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Evaluation of anti-obesity properties association with reducing hypertension and diabetic through Molecular Docking

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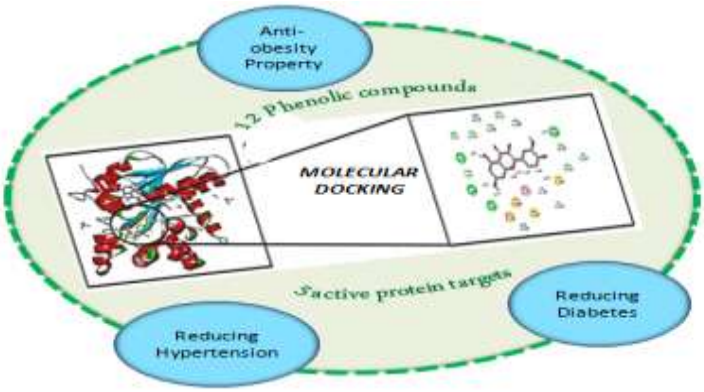
ABSTRACT
The hypertension and diabetes are the two major concerns whose incidences are rapidly rising.However, its association and rising cases of obesitymake the scenario even more troublesome.Thus, diabetes, hypertension, and obesity are three diseases that are linked to one another.The proposed invention focuses on predicting the factors that are related between hypertension, diabetes andanti-obesity properties. The research work wants to find out the important factors that can support for reducing hypertension and diabetes through molecular docking.Auto Dock Vinawas used to evaluate selected hypertension targeted molecules against phenolic compound ligands, and Discovery studio visualizer was used to create 3D and 2D interaction photos. Five out of 12 phenolic compounds were found to form conventional hydrogen bonds, and only Caffeic acid formed the highest number of hydrogen bonds. However, the binding energy and inhibition constant of all twelve phenolic compoundswere determined. Interestingly, daidzinshowed the lowest binding energy of -5.06 kcal/mol and inhibition constant of 192.57µM.The results of our investigation suggested that five specific phenolic compounds can have a good impact against 6 active protein targets, pertaining to the significant binding energies of phenolic compoundsduring blind docking. Specifically, daidzincould be a good anti-obesityfactorfor reducing diabetes and hypertension.

Keywords: Hypertension, diabetes, molecular docking, Auto Dock Vina, Caffeic acid, daidzin

Graphical abstract



I. INTRODUCTION

Obese and diabetes mellitus(DM) are important health concerns worldwide; their incidence is increasing at ancaring high rate, generating big social costs. Obesity is frequently observed among those who live long-term sedentary lifestyles,consume large amounts of fast food, or suffer from genetic diseases or disorder. Obese is a complex disease commonly accompanied by insulin resistance, high oxidative stress, and enhanced inflammatory expression.According to the International Obesity Taskforce, more than 300 million people and who have a body mass index greater than 30 kg/m2 are categorized as obesity. The number of obese-born children of developing countries is increasing, as is

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the number of obese adults in developed countries.One of three children born in the early current century is expected to develop obesity-related diabetes.

Obesity causes the development of metabolic disorders such as DM, hypertension, cardiovascular diseases, and inflammation-related pathologies. It is expected that in 20 years nearly 600 millionadults will become diabetic because of the increasing obesity Diffusion and high population growth.Obesity is now a global problem and is associated with a number of chronic conditions including osteoarthritis, obstructive sleep apnea, gallstones, fatty liver disease, reproductive and gastrointestinal cancers, dyslipidemia, hypertension, type 2 diabetes, heart failure, coronary artery disease, and stroke.According to the World Health Organization, obesity is one of the most prevalent health concerns nowadays, and it is believed to be one of the major causes of cancer and a variety of other minor illnessIn addition to insulin resistance, increased oxidative stress, and increased expression of inflammatory markers, obesity is a complex condition.Obesity and overweight are now understood to be risk factors for a number of chronic diseases, including diabetes, high blood pressure, cardiovascular disease, and cancer. Diabetes mellitus is another condition that increases the chance of hidden renal failure. Hence, diabetes mellitus and advanced age may operate as risk factors for hidden renal failure. Given the high prevalence of type II diabetes in the elderly population.Diabetes is widely acknowledged as an epidemic that is just beginning to spread and that affects almost every nation, demographic, and economy in the world.

In the field of molecular modeling, docking is a method which predicts the preferred orientation of one molecule to a second when a ligand and a target are bound to each other to form as stable complex. Knowledge of the preferred orientation in turn may be used to predict the strength association or binding affinity between two molecules using for example scoring functions. A number of different types of antiobesity factor analysis systems that are known in the prior art.Uncovering antiobesity-related hypertension targets and mechanisms of metformin, an antidiabetic medication Metformin, a common clinical drug used to treat diabetes mellitus, is found with potential antiobesity actions as reported in increasing evidences. However, the detailed mechanisms ofmetformin-antiobesity-related hypertension remain unrevealed. We have utilized the bioinformatics strategy, including network pharmacology and molecular docking analyses, to uncover pharmacological targets and molecular pathways of bioactive compounds against clinical disorders, such as cancers, coronavirus disease 2019. In this report, the in-silico approaches using network pharmacology and molecular docking was utilized to identify the core targets, pharmacological functions and mechanisms of metformincompunds against obesity related hypertension.

The mechanisms through which obesity causes hypertension are complex and include sympathetic nervous system over-activation, stimulation of the renin-anguiped cytokines, insulin resistance and structural and functional renal changes. The proposed invention focuses on predicting the importance of molecular docking in reducing hypertension and diabetes by concentrating on anti-obesity. Thus, the present invention relates to the field of designing & implementing a framework of evaluating anti-obesity aspects for reducing hypertension and diabetes.

II. MATERIALS AND METHODS

2.1 Ligand/ Molecule preparation

PubChem was used to obtain the SDF files of the12 phenolic compounds such as Cyanidin-3-glucoside,Caffeic acid 4-O-hexoside, Caffeic acid 3-O-(6’’-succinyl glucoside), Daidzin, Pelargondin 3-glucoside, Pelargondin 3-(6”-malonyl-glucoside), Apigenin-O-hexoside, Caffeic acid, 5-O-caffcoylquinic acid, Cyanidin-3-O-(6”-caffeoyl-glucoside), Cyanidin-3-O-(6”-malonyl-glucoside, P-cumaric acid and discovery visualizer was utilized for converting the SDF files into PDB files. SDF files cannot be used directly for docking studies.

2.2 Target/ receptor preparation

PDB web citation (https://www.rcsb.org/) was used to obtain X-ray crystal structures of Glucokinase, AMP-activated protein kinase, Insulin receptor, Protein kinase B, insulin receptor protein kinase. First, the Auto Dock Tool (ADT) was used to remove all HOH molecules from the protein, assign hydrogen polarities, and add Kollman charges and polar hydrogen atoms. Gasteigercharges were also applied to the prepared protein.

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2.3 Analysis of molecular docking

AutodockVina software approaches were used to predict the interaction energies between phenolic compounds and diabetis-hypertension proteins. Interactions were analysed using the Lamarckian genetic approach (LGA). AutoDockVina uses the method below to compute the ligand and receptor interaction binding energy (DG):

$$\Delta G_{binding} = \Delta G_{gauss} + \Delta G_{repulsion} + \Delta G_{H\text{-}bond} + \Delta G_{hydrophobic} + \Delta G_{tors}$$

The dispersion of two Gaussian functions is referred to as ΔGgauss. Grepulsion: the square of the distance is repelled if the distance is larger than a threshold value. Ghbond: a ramp function that may be used to model metal ion interactions. ΔGhydrophobic: ramp function, Gtors: proportional to the number of rotatable bonds.

During the modification of the native PDB file of the chosen 3D structure of target proteins, water (HOH) was also removed. The pharmaceutical phenolic compounds were given hydrogen atoms;Kollman unified charges, default solvation parameters, and a Gasteiger charge in all twelve docking studies. In all docking experiments, the grid box was intended to enclose the maximum area of the protein, resulting in blind docking. The values for the X, Y, and Z axes of a grid point were set to 1260 X 1260 X 1260. In the default setting, the grid point spacing was set to 0.575. The Lamarckian genetic algorithm (LGA) was utilized to calculate flexible docking calculations between protein and pharmaceutical phenolic molecules. The obtained conformations of selected diabetic-hypertension targeted proteins and drug molecules complexes were subjected to additional analysis and were thoroughly examined for the formation of various types of interactions using Discovery Studiomolecular visualization software after the docking steps were completed successfully.

III. RESULTS

We discovered that fivepharmaceutical phenolic compounds interact with all five diabetic-hypertension targeted proteins in some way after looking at molecular interaction findings from docking experiments with various drugs. The final intermolecular energy, inhibition constants, and hydrogen bond formation during the interaction of ligand and receptor molecules could all be used to evaluate molecular docking data.

Figure 1:Molecular Docking Simulation analysis. Interaction of Daidzin with (a) Glucokinase (b) AMP-activated protein kinase (c) Insulin receptor (d) Protein kinase B (e) insulin receptor protein kinase.

Phenolic compounds	Lowest Binding Energy (Kcal/mol)	Inhibition constant (μM)	Hydrogen bonding
Cyanidin-3-glucoside	-4.95	745.02	NO Hydrogen bonds
Caffeic acid 4-O-hexoside	-4.64	920.11	
Caffeic acid 3-O-(6''-succinyl glucoside)	-4.60	918.09	ASN 247, VAL 248
Daidzin	-5.06	192.57	HIS 135, ASN 146
Pelargondin 3-glucoside	-4.82	909.91	
Pelargondin 3-(6''-malonyl-glucoside)	-4.83	920.66	HIS 135
Apigenin-O-hexoside	-4.21	905.32	ASN 257
Caffeic acid	-3.52	1089.2	ARG 265, TYR 255, GLU 262, HIS 254, TRP 277
5-O-caffcoylquinic acid	-4.63		NO Hydrogen bonds
Cyanidin-3-O-(6''-caffeoyl-glucoside),	-4.98	849.43	HIS 354, ASN 216
Cyanidin-3-O-(6''-malonyl-glucoside,	-4.97	852.13	NO Hydrogen bonds
P-cumaric acid	-4.06	958.06	ASP 145

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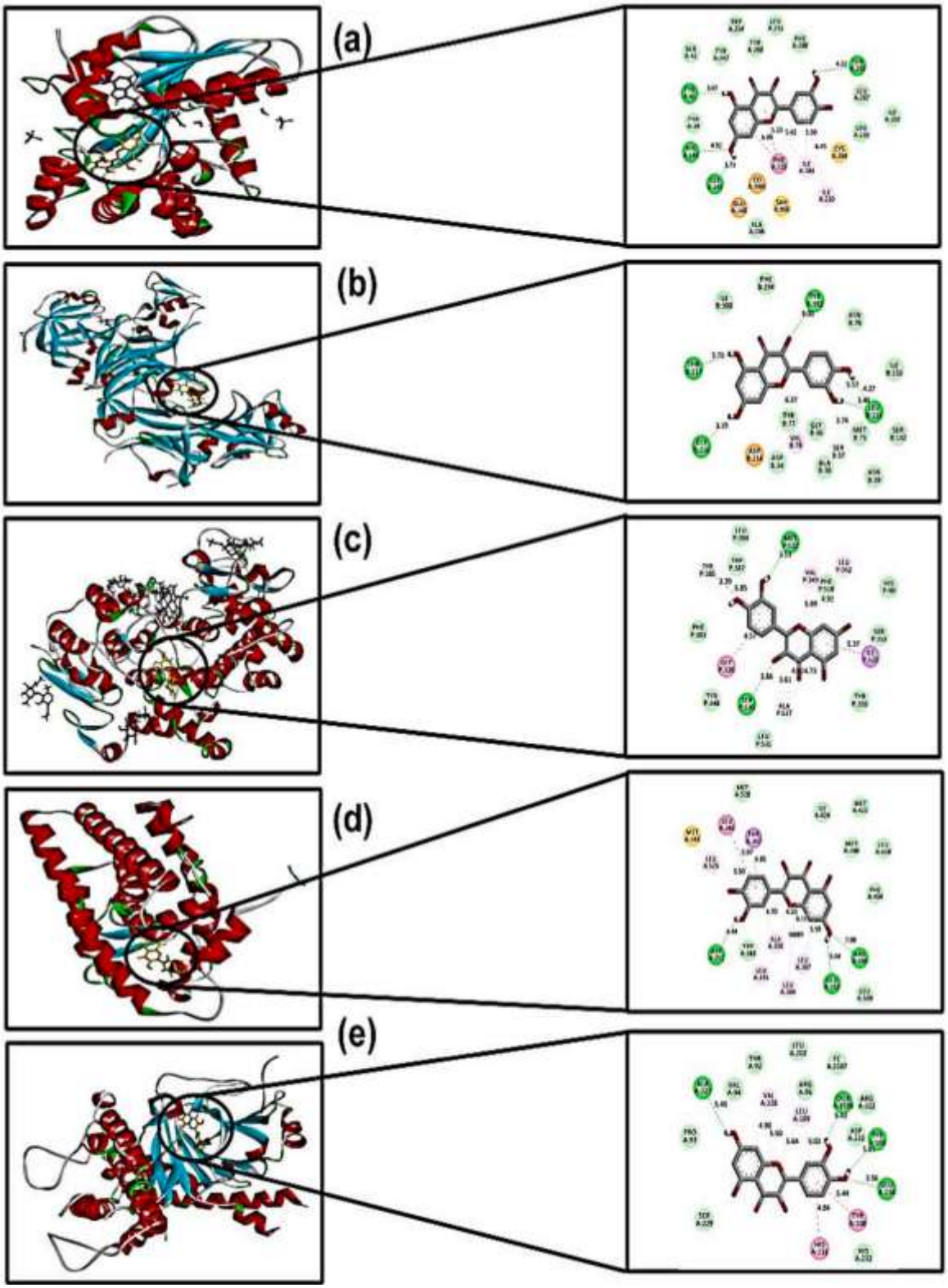

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During blind docking of all twelve pharmaceutical phenolic compounds, it was observed that 5 phytochemicals out of 12were found to form conventional hydrogen bonds, and out of 5, it was observed that only Caffeic acidformed the highest number of hydrogen bonds. However, the binding energy and inhibition constant of all twelve phenolic compounds, as shown in Table 1. Interestingly, Daidzin showed the lowest binding energy of -5.06 kcal/mol and inhibition constant of 192.57μM (Table1; Figure 1).

IV. DISCUSSION

The interaction energies evaluated from molecular docking using metformin phenolic compounds against Glucokinase, AMP-activated protein kinase, Insulin receptor, Protein kinase B; insulin receptor protein kinaserevealed that all twelvemetformin phenolic compounds interacted with all six diabetic-hypertension targeted molecules. Metformin phenolic compounds have good anti-obesity properties. Similarly, the results of our investigation suggest that metformin phenolic compounds can have a good impact on diabetes and hypertension. All the phenolic compounds showed significant binding energies during blind docking. As a result, Daidzincan be a good medicinal component for anti-obesity associated with diabetes and hypertension.

REFERENCES

[1]. N. Cardullo, V. Muccilli, L. Pulvirenti, A. Cornu, L. PouysD. Deffieux, S. Quideau, C. Tringali, C-glucosidicellagitannins and galloylated glucoses as potential functional food ingredients with anti-diabetic properties: a study of α-glucosidase and α-amylase inhibition, Food Chem. 313 (2020) 126099.

[2]. N. Cardullo, V. Muccilli, L. Pulvirenti, A. Cornu, L. Pouys D. Deffieux, S. Quideau, C. Tringali, C-glucosidicellagitannins and galloylated glucoses as potential functional food ingredients with anti-diabetic properties: a study of α-glucosidase and α-amylase inhibition, Food Chem. 313 (2020) 126099.

[3]. M.H. Rahuman, S. Muthu, M.M. Wezhli, J. Charles, H. Umamahesvari, Vibrational

[4]. (FT-IR, FT Raman), electronic and docking studies and wave function analysis with quantum chemical computation on 3-Bromophenyl acetic acid: a potential amidase inhibitor, in: Materials Today: Proceedings, 2020.

[5]. R.O. Oyewole, A.K. Oyebamiji, B. Semire, Theoretical calculations of molecular descriptors for anticancer activities of 1, 2, 3-triazole-pyrimidine derivatives against gastric cancer cell line (MGC-803): DFT, QSAR and docking approaches, Heliyon 6 (2020).

[6]. A.R. Jo, J.H. Kim, X.-T. Yan, S.Y. Yang, Y.H. Kim, Soluble epoxide hydrolase inhibitory components from Rheum undulatum and in silico approach, J. Enzyme Inhib. Med. Chem. 31 (2016) 70–78.

[7]. X.-D. Hou, X.-Q. Guan, Y.-F. Cao, Z.-M. Weng, Q. Hu, H.-B. Liu, S.-N. Jia, S.- Z. Zang, Q. Zhou, L. Yang, Inhibition of pancreatic lipase by the constituents in St. John's Wort: in vitro and in silico investigations, Int. J. Biol. Macromol. 145 (2020) 620–633.

[8]. F. Shamsa, H. Monsef, R. Ghamooshi, M. Verdian-rizi, Spectrophotometric determination of total alkaloids in some Iranian medicinal plants, Thai. J. Pharm. Sci. 32 (2008) 17–20.

[9]. V.L. Singleton, J.A. Rossi, Colorimetry of total phenolics with phosphomolybdicphosphotungstic acid reagents, Am. J. Enol. Vitic. 16 (1965) 144–158.

[10]. T.A. Olasehinde, E.C. Odjadjare, L.V. Mabinya, A.O. Olaniran, A.I. Okoh, Chlorella sorokiniana and Chlorella minutissima exhibit antioxidant potentials, inhibit cholinesterases and modulate disaggregation of β-amyloid fibrils, Electron. J. Biotechnol. 40 (2019) 1–9.

[11]. S. Liu, D. Li, B. Huang, Y. Chen, X. Lu, Y. Wang, Inhibition of pancreatic lipase, α-glucosidase, α-amylase, and hypolipidemic effects of the total flavonoids from Nelumbonucifera leaves, J. Ethnopharmacol. 149 (2013) 263–269.

[12]. N. Alias, T. Leow, M. Ali, A. Tajudin, A. Salleh, R. Rnzra, Anti-obesity potential of selected tropical plants via pancreatic lipase inhibition, Adv. Obes. Weight Manag. Control 6 (2017).

[13]. D.M. Quinn, K. Shirai, R.L. Jackson, J.A. Harmony, Lipoprotein lipase-catalyzed hydrolysis of water-soluble p-nitrophenyl

esters. Inhibition by apolipoprotein C-II, Biochemistry 21 (1982) 6872–6879.

[14]. A. Daina, O. Michielin, V. Zoete, SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules, Sci. Rep. 7 (2017) 1–13.

[15]. M.S. Ali, J. Muthukumaran, H.A. Al-Lohedan, Molecular interactions of ceftazidimewith bovine serum albumin: spectroscopic, molecular docking, and DFT analyses, J. Mol. Liq. 313 (2020) 113490.

[16]. O. Trott, A.J. Olson, AutoDockVina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading, J. Comput. Chem. 31 (2010) 455–461.

[17]. S. de Ferranti, D. Mozaffarian, The perfect storm: obesity, adipocyte dysfunction, and metabolic consequences, Clin. Chem. 54 (2008) 945–955.

[18]. D. Kalita, D.G. Holm, D.V. LaBarbera, J.M. Petrash, S.S. Jayanty, Inhibition of α-glucosidase, α-amylase, and aldose reductase by potato polyphenolic compounds, PLoS One 13 (2018), e0191025.

[19]. M. Patil, R. Patil, B. Bhadane, S. Mohammad, V. Maheshwari, Pancreatic lipase inhibitory activity of phenolic inhibitor from endophyticDiaporthearengae, Biocatal. Agric. Biotechnol. 10 (2017) 234–238.