Original article

The potential of Paritaprevir and Emetine as inhibitors of SARS-CoV-2 RdRp

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA-dependent RNA polymerase (RdRp) is a well-characterized therapeutic target which is a key player driving the viral replication and transcription machinery. The recent elucidation of the experimental structure of SARS-CoV-2 RdRp enzyme complexed with triphosphate form of Remdesivir (RTP) has opened an avenue for structure-based identification of potent inhibitors. Given the high mortality rate of the coronavirus disease 2019 (COVID-19) and lack of effective therapeutics against it, an alternative for safe and speedy drug discovery needs to be sought after. One promising strategy could be to explore the possibility for repurposing the Food and Drug Administration (FDA) approved antiviral drugs and antiviral phytocompounds. In the present study, a set of FDA approved antiviral drugs and antiviral phytocompounds were screened for their ability to bind within the RdRp enzyme active pocket. The top 3 hits among the FDA approved drugs were Paritaprevir (D33), Rilpivirine (D19) and Simeprevir (D31) which scored binding energies between $-8.08$ kcal/mol and $-10.46$ kcal/mol. Emetine (P5), 7,4-di-O-galloyltricetifavan (P28) and Oleanolic acid (P17) were the top three phytocompounds hits and exhibited binding energies ranging from $-7.81$ kcal/mol to $-8.17$ kcal/mol. These drugs and phytocompounds were able to establish hydrogen bonds with the catalytic residues-Asp760 and Asp761 and hydrophobic interactions with neighbouring residues. Further, the physicochemical properties of the molecules were evaluated. These identified potential inhibitors warrant further experimental investigations before their acceptance as drug candidates for the treatment of the disease.

1. Introduction

The novel coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a pandemic known as coronavirus disease 2019 (COVID-19). Since its first report from Wuhan, Hubei Province of China in December 2019 (Chan et al., 2020), the disease has spread rapidly across nations with unprecedented deaths and infections worldwide. The human-to-human SARS-CoV-2 infection and the paucity of effective prophylactics, drugs and vaccines have made it difficult to control the pathogenesis of the disease caused by the virus (Chen et al., 2020). SARS-CoV-2 belongs to the Betacoronavirus genus and it is a positive-stranded RNA virus whose replication and transcription processes are mediated by non-structural proteins (nspS) which are formed from the cleavage of viral polyproteins (pp1a and pp1ab) (Ziebuhr, 2005). The multi-domain protein known as RNA-dependent RNA polymerase (RdRp) catalyses the formation of phosphodiester bonds between ribonucleotides in presence of divalent metal ion using RNA as template (Jia and Gong, 2019; Venkataraman et al., 2018). RdRp (nsp12) is the most essential component of the replication/transcription machinery. While nsp12 catalyses the synthesis of viral RNA, nsp7 and nsp8 are key cofactors which help the RNA polymerase in its catalytic
functions and confers processivity to it (Subissi et al., 2014). The replication fidelity is maintained by the exonuclease activity with the proofreading function of the nsp14 (ExoN) (Ma et al., 2015). The SARS-CoV-2 RdRp structure consists of three important domains-a) "right hand" RdRp domain (residues Ser367-Phe920) b) nidovirus-unique N-terminal extension domain (residues Asp600-Arg249) that possesses a nidovirus RdRp-associated nucleotidyltransferase (NiRAN) architecture (Lehmann et al., 2015) c) the interface domain (residues Ala250-Arg365) that connects the RdRp domain and NiRAN domain (Gao et al., 2020). The polymerase (RdRp) domain has a conserved structure of a typical viral polymerase family (McDonald, 2013) and consists of three subdomains-a) fingers subdomain (residues Leu366-Ala581 and Lys621-Gly679) b) a palm subdomain (residues Thr582-Pro620 and Thr680-Gln815) c) a thumb subdomain (residues His816-Glu920). The catalytic residues of the polymerase enzyme are composed of Ser759, Asp760 and Asp761 which are located in the motif C of the palm subdomain of the RdRp domain (Gao et al., 2020).

The RdRp enzyme is a good therapeutic target since it plays a key role in driving viral replication and transcription processes (Pachetti et al., 2020). A few inhibitors have been designed against the target enzyme. For example, Remdesivir (RDV) which is an investigational drug and it is a nucleotide analog inhibitor of RdRp (Wang et al., 2020) which has been previously developed for the treatment of Ebola virus disease (EBV) (Siegel et al., 2017). The molecule competes with the natural substrate, adenosine triphosphate (ATP) during RNA biosynthesis and exhibits broad-spectrum activity against several RNA viruses including severe acute respiratory syndrome coronavirus (SARS-CoV) and middle east respiratory syndrome coronavirus (MERS-CoV) (Agostini et al., 2018). The current scenario warrants safe and speedy identification of therapeutic drugs or vaccines to treat the infections. One effective strategy perhaps could be the use of broad-spectrum antivirals or molecules having known antiviral activity. The existing marketed antiviral drugs approved by the Food and Drug Administration (FDA) could be repurposed for COVID-19 (Jeon et al., 2020). Further, the phytochemicals having demonstrated antiviral activity can be explored to identify lead molecules (ul Qamar et al., 2020).

In the present study, a set of antiviral phytochemicals and FDA-approved antiviral drugs have been tested for their suitability as SARS-CoV-2 RdRp inhibitors through molecular docking approach. The binding affinity of the compounds with the target enzyme was evaluated and some promising leads have been suggested which can be developed as drug candidates against SARS-CoV-2 infection in humans.

2. Materials and methods

2.1. Retrieval of antiviral compounds

The information about 110 antiviral compounds consisting of 56 phytochemicals and 54 FDA approved antiviral compounds were collected through literature search (De Clercq and Li, 2016; Kalliyaperumal et al., 2020; Naithani et al., 2008). The three-dimensional structures of the compounds were retrieved from PubChem database (Kim et al., 2016) and saved in SDF format. The compounds whose structures were not available in PubChem database were modelled using ACD/ChemSketch (Freeware) 2019.1.2 tool and were converted into a three-dimensional form using Open Babel version 2.4.1 program (O’Boyle et al., 2011) and subsequently, the structures were optimised using Merck molecular force field 94 (MMFF94) (Halgren, 1996) with steepest descent algorithm.

2.2. Retrieval of SARS-CoV-2 RdRp structure

The three-dimensional structure of the target enzyme, RdRp was retrieved from Protein data bank (http://www.rcsb.org/) using PDB ID: 7BV2. The cryo-electron microscopy (cryo-EM) structure contains RdRp (nps12) complexed with bound cofactors nsp7 and nsp8, template-primer RNA and triphosphate form of Remdesivir (RTP) and has been solved at a resolution of 2.50 Å (Yin et al., 2020).

2.3. Ligand and protein preparation

The protein was prepared for molecular docking using AutoDockTools-1.5.6. The cofactors, ions, heteroatoms including water molecules were removed and polar hydrogen atoms and Kollman charges were added to the protein and the prepared structure was saved in PDBQT format. Similarly, ligands were prepared by addition of hydrogen atoms, Gasteiger charges and assignment of the number of torsions and the prepared ligand structures were saved as PDBQT file.

2.4. Molecular docking studies

Each compound was docked into the active site pocket of the enzyme by defining a grid box around the co-crystal ligand using AutoDock 4.2 software (Morris et al., 2009). The grid box is centred at xyz coordinates of 92.5053, 93.2594 and 103.4061, number of grid points of 60 × 60 × 60 with a grid spacing of 0.3750 Å. The

| List of Abbreviations |
|-----------------------|
| COVID-19 | Coronavirus disease 2019 |
| FDA | Food and Drug Administration |
| HBA | Hydrogen bond acceptor |
| HBD | Hydrogen bond donor |
| LogP | Octanol-water partition coefficient |
| LogS | Aqueous solubility |
| MW | Molecular weight |
| MERS-CoV | Middle east respiratory syndrome coronavirus |
| Nsp | non-structural protein |
| NiRAN | Nidovirus RdRp-associated nucleotidyltransferase |
| RdRp | RNA-dependent RNA polymerase |
| RB | Rotatable bonds |
| RDV | Remdesivir |
| RTP | Triphosphate form of Remdesivir |
| SARS-CoV-2 | Severe acute respiratory syndrome coronavirus 2 |
| SARS-CoV | Severe acute respiratory syndrome coronavirus |
| TPSA | Topological polar surface area |

In the present study, a set of antiviral phytochemicals and FDA-approved antiviral drugs have been tested for their suitability as SARS-CoV-2 RdRp inhibitors through molecular docking approach. The binding affinity of the compounds with the target enzyme was evaluated and some promising leads have been suggested which can be developed as drug candidates against SARS-CoV-2 infection in humans.
molecular docking was performed using Lamarckian genetic algorithm (LGA) with the given parameters: a) an initial population size of 150 individuals b) a maximum number of 2,500,000 energy evaluations c) a maximum number of 27,000 generations d) gene mutation rate of 0.02 and e) crossover rate of 0.8. The number of genetic algorithms (GA) runs was set to 50. The conformations were clustered based on root mean square deviation (RMSD) cut-off value of 2.0 Å. The best docking pose for each compound was considered based on the lowest binding energy score and was further evaluated using LigPlot + version 1.4.5 program (Laskowski and Swindells, 2011) for studying the molecular interaction (hydrogen bonds and hydrophobic interactions).

2.5. Evaluation of physicochemical properties of the compounds

The physicochemical properties of the compounds such as molecular weight (MW), octanol–water partition coefficient (LogP), number of hydrogen bond acceptor (HBA), number of hydrogen bond donor (HBD), aqueous solubility (LogS), topological polar surface area (TPSA) and drug-likeness scores were determined using OSIRIS DataWarrior version 5.0 tool (Sander et al., 2015).

3. Results

A total of 110 compounds consisting of 54 FDA approved antiviral compounds (Suppl. Table 1) and 56 antiviral phytocompounds (Suppl. Table 2) and were screened for their ability to bind to the active site pocket of the RdRp enzyme through molecular docking studies. The binding energy scores of the compounds were compared with the standard inhibitor, triphosphate form of Remdesivir (RTP). Among the set of 54 FDA approved antiviral drugs, top 3 hits identified were Paritaprevir (D31), Rivipivirine (D19) and Simeprevir (D33) (Fig. 1A) which exhibited binding energies of −10.46 kcal/mol, −8.25 kcal/mol and −8.08 kcal/mol respectively (Fig. 1B) and their corresponding inhibition constants were found to be 21.46 nM, 892.59 nM and 1.19 μM. The binding poses and molecular interactions between the hits and the target enzyme are represented in Fig. 1C, D. The first best hit-D33 exhibits six number of hydrogen bonds via Tyr456, Asp623, Ser682, Asp760 and Asp761 and stably held within the active site pocket of the RdRp enzyme. Further, eleven residues (Met542, Arg553, Thr556, Val557, Ala558, Asp618, Tyr619, Lys621, Cys622, Thr680 and Ser681) were observed to participate in hydrophobic interactions. The second best hit-D19 forms one hydrogen bond with Ser814 and hydrophobic interactions via residues-Val557, Ala558, Asp618, Tyr619, Lys621, Cys622, Thr680 and Ser681. The third hit-P17 interacts with the enzyme using three hydrogen bonds with Lys551, Asn691 and Ser759 with bond distances of 2.77 Å and 2.75 Å with the backbone nitrogen (N) atom of Cys622 and the side chain oxygen atom (OD1) of Asp760 respectively. The molecule further establishes strong hydrophobic interactions with the residues- Arg553, Asp618, Tyr619, Lys621, Asp623, Leu758, Ser761, Glu811, Cys813 and Ser814 within the binding site pocket of the enzyme. The second hit-P28 shows strikingly eight number of hydrogen bonds with Lys545, Thr556, Val560, Asp623, Thr680, Ser682, Gly683 and hydrophobic interactions with nine residues-Tyr456, Met542, Val557, Ala558, Gly559, Glu665, Val667, Lys676 and Ser681. The third hit-P17 interacts with the enzyme using the triphosphate form of Remdesivir (D31) and Raltprevir (D33) (Fig. 1A) which exhibited binding energies of −8.11 kcal/mol, −8.17 kcal/mol and −7.81 kcal/mol respectively (Fig. 2B). The inhibition constants for P5, P28 and P21 were found to be 345.72 nM, 1.03 μM and 1.87 μM respectively. The binding poses of the top three hits were further analysed for the chemical nature of interaction with the enzyme (Fig. 2C, D). The first best hit-P5 showed two number of hydrogen bonds of distances 2.77 Å and 2.75 Å with the backbone nitrogen (N) atom of Cys622 and the side chain oxygen atom (OD1) of Asp760 respectively. The molecule further establishes strong hydrophobic interactions with the residues- Arg553, Asp618, Tyr619, Lys621, Asp623, Leu758, Ser761, Glu811, Cys813 and Ser814 within the binding site pocket of the enzyme. The second hit-P28 shows strikingly eight number of hydrogen bonds with Lys545, Thr556, Val560, Asp623, Thr680, Ser682, Gly683 and hydrophobic interactions with nine residues-Tyr456, Met542, Val557, Ala558, Gly559, Glu665, Val667, Lys676 and Ser681. The third hit-P17 interacts with the enzyme using three hydrogen bonds with Lys551, Asn691 and Ser759 with bond distances of 2.81 Å, 2.66 Å and 2.70 Å respectively. The residues such as Arg553, Tyr619, Pro620, Lys621, Cys622 and Asp760 are involved in hydrophobic interactions with different moieties of P17. The binding of the control inhibitor (RTP) with the enzyme is predominantly favoured by nine number of hydrogen bonds via residues-Ser549, Lys551, Arg555, Leu758, Asp760, Asp761 and Ser814 and only two residues-Ser759 and Cys813 contributes towards hydrophobic interactions. The binding energy and inhibition constant for the control were −4.6 kcal/mol and 887.56 μM respectively.

The physicochemical properties of the compounds are important as they determine the pharmacokinetics, pharmacodynamics and bioavailability of a drug. The physicochemical properties of the top hits along with the control were evaluated using DataWarrior (Table 1). The results show that the molecular weight (MW) for the drugs (D33, D19 and D31) ranged from 366.427 Da to 765.889 Da and the phytocompounds (P5, P17 and P28) have MW between 456.708 Da and 562.482 Da. The control (RTP) has MW of 531.203 Da. The control shows the lowest octanol–water partition coefficient (LogP) of −10.978 whereas P17 shows the highest LogP of 6.0643. The maximum number of hydrogen bond acceptors were found to be 18 in case of control whereas P17 possesses the minimum number of HBA (N = 3). Similarly, the number of hydrogen bond donors were calculated for the mole-

| Molecule Name | MW | LogP | LogS | HBA | HBD | TPSA | RB | Druglikeness |
|---------------|----|------|------|-----|-----|------|----|--------------|
| D19           | 366.427 | 4.7377 | −7.081 | 6 | 2 | 97.42 | 5 | −5.0142 |
| D31           | 749.951 | 5.3017 | −6.548 | 12 | 2 | 193.51 | 7 | 5.069 |
| D33           | 765.889 | 4.7202 | −7.608 | 14 | 3 | 198.03 | 6 | −0.04683 |
| P5            | 480.647 | 4.9095 | −4.066 | 6 | 1 | 52.19 | 7 | 3.8313 |
| P17           | 456.708 | 6.0643 | −6.128 | 3 | 2 | 57.53 | 1 | −1.782 |
| P28           | 562.482 | 4.8073 | −4.985 | 12 | 6 | 192.44 | 8 | −1.6152 |
| RTP           | 531.203 | −10.978 | 1.824 | 18 | 7 | 318.94 | 8 | −33.957 |

**Table 1** Physicochemical properties of top hit molecules (FDA approved antiviral drugs-D19, D31 and D33 and antiviral phytocompounds-P5, P17 and P28) along with the control (RTP).

- **MW**: Molecular weight.
- **LogP**: Partition coefficient between n-octanol and water.
- **LogS**: Aqueous solubility at 25 °C and pH = 7.5.
- **HBA**: Number of hydrogen bond acceptor.
- **HBD**: Number of hydrogen bond donor.
- **TPSA**: Topological polar surface area (Å²).
- **RB**: Number of rotatable bonds.
cules and it was found that control has the maximum number of hydrogen bond donors ($N = 7$) and P5 has the minimum number of HBD ($N = 1$). Other physicochemical properties include aqueous solubility ($\log S$), topological polar surface area (TPSA), number of rotatable bonds (RB) and druglikeness score. All the molecules have $\log S$ value $\leq -4$ except for the control. The TPSA ranged between 52.19 Å² for P5 and 318.94 Å² for the control. The maximum number of RB were found to 8 in case of control whereas P17 has the minimum number of RB ($N = 1$). The druglikeness score is highest for D31 (5.069) and lowest for the control ($-33.957$).

4. Discussion

SARS-CoV-2 RdRp is a promising therapeutic target which can be used for screening of potential drug molecules against the viral infections in humans. The enzyme is a key player regulating the replication and transcription machinery within the host cell (Pachetti et al., 2020). The enzyme contains 932 amino acid residues and has three different domains- a) RdRp domain (residues Ser367-Phe920) b) NiRAN domain (residues Asp60-Arg249) c) the interface domain (residues Ala250-Arg365) that connects the RdRp domain and NiRAN domain (Gao et al., 2020). The RdRp domain can be utilised for the identification of potential inhibitors against the polymerase enzyme. The RdRp domain consists of three subdomains-a finger, a palm and a thumb subdomain. RdRp has been earlier targeted with an investigational drug known as Remdesivir which inhibited MERS-CoV and SARS-CoV replication in tissue cultures and exhibited efficacy in nonhuman animal models (Martinez, 2020). Remdesivir is a nucleotide analog prodrug which was previously developed for treatment against Ebola virus infection. It is metabolized into the active triphosphate form.

Fig. 1. Molecular interaction studies between FDA approved antiviral drugs and SARS-CoV-2 RdRp enzyme (A) Chemical structures of top three hits- Paritaprevir (D33), Rilpivirine (D19) and Simeprevir (D31) (B) Binding energy evaluation of the hits and control (RTP) (C) Binding poses of the drugs-D33 (yellow stick), D19 (spring green stick) and D31 (pink stick) (D) LigPlot + molecular interaction profile illustrating hydrogen bonds with green dashed lines and hydrophobic interacting residues with red radiating arcs.
which competes with adenosine triphosphate (ATP) and causes premature chain termination during viral RNA biosynthesis process (Gordon et al., 2020). The investigational drug also showed remarkable inhibition potential against COVID-19 virus replication under *in vitro* conditions (Wang et al., 2020) but exhibited moderate efficacy in the United states trial conducted by the US National Institute of Allergy and Infectious Diseases (NIAID) with 31% recovery in patients than those received placebo. Therefore, there is a scope of investigating other antiviral drugs against COVID-19.

Attempts have been made previously to identify SARS-CoV-2 RdRp enzyme inhibitors through virtual screening using a homology model derived structure of the enzyme (Elfiky, 2020; Wu et al., 2020). The recently solved three-dimensional cryo-EM structure of RdRp complexed with the template-RNA primer and triphosphate form of Remdesivir (RTP) (PDB ID: 7BV2) has provided mechanistic insights into the inhibition of polymerase activity exhibited by RTP (Yin et al., 2020) and opened an avenue for structure-based identification of novel inhibitors against the enzyme. One of the hurdles faced in structure-based drug discovery for RdRp is that Remdesivir along with a majority of other inhibitors is incorporated during the RNA synthesis process but such nucleotide analog inhibitors are easily excised from the nascent RNA chain by the proofreading and high fidelity activity of RdRp and nsp14 protein. Nsp14 is a bifunctional protein with an exonuclease activity in N-terminal region and a guanine-N7-methyltransferase (N7-MTase) activity in C-terminal region and therefore confers replication fidelity to the RdRp enzyme (Bouvet et al., 2012). It is worth exploring the nonnucleoside analog inhibitors which can inhibit the viral replication process. The rapid spread of SARS-CoV-2 infection worldwide and lack of effective drugs and vaccines to combat the disease necessitates a safe and rapid discovery of drugs. One effective and promising approach is a repurposing of FDA approved antiviral drugs or using phytochemicals having previously reported antiviral activities.

In the present study, a total of 110 known antiviral compounds (54 FDA approved drugs and 56 antiviral phytocompounds) were subjected to a virtual screening procedure. Few promising hits such as Paritaprevir (D33), Rilpivirine (D19), Simeprevir (D31), Emetine (P5), 7,4-di-O-galloyltriisoflavone (P28) and Oleanolic acid (P17) were identified as potential inhibitors of SARS-CoV-2 RdRp enzyme.

![Molecular interaction studies between antiviral phytocompounds and SARS-CoV-2 RdRp enzyme](image-url)

**Fig. 2.** Molecular interaction studies between antiviral phytocompounds and SARS-CoV-2 RdRp enzyme (A) Chemical structures of top three hits: Emetine (P5), 7,4-di-O-galloyltriisoflavone (P28) and Oleanolic acid (P17) (B) Binding energy evaluation of the hits and control (RTP) (C) Binding poses of the phytocompounds-P5 (orange stick), P28 (orchid stick) and P17 (salmon stick) (D) LigPlot + molecular interaction profile illustrating hydrogen bonds with green dashed lines and hydrophobic interacting residues with red radiating arcs.
(P5), 7,4-di-O-galloylitricefavan (P28) and Oleanolic acid (P17) were identified which exhibited higher binding affinity to the RdRp enzyme compared to Remdesivir. It is interesting to know that D33 and D31 are potent Hepatitis C virus (HCV) NS3/4A protease inhibitors and D19 is a nonnucleoside reverse transcriptase inhibitor (NNRTI) and an FDA approved drug against HIV infection (De Clercq and Li, 2016). The phytopharmaceutical P5 is an alkaloid isolated from the roots of Cephaelis ipecacuanha (Family: Rubiaceae) and has been found earlier to effectively inhibit herpes simplex virus (HSV) (Hanisch et al., 1966; Kalyaperumal et al., 2020). P28 is a flavan derivative isolated from the methanolic extract of leaves of Pithecellobium clypearia (Family: Fabaceae) and have antiviral activity against the respiratory syncytial virus (RSV) with 50% inhibition concentration (IC_{50}) value of 10 μg/ml (Li et al., 2006). P17 is a tripterpenoid extracted from the leaves and twigs of Prosopis glandulosa (Family Leguminosae) and previously reported to effectively inhibit HIV-1 replication in infected H9 cells with a half maximal effective concentration (EC_{50}) value of 1.7 μg/ml (Kashiwada et al., 1998). The present study reveals that the best hit molecule-D33 among FDA approved drugs showed six number of hydrogen bonds, three of which are established with the catalytic residues-Asp760 and Asp761 found within the Motif C of the RdRp domain (Gao et al., 2020) whereas the best hit molecule among the phytochemical was P5 which shows one hydrogen bond with the catalytic residue-Asp760. These hits are more likely to compete with the binding of physiological nucleotides within the active site pocket of the enzyme required for the synthesis of the viral RNA. The experimental structure of RdRp complexed with Remdesivir showed one hydrogen bond with catalytic residue Asp760 which is also found among nine hydrogen bonds in the present modelling studies between the enzyme and Remdesivir. Some physicochemical properties such as molecular weight, octanol–water partition coefficient, number of hydrogen bond acceptor groups, and number of hydrogen bond donor groups, aqueous solubility, topological polar surface area and drug-likeness scores were also evaluated for the best hits. While molecular weight determines the diffusion of a molecule across the lipid bilayer, the octanol–water partition coefficient influences the lipophilicity and absorption of the drug. The number of hydrogen bond acceptor or donor groups is more likely to influence the permeability of the drug molecules and aqueous solubility may affect their distribution characteristics. The topological polar surface area is more likely to determine the oral bioavailability of the drug (Gurung et al., 2016). These properties greatly influence the pharmacokinetics and pharmacodynamics of a drug and subsequently the bioavailability of a drug. Such preliminary in silico investigation of the physicochemical properties would assist in the experimental studies and optimization of the drugs based on the activity and the pharmacophysical descriptors of the molecules (structure–activity relationship studies).

5. Conclusion

Using the recently solved structure of RdRp complexed with triphosphate form of Remdesivir (RTP), potential inhibitors were identified which include three FDA approved drugs- Paritaprevir (D33), Rilpivirine (D19) and Simeprevir (D31) and three antiviral phytochemicals- Emetine (P5), 7,4-di-O-galloylitricefavan (P28) and Oleanolic acid (P17). The molecules identified in the present study need further experimental studies to confirm their suitability for the treatment of SARS-COV-2 infection in humans.

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 associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.sjbs.2020.11.078.

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