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Therapeutic capability of five active compounds in typical African medicinal plants against main proteases of SARS-CoV-2 by computational approach

Oluwasayo Peter Abodunrin [a,*], Olayinka Fisayo Onifade [b], Abayomi Emmanuel Adegboyega [c]

[a] Radiation and Health Physics, Physical Sciences Department, Bells University of Technology, Ota, Nigeria
[b] Phytomedicine, Biochemistry and Bioinformatics, Chemical Sciences Department, Bells University of Technology, Ota, Nigeria
[c] Department of Biochemistry, Faculty of Basic Medical Sciences, University of Jos, Jos, Nigeria

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ABSTRACT

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a pandemic cause of Corona Virus Disease (COVID-19), that has claimed numerous human lives across the globe. Main protease being the active protein of SARS-CoV-2 requires urgent mitigating effect against the spread of the virus. The therapeutic roles of the active compounds present in ten typical African medicinal plants were investigated in this study. Five active compounds *Curcuma longa* (Curcumin and Bisdethoxy curcumin), Garcinia kola (kolaviron), *Zingiber officinale* (Gingerol) and *Vernonia amygdalin*a (Artemisinin) were selected and docked against Main protease through receptor grid generation, protein ligand docking, receptor ligand complex pharmacophore and binding free energy. The results obtained revealed Curcumin had the highest binding score of −8.628 kcal/mol while artermisinin presented the least with −4.123 kcal/mol. The outcome of the pharmacokinetic prediction in this study revealed high transport capacity across the gastrointestinal tract and high blood brain barrier permeability for curcumin, bisdemethoxy curcumin, gingerol and artemisinin. The exemption is gingerol with low LD_{50} value (250 mg/kg), the LD_{50} of all active compounds ranged from 2000 to 4228 mg/kg. Adsorption, distribution, metabolism, excretion and toxicity (ADMET) properties exhibited by all compounds portrayed them as non-hepatotoxic, non-cytotoxic, non-mutagenic and non-carcinogenic. The active compounds exhibited drug-likeness features against Main protease of Covid-19.

1. Introduction

The Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) as well as Middle East Respiratory Syndrome Coronavirus (MERS-CoV) are member of Coronaviridae family, which affects species ranging from human beings to animals, causing dreadful respiratory diseases [1]. Coronavirus 2019 (COVID-19) emerged from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as a pandemic [2] discovered in Wuhan, Hubei province China, where it was spontaneously transferred from animal source like bats as possible sources to human being [3–5]. The infection leads to severe respiratory disease after an incubation period of 2–14 days [6]. The mode of transmission among human beings has been confirmed to be based on contaminated hands, infected surfaces and salivary or airway droplets [7]. The death rate has risen to 5, 620,865 with infection cases at 360,578,392 as at 4:37 p.m. CET, January 27, 2022 [8]. When infecting human cells, SARS-CoV-2 attaches itself with angiotensin converting enzyme 2, ACE2 [9,10]. ACE2 functions through the decrease blood pressure by lowering the angiotensin 2 [11,12]. The inflammatory around the lung, through animal research, has been shown as been reversible by improving the expression of ACE2 [13]. Viral proteases enzymes are major drug target; they function essentially, in viral protein maturation through proproteins removal after translation processes in the cytosol of the host cell. SARS-CoV-2 has become medically important coronaviruses because of the resulting health challenges [14,15]. The viral particles of coronavirus contain 4 major structural proteins: spike, membrane, envelope and nucleocapsid protein. Spike is a vital target for virus entrance into human cells via interaction with the ACE2. Nonstructural proteins possess enzymatic activities like proteases alongside RNA polymerase that redirected its activities. The blocking of the enzymatic regulations is useful when

* Corresponding author. Radiation and Health Physics Division, Physical Sciences Department, Bells University of Technology, Ota, 112233, Nigeria.
E-mail address: opabodunrin@bellsuniversity.edu.ng (O.P. Abodunrin).

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developing antiviral drugs against SARS-CoV2. SARS-CoV-2 is a positive-stranded large RNA genome enveloped betacoronavirus consisting approximately 30 kb of encoded proteins [16–18]. One of them, Main protease (3 chymotrypsin-like protease) being a cysteine protease, aids maturation cleavage of repeating amino acid units linked by a peptide bond in the process of virus reprodution [19–21]. Main protease is a homodimer consisting of two promoters: papin-like cyctseine protease (PL^{pro}) and 3 chymotrypsin-like protease ($3CL^{pro}$) alongside three domains; domain I (residue 8–101), domain II (residue 102–184), and domain III (residue 201–303). Domains I and II, are made up of six antiparallel β-barrels. An antiparallel globular cluster of five α helices forms domain. Domain III is involved in indirect interaction with substrate crucial for enzymatic activity of proteins through the removal of inactive protease [22]. Main protease is an upstream enzyme that involves in the SARS-CoV-2 replication and transcription [23]. The presence of computational model through *in-silico* screening of potential inhibitory role against the Main protease becomes possible.

Applications of plant extracts in medicine have being historically common due to their effectiveness against numerous infections majorly in Africa [24]. Approximately 70% of medications are synthesized directly or indirectly from the active ingredient present in plant extracts nevertheless the high rate of consumption for health improvement is observed in rural environment [24,25]. Plant extracts are readily available, safe, natural and affordable with limited side effect as compared to synthesized drugs. Plants generally are composed of phytochemical constituents present in different sections ranging from flower, leaf, stem and roots which serves as bioactive compounds responsible for numerous therapeutic role like anti diabetic, anti-inflammatory, antiviral and anti-microbial effects [26]. There are common plants used in Nigeria due to their bioactive compounds and previous infection treatment history. Bitter kola (*Garcinia kola*) is found majorly in moist forests of Central and Western African countries belonging to the family Guttiferae [27]. The entire parts of the plant are of importance, it is orally applied to alleviate poor health status ranging from erectile dysfunction, cough, gastric problems and high blood pressure. The major biflavonoids present in *Garcinia kola* is kolaviron responsible for its anti-inflammatory, anti-microbial and wound healing features [28,29]. Bitter leaf (*Vernonia amygdalina*) is a small shrub of tropical Africa origin belonging to the daisy family. *Vernonia amygdalina* is major traditional dish in some region in Nigeria due to its nutritional composition. The presence of artemisinin a bioactive terpenoid present in bitter leaf could be responsible for its usefulness in orthodox medication, being responsible for treating chicken pox, stomach ache, measles, pneumonia and cancer [30]. Ginger (*Zingiber officinale)* and turmeric *(Curcuma longa)* are used as cuisines and medicinal spices globally [31,32]. They are perennial plants of tropical and subtropical Asia Origin. *Zingiber officinale* contains gingerol as the bioactive compound of phenolic compound and terpeniods while *Curcuma longa,* curcumin being its bioactive ingredient of polyphenol making them responsible for various therapeutic functions in aliments like cough, cold, fever, arthritis and cancer [30,31]. This study was aimed at characterizing the potency of these medicinal plants against SARS-CoV2 protease through molecular docking, pharmacophore modelling and ADMET studies.

2. Methods

2.1. Protein preparation

The crystal structure of Main protease (PDB ID: 6LU7) resolution 2.16 Å was retrieved from Protein Data Bank (PDB) repository. The sample was prepared employing protein preparation wizard panel of Glide [33] to assign bond orders, add hydrogen, create disulfide bonds and, fill missing loops and side chains with prime. Water molecules outside 3.0 Å of the heteroatoms were detached and the structure minimized and optimized employing OPLS3 and PROPKA respectively [33,34]. Afterwards, the receptor grid file was created to define the binding pocket of the ligands.

2.2. Ligand preparation

About sixteen compounds from reviews on phytochemistry and medicinal importance of selected herbs commonly used in treating various infections and ailments in Nigeria [30]. Their structures including that of the standard inhibitor also known as (1s, 2s)-2-({n-[(Benzyloxy)carbonyl]-L-Leucyl}amino)-1--Hydroxy-3-[(3s)-2-Oxopyrrolidin-3-Yl]propane-1-Sulfonic Acid (K36) were downloaded from the PubChem database were prepared for molecular docking using Ligprep module [35]. Low-energy 3D structures having appropriate chiralities were generated. Possible ionization states for each ligand structure were generated at physiological pH of 7.2 ± 0.2. Also generated were stereoisomers for each ligand by maintaining specified chiralities and varying others.

2.3. Receptor grid generation

Receptor grid generation permits specifying the size and position of the protein's active site for ligand docking. The scoring grid was specified with respect to the co-crystalized ligand (inhibitors N_3) applying the receptor grid generation tool of Schrödinger Maestro 12.5. The van der Waals (vdW) radius scaling factor of nonpolar receptor atoms of 1.0 and partial charge cut-off of 0.25 were applied.

2.4. Protein-ligand docking

Molecular docking studies were undertaken with the generated receptor grid file using Glide tool of Schrödinger Maestro 12.5. The ligands already prepared were docked applying standard precision (SP), setting ligand sampling to flexible, with the ligand sampling set to none (refine only). The vdW radius scaling factor and partial charge cut-off for ligand atoms were 0.80 and 0.15 respectively.

2.5. Receptor-ligand complex pharmacophore modelling

A receptor-ligand complex pharmacophore model was developed with PHASE using the first 3 compounds having the top binding affinity towards the target protein. Auto (E-pharmacophore) method was applied; hypothesis set at 7 as the highest number of features being generated, 2.0 as lowest feature to feature distance, 4.0 as lowest feature to feature distance for feature of the same type and donor as vector.

2.6. Binding free energy calculation

The Prime MM-GBSA panel was used to determine the binding free energy for ligand–protein complexes employing the MM-GBSA technology available with Prime [36]. The binding free energy of the protein-ligand complexes was then used to obtain stability of their complexes via Prime MM-GBSA program (Schrödinger suite version 2020–3). Prior to this, the ligands were prepared by ligprep, while the respective proteins were prepared using the protein preparation wizard methods as discussed earlier. The active sites of the proteins were predicted by sitemap. Hence, the compounds were docked with proteins using glide SP docking. With OPLS3 force field selected and VSGB employed as the continuum solvent model, others were set as default [36].[1]

2.7. Pharmacology parameters

The absorption, distribution, metabolism, excretion and toxicity

[1] The authors contributed equally to this work.

(ADMET) features of the test compounds were obtained employing *in silico* integrative model predictions on the SwissADME and PROTOX-II software respectively.

3. Results

3.1. 2D structures of some active compounds present in the medicinal plants

The 2D structures of the five most bioactive constituents of African medicinal plants, namely, curcumin, kolaviron, bisdemethoxycurcumin, gingerol, and artemisinin were modeled and used as ligands for docking studies against Main protease of SARS-CoV-2 (Fig. 1). In the molecular docking of the plants active compound against SARS-CoV-2 Main protease, several active compounds exhibited numerous level of binding affinity against the protein of interest, as represented in Table 1. The binding affinities ranging from −8.628 to −2.236 kcal/mol of the change in Gibbs free energy (ΔG) against SARS-CoV-2 Main protease. Curcumin has the greatest binding affinity with −8.628 kcal/mol. The binding affinity of kolaviron is −7.027 kcal/mol, (1s,2s)-2-({n-[(Benzyloxy)carbonyl]-L-Leucyl}amino)-1-Hydroxy-3-[(3s)-2-Oxopyrrolidin-3-Yl]propane-1-Sulfonic Acid the standard ligand is −6.541 kcal/mol, bis-demethoxy curcumin is −4.975 kcal/mol, gingerol is −4.252 kcal/mol and arteminsin with the least binding affinity of −4.123 kcal/mol among the top five compounds.

Table 1
The docking score (kcal/mol) of the active compound of medicinal plants against main proteinase of SARS-CoV-2.

Active compound	Main proteinase of SARS-CoV-2	PubChem ID
Curcumin	−8.628	969516
Kolaviron	−7.027	155169
(1s,2s)-2-({n-[(Benzyloxy)carbonyl]-L-Leucyl}amino)-1-Hydroxy-3-[(3s)-2-Oxopyrrolidin-3-Yl]propane-1-Sulfonic Acid (standard inhibitor) (K36)	−6.541	118737648
Bis-demethoxycurcumin	−4.975	5315472
Gingerol	−4.252	442793
Artemisinin	−4.123	68827
Nimbic acid	−3.965	25446
Thymoquinone	−3.931	10281
Paradol	−3.924	94378
Nimbolide	−3.883	12313376
Ibuprofen	−3.727	3672
Geraniol	−3.42	637566
Beta-Pinene	−3.188	14896
Citral	−3.061	638011
Limonene	−2.9	22311
Allicin	−2.236	65036
Alpha-Pinene		6654

3.2. Molecular modeling of biological interactions

The molecular interaction among the standard inhibitor (K36), *Vernonia amygdaline*, *Garcinia kola*, *Zingiber officinale* and *Curcuma longa*

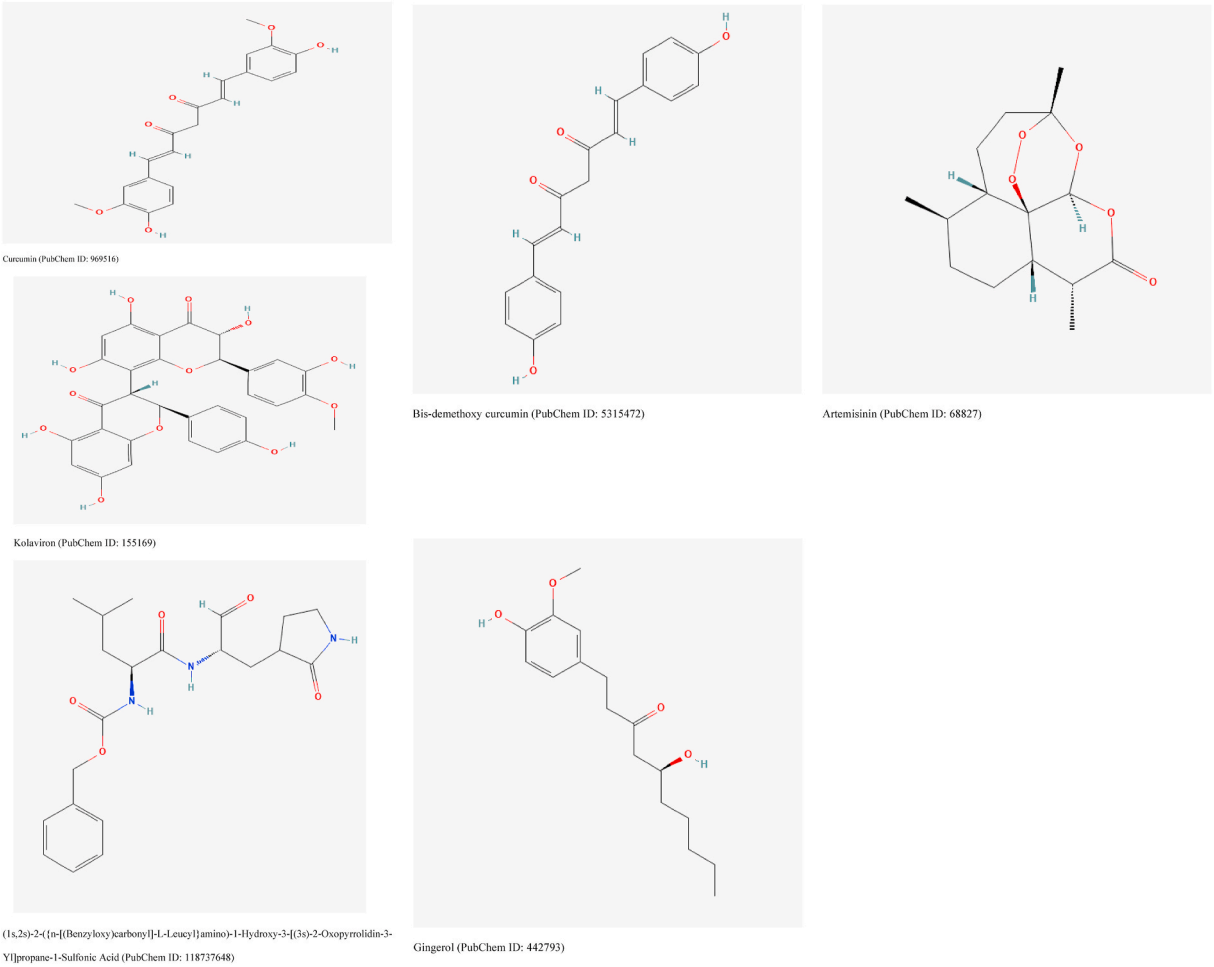

Fig. 1. 2D Structures of active compound present in medicinal plants.

with the SARS-CoV-2 Main protease, showing the binding pocket of the enzyme comprising of various amino acid residue as shown in Fig. 2. Artemisinin formed hydrogen bond with GLN 189 and GLU 166; the hydrogen bond was formed in gingerol at THR 190 and GLN 189; bis-demethoxycurcumin formed hydrogen bond with THR 26, THR 190, GLN 189 and GLU 166; moreso, curcumin bonded at the position THR 26, GLY 143, GLN 189 and THR 190 with hydrogen; kolaviron formed hydrogen bond also at GLU 166 and GLY 143 while (1s,2s)-2-({n-[(Benzyloxy)carbonyl]-L-Leucyl}amino)-1-Hydroxy-3-[(3s)-2-Oxo-pyrrolidin-3-Yl]propane-1-Sulfonic Acid (standard K36) binds with hydrogen bond at GLN 189 and HIS 41.

3.3. Adsorption, distribution, metabolism, excretion and toxicity (ADMET) properties

The SwissADMET predictions of lipophilicity, solubility, drug-likeness and oral bioavailability of the selected bio active compounds are presented as Table 2, the pharmacokinetic features as Table 3 while the protox II predicted toxicity profile are as presented in Table 4. The water solubility, Log S, of curcumin, kolaviron, bisdemethoxy curcumin and -Gingerol were predicted to be moderately soluble while artemisinin is soluble. Additionally, the Lipohilicity (Log P) are of the range −0.48 for kolaviron to 2.62 for artemisinin. In terms of drug-likeness, the outcome of this study indicated that kolaviron violated three of the Linpinski rules, while curcumin, bisdemethoxy curcumin, gingerol and artemisinin fully obeyed the rules. Additionally, the bioavailability scores of curcumin, bisdemethoxy curcumin, gingerol and artemisinin is 0.55 while that of artemisinin is 0.17 (see Table 5).

The pharmakokinetic prediction in Table 3 portrayed high transport capacity across the gastrointestinal tract and high blood brain barrier (BBB) for curcumin, bisdemethoxy curcumin, gingerol and artemisinin. However, none of the active compounds is substrate to permeability of the glycoprotein (P-gp). Furthermore, bisdemethoxy curcumin, gingerol and artemisinin are predicted to be able to inhibit CYP1A2; curcumin, kolaviron and bisdemethoxy curcumin are predicted to inhibit CYP2C9 and CYP3A4. Moreover, curcumin, kolaviron, bisdemethoxy curcumin gingerol and artemisinin were predicted not to inhibit CYP2C19 and CYP2D6.

As presented in Table 4, the protoxll-predicated toxicity profile of the compounds showed that curcumin, kolaviron, bisdemethoxy curcumin, gingerol and artemisinin do not tend to be hepatotoxic, carcinogenic, mutagenic and cytotoxic. However, curcumin, kolaviron, gingerol and artemisinin are predicted to have immunotoxic potentials. The exemption of gingerol with low LD_{50} value (250 mg/kg), the LD_{50} of the active compound ranged from 2000 to 4228 mg/kg. Moreso, curcumin and kolaviron belong to the acute oral toxicity class 4, bisdemethoxy curcumin and artemisinin to class 5, and gingerol to class 3.

3.4. Receptor-ligand pharmacophore modelling

The active compounds produced pharmacophore models against SARS-CoV-2 Main protease. The model revealed four sorts of characteristics:D: Hydrogen Acceptor, A: Hydrogen Donor, H: hydrophobic, and R: Aromatic ring which are presented in figure below: Kolaviron formed two hydrogen bond donor, two hydrogen bond acceptor and one aromatic ring with the enzyme. Curcumin and bisdemethoxy curcumin uses two hydrogen donor, hydrogen acceptor and aromatic rings; the standard inhibitor requires one hydrogen donor, one hydrogen acceptor and one aromatic ring (see Fig. 3).

3.5. Binding free energy calculation

The binding free energy of the protein-ligand complexes was employed to determine the stability of their complexes via Prime MM-GBSA program (Schrödinger suite version 2020–3) (see Fig. 4).

4. Discussion

The Coronaviruses are the virus with positive-polarity RNA genome, making them to depend less on the host cell during replication. The replication occurs in the cytoplasm of the epithelial cells of the respiratory system and the gastrointestinal system [16,18]. The computational approach of drug design against covid-19 is essential to reduce cost, save time and improve output. NADPH and dTDP-4-dehydro-6-deoxy-L-mannose show a significant interaction *in silico* with the active site of Mpro, with a binding energy of 8.5 and 8.6 kcal/mol, respectively [37]. This study involved five approaches comprising of protein and ligand preparation, receptor grid generation, protein-ligand docking, receptor ligand pharmacophore, binding free energy and pharmacology parameters. In this study, 5 major bioactive compounds of plant extract in addition with standard ligand were docked against SARS-CoV-2 Main protease, curcumin had the highest docking score of −8.62 kcal/mol, followed by kolaviron with −7.027 kcal/mol as compared with the standard ligand (K36) −6.541 kcal/mol. The presence of flavonoinds and curcumin in *Curcuma longa* has been shown to be responsible for its chemopreventive and physiological effects in many

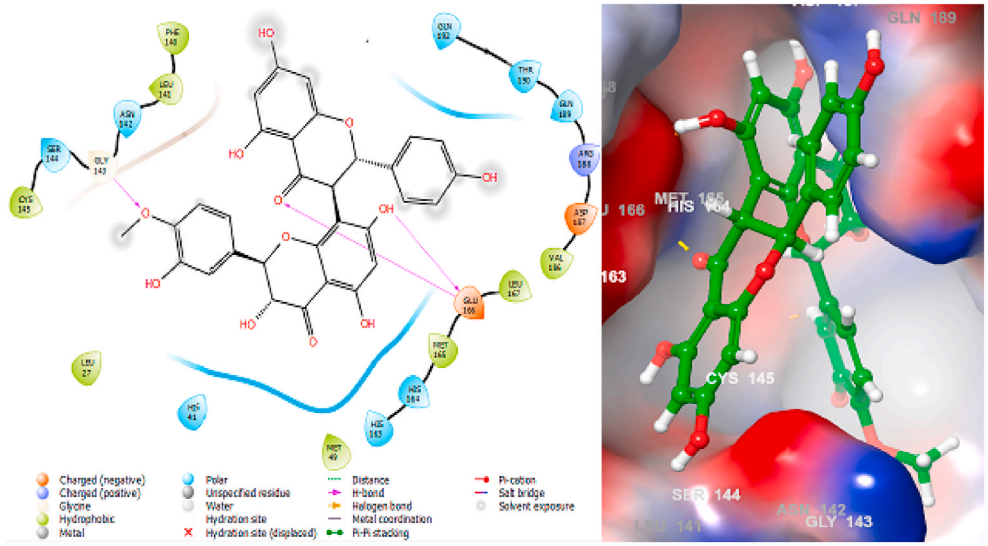

Fig. 2a. 3D representations of SARS-CoV-2 3C-like Protease-kolaviron.

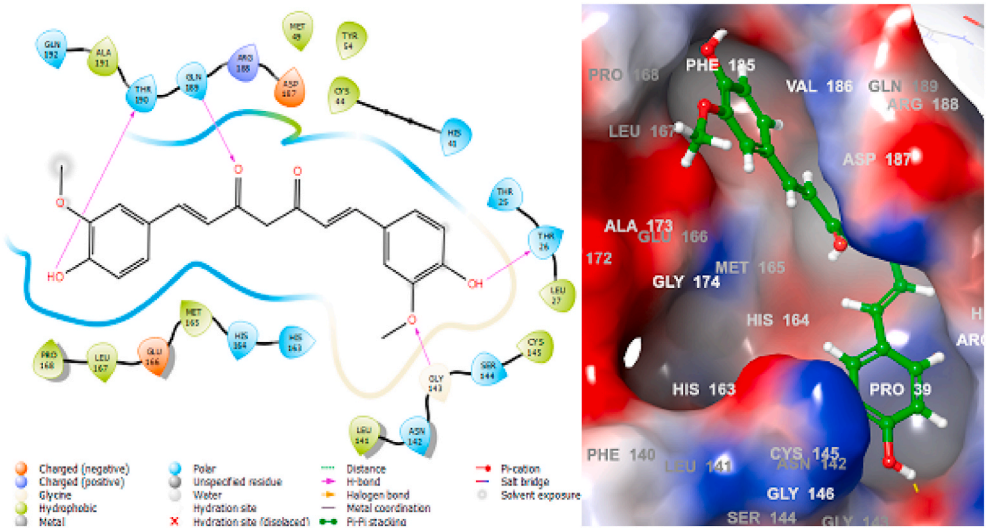

Fig. 2b. 2D and 3D representations of SARS-CoV-2 3C-like Protease-curcumin.

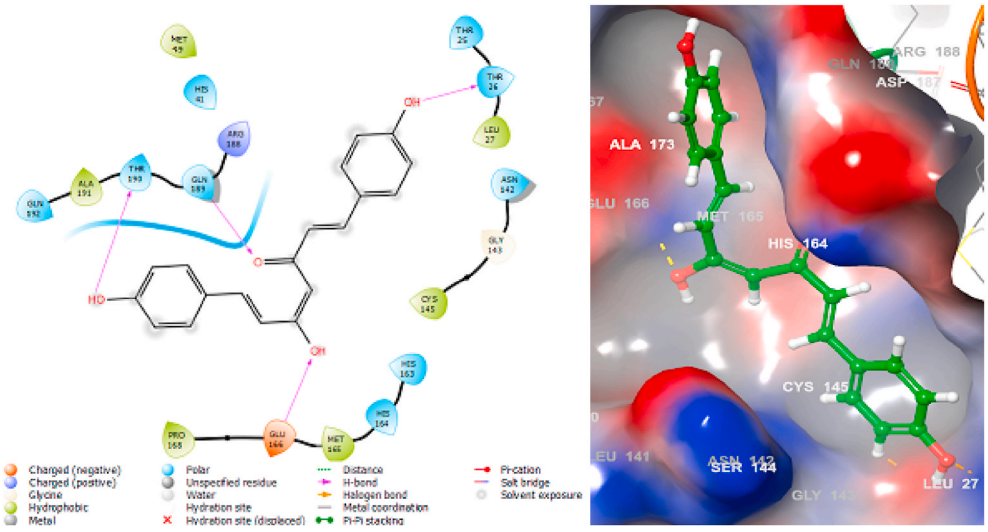

Fig. 2c. 2D and 3D representations of SARS-CoV-2 3C-like Protease-Bisdemethoxycurcumin.

tumor bioassays and the decreased tumor cell growth [38]. Curcumin has been reported to possess antioxidant, anti-inflammatory and anti-bacterial properties [38]. *In-silico* approach recently found curcumin as safe, being able to also interact in molecular mechanisms with proteins [39]. The docking score obtained for curcumin being higher than the standard ligand K36 may inform its level of interaction with the active site of Main protease of Sars-Cov-2 by forming hydrogen bonds [40,41]. The protoxll-predicted toxicity profile of curcumin inferred is non-hepatotoxic, non-cytotoxic, non-mutagenic with the LD_{50} prediction at 2000 mg/kg body weight suggesting that curcumin have good therapeutic properties with drug-likeness for oral drug development [41–43]. Kolaviron is the active ingredient of Garcinia kola known to possess biflavonoids responsible for its numerous health benefits; the high docking score may account for its interactions with Main protease of covid-19 making it pharmacologically active with numerous pharmacokinetic properties both in-vivo and in-silico [44,45]. Bisdemethoxy curcumin is a derivative of curcumin, composing of polyphenol and possess anti-cancer and hepatoprotective effect in-vivo [46]. Furthermore, the in-silico ADMET studies have predicted its role as antiviral among many therapeutic functions [47]. Gingerol the active ingredient of Zingiber officinale serves as anti-inflammatory agent; gingerol intreacts with main protease of covid-19 on the carboxyl and hydroxyl ends of the chains which can serve as potential drug target [48]. Artemisinin the active component of *Vernonia amygdalina* and an active anti-malaria component [4,49,50], though had the least docking score, interact with SARS-CoV-2 Main protease on Glu 166 and Gln 189 making it a potential drug target [51].

These six compounds interacted with important active site amino acids residues of the enzyme; curcumin, kolaviron, bisdemethoxy curcumin, gingerol, artemisinin and the standard ligand formed one or more hydrogen bonds with Gln 189. Additionally, curcumin, bisdemethoxy curcumin, gingerol, artemisinin, standard K36 formed hydrogen bond with amino acid GLN 189 [52]. There were hydrogen interaction with curcumin and kolavion on amino acid GLY143, bisdemethoxy curcumin and artemisinin on GLU 166 [53,54]. Curcumin and bisdemethoxy curcumin formed hydrogen bonds on THR26, finally bisdemethoxy curcumin and gingerol interacted with hydrogen bonds at the THR 190 amino acid pocket of the 6LU7 protein of the Main protease of covid 19.

The drug-likeness features which include flexibility, lipophilicity, water solubility, molecular size, plasma protein binding, and saturation of the compound polarity, determine the orally bioavailability of a

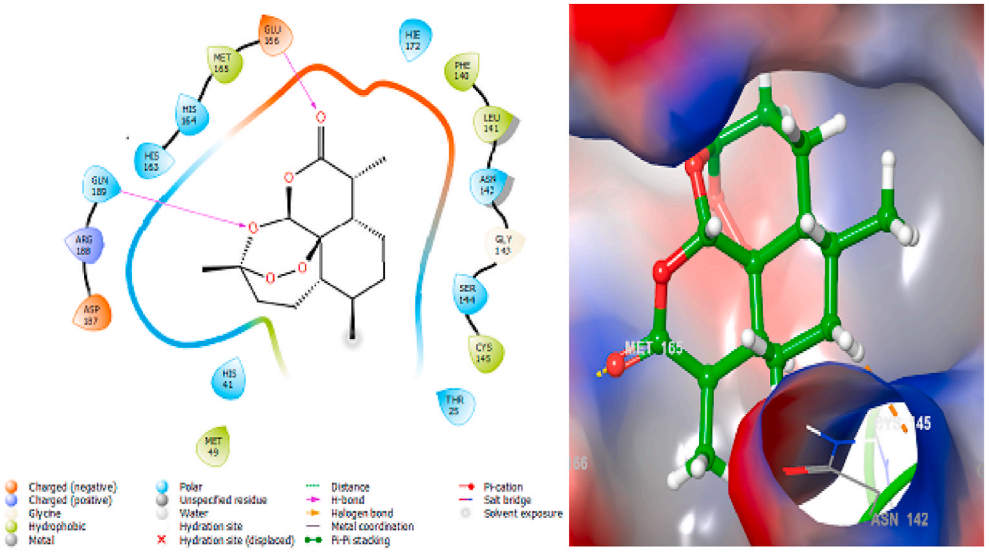

Fig. 2d. 2D and 3D representations of SARS-CoV-2 3C-like Protease-Artemisinin.

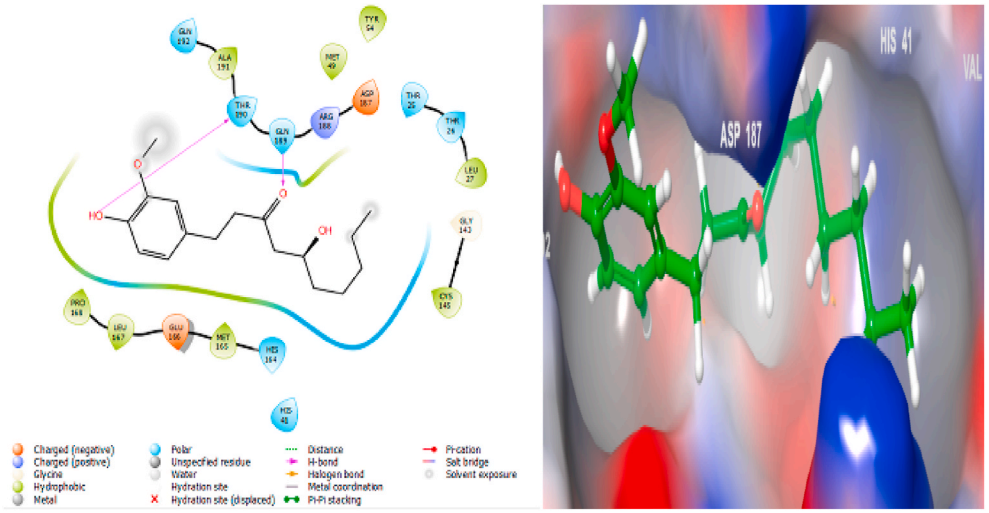

Fig. 2e. 2D and 3D representations of SARS-CoV-2 3C-like Protease-Gingerol.

compound [55,56]. Curcumin, bisdemethoxy curcumin, gingerol and artemisinin possess high water solubility, vital transport factor within the blood, however kolaviron is poorly soluble. Furthermore, curcumin, bisdemethoxy curcumin, gingerol and artemisinin obeyed both Vebers and Lipinski rule of five making them orally active. In Veber's rule, compounds that meet only the two criteria of $\leq$10 rotatable bonds and polar surface area $\leq$140 Å are projected to have good oral bioavailability while the Lipinski rule constitutes octanol/water partition coefficient (C logP) $\leq$ 5, number of hydrogen bond acceptors (HBA) $\leq$ 10, the criteria of molecular weight (MW) $\leq$ 500 with an orally active drug not violating beyond one of these criteria [11]. The toxicity profile of active compounds of curcumin, bisdemethoxy curcumin, gingerol and artemisinin are not likely to produce any toxic effect on the Hepatocyte and cytosol. Moreso, of all the active compounds gingerol is the most toxic compound with the LD_{50} of 250 mg/kg, while other active compounds belonging to oral toxicity class 5 are relatively safe, with LD_{50} ranging from 2000 to 4228 mg/kg. The pharmacokinetic properties of curcumin, bisdemethoxy curcumin, gingerol and artemisinin include the underlying role offered by drug-metabolising enzymes like cytochrome P-450 thereby inhibiting the metabolism of drugs being substrates of one or more of the enzymes, resulting in certain degrees of drug-drug interaction [54,57,58].

Binding free energy determines the stability of the protein-ligand complexes [58]; as the binding free energy increases, the ligand-bound protein becomes more stable and favorable. Curcumin exhibited the highest stability of Main protease, followed by kolaviron, the standard, bisdemethoxy curcumin, gingerol and artemisinin. The visualization in the scatter plot is thus a validation of how reliable the docking procedure is in predicting the active site of the protein. Moreso, the main donors to the free binding energy are covalent energy, Coulomb energy, lipophilic bonding, hydrogen bonding and van der Waals energy.

5. Conclusion

The potency of the active ingredients from ten medicinal plants common in Southwest Nigeria against Covid-19 virus has been determined. Five out of sixteen active compounds from the ten medicinal plants demonstrated positive inhibitory role against Main protease of Covid-19. These include curcumin, kolaviron, bisdemethoxy curcumin, gingerol and artemisinin. These active compounds recorded various docking scores against main protease of Covid-19 with curcumin being

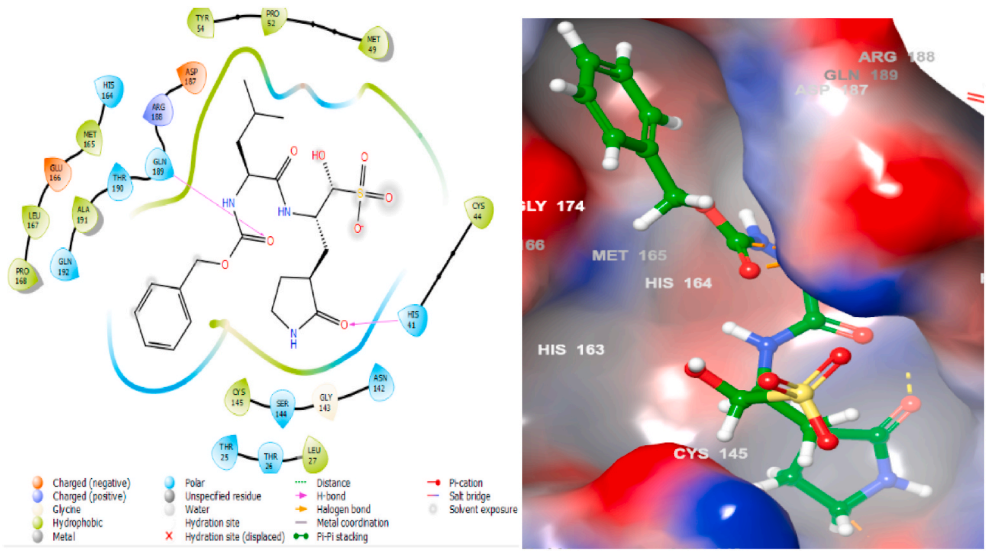

Fig. 2f. 2D and 3D representations of SARS-CoV-2 3C-like Protease-standard inhibitor.

Table 2
SwissADMET prediction outputs of selected active compounds.

AC	Molecular weight	Mean logp (0–3)	Silicos-IT Log SW (−0.7 to +6.0)	Silicos-IT class	Lipinski violations (>500 g/mol)	Veber violations (<140 Å^2)	Bioavailability Score (100%)
A	368.38	1.47	−4.45	MS	0	0	0.55
B	588.52	−0.48	−5.76	MS	3	1	0.17
C	308.33	2.13	−4.23	MS	0	0	0.55
D	294.39	2.14	−4.58	MS	0	0	0.55
E	282.33	2.62	−2.03	S	0	0	0.55

A = Curcumin, B=Kolaviron, C=Bisdemethoxycurcumin, D = Gingerol, E = Artemisinin, AC = Active compound; S=Soluble; MS = Moderately Soluble.

Table 3
Pharmacokinetics prediction output of selected active compounds.

AC	GI A	BBBP	Pgp	CYP1A2I	CYP2C19I	CYP2C9I	CYP2D6I	CYP3A4I
A	High	No	No	No	No	Yes	No	Yes
B	Low	No	No	No	No	Yes	No	Yes
C	High	Yes	No	Yes	No	Yes	No	Yes
D	High	Yes	No	Yes	No	No	No	No
E	High	Yes	No	Yes	No	No	No	No

A = Curcumin; B=Kolaviron; C=Bisdemethoxy curcumin; D = Gingerol; E = Artemisinin AC = Active compound; GIA = GI Absorption; BBB=BBB permeant; Pgp = Pgp substrate; CYP1A2I = CYP1A2 inhibitor; CYP2C19I = CYP2C19 inhibitor; CYP2C9I = CYP2C9 inhibitor; CYP2D6I = CYP2D6 inhibitor; CYP3A4I = CYP3A4 inhibitor.

Table 4
Protoxll-predicated toxicity profile of selected active compound.

AC	H T	C T	IT	MT	CT	LD_{50} (mg/kg)	PTC
A	Inactive	Inactive	Inactive	Inactive	Inactive	2000	4
B	Inactive	Inactive	Inactive	Inactive	Inactive	2000	4
C	Inactive	Inactive	Active	Inactive	Inactive	2560	5
D	Inactive	Inactive	Inactive	Inactive	Inactive	250	3
E	Inactive	Inactive	Inactive	Inactive	Inactive	4228	5

A = Curcumin; B=Kolaviron; C-Bisdemethoxy curcumin, D-Gingerol, E− Arteminsinin
HT=Hepatotoxicity; CT=Carcinogenicity; IT=Immunotoxicity, CT=Cytotoxicity; PTC=Predicted Toxicity Class.

the highest having −8.62 kcal/mol followed by kolaviron with −7.027 kcal/mol, the standard ligand with −6.541 kcal/mol, bisdemethoxy curcumin with −5.641 kcal/mol, gingerol with −4.975 kcal/mol and artemisinin with −4.252 kcal/mol. These five active compounds retain a favorable ADMET profile with none exhibiting any affinity towards cytotoxicity, hepatotoxicity, mutagenicity and carcinogenicity. As a result, these active compounds may be investigated further through experimental studies and possibly developed into novel drugs or supplements for the treatment of Covid-19.

Ethics approval and consent to participate

Not applicable.

Sources of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Consent for publication

Not applicable.

Table 5
Binding free energy calculations of top five hit compounds against main protease.

AC	ΔGBind[a]	ΔG_Coulomb[b]	ΔG_Covalent[c]	ΔG_Hbond[d]	ΔG_Lipo[e]	ΔG_Packing[f]	ΔG_vdW[g]
A	−59.50	−36.72	7.61	−2.49	−17.82	−0.81	−41.05
B	−61.33	−41.99	6.91	−3.84	−7.34	−4.52	−39.90
C	−42.99	28.22	6.75	−1.32	−20.49	−0.34	−53.66
D	−52.87	−28.69	4.06	−2.43	−13.31	−1.33	−29.12
E	−45.10	−17.89	7.47	−1.62	−16.75	−0.51	−33.12
F	−22.12	1.34	−0.01	−1.13	−7.20	0	−26.67

AC-Active compound A-Curcumin B-Kolaviron C- (1s,2s)-2-({n-[(Benzyloxy)carbonyl]-L-Leucyl}amino)-1-Hydroxy-3-[(3s)-2-Oxopyrrolidin-3-Yl]propane-1-Sulfonic Acid D-Bis Demethoxy curcumin E-Gingerol F-Artemisinin.

[a] MM-GBSA free energy (kcal/mol) of binding.
[b] Contribution to the MM-GBSA free energy of binding (kcal/mol) from the Coulomb energy.
[c] Contribution to the MM-GBSA free energy of binding (kcal/mol) from hydrogen bonding.
[d] Contribution to the MM-GBSA free energy of binding (kcal/mol) from lipophilic binding.
[e] Contribution to the MM-GBSA free energy of binding (kcal/mol) from packing binding.
[f] Contribution to the MM-GBSA free energy of binding (kcal/mol) from solvent GB binding.

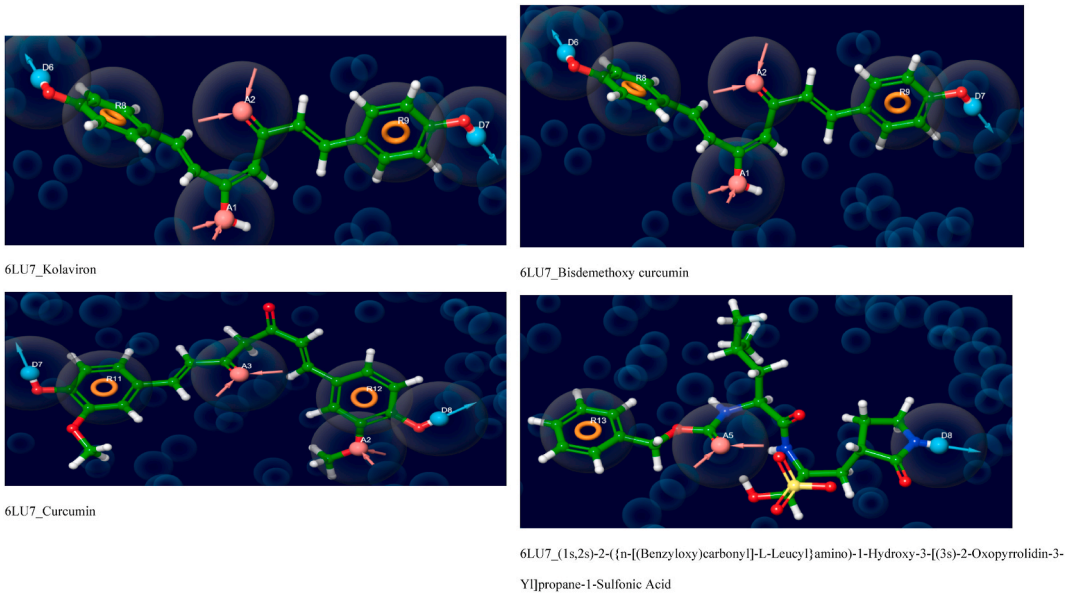

Fig. 3. Pharmacophore models of kolaviron, curcumin, Bisdemethoxy curcumin and (1s,2s)-2-({n-[(Benzyloxy)carbonyl]-L-Leucyl}amino)-1-Hydroxy-3-[(3s)-2-Oxopyrrolidin-3-Yl]propane-1-Sulfonic Acid on SARS-CoV-2 Main proteinase.

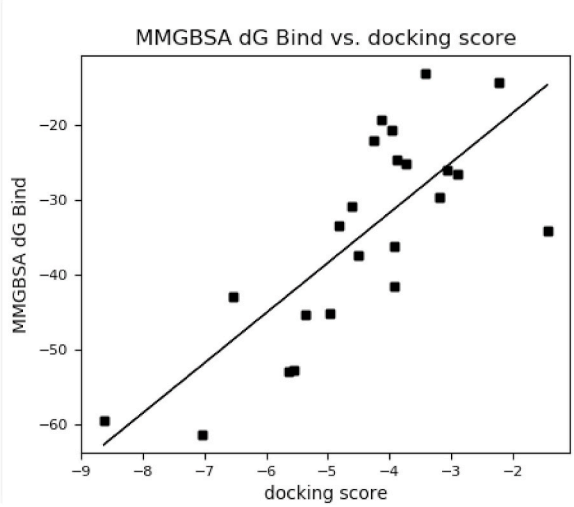

Fig. 4. Binding free energy MMGBSA dG Bind (Δ*G*bind) versus docking score (kcal/mol).

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Authors' contributions

Conception and design of the study: OP and OF. Acquisition of data, analysis and interpretation of data: OP, OF and AE. Drafting the article, revising it critically for important intellectual content: OP, OF and AE. Final approval of the version to be submitted: OP, OF and AE.

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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