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Research Article

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Molecular Docking Analyses of Phytochemicals from African Herbal Plants Exhibit Inhibitory Activity against Therapeutic Targets of Sars-COV-2

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Abstract

Viral diseases remain the leading cause of death due to infectious agent globally. Presently, global public health threat of international concern is the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the causative agent of coronavirus disease-2019 (COVID-19) of worldwide prevalence. Plants worldwide including plants of African ethno-pharmacological relevance are a natural source of abundant and diverse phytochemicals with bioactivity against microorganisms including viruses. We selected 13 plants used in African traditional medicine for the treatment of viral diseases to screen for phytochemicals capable of interfering with SARS-CoV-2 therapeutic targets using AutoDocking Vina in silico approach. 25 phytochemicals from these plants that passed the Lipinski rule of drug-likeness were assessed for antiviral activity against three SARS-CoV-2 therapeutic targets, namely: spike glycoprotein, Papain-like protease and 3C-like proteinase. The crystal structure of the viral protein targets were obtained from the protein databank website (https://www.rcsb.org/). The active sites of the target proteins were predicted using SCFBio Server (http://www.scfbio-iitd.res.in/dock/ActiveSite.jsp) from the pdb file as input. The antiviral herbal phytochemical compounds were then docked with Papain-like protease, 3C-like proteinase and spike glycoprotein. The Autodocking hit results generated six lead phytochemicals out of the twenty-five (25) phytochemicals obtained from the African traditional herbs with potential anti-SARS-CoV-2 activity. The lead molecules with their binding affinities against Papain-like protease and 3C-Like Proteinase are as follows: Ginsenosides (-9.9), ursolic acid (-9.4), oleanolic acid (-9.4), cynarine(-8.9), glabridin (-8.5) and cinnamoyl-echinadiol (-8.2). We advocate for further in vitro and in vivo studies to evaluate the activity of these lead compounds with a view to optimized drug intervention against COVID-19 pandemic.

Keywords: Coronavirus Disease-2019, SARS-CoV-2, Spike Glycoprotein, Papain-Like Protease, 3C-Like Proteinase.

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the causative agent of coronavirus disease 2019 (COVID-19), a viral disease recently declared a global public health emergency by the World Health Organization [1]. The Coronaviruses are enveloped, positive-sense single-stranded RNA viruses with a nucleocapsid of helical symmetry. The virus; SARS-CoV-2 encodes several proteins some of which are essential to viral entry and replication. Among these proteins is are 3C-Like protease (3CLPro) and spike protein. The SARS 3CLPro is a cysteine protease indispensable to the viral life cycle while the spike protein uses angiotensin converting enzyme 2 as a receptor to mediate virus cell entry. These proteins make attractive targets for drug development. Coronaviruses have widely been known to cause respiratory

and intestinal infections in humans after the outbreak of "severe acute respiratory syndrome (SARS)"in Guangdong, China. SARS was caused by SARS-CoV during 2002 and 2003, and it emerged in a market where civets were sold out. Only a decade later, the world witnessed another outbreak of "Middle East respiratory syndrome (MERS)" caused by MERS-CoV in the Middle East [2]. Coronavirus disease-2019 (COVID-19) outbreak was first reported December 2019 in Wuhan China and the disease has spread worldwide with over 3 million cases cases and 200,000 mortality. The country's worst hit (reporting over 10,000 cases) are USA, Italy, Spain, China, Germany, France, Iran, UK, Switzerland, Belgium, Netherlands, Turkey, Austria [3, 4]. As at April 30th, 2020 the Nigerian Centre for Disease Control (NCDC) reported over 1550 confirmed cases with 44 fatalities in Nigeria [5]. The widely accepted theory on source of COVID-19 infection relates to animal-human transmission as the virus jumps the species-barrier at a local fish and wild animal market in Wuhan of Hubei province in China. Studies have now established the disease ongoing spread is via humans by way of aerosolized droplets or through direct contact, with an average incubation day of 6.4 (range 2-14 days) and a basic reproduction number of 2.24-3.58 [6]. The infection is majorly characterized by pneumonia, fever, muscle soreness, abnormal respiratory distress syndrome (ARDS) and other rare symptoms such as diarrhoea, haemoptysis, headache, sore throat and shock [7].

Isolation of confirmed and suspected cases and their contacts is the central plank in the control of transmission, adopted by countries worldwide, the success of this approach is yet to be verified. In the meantime, no drug or vaccine is available for the treatment of confirmed cases and prevention of COVID-19 in the uninfected, presently clinicians are repurposing (repositioning) drugs developed for existing medical conditions such as that for malaria (chloroquine (CQ) / hydroxychloroquine (HCQ)), Human Immunodeficiency Virus (HIV) and EBOLA (Remdesivir) , anti-staphylococcal drug (teicoplanin) in the management of COVID-19. Earlier studies had shown CQ as a potent inhibitor of most coronaviruses, including SARS-CoV-1[8]. The antiviral properties of CQ and HCQ and their potential benefits in inhibiting the replication of SARS-CoV-2 has given the medical world a ray of hope in the fight against COVID-19. Preliminary trials of chloroquine repurposing in the treatment of COVID- 19 in China have been encouraging, leading to several new trials. Hitherto, no clinical trial hasindicated CQ treatment of any acute virus infection, however a modest treatment effect of CQ was observed with chronic hepatitis C virus (HCV) infection [9]. The pandemic is still ongoing, hence the need to urgently find new preventive and therapeutic agents as soon as possible. Development of these treatments may require years, meaning that a more immediate remedy should be found in earnest. Recently, the Nigerian minister of health encouraged the use of African indigenous herbal plants in fighting this new viral infection. Plants are a natural resource for abundant and diverse bioactive compounds evident by its deployment in the traditional pharmacopeia of almost all cultures and society. Innovative therapeutic approaches in modern science involve the screening of plants phytochemicals/ secondary metabolites for bioactive molecules able to interfere with microbial disease processes. Investigation of African folk/traditional medicines used in the treatment of viral diseases necessitated our study of phytochemicals from 13 different African plants species, namely. We hypothesize that the antiviral effects of these plants represent a potentially valuable resource for therapeutic intervention against SARS-CoV-2. Hence, the application of bioinformatics molecular docking tool AutoDock Vina to quickly screen African herbal plants for molecules with the potential to directly inhibit targets in SARS-CoV-2 the causative agent of COVID-19.

Materials and Methods

Literature Search and Analysis

Literature search and compound selection in google search engine concerning natural compounds against SARS or MERS coronavirus activity was selected using the query "coronavirus AND inhibitor AND (SARS OR MERS OR SARS-CoVOR MERS-CoV)." After careful reading of the studies returned by this search, the natural compounds that had biologically confirmed antiviral activities were compared? existing medicinal plants in Pubchem (https://pubchem.ncbi.nlm.nih.gov/) and NCBI (https://www.ncbi.nlm.nih.gov) for Natural compounds in herbs associated with antiviral activity were examined in a stepwise manner viz:- Discovery Studio Visualized; Protein Data Bank (https://www.rcsb.org/); Open babel GUI software; Supercomputing Facility for Bioinformatics & Computational Biology (http://www.scfbio-iitd.res.in/dock/ActiveSite.jsp) and Auto dock Vina as shown below in Figure 1.

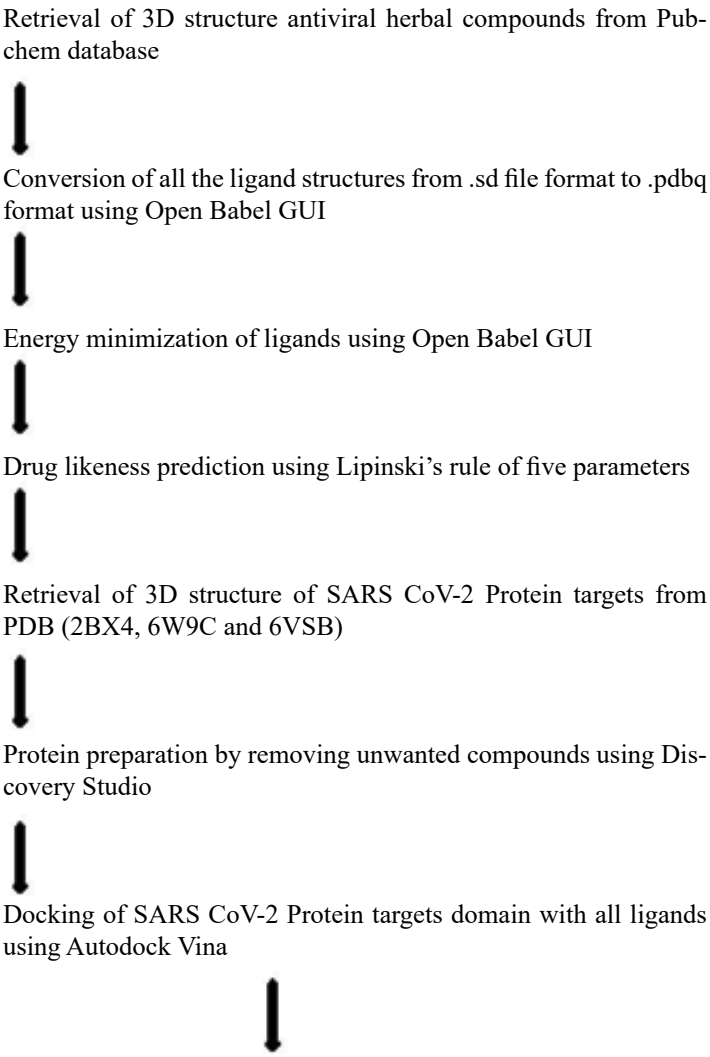

Figure 1: Flow Chart for the Collection and Sorting of Antiviral Herbal Compounds from NCBI.

Phytochemicals Hits Screening, Preparation and Optimization

A literature review of African Traditional Medicines with antiviral activities was conducted and a list of herbs with antiviral activities was produced. Further research was done on the list to produce the phytochemical bioactive compounds responsible for the antiviral activity using the websites Pubchem (https://pubchem.ncbi.nlm.nih.gov/) and NCBI (https://www.ncbi.nlm.nih.gov). The 3D chemical structures and the physiochemical properties of these antiviral phytochemical compounds were downloaded from the PubChem database (www ncbi.nlm.nih.gov/pubchem) in .sdf format. The energy of the compounds where minimized and converted to .pdbq format using Open Babel software. Summary of all the antiviral phytochemical compounds used in these studies are represented in table 1. Lipinski's rule of five parameters such as molecular weight, log P, and number of hydrogen bond donors and number of hydrogen bond acceptors were taken from the PubChem database for the herbs derived phytochemical compounds [10-15].

Table 1: List of Antiviral Phytochemical Bioactive Compounds from Herbs That Passed Lipinski Rules

S/N	*COMPOUND*	*HERBS*	*MOLECULAR MASS*	*LOG P*	*H- BOND DONORS*	*H-BOND ACCEPTORS*	*MOLAR REFRACTIVITY*
1	Carvacrol	Oregano	150.00	2.82	1	1	46.93
2	Safficinolide	Sage	344.00	3.51	1	5	92.08
3	Apigenin	Basil (holy)	270.00	2.42	3	5	70.81
3	Ursolic	Basil (holy)	456.00	7.09	2	3	132.61
4	Trans-Anethole	Fennel	148.00	2.73	0	1	47.70
5	Allicin	Garlic	162.00	2.62	0	1	46.00
6	Allyl Propyl Disulfide	Garlic	148.00	2.96	0	0	45.40
7	Diallyl Trisulfide	Garlic	178.00	3.39	0	0	52.90

8	Alanine, 3-(2-Propenyl-sulfinyl)	Garlic	177.00	0.20	3	4	43.82
9	(1s,2r,4s)-(-)-Borneol	Lemon grass	154.00	2.19	1	1	45.24
10	Methyleugenol	Lemon grass	178.00	2.43	0	2	53.45
11	3,7-Dimethyloc-ta-1,6-Diene	Lemon grass	138.00	3.55	0	0	48.03
12	Neral	Lemon grass	152.00	2.88	0	1	48.49
13	Nerol	Lemon grass	154.00	2.67	1	1	49.51
14	Menthol	Peppermint	156.00	2.44	1	1	47.35
15	Rosmarinic	Peppermint	360.00	1.76	5	8	89.80
16	Oleanolic Acid	Rosemary	456.00	7.23	2	3	132.68
17	(8Z,13Z)-8,13-Pentadecadien-11-Yn-2-One	*Echinacea*	218.00	4.05	0	1	70.11
18	Chlorogenic Acid	*Echinacea*	354.00	-0.65	6	9	82.52
19	Cynarine	*Echinacea purpurea*	516.00	1.03	7	12	125.20
20	Cinnamoyl Echi-nadiol	*Echinacea purpurea*	384.00	4.53	1	4	110.58
21	Sambucus Nigra Degraded Cyano-genic Glycosides (2'-Epimer)	Sambucus nigra	353.00	-0.32	2	9	81.67
22	Liquiritigenin	Licorice	256.00	2.80	2	4	68.53
23	Glabridin	Licorice	324.00	4.00	2	4	91.89
24	Zingerone	Ginger	194.00	1.92	1	3	53.66
25	Ginsenosides	Ginseng	444.00	7.53	2	2	134.29

Protein Retrieval and Preparation

The crystal structures of the three main protein targets of SARS-CoV-2 where searched and downloaded in .pdb format via protein data bank website (https://www.rcsb.org/) namely:-

1. 3C-Like Proteinase SARS CoV-2
(2BX4)
2. Papain-like proteinase SARS CoV-2
(6W9C)
3. Spike glycoprotein SARS CoV-2
(6VSB)

The unwanted molecules such as water, ligand in complex with the protein structures retrieved were removed using discovery studio visualizer software (Version 17.2.0) and Open babel software was used to convert the proteins from .pdb to .pdbq format.

Active Site Prediction

A search tool that determines the total number of active sites along with information on their amino acid sequence, cavity points and the average volume of the cavity was employed. The active sites of the target proteins were predicted using SCFBio Server (http://www.scfbio-iitd.res.in/dock/ActiveSite.jsp) using a .pdb file as input.

Docking Studies with AutoDock Vina

Molecular docking studies were performed for the selected antiviral phytochemical compounds with the selected target proteins of SARS CoV-2 by an automated docking tool, AutoDock Vina. Autodock Vina works by Lamarckian Genetic Algorithm. The precise interaction of bioactive agents or candidate molecules with their targets is important in the drug development process. AutoDock Vina combines two methods to achieve these goals Rapid grid-based energy evaluation and efficient search of torsional freedo

Results

Drug-Likeness Result

In silico study of the selected antiviral herbal compounds on the three main protein targets of SARS Cov-2 (3CLP, PLO, Spike Glycoprotein) using AutoDock Vina showed the following results and compounds which follow Lipinski's rule of five were all subject-

ed to docking experiment. Twenty-five (25) antiviral herbal compounds satisfied Lipinski's rule of five for drug-likeness (Table1). Lipinski rule of 5 is used to distinguish between drug like and non-drug like molecules and to predicts high probability of success or failure due to drug likeness for molecules complying with 2 or more of rules which are; Molecular mass less than 500 Dalton; High lipophilicity (expressed as LogP less than 5); Less than 5 hydrogen bond donors; Less than 10 hydrogen bond acceptors and Molar refractivity should be between 40-130 [16-24]. These filters serve as checks in early preclinical development which could reduce cost late-stage preclinical and prevents clinical trial failures.

Autodock Vina Docking

The whole docking procedure was done sequentially (Figure 1). The antiviral herbal phytochemical compounds that passed the Lipinski rule of 5 drug-likeliness were docked with Papain-like protease, 3C-like proteinase and spike glycoprotein separately. The docking results are summarized in Table1. The ligands with binding affinity >8 will be subjected to further interaction analysis. The findings of the results are solely based on the docking energy value and the interaction at the binding sites. The more negative the value, the more stable the complex is and more binding affinity. According to the energy funnel theory less energy depicts highly stable conformation. Hence more energy would be needed to break the complex that means high dissociation energy.

Inhibition of Papain-like Protease

All the selected ligands were docked with Papain-like protease and 3C-Like Proteinase, Table 2. The docking of ligands was carefully observed and their interaction and orientations were also monitored. Ginsenosides had the highest binding energy (-9.9), second to that Ursolic also scored high (-9.4) followed by Oleanolic acid (-9.4). Ginsenosides inhibit the most because the strength and the catalytic activity of a binding complex are predicted by their hydrogen bonds between them. The amino acid residues with which hydrogen bonds formed are shown in figures 2, 3 and 4 with residues in the active sites of Papain-like protease. Ursolic binds in the catalytic site with a greater number of hydrogen bonds when compared to other compounds as having better antiviral property and possible activity.

Table 2: AutoDock Vina Score of Antiviral Herbal Compounds on Papain-Like Protease with Binding Affinity >8

S/No	African Herb	Active Compound	Country Found	Binding Affinity	Rmsd/Ub	Rmsd/Lb
1	Ginseng *(Pinax ginseng)*	Ginsenosides	Uganda, South Africa	-9.9	22.018	19.332
2	Basil Holy *(Ocimum tenuiflorum)*	Ursolic	Nigeria	-9.4	13.971	11.308
3	Rosemary *(Salvia Rosmarinus)*	Oleanolic Acid	Nigeria, Sub-Saharan Africa	-9.4	8.076	2.523
4	Purple coneflower *(Echinacea purpurea)*	Cynarine	Nigeria Sub-Saharan Africa	-8.9	5.449	3.377
5	Licorice *(Glycyrrhiza glabra)*	Glabridin	Nigeria, Ghana, North Africa	-8.5	6.286	4.595
6	*Echinacea purpurea Purple coneflower*	-Cinnamoyl -Echinadiol	Sub-Saharan Africa	-8.2	2.134	1.512

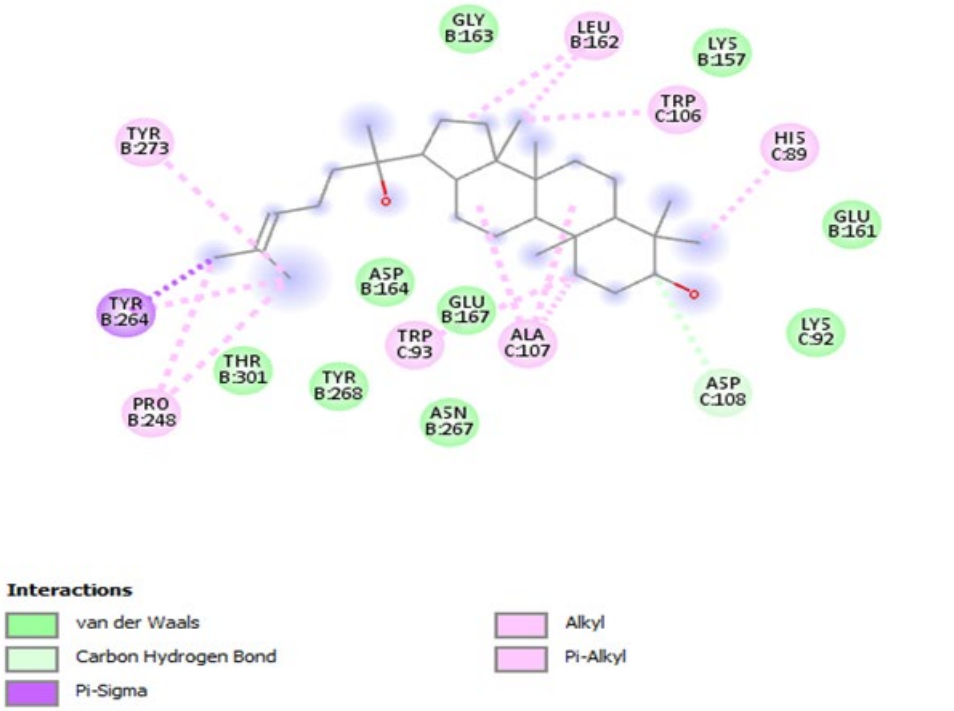

Figure 2: Papain-like protease in complex with ginsenosides

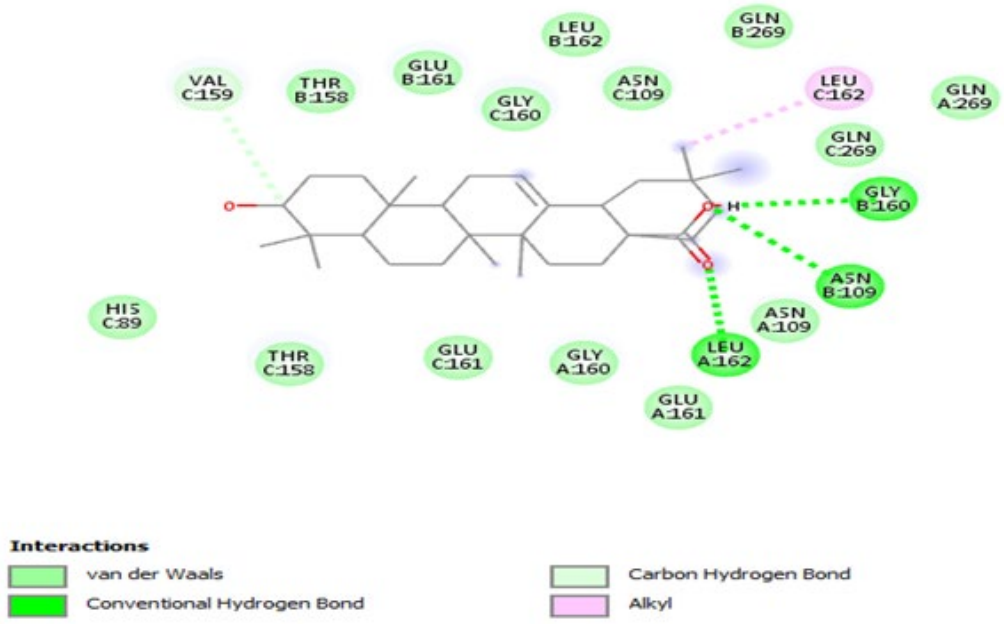

Figure 3: Papain-like protease in complex with Ursolic

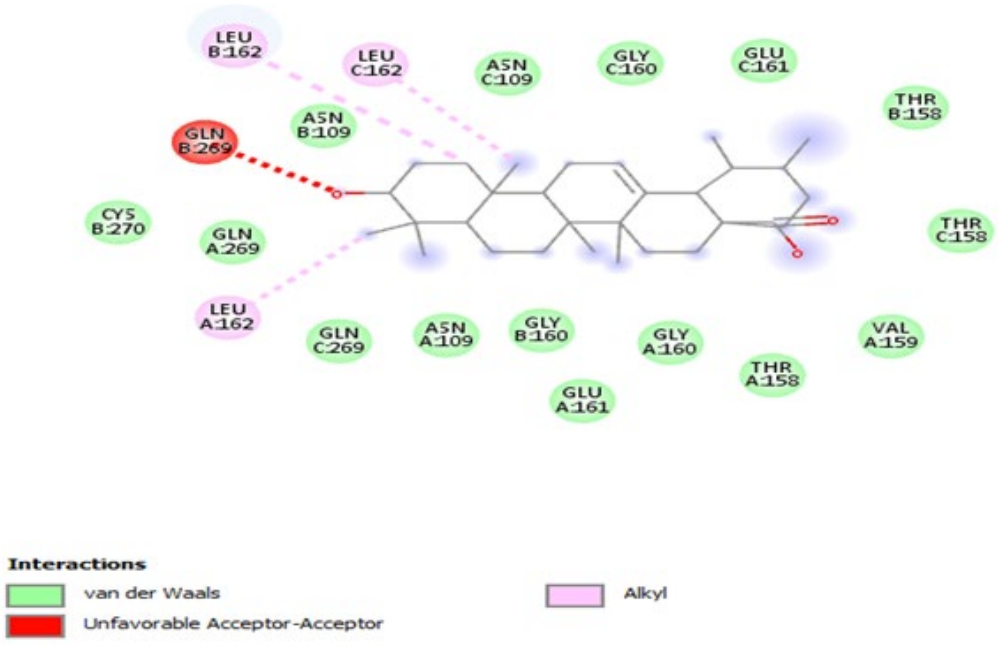

Figure 4: Papain-like Protease in Complex with Oleanolic acid

Inhibition of 3C-Like Proteinase

All the selected ligands were docked with 3C-Like Proteinase and the results are shown in Table 3. The docking of ligands was carefully observed and their interaction and orientations were also monitored. Table 3, Result showed that Ursolic having highest binding energy (-8.4) and the second one, Neral (-9.3) scored well. Now, the result showed that ursolic is a potent inhibitor when compared with the 3C-Like Proteinase.

The strength and the catalytic activity of a binding complex are predicted by their hydrogen bonds between them. The amino acid residues with which hydrogen bonds formed are shown in figures 5 and 6. These residues are in the active site region of 3C-Like Proteinase.

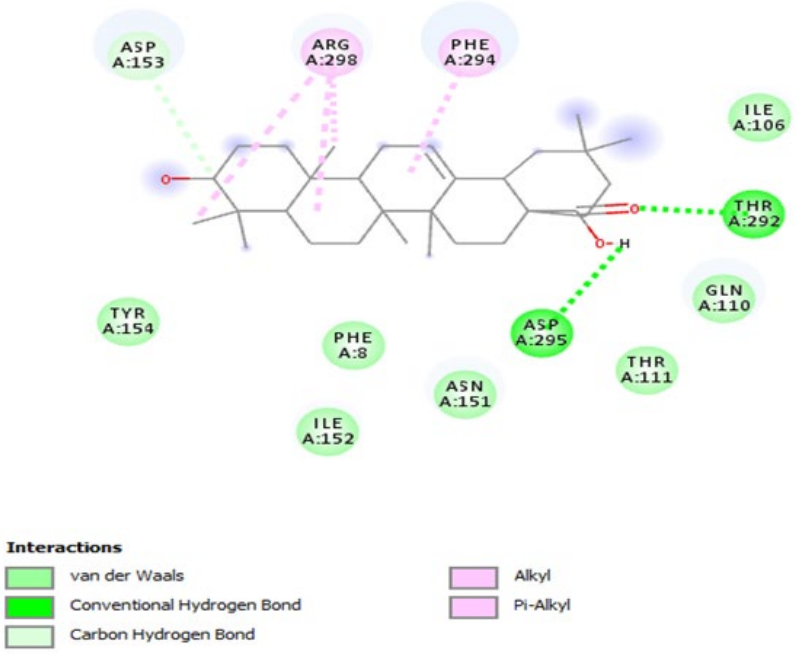

Figure 5: 3C-Like Proteinase in complex with Ursolic

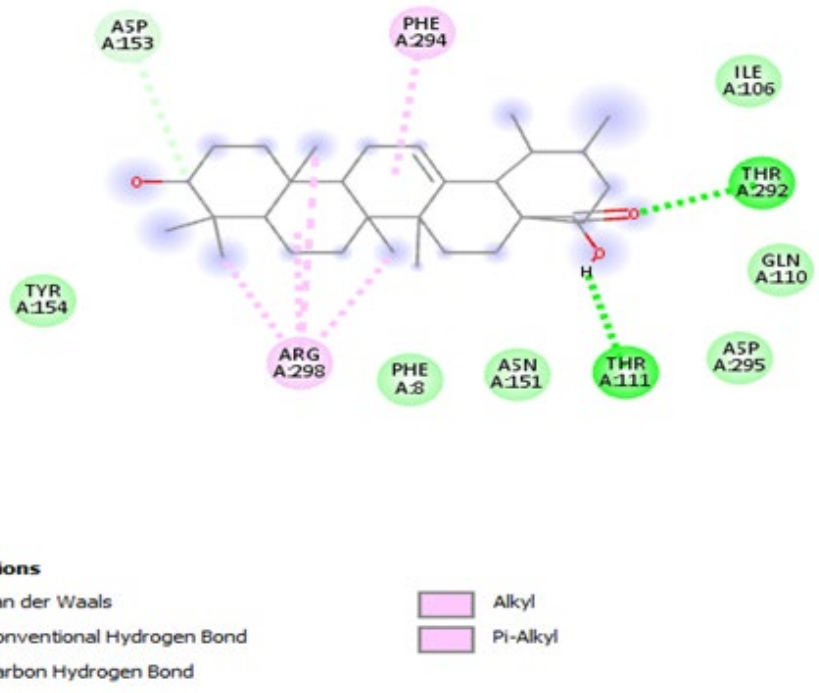

Figure 6: 3C-Like Proteinase in complex with Neral

Inhibition of Spike Glycoprotein

All the selected ligands were docked with spike glycoprotein where the docking of ligands was carefully observed and their interaction and orientations were also monitored. The output showed that Cynarine having highest binding energy (-9.1) second to that Oleanolic acid also scored high (-8.5) and third one the Ursolic (-8.3) scored well as shown in table 4. Hence Cynarine inhibit the most. Now, the result showed that Cynarine is a potent inhibitor when compared with the spike glycoprotein. The strength and the catalytic activity of a binding complex are predicted by their hydrogen bonds between them. The amino acid residues with which hydrogen bonds formed are shown in figures 4, 5, and 6.

ADMET Screening of Natural Compounds

Since traditional African herbal treatments are always taken orally after boiling with water, an in silico integrative model of absorption, distribution, metabolism and excretion (ADME) was used to screen for natural compounds that may be bioactive via oral administration. The indices used for the screening include evaluation of oral bioavailability, GI absorption, drug-like value, and BBB-Permeant. The threshold values indicating effectiveness for these four indices were > 30%, > 0.4, > 0.18 and Yes, respectively, as recommended by Hu et al [26]. The values of these four indices can be obtained from the NCBI database as seen in Table 3.

Table 3. ADMET Screening of Natural Compounds in African Herbs Using Swiss Tool

S/N	Active Compound	Herbs	Formula	Mw	Bioavailability Score	Drug-Like Values	BBB Permeant	GI - Absorption
1	Ginsenosides	Ginseng (Pinax ginseng)	C30H52O2	444.73	0.55	2	No	Low
2	Ursolic	Basil Holy (Ocimum tenuiflorum)	C30H48O3	456.7	0.56	2	No	Low
3	Oleanolic Acid	Rosemary (Salvia Rosmarinus)	C30H48O3	456.7	0.56	2	No	Low

4	Cynarine	Purple cone-flower (Echinacea purpurea)	C25H24O12	516.45	0.11	2	No	Low
5	Glabridin	Licorice (Glycyrrhiza glabra)	C20H20O4	324.37	0.55	1	Yes	High
6	Cinnamoyl Echinadiol	Echinacea purpurea Purple cone-flower	C24H32O4	384.51	0.55	2	Yes	High
7	Neral	Lemon Grass	C10H16O	152.23	0.55	1	Yes	High
8	Apigenin	Basil (Holy)	C15H10O5	270.24	0.55	0	Yes	High

Discussion

In this work, we undertook a multiple step selection process and screened 25 herbal plants with a high probability of directly inhibiting SARS-CoV-2 possibly providing instant help in the prevention and treatment of the pneumonia. In Africa, Nigeria in particular at this point, viral spread is ongoing and has affect persons worldwide. Two principles guided our screening work. The first is that the anti-coronavirus components contained in the source plants should be absorbable via oral prescription. This principle requires that the herbs selected should contain biologically proven anti-coronavirus ingredients, and that these natural compounds should pass the drug-likeness test. Therefore, we conducted a three-step screening process. In silico, studies of the selected antiviral herbal compounds on the three main protein targets of SARS Cov-2 (3CLP, PLO, Spike Glycoprotein) using AutoDock Vina with exciting results. Compounds which obey Lipinski's rule of five were all subjected to docking experiment. Twenty-five (25) antiviral herbal compounds satisfied Lipinski's rule of five for drug-likeness as earlier stated, Table 1.

The Lipinski rule of 5, is too distinguished between drug like and non-drug-like molecules which is known to predict with high probability of success or failure. These filters are used as cut-off points or criteria for preclinical development to reduce wastages in clinical trials. The whole docking procedure was done sequentially. The second step was the antiviral herbal phytochemical compounds that passed the Lipinski rule of 5 drug-likeliness were docked with Papain-like protease, 3C-like proteinase and spike glycoprotein separately.

There were 25 overlapping compounds. This method was an expeditious way to identify natural components having a high possibility of anti-coronavirus (2019-nCoV) activity. This is important, as the anti-coronavirus effects of the selected compounds have been biologically confirmed, and the genetic similarities between coronavirus (2019-nCoV) and SARS or MERS coronavirus are high [24, 25]. Among the 25 compounds highlighted by our first step, only 6 passed this screening, showing the necessity of such a test.

All 6 compounds could bind to the proteins as predicted for the new coronavirus. We believe that the high success rate of our docking screening was due to the high genetic similarity between the new coronavirus and the SARS or MERS virus [24, 25]. The ligands with binding affinity >8 were subjected to further interaction analysis. The findings of the results are solely based on the docking energy value and the interaction at the binding sites. The more negative the value, the more stable the complex is and more binding affinity. According to the energy funnel theory less energy depicts highly stable conformation. Hence more energy would be needed to break the complex that means high dissociation energy. The docking results are summarized in in a tabular form Tables 1 and 2.

Inhibition of Papain-like Protease

The selected ligands were docked with Papain-like protease, their interaction and orientations were carefully monitored as showed in table2. Amongst the compounds with anti-viral activities, Ginsenosides had the highest binding energy (-9.9), followed by Ursolic with (-9.4) scores while Oleanolic acid. It means Ginsenosides inhibit the most because the strength and catalytic activity of a binding complex are predicted by their hydrogen bonds between them. The amino acid residues with which hydrogen bonds formed are shown in figures 3-6 explained this clearly [26-35]. These residues are in the active site region of Papain-like protease. Also, Ursolic binds in the catalytic site with a greater number of hydrogen bonds when compared to other compounds under study it therefor has high antiviral property.

Conclusion

In this study, 25 phytochemical hit molecules obtained from 13 different plant species contained in African traditional medicine pharmacopoeia with reported antiviral efficacy were screened through computer-aided drug discovery (CADD) with the molecular docking tool AutoDock Vina. Six lead molecules showed the highest binding affinity and strong interactions with three therapeutic targets (Papain-like protease, 3C-Like protease and spike glycoprotein) of SARS-CoV-2. These compounds displayed appreciable non-covalent interactions such as Hydrogen bonding,

Van der Waals forces, electrostatic and hydrophobic interactions. Lipinskis rule indicated the pharmacokinetic efficacy of these lead compounds especially against Papain-like protease. Further study into the absorption, distribution, metabolism, excretion, toxicity (ADMET) of these lead compounds, in vitro and in vivo experiments are needed to validate utilization and sourcing of COVID-19 therapeutic interventions from these plants [27-46].

Author Contributions

Conceptualization, Goni Abraham Dogo and John Chinyere Aguiyi; Data curation, Uchechukwu Oheari; Formal analysis, Uchechukwu Oheari; Funding acquisition, John Chinyere Aguiyi; Investigation, Goni Abraham Dogo and Uzal Umar; Methodology, Goni Abraham Dogo, Uchechukwu Oheari and Aboi Madaki; Project administration, Goni Abraham Dogo; Supervision, John Chinyere Aguiyi; Visualization, Uzal Umar; Writing – original draft, Goni Abraham Dogo, Aboi Madaki, John Chinyere and Uchechukwu. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

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