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In silico screening of natural compounds for antiviral activity against the influenza virus

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ABSTRACT

Influenza A viruses are major pathogens responsible for significant global morbidity and mortality, necessitating the development of novel antiviral agents targeting drug-resistant strains. This study has assessed the antiviral potential of various natural compounds against influenza A by performing molecular docking analyses in order to evaluate their binding affinities with neuraminidase (Protein Data Bank identifier: 3TI6); a critical viral enzyme that facilitates progeny virion release and dissemination. A total of 5,749 unique phytoconstituents were computationally screened, yielding five candidates with high binding affinities: pentagalloylglucose (-15.238 kcal/mol), stachyurin (-12.833 kcal/mol), osyritin (-12.398 kcal/mol), stachysoside A (-12.166 kcal/mol), and repandusinic acid A (-11.911 kcal/mol). Molecular dynamics simulations of repandusinic acid A corroborated the docking results and geometry optimization data, demonstrating enhanced structural stability and conformational flexibility relative to analogous compounds, with a root mean square deviation of 0.147 Å. These findings indicate that the identified bioactive compounds, particularly repandusinic acid A, hold promise as antiviral agents targeting neuraminidase. However, extensive experimental validation is required in order to elucidate their therapeutic efficacy, toxicity profiles, and pharmacokinetic parameters in clinical contexts.

1. Introduction

Influenza viruses primarily comprise types A and B, which are responsible for seasonal epidemics and recurring global pandemics.

PHARMAKEFTIKI, 37, 2S, 2025 | 269-273

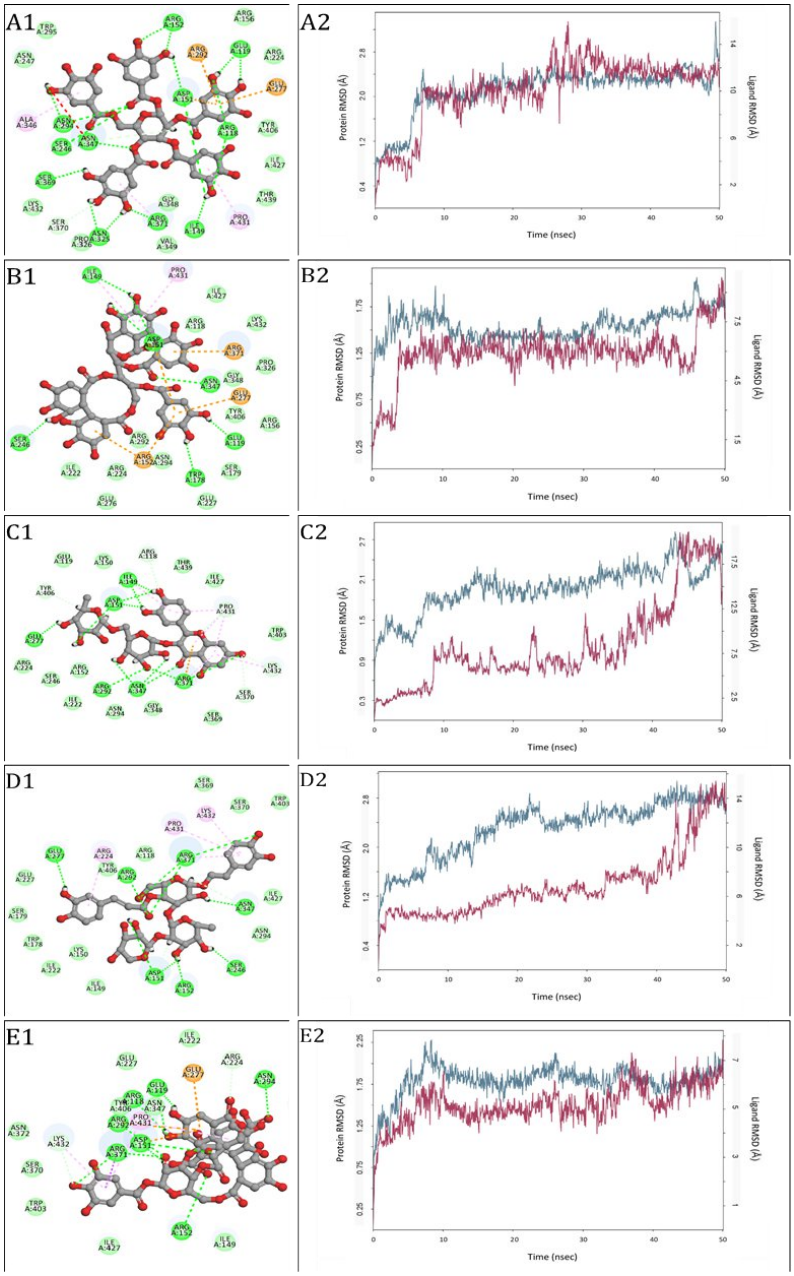

Figure 1. *Molecular docking and molecular dynamics (MD) analysis of natural compounds targeting the influenza virus neuraminidase. (A–E): Molecular docking and MD simulations of five top-ranking natural compounds interacting with the influenza virus neuraminidase (Protein Data Bank identifier: 3TI6). The recorded binding affinities were as follows: (A), pentagalloylglucose (-15.238 kcal/mol); (B), stachyurin (-12.833 kcal/mol); (C), osyritin (-12.398 kcal/mol); (D), stachysoside A (-12.166 kcal/mol); (E), repandusinic acid A (-11.911 kcal/mol). Repandusinic acid A (−11.911 kcal/mol) maintained conformational integrity throughout a 100-nanosecond MD simulation, with a root mean square deviation (RMSD) of 0.147 Å, suggesting stable target engagement under physiological conditions. The right panel illustrates the RMSD profiles of ligand–protein complexes over time, identifying repandusinic acid A as the most structurally stable compound.*

PHARMAKEFTIKI, 37, 2S, 2025 | 269-273

Their high mutation rates and propensity for genetic reassortment pose persistent threats to the efficacy of preventive and therapeutic measures. Transmission occurs *via* respiratory droplets expelled from infected individuals, with acute-onset symptoms including fever, cough, and myalgia[1].

The causative agent of influenza is an enveloped virus classified within the family *Orthomyxoviridae*, characterized by a segmented RNA genome enclosed within a lipid bilayer and studded with glycoproteins such as neuraminidase and hemagglutinin[2]. Existing antiviral therapies target neuraminidase and the M2 protein; however, the emergence of drug-resistant strains has compromised their clinical utility. For example, the prevalence of resistance to oseltamivir among influenza A(H1N1) variants rose markedly within a year of emergence[3]. This landscape highlights the critical need for novel antiviral agents with alternative mechanisms of action.

Natural products have gained attention as promising sources of structurally diverse antiviral candidates[4]. The present study aimed at evaluating the antiviral potential of selected natural compounds against influenza virus through *in silico* methods, specifically molecular docking, in order to determine their binding affinities to neuraminidase and nominate viable leads for further development.

2. Methodology

This study has employed *in silico* approaches for the characterization of the interactions between natural compounds and influenza viral proteins. A total of 12,971 phytochemicals were initially sourced from 200 medicinal plants prevalent in the Middle East. After excluding redundant molecular structures, 5,749 unique ligand conformations remained. Ligand structures were optimized by using the Ligand Preparation (LigPrep) module within the Glide suite. Calculations were performed at physiological pH (7.0), incorporating partial atomic charges and low-energy conformations *via* the Optimized Potentials for Liquid Simulations version 4 (OPLS4) force field. The extensive atomic content of these compounds typically precludes their routine application in docking workflows, but their inclusion was justified by the exploratory nature of the study.

The crystal structure of the influenza virus neuraminidase (PDB ID: 3TI6) was retrieved from the Protein Data Bank. Protein structure optimization was executed by using the Protein Preparation Wizard in Glide, involving bond order validation, addition of missing hydrogen atoms, and energy minimization at pH 7 using OPLS4, yielding a root mean square deviation (RMSD) of 0.30 Å. This step ensured compatibility of the receptor model for accurate docking simulations.

Docking studies have estimated the protein–ligand binding affinities by using Glide software. The neuraminidase active site was defined by seven functionally critical residues: Arg118, Arg152, Arg292, Glu119, Glu227, Asp151, and Tyr402. Residue assignments reflected their catalytic and interaction roles.

In an attempt to validate docking outcomes and to assess complex stability, molecular dynamics (MD) simulations were conducted on the top-scoring ligand. A 100-nsec MD run was performed in order to monitor temporal fluctuations of the ligand–protein complex. RMSD values were tracked for both protein backbone and ligand positions, thereby providing insights into conformational integrity under simulated physiological conditions.

3. Results and Discussion

From the 5,749 compounds screened, five emerged as potent neuraminidase inhibitors, exhibiting binding affinities ranging from -15.238 to -11.911 kcal/mol (Figure 1). Repandusinic acid A exhibited a strong binding affinity (-11.911 kcal/mol) and demonstrated the highest structural stability during the undertaken MD simulation, as reflected by its lowest RMSD values among the tested compounds. As an ellagitannin, its polyphenolic scaffold and abundance of hydroxyl moieties contribute to its enhanced bioactivity[5]. Other notable ligands included pentagalloylglucose, stachyurin, osyritin, and stachysoside A; all of which interacted favourably with key neuraminidase residues – specifical-

PHARMAKEFTIKI, 37, 2S, 2025 | 269-273

ly, Arg118, Asp151, and Glu227[6]. These interactions are essential for the enzymatic function of neuraminidase and imply a potential to inhibit viral replication[7].

MD simulations corroborated the docking predictions, thereby confirming the stability of repandusinic acid A over 100 nsec, with minimal deviation from its native conformation. Stability under such conditions is imperative for therapeutic viability, as unstable compounds may degrade or lose efficacy in biological systems. Natural products such as repandusinic acid A offer intrinsic advantages over synthetic molecules, including diverse chemical frameworks and reduced likelihood of resistance development. Their mechanisms may diverge from conventional antiviral pathways, making them particularly suited for combating drug-resistant influenza strains[4].

Notably, strains such as influenza A(H1N1) have exhibited rapid resistance to existing antivirals, reinforcing the need for alternative therapies. Literature further supports the antiviral promise of natural compounds with novel modes of action[7]; for instance, alkaloids have been shown to inhibit viral enzymes implicated in replication[8]. Recent reports affirm the broad-spectrum antiviral activity of phytochemicals – such as alkaloids, flavonoids, phenolic acids, lignans, coumarins, terpenes, and proteinaceous agents – against respiratory viruses including influenza A and SARS-CoV-2. In fact, their demonstrated efficacy against SARS-CoV-2 underscores the possibility of dual utility for future outbreaks[9].

4. Conclusion

This study has identified five natural compounds with strong affinity for influenza virus neuraminidase through *in silico* screening, notably highlighting the stability and therapeutic promise of repandusinic acid A through molecular dynamics simulation. Further empirical studies are warranted in order to establish clinical efficacy, safety profiles, and pharmacokinetic properties.

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Conflicts of interest

None exist.

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PHARMAKEFTIKI, 37, 2S, 2025 | 269-273

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