Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Polyacylated anthocyanins constructively network with catalytic dyad residues of 3CL^{pro} of 2019-nCoV than monomeric anthocyanins: A structural-relationship activity study with 10 anthocyanins using *in-silico* approaches

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ABSTRACT

Coronavirus epidemic 2019 (COVID-19), caused by novel coronavirus (2019-nCoV), is newly increasing worldwide and elevating global health concerns. Similar to SARS-CoV and MERS-CoV, the viral key 3-chymotrypsin-like cysteine protease enzyme (3CL^{Pro}), which controls 2019-nCoV duplications and manages its life cycle, could be pointed as a drug discovery target. Herein, we theoretically studied the binding ability of 10 structurally different anthocyanins with the catalytic dyad residues of 3CL^{pro} of 2019-nCoV using molecular docking modelling. The results revealed that the polyacylated anthocyanins, including phacelianin, gentiodelphin, cyanodelphin, and tecophilin, were found to authentically bind with the receptor binding site and catalytic dyad (Cys145 and His41) of 2019-nCoV-3CL^{pro}. Our analyses revealed that the top four hits might serve as potential anti-2019-nCoV leading molecules for further optimization and drug development process to combat COVID-19. This study unleashed that anthocyanins with specific structure could be used as effective anti-COVID-19 natural components.

1. Introduction

Nowadays, novel coronavirus (2019-nCoV) was reported in late 2019 and emerged as a hot research topic. The 2019-nCoV gained the immense attention of scientists all over the world. The discovery of its whole-genome sequence has helped researchers to quickly identify the virus in patients and try to control its symptoms [1,2]. The 2019-nCoV belongs to the β-coronavirus group, sharing ancestry with bat coronavirus HKU9-1, similar to SARS-coronaviruses that despite of sequence diversity its spike protein interacts with the human ACE_2-receptor [3]. By July 1, 2020, the global death toll reached 509,112 with 10,449,151 confirmed cases in 213 countries (https://www.worldometers.info/coronavirus).

Recent findings revealed that 2019-nCoV genes share >80.0% nucleotide identity, and 89.1% nucleotide similarity with SARS-CoV genes [4,5]. Generally, on the transcription of gene, ~800 kDa of polypeptide obtains from β-coronaviruses, which is proteolytically breakdown into numerous proteins. In addition, it was found that papain-like protease (3CL^{Pro}) controls the virus replication through leading the proteolytic processing. The 3CL^{Pro} cleaves the polyprotein at 11 different sites to produce numerous non-structural proteins [6]. Consequently, 3CL^{Pro} plays a key role in the virus duplication and unlike structural/accessory protein-encoding genes located at the 3' end which shows great variability [7]. Hence, it may be a potential target for the inhibitor of anti-COVID-19.

Studies based on the structural analysis have identified the potential inhibitors of MERS-CoV 3CL^{pro} and SARS-CoV [8].

Abbreviations: COVID-19, Coronavirus epidemic 2019; 2019-nCoV, Novel coronavirus; MOE 09, Molecular Operating Environment; 3CL^{pro}, Papain-like protease; MD, Molecular dynamic simulations.

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1093-3263/

Bioactive substances, especially anthocyanins, have drawn considerable attention owing to their potential for drug development against various diseases without exerting any side effects [9–12]. Anthocyanins belong to the widespread category of phenolic compounds, collectively known as flavonoids, and are mainly soluble in water with multifunction and health-promoting effects [13–15]. Anthocyanins have been found in 27 families of plants which have several protective effects, such as anti-inflammatory, anti-mutagenic [16], anti-oxidants, and most recently antiviral effects [17]. Moreover, in order to speed up the drug approval process and to find more effective inhibitors through new platforms as well as to improve the state of antiviral treatment, the method of computational drug discovery is highly reliable [18]. The discovery of new allosteric compounds against COVID-19 can help to eradicate the global epidemic. Thus, the first step is to find out the suitable molecules that have high efficiency of binding residues with the $3CL^{Pro}$. The initial screening of molecules through computational techniques will save time and efforts to develop fast and authentic therapies against COVID-19. Furthermore, this step will help to develop more effective *in vivo* trails for COVID-19.

Keeping in mind the literature review and to the best of our knowledge, few studies are available on the screening of various anthocyanins using computational approach against different viruses [19] but no report is available against COVID-19. Most importantly, it was hypothesized that the biological activities, including antiviral effects, of anthocyanins are structural-dependent. For example, it was found that hydroxyl (-OH) or methoxyl (-OCH_3) substitutions on the flavan nucleus, the number of −OH moieties in the molecule, the degree of methylation of −OH−moieties, the nature and/or the number of sugar moiety attached to aglycone molecule, and the specific position of these attachments are the main factors affecting the biological activity of anthocyanins [20–22]. Therefore, we selected 10 different anthocyanins in order to represent the different glycosylation and acylation patterns with various flavan and sugar moieties of anthocyanins. Therefore, this study was conducted to gain structural insights regarding the potential anti-COVID-19 effects of 10 structurally different anthocyanins that can target the $3CL^{Pro}$ of 2019-nCoV using *in silico* approaches (molecular docking and drug scan). The consequences of this research will help the researcher to improve the natural therapeutics against COVID-19.

2. Materials and methods

Simulation screening approach based on the structure was done using a high performance computational work station with the subsequent stipulations (Intel(R) Core(TM) i7-3210 M CPU @ 2.50 GHz, 5 Core(s) processor with 4.00 GB RAM and 64-bit Windows-10 Operating System). This simulation was conducted using Molecular Operating Environment (MOE 09).

2.1. Ligand database arrangement

The structures of 10 anthocyanins, including, cyanidin 3-glucoside (PubChem CID-441667), cyanidin 3-rutinoside (PubChem CID- 29232), pelargonidin 3-glucoside (PubChem CID-443648), cyanidin 3-O-[2″-O-(xylosyl) glucoside] 5-O-(6‴-O-malonyl) glucoside (PubChem CID-44256799), delphinidin 3-sambudiglucoside (PubChem CID-443648), cyanodelphin (PubChem CID-101193633), gentiodelphin (PubChem CID-11979365), phacelianin (PubChem CID-102176728), protocyanin (PubChem CID-100916164), and tecophilin (PubChem CID-122205992), were obtained from PubChem database. Remdesivir (PubChem CID-121304016) was used as a positive control. The optimization of anthocyanin and remdesivir structure for docking was done by adding partial charges as well as energy minimization using Protonate-3D and MMFF94X force field. The storage of optimized ligand files of 10 anthocyanins and remdesivir was done in the ligand database that was further used as a source of input file to conduct the docking studies.

2.2. Refinement of $3CL^{pro}$ of 2019-nCoV structure

The 3D structure of $3CL^{pro}$ of 2019-nCoV (PDB: 6y84) was obtained from the Protein Data Bank (http://www.rcsb.org) with a resolution of 2.16 Å. The water molecules and already bound ligands were removed from the structure to refine the structure of $3CL^{pro}$. Energy minimization and 3D protonation were conducted using MOE, and the minimized structure was then used in the subsequent steps [23].

2.3. Molecular docking and drug likeness analyses

The 10 anthocyanins with different structures and remdesivir were docked with the allosteric ligands of $3CL^{pro}$-2019-nCoV using MOE docking tool. Identification of potent binding sites was done using MOE site finder tool and subsequently taken by docking process. Ten suitable docked poses were produced by applying a scoring function London dG. Force field algorithm was then applied to refine the docking process and to keep the receptor rigid. From these, the most suitable molecules and interacting ligands were scrutinized based on RMSD (Root-Mean-Square Deviation) which is generally measured in terms of docking score, Angstrom (Å), and co-crystallized ligand. The LigX tool of MOE was used to analyze the ligand receptor binding, which revealed the potential residues interacting with ligands graphically. It also produces 2D-images signifying the forces stabilizing ligand molecules within the receptor's binding pockets [24]. For the analysis of drug likeness of 10 anthocyanins, all anthocyanins were filtered based on bearing appropriate molecular attributes to be anti-COVID-19 drug candidates. The predicted pharmacophore of phacelianin was also created [25].

2.4. Molecular dynamics simulations

To verify the results of the current study and to assess the binding performance and stability of phacelianin, molecular dynamic simulations (MD) based on clear solvent molecular dynamics were conducted using the homology model of SARS-CoV-2 $3CL^{pro}$. GROMOS software was used to run 50 ns of MD simulations following the previous protocol [26].

3. Results and discussion

Analysis of allosteric binding of 10 structural different anthocyanins with SARS-CoV-2 $3CL^{pro}$ showed several poses. We used the best pockets with low S-score to analyze the anti-COVID-19 potential of anthocyanins. Iterative docking of the best docked molecules within receptor pocket originally occupied by co crystallized inhibitor. The chemical structures of 10 structurally different anthocyanins and remdesivir used in this study are portrayed in Fig. 1. By analyzing the physicochemical parameters of SARS-CoV-2 $3CL^{pro}$, it was found that the enzyme consisted of 306 residues with chain type of polypeptide (L) with a molecular weight of 33.796 kDa, categorizing the protein as a stable, hydrophilic molecule capable of establishing H-bonds with other ligands (Fig. 2). Recently, it was found that the sequence of SARS-CoV-2 $3CL^{pro}$ clustered with bat SARS-like coronaviruses and sharing 99.02% sequence identity [3]. Furthermore, it was found that SARS-CoV-2 is more comparable to SARS-CoV than MERS-CoV, and shares

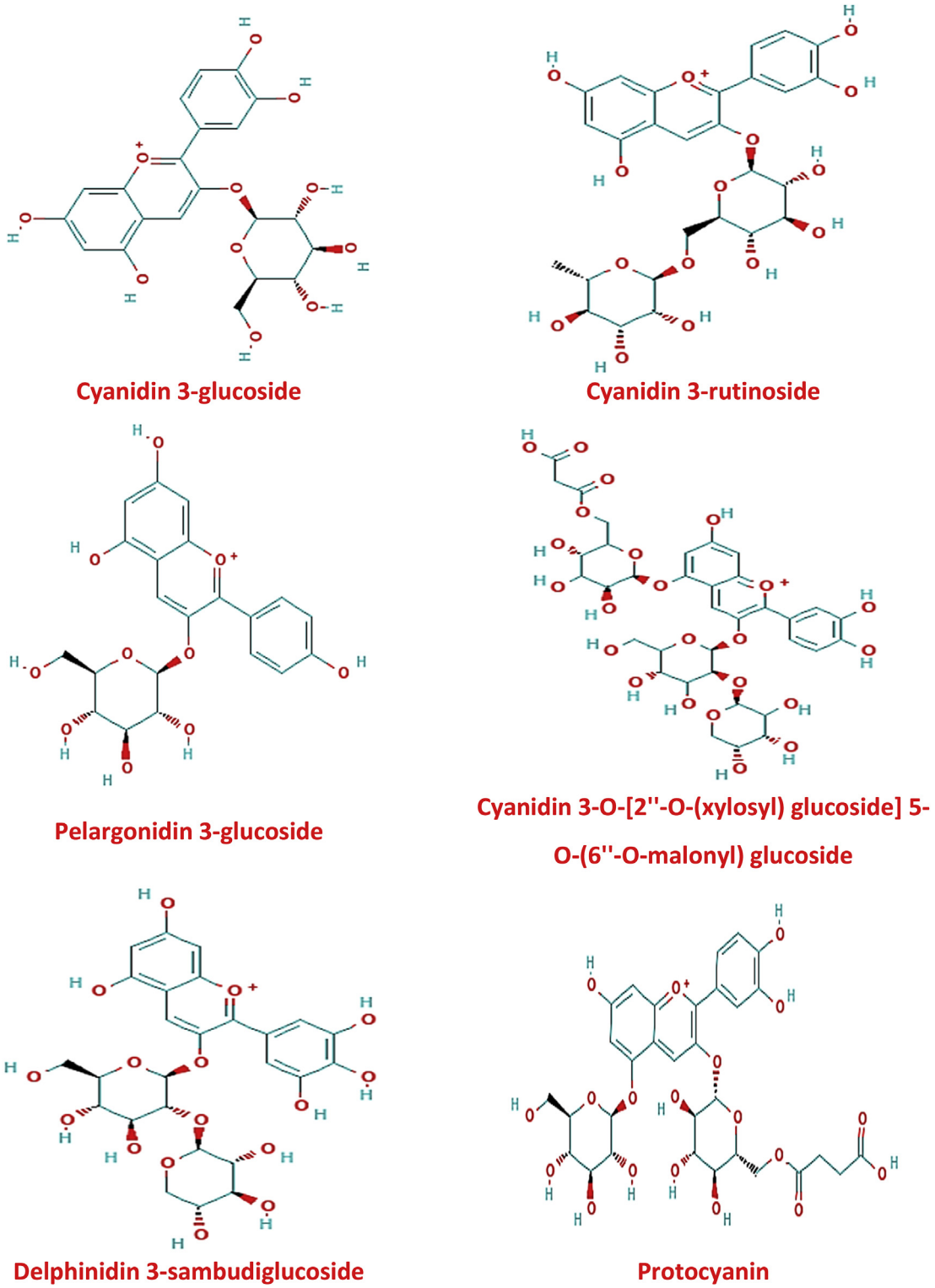
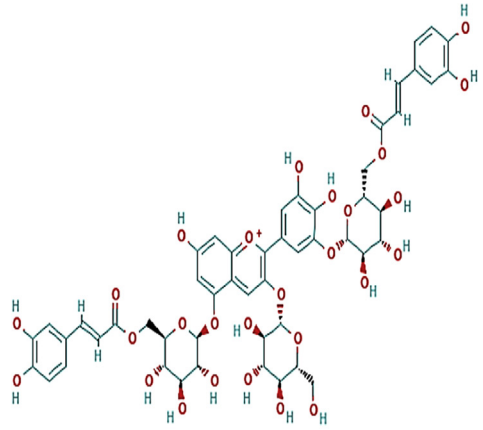


Fig. 1. 2D-chemical structures of 10 structurally different anthocyanins and remdesivir as a control.

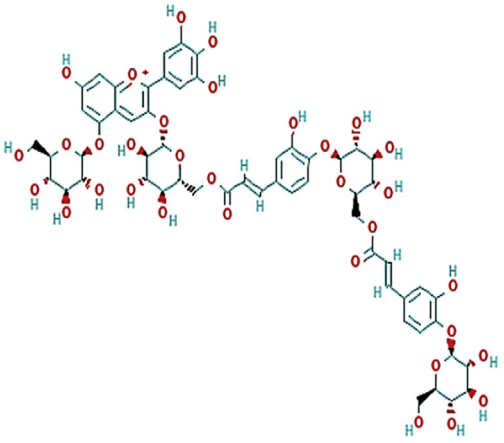
a mutual forebear with bat coronaviruses [26,27]. The results also discovered that SARS-CoV-2 has a Cys-His catalytic dyad (Cys145 and His41), reliable with SARS $3CL^{pro}$ (Cys145 and His41), TGEV $3CL^{pro}$ (Cys144 and His41), and HCoV $3CL^{pro}$ (Cys144 and His41) [28]. It was disclosed that the SARS-CoV-2 $3CL^{pro}$ receptor-binding pocket conformation resembles with the binding pocket of SARS-CoV $3CL^{pro}$ and increases the possibility that inhibitors intended for SARS-CoV $3CL^{pro}$ may also inhibit the activity of SARS-CoV-2

$3CL^{pro}$.

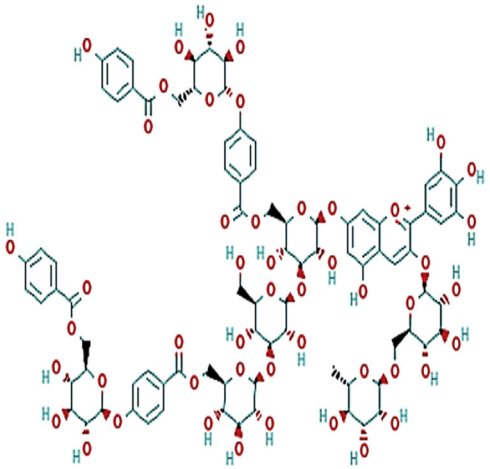
To manage with the constant need of a novel and effective small molecule as anti-COVID-19 therapeutics with negligible side effects, research is now directing more on computational drug discovery [29]. To fasten the drug approval procedure and to discover more efficacious inhibitors with a novel structure that can improve the antiviral therapeutics status, computational drug discovery approaches are highly reliable. From the ground-breaking



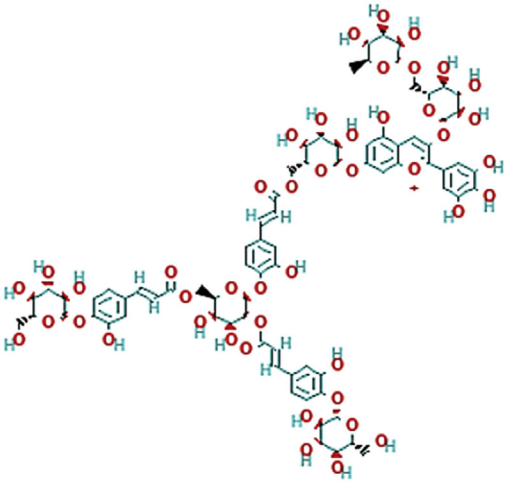
Gentiodelphin



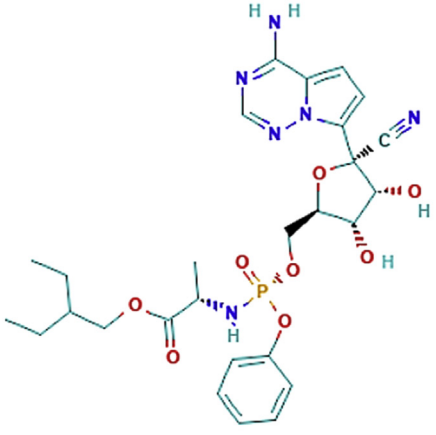
Phacelianin



Cyanodelphin

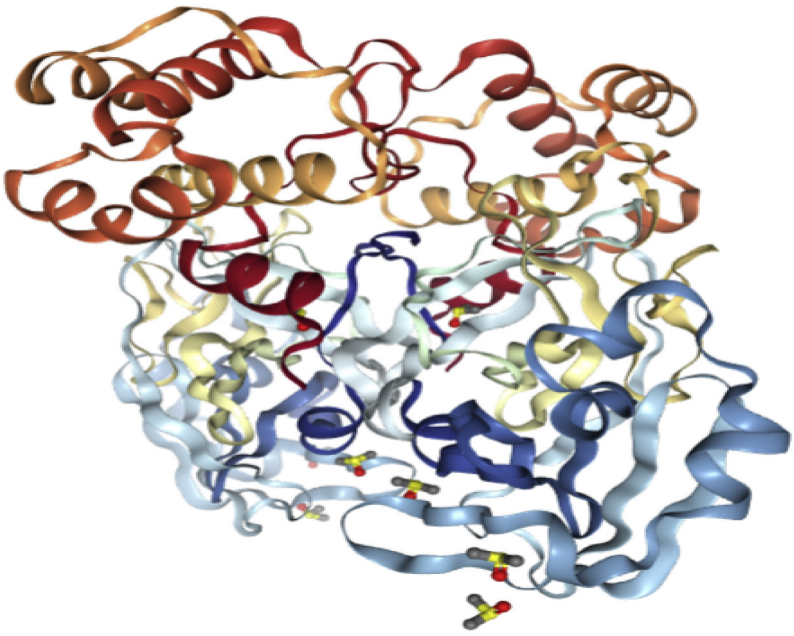


Tecophilin



Remdesivir

Fig. 1. (*continued*).



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SGFRKMAFPS GKVEGCMVQV TCGTTTLNGL WLDDVVYCPR HVICTSEDML
           HHHHTTEEEE EETTEEEEEE EETTEEEEEG GGG  TTGGG

NPNYEDLLIR KSNHNFLVQA GNVQLRVIGH SMQNCVLKLK VDTANPKTPK
S  HHHHHHT   GGGEEEEE TTEEE EEEE EEETTEEEEE ESS  TT  E

YKFVRIQPGQ TFSVLACYNG SPSGVYQCAM RPNFTIKGSF LNGSCGSVGF
EEE    TT  EEEEEEEETT EEEEEEEEE   TTS B      TT TT EEE

NIDYDCVSFC YMHHMELPTG VHAGTDLEGN FYGPFVDRQT AQAAGTDTTI
EEETTEEEEE EEEEEE TTS  EEEE TTS  BSTT  SSSS         B

TVNVLAWLYA AVINGDRWFL NRFTTTLNDF NLVAMKYNYE PLTQDHVDIL
HHHHHHHHHH HHHTT  TT   S    HHHH HHHHHHTTB     HHHHHHT

GPLSAQTGIA VLDMCASLKE LLQNGMNGRT ILGSALLEDE FTPFDVVRQC
HHHHHHH    HHHHHHHHHH HHHH  TT   BTTBSS       HHHHHHHH

SGVTFQ
HT
```

Fig. 2. The 3D-chemical structures of $3CL^{pro}$ enzyme of 2019-nCoV and its sequence.

detail of structural diversity among anthocyanins, virtual screening was done to discover novel allosteric compounds as anti-COVID-19. The allosteric regulation has been reported as an effective strategy to attain irreversible inhibition. The spatial orientation and dock score of current reported four top-ranked leads to the efficient binding of functional residues with maximum binding affinity. These anthocyanins meet the drug likelihood criteria are tabulated in Table 1 and may prove excellent ready to use as a starting point. Previously, multiple studies confirmed the potential antiviral effects of anthocyanins [30–32].

Binding affinity analysis of 10 structural different anthocyanins and/or remdesivir through LigX is portrayed in Fig. 3. It was revealed that 10 anthocyanins differentially interacted with different residues of SARS-CoV-2 $3CL^{pro}$ in a structural-dependent manner. In details, phacelianin showed the best anthocyanins, where it could bind with 19 amino acid residues of SARS-CoV-2 $3CL^{pro}$ and there are 4 H-bonding forces have been occurred. Most importantly, phacelianin directly interacted with His41 and Cys145 through H-bonding forces, showing its ability to interact with the catalytic dyad residues of $3CL^{pro}$. Structurally, phacelianin

Table 1
The top five poses of the interaction between 10 structural different anthocyanins or remdesivir with the catalytic dyad residues of $3CL^{pro}$ of 2019-nCoV and their docking properties.

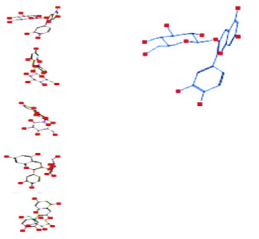
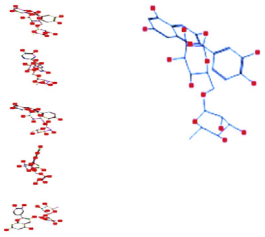
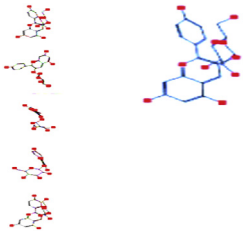
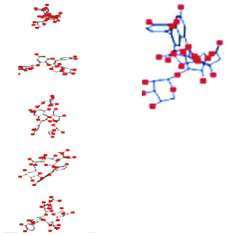
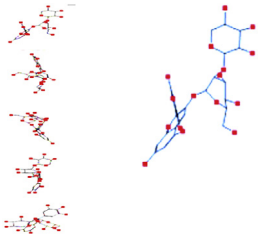
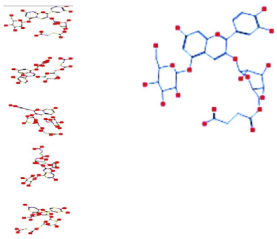
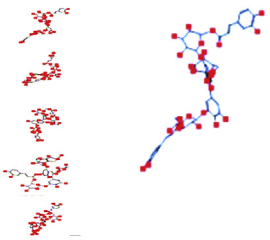
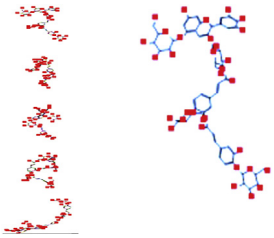
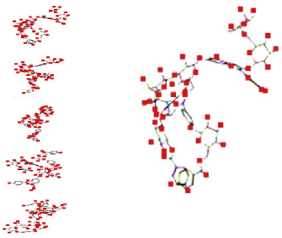
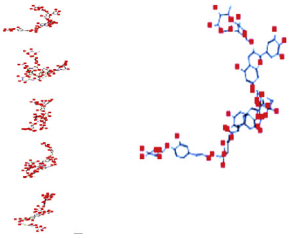
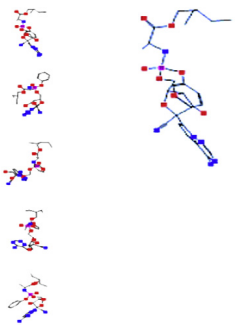
Anthocyanins	Mol	S	E-conf	E-place	E-score
Cyanidin 3-glucoside		**−16.63**	**−87.31**	**−86.57**	**−14.17**
Cyanidin 3-rutinoside		−22.96	0.76	−118.85	−17.02
Pelargonidin 3-glucoside		−17.14	−180.77	−100.22	−13.59
Cyanidin 3-O-[2″-O-(xylosyl) glucoside] 5-O-(6″-O-malonyl) glucoside		−20.06	−171.52	−59.58	−13.81
Delphinidin 3-sambudiglucoside		−16.98	59.85	−76.90	−15.88
Protocyanin		−22.62	−92.65	−47.68	−13.72

Table 1 (*continued*)

Anthocyanins	Mol	S	E-conf	E-place	E-score
Gentiodelphin		−30.02	−55.44	−122.81	−12.70
Phacelianin		−36.30	294.18	−94.72	−14.59
Cyanodelphin		−33.36	466.05	−71.01	−14.04
Tecophilin		−35.53	126.04	−61.39	−9.72
Remdesivir		−23.89	2.64	−68.15	−11.43

Mol: An output pose.
S: The final score, which is the score of the last stage that was not set to None.
E-conf: The energy of the conformer.
E-place: Score from the placement stage.
E-score: Score from the rescoring stage.

is a polyacylated anthocyanin that has linear (poly) acylated chains on the C-ring and linked to a flavonoid moiety with sufficient conformational flexibility [33].

Likewise, gentiodelphin, cyanodelphin, and tecophilin directly networked with His41 via H-bonding and indirectly assembled with Cys145. Results also showed that pelargonidin 3-glucoside, cyanidin 3-rutinoside, cyanidin 3-O-[2″-O-(xylosyl) glucoside] 5-O-(6″-O-malonyl) glucoside, and delphinidin 3-sambudiglucoside have been secondarily interacted with both of His41 and Cys145, showing their partial influence on the catalytic dyad residues of $3CL^{pro}$. On the other hand, cyanidin 3-glucoside and protocyanin neither interact with His41 nor Cys145; however, both of these have been networked with 7 and 8 amino acid residues of $3CL^{pro}$ via H-bonding and metal contact, respectively. The crucial catalytic residues of pocket spatial position of phacelianin is stabilized within the pocket with the lowest S-score (−36.30) and interacted

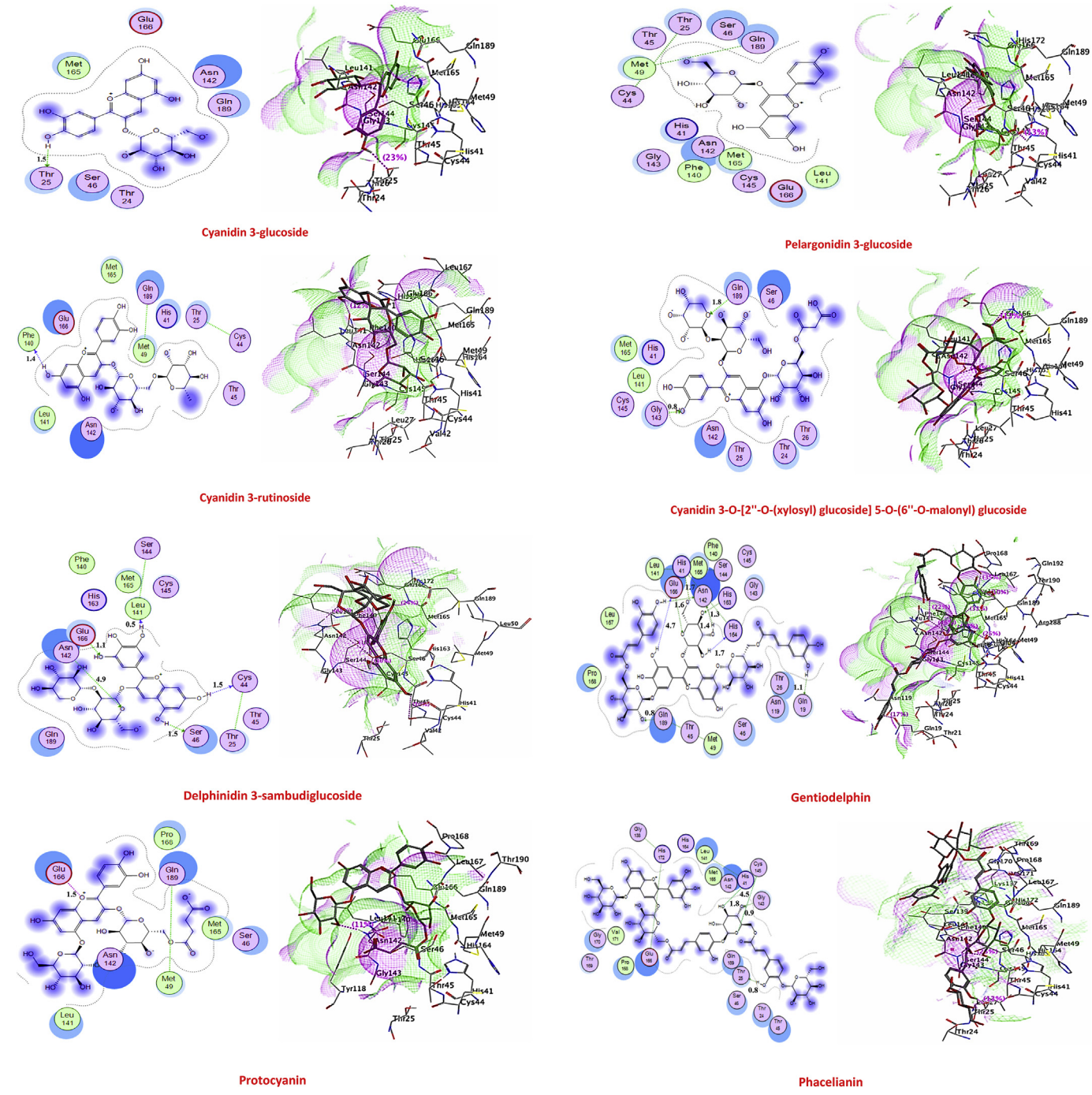


Fig. 3. LigX interaction diagram representing binding pattern of 10 structural different anthocyanins and remdesivir with binding pocket residues of $3CL^{pro}$ enzyme of 2019-nCoV.

with Cly138, His 172, His 164, Leu 141, Met 155, Asn 142, His41, Cys145, Gly 143, Gly 170, Val 171, Thr159, Pro 153, Glu 155, Gln 189, Thr25, Ser 46, Thr24, and Thr45. The difference in the binding ability of each anthocyanin with SARS-CoV-2 $3CL^{pro}$ may be due to their structure-based relationship activity.

These results identified at least four novel non-toxic and drug-gable natural anthocyanins that are predicted to bind with the receptor binding site and catalytic dyad (Cys-145 and His-41) of SARS-CoV-2 $3CL^{pro}$ (Fig. S1). Among these anthocyanins, phacelianin strongly interacted with the catalytic dyad residues (Cys-145 and His-41) of SARS-CoV-2 $3CL^{pro}$, with sense binding affinity and docking score. Previously, phacelianin, gentiodelphin, cyanodelphin, and tecophilin which could be extracted from the blue flowers, such as the blue petals of *Phacelia campanularia*, *Gentiana makinoi*, and *Delphinium hybridum*, showed some biological activities [17,33]. Looking at the antiviral drug potential of the aforenoted anthocyanins, the current study is an endeavor to exploit the chemical nature of three anthocyanins as anti-COVID-

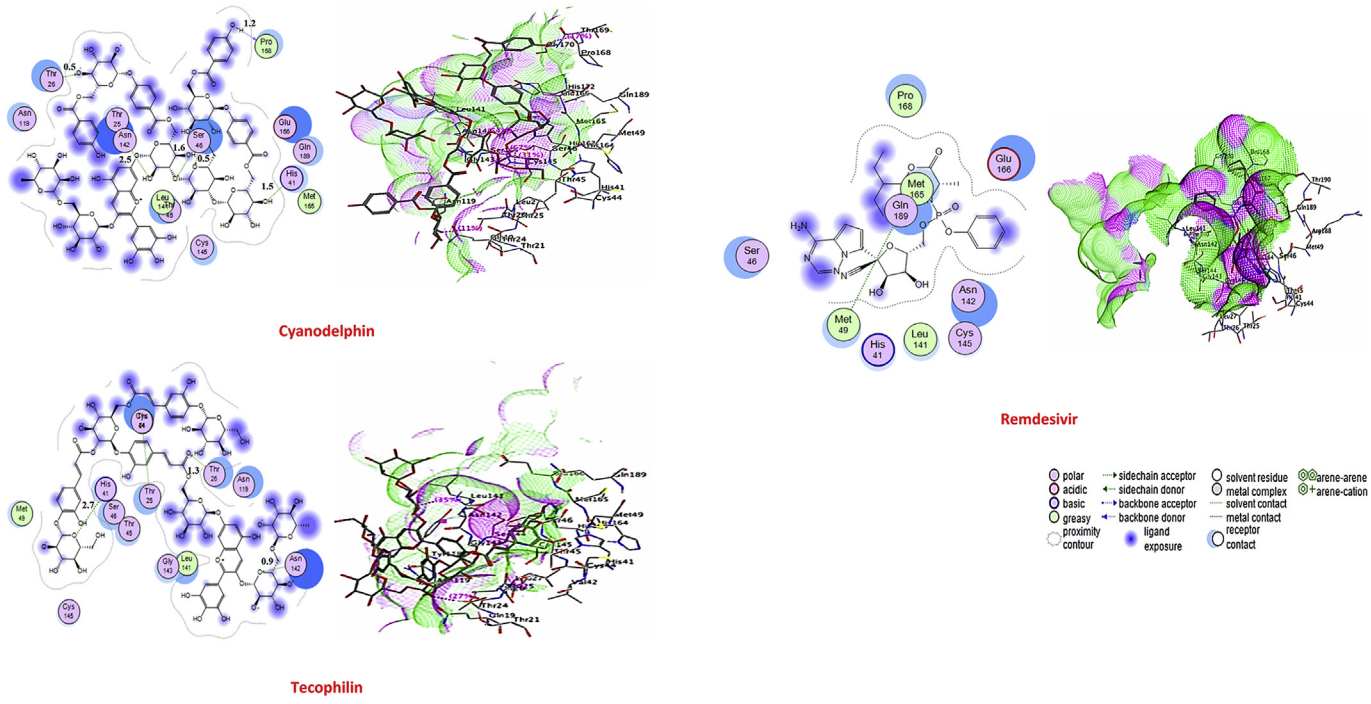


Fig. 3. (*continued*).

19. The current molecular docking study unleashed the importance of the binding of anthocyanins with SARS-CoV-2 $3CL^{pro}$, which successfully blocked both His41 and Cys145. Comparing with remdesivir as an antiviral control-based drug, polyacylated anthocyanins such as phacelianin, gentiodelphin, cyanodelphin, and tecophilin blocked the catalytic dyad residues of SARS-CoV-2 $3CL^{pro}$ better than remdesivir, where these anthocyanins directly interacted with His41 and Cys145. Inversely, the monomeric anthocyanins exerted the same effects with remdesivir as both of them weakly interacted with the catalytic dyad residues of SARS-CoV-2 $3CL^{pro}$. This mostly because of the different mode of action of remdesivir on SARS-CoV-2. It was recently disclosed that remdesivir could mitigate SARS-CoV-2 by acting as RdRp inhibitors [34,35].

On the other hand, it was recently reviewed that anthocyanins are more bioavailable than previously envisaged [36]. The vast majority of animal and human pharmacokinetics studies suggested that anthocyanins are directly absorbed through stomach transporters, intestinal glucose transporters, and tight junction permeability sites, and their metabolites could be identified in the blood within 30–90 min of consumption. In total around 16 phenolic catabolites were derived from anthocyanins, where ferulic, isoferulic benzoic, phenylacetic, and caffeic acid derivatives were the main anthocyanins' metabolites. Meanwhile, the health effects of anthocyanin's intake are probably a consequence of the biological activity of their metabolites, showing the importance of consuming anthocyanins-rich diets [22,36].

To verify the drug ability of selected anthocyanins, ligand properties were calculated with the LigX tool of MOE. All selected anthocyanins showed positive results and fulfilled the criteria of the Lipinski's rule of five [24]. The rule describes that potential drug like compounds should not have more than 5 H-bond donors, maximum 10 H-bond acceptors, and an octanol water partition coefficient log P not greater than 5. These results suggest that natural products identified in our study, especially phacelianin, gentiodelphin, cyanodelphin, and tecophilin, may prove more useful candidates for COVID-19 drug therapy. To further examine the molecular docking results, phacelianin was subjected to MD simulation and RMSD, the radius of gyration (RoG), and H-bond parameters were expressed [37]. Phacelianin-SARS-CoV-2 $3CL^{pro}$-complex did not show any obvious fluctuations, referring to the stability of anthocyanin-enzyme complexes with average RMSD values of 1.6 ± 0.01 Å (Fig. S2A). It was also suggested that the normal behavior for phacelianin-SARS-CoV-2 $3CL^{pro}$ complex; where it was remained compact and stable throughout the 50 ns of MD simulations (Fig. S2B). Likewise, H-bonds, which are the key stabilizing forces in proteins, suggested that the phacelianin-SARS-CoV-2 $3CL^{pro}$ complex remains stable throughout the simulation, with no obvious fluctuations (Fig. S2C). It can be concluded from this study that each of phacelianin, gentiodelphin, cyanodelphin, and tecophilin and their sources such as pomegranates may serve as possible anti-SARS-CoV-2 drug sources. Phacelianin is a form of anthocyanins flavonoid. Hydroxy groups (-OH), ketone groups (=O) and O^{+} groups in phacelianin are predicted to play a key role in the interaction with the amino acid residue at the active site of SARS-CoV-2 $3CL^{pro}$ (Fig. 4).

4. Conclusion

In conclusion, our study revealed that some medicinal plants rich in anthocyanins, especially phacelianin, gentiodelphin, cyanodelphin, and tecophilin, could be theoretically used to treat the outbreak of COVID-19. We screened the structural relationship activity of 10 anthocyanins as potential antiviral components. We found that the polyacylated anthocyanins are better than both of diacylated and monomeric anthocyanins that may inhibit SARS-CoV-2 $3CL^{pro}$ and then the virus replication. Further, *in vitro* and *in vivo* studies are needed to transmute these potential anthocyanins inhibitors into clinical drugs. We predict that the understandings obtained in the current study may evidence valued for discovering and unindustrialized novel natural anti-COVID-19 therapeutic agents in the near future.

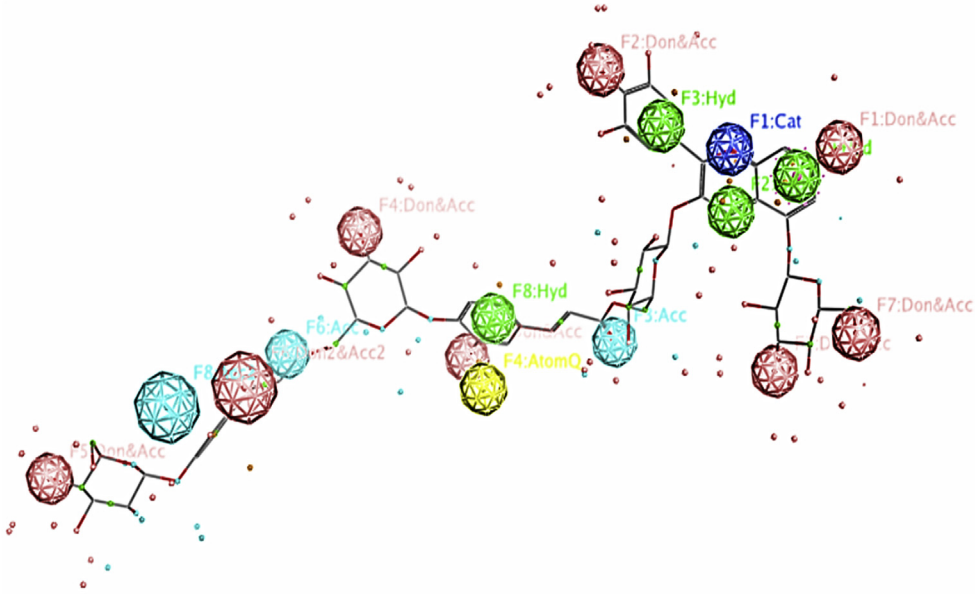


Fig. 4. Phacelianin mapped to the suspected pharmacophore model.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jmgm.2020.107690.

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