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Identification of Promising High-Affinity Inhibitors of SARS-CoV-2 Main Protease from African Natural Products Databases by Virtual Screening

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Abstract

With the rapid spread of the novel Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2), the causative agent of COVID-19 pandemic, poses a serious threat to global public health and still requires further investigations into potential therapeutic agents. The availability of SARS-CoV-2 genomic data and efforts to determine the structure of the viral proteins facilitated the identification of potent inhibitors using structure-based methods and bioinformatics tools.

Some drugs candidates have been proposed to treat COVID-19, but their effectiveness has not been approved. However, it is important to find new targeted drugs to overcome the problem of drug resistance. Several viral proteins such as proteases, polymerases or structural proteins have been considered as potential therapeutic targets. However, the viral target must be essential for host invasion and meet certain drug eligibility criteria.

In this work, we selected the validated pharmacological target main protease Mpro and we performed high throughput virtual screening of Natural Products from African Databases such as NANPDB, EANPDB, AfroDb, and SANCDB to identify the most promising inhibitors with the best pharmacological properties.

In total, 8741 Natural Products NPs were virtually screened against the main protease of SARS-CoV-2. Two hundred and five (205) compounds showed high-affinity scores (less than -10.0 Kcal/mol), among which fifty-eight (58) filtered through Lipinski's rules. Those NPs showed better affinity than known inhibitors (i.e., ABBV-744, Onalespib, Daunorubicin, Alpha-ketoamide, Perampanel, Carprefen, Celecoxib, Alprazolam, Trovafloxacin, Sarafloxacin, Ethyl biscoumacetat). Detail of their interactions with the protein were illustrated and discussed with comparative inhibitors. Those promising compounds could be considered for further investigations toward the development of SARS-CoV-2 drug.

Keywords: SARS-CoV-2; Main protease; Natural products; Virtual screening

KAbbreviations: NP: Natural Products; SARS-CoV-2: Severe Acute Respiratory Syndrome Corona Virus 2

Introduction

On January 30th, 2020, the World Health Organization (WHO) declared the outbreak of the spread of coronavirus (COVID-19) as an international public health emergency [1]. In March 2020 the WHO classified the COVID-19 as a pandemic showing the rapid spread of the threat due to the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [2].

This infection infected more than 667,000,000 people and caused more than 6,7 million deaths worldwide in January 2023. Although not spared, the Africa continent had more than 258,000 deaths and more than 12,700,000 cases at the beginning of August 2021. The rapid spread of the pandemic caused a serious threat to public health, requiring rapid research into therapeutic agents. The development of new drugs requires too much time and money by conventional methods [3]. With omics technologies and bioinformatics tools, the time and costs are considerably reduced. In the COVID-19 pandemics, the rapid availability of SARS-Cov-2 genomic data and the protein structures facilitated the identification of therapeutic targets and inhibitors. Thus, many inhibitors have been proposed to treat the COVID-19. Those molecules were from Natural Compounds or from Approved Drugs. but their efficiency has not been evaluated yet [4-6]. Several viral proteins such as proteases, polymerases or structural proteins have been considered as potential therapeutic targets [7].

Natural Products (NPs) are broadly defined as chemical substances produced by living organisms. Some definitions include all small molecules resulting from metabolic reactions, while others classify as "NPs" only the secondary or non-essential metabolism products [8,9]. In this document, the term Natural Products will designate extracted bioactive compounds from Plants stored in an African Data base. The bioactive compounds have benefited mankind in food, pesticides, cosmetic products, and especially in drugs [10]. The crude extracts from Plants used in traditional medicine contain many pharmacological active compounds [11,12]. They have shown their healing power in reducing diseases since ancient civilization [13]. These crude medicines can lead to the discovery of other active molecules and eventually to the development of chemical pure drugs that have real beneficial effects. Currently, many prescribed medicines are derived from investigations on natural products. The oldest examples of drugs based on natural products are analgesics. Salicin, a natural product hydrolyzed into

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acetylsalicylic acid, better known as aspirin, is a synthetic derivate used as an analgesic [13]. Some of the notable approved drugs, either from pure or derived NPs, include lefamulin, the aminoglycoside antibiotic plazomicin; tafenoquine succinate, an antimalarial agent; and aplidine, an anticancer agent [14]. These findings are positive proofs that NPs could be used to find efficient drugs.

In the early 2000s, the main protease (Mpro, nsp5) also named chymotrypsin-like protease (3CLpro) attracted particular attention as therapeutic targets after the first SARS-CoV epidemic [15]. Indeed, many studies demonstrated that this protease is a interesting therapeutic target due to its essential role in viral replication [16,17]. Other important coronaviral therapeutic targets include Spike protein (S), RNA-dependent RNA polymerase (RdRp, nsp12), NTPase/helicase (nsp13), and papain-like protease (PLpro, part of nsp3) [18,19]. Mpro plays a central role in mediating viral replication and transcription functions through extensive proteolytic processing of two replication polyproteins, pp1a (486 kDa) and pp1ab (790 kDa) [20]. It exists only in viruses and is not present in humans. Interestingly, it is the most conserved enzyme among SARS-CoV-2 related viruses [21]. The sequence of the Mpro enzyme shows high identity (>96%) with the SARS-CoV, except for one key residue (Ala285Thr), which may contribute to the high infectivity of the SARS-CoV-2 virus [22]. The functional centrality of Mpro in the viral life cycle makes it an interesting target for drug development against SARS and other CoV infections. Therefore, its inhibition may block the production of infectious virus particles and thus alleviate disease symptoms [23]. By capitalizing on this knowledge, Mpro have been chosen as the most attractive target drug discovery against SARS in this work.

In this study, we carried out investigations of potential inhibitors of Mpro of SARS-CoV-2 by high-throughput virtual screening of NPs from African Databases. Details of interactions between the target et the molecules were analyzed to propose the promising inhibitors of SARS-Cov-2 [24].

Materials and Methods

Compounds datasets

We used four African databases of Natural Products: AfroDb, EANPDB, NANPDB and SANCDB [9,10,25-27]. Because the databases did not have the same formats, they were prepared differently. The molecules of the AfroDb and EANPDB databases were prepared using PyRx-Python Prescription 0.8 while those of SANCDB and NANPDB were formatted by Open Babel using homemade scripts [28]. Then all compounds in SDF (Standard Delay Format) format were converted into the pdbqt format. The compounds (Alpha-ketoamide 13b, Daunorubicin, Onalespib, and ABBV-744), were prepared using AutoDockTools to be used as controls.

Protein preparation

The main protease (Code PBD: 6Y2F), in complex with alpha-ketoamide 13b (αk-13b) was loaded into PyMol to delete the ligand [29]. The protein structure without the ligand was prepared with AutoDockTool-1.5.7 (ADT). ADT is being distributed free of charge as part of the MGLTools packages. ADT was used to remove non-polar Hydrogens, to add the Gasteiger charges, and to assign Solvation parameters and Atom Types. The resulting file was used as the receptor in the virtual screening process. The Computed Atlas of Surface Topography of protein (CASTp) server is an online tool that locates and measures pockets and voids on 3D protein structures [30]. It was used to determine the ligand-binding pocket size. Based on the pocket size and taking into account of the alpha-ketoamide 13b position in the crystal structure, the grid box coordinates were set as following: center_x=-0.000, center y=-0.704, center_z=-0.000 and size_x=40, size_y=40, size_z=40.

Virtual screening

Virtual screening is a widely used technique for identifying the top compounds against specific proteins from a library of compounds [31]. The sum of 8741 molecules was virtually screened with the main protease Mpro using AutoDock Vina 1.1.2 in Command Line. After the preparation of the protein and ligands in pdbqt format, all the files were put in the same folder, with a configuration file containing the receptor name, the grid box coordinates, the list of ligands [32,33]. The Vina script was launched with default parameters.

Lipinski's rule of five verification

Lipinski's rule helps to distinguish drug-like from non-drug-like molecules [34,35]. It states that a drug-like molecule must have at least two of the following rules: Molecular weight less than 500 Dalton, high lipophilicity (expressed as LogP less than 5), less than 5 hydrogen bond donors; less than 10 hydrogen bond acceptors; molar refractivity must be between 40 and 130 [34,35]. The SwissADMET server was used to compute the related parameters to Lipinski's rules [36].

Determination of Protein-ligand interactions

The interactions between the protein and the NPs were determined using the Ligplot+ v.2.2.4 software [37]. PyMol-2.0 was used to illustrate and highlight the interactions [29].

Results

Datasets of natural compounds

In this study, we used four African Databases of bioactive Compounds suitable for virtual screening: AfroDb, SANCDB, NANPDB and EANPDB. AfroDb is a collection of NPs from African medicinal plants with known bioactivities [38]. It represents the largest diversified collection of 3D structures of natural products covering the entire African continent. The compounds with a large number of tested biological activities are included in the ZINC database. The South African Natural Compounds Database SANCDB is a fully referenced database of NPs from sources in South Africa [27]. The Northern African Natural Products Database (NANPDB) is the largest collection of NPs produced by indigenous organisms of North Africa [9]. The Eastern Africa Natural Products Database EANPDB (http://african-compounds.org) containing the structural and bioactivity information of 1870 unique isolated molecules from about 300 source species from the Eastern African region. In total, 8741 NPs were obtained from the different databases (Table 1).

Database	SANCDB	NANPDB	EANDPB	AfroDb	Total
Number of NPs	1134	4912	1815	880	8741
References	Hatherley et al., 2015 [10]	Ntie-Kang et al., 2017 [25]	Simoben et al., 2020 [9]	Ntie-Kang et al., 2013 [26]	

Table 1: Summary of databases used for virtual screening.

SARS-CoV2 active site

The structure of SARS-CoV-2 (code PDB: 6Y2F) was used for the virtual screening. The protein was prepared as described above and the binding pocket was determined using CASTp server. ADT was used to prepare the Grid box corresponding to the CASTp results. The Figure 1 presented the localization of binding area for the screening.

The structure was constituted of two chains (A and B) surrounding a catalytic dyad (His41-Cys145). The structure was very similar to that of the SARS protease [39]. It was composed of three domains: the domain I (residues 1-101), domain II (residues 102-184) mainly made of antiparallel β-sheets, and an α-helical domain III (residues 201-301) [40,41]. The catalytic domain III contains the Ser284-Thr285-Ile286 segment, an additional domain far from the catalytic dyad. One major difference with SARS-CoV-I is the substitution of the Thr285 residue by Ala 23 [22]. The Figure 1A showed the binding pocket of Mpro represented by the Red surface. The molecular surface area of the pocket was 1738.8 Å3. This pocket was located between the two protomers. It was used to define a grid box covering the amino acids of the binding site (Figure 1B). The grid box volume was made large enough to allow a number of NPs to dock to the cleft. Indeed, a molecule able to strongly interact between the two protomers could inactivate the enzyme activity, even preventing the protein dimerization [42].

In total, 8741 molecules were screened against the SARS-CoV-2 Mpro among which two hundred and five (205) molecules presented affinity scores that ranged between -12.1 Kcal/mol and -10.0 Kcal/mol. Among them, fifty-eight passed through the Lipinski's rule and twelve (12) did not present any violation of the rule. Those molecules got affinity scores ranging from -11.2 Kcal/mol and -10.0 Kcal/mol (Table 2). The molecules ABBV-744, Daunorubicin and Onalespib described as potent inhibitors of Mpro were also screened as controls using the same docking parameters (Table 2) [43].

The Table 2 showed for each molecule, the parameters of Lipinski which are molecular weight, logP, number of hydrogen bonds donor and number of hydrogen bonds acceptor. The twelve NPs presented in the Table 2 did not showed any violation of Lipinski's rules indicating improved pharmaceutical properties. Moreover, those compounds presented higher affinity scores than standard inhibitors used as controls [43]. The results illustrated that these NPs could be considered as promising inhibitors of Mpro from SARS-CoV-2.

The Table 3 presented the details of the interactions between Mpro and the twelve identified compounds. The analysis of the interactions showed that the inhibitors interact mostly with residues Arg4, Leu282, Gly283, Glu288 of Mpro which are key residues of Mpro.

The interactions between Mpro and the top four inhibitors based on their affinity scores, docked poses and interactions with key amino acids were presented on the Figure 2. The LigPlot+ program was used to map the 2D interactions between Mpro and the top four compounds (Figure 3). The details of the other compounds are presented on Figure 4. The analysis of the interaction's details was summarized in Table 4 which revealed that the main residues of Mpro interacting with the ligands were Arg4, Lys5 Glu283, Gly283 and Glu288 involved in the catalytic domain surrounding the active site dyad (His41-Cys145).

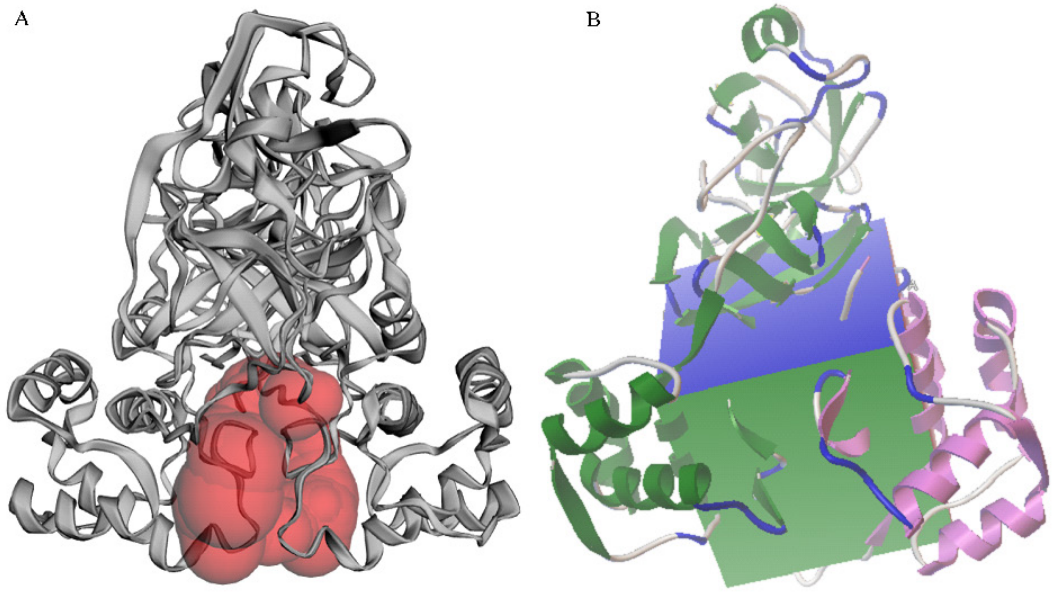

Figure 1: Binding pocket (Red surface) of SARS-CoV-2 Mpro determined by CASTp server (A), highlighted in the Grid box prepared by AutoDockTools (B). The Figure highlights also the two chains of the protein (chain A in purple and chain B in green).

No	Compounds	Mw (Dalton)	Log(P)	Hydrogen donor	Hydrogen acceptor	Affinity (Kcal/mol)
1	Sphaeropsidin A (NA)	346.42	2.27	2	5	-11.2
2	Gypsogenic acid (NA)	486.68	2.98	3	5	-10.6
3	Yardenone (SANC00595)	488.7	4.51	0	5	-10.5
4	A-homo-3a-oxa-5beta-olean-12-en-3-one-28-oic acid (EA)	470.691	-3.503	1	5	-10.4

5	Epigallocatechin (NA)	306.27	0.42	6	7	-10.4
6	Neopellitorine B (NA)	235.37	3.6	0	1	-10.4
7	Caretroside A (NA)	402.48	2.2	3	6	-10.3
8	Pallidol (NA)	454.47	2.51	5	6	-10.3
9	Maslinic acid (NA)	472.7	3.38	3	4	-10.2
10	Cabralealactone (NA)	414.62	3.86	0	3	-10.2
11	Olibanumol H (NA)	460.73	4.3	3	3	-10.1
12	Clionamine D (SANC00290)	401.54	2.43	2	5	-10
Known Mpro Inhibitors used as controls						
1	Alpha-ketoamide 13b	593.7	3.96	4	7	-9.2
2	Daunorubicin	527.5	2.66	5	11	-9.1
3	Onalespib	409.5	3.84	2	5	-8.4
4	ABBV-744	491.6	3.65	3	5	-8

Table 2: List of the most promising potent inhibitors of SARS-CoV-2 Mpro from African Natural Compounds.

Molecules	**Interactions with Protein via**	
	Chain A	**Chain B**
Sphaeropsidin A	Arg-4, Lys-5	Glu-288
Gypsogenic acid	Arg-4	Glu-283
Yardenone	Arg-4, Gly-283	Arg-4
A-homo-3a-oxa-5beta-olean-12-en-3-one-28-oic acid	None	Arg-4, Glu-288
Epigallocatechin	Lys-137, 2Glu-288, Asp-289, Glu-290	Arg-4
Neopellitorine B	Lys-137, Thr-169, Leu-287, Asp-289	Thr-280, 2Glu-283
Caretroside A	Glu-288	Trp-207, Gly-283, Lys-5
Pallidol	Phe-3, Asp-289	Lys-5, Glu-288
Maslinic acid	Phe-3	Leu-282
Cabralealactone	Arg-4	Leu-282
Olibanumol H	Arg-4, Gly-138	Lys-5, 2Phe-3
Clionamine D	Phe-3, Leu-282	Phe-3, Leu-282

Table 3: Interacting residues of Mpro with the inhibitors.

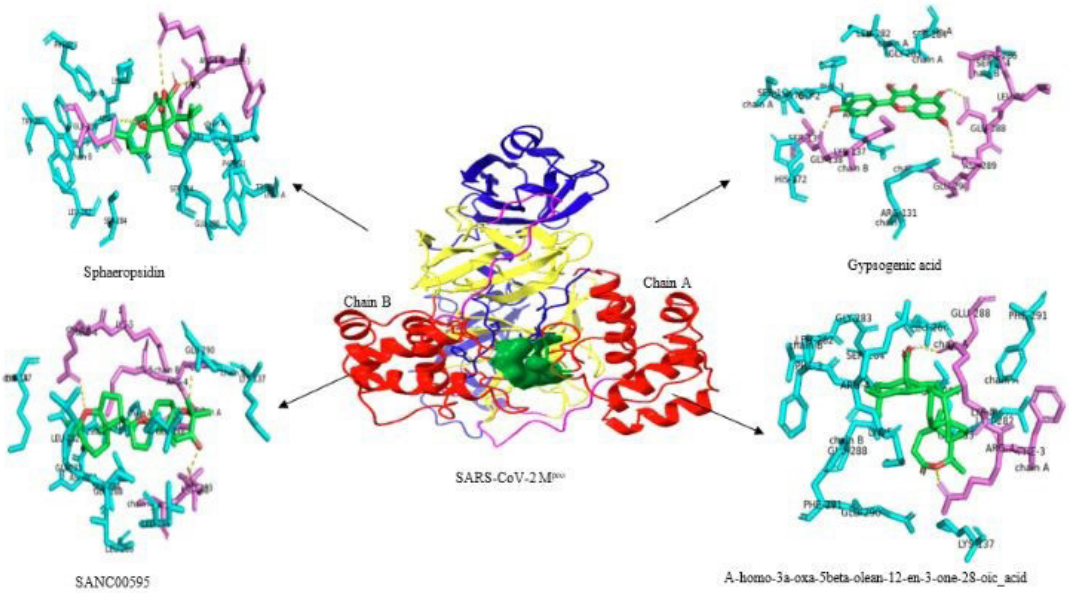

Figure 2: Details of Mpro interactions with the top four inhibitors; (A) Sphaeropsidin A; (B) Gypsogenic acid; (C) Yardenone (SANC00595); and (D) A-homo-3a-oxa-5beta-olean-12-en-3- one-28-oic acid. The ligands are illustrated in green stick surrounded by polar residues (magenta) establishing hydrogen bonds (yellow) with the protein and non-polar residues (cyan). The interacting residues of Mpro are labeled and numbered.

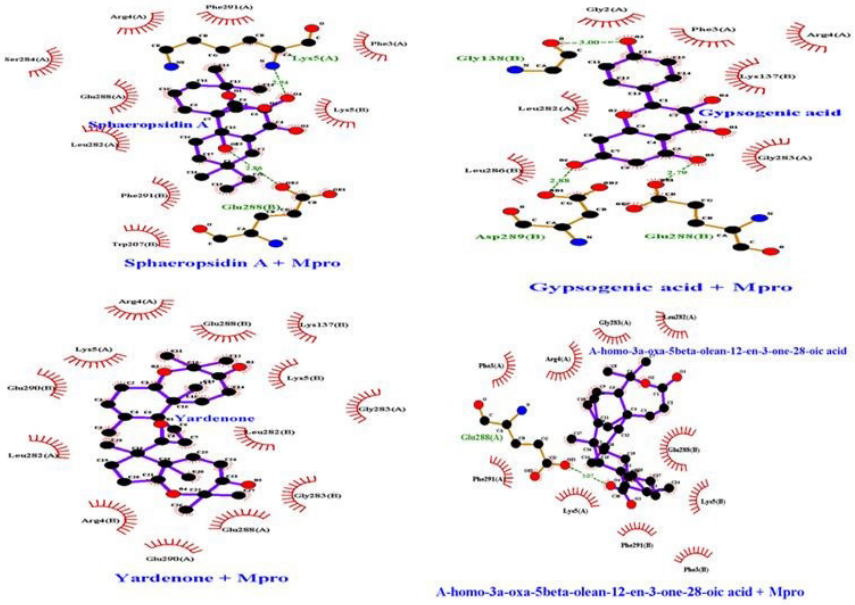

Figure 3: 2D interactions map between Mpro and the top four compounds by the LigPlot+ program.

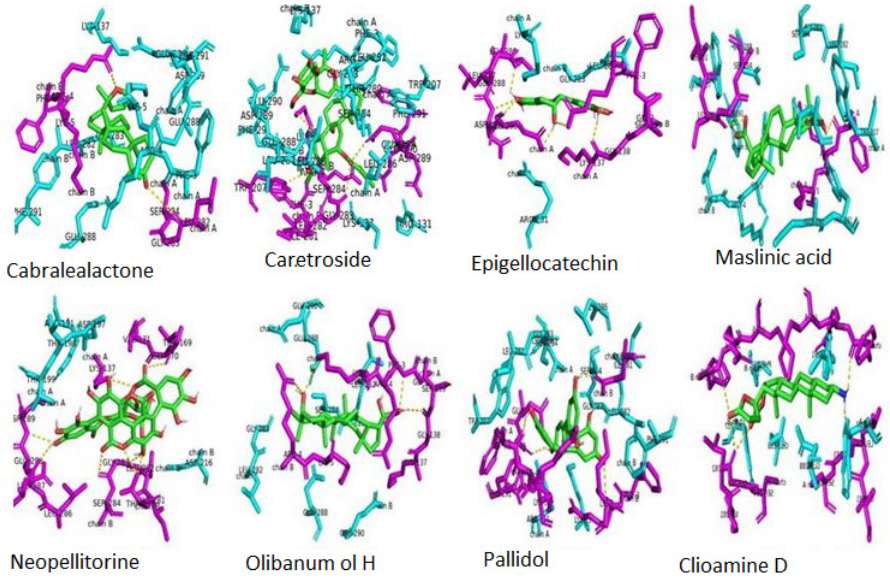

Figure 4: Interactions details between the others compounds and Mpro. Each ligand is illustrated in green stick surrounded by polar residues (magenta) establishing hydrogen bonds (yellow) with the protein and non-polar residues (cyan).

	Number of H Bonds	Mpro Residues involved in	
		H Bonds	VdW interactions
Sphaeropsidin A	3	Arg-4, Lys-5 (Chain A)	Phe-291, Phe-3, Ser-284, Glu-288, Leu-282, (Chain A)
		Glu-288 (Chain B)	Lys-5, Trp-207, Phe-291 (Chain B)
Gypsogenic acid	2	Arg-4 (chain A)	Gly-283, Phe-3, Gly-2, Leu-282 (Chain A)
		Glu-283 (chain B)	Leu-286, Lys-137 (Chain B)
Yardenone	3	Arg-4, Gly-283 (Chain A)	Lys-5, Leu-282, Glu-290, Glu-288, Gly-283 (Chain A)
		Arg-4 (chain B)	Glu-290, Gly-283, Leu-282, Lys-5, Lys-137, Glu-288 (Chain B)
A-homo-3a-oxa-5beta-olean-12-en-3-one-28-oic acid	2	Arg-4, Glu-288 (chain B)	Leu-282, Gly-283, Arg-4, Phe-3, Phe-291, Lys-5 (Chain A)
			Phe-291, Phe-3, Lys-5, Glu-288 (Chain B)

Table 4: Summary of interactions between Mpro and the top four compounds.

Discussion

Discovering new drugs capable of inhibiting the infection caused by SARS-CoV-2 is a worldwide imperative to finally end this public health emergency. Many studies have demonstrated that the Mpro protein is an attractive target for SARS-CoV-2 because it plays a significant role in viral replication, it is conserved compared to other related viruses, and differs from human proteases in its cleavage specificity [20,21]. Many crystal structures are available for this interesting target, making it well suitable for structure-based drug design [24,44]. Since Africa is a continent rich in plant diversity, the first choice for care comes from natural products, which are readily available and less expensive [8]. African NPs have been shown to have antiviral, antifungal and antibacterial properties [45]. These molecules are increasingly characterized and recorded in databases, becoming suitable candidates for high-throughput virtual screening against validated drug targets.

In this study, we screened out 8741 NPs from African databases: AfroDb (880), EANPDB (1815), NANPDB (4912) and SANCDB (1134) with the SARS-CoV-2 Mpro (code PDB: 6Y2F). Results showed that twelve (12) compounds (Table 2): Sphaeropsidin A, Gypsogenic acid, Yardenone, A-homo-3a-oxa-5beta-olean-12-en-3-one-28-oic acid, Epigallocatechin, NeopellitorinB, Caretroside A, Pallidol, Maslinic acid, Cabralealactone, Tribulus saponin aglycone 3, Olibanumol H and Clionamine D had high affinity values of -11.2 to -10.0 Kcal/mol for SARS-CoV-2 Mpro. These molecules show better affinity values than standard Mpro inhibitors such as 6-Deaminosinefungin (-8.1 Kcal/mol) and UNII-O9H5KY11SV (-8.4 Kcal/mol). Daunorubicin (-9.33 Kcal/mol), Onalespib (-8.21 Kcal/mol), ABBV-744 (-7.79 Kcal/mol) identified by Fakhar et al. [43] in the same conditions (Table 2). Furthermore, these molecules showed improved pharmaceutical properties, which were confirmed by Lipinski's parameter values. The 12 identified NPs showed their potential utility as interesting prodrugs of Mpro.

Analysis of their interactions with Mpro revealed that they primarily bind to protein residues Arg4, Lys5 Glu283, Gly283 and Glu288 involved in the catalytic domain around the active site dyad (His41-Cys145). Therefore, the identified compounds may actually block the enzyme's activity. It would be interesting to perform biological tests on the identified NP and SARS-Cov-2 proteins.

Many of the 12 NPs identified here have previously shown efficiency in other studies: Sphaeropsidine A against drug-resistant cancer cells; Gypsogenic acid against Bacillus subtilis and Bacillus thrungiensis also as potential antineoplastic agent ; Yardenone antagonizes the activation of hypoxia-inducible factor 1 (HIF-1) in breast and prostate tumor cells ; Epigallocatechin extracted from Acacia karroo, has been used medicinally to treat diarrhea, colds, dysentery, conjunctivitis and hemorrhages. Acacia karroo and other native plant species such as Artemisia afra, Ziziphus mucronata and Eucomis autumnalis have been widely used to treat symptoms of listeriosis; A-homo-3a-oxa-5beta-olean-12-en-3-one-28-oic Acid, extracted from Albizia gummifera has been used in indigenous medicine for various nutrients [46-48].

This study's findings imply that the inhibitors identified were promising inhibitors of SARS-Cov-2 main protease Mpro interesting for the development of efficient drugs against SARS-Cov-2. Further investigations are needed to deepen these findings in the process of drug development. The preliminary results of this study show that the identified inhibitors are promising inhibitors of the main protease Mpro, which is of great interest for the development of effective drugs against SARS-Cov-2, the causative agent of COVID-19. Biological assay is planned to evaluate the effect of these promising inhibitors of SARS-Cov-2.

Conclusion

In this preliminary study, a total of 8,741 Natural Products were subjected to virtual screening against the primary protease of SARS-CoV-2. From this 205 compounds demonstrated high-affinity scores and out of these, 58 compounds successfully met the filtration criteria and finally we identified twelve (12) NPs (Sphaeropsidin A, Gypsogenic acid, Yardenone, A-homo-3a-oxa-5beta-olean-12-en-3-one-28-oic acid, Epigallocatechin, Neopellitorine B, Caretroside A, Pallidol, Maslinic acid, Cabralealactone, Tribulus saponin aglycone 3, Olibanumol H, Clionamine D) from African databases of bioactive molecules which promising inhibitory effect on the main protease Mpro, the most attractive target of SARS-CoV-2. Further investigations need to be pursued to foster the way into the development of new drugs against the COVID-19 virus.

Competing interests

The authors have no competing interests to declare that are relevant to the content of this article.

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