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In silico evaluation of therapeutic potentials of Syringic acid against some selected diseases

Md. Riad Chowdhury,* Kamrul Hasan Chowdhury, Nujhat Binte Hanif

ABSTRACT

In the past few years several developments in medications have been made for the better treatment of certain diseases like Breast Cancer, Alzheimer's disease, Tuberculosis, Obesity and Malaria. Phytochemicals possessing various medicinal properties have opened up the door to discover or design novel drug against these diseases. Syringic acid is such a natural compound found in many plants with a vast range of therapeutic potentials against several diseases. The present study aims to reveal Syringic acid as a potent inhibitor against Breast Cancer, Alzheimer's disease, Tuberculosis, Obesity and Malaria comparing to the standard drugs of each disease. Molecular docking of syringic acid with critical proteins associated with the diseases was done using Schrödinger Maestro (v11.1). QikProp module of Schrödinger Maestro was used for ADME prediction and the toxicity of the ligand was evaluated by ProTox online databases. Syringic acid was found to exhibit acceptable ADME properties with no carcinogenicity and mutagenicity. Molecular docking result also showed higher scores compared to the commercially available standard drugs against four out of five diseases. The best docking scores were found against Breast cancer, Alzheimer's disease, Obesity and Malaria which are -6.801 kcal/mol, -5.285 kcal/mol, -5.491 kcal/mol and -4.141 kcal/mol respectively. Syringic acid can be a stronger inhibitory potential agent against selected diseases than the standard drugs. Further clinical studies are required to consider syringic acid as an effective candidate drug for the better treatment of the mentioned diseases.

Keywords: Syringic acid, Molecular docking, ADME/T, *In silico*.

*Correspondence to:
Md. Riad Chowdhury, Department of Pharmacy, International Islamic University Chittagong, Chittagong-4318, Bangladesh
riadchy01@gmail.com

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INTRODUCTION

Syringic acid is a phenolic compound which occurs in olives, dates, acai palm, grapes, pumpkins, honey and many other plants.[1,2] It exhibits many pharmacological properties including antioxidant, anti-inflammatory, anti-proliferative, anti-microbial and anticancer activity.[3,4] Along with these multi-pharmacologic activities of syringic acid, it can be considered for the evaluation as a novel drug against several diseases. Some diseases captured in this study are breast cancer, tuberculosis, alzheimer's disease, obesity and malaria.

Breast cancer is the most common cause of death due to cancer among women worldwide.[5] The treatments include surgery, radiotherapy, chemotherapy with antracycline, endocrine therapy with tamoxifen and anti-HER2-therapy with trastuzumab.[6] In case of tuberculosis, it is estimated that more than 8 million people suffer from TB each year and the death rate is approximately 2 to 3 millions.[7] Moreover, the rate is increasing due to multidrug-resistant strains of *M. tuberculosis*.[8] Similarly another infectious disease is Malaria that causes half a million deaths in 219 millions cases per year.[9] Again, alzheimer's disease a neurodegenerative disorder is responsible for 50-60% of the dementia cases.[10] The risk of this disease increases substantially due to obesity.[11]

Molecular docking is a significant computational approach in lead optimization which predicts binding affinity between the selected compound and target protein. Therapeutic potential of any compound can be evaluated initially through molecular docking that ultimately saves time and cost in drug discovery. Since syringic acid possesses several types of activity, current study focuses on evaluating its pharmacologic properties against above mentioned diseases using computational approach.

MATERIALS AND METHODS

Ligand Preparation: The structure of Syringic acid (CID: 10742) was retrieved in SDF format from PubChem database (www.pubchem.ncbi.nlm.nih.gov) and three-dimensional structure was prepared by using LigPrep wizard of Schrödinger maestro. Possible ionization state was generated using Epik at pH 7.0±2.0 for proper calculation of tautomer and better understanding of protonation state in biological condition.[12] Up to 32 stereoisomers were generated per ligand retaining specific chiralities. Assigning the bond orders the structure was minimized at OPLS3 force field.[13] Similar methods and parameters are also used for the preparation of standard drug compounds for comparison purpose.

Department of Pharmacy, International Islamic University Chittagong, Chittagong-4318, Bangladesh

Protein preparation: The receptors used for molecular docking were downloaded from RCSB Protein Data Bank: [14] human estrogen receptor alpha (PDB id: 3ERT)[15] against breast cancer, mycolic acid cyclopropane synthase(PDB id: 1KPI)[16] against tuberculosis, BACE1 (PDB id: 4IVT)[17] against Alzheimer's disease, fat mass and obesity (FTO) protein (PDB id: 3LFM)[18] against obesity and plasmepsin II (PDB id: 1SME)[19] against malaria. Protein preparation wizard in Schrödinger Maestro (v11.1) was used for structure refinement of proteins where bond orders were assigned along with the addition of hydrogens to overwhelming atoms. Also the selenomethionines were transformed into methionines and water molecules were deleted. Finally creating zero order bonds to metals and disulfide bonds, minimization was performed utilizing default constraint of RMSD 0.30 Å and force field OPLS3.

Active Site Selection: The active sites on target receptors were selected by PockDrug server which estimates pocket druggability using ligand proximity method.[20] Setting proximity threshold to 5.5Å, the pocket with highest probability of druggability was selected.[21]

Receptor Grid Generation: In Glide, grids were generated maintaining the default parameters of van der Waals scaling factor 1.00, partial charges cutoff 0.25 and an OPLS3 force field. A bounding box for individual receptor was set to such extend that it covers the entire active site for docking experiment.

Docking Simulation: Standard precision ligand docking was performed in Glide of Schrodinger maestro (v11.1) where penalties were employed to non-cis/trans amide bonds. Van der Waals scaling factor and partial charges cutoff were set to 0.80 and 0.15 respectively. Energy minimized posture was applied for final scoring and expressed as glide score. The poses and glide score value of syringic acid and standard drug compounds with each selected receptor was recorded.

ADME/T Analysis: ADME properties determine the drug-like activity of ligand molecule based on Lipinski's rule of five.[22] According to this rule, physicochemical parameter ranges include molecular weight ≤ 500, H-bond donor ≤ 5, H-bond acceptor ≤ 10, log P ≤ 5 and molar refractivity 40-130. The QikProp module of Schrödinger maestro (v11.1) was used to predict the absorption, distribution, metabolism and excretion (ADME) of syringic acid. Also the toxicity of the ligand was evaluated using SMILES (simplified molecular-input line-entry system) in ProTox online database.[23]

RESULTS

Docking Simulation

In this study, molecular docking simulation was performed to analyze the interaction of syringic acid (Figure 1) with five receptors targeted for the treatment of specific diseases. Comparing to the standard drug, glide scores of syringic acid were tabulated in Table 1 and also, the interactions with bond distances were explained by analysis from Table 2. Hydrogen and hydrophobic interactions are displayed in Figure 1. Four out of five docking results of syringic acid have exhibited higher scores than standard drugs. Among them, the best result found was against breast cancer which is -6.801 kcal/mol. It forms two hydrogen bonds with Arg-394 and Glu-353 also three hydrophobic interactions with Leu-346, Ala-350 and Leu-387. Again, syringic acid possesses almost similar docking scores against Alzheimer's disease and obesity which are -5.285 kcal/mol and -5.491 kcal/mol respectively. When bound to BACE1 receptor, it forms two hydrogen bonds with Asp-32 and Phe-108 as well as two pi-pi stacking interactions with Phe-108 and Tyr-71. In case of fat mass and obesity (FTO) protein, amino acid Glu-234, Tyr-106 and Arg-96 was found in H-bonding interaction and His-231, Tyr-108 in hydrophobic interaction with syringic acid. The lowest docking score (-4.141 kcal/mol) obtained was when ligand binds to plasmepsin II by two H-bonds with Thr-217 and Asp-34 and a hydrophobic bond withVal-78 for anti-malarial activity. However,

Table 1 Docking scores comparison between syringic acid and standard drugs

	Docking Scores (kcal/mol)	
Diseases	**Syringic acid**	**Standard Drugs**
Breast cancer	-6.801	-4.819 (Tamoxifen)
Tuberculosis	-6.886	-7.016 (Thiacetazone)
Alzheimer's Disease	-5.285	-4.129 (Galantamine)
Obesity	-5.491	-3.881 (Orlistat)
Malaria	-4.141	-3.896 (Primaquine)

Table 2 Interactions and bond distances of syringic acid with the receptor binding site

	Hydrogen bond interactions of Syringic acid		Hydrophobic interactions of Syringic acid	
Diseases	**Amino acid residue**	**Distance (Å)**	**Amino acid residue**	**Distance (Å)**
Breast cancer	Arg-394	2.65	Leu-346	5.05
(PDB ID: 3ERT)	Glu-353	1.60	Ala-350	5.04
	-	-	Leu-387	5.24
Tuberculosis	Tyr-41	1.84	Phe-215	4.09
(PDB ID: 1KPI)	Tyr-24	2.02	-	
Alzheimer's Disease	Asp-32	1.72	Tyr-71	5.52
(PDB ID: 4IVT)	Phe-108	2.04	Phe-108	5.34
Obesity	Glu-234	2.98	Tyr-108	4.99
(PDB ID: 3LFM)	Tyr-106	1.79	His-231	3.90
	Arg-96	2.75	-	
Malaria	Thr-217	1.89	Val-78	5.10
(PDB ID: 1SME)	Asp-34	1.75	-	

Table 3 Molecular properties of syringic acid

Molecular properties	
Molecular weight	198.17 g/mol
Hydrogen bond donor	2
Hydrogen bond acceptor	5
High lipophilicity	1.02
Molar refractivity	48.41
Mutagenicity	Non Mutagen
Carcinogenicity	Non Carcinogen

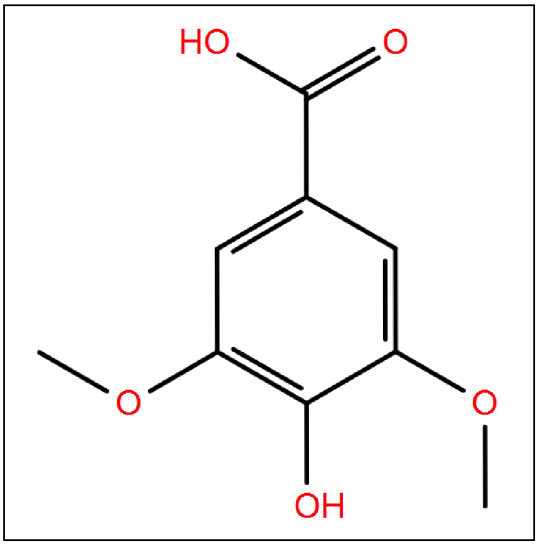

Figure 1 2D structure of Syringic acid

this score is still higher than the standard drug selected for comparison. At last, the interaction that shows low docking score than standard drug is when syringic acid binds to the receptor mycolic acid cyclopropane synthase against tuberculosis. The interaction revealed a score of -6.886 kcal/mol forming two H-bonds with Tyr-24 and Tyr-41 also a pi-pi stacking with Phe-215.

ADME/T Analysis

ADME property characterizes the drug-like activity of ligand molecules. Pharmacokinetic properties of syringic acid given in Table 3 show that the compound follow Lipinski's rule of five. Also the predicted toxicity shows that the compound is non-carcinogenic and non-mutagenic.

DISCUSSION

Molecular docking provides information about the relative orientation of a ligand molecule when it is bound to a protein.[24] Such information can be used to understand the pharmacological activity of natural compounds at biological condition and discover novel compounds with more potency and selectivity. From this aspect, *in silico* molecular docking study of syringic acid was carried out to analyze its mechanism of action against five diseases namely breast cancer, Alzheimer's disease, tuberculosis, obesity and malaria. The study revealed that syringic acid possesses higher scores against four selected diseases when compared to the available standard drugs. The docked poses were further analyzed for interactions with amino acid residues of the receptor. Syringic acid was found to have shorter hydrogen bond interactions with the receptor active site which suggest that it has a stronger binding affinity.

Furthermore, pharmacokinetic and toxicological properties of a compound are the significant parameters in drug discovery process. Thus, syringic acid was subjected to the analysis of absorption,

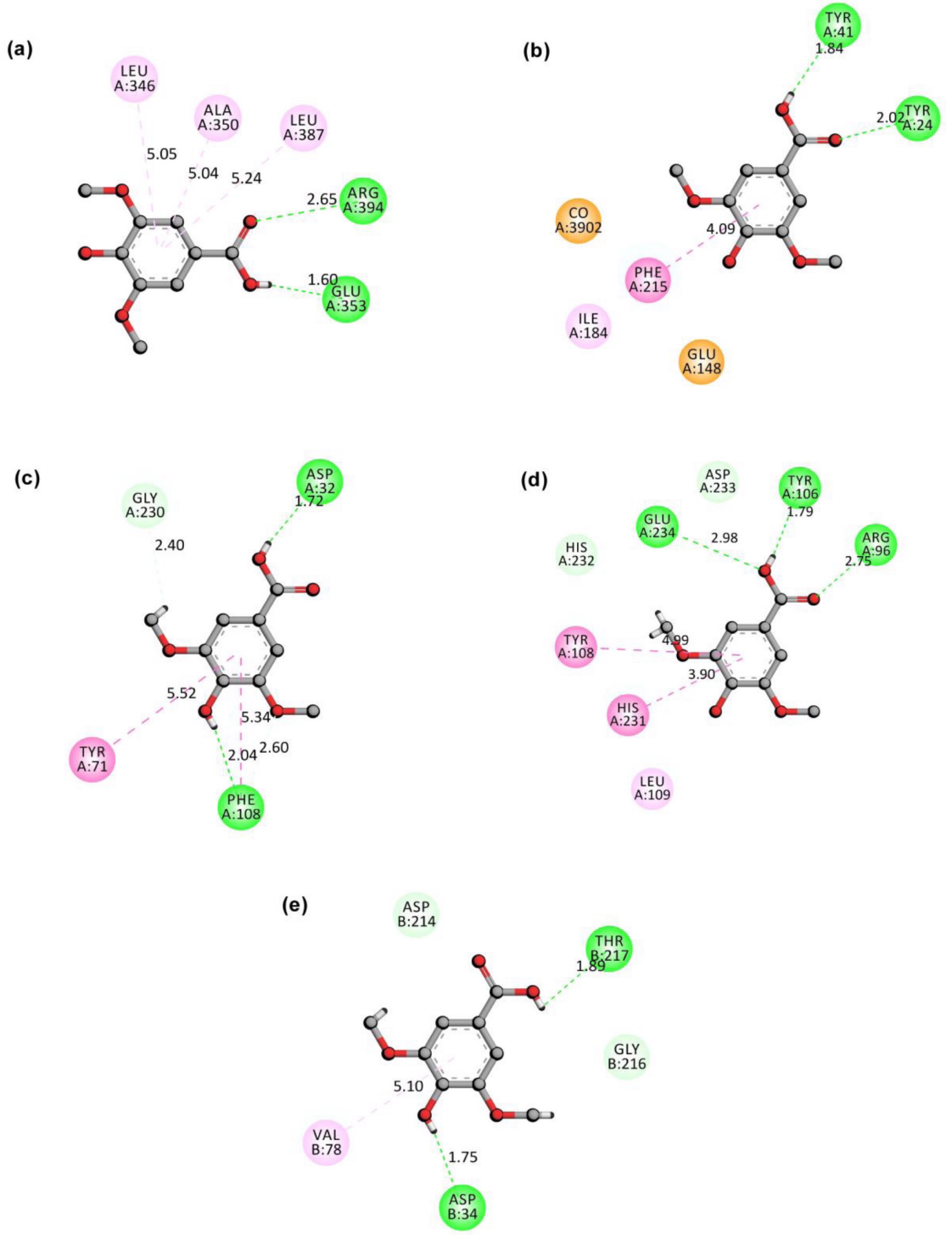

Figure 2 Ligand interaction diagram of syringic acid with selected receptors. a) Syringic acid with 3ERT; b) Syringic acid with 1KPI; c) Syringic acid with 4IVT; d) Syringic acid with 3LFM; e) Syringic acid with 1SME

distribution, metabolism and excretion based on Lipinski's rule of five and exhibited good oral bioavailability. In addition, the compound is considered to be safe as it does not show any mutagenicity or carcinogenicity through toxicity analysis.

CONCLUSION

In conclusion, the docking study of syringic acid with several targets revealed that it is a promising candidate against selected diseases. It showed good docking scores comparing to the standard drugs. Also syringic acid has an acceptable druglike property with no carcinogenicity or mutagenicity. Thus it can be considered for further *in vitro* and *in vivo* analysis of therapeutic potentials.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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