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Exploration of date palm (*Phoenix dactylifera*) bioactivity as anti-SARS-CoV-2: *in silico* study

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Abstract: The COVID-19 pandemic has accelerated the search for effective antiviral agents, with particular interest in natural compounds. This study explores the potential of compounds found in date palm (*Phoenix dactylifera*) fruit as antiviral agents against SARS-CoV-2, utilizing molecular docking techniques. Computational tools including Autodock Vina, DS Visualizer, Autodock Tools, Python, and Marvin Sketch were employed for this analysis. The results indicate that apigenin, diosmetin, and luteolin exhibit promising antiviral activity. Specifically, the binding energies of apigenin to the 3CL-Pro, Nsp3, PD-ACE-2, and RBD-S proteins were -7.6 kcal/mol, -8.7 kcal/mol, -5.7 kcal/mol, and -7.0 kcal/mol, respectively. Diosmetin displayed binding energies of -6.7 kcal/mol, -8.5 kcal/mol, -5.6 kcal/mol, and -7.2 kcal/mol with the same proteins, while luteolin showed binding energies of -7.9 kcal/mol, -8.6 kcal/mol, -5.7 kcal/mol, and -7.3 kcal/mol. For comparison, the binding energies of nirmatrelvir were -7.2 kcal/mol, -7.5 kcal/mol, -5.1 kcal/mol, and -6.3 kcal/mol, and those of ritonavir were -7.0 kcal/mol, -8.2 kcal/mol, -5.6 kcal/mol, and -6.7 kcal/mol with the respective proteins. These findings suggest that apigenin, diosmetin, and luteolin have stronger binding affinities than nirmatrelvir and ritonavir in silico, highlighting their potential for further development as antiviral agents.

Keywords: Phoenix dactylifera, molecular docking, SARS CoV-2

Introduction

The Coronavirus Disease 2019 (COVID-19), declared a pandemic by the World Health Organization (WHO) in March 2020, has become a global crisis, spreading rapidly across the world and resulting in significant loss of life [1]. Governments have implemented various strategies to reduce the number of COVID-19 cases, yet there remains an urgent need for the development and innovation of effective treatments.

Natural compounds present a promising avenue for drug development. One plant with notable potential as an antiviral agent is the date palm (*Phoenix dactylifera*). Dates are well-documented for their health benefits, including antioxidant, antimutagenic, antimicrobial, anti-inflammatory, antihyperlipidemic, gastroprotective, hepatoprotective, nephroprotective, anticancer, antifibrotic, antiproliferative, and immunostimulant activities. They contain a variety of nutraceutical compounds, such as anthocyanins, phenolics, sterols, carotenoids, and flavonoids, which possess antiradical properties and offer protection against oxidative damage [2]. Among these, the phenolic compounds apigenin, diosmetin, and luteolin have shown potential for therapeutic applications [3].

However, the antiviral activity of date palm compounds against SARS-CoV-2 has not been extensively studied. This study aims to evaluate the potential of apigenin, diosmetin, and luteolin as anti-SARS-CoV-2 agents using molecular docking techniques. Molecular docking is a computational method that calculates the binding affinity and predicts the binding sites of compounds with target proteins. This approach serves as a preliminary step to identify promising orientations of candidate compounds relative to known drugs [4]. SARS-CoV-2, a member of the Coronaviridae family, is an RNA virus capable of infecting birds, mammals, and humans, leading to a range of acute to chronic diseases. Several structural and nonstructural proteins, such as 3CL-Pro, Nsp3, PD-ACE-2, and RBD-S, have been identified as potential targets for antiviral drug development [5].

Method

Tools and software

Data and information were obtained from experimental results using the molecular docking

Table 1. Binding energy data between test compounds and target proteins (kcal/mol)

Comp/Protein	3Cl-Pro	Nsp3	PD-ACE-2	RBD-S
Apigenin (A)	-7.6	-8.7	-5.7	-7.0
Diosmetin (D)	-6.7	-8.5	-5.6	-7.2
Luteolin (L)	-7.9	-8.6	-5.7	-7.3
Nirmatrelvir (N)	-7.2	-7.5	-5.1	-6.3
Ritonavir (R)	-7.0	-8.2	-5.6	-6.7
	L>A>N>R>D	A>L>D>R>N	A=L>D=R>L	L>D>A>R>N

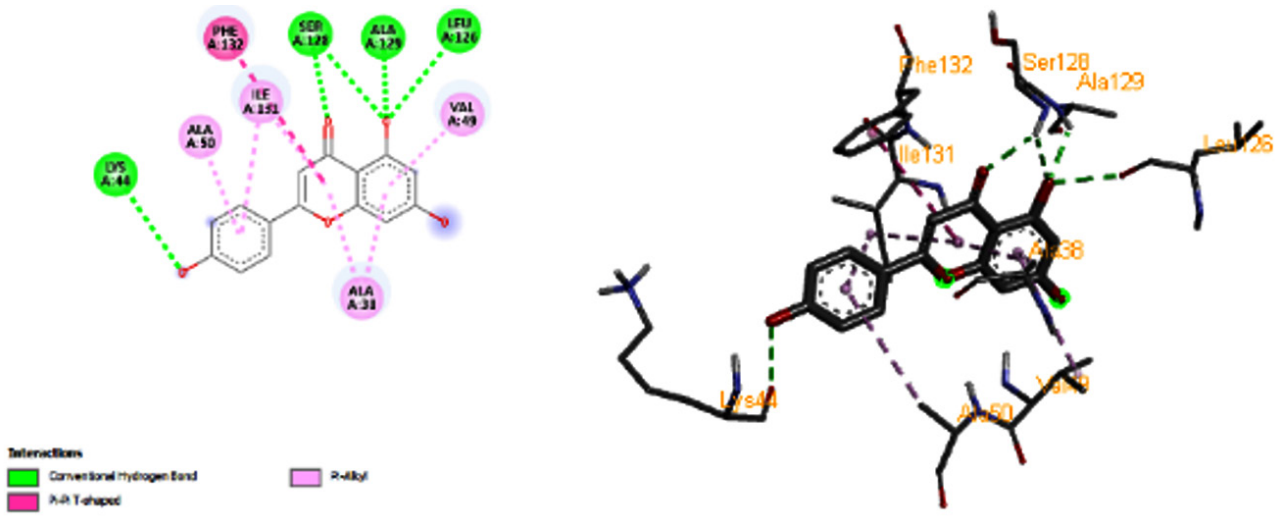

Figure 1. Apigenin with Nsp3 2D (left) and 3D (right) visualization

method. The computational tools and software utilized included Autodock Vina, DS Visualizer, Autodock Tools, Python, and Marvin Sketch.

Molecular docking

The protein structures of 3CL-Pro, Nsp3, PD-ACE-2, and RBD-S were retrieved from the Protein Data Bank (PDB) (www.rcsb.org). Preprocessing of the proteins and ligands was performed using DS Visualizer. Native ligands were extracted from the target protein files, while test ligands were downloaded from PubChem (http://pubchem.ncbi.nlm.nih.gov). The proteins were saved under the name "receptor.pdb," native ligands as "native_ligand.pdb," and test ligands as "ligand.pdb." These files were then converted to PDBQT format using Autodock Tools. The processed protein and ligand files were stored in the Vina folder.

A new text file, named "conf.txt," was created and populated with the necessary information for the docking process. The docking conformations were selected based on an RMSD value of <2Å. Visualization of the docking results, including the interactions between the test protein and test ligand, was conducted using DS Visualizer. The data were further analyzed by selecting the most stable conformation with the lowest docking score [6].

Results

The validation results demonstrated that the RMSD values for all proteins were less than 2.00 Å, confirming the accuracy of the docking simulations. The binding affinities of apigenin from date fruit with the proteins 3CL-Pro, Nsp3, PD-ACE-2, and RBD-S were -7.6 kcal/mol, -8.7 kcal/mol, -5.7 kcal/mol, and -7.0 kcal/mol, respectively. For diosmetin, the binding affinities with the same proteins were -6.7 kcal/mol, -8.5 kcal/mol, -5.6 kcal/mol, and -7.2 kcal/mol, respectively. Similarly, luteolin showed binding affinities of -7.9 kcal/mol, -8.6 kcal/mol, -5.7 kcal/mol, and -7.3 kcal/mol with the respective proteins (Table 1).

The test compound with Nsp3 protein exhibited the highest affinity, indicating its strong potential as an antiviral agent. Among the tested compounds, apigenin demonstrated the highest docking score with

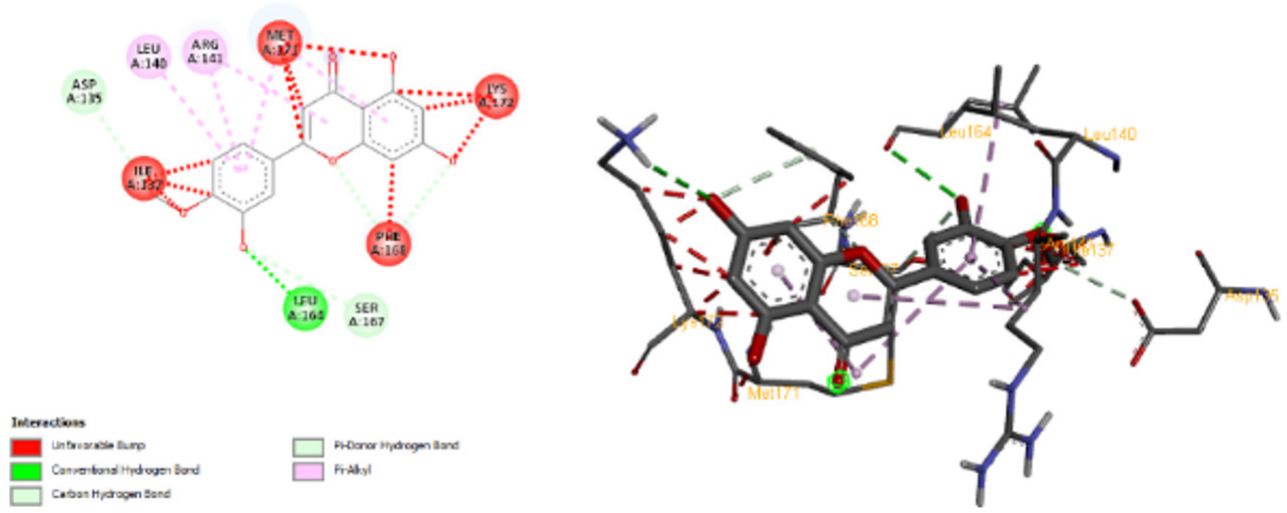

Figure 2. Diosmetin with Nsp3 2D (left) and 3D (right) visualization

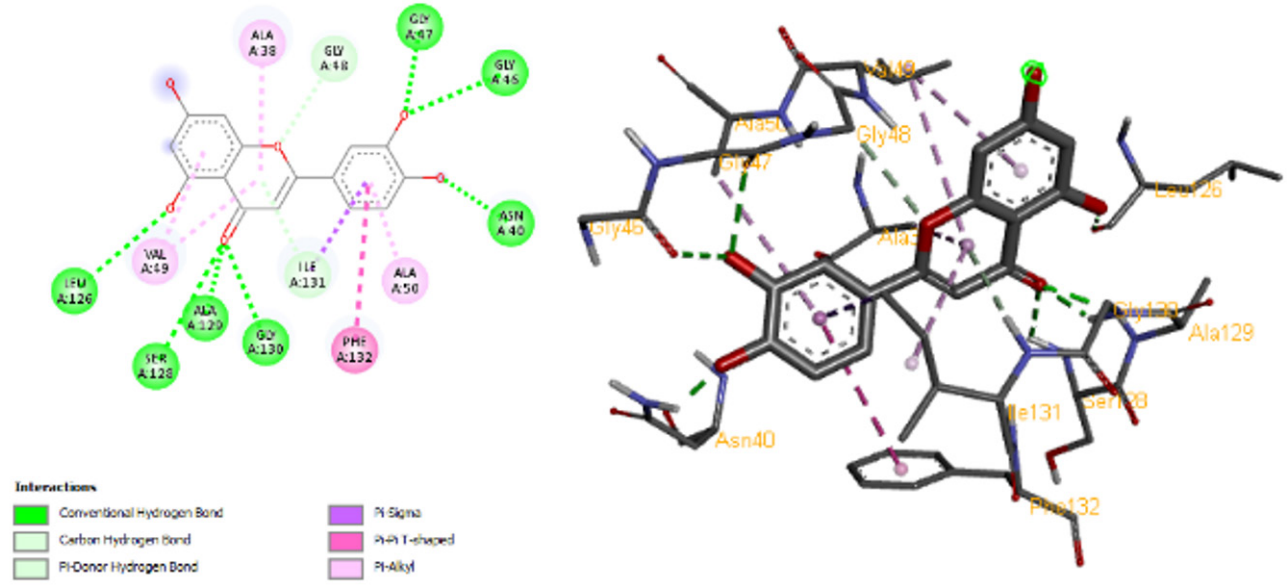

Figure 3. Luteolin with Nsp3 2D (left) and 3D (right) visualization

Nsp3 at -8.7 kcal/mol. Visualization of the binding interaction (Figure 1) revealed that apigenin forms hydrogen bonds with the amino acids Ser A:128, Ala A:126, Leu A:126, and Lys A:44 at the active site. As shown in Figure 1, apigenin forms more hydrogen bonds with Nsp3 compared to diosmetin and luteolin, suggesting a stronger affinity than both nirmatrelvir and ritonavir.

Diosmetin also exhibited a strong binding affinity with Nsp3, with a free energy of -8.5 kcal/mol. The 2D visualization (Figure 2) showed that diosmetin forms a hydrogen bond with the amino acid Leu A:164 at its active site. When compared to nirmatrelvir and ritonavir, diosmetin demonstrated superior binding affinity.

Luteolin showed a relatively high binding affinity with Nsp3, with a free energy of -8.6 kcal/mol. The 2D visualization (Figure 3) indicated that luteolin forms hydrogen bonds with several amino acids, including Gly A:47, Gly A:46, Asn A:40, Leu A:126, Ser A:128, Ala A:129, and Gly A:130 at the active site.

Discussion

The differences in free energy of binding observed in the results are likely due to variations in ligand interactions with amino acids within the receptor. Apigenin docking with the Nsp3 protein resulted in the lowest docking score of -8.7 kcal/mol, indicating

the strongest activity among the tested compounds. Apigenin, known for its inhibitory effects on SARS-CoV-2, interacts effectively with the Nsp3 protein. A lower binding affinity value suggests that the functional group requires or releases less energy to transfer electrons, resulting in a more negatively charged state that facilitates interaction with positively charged amino acid atoms. Consequently, a lower affinity value indicates a more stable molecular complex.

The docking score, or binding energy, reflects the strength of the interaction between the test compound and the target receptor. A lower docking score signifies a higher binding affinity between the test compound and the receptor [7]. When compared to the standard compounds nirmatrelvir and ritonavir, apigenin, diosmetin, and luteolin exhibit superior binding affinity. These findings suggest that compounds found in dates have significant potential as SARS-CoV-2 antiviral agents.

Conclusion

Compounds in date fruits with the greatest potential in inhibiting the SARS-CoV-2 virus are apigenin compounds, followed by diosmetin and luteolin. The antiviral potential of the test compounds showed stronger binding energy than ritonavir and nirmatrelvir drugs.

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Declaration of interest

The authors declare no conflict of interest.

Authors contribution

NHA, RF conducted the literature search, study design, data collection, data analysis, data interpretation, and writing of the publication manuscript.

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