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RESEARCH ARTICLE

Can *Costus afer* be used for co-treatment of COVID-19, its symptoms and comorbidities? A novel approach for combating the pandemic and implications for sub-Saharan Africa

Jannat, K.[1¶], Hasan, A.[1¶], Bondhon, T.A.[1¶], Mahboob, T.[2], Paul, A.K.[1], Jahan, R.[1], Nissapatorn, V.[2*], Pereira, M.L.[3], Wiart, C.[4], Rahmatullah, M.[1*]

[1]Department of Biotechnology & Genetic Engineering, University of Development Alternative, Lalmatia, Dhaka, Bangladesh
[2]School of Allied Health Sciences, World Union for Herbal Drug Discovery (WUHeDD) and Research Excellence Center for Innovation and Health Products (RECIHP), Walailak University, Nakhon Si Thammarat, Thailand
[3]CICECO-Aveiro Institute of Materials & Department of Medical Sciences, University of Aveiro, Aveiro, Portugal
[4]School of Pharmacy, University of Nottingham Malaysia Campus, Selangor, Malaysia
[¶]These authors contributed equally to this work
*Corresponding author: nissapat@gmail.com; rahamatm@hotmail.com

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ABSTRACT

Despite the huge loss of lives and massive disruption of the world economy by the COVID-19 pandemic caused by SARS-CoV-2, scientists are yet to come out with an effective therapeutic against this viral disease. Several vaccines have obtained 'emergency approval', but difficulties are being faced in the even distribution of vaccines amongst high- and low-income countries. On top of it, comorbidities associated with COVID-19 like diabetes, hypertension and malaria can seriously impede the treatment of the main disease, thus increasing the fatality rate. This is more so in the context of sub-Saharan African and south Asian countries. Our objective was to demonstrate that a single plant containing different phytoconstituents may be used for treatment of COVID-19 and comorbidities. Towards initial selection of a plant, existing scientific literature was scanned for reported relevant traditional uses, phytochemicals and pharmacological activities of a number of plants and their phytoconstituents pertaining to treatment of COVID-19 symptoms and comorbidities. Molecular docking studies were then performed with phytochemicals of the selected plant and SARS-CoV-2 components – Mpro, and spike protein receptor binding domain and hACE2 interface using AutoDock Vina. We showed that crude extracts of an indigenous African plant, *Costus afer* having traditional antidiabetic and antimalarial uses, has phytochemicals with high binding affinities for Mpro, and/or spike protein receptor binding domain and hACE2 interface; the various phytochemicals with predicted high binding energies include aferoside C, dibutyl phthalate, nerolidol, suginal, and ±-terpinene, making them potential therapeutics for COVID-19. The results suggest that crude extracts and phytochemicals of *C. afer* can function as a treatment modality for COVID-19 and comorbidities like especially diabetes and malaria.

Keywords: *Costus afer*; COVID-19; SARS-CoV-2; molecular docking; Aferoside C.

INTRODUCTION

The coronavirus pandemic caused by the Severe Acute Respiratory Syndrome Corona Virus-2 (SARS-CoV-2) has now caused considerable disruptions in the world economy and the world population. As of September 2, 2021 the virus has infected 219,291,026 persons and caused the deaths of 4,545,613 people (https://www.worldometers.info/coronavirus/). COVID-19 has no available allopathic drugs. Several vaccines have obtained emergency approvals, but it will be a daunting task to vaccinate the world's current population of 7.8 billion, and maintaining vaccine efficacy against quite rapidly emerging new variant strains of the virus.

Although till now, COVID-19 (the disease caused by SARS-CoV-2) cases had been low in Africa, the continent and particularly the sub-Saharan countries along with South Africa are now witnessing a surge in COVID-19 cases, which might dramatically impact the continent considering that most countries (including most sub-Saharan countries) are

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economically under-developed and may be ill-equipped to deal with COVID-19 diagnostics and treatment (Nuwagira & Muzoora, 2020). On top of COVID-19, sub-Saharan African countries suffer from a number of diseases (comorbidities) like malaria, human immunodeficiency virus (HIV), tuberculosis (TB), cholera, and Ebola (Orish, 2015), and non-infectious diseases like diabetes (International Diabetes Federation, 2017), which can complicate COVID-19 treatment and increase the number of fatalities.

Leaving aside other disorders, sub-Saharan African (SSAn) countries may have to cope with three epidemiological disorders at the same time, which disorders are syndemic in the form of COVID-19 (and its symptoms), malaria, and diabetes. No single allopathic medicine can deal with these three disorders (and these disorders-induced secondary complications) by itself. However, plants with their diverse array of phytochemicals can form a viable substitute.

The African continent contains possibly about 35,000 floral species (Couvreur, 2015) and a number of medicinal plants are used in the various African traditional medicinal (ATM) systems to treat many symptomatic disorders associated with COVID-19. African traditional medicines also use plants for the treatment of viral diseases other than COVID-19, like dengue and chikungunya, as well as non-viral diseases like diabetes and malaria. As such, ATMs need to be examined more closely regarding COVID-19, a view endorsed by WHO (WHO, 2020). A large percentage of COVID-19 patients die when comorbidities are present and this is an aspect which should not be overlooked.

Our initial literature search was for plants, which are used in ATM for the treatment of diabetes, malaria, and as many COVID-19 symptoms as possible. The next stage was to examine the reported phytochemicals and pharmacological activities of any selected plants that supported the plant's traditional/ethnic uses. In the final stage, molecular docking studies were conducted on reported phytochemicals of the plant with the main protease Mpro of SARS-CoV-2, which plays a vital role in viral replication and the interface between receptor binding domain (RBD domain) of the Spike protein (S) and its human angiotensin converting enzyme 2 receptor (hACE2), which plays the major role for binding and subsequent cellular entry of the virus. These two proteins of SARS-CoV-2 form major therapeutic targets for their importances in viral replication and viral entry, respectively, and are used in various computational studies for drug discovery against the virus (Wu *et al*., 2020).

As far back as human history has been recorded, it shows that human beings suffered from diseases and plants have always formed the source of drugs. The practice has continued till now, and about 25% of the drugs in current use in conventional or allopathic medicine are plant-derived. These drugs include digoxin, artemisinin, vincristine, vinblastine, and atropine, to name only a few (Rates, 2001). Ethnopharmacological approaches to new drug discovery encompasses field observations of traditional medicinal practices, followed by phytochemical and pharmacological research (Süntar, 2020). Because of the huge costs involved in clinical trials and the time required to conduct these trials, prior *in silico* studies are generally conducted using a variety of programs to learn more about the drug-potential of a phytochemical or its chemical derivatives.

In the present study, we have combined these approaches by first searching out the traditional uses of a plant followed by searches of its phytoconstituents and pharmacological activities. Following preliminary confirmation of the suitability of the plant through literature searchs as per our requirements of being a potential anti-COVID-19 plant (reported ability to alleviate at least a few COVID-19 symptoms as well as one or two comorbidities), the plant *Costus afer* was selected and a number of the phytochemicals of the plant were subjected to molecular docking analysis with two major proteins of SARS-CoV-2, as described before. Phytochemical screening through molecular docking with main protease Mpro of SARS-CoV-2 for discovery of anti-COVID-19 drugs has been done before in a number of studies (Garg *et al*., 2020; Joshi *et al*., 2020; Mahmud *et al*., 2021); the same applies to molecular docking studies with spike protein receptor binding domain (Basu *et al*., 2020; Pushkaran *et al*., 2021).

MATERIALS AND METHODS

Literature search

Existing peer-reviewed scientific literature was scanned through various search engines like PubMed, SCOPUS, and Google Scholar to find out review papers and papers dealing with ethnic uses, phytochemicals, and pharmacological activity studies of the plant *Costus afer*. A number of search terms were used like [*Costus afer*, review], [*Costus afer*, ethnobotanical uses, Africa]. For data pertaining to COVID-19, search terms like [COVID-19], and [COVID-19, comorbidities] were used. Boolean operators were used in the search. Selection of articles and their inclusions were prioritized on the basis of their containing search terms in their title, keywords, abstract or full text. We used a narrative mode to present the relevant reports; any meta-analysis was not done because of the scarcity of ethnic, phytochemical and pharmacological reports.

Three-dimensional structure of COVID-19 major protease (3C-like protease or Mpro)

We used the pdb file (6LU7) of the main protease of SARS-CoV-2 (Mpro) in the present study (Liu *et al*., 2020) following removal of the inhibitor (known as N3) from the pdb file prior to using the protein's structure in our molecular docking studies with the phytochemicals. Monomeric form of the protease was used for molecular docking (Zhavoronkov *et al*., 2020). Any water or other molecules bound to the monomeric structure was removed prior to molecular docking.

Structure of receptor binding domain (RBD) of spike protein bound to ACE-2

The structure of novel coronavirus SARS-CoV-2 spike protein receptor-binding domain complexed with its receptor ACE2 was retrieved from the Protein Data Bank (pdb id 6LZG). This structure demonstrates the interaction between Receptor Binding Domain (RBD) of Spike protein and its human receptor, human ACE2 (hACE2). The key residues of RBD that are involved in the interaction are as follows: Lys417, Tyr449, Leu455, Ala475, Glu484, Phe486, Asn487, Tyr489, Gln493, Ser494, Gly496, Gln498, Thr500, and Gly502 (Boison *et al*., 2019; Muhseen *et al*., 2020). The authors of the paper targeted the interface between RBD domain of the Spike protein and hACE2. Our intention was to examine for possible disruption in the protein-protein interaction between the Spike protein of SARS-CoV-2 and hACE2 through binding of phytochemicals to this binding region (RBD). Any disruption in this protein-protein interaction will make it difficult for spike protein to bind to hACE2 and thus cause SARS-CoV-2 to lose its ability to enter the human body. It would be further advantageous if the same phytochemical or phytochemical(s) from a single plant can bind to both Mpro and RBD of S protein.

Compounds used in docking studies

A total of 26 phytochemicals present in *Costus afer* were selected from several papers listing the phytoconstituents of the plant (Ogukwe *et al*., 2018; Boison *et al*., 2019). The selection was rather random and did not follow any set rules except for what seemed likely to bind to Mpro of SARS-CoV-2 or the RBD of S protein-hACE2 interface based on the phytochemical structure. Along with the phytochemicals, a control antiviral drug lopinavir was used as standard. Lopinavir is a drug currently under investigation against COVID-19 and has also been tested previously for use against Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) viruses (Meini *et al*., 2020; Yao *et al*., 2020). Ligand molecules were downloaded from Pubchem (Ihlenfeldt, 2008) in sdf format. They were optimized with the force field type MMFF94 using Openbable softwares and saved as pdbqt format.

Ligand molecular docking studies

Molecular docking (blind) was conducted using AutoDock Vina (Trott & Oslon, 2010). In blind docking there is no assumption on the binding site (Meng *et al*., 2011). We report ΔG values as an average of the top values from the docking program. In our figures, we show the pose of some phytochemicals bound to SARS-CoV-2 main protease as well as RBD of S protein-hACE2 interface, as obtained from PyMOL and displayed in Discovery Studio (Studio, 2015) as shown before in our previous studies (Hasan *et al*., 2020; Bondhon *et al*., 2021). It is to be noted that the lower the predicted binding energies (ΔG) of a phytochemical to Mpro or RBD of S protein, the higher will be the binding affinity of the phytochemical to the protein.

Lipinski's rule of five

Lipinski's rule of 5 or Ro5 (Giménez *et al*., 2010; Fernandes *et al*., 2016) was followed to determine the drug like properties of the phytochemicals of *Costus afer* in the present work. The rule states that molecules, which are poorly absorbed by intestinal wall (that is oral bioavailability is not good) would present any two or more of these characteristics: molecular weight more than 500, lipophilicity (log P >5), hydrogen-bond (HB) donor groups (expressed as the sum of OHs and NHs groups) more than 5, more than 10 HB acceptor groups (expressed as the sum of Os and Ns atoms), and molar refractivity outside a range of 40-130. Lipinski's rule has its violations and it may be mentioned that a number of drugs (like artovastatin and montelucast) have more than two violations of the rule (Giménez *et al*., 2010). From 2000 to 2014, out of the 38 central nervous system drugs introduced, 32% violated one or more aspects of Lipinski's rule (Bondhon *et al*., 2021). Lipinski's Ro5 still is advantageous for giving general ideas on the drug suitability of a given compound.

Biological activity prediction (ADME analysis)

The phytochemicals were evaluated for potential bio-activity (ADME or absorption, distribution, metabolism and excretion). The various parameters were evaluated with the aid of the software Molinspiration (www.molinspiration.com, Nova Ulica, Slovensky Grob, Slovak Republic) (Rakib *et al*., 2020).

Results and Discussion

Costus afer Ker-Gawl (Costaceae/Zingiberaceae) is commonly known in English as ginger lily and spiral ginger. It is an evergreen perennial. Its habitat ranges from Senegal and Ethiopia to Angola, Malawi, and Tanzania in sub-Saharan Africa. It can grow up to 4 meters high [https://pfaf.org/user/Plant.aspx?LatinName=Costus+afer].

Ethnic uses

A paper by Boison and colleagues published in 2019 (Boison *et al*., 2019) summarizes the various ethnic uses of this plant. These include "inflammation, arthritis, stomach-ache, cough, sore throat, measles, malaria, chicken pox, influenza, genital herpes, purgative, laxative, diabetes mellitus, wound healing, diuretic, aperient, jaundice, fever, leprosy, gastric ulcer, colic, hypertension, hemorrhoids, toothache, Central Nervous System (CNS) depression, helminthic disorder, hepatic disorder, miscarriage, gonorrhea, impotency, ear infection, conjunctivitis, and oligospermia". The common symptoms of non-complicated COVID-19 as mentioned before (Sheikhi *et al*., 2020) are marked in bold in the ethnic uses of *C. afer* in Africa as summarized by Boison *et al*. (2019) and given above, along with bold markings of disorders during moderate to severe COVID-19 infections. Also, to be mentioned is that inflammation, influenza, stomach ache, and other types of pain can also develop in COVID-19 patients like myalgia, arthralgia, headache, and chest pain (Weng *et al*., 2021). Among them, the most important comorbidities are possibly diabetes, malaria, and hypertension. CNS involvement and neurological manifestations are also increasingly described in COVID-19 patients (Asadi-Pooya and Simani, 2020), as well as jaundice (Fierro, 2020).

Pharmacological activity validations of ethnic uses

Pharmacological activity studies with *Costus afer* crude extracts or phytochemicals, which are relevant to COVID-19 symptoms and comorbidities are summarized in Table 1. It is to be noted that this is not an exhaustive review, rather some articles were chosen, which the authors (in their opinion) thought best described the subject. One thing is clear from ethnic literature and pharmacological activity studies (cited and not cited) that two of the disorders most studied and validated by researchers are the use of the plant against diabetes and malaria.

Molecular docking studies

Altogether 26 phytochemicals of *Costus afer* were evaluated for their binding affinities to Mpro and RBD of S protein of SARS-CoV-2. The results are shown in Table 2 and the phytochemical structures are shown in Figure 1. Among the 26 phytochemicals, the steroidal saponin aferoside C showed the least predicted binding energy (that is stronger binding affinity) for both Mpro and S proteins, with ΔG values at -8.8 and -10.4 kcal/mol, respectively. Besides aferoside C, none of the other phytochemicals showed any significant predicted binding energies with Mpro. However, suginal, dibutyl phthalate, nerolidol, and alpha-terpinene showed high binding affinities for RBD of S protein, with predicted ΔG values of -8.2, -7.2, -7.2, and -7.1 kcal/mol, respectively. The results indicate that at least five phytochemicals of *C. afer* may have the potential to block viral entry into human cells.

Like Mpro of SARS, Mpro of SARS-CoV-2 is catalytically active as a dimer. Each monomeric unit contains three domains, namely, domain I consisting of amino acid residues 8-101, domain II (amino acid residues 102–184), and domain III (amino acid residues 201–306) (Zhang *et al*., 2020). Although domain III does not directly participate in interacting with the substrate, removal of domain III results in an inactive protease for domain III is involved in regulating dimerization of Mpro (Amin *et al*., 2021) and dimerization is necessary for the protease to be catalytically active (Gimeno *et al*., 2020).

Table 1. Reported pharmacological studies with *Costus afer* relevant to COVID-19 symptoms and comorbidities

COVID-19 symptom or comorbidity	Pharmacological activity studies	References
Analgesic and anti-inflammatory effect	Using rat models, it was shown that leaf ethanol extract and stem juice demonstrated antinociceptive activities.	(Ijioma *et al*., 2014)
	Hexane fraction of 70% methanolic leaf extract showed anti-inflammatory properties *in vitro* screening assays like anti-denaturation of protein, erythrocyte stabilization assay, and anti-proteinase activity.	(Anyasor *et al*., 2015)
	Anti-inflammatory effect observed in carrageenan, arachidonic acid, formaldehyde, and Complete Freund's Adjuvant-induced arthritis in male albino rats with hexane fraction of leaves.	(Anyasor *et al*., 2014)
Hepatoprotective	Aqueous extract of stems significantly reduced total bilirubin concentrations in serum of high fat diet-induced hyperlipidemic rats.	(Chioma *et al*., 2020)
	Hepatoprotective activity seen in rats with aqueous leaf extract against cyclosporine A induced hepatotoxicity.	(Ezejiofor & Orisakwe, 2015)
	Oral administration of aqueous fraction of methanolic extract of leaves protected rats against diethylnitrosoamine-induced hepatocellular carcinoma.	(Anyasor *et al*., 2014, 2020)
CNS depression	Although leaf extract had little effect on gait even at a dose of 800 mg/kg body weight, it potentiated the effect of phenobarbitone in albino mice.	(Ezejiofor & Igweze, 2016)
Diabetes	In alloxan-induced diabetic rats, leaf extract at 375, 750 and 1125 mg/kg significantly reduced blood glucose levels.	(Uwah *et al*., 2015)
	Ethyl acetate extract of rhizome and methanol extract of leaf reportedly showed inhibition of α-glucosidase and α-amylase enzymes.	(Ezejiofor *et al*., 2017)
	In streptozotocin-induced diabetic rat model, leaf extract demonstrated significant improvement of diabetes-induced dyslipidemia.	(Ekpe *et al*., 2018)
	Leaf extract of the plant was able to reverse alloxan-induced damage of pancreatic β-cells.	(Ezejiofor *et al*., 2014)
Malaria	Aqueous extract of stems showed anti-plasmodial effect against *Plasmodium berghei berghei* infected albino mice.	(Kingsley & Umukoro, 2019)
	Ethanol extract of aerial parts of the plant reportedly demonstrated strong anti-plasmodial activity *in vitro* against field isolates and chloroquine sensitive 3D7 strains of *Plasmodium falciparum* using *Plasmodium* lactate dehydrogenase (pLDH) assay. No toxicity of the extract was observed.	(Tiko *et al*., 2020)
	Methanol stem extract of the plant and residual aqueous fraction showed significant and dose-dependent inhibitions of schizont growth in chloroquine-sensitive, chloroquine-resistant, and artemether-resistant *Plasmodium falciparum* strains with IC_{50} values of 8.86 and 10.51, 11.27 and 15.05, and 10.30 and 11.23 µg/mL against chloroquine-sensitive, chloroquine-resistant and artemether-resistant strains, respectively.	(Jimoh *et al*., 2019)

As shown in the 2D and 3D interactions in Figure 2, aferoside C interacts with amino acid residues Leu141, Asn142, Gly143, Cys145, Pro168 and Ala191 of Mpro. Thus, besides interacting with one of the catalytic dyad amino acids (Cys145), aferoside C binds essentially with domain II amino acids of Mpro (Cys145 is also a domain II amino acid). Common amino acid residues of Mpro interacting with aferoside C and the irreversible inhibitor N3 of Mpro are depicted in bold. Pymol diagram of polar interactions between Mpro amino acid residues and aferoside C are shown in Figure 3.

Fourteen amino acids of the spike protein receptor binding domain (S-RBD) of SARS-CoV-2 have been identified contributing to the binding and stability of the complex. These amino acids of S-RBD are Phe486, Asn487, Ala475, Glu484, Tyr489, Leu455, Gln493, Tyr453, Ser494, Tyr449, Gln498, Gly496, Gly446 and Asn501. Amino acid residues on ACE-2 like Lys353 and Lys31 are said to contribute to the hotspot residues that ultimately bind the S protein (Yi *et al*., 2020). The 2D and 3D interactions of aferoside C and dibutyl phthalate with S protein RBD-hACE2 receptor interface are shown in Figures 4 and 5, respectively. Aferoside interacts with Gly446, Gly447, Tyr449, and Phe486 amino acid residues of S-RBD (the important amino acid residues are shown in bold). Dibutyl phthalate interacts with Phe486 and Tyr489 amino acid residues of S-RBD. Taken together, the binding affinities of aferoside C as shown in Table 2 and the various Figures (2D, 3D, and Pymol) demonstrated tight interactions of the phytochemical with both Mpro and RBD of S protein-hACE2 interface and thus can be considered as a potential therapeutic against SARS-CoV-2. Although dibutyl phthalate, suginal, nerolidol, and α-terpinene did not demonstrate high binding affinities with Mpro, yet considering their predicted

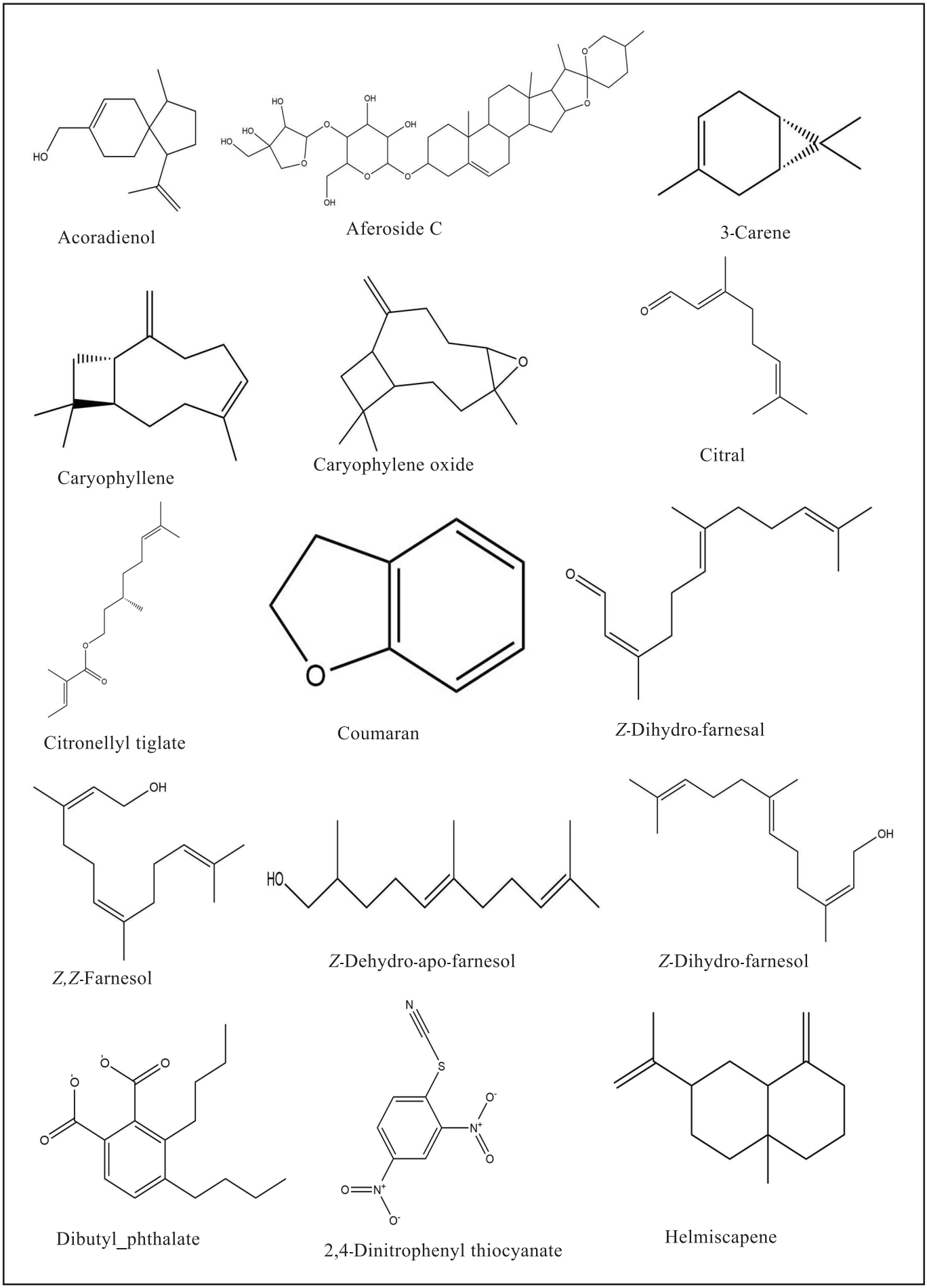

Figure 1. Structures of *Costus afer* phytochemicals used in molecular docking studies.

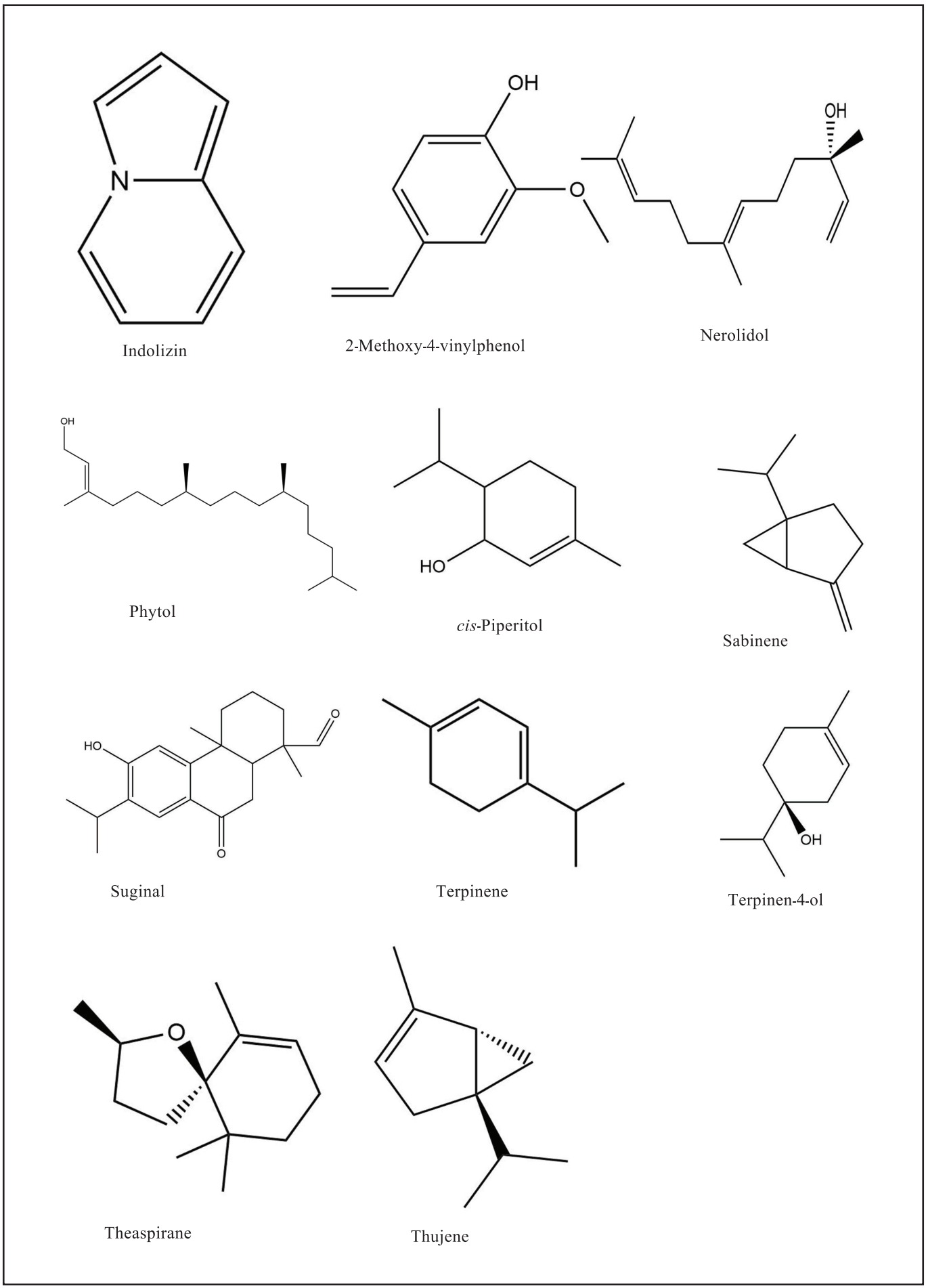

Figure 1. (continued).

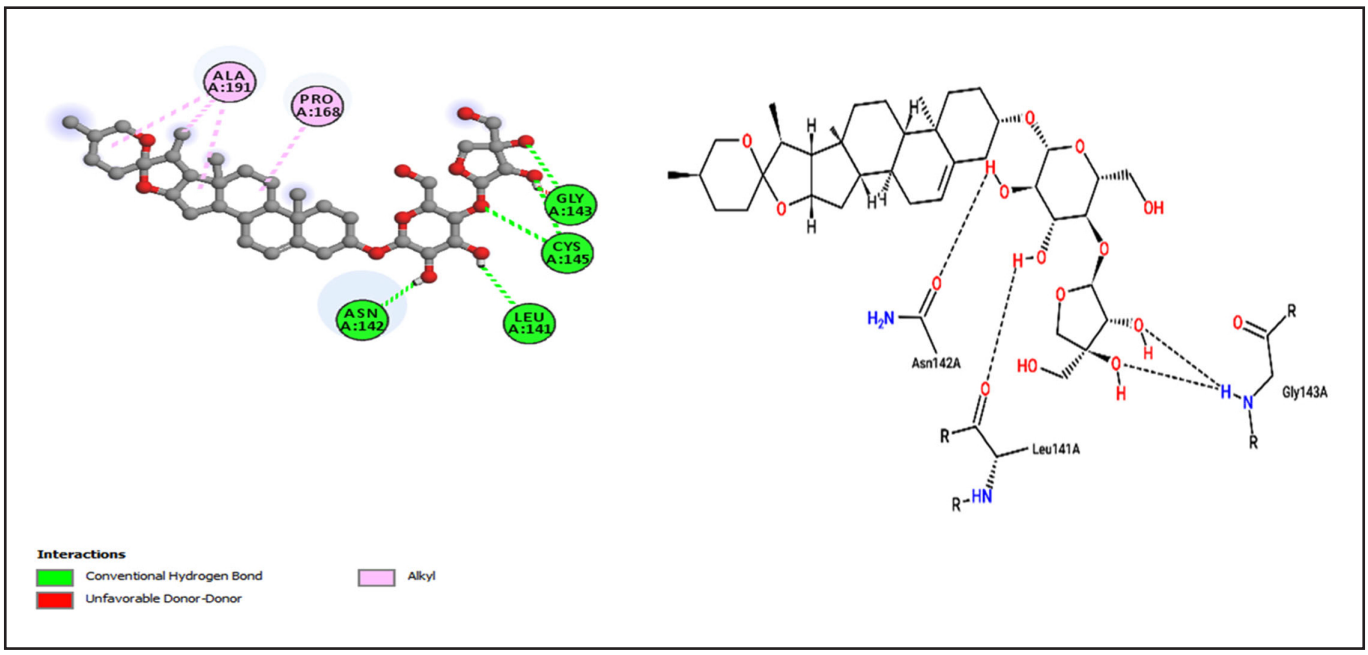

Figure 2. Depictions of aferoside C interactions with Mpro of SARS-CoV-2.

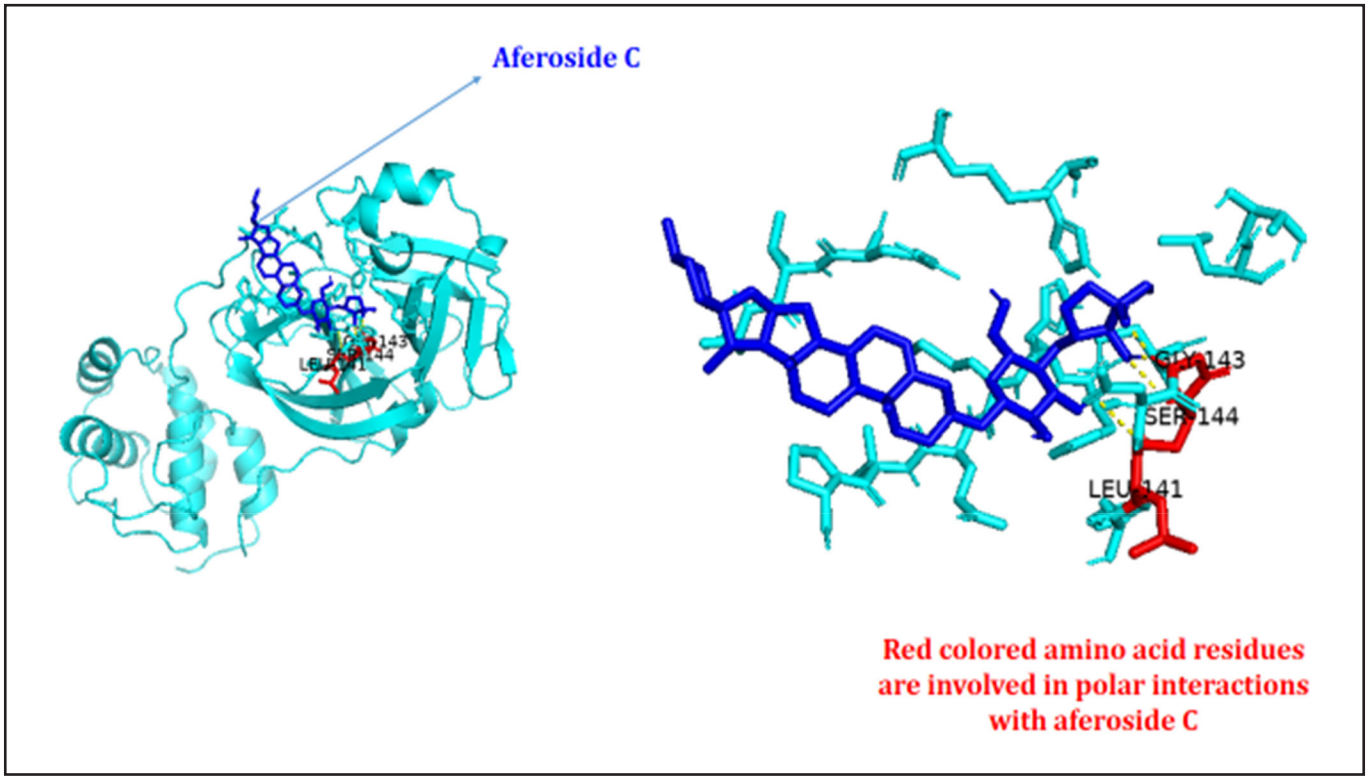

Figure 3. Pymol diagram depicting polar interactions between aferoside C and Mpro.

low binding energies (that is high binding affinities) with S protein RBD-hACE2 interface (especially suginal), also makes them attractive candidates as therapeutics against SARS-CoV-2 for potential ability to block viral entry into human host cells.

Physico-chemical properties of selected phytochemicals and ADME analysis

Physicochemical properties of selected phytochemicals demonstrating high binding affinities for Mpro and/or S protein RBD-hACE2 interface including violations of Lipinski's Ro5 were analyzed as mentioned before (Daina *et al*., 2017; Rakib *et al*., 2020). Interestingly, dibutyl phthalate, suginal, and nerolidol had zero violations of Lipinski's Ro5; aferoside violated all 5 rules. The results are shown in Table 3. However, it has to be pointed out that Lipinski's rule of five, although applicable to "orally bioavailable small-molecule drug design", is not applicable for "natural product and semi-synthetic natural product drugs" (Zhang and Wilkinson, 2008). New molecular entities (NMEs), especially biological, are

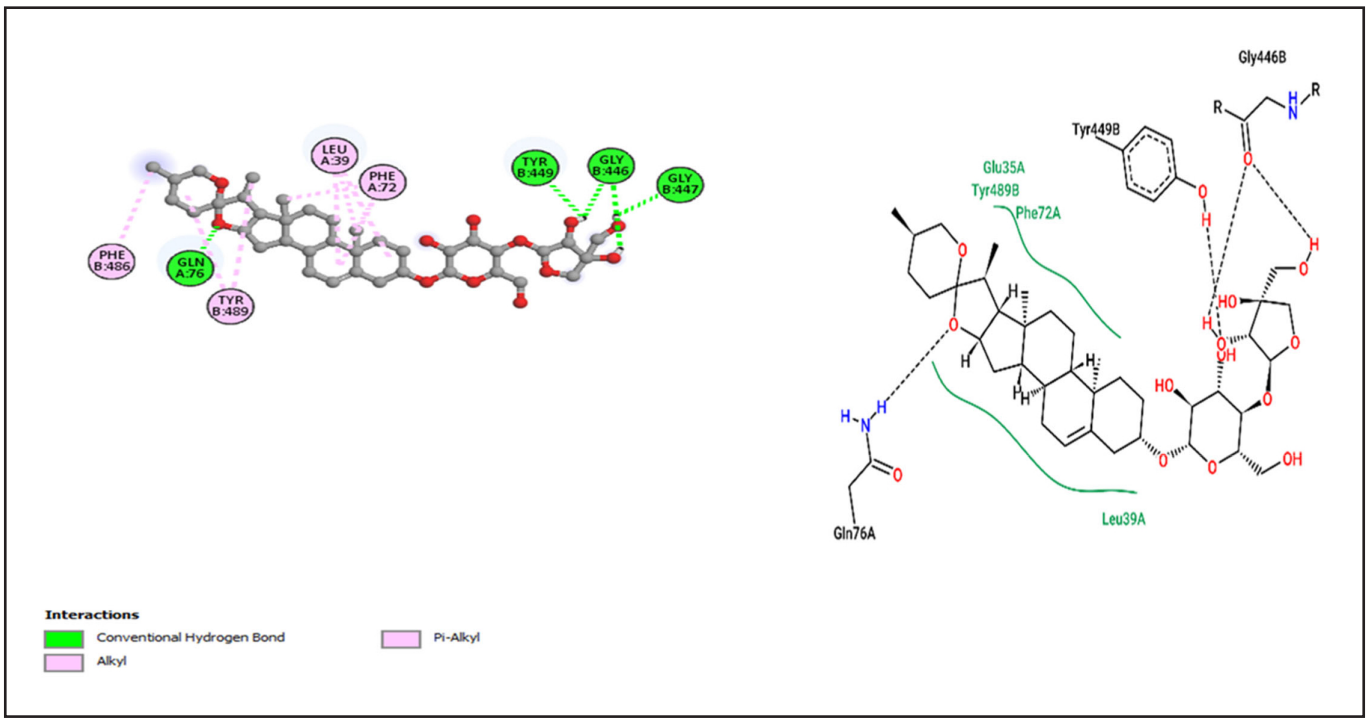

Figure 4. Depictions of aferoside C interactions with RBD of S protein of SARS-CoV-2.

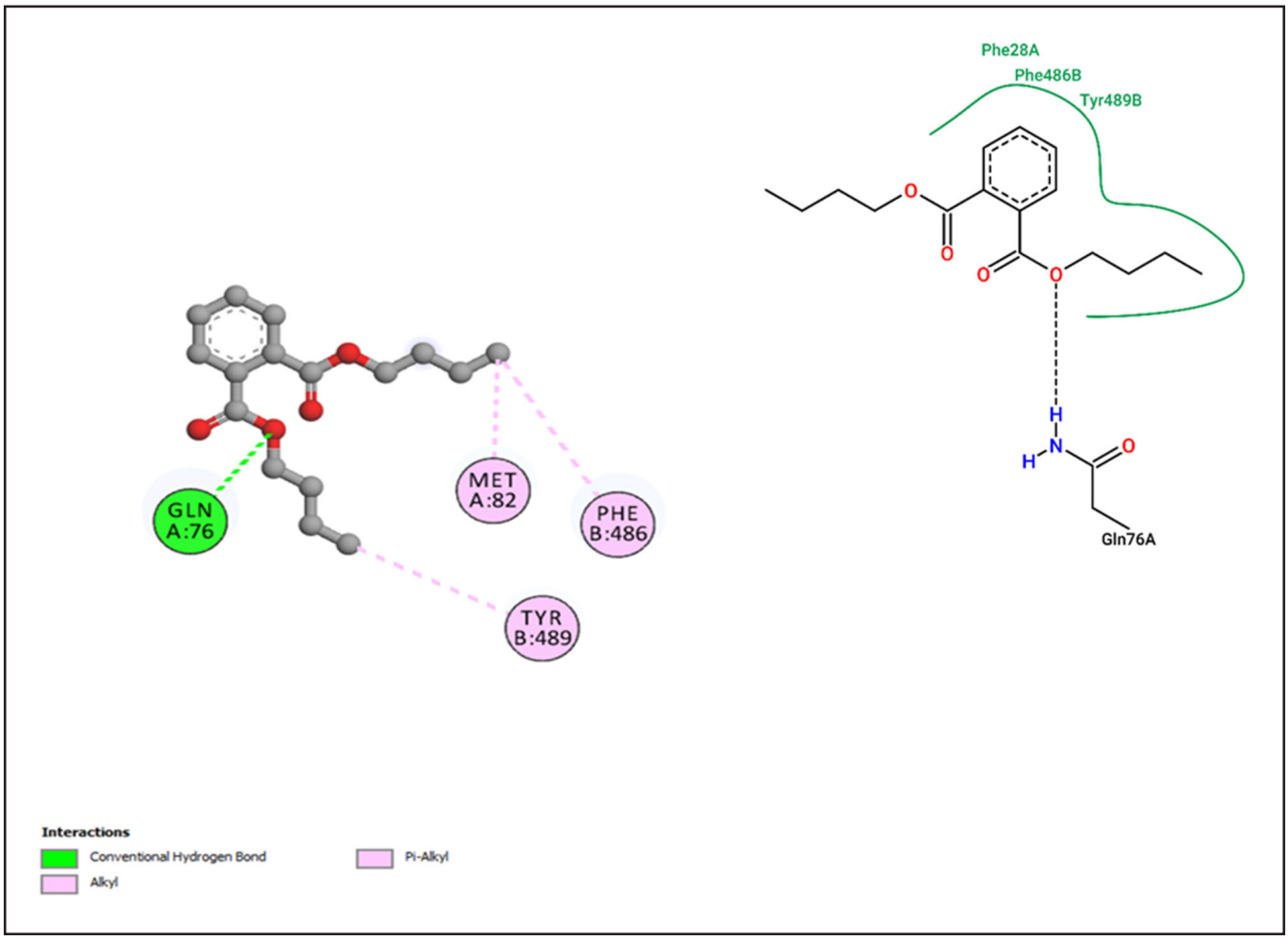

Figure 5. Depictions of dibuytl phthalate interactions with RBD of S protein of SARS-CoV-2.

Table 2. Binding energies of *Costus afer* phytochemicals to Mpro (without bound N3) and spike protein RBD-ACE2 interface

Phytochemicals	Binding energy (ΔG = akcal/mol)	
	Mpro (without N3)	Spike protein (S)
Beta-Acoradienol	-4.5	-6.5
Aferoside C	-8.8	-10.4
3-Carene	-4.9	-5.3
Caryophyllene	-6.0	-6.2
Caryophyllene oxide	-6.3	-6.5
Citral	-4.2	-6.3
Citronellyl tiglate	-4.2	-6.5
Coumaran	-4.7	-6.2
Z-Dihydro-farnesal	-4.4	-5.5
Z,*Z*-Farnesol	-5.0	-6.7
Z-Dehydro-apo-farnesol	-4.6	-6.8
Z-Dihydro-farnesol	-4.6	-5.5
Dibutyl phthalate	-4.9	-7.2
2,4-Dinitrophenyl thiocyanate	-5.0	-5.6
Beta-Helmiscapene	-5.8	-6.6
Indolizin	-4.6	-5.8
2-Methoxy-4-vinylphenol	-5.3	-6.5
Nerolidol	-5.4	-7.2
Phytol	-4.5	-5.0
cis-Piperitol	-4.8	-6.4
Sabinene	-4.5	-6.3
Suginal	-6.5	-8.2
Alpha-Terpinene	-5.1	-7.1
Terpinen-4-ol	-5.1	-6.5
Theaspirane	-5.8	-5.9
Alpha-Thujene	-4.8	-6.7

increasingly being approved by the US Food and Drug Administration as parenteral drugs [https://dcatvci.org/4793-parenteral-drugs-tracking-new-drug-approvals] and that can possibly apply to biological compounds like aferoside C.

Taking all the results into account, five phytochemicals of *C. afer* stand out (among the phytochemicals tested) for their strong binding affinities to Mpro or S protein RBD-hACE2 interface or both suggesting that they have the potential to be COVID-19 therapeutics. These phytochemicals are aferoside C, suginal, dibutyl phthalate, nerolidol, and alpha-terpinene. Phthalic acid esters may have antiviral activity as demonstrated for 2"-(methoxycarbonyl)-5"- methylpentyl 2'-methylhexyl phthalate from the aerial parts of the Bangladeshi mangrove fern *Acrostichum aureum*, which was found to show antiviral activity against dengue, chikungunya, and human parainfluenza virus (Uddin *et al*., 2013). Any antiviral activities of the other four compounds have not been reported to our knowledge. The limitation of this study is that it relies on only *in silico* studies to determine anti-SARS-CoV-2 potential of various phytochemicals present in *Costus afer*. It was also not possible in this study to evaluate all phytochemicals of the plant for their anti-SARS-CoV-2 potential. The strong points in the study are (I) to highlight the fact that COVID-19 comorbidities should be taken into account during its treatment to decrease the mortality rate and notes the weakness of conventional treatment in trying to deal with both COVID-19 and comorbidities, given the fact that till now there is not a single drug against COVID-19 with or without comorbidities; (II) this study points to an alternative method of treatment of COVID-19 and a number of major comorbidities like malaria and diabetes with the use of a single plant (crude extract primarily), which even though some researchers might find it traditional, but traditional approaches have been endorsed by WHO to treat COVID-19 following appropriate clinical trials and toxicity determinations; and (III) last but not the least, the present study points to a pragmatic way of using a three pronged approach of ethnic use reports, pharmacological activity reports, and *in silico* studies with reported phytochemicals of a given plant to come to a rational conclusion of the suitability of a plant's crude extract(s) and or phytochemicals to treat COVID-19. The value of this approach is that instead of costly imported synthetic drugs, this approach can be used to identify readily affordable and available medicinal plants in one's own country, region or vicinity for further quick analysis, which may turn out to be the key in saving lives during pandemics caused by new and emerging infectious agents. A further point is that many conventional (allopathic) drugs are phytochemicals (like artemisinin), and this approach presents a quick route of discovery of allopathic drugs.

CONCLUSION

From a combination of previously published ethnic uses and pharmacological activity studies on *Costus afer*, a number of phytochemicals reported from the plant were evaluated in molecular docking studies for their predicted binding energies to SARS-CoV-2 Mpro, and the spike protein (S) receptor binding domain (RBD) interface with the virus' human receptor ACE2 (hACE2). Our results indicate that if both ethnic uses of the plant and currently done *in silico* studies are validated through actual laboratory studies and clinical trials, the plant and its phytochemical(s) may prove to be an asset in the simultaneous treatment of COVID-19 and major comorbidities like malaria and diabetes. As such, the plant holds immense potential for particularly Sub Saharan and South Asian countries, which are fast becoming new epicenters for COVID-19 and in which countries, malaria and diabetes are still rampant.

Table 3. Physico-chemical properties of selected compounds of *Costus afer*

Compound Name	Molecular weight	Number of H-Bond Acceptors	Number of H-Bond Donors	Log P	Molar Refractivity	Number of Violation
Aferoside C	708.88	12	6	5.25	180.43	5
Caryophylene oxide	220.35	1	0	3.15	68.27	0
Caryophyllene	204.35	0	0	3.29	68.78	0
Suginal	314.42	3	1	2.72	92.26	0
Dibutyl phthalate	278.34	4	0	2.97	77.84	0
Nerolidol	222.37	1	1	3.64	74.00	0

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Conflicts of interest

All authors declare that they have no conflicts of interest.

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