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Original article

Docking Studies on the Effects of Some Bioactive Compounds from *Pistacia atlantica* Desf. against Main Protease SARS-CoV2

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Abstract

Novel coronavirus which was named later as SARS-CoV2 appeared in Wuhan, China, in the end of December 2019. Actually, no precise drugs are existed and research concerning SARS-CoV2 treatment is deficient. SARS-CoV2 main protease (Mpro) was crystallized by Liu et al. (2020) and represented a crucial drug target. The present work aimed to evaluate some bioactive compounds from Pistacia atlantica as possible SARS-CoV2 Mpro inhibitors, based on molecular docking approach. Molecular docking was carried out using AutoDock Vina software. The results indicated that Beta-Eudesmol, Elemol, Verbenol, Pinocarvone, Myrtenal, Myrtenol and Trans-Carveol have a potential inhibitor activity of SARS-CoV2 Mpro. Nevertheless, further investigations are required to develop and optimize drug process to combat SARS-CoV2.

Keywords: SARS-CoV2, molecular docking, bioactive compounds, *Pistacia atlantica*.

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INTRODUCTION

The genus *Pistacia* belongs to the *Anacardiaceae* family, it has a remarkable ecological amplitude and plasticity. Previous studies qualify *P. atlantica* Desf. as a precious species, due to its several therapeutic properties and attracts the attention in medical and pharmaceutical eras (Daget and Godron, 1974; Monjauze, 1980; Benhassaini, 2003; El Oualidi et al., 2004). In addition, this specie contains several secondary compounds including flavonoids, floroglucides, coumarins, tannins, anthracene derivatives, sugars, saponins, phenolic and alcaloids carbohydrates. Therefore, these compounds have antipyretic, antidiabetic, antiradical, cytotoxic activities (Hamdan and Afifi, 2004; Topçu et al., 2007; Benhammou et al., 2007, Benhammou et al., 2008), antioxidants, antimicrobial and anti-inflammatory (Farhoosh, 2008).

Until now, very few studies have investigated the antiviral potency of *P. atlantica* Desf., whereas, the antiviral properties of other *Pistacia* have been evaluated (Karimi et al., 2019). In the actual context, novel Coronavirus SARS-CoV-2 appeared in China at the end of December 2019 (Xu et al., 2020). Coronaviruses are RNA viruses that have huge viral RNA genomes (Chen and Liu, 2020). They encoded genes for an RNA polymerase, spike protein with trimeric structural (Xue et al., 2008; Chen et al., 2020), Membrane protein (M), Nucleocapsid protein (N), Envelop protein (E) and some nonstructural proteins (Boopathi et al.,2020). The main protease (Mpro) plays an important role in polyprotein and virus maturation. According to the three-dimensional structure of SARS-CoV-2Mpro made by Jin and al. (2020), SARS-CoV-2Mpro was composed with three regions in which the second region is the important binding of the inhibitors (Yang et al., 2003; Zhao et al., 2008). SARS-CoV-2Mpro is an attractive target for designing a therapeutic approach (Anand et al., 2003; Yang et al., 2003; Pillaiyar et al., 2016).

The characteristic of this novel virus is its rapid extension and cause a world pandemic. In this situation, finding a novel drug seems to be very urgent. Molecular docking is one of the promising tools which were employed for screening and developing a new drug. Also, this approach helps therapists how to administrate the drug in first instance (Liu et al., 2005). This tool is based on the study of the interaction established between drug (ligand) and target protein (receptor) (Mcconkey et al.,1983).

In this study, we selected Terpenoids compounds of *P. atlantica* Desf. as inhibitors against SARS-CoV-2Mpro using docking molecular approach.

MATERIAL and METHODS

Data set

The leaves of *P. atlantica Desf* contain 49 identified compounds. According to Ait Said et al. (2011) these compounds were regrouped into: monoterpenes (8 hydrocarbons and 14 oxygenated) and sesquiterpenes (16 hydrocarbons and 9 oxygenated). In this study, we selected twenty terpenoids components based on conducted the docking study.

Docking protocol

Docking calculations need a receptor and ligand representations in a file format called pdbqt which is a modified protein data bank (Berman et al., 2000). The format contains atomic charges, atom type definitions and, for ligands, topological information (rotatable bonds). These files preparations are carried out using Autodock 1.5.4 MGL Tools (Sanner, M. F., 1999). Ligands for subsequent docking runs can be prepared one by one through PyMol (DeLano, 2002) and Autodock 1.5.4 MGL Tools. The bioactive conformations were simulated using AutodockVina (Trott and Olsan, 2010). AutodockVina is a program for molecular docking and virtual screening for drug. It is used in many studies (Trott and Olsan, 2010; Sandeep et al., 2011; Jaghoori et al., 2016).The crystal structure of SARS-CoV-2main protease(PDB entry code: 6lu7) obtained from the protein database (http://www.rcsb.org) with original ligand and water were eliminated.

The best conformations of the ligands were analyzed for their binding interactions and were evaluated by the binding free energies (Docking affinity, kcal/mol) and bonds interactions between ligand atom and active site residues. Subsequently, the results were analyzed using PyMol and LigPlot+ (Laskowski and Swindells, 2011).

RESULTS

The results are presented in Table 1 and Table 2 demonstrated seven compounds generating the highest binding energy with SARS-CoV-2 main protease: Beta-Eudesmol (-5.5kcal/mol) forming a hydrogen bond with the main protease at (Ser158, Lys102, Asp153), Elemol (-5.2kcal /mol) constituting a hydrogen bond at Ser 158, Verbenol (- 5.2kcal/mol) forming hydrogen bond at Thr111, Pinocarvone (-5.1 kcal/mol) and creating a hydrogen bond at Trp207. Myrtenal (-4.9 kcal/mol) at Thr292, Myrtenol (-4.9 kcal/mol) creating a hydrogen bond at Asn151, Thr111, finally Trans-Carveol (- 4.9 kcal/mol) forming a hydrogen bond with the main protease at Lys (Figure 2).

Table 1. The properties of terpenoids from the *Pistacia atlantica* leaf.

Ligand	Molecular Formula	Weight (g/mol)	Hydrogen Bond Donor	Hydrogen Bond Acceptor	Topological Polar Area (Å²)
Beta-Eudesmol	$C_{15}H_{26}O$	222.37	1	1	20.2
Elemol	$C_{15}H_{26}O$	222.37	1	1	20.2
Verbenol	$C_{10}H_{16}O$	152.23	1	1	20.2
Pinocarvone	$C_{10}H_{14}O$	150.22	0	1	17.1
Myrtenal	$C_{10}H_{14}O$	150.22	0	1	17.1
Myrtenol	C10H16O	152.23	1	1	20.2
Trans- Carveol,	$C_{10}H_{16}O$	152.23	1	1	20.2
Trans-Pinocarveol,	$C_{10}H_{16}O$	152.23	1	1	20.2

Ligand	Molecular Formula	Weight (g/mol)	Hydrogen Bond Donor	Hydrogen Bond Acceptor	Topological Polar Area (Å²)
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Pinocarvone	$C_{10}H_{14}O$	150.22	0	1	17.1
Myrtenal	$C_{10}H_{14}O$	150.22	0	1	17.1
Myrtenol	C10H16O	152.23	1	1	20.2
Trans- Carveol,	$C_{10}H_{16}O$	152.23	1	1	20.2
Trans-Pinocarveol,	$C_{10}H_{16}O$	152.23	1	1	20.2

Table 2. The interactions of *Pistacia atlantica* terpenoids molecules with the COVID 19 main protease.

Ligand	Docking affinity Kcal/mol)	Distance from rmsd l.b.	Best mode rmsd u.b.	Residues Hydrogen bond interaction	Distance (Å)
Beta-Eudesmol	- 5.5	0	0	Ser 158 Lys 102 Asp 153	2.87 2.98 2.94
Elemol	- 5.2	0	0	Ser 158	2.91
Verbenol	- 5.2	0	0	Thr 111	3.32
Pinocarvone	- 5.1	0	0	Trp207	3.09
Myrtenal	- 4.9	0	0	Thr 292	3.05
Myrtenol	- 4.9	0	0	Asn 151 Thr 111 Thr 111	2.92 2.92 3.04
Trans- Carveol	- 4.9	0	0	Lys 5	2.86

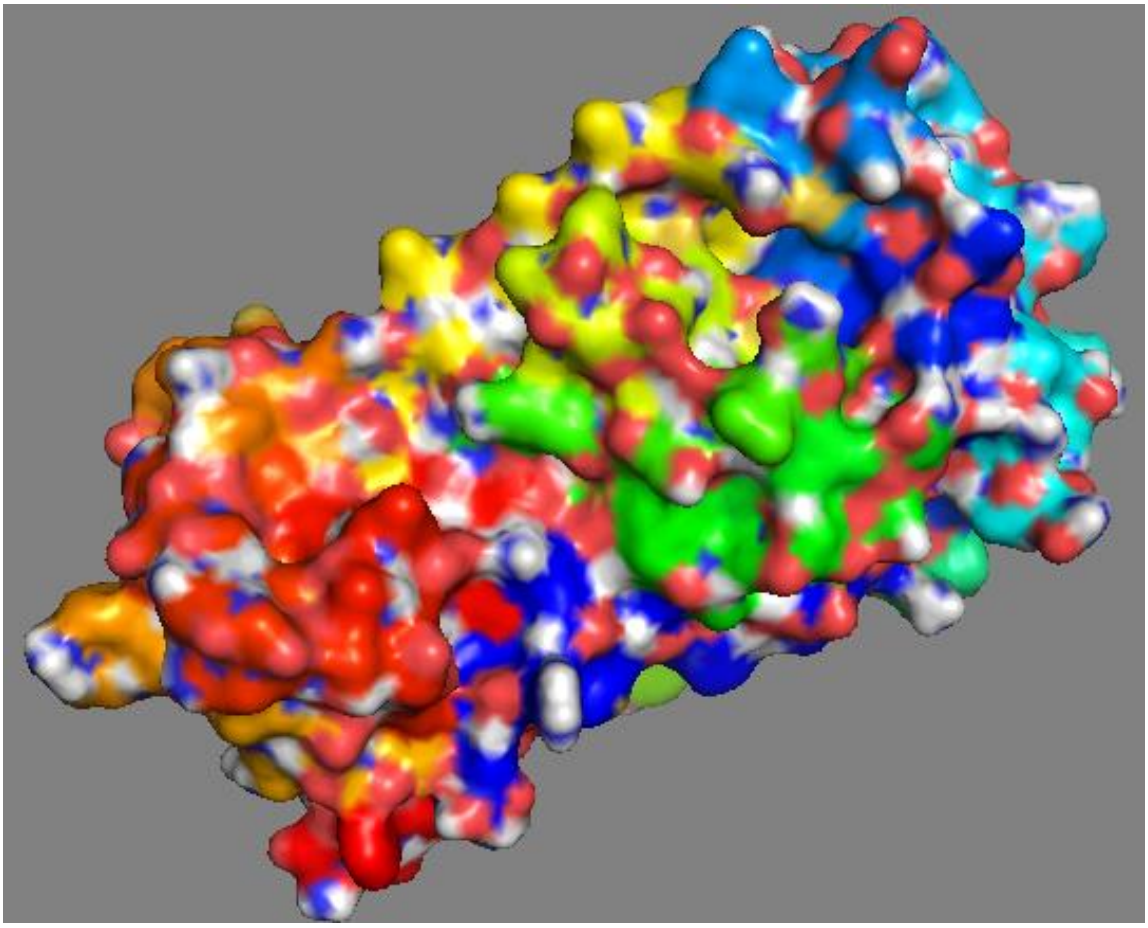

Figure 1. 3D structure of 2019-nCoV (https://www.rcsb.org/)

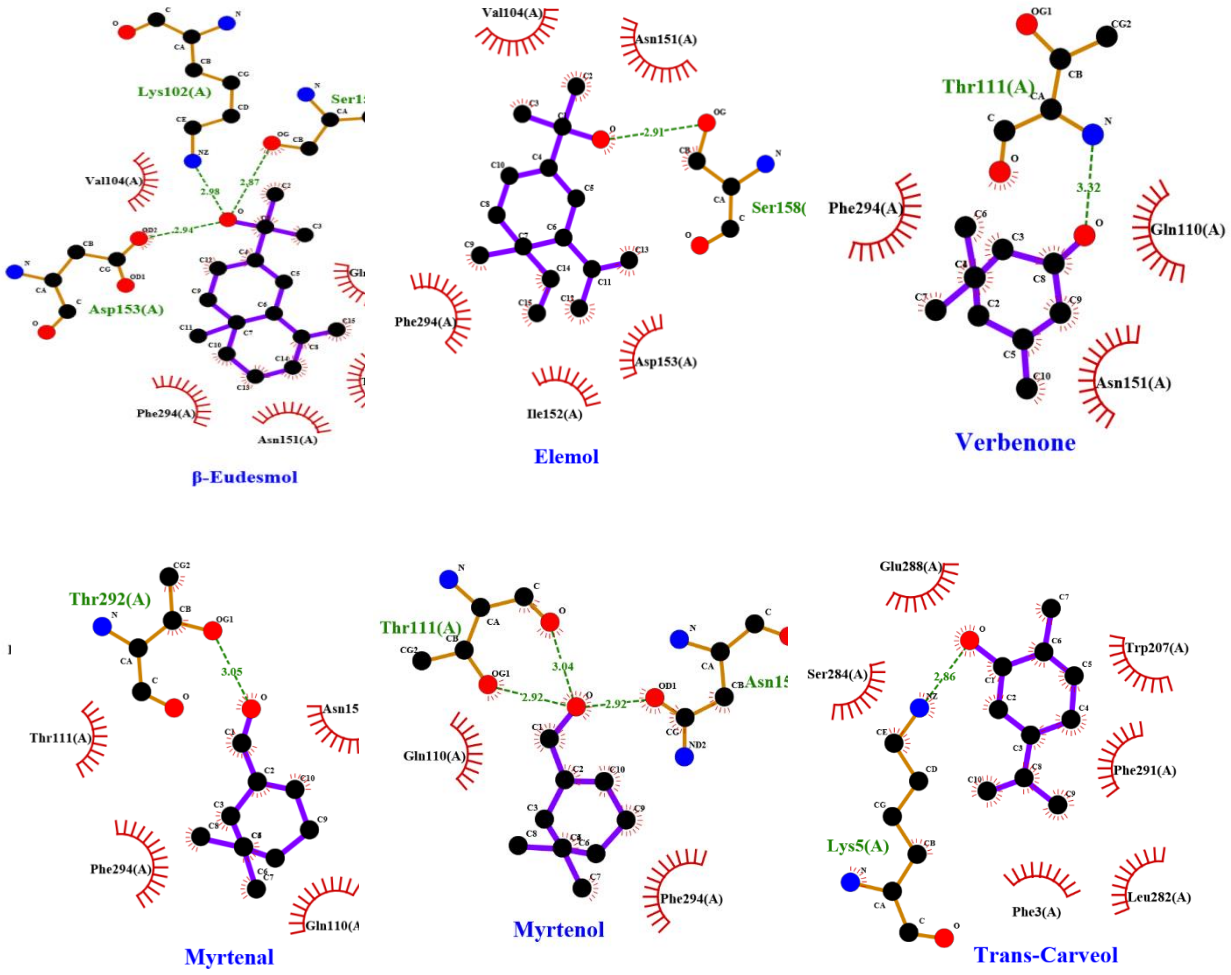

Figure 2. 2 D View of the binding conformation of the ligands interaction with a target (2019-nCoV) main protease.

Discussion

In this study, twenty terpenoids components provided from *P. atlantica* Desf. were docked. seven compounds engendered highest energy and stable binding with SARS-CoV-2 main protease. These results can be explained by the presence of sesquiterpenes compounds in natural products generated an antiviral activity (Vieira et al., 2014). Generally, these compounds were associated with divers' biological activities.

According to Fatemeh et al. (2018), mono, di and triterpenoids are associated with anti-inflammatory and antimicrobial effects. Also, hydroxy groups in terpenoids compounds play a signifying role in the interactions with the active site of SARS-CoV-2Mpro (Aziz et al., 2018).

The molecular weight of terpenoids of *P. atlantica* Desf. have low weight compared with isotymol (220.31g/mol) that has signaled by Abdelli et al. (2020), which has inhibitor effect against Coronavirus. Researches were oriented toward small compounds which formed the strong Hydrogen bonds (Pant et al.,2020).

The study results indicated that Beta-Eudesmol, Elemol, Verbenol, Pinocarvone, Myrtenal, Myrtenol and Trans-Carveol from *P. atlantica* Desf have a potential inhibition of SARS-CoV-2Mpro, which should be explored in further investigations.

CONCLUSION

In this research the inhibitory potential of the terpenoids compounds of *P. atlantica* have studied againstSARS-CoV-2 main protease using molecular docking approach. Natural products with antiviral potency have to pay attention for researchers. Nevertheless, no earlier reports have found the antiviral activity of *P. atlantica*, except Karimi et al (2020), Consequently, *P. atlantica* offers an alternative inhibitor source against this novel coronavirus.

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