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In silico binding studies with compounds present in essential oil of *Tasmannia lanceolata* leaves to 3C-like protease of SARS-CoV-2

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Abstract
The current pandemic of COVID-19 caused by the coronavirus SARS-CoV-2 has as of December 2, 2020 resulted in 64,504,648 infected cases resulting in 1,493,082 deaths. Although at least three vaccines against the virus are on their way to get emergency approval from the United States Food and Drug Administration possibly by December 15, 2020, this may not be the final answer to the COVID-19 problem. Out of the three vaccines, two needs low temperatures for storage and the facility may not be available in the less developed countries. The less developed countries are not in a position to compete with the developed countries regarding vaccine availability for their people any time soon. Adverse effects, if any, of these vaccines are yet to be determined. The world population is now 7.8 billion. Importantly, all three vaccines need two doses to work effectively. The situation calls for the manufacture of 15.6 billion units to be given twice to far-flung people all over the world, which is not an easy task. The alternative search for more affordable and viable drugs led us to examine the binding of essential oil (EO) components of leaves of the plant *Tasmannia lanceolata* (Poiret) A.C. Smith (Winteraceae family) to the 3C-like protease of SARS-CoV-2, also known as the main protease or Mpro in molecular docking studies *In silico* and the process inhibit the protease, which plays a vital role in viral replication. Several compounds, including alloaromadendrene, cubebol, spathulenol, caryophyllene oxide and guaiol showed promising binding affinities to Mpro with binding energies at or below -6.3 kcal/mol. The compounds can be used in further studies through the synthesis of various derivatives and evaluation of their potential as possible anti-COVID-19 drugs.

Keywords: Molecular docking, *Tasmannia lanceolata*, SARS-CoV-2, Mpro, essential oil

Introduction
The current pandemic of COVID-19 caused by the corona virus SARS-CoV-2 has as of December 2, 2020 resulted in 64,504,648 infected cases resulting in 1,493,082 deaths. Infection of humans by corona viruses (CoVs) is not new; prior to SARS-CoV-2, six CoVs were already known to infect humans including HCoV-229E, HCoV-NL63, HCoV-OC43, HCoV-HKU1, SARS-CoV, and MERS-CoV. The first four of the six corona viruses cause only mild upper respiratory tract illnesses; however, SARS-CoV (Severe Acute Respiratory Syndrome coronavirus, emerged in 2002) and MERS-CoV (Middle East Respiratory Syndrome corona virus, emerged in 2012) have caused high mortality rates but not as much as SARS-CoV-2 [1].
At least three vaccines against SARS-CoV-2 (manufactured by Moderna, Pfizer-BioNTech, and Astrazeneca-Oxford University) are on their way to get emergency approval from the United States Food and Drug Administration possibly by December 15, 2020 (UK has authorized Pfizer's vaccine for emergency use on December 2, 2020) [2], but this may not be the final answer to the COVID-19 problem. Out of the three vaccines, two needs very low temperatures for storage, which facility may not be available in the less developed countries; the less developed countries are not in a position to compete with the developed countries regarding procurement of vaccines for their people any time soon; any adverse effects of the vaccine(s) are yet to be determined; it has to be remembered that the world population is now 7.8 billion and since all three vaccines need two doses to work effectively, the situation calls for manufacture of 15.6 billion units to be given twice to far flung people all over the world, which is not an easy task and since all 15.6 billion units of the vaccine (s) cannot be

manufactured or administered within a few days, an unenviable task remains for the authorities concerned to decide who gets the vaccine first.

The situation calls for discovery of anti-SARS-CoV-2 drugs as another safety measure to stop the COVID-19 pandemic. A number of drug targets in the virus can be utilized, of whom the most promising target appears to be the chymotrypsin like protease (or main protease Mpro, otherwise known as 3CLpro), also known as the 3C-like protease of which the crystal structure is known [3]. Inhibition of this homodimeric cysteine protease can inhibit replication of the virus through stoppage of cleavage of viral polyproteins into individual polypeptides, which are necessary for replication and transcription [4-8].

The catalytically active 3C-like protease is present in the virus as a dimer with the two amino acids His41 and Cys145 playing the major role in the proteolytic process [9]. Dimerization possibly provides a 'substrate-binding cleft' between the two monomers [10]. However, in the dimer, the His-Cys dyads are located symmetrically at opposite ends of the cleft, which is suggestive of individual proteolytic action [11]. The main protease monomer consists of three domains. Domains 1 and 2 comprise of amino acid residues 8-101 and 102-184, respectively; they form a chymotrypsin-like fold and acts as the catalytic domain [12]. Domain 3 comprises of residues 200-303. As has been reported previously, the first seven amino acids at the N-terminus reportedly form the N-finger and play a significant role in the formation of the active site of the 3C-like protease [13].

In silico approaches like molecular docking is an effective tool in the identification of compounds, which can be potential therapeutics for COVID-19. This is more so in the absence of virology labs with the required bio-safety levels (BSLs). However, wet lab experiments for virucidal activity followed by clinical trials still remain a necessity following *in silico* identification of potential therapeutics. A large number of *in silico* studies are going on against various targets of SARS-CoV-2 using phytochemicals, other anti-viral drugs and computer-designed inhibitors of SARS-CoV-2. The phytochemicals so far reported with the highest ability to inhibit 3CLpro *in silico* (Betulinic acid, kaempferol, quercetin) mainly interacted with the regions between domains 2 and 3 [14]; this region is important for 3CLpro to form a dimer [9].

Our laboratory has also been screening phytochemicals from various sources through *in silico* studies to evaluate their binding energies to the 3C-like protease of SARS-CoV-2 with the assumption that a strong binding can lead to inhibition of the protease with consequential inhibition of viral replication [15-20]. Essential oils and at least some of their components have always been at the forefront of anti-viral studies; the same applies to in the case of COVID-19 [21-23]. The alternative search for more affordable and viable drugs led us to examine the binding of essential oil (EO) components of leaves of the plant *Tasmannia lanceolata* (Poiret) A.C. Smith (Winteraceae family) to the 3C-like protease of SARS-CoV-2 in molecular docking studies.

The plant is known in Tasmania as 'mountain pepper', and is an evergreen shrub often used as a culinary spice. The Aboriginal people in Tasmania and southeast Australia use leaves and fruits of the plant as a food flavoring, as well as in traditional medicine as a treatment for skin disorders, venereal diseases, colic and stomach ache [24]. The dried leaves of *Tasmannia lanceolata* (Poiret) A.C. Smith (Winteraceae family) contain 0.67% w/w vitamin D_2 [25]. Methanolic extract of the berries (fruit) has been shown to be non-toxic and effective against a number of bacteria and fungi, thus indicating their potential use as a preservative and for medicinal purposes [26]. Fruit extracts of the plant also strongly inhibited growth of *Proteus mirabilis*, which is a bacterial trigger for rheumatoid arthritis [27]. CO_2 extracts of its leaves improve stretch marks and skin texture, as shown in a recent clinical study [28]. Polyphenol-rich extracts from its leaves contain antioxidant properties and display cytoprotective effects *in vitro* [29, 30].

Methods

Three-dimensional structure of SARS-CoV-2 major protease (3C-like protease)

We have used the pdb file (6LU7) of the main protease or SARS-CoV-2 3C-like protease (or main protease Mpro) as published earlier [31]. An inhibitor (called N3) was removed from the pdb file before using the protein's structure. Monomeric form of protein was used for molecular docking.

Compounds used in docking studies

We studied 37 compounds reportedly present in EO of leaves of *Tasmannia lanceolata* [32]. Ligand molecules were downloaded from Pubchem [33] in sdf format. They were optimized with the force field type MMFF94 using Openbabel software and saved as pdbqt format.

Ligand molecular docking studies

Molecular docking (blind) studies were conducted using AutoDock Vina [34]. We report ΔG values as an average of values from five independent runs of the docking program. In our figures, we show the pose of phytochemicals bound to SARS-CoV-2 main protease as obtained from PyMOL and displayed in Discovery Studio [35].

Lipinski's rule of five

Lipinski's rule of five was followed to predict the drug-likeliness properties of the phytochemicals tested; the following five principles were followed:

i) Molecular weight to be not more than 500
ii) Number of H-bond acceptors $\leq$ 10
iii) Number of H-bond donors $\leq$ 5
iv) Lipophilicity (Log P value) < 5
v) Molar refractivity between 40 to 130 [36-38]

Results and Discussion

Altogether, 37 compounds present in EO from leaves of *Tasmannia lanceolata* were examined in the present study for their binding affinities to the 3C-protease of SARS-CoV-2. Their structures are shown in Figure 1 and their binding energies (ΔG = kcal/mol) are shown in Table 1.

Table 1: Binding data of docking result of *Tasmannia lanceolata* phytochemicals and 3C-like protease of SARS-CoV-2

Compounds	Binding Affinity (ΔG = kcal/mol)
α-Pinene	-4.9
Sabinene	-4.5
β-Pinene	-5.1
Myrcene	-4.0
α-Phellandrene	-4.8
p-Cymene	-5.1
Limonene	-4.9
β-Phellandrene	-4.8
1,8-Cineole	-5.1
trans-β-Ocimene	-4.2
Terpinolene	-4.9
Linalool	-4.3
α-Terpineol	-5.2
Piperitone	-4.5
Safrole	-4.9
α-Cubebene	-6.3
Eugenol	-5.5
α-Copaene	-5.9
Methyl eugenol	-4.9
α-Gurjunene	-6.4
Iso-caryophyllene	-6.2
Alloaromadendrene	-6.3
Germacrene D	-5.8
Muurola-4[14],5-diene	-6.1
Bicyclogermacrene	-6.0
Cubebol	-6.7
cis-Calamenene	-6.1
Cadina-1,4-diene	-5.7
Elemol	-5.5
Palustrol	-6.1
Spathulenol	-6.5
Caryophyllene oxide	-6.3
Viridiflorol	-6.0
Guaiol	-6.3
β-Cedrene epoxide	-6.0
Drimenol	-5.8
Polygodial	-5.9

Overall, the EO components from *Tasmannia lanceolata* did not exhibit any remarkable or high binding affinities to the SARS-CoV-2 3C-like protease or Mpro. Out of the 37 compounds tested *in silico* molecular docking studies, only 14 compounds demonstrated binding affinities of -6.0 kcal/mol or higher. Among these 14 compounds, the highest binding affinities were observed with cubebol and spathulenol at -6.7 and -6.5 kcal/mol, respectively. A binding affinity of -6.4 kcal/mol was shown by α-gurjunene. Several other compounds showing binding affinities of -6.3 kcal/mol included α-cubebene, Alloaromadendrene, caryophyllene oxide and guaiol.

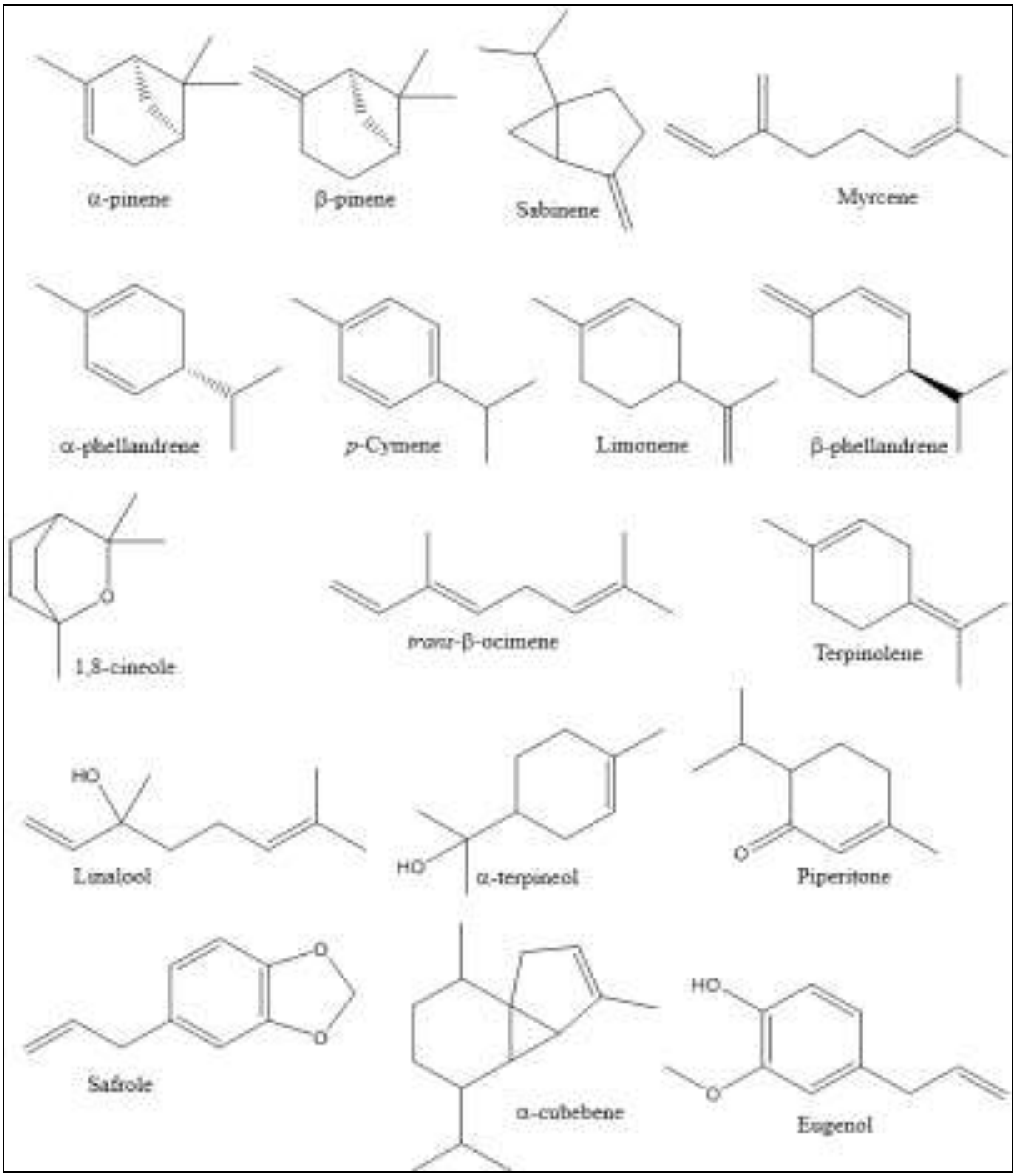

Fig 1: Structures of various compounds of *Tasmannia lanceolata*

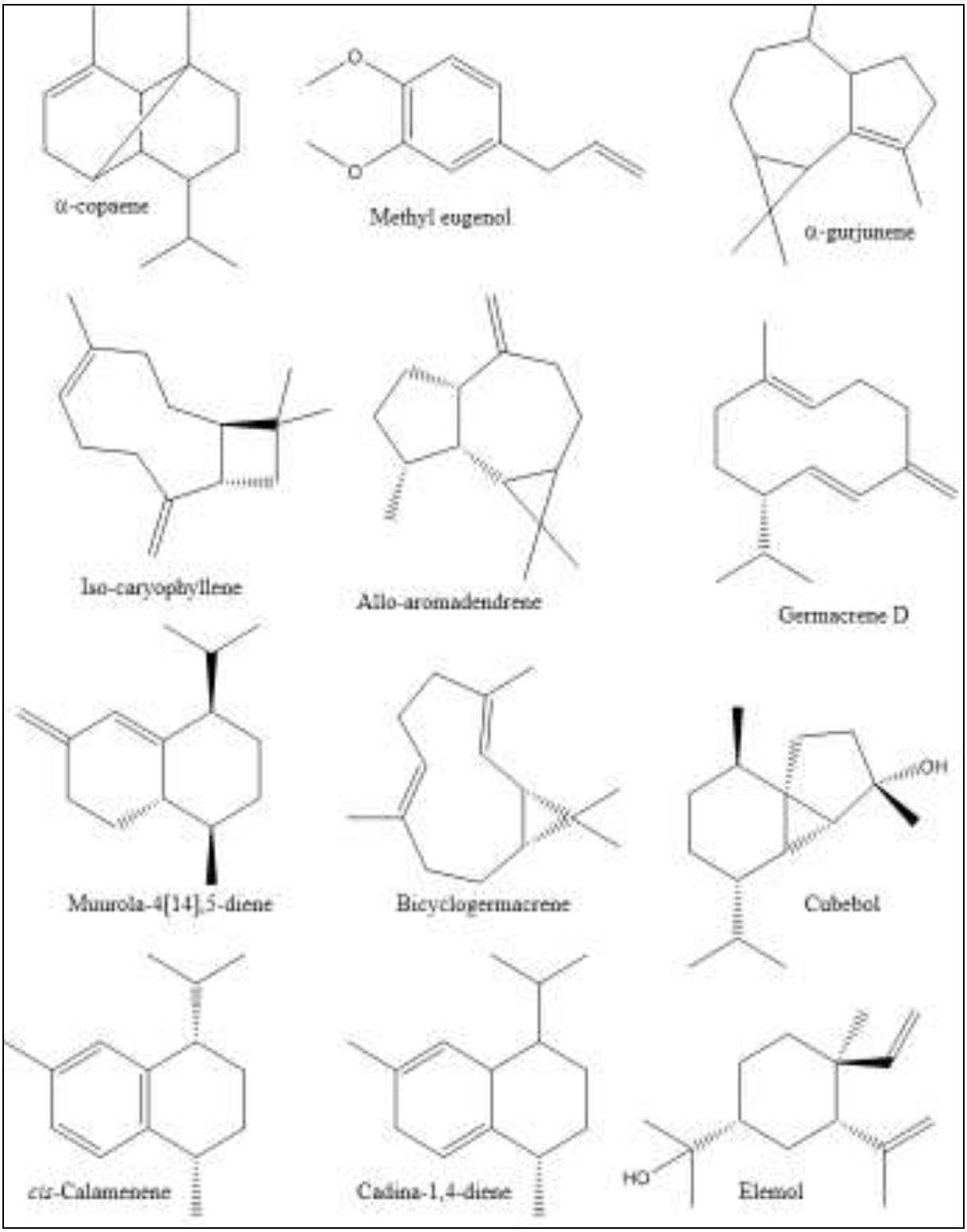

Fig 1: Continued

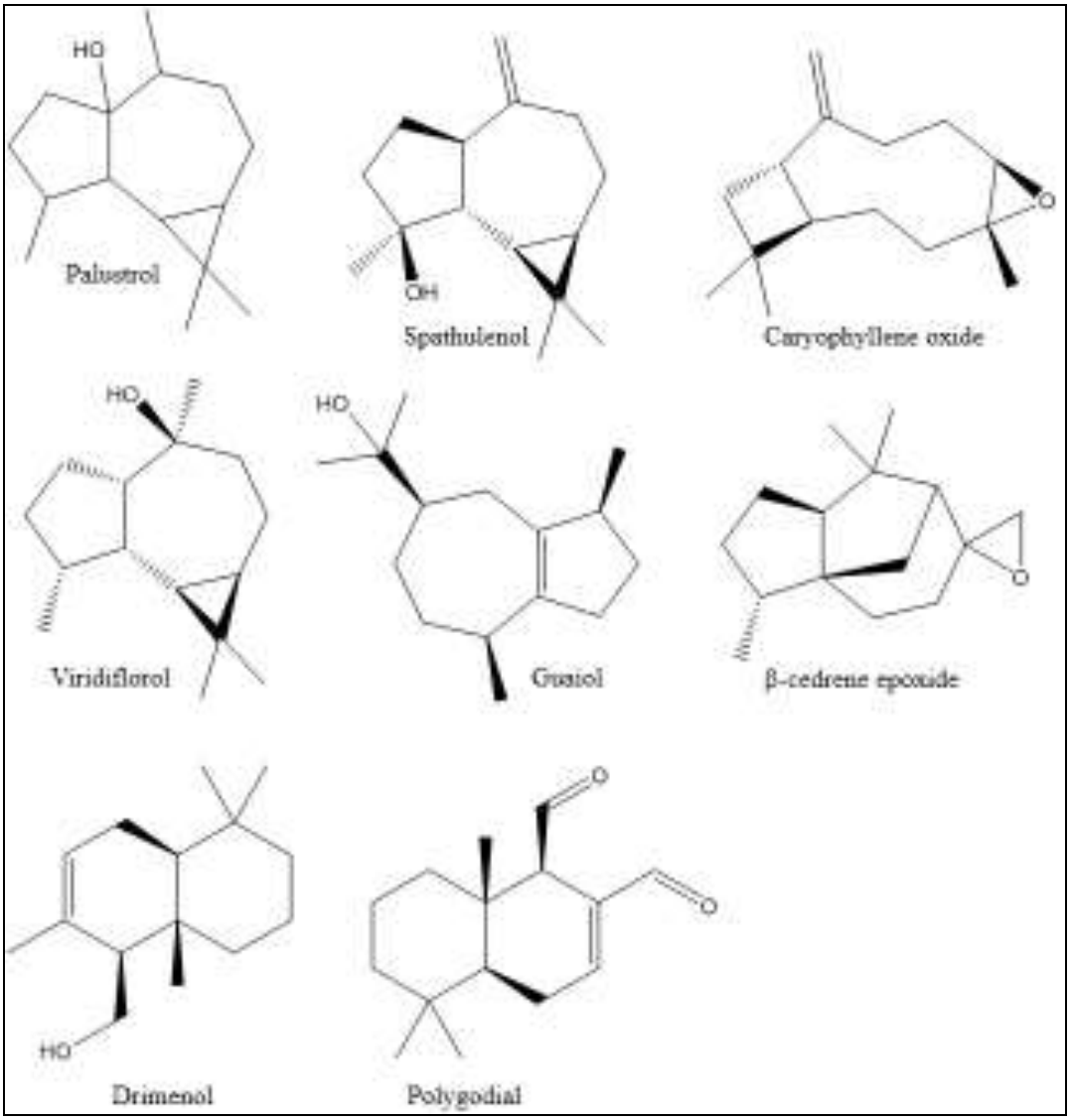

Fig 1: Continued

The interactions of cubebol, spathulenol, α-gurjunene, α-cubebene, Alloaromadendrene and guaiol with amino acid residues in SARS-CoV-2 protease are shown in Figures 2-7. What is important is that none of the compounds interacted with the His41-Cys145 at the active site of the protease. These compounds appeared to have a common interaction affinity with amino acid residues Val104, Ile106, and Phe294 of the protease. An exception to this was guaiol, which interacted with Leu271 and Asn274 (Domain 3) of the protease. However, interactions with Domain 1 and/or Domain 2 amino acids (Domains 1 and 2 comprise of residues 8-101 and 102-184, respectively; they form a chymotrypsin-like fold responsible for catalysis) possibly can be responsible for protease inhibitory activity, even if the activity is weak.

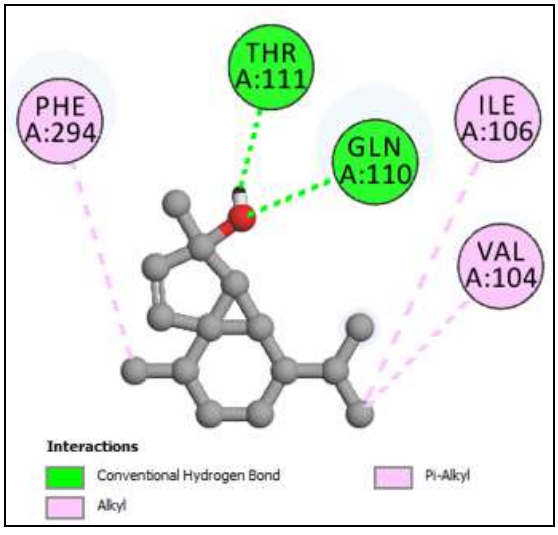

Fig 2: Interaction of cubebol with Mpro

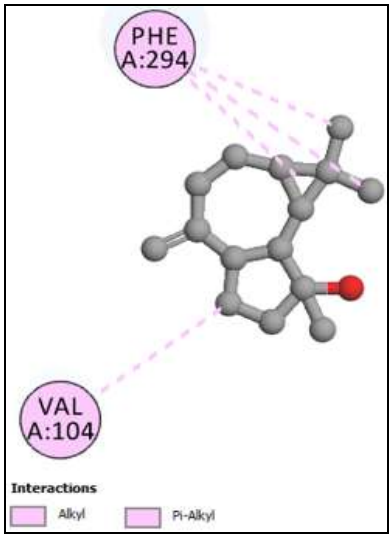

Fig 3: Interaction of spathulenol with Mpro

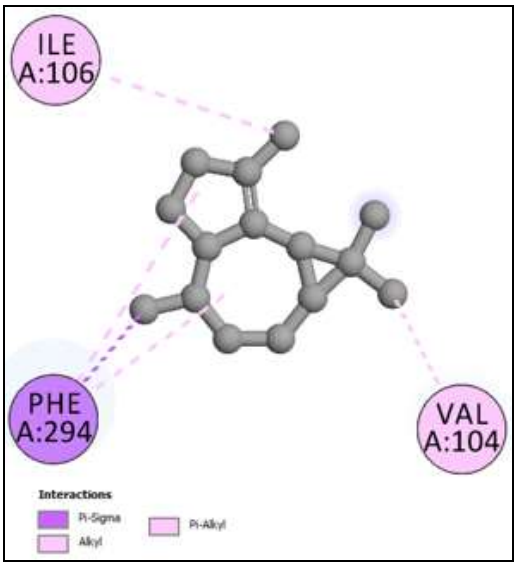

Fig 4: Interaction of α-gurjunene with Mpro

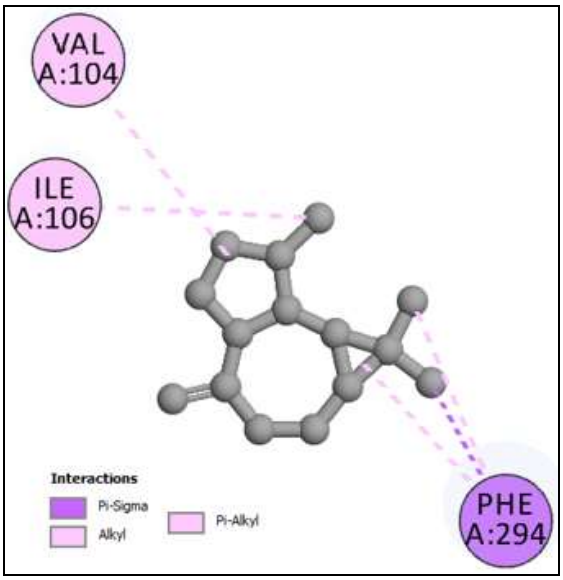

Fig 6: Interaction of Alloaromadendrene with Mpro

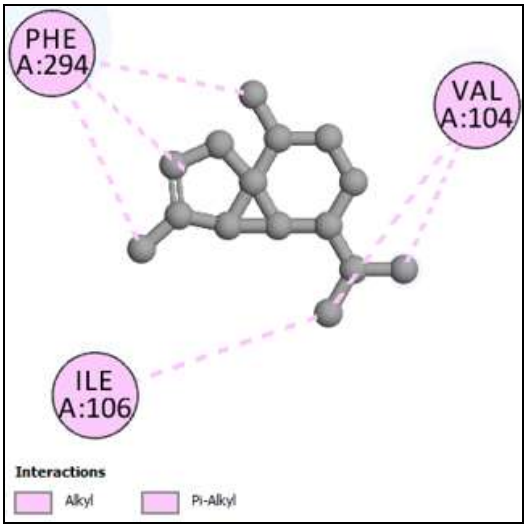

Fig 5: Interaction of α-cubebene with Mpro

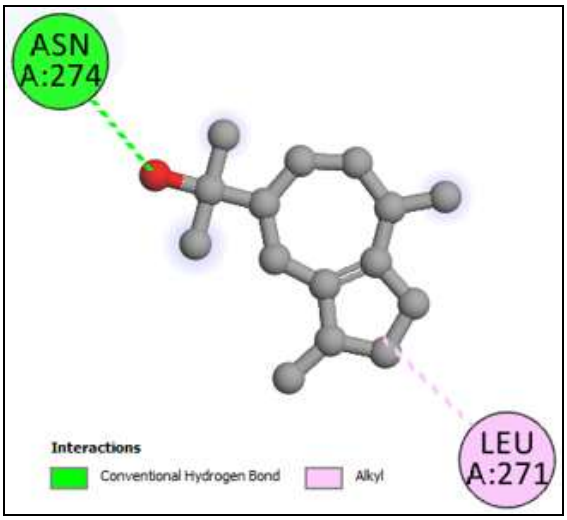

Fig 7: Interaction of guaiol with Mpro

The results of some of the components of *Tasmannia lanceolata* leaf EO regarding Lipinski's rule of five are given in Table 2. The results show that all the compounds fall within Lipinsky's rule of 5 with 0 violations. The results in Table 2, when taken in combination with Table 1 results, indicate that cubebol and spathulenol along with α-gurjunene, α-cubebene, Alloaromadendrene, and guaiol merits further investigation for any SARS-CoV-2 virucidal activity in wet lab tests.

Table 2: Lipinski's rule of five applied to selected compounds of *Tasmannia lanceolata*

Compounds	Molecular weight	Number of H-Bond Acceptors	Number of H-Bond Donors	Log P	Molar Refractivity	Number of Violation
α-Cubebene	204.35	0	0	3.41	67.14	0
α-Copaene	204.35	0	0	3.40	67.14	0
α-Gurjunene	204.35	0	0	3.26	67.14	0
Iso-caryophyllene	204.35	0	0	3.29	68.78	0
Alloaromadendrene	204.35	0	0	3.27	67.14	0
Germacrene D	204.35	0	0	3.32	70.68	0
Muurola-4[14],5-diene	204.35	0	0	3.33	69.04	0
Bicyclogermacrene	204.35	0	0	3.35	68.78	0
Cubebol	222.37	1	1	3.09	68.82	0
cis-Calamenene	202.34	0	0	3.19	68.07	0
Spathulenol	220.35	1	1	2.88	68.34	0
Cadina-1,4-diene	204.35	0	0	3.39	69.04	0
Palustrol	222.37	1	1	3.11	68.82	0
Guaiol	222.37	1	1	3.29	70.72	0
Drimenol	222.37	1	1	3.02	70.16	0
Polygodial	234.33	2	0	2.25	69.40	0

Eucalyptus essential oil inhalation has been proposed to bring relief to some of COVID-19' symptoms such as pain, cough, respiratory inflammation, cytokine storm and dyspnea [39]. *In vitro* anti-microbial and anti-viral activities have been reported for EO obtained from leaves of *Salvia cedronella* Boiss. The main components of the EO, which showed activity against influenza and herpes simplex virus (HSV), were 1,8-cineole, α-pinene, caryophyllene oxide and sabinene [40]. It is possible that EO of *Tasmannia lanceolata* may be able to provide at least symptomatic relief if not total cure of COVID-19.

Conclusion

Molecular docking results indicate that several components of EO obtained from *Tasmannia lanceolata* leaves may be suitable candidates for further structural modifications and future preclinical studies related to the development of therapeutics for COVID-19.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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