

Potential anti-COVID-19 activity of Egyptian propolis using computational modeling

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Aim: To investigate the prospective anti COVID-19 activity of Egyptian propolis. **Material & methods:** Propolis samples were collected from different Egyptian geographical areas and characterized using standardized methods, scanning electron microscope and gas chromatography/mass spectrometry along with computational modeling to predict the anti-COVID-19 activity. **Results & conclusion:** Gas chromatography/mass spectrometry analysis of Menoufia propolis proved the presence of Octatriacontyl pentafluoropropionate (4.2%). Docking analyses declared that Octatriacontyl pentafluoropropionate is well oriented inside the enzyme pockets, in addition to excellent binding manner with the active site of the target macromolecules (RNA-dependent RNA polymerase, Spike protein S1 and main protease) in relation to some broad-spectrum antiviral agents. Menoufia propolis could be a promising candidate in the combat against the pandemic COVID-19.

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Recently coronavirus SARS-CoV-2 (COVID-19) has emerged as a new and even fatal disease to humans. It is proved to be originally linked with several pneumonia cases in Wuhan, China. Global clinical cases reached 1,382,658 deaths [1,2]. COVID-19 is genetically related to the beta-coronavirus group, as SARS-coronaviruses, its spike protein has the ability to bind to the human ACE-2 receptor. Coronavirus (CoV) cell infection starts by viral entry, through recognition of ACE-2 and then CoV membrane fuses with the host cell membrane [3]. COVID-19 is a single-stranded RNA virus with a 5'-untranslated region (UTR), nonstructural proteins (nsps) encoded in a replicase complex (orf1ab), gene of a spike protein (S), gene of envelope protein (E), gene of a membrane protein (M), gene of a nucleocapsid protein (N), 3'-UTR, and several unidentified nonstructural open reading frames [1]. Broad-spectrum antiviral agents (BSAAs) are now being considered as potent drug candidates [4]. BSAAs have an advantage of targeting more than two viral families and prevent the viral replicative mechanisms [5]. By spanning Phase II through IV only few existing BSAAs are now being under test in clinical trials. Umifenovir can inhibit the viral entry through membrane fusion inhibition. Umifenovir has been considered in a Phase IV clinical trials combined with different drugs as a potential treatment for pneumonia associated with COVID-19 (ClinicalTrials.gov ID: NCT04255017) [6]. Remdesivir (RNA-dependent RNA polymerase inhibitor) is being considered for mild-to-moderate SARS-CoV-2 in Phase III level clinical trials (ClinicalTrials.gov Identifier: NCT04252664) [7].

Propolis is a well-known natural product and has been used in folk medicine for centuries. It is a resinous material collected from different plant parts by honeybees (*Apis mellifera* L) [8]. Recently propolis has attracted great interest as a potential antimicrobial agent [9]. Propolis composition is primarily affected by the geographical and climatic changes as well as the botanical origin [10]. Propolis' biological activities are correlated with the presence of flavonoids, aromatic acids, diterpenic acids and phenolic compounds [11]. Propolis ethanolic extract has been reported to possess various biological activities, such as antibacterial, antifungal, antiviral, antioxidant,

anti-inflammatory, antihepatotoxic and antitumor [7]. Sforcin [12] reported the safety profile of the propolis as a nontoxic compound to humans or mammals with DL50 ranged from 2 to 7.3 g/kg in mice; however for humans DL50 reached 1.4 mg/kg (~70 mg/day).

Novelty impeded in the present work is that propolis samples from different Egyptian geographical areas were collected and comparative chemical composition was conducted through analytical and chromatographic methods with concomitant to the anti-COVID-19 activity.

Materials & methods

Propolis samples

Propolis samples were collected from different geographic areas in north Egypt namely: Alexandria (31.21564°N, 29.95527°E), Tanta (30.79611491°N, 30.99517822°E) and Menoufia (30.637468°N, 30.914927°E). The samples were collected and kept in dark sterile glass containers until further use.

Propolis analysis

Scanning electron microscopic examination of propolis samples

Propolis samples were examined using scanning electron microscope JEOL JSM-6390LV (USA). Each sample was oven dried (105°C/45 min), then coated with metallic gold ions and stored in plastic boxes, which were sealed with parafilm (PARAFILM 1M) to prevent moisture absorption and left at room temperature for 24 h. The samples were then analyzed at different magnifications (Voltage 12 kV, Working Distance 12 mm, Spot size 44, Vacuum Mode HV) [13].

Preparation of the propolis extract

Propolis samples were chopped into small pieces and extracted (20% w/v) by maceration with ethanol (99.9%) for 7 days in the dark with continuous stirring followed by sonification for one hour at 70°C [14] then filtered through a Whatman filter paper No. 1 and the extracts were stored in a dark jar at 4°C for further analysis.

Chemical analysis

Qualitative method

Standard procedures were used to determine the presence or absence of different secondary metabolites of propolis ethanolic extracts such as phenolic compounds, terpenoids, steroids, flavonoids, tannins and glycosides [15].

Quantitative method

Gas chromatography/mass spectrometry analysis of different propolis samples

About 2 mg of the propolis ethanolic extract was dissolved in 20 µl dry pyridine, then 30 µl N,O-bis(trimethylsilyl)trifluoroacetamide (BSTFA) were added. The mixture was heated at 80°C for 20 min and diluted with 100 µl pyridine then each sample was analyzed using gas chromatography/mass spectrometry (GC/MS). Compounds identification was done using computer search user-generated reference libraries, incorporating mass spectra (Wiley 138 and Nist 98 libraries) [16].

Molecular modeling

In the current study, molecular docking was performed to predict the binding affinity of the test compounds toward the target enzymes RNA-dependent RNA polymerase (RdRp), Spike protein S1 and main protease (3CLpro, or 3-chymotrypsin-like protease). This study could describe mode of binding of screened compounds to the active site of target macromolecules and type of interactions of different conformations. The scoring function (S) could compute the binding energy to select orientations with the lowest energy state. It also could be used as indicator of relative strength of interactions with the active site [17].

Molecular Operating Environment (MOE) software was utilized in all the docking experiments, with the x-ray crystal structures of the docking targets; optimized SARS-CoV-2 RdRp (PDB ID: 7BTF), SARS-CoV-2 Spike protein S1 (PDB ID: 6VW1) and SARS-CoV-2 3CLpro (PDB ID: 6Y2G) models were obtained from the Protein Data Bank (PDB) website.

Molecular docking results are often validated using a training set of experimental ligand–protein complexes, and the accuracy of these docking programs is mainly dependent on the used training set [18]. Due to the lack of known ligands, it is important to ensure that the used software is able to replicate the binding mode of a known experimental

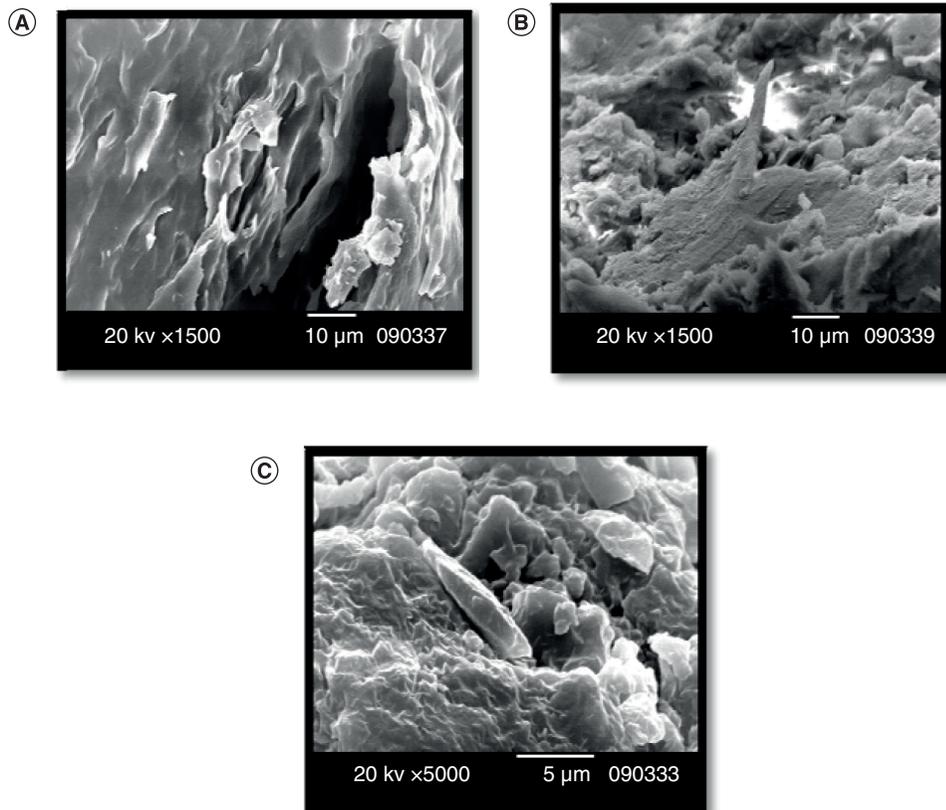


Figure 1. Egyptian propolis analyses and potential anti COVID-19 effect. Scanning electron micrographs of the Propolis' samples: Alexandria (A), Tanta (B) and Menoufia (C).

inhibitor for the studied enzymes. Although neither an effective antiviral drug nor a vaccine against COVID-19 is currently available, several reports have indicated that RdRp inhibitors (remdesivir), influenza glycoproteins inhibitors (umifenovir), in addition to HIV-1 protease inhibitors (lopinavir) have the potential for designing active SARS-CoV-2 inhibitors [19,20]. In the attempt to have reference values (positive control), remdesivir, umifenovir and lopinavir antiviral drugs were considered as comparative standards for the molecular docking.

Results

Propolis analysis

Propolis used in the present study was collected from different geographic areas namely: Alexandria, Tanta and Menoufia. Alexandria and Menoufia propolis were dark brown while Tanta propolis was light brown. Propolis classification showed variations according to the botanical origin due to the difference in the dominant pollen grains [21]. Pollen grain analysis was investigated according to Temizer *et al.* [21], which revealed the relatedness of Alexandria propolis to the family Cyperaceae (that was occasionally found in Tanta propolis) while that of Tanta and Menoufia were related to the family Asteraceae.

Scanning electron microscopic examination of propolis samples

Scanning electron microscopic analysis of the propolis samples under test (Figure 1A–C) showed 3D structures and morphological features of the propolis samples. It was revealed that no foreign materials were detected and wrinkled surfaces covered with wax layers were observed.

Table 1. Qualitative chemical analysis of the propolis samples.

Content	Alexandria	Tanta	Menoufia
Glycosides	+	+	-
Flavonoids	+	+	+
Phenols	-	+	-
Steroids	-	-	-
Tannins	-	+	+
Terpenoids	+	+	+

(+): Present, (-): Absent.

Chemical analysis of the propolis

Qualitative analysis

The qualitative chemical analysis for the tested propolis samples showed variations among the samples that were geographically different. Steroids were not detected in all the tested samples. In the present study a detailed investigation on the composition of the Egyptian propolis collected from specific areas was analyzed (Table 1).

Quantitative analysis

GC/MS analysis

On referring the results of the present work to the data base with the corresponding acquisition time (Figures 2A–C), 26 compounds have been identified. It was revealed that the common detected components in the tested extracts were heptacosane, octacosanol and pinocembrin that were in average concentrations except for that of Menoufia and Alexandria propolis, respectively (Table 2). The presence of unusual substances such as sterol precursors and some alcohols may be due to the different geographic areas of propolis in Egypt.

Anti-COVID-19 activity using molecular docking

In the current study, molecular docking was performed to predict the binding affinity of the test compounds toward the target enzymes RNA-dependent RNA polymerase, spike protein S1 and main protease (Table 3). Results of the docking studies showed that most compounds possessed promising binding scores, in addition to excellent binding manner with the active site of target macromolecules in comparison to the reference antiviral drugs remdesivir, lopinavir and umifenovir. The binding interactions of test compounds were investigated to study their modes of binding and orientations related to their antiviral activity.

RNA-dependent RNA polymerase inhibition screening

Considering RNA-dependent RNA polymerase inhibition screening, interestingly, octacosane, heptacosane, hexadecaneperoxoic acid, 1,1-dimethyl-3-[(1-oxohexadecyl)oxy] propyl ester, oxalic acid, dodecyl 2-phenylethyl ester, octatriacontyl pentafluoropropionate and octacosanol possessed remarkable binding scores higher than the reference remdesivir. While, heneicosane, bis(2-ethylhexyl) ester, octadecane, 3-ethyl-5-(2-ethylbutyl) and Pregn-5-en-20-one, 11-(acetyloxy)-3,14-dihydroxy-12-(2-hydroxy-3-methyl-1-oxobutoxy)-, (3 β ,11 α ,12 β ,14 β) showed significant binding scores which are quite similar to remdesivir (Table 3).

The binding site of RdRp was explored computationally, which provides some insights in the discovery of antiviral drugs. The interaction of RdRp with the reference drug remdesivir showed hydrogen bond interaction with Glu167, Asp618, Lys621 and Lys798 (Figure 3A). Docking results for octatriacontyl pentafluoropropionate declared that this compound is well oriented inside the enzyme pockets and showed hydrogen bond interaction with Lys798 (Figure 3B).

Spike protein S1 inhibition screening

Results of spike protein inhibition screening indicated that most compounds exhibited significant binding scores similar to those exhibited by the reference drug umifenovir. n-hexadecanoic acid, heneicosane, octacosane, heptacosane, hexadecaneperoxoic acid, 1,1-dimethyl-3-[(1-oxohexadecyl)oxy]propyl ester, oxalic acid, dodecyl 2-phenylethyl ester, bis(2-ethylhexyl) ester, octacosanol, octadecane, octatriacontyl pentafluoropropionate and 3-ethyl-5-(2-ethylbutyl) showed the best scoring results (higher than Umifenovir). While, tetradecanoic acid, hexadecanoic acid, methyl ester, pinostrobin chalcone, trans-13-octadecenoic acid, estra-1,3,5(10)-trien-17-one, 3-

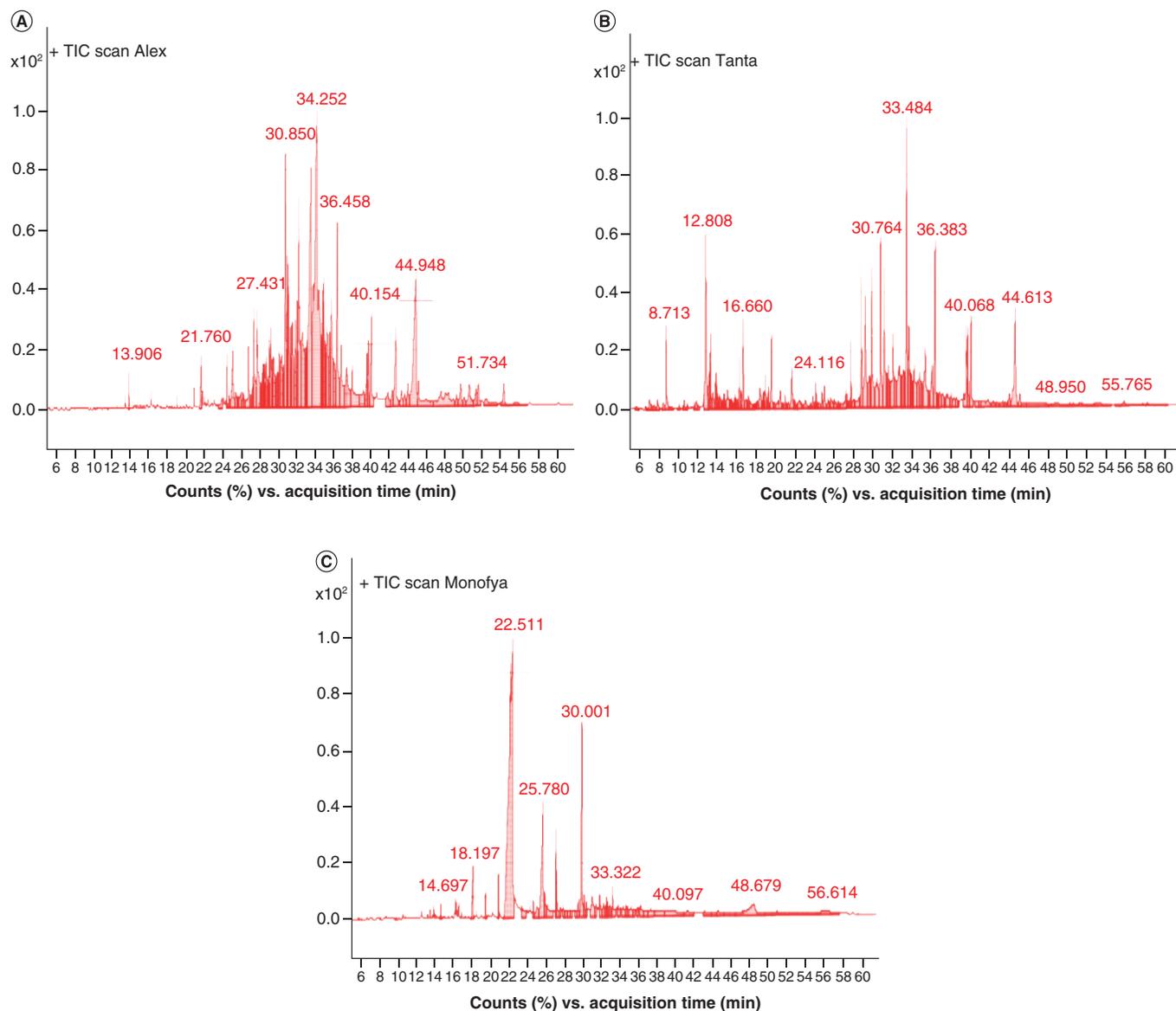


Figure 2. Egyptian propolis analyses and potential anti COVID-19 effect. Gas chromatography chromatogram of the different propolis samples: Alexandria (A), Tanta (B) and Menoufia (C).

hydroxy-2-methoxy, pregn-5-en-20-one, 11-(acetyloxy)-3,14-dihydroxy-12-(2-hydroxy-3-methyl-1-oxobutoxy)-, (3 β ,11 α ,12 β ,14 β) and cyclohexamine, N-n-butyl-1-[2-thionaphthenyl] possessed comparable binding scores to umifenovir.

The interaction of spike protein S1 with the reference drug Arbidol[®] (umifenovir) revealed hydrogen bond interaction with Phe456, in addition to hydrophobic interaction with Lys458 and Asn481 (Figure 4A). Docking results for octatriacontyl pentafluoropropionate showed hydrogen bond interaction with Asp420, in addition to H-arene interaction with Tyr505 (Figure 4B).

Main protease enzyme inhibition

Regarding main protease enzyme, octacosane, hexadecaneperoxoic acid, octatriacontyl pentafluoropropionate and 1,1-dimethyl-3-[(1-oxohexadecyl)oxy] propyl ester showed the highest binding scores and good binding profile in comparison to the reference drugs lopinavir.

The interaction of 3CLpro with the reference drug KALETRA[®] (lopinavir) displayed hydrogen bond interaction with Glu166 and hydrophobic interaction with Thr26 and Asn142 (Figure 5A). Docking results for octatriacontyl

Table 2. Gas chromatography/mass spectrometry analysis of the propolis samples under test.

Probable compound	Relative percentage (%)		
	Alexandria	Tanta	Menoufia
Acids			
n-Hexadecanoic acid	15.30	-	65.80
trans-13-octadecenoic acid	13.40	-	2.20
Benzoic acid	-	77.50	-
Trans-caffeic acid	-	62.20	-
Tetradecanoic acid	-	-	5.50
Alkanes			
Heneicosane	-	5.1	-
Octacosane	-	53	-
Heptacosane	70.60	54.5	-
Esters			
Hexadecanoic acid, methyl ester	-	-	1.60
Methyl pentafluoropropionate	-	2.90	-
Pinostrobin chalcone	-	49.90	17.60
Hexadecaneperoxoic acid, 1,1-dimethyl-3-[(1-oxohexadecyl)oxy]propyl ester	-	-	4.20
Oxalic acid, dodecyl 2-phenylethyl ester	-	-	3.40
Triterpenoids			
R1-Barrigenol	8.60	-	-
α -Eudesmol	-	26.10	-
β -Eudesmol	-	28.70	-
Alcohol			
Octacosanol	34.90	58.80	-
Flavonoids			
Pinocembrin	-	57.00	17.60
Not specified			
Octatriacontyl pentafluoropropionate	-	-	4.2
Bicyclo[2.2.2]octa-2,5-diene, 1,2,3,6-tetramethyl	-	-	1.30
Estra-1,3,5(10)-trien-17-one, 3-hydroxy-2-methoxy	14.60	-	-
4 β -Methylandrosterane-2,3-diol-1,17-dione	27.20	-	-
Pregnan-20-one, 3,17-dihydroxy-, (3 β ,5 β)	11.60	-	-
Octadecane, 3-ethyl-5-(2-ethylbutyl)	22.30	-	-
Pregn-5-en-20-one, 11-(acetyloxy)-3,14-dihydroxy-12-(2-hydroxy-3-methyl-1-oxobutoxy)-, (3 β ,11 α ,12 β ,14 β)	34.90	-	-
Cyclohexamine, N-n-butyl-1-[2-thionaphthenyl]	25.40	-	-

(-): Not detected.

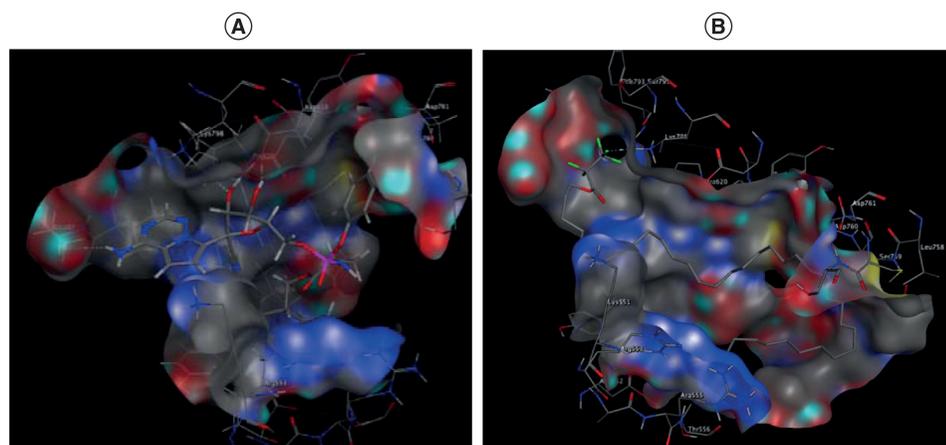
pentafluoropropionate revealed hydrogen bond interaction with Met49 (Figure 5B).

Discussion

In the present study, Egyptian propolis samples were analyzed and investigated for their anti-COVID-19 activity using molecular docking. Pollen grain analysis was investigated according to Temizer *et al.* [22] which revealed that the family Cyperaceae was dominant in Alexandria propolis while family Asteraceae was dominant in Tanta and Menoufia propolis samples. Scanning electron microscope analysis of propolis samples revealed that all the propolis samples have a putative gel like morphology. Rahim *et al.* [23] stated that the propolis samples with a homogenized flat topography (with intervals of flaking out and crumpled-like surface topography) may act as building blocks of the hive. Further chemical analysis was applied on the propolis samples, which revealed that the presence of tannins, phenols and steroids varies among the samples which prove that the propolis composition differs according to the correspondence area and the environmental conditions including flora [24]. GC/MS analysis revealed that acids were the main component in the propolis samples. Hegazi *et al.* [24] reported that the characteristic groups

Table 3. The binding scores of test compounds toward three protein targets (RNA-dependent RNA polymerase, spike protein S1 and main protease) from 2019-nCoV.

Test compound	Propolis sample source	Binding score (kcal/mol)		
		RNA-dependent RNA polymerase	Spike protein S1	Main protease
Remdesivir		-6.77		
KALETRA® (lopinavir)				-8.18
Arbidol® (umifenovir)			-5.56	
n-Hexadecanoic acid	Alexandria, Menoufia	-5.70	-5.64	-6.28
Benzoic acid	Tanta	-3.91	-4.16	-3.70
Trans-caffeic acid	Tanta	-4.8	-4.76	-4.48
Tetradecanoic acid	Menoufia	-5.34	-5.23	-5.84
Heneicosane	Tanta	-6.19	-5.68	-6.44
Octacosane	Tanta	-6.87	-5.99	-7.39
Heptacosane	Alexandria, Tanta	-6.91	-5.80	-6.95
Hexadecanoic acid, methyl ester	Menoufia	-5.63	-5.27	-6.28
Pinostrobin chalcone	Tanta, Menoufia	-5.59	-5.50	-5.44
Hexadecaneperoxoic acid, 1,1-dimethyl-3-[(1-oxohexadecyl)oxy]propyl ester	Menoufia	-8.04	-6.56	-7.35
Oxalic acid, dodecyl 2-phenylethyl ester	Menoufia	-6.94	-5.95	-6.94
trans-13-octadecenoic acid	Alexandria, Menoufia	-5.97	-5.29	-6.06
Methyl pentafluoropropionate	Tanta	-3.54	-3.55	-3.40
R1-Barrigenol	Alexandria	-5.58	-4.44	-5.81
α-Eudesmol	Tanta	-4.47	-4.57	-4.61
β-Eudesmol	Tanta	-4.96	-4.96	-4.77
Octacosanol	Alexandria, Tanta	-6.96	-6.26	-6.77
Pinocembrin	Tanta, Menoufia	-4.93	-4.78	-5.29
Bicyclo[2.2.2]octa-2,5-diene, 1,2,3,6-tetramethyl	Menoufia	-3.84	-3.93	-4.23
Estra-1,3,5(10)-trien-17-one, 3-hydroxy-2-methoxy	Alexandria	-5.31	-5.26	-6.16
Pregnan-20-one, 3,17-dihydroxy-, (3β,5β)	Alexandria	-5.06	-4.36	-5.53
Octadecane, 3-ethyl-5-(2-ethylbutyl)	Alexandria	-6.11	-5.83	-6.55
4β-Methylandrostan-2,3-diol-1,17-dione	Alexandria	-4.72	-4.64	-5.38
Octatriacontyl pentafluoropropionate	Menoufia	-8.20	-6.96	-7.35
Pregn-5-en-20-one, 11-(acetyloxy)-3,14-dihydroxy-12-(2-hydroxy-3-methyl-1-oxobutoxy)-, (3β,11α,12β,14β)	Alexandria	-6.63	-5.03	-6.08
Cyclohexamine, N-n-butyl-1-[2-thionaphthenyl]	Alexandria	-4.90	-5.51	-5.33

**Figure 3.** Egyptian propolis analyses and potential anti COVID-19 effect. Mode of binding of remdesivir (A), and octatriacontyl pentafluoropropionate (B) inside RNA-dependent RNA polymerase active site from 2019-nCoV.

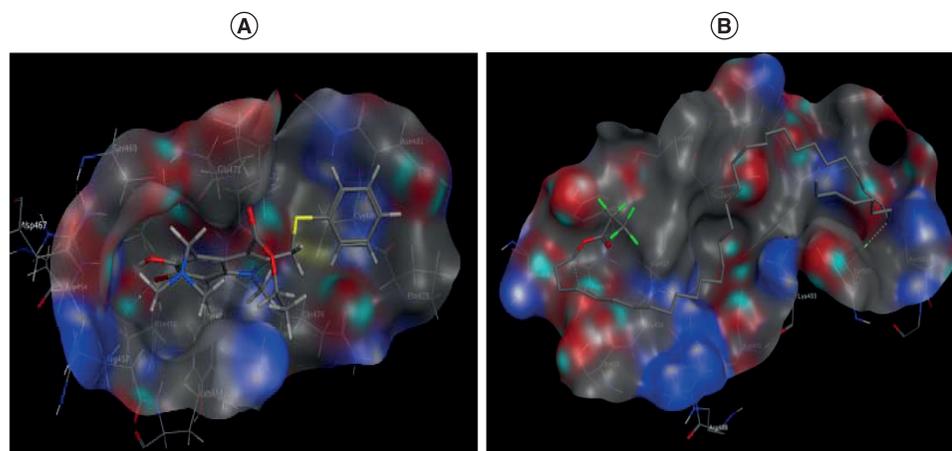


Figure 4. Egyptian propolis analyses and potential anti COVID-19 effect. Mode of binding of umifenovir (A) and octatriacontyl pentafluoropropionate (B) inside spike protein S1 active site from 2019-nCoV.

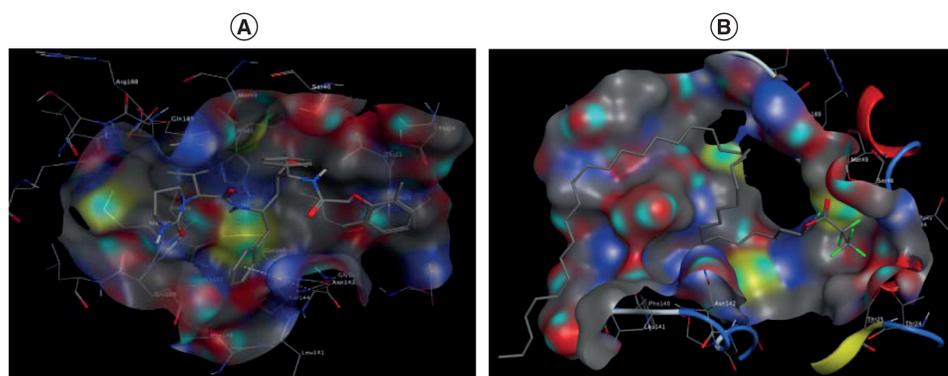


Figure 5. Egyptian propolis analyses and potential anti COVID-19 effect. Mode of binding of lopinavir (A), and octatriacontyl pentafluoropropionate (B) inside main protease 3CLpro active site from 2019-nCoV.

of poplar propolis were aliphatic, aromatic acids, aromatic acid esters and flavonoids and it was characterized by the presence of some triterpenoids. Ibrahim *et al.* [25] found that 11 phenolic compounds in propolis samples that were collected from Abees Apiculture Unit, Agricultural Research Farm, University of Alexandria, Alexandria. The phenolic compounds were identified as pinostrobin; izalpinin; tectochrysin; pinocembrin; galangin; chrysin; quercetin-3,3'-di-O-methyl ether; kaempferol-3-O-methyl ether; quercetin-3,7-di-O-methyl ether; isoferulic acid; and galangin-5-O-methyl ether that were not detected in Alexandria propolis (collected from newly reclaimed lands) that was investigated in the present study (Figure 2A & Table 2) which confirmed the relatedness between the chemical constituents, the botanical origin and the seasonal variations.

In the current study, molecular docking was performed to predict the binding affinity [26] of the propolis compounds toward RNA-dependent RNA polymerase, spike protein S1 and main protease (Table 3). Most of the tested fractions showed promising binding scores in relation to the reference antiviral drugs namely: remdesivir, lopinavir and umifenovir. In a trial to investigate the binding interactions of the tested fractions; the modes of binding and orientations were investigated in relation to their antiviral activity. Octatriacontyl pentafluoropropionate showed hydrogen bond interaction with Lys798, Asp420 and Met49, in addition to H-arene interaction with Tyr505 inside RNA-dependent RNA polymerase, spike protein S1 and main protease enzymes pockets, respectively.

Conclusion

Data from the present study concluded that Egyptian propolis samples proved to have variable chemical composition according to the botanical origin and geographical distribution. Menoufia propolis reported high anti-COVID-19

activity in relation to the tested BSAA and it is recommended as a promising candidate in the combat against the pandemic COVID-19.

Summary points

- The present study aimed to investigate the prospective anti-COVID-19 activity of Egyptian propolis.
- Propolis samples were collected from different Egyptian geographic areas.
- Qualitative and quantitative propolis analyses were evaluated. Gas chromatography/mass spectrometry proved the presence of octatriacontyl pentafluoropropionate (4.2%).
- Computational modeling of propolis fractions was evaluated in relation to some known antiviral drugs namely: remdesivir, lopinavir and umifenovir.
- Most of the tested compounds showed a promising binding score.
- Docking analyses declared that octatriacontyl pentafluoropropionate is well oriented inside the enzyme pockets and showed hydrogen bond interaction with Lys798, in addition to excellent binding manner with the active site of the target macromolecules (RNA-dependent RNA polymerase, Spike protein S1 and main protease) in relation to some broad-spectrum antiviral agents.
- Menoufia propolis could be recommended as a promising candidate in the combat against the pandemic COVID-19.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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References

- 1 Lu R, Zhao X, Li J *et al.* Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *The Lancet* 395(10224), 565–574 (2020).
- 2 Sher M, Shah K, Khan ZA, Khan H, Khan A. Computational and theoretical modeling of the transmission dynamics of novel COVID-19 under Mittag-Leffler power law. *Alex. Eng. J.* 59(5), 3133–3147 (2020).
- 3 Belouzard S, Chu VC, Whittaker GR. Activation of the SARS coronavirus spike protein via sequential proteolytic cleavage at two distinct sites. *Proc. Natl Acad. Sci. USA* 106(14), 5871–5876 (2009).
- 4 Andersen PI, Ianevski A, Lysvand H *et al.* Discovery and development of safe-in-man broad-spectrum antiviral agents. *Int. J. Infect. Dis.* 93, 268–276 (2020).
- 5 Bösl K, Ianevski A, Than TT *et al.* Common Nodes of Virus–Host Interaction Revealed Through an Integrated Network Analysis. *Front. Immunol.* 10, 2186 (2019).
- 6 NIH Clinical Trials (a). A prospective/retrospective, randomized controlled clinical study of antiviral therapy in the 2019-nCoV pneumonia. (2020). <https://clinicaltrials.gov/ct2/show/NCT04255017>
- 7 NIH Clinical Trials (b). Mild/moderate 2019-nCoV remdesivir RCT. (2020). <https://clinicaltrials.gov/ct2/show/NCT04252664>
- 8 Anjum SI, Ullah A, Khan KA *et al.* Composition and functional properties of propolis (bee glue): a review. *Saudi J. Biol. Sci.* 26(7), 1695–1703 (2019).
- 9 Gezgin Y, Kazan A, Ulucan F, Yesil-Celiktas O. Antimicrobial activity of propolis and gentamycin against methicillin-resistant *Staphylococcus aureus* in a 3D thermo-sensitive hydrogel. *Ind. Crops Prod.* 139, 111588 (2019).
- 10 Kuropatnicki AK, Szliszka E, Krol W. Historical aspects of propolis research in modern times. *Evid. Based Complement. Alternat. Med.* 2013, 964149 (2013).
- 11 El-Guendouz S, Lyoussi B, Miguel MG. Insight on propolis from mediterranean countries: chemical composition, biological activities and application fields. *Chem. Biodivers.* 16(7), e1900094 (2019).
- 12 Sforcin JM. Propolis and the immune system: a review. *J. Ethnopharmacol.* 113(1), 1–14 (2007).
- 13 Machado BAS, Silva RPD, de Abreu Barreto G *et al.* Chemical composition and biological activity of extracts obtained by supercritical extraction and ethanolic extraction of brown, green and red propolis derived from different geographic regions in Brazil. *PLoS One* 11(1), e0145954 (2016).
- 14 Kourkoutas Y, Chorianopoulos N, Karatzas KA, Banat IM. Bioactive natural products. *Biomed. Res. Int.* 4302706, 2016, 110–117 (2016).
- 15 VijayaSekhar VE, Prasad MS, Joshi DS, Narendra K, Satya AK, Rao KSS. Assessment of phytochemical evaluation and in-vitro antimicrobial activity of *Cassia angustifolia*. *Int. J. Pharmacogn. Phytochem. Res.* 8(2), 305–312 (2016).

- 16 Abdulkhani A, Hosseinzadeh J, Ashori A, Esmaeeli H. Evaluation of the antibacterial activity of cellulose nanofibers/polylactic acid composites coated with ethanolic extract of propolis. *Polymer Composites* 38(1), 13–19 (2017).
- 17 Pagadala NS, Syed K, Tuszyński J. Software for molecular docking: a review. *Biophys. Rev.* 9(2), 91–102 (2017).
- 18 Li Y, Fu X, Duan D, Liu X, Xu J, Gao X. Extraction and identification of phlorotannins from the brown alga, *Sargassum fusiforme* (Harvey) Setchell. *Mar. Drugs* 15(2), 49 (2017).
- 19 Elfiky AA. SARS-CoV-2 RNA dependent RNA polymerase (RdRp) targeting: an *in silico* perspective. *J. Biomol. Struct. Dyn.* 1–9 (2020).
- 20 Gentile D, Patamia V, Scala A, Sciortino MT, Piperno A, Rescifina A. Putative inhibitors of SARS-CoV-2 main protease from a library of marine natural products: A virtual screening and molecular modeling study. *Mar. Drugs*. 18(4), 225 (2020).
- 21 Temizer IK, Güder A, Çelemlı ÖG Botanical origin and antioxidant activities of propolis from the Irano-Turanian region. *İstanbul J. Pharmacy* 47(3), 107–111 (2017).
- 22 Barth OM, de Janeiro R. Palynology as a tool to distinguish between propolis and geopropolis: southern Brazilian samples. *Open Access Library J.* 2(12), 1 (2015).
- 23 Rahim MKA, Sulaiman SA, Sirajudeen KNS, Ghazali FC. Microscopic and micro-diffraction analysis of *Trigona apicalis* Propolis: a journey towards therapeutics discovery. *Ann. Microscopy* 12 (2012).
- 24 Hegazi A, Abdou AM, Abd Allah F. Egyptian propolis 11: Its antimicrobial activity with comparison with different localities. *Int. J. Curr. Microbiol. Appl. Sci.* 3(9), 530–538 (2014).
- 25 Ibrahim RS, Wanas AS, El-Din AS, Radwan MM, Elsohly MA, Metwally AM. Isolation of eleven phenolic compounds from propolis (bee glue) collected in Alexandria, Egypt. *Planta Medica.* 80(10), PE5 (2014).
- 26 Shah K, Khan ZA, Ali A, Amin R, Khan H, Khan A. Haar wavelet collocation approach for the solution of fractional order COVID-19 model using Caputo derivative. *Alex. Eng. J.* 59(5), 3221–3231 (2020).