categorized as anti-inflammatory substances which could inhibit inflammation by different acting mechanisms [42,43]. It is worth perceiving, those compounds have not only anti-inflammatory properties but also other biological activities such as antibacterial, antiviral, antioxidant, and inhibition of enzyme [44]. In the light of high-risk epidemic virus impact on human society, neither unique vaccine nor specific treatment to be used so far, thus some scientists delicate in exploring the potential drug against virus infection. Interestingly, combinations of some natural compounds performed in enzymatic assay have been reported to observe the unexpected and effective results in previous studies [45,46]. Furthermore, the investigation showed that anti-SARS-CoV-2 treatment could propose separately from two optional sites, one is from Host-based side ACE2 and the other one is Virus-based side (targets as shown in this study). The first line emphasizes when host was infected by virus, the immune cells would attack the pathogens to destroy them and produce the equivalent antibody for defending and protecting the host. In the second step, applicable
drug would help the host to prevent or cease virus invasion via interfering virus cell cycle or thwart the S-protein attached the host cell membrane by inhibiting interaction between the virus and the host cell receptor [47]. Therefore, some antiviral drugs were available to suppress the coronavirus reproduction i.e. Remdesivir which is an adenosine analogue can insert the viral RNA and lead to stopping viral mutation. Besides, the Chloroquine also has revealed that it could interfere the glycosylation of SARS-CoV-2 and block the virus’ membrane to fuse into host cell [48]. Remarkably, some clinical drugs such as protease inhibitor (Paxlovid) [49], adenosine analogue (Remdesivir) [50], and antiretroviral drug (Darunavir) [51] were used in this study as the positive control to do the comparisons with tested natural compounds for partial validation of virtual screen. Additionally, RdRp also plays the other core character at SARS-CoV-2 replication; thereby, a plethora of researches was dedicated in inhibiting the activity of RNA-directed 5’−3’ polymerase [52]. Due to time consuming of new drug discovery and development, the current anti-virus drugs repossession were considered at the beginning of COVID-19 pandemic for an urgent need. Hence, nucleotide inhibitors such as Sofosbuvir, Ribavirin, Galidesivir, Remdesivir, Favipiravir, Cefuroxime, Tenofovir, and Hydroxychloroquine have been demonstrated at in silico study against RdRp to restrict COVID-19 replication [53]. Unfortunately, based on the adverse or side effects from the repurposed drugs, phytomedicines such as natural products, essential oil, and extraction from herbal plants might play a vital role to moderate those effects and conduct the therapeutic regimes due to less adverse effect of phytomolecules. In computational screen, accumulative evidence demonstrated that Gingerol, Rutin, Luteolin, Alovianolic acid A, rosmarinic acid, and p-coumaric acid exerted an unexpected stronger binding affinity with RdRp when compared with repurposed anti-virus drugs [54,55]. It is worth to mention that essential oil compounds were reported as an anti-COVID-19 RdRp treatment via molecular docking aspect [56]. Especially, the previously research portrayed in molecular docking perspective that is small interfering RNA (siRNA) also was applied in silencing the post-transcriptional gene of COVID-19 by encoding RdRp gene sequence and turning off gene expression [57].

Taken a deep insight of drug development, anti-COVID-19 regime could be divided into three strategies such as virus entry, virus proliferation, and immune evasion which could attribute to interact with ACE2-RBD, proteases as well as RdRp, and endoribonuclease. Thereby, according to National Institutes of Health COVID-19 treatment guidelines, a plenty of antiviral drugs are approved by EAU or under evaluated for combating with COVID-19 such as Remdesivir, Chloroquine, Hydroxychloroquine, Azithromycin, Ivermectin, HIV protease inhibitors, and Nitozoxanide etc.; moreover, Zanamivir, Indinavir, Saquinavir, and Remdesivir are among the exciting hits on the Mpro proteinase [58]. Unfortunately, those drugs still bring some undesirable adverse effects to patients. Taking Remdesivir for an instance, it can cause the gastrointestinal symptoms (disorder), elevated transaminase levels as well as prothrombin time, and hypersensitivity reactions [59,60]; moreover, if taking Chloroquine or Hydroxychloroquine for the treatment of COVID-19 patients that would induce some cardiovascular problems such as QTc prolongation, Torsades de Pointes, ventricular arrhythmia, and cardiac deaths [61]. Clinically, the adverse effects of Ivermectin would be dizziness, pruritis, nausea, diarrhea, and neurological side effects [62]; additionally, the HIV protease inhibitors would induce nausea, vomiting, and diarrhea [63]. Therefore, in previous research indicated that a traditional Chinese medicine formula could disrupt the progression of COVID-19 [64]; and this formula was composed of several bioactive compounds i.e. alkaloids, flavones, and flavonoids as well as those phytochemicals have been studied in numerous pharmaceutical activities such as anti-virus, anti-inflammatory, antioxidant etc.[65–71]. Remarkably, the investigation showed that 3CLpro and PLpro are the crucial targets to discover and develop the anti-coronavirus (SARS-CoV, MERS-CoV) drug design [72]. Furthermore, many studies have demonstrated that the bioactivities of several chemicals such as polyphenols (Catechin galate, ECGC, Gallicatechin galate (GCG), 4-O-methylbavachalcone, Resveratrol, Tannic acid, 3-isooheflavin-3-galate (TF2B); flavonoids (Herbacetin, Bavachinin, Nebioavaisofflane, Apigenin, Luteolin, Myricetin, Scutellarein, Sinigrin, Hesperetin, Quercetin); benzopyrans (Psoralidin, Corylifol A, Pectolinarin); protease (Tomentin); chalcones (Isoboavachalcone); indoles (Indigo); saccharides (Rhoifolin), tetra-O-galloyl-beta-D-glucose (TTG); Glucosinolates (sinigrin); and Anthraquinones (aloe emodin) have been suggested to inhibit Mpro and PLpro which are an essential role to impact the coronavirus cell cycle by in vitro and in silico study [72–79]. Particularly, flavonoids (Herbacetin, Rhoifolin, and Pectolinarin) were found to efficiently block the enzymatic activity of SARS-CoV Mpro [23]; additionally, Kaempferol, Quercetin, and Rutin have the potential to be developed as novel inhibitors of SARS-CoV-2 Mpro with a comparable/higher potency as that of Remdesivir [80]. Furthermore, four HCV protease inhibitor drugs, Simeprevir, Vaniprevir, Paritaprevir, and Grazoprevir with Remdesivir inhibit the SARS-CoV-2 PLpro [81]. One study showed that Amentoflavone, Rubiosanidine B, Savinin, Psoralidin, Hirsutene, and Papyriflavonol A are good drug candidate for the search of antibiotics against PLpro and Mpro [82]. Nine natural biflavones were also confirmed to be effective PLpro inhibitors with IC50 values ranging from 9.5 to 43.2 μM via anti-proteolytic activity determination [83].

Considering first location of SARS-CoV-2 infection occurred in the airway mucosa or lung of most patients, and most oral drugs can’t attain the sufficient anti-viral concentration. The in situ (local) drug administration by inhalation spray can afford a locally effective dose to solve some of liabilities such as instability, poor solubility, low bioavailability, poor selectivity, and multiple modes of assay interference particular in curcinomids. Fascinatingly, a curcumin-based spray formulation for anti-SARS-CoV-2 treatment was developed and has finished phase 2 clinical trial [84], and delivers a very important application value in drug formulation and treated strategy designs for the anti-SARS-CoV-2 candidate that targeting on viral S-protein, especially infected prevention.

Of note, PLpro of SARS-CoV-2 is not only a core character in virus translation/rePLICATION but also is a serious issue to explore from immune evasion standpoint. Thereby, PLpro of SARS-CoV-2 could reverse the post-translational modification of cellular proteins conjugated with ubiquitin or (Ub) or Ub-like interferon-stimulated gene product 15 (ISG15) via deubiquitination and delSGylation process [85]. Additionally, Pro-ISG15 cleavage assays further demonstrated that several biflavones exhibited potent inhibitory effects against PLpro-mediated delSGylation, a key process involved in viral immune evasion [83]. Furthermore, ORF8-IRF3 (open-reading frame 8-interferon regulatory factor 3) complex could induce the endoplasmic reticulum stress that COVID-19 virus should evade from host immune response [86]. Moreover, a computational molecular study found that the potent inhibitors (Quercetin, 3-O-“(6-galloyl)-betao-galactopyranosid, Tribuloside, and Rutin) could prevent the immune evasion of Covid-19 [87]. And NSP10–NSP16 were demonstrated that they could avoid SARS-CoV-2 from detecting by immune recognition of host cell, a pervious study suggested that Mitocurcumin (MC) could potentially inhibit the activity of NSP3 [88]. Taken a deep insight into long COVID and multi-system inflammatory syndrome in Children (MIS-C) has been realized a critical and emerging issue for society health. Clinically, the common diagnosis of MSI-C contains fever, severe illness, and the involvement of two or more organ systems failure; while some clinical characters of MIS-C resemble Kawasaki Disease, toxic shock syndrome (TSS), and secondary hemophagocytic lymphohistiocytosis/macrophage activation syndrome [89].
Clinically, dexamethasone (a synthetic corticosteroid) would limit the production of and damaging effect of the cytokines and may be useful for the short-term in severe, intubated, COVID-19 patients, but will also inhibit the protective function of T cells and block B cells from making antibodies, potentially leading to increased plasma viral load that will persist after a patient survives SARS. These corticosteroids could be given together with the natural flavonoid quercetin and luteolin because of theirs antiviral and anti-inflammatory properties, especially its ability to inhibit mast cells, which are the main source of cytokines in the lungs [90]. Moreover, phytochemicals flavonoids exhibit a high safety profile, suitable bioavailability, and no significant adverse effects [91]. Notably, there severe inflammation and cytokine storms are the most fatal etiology of COVID-19. There are several scientific reports of phytochemicals can bind and affect COVID-19 relative cytokines pathways, such as curcumin, quercetin, kaempferol, and luteolin can form interaction with TNF, IL-6, and nuclear factor kappa-light chain enhancer of activated B cells (NF-κB) [92–94]. As anti-inflammatory role of dexamethasone, phytochemicals can also interfere cytokine production, affect inflammatory response and attenuate immunity with less intense of adverse effect when compared with dexamethasone.

The adjuvant co-supplementation of 168 mg curcumin, 260 mg quercetin, and 9 μg (360 IU) of cholecalciferol (Vitamin D3) may possibly have a therapeutic role in the early stage of COVID-19 infection including resolution of acute symptoms, and modulation of the hyperinflammatory response to moderate symptoms of COVID-19 [95].

Focused on flavonoids, especially epicatechin, EGCG, hesperidin, naringenin, quercetin, rutin, luteolin, baicalin, diosmin, genistein, biochanin A, and silymarin, which can counteract the virus-mediated elevated levels of inflammatory cytokines leading to multiple organ failure in silico, in vitro, and in vivo findings [96]. Flavonoids such as quercetin, genistein, apigenin, kaempferol, and epigallocatechin 3-gallate modulate the expression and activation of cytokines such as IL-1, TNF-α, IL-6, and IL-8; regulate the gene expression of many pro-inflammatory molecules such as NF-κB, activator protein-1 (AP-1), intercellular adhesion molecule-1 (ICAM), vascular cell adhesion molecule-1 (VCAM), and E-selectins; and also inhibits inducible nitric oxide (NO) synthase, cyclooxygenase-2 (COX-2), and lipoxigenase, which are pro-inflammatory enzymes [97]. Based on the observations, taken 1000 mg quercetin daily plus the antiviral drugs Remdesivir or Favipiravir is safe and effective in lowering the serum levels of ALP, q-PCR, and LDH as critical markers involved in COVID-19 severity [98]. There is evidence that vitamin C and quercetin co-administration exerts a synergistic antiviral action due to overlapping antiviral and immunomodulatory properties and the capacity of ascorbate to recycle quercetin, increasing its efficacy as an adjunct to Remdesivir [99]. Squalene has been applied as an adjuvant of COVID-19 vaccine to augment protective immunity [100]. There are several clinical trials of phytochemicals used for the COVID-19 treatments within three years, include quercetin, isorhamnetin, and curcumin. The treated dose of quercetin between 400 and 1000 mg/daily (NCT04578158, NCT04377789, NCT04861298), isorhamnetin between 500 and 1000 mg/daily (NCT04622865, NCT04536090), and curcumin between 150 and 500 mg/daily [94]. Some of those clinical trial of all three phytochemicals have been entered phase 2 or phase 3, indicating those phytochemicals have the potential to be the candidate drugs for COVID-19 treatment. Of note, the most use dosage of phytochemicals is higher due to lower bioavailability, less toxicity, and few adverse events. Moreover, herb-herb interactions or herb-drug interactions need to be taken into deep insight.

Unfortunately, there are not any appropriate approach as well as precision medicine to combat SARS-CoV-2 infection. Hereafter, this study was tried to find the candidate phytotherapeutics for battling the COVID-19 pandemic crisis. Henceforth, the search of anti-COVID from natural compounds (phytochemicals) as phytotherapeutics according to anti-inflammation, or underwent anti-virus drugs to investigate the potential hits against the epidemic virus particular SARS-CoV-2 for discovery and development of new drug. Notably, compared with in silico results, the reconfirmation of Vitamin K, Amentoflavone, EGCG, Sapogenins, Aconitine, Curcumin, Arachidonic acid, and Rutin have highly prospective to become a hit of natural products against the epidemic virus particular SARS-CoV-2 (COVID-19) based on multi-targets effects for blocking viral infection through invasion/activation, transcription/reproduction, and posttranscriptional cleavage.

Until now, in the face of the rapid mutation of SARS-CoV-2 and the continuous emergence of new mutant variants, based on the single targeting vaccination or treated strategies to fight with COVID-19 can only acquire a limited result. It is important and urgent to formulate the more comprehensively integrated therapeutic or preventive strategies for SARS-CoV-2 infection, replication, immune evasion and host immune response. Conclusively, this study provides a new or novel in silico evidence-based therapeutic perspective for developing the multi-target or cocktail therapies as HIV for combatting the COVID-19 pandemics.

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Conflicts of Interest

The authors declare no conflict of interest.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jiph.2022.11.022.

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