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Phytochemical compounds present in COVI-MXG herbal preparation inhibits RNA-Dependent RNA polymerase from SARS-CoV-2: A molecular docking study

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Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has been identified as the agent responsible for COVID-19 pandemic. Currently, no therapeutic agents have proven effective in combating the virus. Managing the infection is mainly palliative in nature, involving infection prevention strategies and supportive therapy anchored on drugs that practitioners have had previous usage experience. Previously exploited therapeutic agents include antiviral and antimalarial agents (remdesivir, hydroxychloroquine, chloroquine, lopinavir, umifenovir, favipiravir, and oseltamivir). Micronutrients (zinc, selenium) have also been used. There are claims of herbal preparations that are thought to be beneficial. The self-formulated herbal preparation, COVI-MXG contains a unique combination of five plants. In silico methodologies were used to evaluate the phytochemical constituents. This was to determine possible antiviral activity, safety during usage and pharmacokinetic properties. Docking studies of selected phytochemical compounds in COVI-MXG evaluated against the COVID-19 viral protein target showed binding affinity ranging from -8.1 to -4.2 Kcal/mol. Blood brain barrier permeability and gastrointestinal absorption rates varied to different degrees. Toxicity class varied from 3 to 5. LD^{50} values were relatively high. COVI-MXG contained phytochemical compounds with better binding affinities for SARS-CoV-2 protein (7BV2) than currently employed therapeutic agents (remdesivivr, hydroxychloroquine, chloroquine, lopinavinavir, umifenovir, favipiravir, oseltamivir) which were included in the virtual screening. The phytochemical compounds showed excellent interactions with amino acid residues in the catalytic nsp12 domain. This excellent interaction is likely to result in a better therapeutic outcome in the management of COVID-19. In silico predictions for stability and pharmacokinetic parameters predicted that the formulation can be administered orally.

Key words: COVID-19, SAR-CoV-2, COVI-MXG, zinc.

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) which is the causative agent of the COVID-19 pandemic was first identified in central regions of China. The infection has rapidly affected almost all countries of the world. The disease is associated with high mortality and enormous public health implications.

At the moment, there are no therapeutic agents or vaccines that have proven effective in combating the virus (Li et al., 2020; Ali and Alharbi, 2020). Management of the infection is mainly palliative and involves strategies such as prevention of the infection, supportive therapy anchored on drugs with which practitioners have had previous experience with their usage. In this regard, various therapeutic agents have been exploited. Included amongst these agents are antiviral and antimalarial agents (remdesivir, hydroxychloroquine, chloroquine, lopinavir, umifenovir, favipiravir, and oseltamivir). Micro-nutrients such as zinc and selenium have also been used. However some therapeutic agents have been re-positioned for the management of COVID-19 and this includes, antiviral agents (Remdesivir, Lopinavir, Umifenovir, Favipiravir, and Oseltamivir), and antimalarial agents (hydroxychloroquine, chloroquine) and other supportive agents such as zinc and selenium. Due to these difficulties, attention has shifted to the use of herbal medicines and/or purified natural products. This approach is based on the thinking that these natural products may be helpful in guiding development of novel and effective therapeutic agents against the virus. It has been reported that between 85 and 92% of patients in some cities in China resort to herbal drugs in addition to other remedies (Mani et al., 2020; Yang et al., 2020). Earlier reports show that even though the herbal medications have relatively good safety margins, the mechanism of activity is poorly understood. It is however thought that the activity might be through viral inhibition (Li et al., 2005).

As a result of these challenges, coupled with the impact of the pandemic, great urgency is involved in the search for effective treatments through innovative and unconventional strategies. One of such techniques involves computational approaches or molecular docking (Ekins et al., 2007; Yuan et al., 2016). Molecular docking is a technique that could be used to predict a protein (enzyme) interaction with a ligand using best-fit orientation (Azamm and Abbasi, 2013). This *in silico* approach has proven to be an excellent tool for rational drug discovery and design. It has many advantages because of the inherent tendency to cut down on the time required for *in vivo* and *in vitro* assays (Valerio Jr., 2012). Furthermore, there is a huge reduction in costs associated with physically screening large libraries and/or banks of compounds or even of plant extracts for compounds that may have biological activity (Chen et al., 2017). Another major advantage of *in silico* or virtual screening techniques is that through the techniques, compounds to be evaluated for *in vitro and in vivo* activities can easily be highlighted as a prelude to other investigations and clinical trials (Yang et al., 2020).

Coronaviruses (CoVs) are a family of positive RNA (+ RNA) viruses that infect vertebrates including humans (Perlman and Netland, 2009). The + RNA virus's enzymes fundamentally catalyse the process of RNA synthesis from RNA templates (Salonen et al., 2005) of which RdRp is at its main catalytic subunit for the synthesis of negative RNA (- RNA). SARS-CoV RNA genome replication and transcription are presumably catalysed by the C-terminal part of non-structural protein 12 (nsp12) RdRp (te Velthuis, 2010a). SARS-CoV-2 requires the viral RNA-dependent RNA polymerase (RdRp) for replication which is a target for antiviral drugs such as Remdesivir and Favipiravir (Yin et al., 2020), hence the selection of this protein as our molecular target.

The self-formulated herbal preparation COVI-MXG contains *Monodora myristica*, *Xylopia aethiopica, Gongronema latifolium, Viscum album* and *Garcinia kola.* There are no literature reports to the effect that this combination of plants and in the proportions has ever been documented for use in the management of COVID-19. The study used *in silico* screening strategies to evaluate the phytochemical compounds present in COVI-MXG for their inhibitory effects on SARS-CoV-2 RdRp.

METHODS

The methods utilized in the evaluations were entirely *in silico*.

Hardware, ligand library and target preparation

The operation system used for the computational analysis/screening consisted of an x64-based computer running on Windows 10 Pro with a 32-Bit operating system.

Twenty one phytochemical constituents (Table 1) in the compound library of compounds in COVI-MXG were downloaded from PubChem (Kim et al., 2019). The discovery studio 4.5 visualizer (BIOVIA, 2016) was then used to optimize these compounds. Also included in the ligand library were nine therapeutic compounds currently in use for the treatment of COVID-19. These included Lopinavir, Remdesivir, Ritonavir, Umifenovir, Favipiravir, Oseltamivir, Quinine, Chloroquine and Hydroxychloroquine. After downloading the crystal structure of the SARS-CoV-2 target with pdb code 7BV2 from the Protein Data Bank (pdb) (https://www.rcsb.org/), the pdb file was then opened in WordPad. Closely following this, the original ligands (remdesivir) and water molecules were eliminated then the file was re-saved.

Virtual screening

The PyRx 0.8 software was used for the *in silico* docking, it is a virtual screening software used to screen libraries of compounds against potential drug targets.

The library of ligands was docked into the protein target and the binding affinities determined in Autodock Tools using PyRx 0.8 package (Dallakyan and Olson, 2015) and Autodock Vina (Trott and Olson, 2010). A grid box (x: 89.4261, y: 86.5813, z: 98.8772) with

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Table 1. Selected phytochemical compounds used in molecular docking studies.

Herbal plant	Phytochemical compound evaluated	Reference
Monodora myristica	Limonene α-pinene α-phellandrene	Dongmo et al. (2019)
Xylopia aethiopica	β-pinene β-phellandrene α-pinene γ-terpinene Trans-pinocarveol p-cymene 1,8-cineole Germacrene D α-cadinol	Noudjou et al. (2007)
Viscum album	Syringin Sinapic acid Myricetin Kaempferol Chlorogenic acid Protocatechuic acid Quercetin Ferulic acid Rosmarinic acid	Pietrzak et al. (2017)
Garcinia kola	Kolaviron	Anchang et al. (2015)

dimensions (Angstrom) (x: 44.1528 y: 48.0231 z: 25.0000) was employed. The ligands were inputted as Structure-data file (.sdf) while the target protein was inputted as Protein Databank File (.pdb file) which was converted to the acceptable.pdbqt file for Autodock Vina. Molecular interactions between protein target and ligands were analysed using PyMol (DeLano, 2002) and discovery studio 4.5 visualizer (Pietrzak et al., 2017).

In silico ADMETox analysis

SwissADME (Daina et al., 2017) was used to study the absorption and distribution of the phytochemical compounds while accessing bioavailability score, blood brain barrier permeability and gastrointestinal tract absorption. ProTox-II (Drwal et al., 2014) was used to study the rodent oral toxicity of the phytochemical compounds. Parameters such as carcinogenicity, hepatotoxicity, mutagenicity, cytotoxicity and immunotoxicity were assessed.

These selected phytochemicals are compounds in the herbal plants showing some antiviral/antimicrobial activity from literature selected for input into the docking studies.

RESULTS

The binding affinities of phytochemical compounds in COVI-MXG for SARS-CoV-2 (7BV2) (which is depicted by the change in binding energy (Kcal/mol)) are shown in Table 2. Kolaviron, the major phytochemical in *G. kola* showed the highest binding affinity of -8.1 Kcal/mol followed closely by phytochemicals in *V. album* (Quercetin, Kaempferol, Myricetin) which all had a binding energy of -7.9 Kcal/mol, Chlorogenic acid (-7.4 Kcal/mol) and Rosmarinic acid (-7.2 Kcal/mol). These molecules showed better binding affinities compared to the highest ranking current therapies- Ritonavir (-6.4 Kcal/mol), Remdesivir (-6.3 Kcal/mol) and quinine (-6.2 Kcal/mol). Three phytochemical compounds in *X. aethiopica* (γ-terpinene, P-cymene and Germacrene D) had a better binding affinity than Favipiravir (-5.2 Kcal/mol) but the same with umifenovir (-5.3 Kcal/mol) while two phytochemical compounds in *M. myristica* (Limonene and α- phellandrene) had the same binding affinity as Favipiravir (Tables 1 and 2). Of the current drug therapies for COVID-19 used in this study, chloroquine was observed to have the lowest binding affinity of -4.2 Kcal/mol.

The molecules exhibited different types of interactions including hydrogen bonding, covalent bonding, alkyl and van der Waal's force interactions with active site residues (Figure 1). It was observed that the compounds interacted with amino acid residues in the finger subdomain of the non-structural protein 12 (nsp12) RdRp domain (Residues 366-920) (Dabbagh-Bazarbachi et al.,

Table 2. Binding affinities of phytochemical compounds to SARS-CoV-2 target (7BV2).

Phytochemicals	Binding affinity (Kcal/mol)	Rank
Kolaviron	- 8.1	1
Quercetin	-7.9	2
Kaempferol	- 7.9	2
Myricetin	- 7.9	2
Chlorogenic acid	- 7.4	3
Rosmarinic acid	- 7.2	4
Ritonavir	**- 6.4**	**5**
Remdesivir	**- 6.3**	**6**
Quinine	**- 6.2**	**7**
Ferulic acid	- 6.1	8
Syringin	- 6.1	8
Hydroxychloroquine	**- 6.0**	**9**
Oseltamivir	**- 5.7**	**10**
Lopinavir	**- 5.7**	**10**
α- cadinol	- 5.6	11
Protocatechuic acid	- 5.5	12
Sinapic acid	- 5.4	13
Umifenovir	**- 5.3**	**14**
γ- terpinene	- 5.3	14
p- cymene	- 5.3	14
Germacrene D	- 5.3	14
Favipiravir	**- 5.2**	**15**
Limonene	- 5.2	15
α- phellandrene	- 5.2	15
β- phellandrene	- 5.0	16
Chloroquine	**- 4.6**	**17**
α- pinene	- 4.5	18
Trans- pinocarveol	- 4.4	19
1,8- cineole	- 4.4	19
β- pinene	- 4.2	20

Molecules in bold are currently used in the therapeutic management of COVID-19.

2014) of which LYS 545 and ARG 555 are of interest. Kolaviron was observed to interact with Asp 760 and Asp 761 residues which are in the catalytic centre of the protein target. Furthermore, the molecules docked properly within the target without large scale conformational changes (Figure 2).

Toxicity predictions (Table 3) showed phytochemical compounds with varying degrees of gastrointestinal absorption rates, blood brain barrier permeability and bio-availability. Toxicity class had a lower limit of 3 with an upper limit of 5. The LD_{50} values were relatively high except for P-cymene which had the predicted toxicity class of 1 and a predicted rodent LD_{50} of 3 mg/kg.

DISCUSSION

Current clinical management of COVID-19 includes antiviral agents (remdesivir, hydroxychloroquine, chloroquine, lopinavir, umifenovir, favipiravir, and oseltamivir), anti-oxidants (ascorbic acid) and micro nutrients (zinc and selenium). Although these drugs are still undergoing clinical trials in different countries, there are reported scientific rationales for their use. This is the reason for their choice as a basis of comparison in this evaluation.

Bioactive compounds present in the self-formulated herbal preparation COVI-MXG showed varying degrees of bonded and non-bonded molecular interactions with the protein target SARS-CoV-2 RdRp (7BV2) (Figure 1) which could inhibit the replication of the virus. RdRp is a major viral enzyme that is critical for viral replication and a first-rate drug target especially for the nucleoside antiviral agents.

As reported by Yin et al. (2020), remdesivir interacts with side chains of LYS 545 and ARG 555 which can be observed in the interactions of kolaviron (Figure 1). This is of great interest as the side chains of amino acid

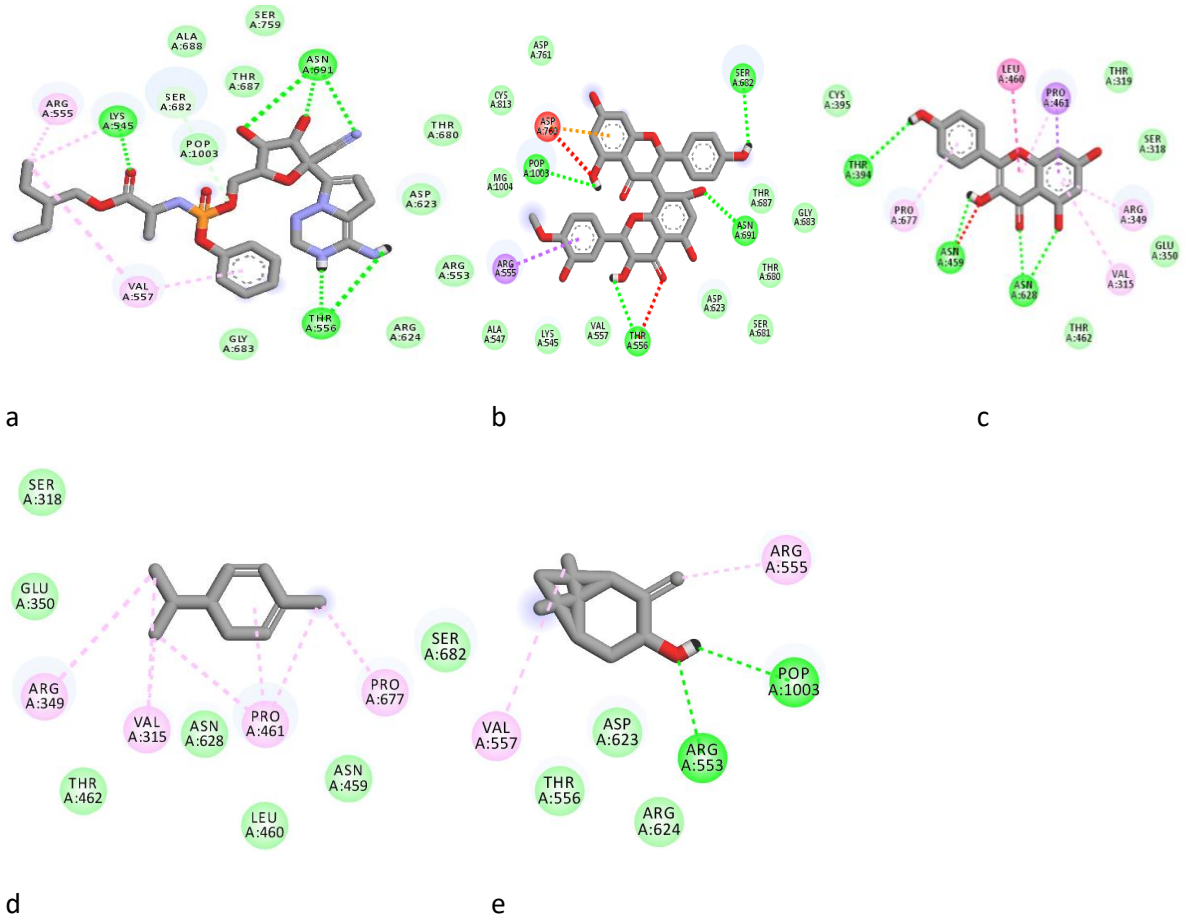

Figure 1. 2D binding interactions of Remdesivir (a), Kolaviron (b), kaempferol (c), α- phellandrene (d) and Trans-pinocarveol (e) to the active site residues of SARS-CoV-2 (7BV2). Ligands are shown in stick forms while amino acid residues are shown in disc forms. Hydrogen- bond interaction with amino acid main chain are indicated by green discontinuous lines, green colored discs shows van der waal's interaction, pink discs shows alkyl interactions while purple discs shows pi- sigma interactions. Discs and lines shown in red colour represent unfavourable bumps and interactions.

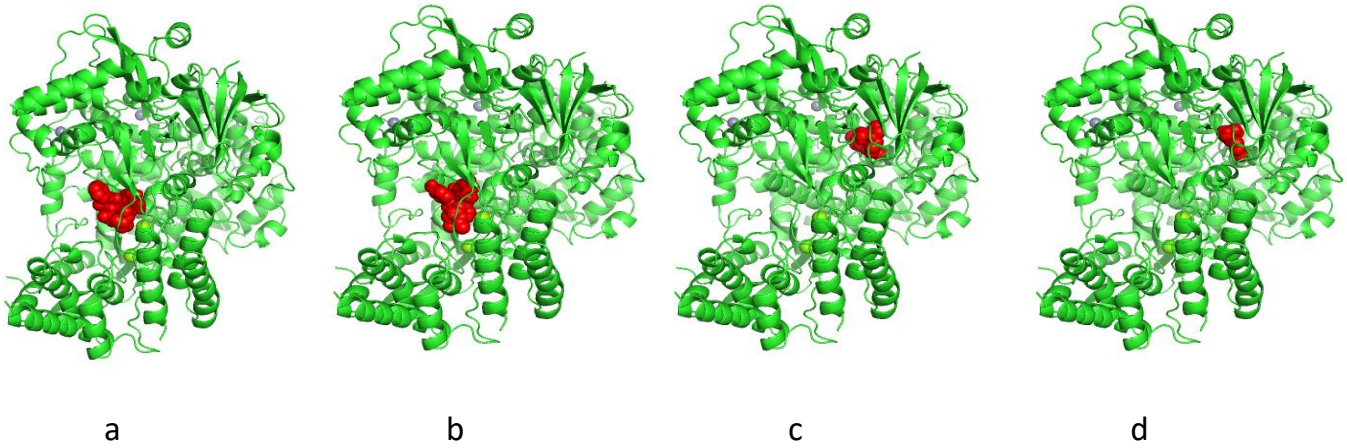

Figure 2. Ribbon representation of 7BV2 in complex with Remdesivir (a), Kolaviron (b), Hydroxychloroquine (c), and α-cadinol (d). There were no large scale changes observed in the conformation of the target upon binding of Ligands. Ligands are shown in red spheres while target (7BV2.pdb) is shown in green ribbons.

Table 3. ADMETox Predictions of Phytochemical Constituents Present in COVI-MXG.

Phytochemicals	GI absorption	BBB permeant	*Bioavailability score	**Predicted toxicity class	Predicted LD_{50} (mg/kg)	Toxicity end points
Kolaviron	Low	No	0.17	4	2000	Inactive
Quercetin	High	No	0.55	3	159	Immunotoxicity
Kaempferol	High	No	0.55	5	3919	Immunotoxicity
Myricetin	Low	No	0.55	3	159	Immunotoxicity
Chlorogenic acid	Low	No	0.11	5	5000	Inactive
Rosmarinic acid	Low	No	0.56	5	5000	Immunotoxicity
Remdesivir				**4**	**1000**	Inactive
Quinine				**3**	**263**	Immunotoxicity
Ferulic acid	High	Yes	0.56	4	1772	Inactive
Syringin	Low	No	0.55	5	4000	Inactive
Hydroxychloroquine				**4**	**1240**	Immunotoxicity& mutagenicity
α- cadinol	High	Yes	0.55	5	2830	Immunotoxicity
Protocatechuic acid	High	No	0.56	4	2000	Carcinogenicity
Sinapic acid	High	No	0.56	4	1772	Inactive
γ- terpinene	Low	Yes	0.55	5	2500	Inactive
p- cymene	Low	Yes	0.55	1	3	Carcinogenicity
Germacrene D	Low	No	0.55	5	5000	Immunotoxicity
Limonene	Low	Yes	0.55	5	4400	Inactive
α- phellandrene	Low	Yes	0.55	6	5700	Inactive
β- phellandrene	Low	Yes	0.55	5	5000	Inactive
Chloroquine				**4**	**311**	Immunotoxicity& mutagenicity
α- pinene	Low	Yes	0.55	5	3700	Inactive
Trans- pinocarveol	High	Yes	0.55	4	1800	Inactive
1,8- cineole	High	Yes	0.55	5	2480	Inactive
β- pinene	Low	Yes	0.55	5	4700	Inactive

BBB permeant: Blood brain barrier permeability; GI absorption: gastrointestinal tract absorption. Molecules in bold are currently used in the therapeutic management of COVID-19. *Bioavailability (F) = 0.85 =Polar surface area (PSA) $\leq$75 A (2), = 0.56 = PSA 75- 150 A (2) = 0.11 = PSA $\geq$ 150 A (2). **Toxicity Class; 1: Extremely toxic; 2: Moderately toxic; 3: Slightly toxic; 4- 6: Non-toxic/ Low toxicity.

residues LYS 545 and ARG 555 are involved in stabilizing income nucleotides for correct positioning for catalysis. Interaction of these phytochemicals compounds with the afore-mentioned residues could inhibit the interaction of the primer strand RNA, thereby inhibiting the catalysis process. In addition, kolaviron could have exhibited better binding affinity compared to the rest of the phytochemical compounds and antiviral agents used in this study due to its interactions with residues ASP 760 and ASP 761. These residues are responsible for coordination of magnesium ions at the catalytic centre of the protein (Yin et al., 2020) and this process has been reported to be vital in the elongation process and RNA maturation (Chaturvedi and Shrivastava, 2005).

Some of the interactions and better binding affinities observed in this study are supported by reported antiviral activities of some of the molecules. For instance literature sources have

elaborately reported on the antiviral activities of kaempferol (Schwarz et al., 2014), limonene (Astani and Schnitzler, 2014) and myricetin (Ortega et al., 2019) against coronavirus as well as herpes simplex virus. Similarly kolaviron a biflavonoid from *G. kola* has also been reported to display antiviral activity (Dongmo et al., 2019). Literature reports also show that Monoterpenes such as γ-terpinene, α-pinene, p-cymene, and 1, 8-cineole display better antiviral activities and low toxicity when in a mixture in comparison to when they are single entities (Astani et al., 2010). This is a desirable and beneficial property in COVI-MXG formulation.

Structure activity relationships affect the position of binding among the evaluated compounds as evident by remdesivir and kolaviron (Figure 2a and b). The other smaller phytochemical compounds shared the same binding pocket with hydroxchloroquine (Figure 2c and d). SARS-CoV-2 RdRp is a moderately stable enzyme. It therefore shows no significant conformational changes in the active site between the apo and active forms (Perlman and Netland, 2009). From the 3D ribbon representation of the interactions (Figure 2), it was observed that there was no large scale conformational changes in the structure of the protein target, which might have been accounted for by its stable nature. Proteins show a rich order of internal motions upon molecular recognition and binding of ligands (Ha and Loh, 2012) which may range from displacements of individual atoms to large scale motions (Grant et al., 2010).

In silico ADMETox profiling of the phytochemical compounds (Table 3) revealed a very promising low toxicity profile for COVI-MXG. Indeed most of the molecules displayed a toxicity class of 3 and above as per the Hodge and Steiner Scale (Hodge and Steiner, 2005). The implication of these findings is that with respect to safety, the phytochemical compounds in COVI-MG compare favorably with the current repurposed drugs used in the management of COVID-19. A notable observation concerns p-cymene, which in this formulation comes from *X. aethiopica.* Its predicted oral toxicity corresponds to toxicity class of 1 and an LD_{50} of 3 mg/kg. However, the point of note is that the toxicity of p-cymene should not pose a problem as it is only present in small amounts (about 7.3%) in *X. aethiopica* fruit oil.

The ProTox II evaluation showed that the key components in COVI-MXG which have been reported to have strong antiviral activities such as kaempferol (Schwarz et al., 2014), limonene (Astani and Schnitzler, 2014), myricetin (Ortega et al., 2019), and monoterpenes (γ-terpinene, α-pinene; 1, 8-cineole) (Astani et al., 2010) are inactive with respect to carcinogenicity, hepatotoxicity, mutagenicity, cytotoxicity and immunotoxicity. Similarly, kolaviron a biflavonoid from *G. kola* which is reported to have strong antiviral activities (Buba et al., 2016; Dongmo et al., 2019) and shows the highest binding affinity to the SARS-COV-2 target protein is inactive with respect to the parameters of the ProTox II evaluation. Although p-cymene, one of the monoterpenes was found to be carcinogenic on the toxicity end points, an explanation has been provided earlier as to why its inclusion in the formulation should not present a major problem. Moreover, these monoterpenes reportedly act better in combination than as single entities (Astani et al., 2010). A notable and curious finding of this *in silico* evaluation was that even though α- and β-Pinene have been reported to possess antiviral and antibacterial activities ((Astani and Schnitzler, 2014; Salehi et al., 2019), they bounded considerably with the molecular target. This was however with much lower affinities than the current drug management of COVID-19 (Table 2).

Although the phytochemical compounds in *G. latifolium* were not included in the docking protocol, they were formulated with the herbal preparation COVI-MXG, as it has been reported that it has constituents that might help alleviate some of the symptoms associated with COVID-19 such as cough, fever and gastrointestinal tract symptoms. In particular, *G. latifolium* has a high total phenolic content which has antioxidant activity and alkaloids which have antipyretic activity. The hydrocyanic acid present in the leaves of *G. latifolium* has been proven to be a successful remedy for cough (Kushi et al., 2012). Furthermore, other literature sources (Ngwu et al., 2018) have reported that *G. latifolium* extract contained limonene, α-Pinene and Cineole which have excellent antioxidant properties.

The formulation of COVI-MXG would afford a synergistic effect, seeing as it contains *G. latifolium* which has an appreciable amount of Zinc (Balogun et al., 2016) and the zinc ionophore activity of quercetin (Dabbagh-Bazzarbachi et al., 2014) which showed a higher binding affinity (Table 2). Zinc has been shown to play an important role in the inhibition of coronavirus RNA polymerase (te Velthuis et al., 2010b).

The pharmacokinetic (ADMET) profile showed a balance in the hydrophilic/hydrophobic affinities of the phytochemical compounds therefore their solubility and permeability propensities. The bioavailability (F) profiling indicated that none of the constituents have a value of 0.85 polar surface area (<75 A (2)) and above, and most of the PSAs are between 0.56 (75- 150 A (2)) and 0.11 (> 150 A (2)). This accounts for the observed gastrointestinal tract absorption, which ranged from low to high, and blood brain barrier permeability. While rapid and sufficient GIT absorption is desired, low blood brain barrier permeability is desired, which is what was obtained with most of the phytochemicals. The implication of these findings predicts that the product will perform optimally following oral administration.

Conclusion

Pharmacokinetic predictions showed that the phytochemical compounds in COVI-MXG have

acceptable degrees of gastrointestinal absorption rates and blood brain barrier permeability. The predicted toxicity classes ranged from 3 to 5 with a high LD_{50} thereby predicting safety during oral use. The phytochemical compounds exhibited considerable binding affinities with the targeted molecular units of the virus. The design and formulation of COVI-MXG afford a synergistic effect of the phytochemicals and zinc which is present in *G. latifolium*. The zinc ionophore activity of quercetin plays an important role in the inhibition of coronavirus RNA polymerase. The findings of this virtual screening predicted the formulation as safe for oral administration and an excellent inhibitory activity against the coronavirus 2 (SARS-CoV-2) RNA-dependent RNA polymerase (RdRp).

ABBREVIATIONS

7BV2.pdb, Pdb code for crystal structure of the SARS-CoV-2 target; **Arg,** arginine; **Asp,** aspartic acid; **Lys,** lysine; **BBB permeant,** blood-brain barrier permeability; **GI absorption,** gastrointestinal tract absorption; **COVID-19,** coronavirus disease 2019; **LD_{50},** lethal dose 50%; **pdb,** protein data bank; **RNA,** ribonucleic acid; **SARS-CoV-2,** severe acute respiratory syndrome coronavirus 2; **Sdf,** structure-data file; **RdRp,** RNA-dependent RNA polymerase.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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