Journal of Chemical Health Risks

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JCHR (2024) 14(4), 490-503 | ISSN:2251-6727

Investigations Using Molecular Docking and Simulation on the Antidiabetic Activity of Resveratrol Aldehyde Molecule.

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(**Received**: 14 April 2024 **Revised**: 01 May 2024 **Accepted**: 18 June 2024)

KEYWORDS

Diabetes, Drug discovery, Resveratrol aldehyde, *in silico*, Drug repurposing, Molecular simulation.

ABSTRACT:

Introduction: Diabetes mellitus (DM) is a heterogeneous group of disorders essentially characterized by variable degrees of impaired secretion (T1DM) and/or action of insulin (T2DM), leading to persistent elevation in blood glucose levels. T2DM is the most prevalent form, with an incidence of 90–95% of all known cases in the population. Due to the development of undesirable side effects associated with the currently prescribed drugs for the treatment of T2DM, the search for novel drugs continues.

Objectives: In the present study, we have investigated the *in silico* interactions of four proteins with synthesized resveratrol aldehyde.

Methods: Molecular docking is one of the most accepted and successful structure-based *in silico* methods, which facilitates predicting the interactions taking place between molecules and biological targets. Peripheral tissue resistance to insulin action, the characteristic feature of T2DM, is known to affect the metabolism of glucose and fat in humans. Several reports suggest that AMP-activated protein kinase, C-reactive protein (CRP), protein tyrosine phosphatase, and glutamine fructose-6-phosphate amidotransferase all play significant roles in the initiation, progression, and onset of T2DM.

Results: All four proteins exhibit a strong affinity for the resveratrol aldehyde. All the proteins, namely, Glutamine fructose-6-phosphate amidotransferase (ΔG:-7.24 kcal/mol), AMP:Activated protein kinase (ΔG:-7.23 kcal/mol), C-Reactive Protein (CRP) (ΔG:-7.11 kcal/mol), and Protein Tyrosine Phosphatase (PTP) (ΔG: -7.38 kcal/mol), showed strong binding affinities with resveratrol aldehyde.

Conclusions: Protein tyrosine phosphatase was a better lead molecule than other proteins, according to the results of the Molecular Docking simulation. Before demonstrating their therapeutic implications against diabetes, through, comprehensive wet-lab validations are necessary.

1. Introduction

Diabetes Mellitus is a heterogeneous group of disorder essentially characterized by variable degrees of impaired secretion (T1DM) and /or action of insulin (T2DM) leading to persistent elevation in blood glucose levels. DM has been recognized as one of the four major non-communicable diseases, namely cardiovascular diseases, cancer, chronic respiratory diseases and diabetes that insist imperative awareness from all key stakeholders worldwide in an effort to tackle its prevalence and associated secondary complications [1] .Additionally, it is included as a top 10 causes of mortality worldwide. DM is established as the third highest risk factor for worldwide premature mortality due to chronic hyperglycemia or severe hypoglycemia. According to International Diabetes Federation (IDF) report 2022, currently 537 million people are living with DM and it is projected that by 2045 about 783 million people will be living with DM [2]. This number is lesser because, for each diagnosed case, there will be one undiagnosed case in first world and eight in the third world countries. Factors driving this striking rise of diabetes incidence in developing countries are flaring of urbanization and lifestyle changes, including increasing

Journal of Chemical Health Risks

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JCHR (2024) 14(4), 490-503 | ISSN:2251-6727

sedentary lifestyles, lack of physical activity, obesity, increased elderly population and the global nutrition transition from nutrient-rich to energy directed foods [3].

T1DM arises due to selective, progressive and irreversible autoimmune destruction of a critical mass of pancreatic beta cells, varying from rapid to slow descend of insulin synthesis and secretion. The chief contributors of T1DM include autoimmunity, genetics and environmental factors. T1DM can develop quickly over weeks or even days. Nearly 90% of T1DM patients have one or more islet cell autoantibodies such as cytoplasmic islet cell antibodies (ICA), anti-insulin antibodies, Glutamate decarboxylase (GADA) and Zinc-transporter 8 (ZnT8). Presence of two or more autoantibodies is an almost certain forecaster of clinical hyperglycemia and T1DM.Increased incidence and prevalence rates of severe hypoglycemic episodes (blood glucose levels below 54mg/dl) may occur in T1DM patients at least one episode once in two years due to therapeutic hyperinsulinemia which in turn may arises due to high dose of insulin administration, incorrect timing related to meals, increase in glucose utilization during or after physical exercise, increase in insulin sensitivity due to weight loss, fall in insulin excretion under pathological conditions such as renal dysfunction or hepatic malfunction etc., T1DM occasionally occurs in association with other autoimmune disorders [4,5].

T2DM is the most prevalent form due to numerous causes, with a frequency of 90-95% of all known cases in the population [6]. It characterizes a whole spectrum of clinical syndromes ranging from insulin secretion defects to the impaired action on vital tissues. In the initial stages, the pancreas secrets more insulin in order to maintain the glucose levels within the physiological range. However, subsequent to the onset of T2DM, the secretion of insulin gradually decreased. The incidence of T2DM at earlier stages frequently goes undiagnosed because the classic symptoms develop gradually as hyperglycemia develops, and the insulin levels in such patients are often within the physiological levels or elevated.

According to American Diabetes Association (ADA) diabetes mellitus can be diagnosed clinically by three ways and each, in the absence of unequal hyperglycemia, must be confirmed, on a subsequent day, by any of the three methods, namely the levels Fasting plasma Glucose (FPG) less than 120mg/dl, two hour Post-prandial glucose less than 140mg/dl and Random less than 180mg/dl. Nowadays, the levels of glycosylated heamoglobin (HbA1c), a measure of percentage of haemoglobin that is bound to glucose for the last three months, is used a reliable and reproducible index of both diagnostic and prognostic value in the field of diabetic treatment. HbA1c percentage of less than 7 is regarded as good glycemic control in diabetic individuals. The classical signs (experienced only by the individual) of DM include polyuria, polydipsia, polyphagia, headache, body pain, whole body itching, discomfort, inactiveness, shortness of breath and the conventional symptoms (detected by someone) include unusual weight loss, frequent infections, foot ulcer and delay in wound healing. The chronic complications of DM include retinopathy, neuropathy, nephropathy, cardiovascular complications, gastrointestinal disorders, skin infections, genital disorders and bone deformities [7]. There is a strong link between T2DM; chronic hyperglycemia induced oxidative stress and inflammation [8, 9].

Chronic hyperglycemia in diabetes is routinely treated with a range of antidiabetic drugs that have different mechanisms of action, such as stimulation of insulin secretion, decrease in insulin resistance, regulation of gluconeogenesis, glycogenesis, glycogenolysis, increased glucose utilization, and decrease in the absorption of glucose in the intestine. However, treatment with insulin injection forms the cornerstone for the treatment of both T1DM and T2DM, and its frequency and success in pharmacotherapy vary in different ethnic subgroups. Most of the currently prescribed drugs for the treatment of diabetes and its secondary complications often elicit unfavorable side effects in addition to the development of drug resistance after prolonged ingestion; hence, the search for novel therapeutics with greater efficiency and without side effects, preferably of plant origin, continues [10]

Since its first exterior in the mid-1970s, molecular docking has established itself as an imperative tool to help in the understanding of interactions between chemical compounds and their molecular targets and for drug discovery. Molecular docking allows understanding the relationships between different molecular targets involved in a given disease, providing meticulous importance to recent drug design strategies, including polypharmacology, drug repurposing, target identification, and prediction of adverse drug reactions. *In vivo* and *in vitro* studies represent the experiments for replicating them in the wet laboratory whereas *in silico* methods do not necessitate cell lines or

Journal of Chemical Health Risks

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JCHR (2024) 14(4), 490-503 | ISSN:2251-6727

experimental animals and have attained vital part of drug design and discovery [11]

Resveratrol (3, 5, 4'-trihydroxystilbene) is a naturally occurring phytoalexin found in grapes (*Vitisvinifera*), a variety of berries, peanuts, and medicinal plants, such as Japanese knotweed (*Polygonumcuspidatum*). It is produced in response to stress, injury, ultraviolet irradiation and fungal (*Botrytis cinerea*) infection as part of their defense mechanism. Red wine is the most important dietary source of resveratrol. Resveratrol is postulated to be an important cause in the "French Paradox", a term coined to depict the study that the French population has a very low incidence of cardiovascular disease even though their diet is rich in saturated fats. Grape skin contains 50-100 mg resveratrol per gram. Scientific interest in resveratrol has continually gained momentum since 1997, when it was first demonstrated to prevent carcinogenesis in mice [12]. In the intervening years, this molecule has received considerable attention for its non-toxic, anti-inflammatory, anti-tumorigenic, and anti-oxidant properties, as well as its ability to increase lifespan in lower organisms and improve general health in mammals [13]. Although almost all the nearly 4000 published studies on resveratrol were performed *in vitro* or in animal models, intense media coverage highlighting its potential applications in the prevention and treatment of age-related diseases has inspired many individuals to try resveratrol supplements and many companies to develop either resveratrol-based drugs or nutraceuticals [14].

AMP-Activated protein kinase (AMPK-2H6D)

AMP-activated protein kinase (AMPK) is a highly conserved fuel-sensor of cellular energy. The activity of AMPK is improved by ATP-depleting conditions such as caloric restriction and physical exercise. AMPK exists as heterotrimers composed of a catalytic alpha subunit, regulatory beta and gamma subunits. In humans, each of these occur a multiple isoforms encoded by distinct genes such that there are at least twelve possible hetero trimeric combinations. The AMPK-signaling pathway symbolizes a mechanism to counter to the fluctuating glucose levels. AMPK ameliorates the pathogenesis of several metabolic disorders, including diabetes mellitus, by controlling the expression and activation of various downstream molecules [15].AMPK controls fatty acid oxidation, muscle glucose uptake, expression of cAMP-stimulated gluconeogenic genes like PEPCK and G6Pase and glucose-stimulated genes linked to hepatic lipogenesis like fatty acid synthase [FAS] and L-type pyruvate kinase. Additionally, the metabolic effects of AMPK activation, especially its ability to cause a metabolic switch from fat synthesis to fat oxidation and to facilitate muscle glucose uptake, would be beneficial in individuals with insulin resistance and /or Type 2 diabetes mellitus [16]. Since Type 2 DM expresses muscle hexokinase and glucose transporters especially Glut4, simulating the effects of intensive exercise training, it can be treated by activating AMPK. Several plant derived molecules such as resveratrol, curcumin, quercetin, ginsenoside, berberine, epigallocatechin, theaflavin, hispidulin,andberberine have been reported to activate AMPK .

C-reactive protein (CRP -1GNH)

C-reactive protein (CRP) was originally discovered by Tillett and Francis (1930) as a substance in the serum of individuals with acute inflammation that reacted with the "c" carbohydrate antigen in the capsule of pneumococcus. CRP is a disc-shaped pentameric protein synthesized by the liver with a molecular weight of 1, 20,000 daltons and consists of five identical sub-units that contain each 206 amino acids. It has little or no carbohydrates. CRP is stable and has a half-life of about 1 hour. Among proinflammatory markers, CRP is emerging as an independent release-sensitive physiological marker of subclinical systemic inflammation associated with hyperglycemia, insulin resistance, and overt T2DM. Insulin resistance is an essential physiological condition for Type 2 diabetes, and it is thought to signify a chronic inflammatory state due to its induction by proinflammatory cytokines such as IL-6 and TNF-alpha, which are produced by the adipocytes [17]. It was observed that elevated CRP concentration is a prime inflammatory interpreter of diabetes, independent of obesity and other physiological markers. The CRP level in T2DM was about 3 times higher than in normal participants, indicating that hyperglycemia itself is a factor that can cause an increase in serum CRP levels in T2DM. Impaired fasting glucose, impaired glucose tolerance, and elevated glycatedHb levels correspond to the highest quartile of CRP. Plasma levels of CRP are considered a strong independent predictor of the risk of future myocardial infarction, stroke, peripheral arterial disease, and vascular death among individuals without known cardiovascular disease [18]. Since there is no known polymorphism or deficiency condition for this highly conserved plasma protein, the structure sheds light on the molecular

Journal of Chemical Health Risks

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JCHR (2024) 14(4), 490-503 | ISSN:2251-6727

mechanisms by which it might carry out its biological function.

Protein tyrosine phosphatases (PTP-2NT7)

Protein tyrosine phosphatases (PTPases) belong to a super family of homologous enzymes that regulates a wide range of events in cellular signal transduction and metabolism. They have been broadly classified into two classes namely intracellular or non-receptor type or major PTP1B type and trans membrane or receptor type or minor LAR-Leukocyte Antigen Related type. They have been implicated in the regulation of insulin action cascade by promoting the dephosphorylation and inactivation of the autophosphorylated insulin receptor kinase domain. The N-terminal domain of PTB1B containing tyrosine residues is essential for interaction with the insulin receptor. Resistant to the action of insulin in its target tissues is the hall mark of T2DM and hence improving tissue sensitivity to insulin is a principal clinical objective to ameliorate chronic hyperglycemia and its secondary complications [19]. Since, PTPases serve as negative regulators of the insulin signaling cascade, PTPase inhibitors may ultimately find an imperative clinical role as novel insulin sensitizers in the management of T2DM and they have been identified as novel targets for the enhancement of insulin action [20].

Glutamine fructose-6-phosphate amidotransferase (GFAT-2ZJ3)

Glutamine: fructose-6-phosphate amidotransferase (GFAT) catalyzes the first dedicated step of the hexosamine biosynthetic pathway and therefore plays an important role in the etiology of type 2 diabetes. The four major hypotheses of chronic hyperglycaemia-induced diabetic complications include increased polyol pathway flux; increased advanced glycation end-products (AGEs) formation, activation of protein kinase C (PKC) isoforms and increased hexosamine pathway flux and a number of clinical trials have investigated specific inhibitors of these mechanisms. In diabetic individuals, the persistently elevated levels of glucose inside the cell are mainly metabolized to glucose-6 phosphate, fructose-6 phosphate, and subsequently to the rest of the glycolytic pathway downstream products. In addition to this, fructose-6-phosphate is also catalyzed by GFAT into glucosamine-6-phosphate through the hexosamine pathway, which ultimately produces uridinediphosphate N-acetylglucosamine (UDP), leading to the induced transcription of Transforming growth factor alpha, Transforming growth factor β1 and Plasminogen activator inhibitor-1. Thus, successful inhibition of this rate-limiting enzyme, GFAT, aids in the prevention of chronic hyperglycaemia-induced elevation in the transcription of TGF-α, TGF-β1, and PAI-1, leading to endurance from several micro- and macrovascular diabetic complications. Additionally, the hexosamine pathway plays an important role in hyperglycaemia- and fat-induced insulin resistance which is the hall mark of T2DM. Therefore, small-molecule inhibitors of GFAT would serve as beneficial tools for the treatment of diabetic complications and the investigation of the effects of the nutrient-sensing hexosamine pathway on insulin resistance [21].

Three types of human GFAT isoforms, namely GFAT, GFAT2, and GFAT1L, have been identified. GFAT2 is of clinically less interest in diabetic states since it is primarily expressed in the brain. The GFAT isoform is principally expressed in liver and fat; thus, it is a leading target for the regulation of obesity and diabetic conditions. The third isoform, GFAT1L, is a splice variant of GFAT1 and largely subsists in muscle cells [22]. GFAT is a 681 amino acid residue that consists of two structurally and functionally distinct domains. The N-terminal glutaminase domain of 27 kDa (residues 1–310) catalyzes the hydrolysis of the glutamine molecule to glutamate and ammonia molecules, whereas the 40 kDa C-terminal isomerase domain (residues 311–680) utilizes ammonia for the conversion of fructose-6-phosphate to glucosamine-6-phosphate. The binding site of the glutamine molecule resides within the N-terminal domain, while the binding site of glutamine 6-phosphate is within the C-terminal domain. The inadequate availability of reported GFAT inhibitors necessitates the imperative search for rational designs of GFAT inhibitor molecules.

2. **Objectives**In view of the beneficial and therapeutic effects of resveratrol aldehyde and the role of AMPK, CRP, PTP, and GFAT in the maintenance of normoglycemia, in the present study an earnest attempt has been made to explore the interaction between resveratrol aldehyde ligand either as an inhibitor or an agonists on the four protein targets chiefly associated with diabetes mellitus. In the *in silico* approach, the docking of the ligand with the targets was demonstrated on the basis of Binding energy. The mode of interaction offers a potential strategy to explore the possible mode of action of resveratrol aldehyde in the treatment of diabetes mellitus and its secondary complications.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(4), 490-503 | ISSN:2251-6727

3. Methods

3.1 Protein Preparation

The target proteins found in the protein data bank (PDB) (http://www.pdb.org) cannot be used reliably for molecular docking because they may be bound to heavy atoms, co-crystallized ligands, water molecules, ions and cofactors. This requires preprocessing, which involves adding hydrogen atoms, removing the water molecules in the binding area, removing the co-bound ligand (s)/ions, and adding polar charges. These files were converted from pdb to pdbqt after preprocessing.

3.2 Ligand and energy minimization

Utilizing Docking Server, the MMFF94 force field, was utilized to reduce the energy of ligand molecules. The ligand atoms were given Gasteiger partial charges. Hydrogen atoms that were not polar were combined and rotatable bonds were defined.

3.3 Ligand-protein docking

Molecular Docking conformations of docked molecules were ordered according to their energies and superposition was used to determine which conformations were most similar to the co-crystallized ligands. Auto dock Vina was used to visualize ligand docking. Using Discovery Studio Visualizer, hydrogen bonds surrounding interacting hydrophobic amino acids were made visible. For measuring binding affinity, Auto dock Vina was used [23]. We used the Lamarckian Genetic Algorithm (LGA) to simulate docking. The initial positions of the Ligand molecules, orientations, and torsion were all determined at random. The 100 distinct runs that made up each docking experiment were each programmed to end after a maximum of 2,500,000 energy evaluations [24].

3.4 Molecular dynamic simulation of the complexed structure of receptor-ligand

By using molecular dynamic simulation, the docking structures with the lowest docking energy were assessed for protein stability and complex motion. The modifications server (http://imods.chaco nlab.org) handled the molecular dynamics. The discovery of these modes is facilitated by iMODS, which also creates workable transition paths between two homologous structures. Using normal mode analysis (NMA), the iMOD server computes the internal coordinates of the protein to assess its stability. The main-chain deformability plot, B-factor values, eigen value, covariance matrix, and elastic network model all serve as representations of the protein's stability [25].

3.5 Resveratrol aldehyde

To create resveratrol aldehyde ligand, resveratrol was subjected to the Vilsmeier reagent (POCl3, DMF, and MeCN). In a nutshell, a solution of Resveratrol (912 mg, 4 mmole) and DMF (464 ml, 6 mmole) in 20 ml of MeCN was kept in an ice water bath. Drop-by-drop additions of freshly distilled POCl3 (0.6 ml, 6 mmole) were then made. At room temperature, the mixture was constantly mixed for one hour. The mixture was then added to cold water, agitated at 40 degrees in a water bath, and extracted with 310 ml of EtOAc before being allowed to evaporate [26,27]. With a yield of 78%, the yellow Resveratrol aldehyde crystals were synthesized. The overall scheme is represented as Scheme 1. The compound structure was drawn and optimized using chemsketch and saved in MDL-Mol (Model Description Language - Mol) format and converted to PDB format using open babel converter program. (Table:1)

4. Results

Drug discovery is concerned with identifying new chemical entities or leads, having a desired pharmacological activity. It is a fact that the bioactive leads could be identified via different approaches, but the implementations of *in silico* methods have reduced the cost and lengthy time required to pass a drug for prescription. The systematic pharmacokinetics and toxicity profile along with efficacy are the paramount determinants for unbeaten drug development. It is obligatory that these areas should be considered at the early stages in the drug discovery process. The diversity of plant species has kept naturally-derived molecules at the core of the drug discovery process with many more molecules to be discovered. Despite the massive researches on medicinal herbs, to scientifically validate their apparent curative properties, there are many concealed potential healing powers beyond their ethnomedicinal uses. Being involved in drug discovery from natural resources for more than a decade, we have recently reported the beneficial and pharmacological properties of resveratrol. A potent *in silico* structure-based technique called molecular docking makes it possible to predict ligand-target interactions at the molecular level. In docking studies, the binding energy (BE) of each bioactive molecule with the protein molecule was calculated using the formula

Journal of Chemical Health Risks

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JCHR (2024) 14(4), 490-503 | ISSN:2251-6727

$$BE = A + B + C - D,$$

where A stands for desolvation energy, B for final total internal energy, C for torsional free energy, and D for the energy of the unbound system.

Among the selected proteins, PTPase showed the highest binding affinity (-7.38 kcal/mol) with resveratrol aldehyde whereas CRP showed the least binding affinity (-7.11 kcal/mol) (Table 3). On looking to the hydrogen bond interaction, PTPase interacted with resveratrol aldehyde via three hydrogen bonds at ARG A: 79, LEU A: 204, and GLU A: 75. The four amino acid residues of the CRP that interact with resveratrol aldehyde include TYR A: 49, THR A: 41, PRO A: 93, and ALA A: 92. GFAT showed six hydrogen bond interactions with resveratrol aldehyde via LYS A: 675, GLN A: 421, SER A: 376, VAL A: 471, and ALA A: 674 (-7.24 kcal/mol). The amino acid residues of AMP activated protein kinase LYS A: 141, ASN A:144, interact with resveratrol via two hydrogen bonds (-7.23 kcal/mol). Molecular docking results are shown in Table 2.

4.1 Molecular dynamics simulation

To examine the mobilities and flexibilities of the amino acid residues during binding, a normal mode analysis (NMA) and molecular dynamics (MD) simulation of the resveratrol aldehyde and four proteins was performed.

4.2 Mobility

The ability of a given molecule to deform at each of its residues is determined by the main-chain(protein backbone) deformability. High deformability zones can be used to guess where the chain pivots are. Figures2. Illustrate how the target protein deforms as it binds to resveratrol aldehyde.

4.3 B-factor

The computed from NMA B-factor is generated by multiplying the NMA mobility by (8pi2) and the experimental B-factor is acquired from the relevant PDB field. The averaged root mean square deviation (RMSD) is provided in the B-factor column. Figures 3 depict the docked complex between proteins and resveratrol aldehyde.

4.4 Eigen values

The motion toughness is represented by the eigenvalue associated with each normal mode. The energy required to deform the structure is exactly proportional to the eigenvalue. The distortion is easier to produce the lower the eigenvalue (Figure 4).

4.5 Variance

Each normal mode's variance is inversely correlated with its eigenvalue.The individual (blue) and cumulative (green) variations are shown as coloured bars in Figures 5.

4.6 Covariance map

When two residues are coupled together, their movements are either correlated (red), uncorrelated (white), or anti-correlated (blue) (Figures 6) [28].

4.7 Elastic network

Figure 7 show how the elastic network model identifies the atom pairs connected by springs.

5. Discussions

When compared to the other four proteins, the synthesized reserveratrol molecule exhibit best binding affinity for the protein tyrosine phosphatase C compared to other proteins. Resveratrol aldehyde may inhibit protein tyrosine phosphatase (PTP), which is thought to be a key player in the tyrosine phosphorylation and dephosphorylation that is a fundamental mechanism of cell development and differentiation, according to molecular docking research [29]. The dephosphorylation of the insulin receptor (IR) by PTPs during its internalization results in gluconeogenesis inhibition and stimulates the synthesis of glycogen and triglycerides. Insulin is a critical regulator of liver homeostasis. Loss of this strict regulation results in increased hepatic insulin signaling, improved insulin-stimulated glucose suppression, decreasedserum and hepatic triglyceride and cholesterol levels, and less protection against reactive oxygen species in protein phosphorylation, which results in over or under activation of key signaling pathways [30]. Insulin receptor substrate deficiency in the pancreas enhances beta -cell function and induces compensatory islet development, which results in a malfunction of insulin secretion [31]. The expression of specific PTPs in muscle and adipose tissue is associated with the onset of T2D. PTP was higher in the muscle cytosol of obese nondiabetic patients compared to lean people [30]. Our findings imply that through binding to this protein, resveratrol aldehyde could sustain blood glucose levels, insulin metabolism, and fat formation.

The HBP pathway's most significant enzyme, GFAT, which catalyses the amidation of fructose-6-phosphate to glucosamine-6-phosphate in the presence of glutamine, was

Journal of Chemical Health Risks

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JCHR (2024) 14(4), 490-503 | ISSN:2251-6727

inhibited by resveratrol aldehyde. HBP is one among the mechanisms via which hyperglycemia mediates peripheral insulin resistance and diabetes consequences. It is thought that glucose fluidity through this channel functions as a system of nutrient sensing. However, it is still unknown how insulin resistance is caused by the signal resulting from elevated HBP flow. In many experimental models, the increased activity of GFAT has been linked to insulin resistance [32, 33] but less is known about the effects of polyphenols on GFAT. Srinivasan *et a* [32]looked into blood pressure, lipid profiles, glucose metabolism, and gene expression.

Flexibility is a key element in the interaction of biological macromolecules with substrates or in protein-protein interactions [34]·A quick and easy server for defining and computing a protein's flexibility is iMODS. NMA, which is integrated with the coordinates of the docked complex, is used to analyze the molecular mobility as well as the structural flexibility [35]· The NMA of proteins is based on the presumption that the maximal movements in a protein, which are functionally significant, are designated by the vibrations normal modes displaying the minimum frequencies [36].The docked complexes' substantial mobility during the NMA research supported the nine proteins' structural adaptability.

The majority of the proteins were found to have different peaks with a deformability index of roughly 1.0. Additionally, our results demonstrate significant deformability in all of the proteins. Deformability, as previously established, is a measure of a protein's flexibility, whereas the B-factor is linked to the protein's mobility [37].

The energy required to distort the structure is strongly related to the eigenvalues produced for the docked proteins. It denotes the protein-ligand complex's motion stiffness. The complex is more easily deformable the lower the eigenvalue [35]· We discovered that all of the complexes exhibited a sizable amount of deformability from the MD investigation of the bound proteins. Additionally, all of the complexes had low eigen values, which showed strong stability and flexibility of the docked protein complexes' molecular motion.

The AMP-Activated protein kinase, CRP, Protein Tyrosine phosphatase, and Glutamine Fructose -6 Phosphate Amidotransferase were found to have the lowest eigen scores indicating easier deformability and motion stiffness of the protein complexes among the four docked complexes. All four complexes' variance maps produced reasonable findings.

The covariance matrices for the complexes of glutamine fructose -6- phosphate amidotransferase and resveratrol aldehyde, AMP-Activated protein kinase, CRP, and protein tyrosine phosphatase displayed strong correlations with little anticorrelations. All the four complexes' elastic maps produced reasonable findings. We hypothesise that the chosen proteins could function as prospective therapeutic targets for resveratrol aldehyde to lessen the harmful effects connected to diabetes mellitus pathology based on the conceivable interactions of the two compounds.

6. Conclusion

Our research showed that resveratrol aldehyde, which was synthesized, *in silico*, has the capacity to interact with and modify the activity of proteins involved in the main types of type 2 diabetes mellitus pathways, including insulin secretion, insulin resistance, and glucose absorption. Resveratrol aldehyde-protein docked complex was shown via MD simulation analyses to be more stable. According to the research, Resveratrol aldehyde appears to have outstanding qualities for oral medications. However, before the manifestation of its therapeutic usage, a holistic strategy to wet-lab trials is necessary to validate the research finding. However, more research utilizing various techniques in both animal models and people is required to corroborate these results and improve our comprehension of the mechanisms of synthesized compounds that underlie their beneficial effects on metabolic health.

Funding

This research received no external funding.

Acknowledgments

Nil

Conflicts of Interest

The authors have no conflicts of interest regarding this investigation**.**

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Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(4), 490-503 | ISSN:2251-6727

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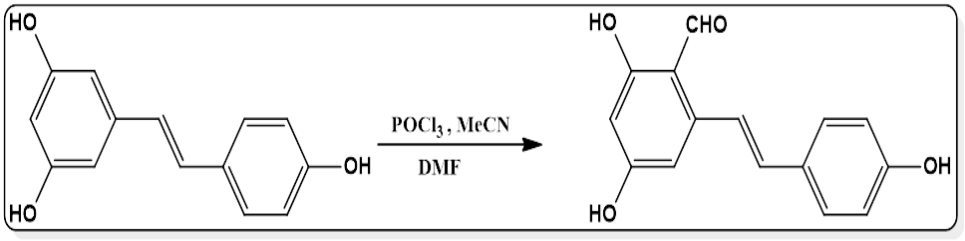
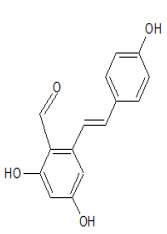
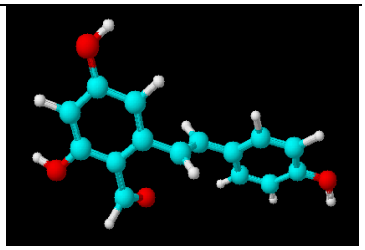


Scheme1. Synthesis of Resveratrol Aldehyde

Table1. 2D and 3D structure of Resveratrol aldehyde

Compound Name	Mol. Formula	SMILES	2D	3D
Resveratrol Aldehyde	$C_{15}H_{12}O_4$	O=Cc1c(cc(O)cc1O)/C=C/c 2ccc(O)cc2		

Journal of Chemical Health Risks

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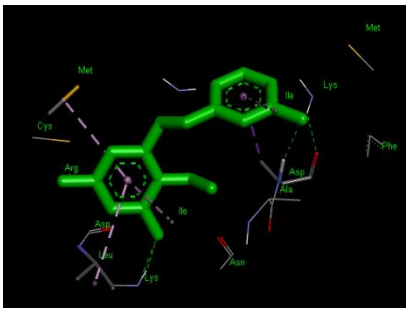
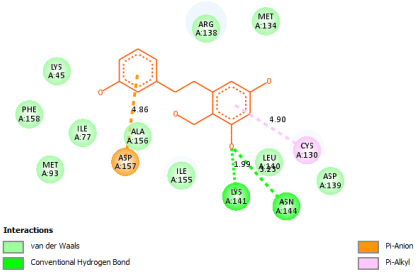
JCHR (2024) 14(4), 490-503 | ISSN:2251-6727

Table 2. Molecular docking results of the selected proteins bind with resveratrol aldehyde.

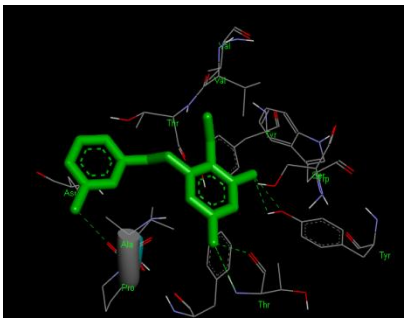
Protein	ID	ΔGb (kcal/mol)	Hydrogen Bonds	Conventional Hydrogen Bonds.	Pi alkyl Interaction.
AMP:Activated protein Kinase	2H6D	-7.23	2	ASN A:144 and LYS A:141	ILE A:77, ILE A:135, MET A:134, CYS A:130, LEU A:140
C-Reactive Protein	1GNH	-7.11	4	TYR A:49,THR A:41, PRO A:93, ALA A:92	TRP A:67
Protein tyrosine phosphatase	2NT7	-7.38	3	ARG A:79, LEU A :204, GLU A:75	LYS A:73
Glutamine fructose-6-phosphate amidotransferase	2Z73	-7.24	6	LYS A: 675, GLN A:421, SER A:376, VAL A:471, ALA A:674 .	LEU A:673

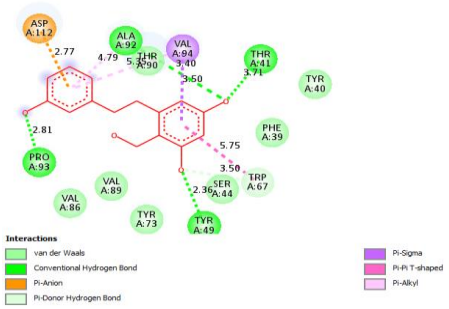
A





B





C

Journal of Chemical Health Risks

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JCHR (2024) 14(4), 490-503 | ISSN:2251-6727

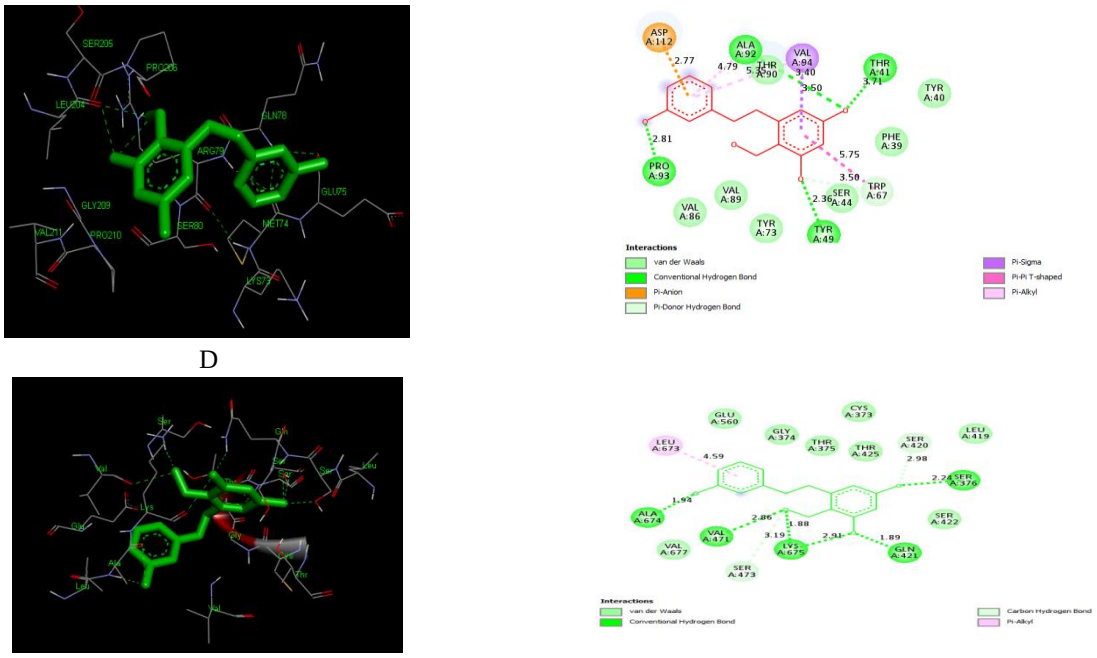

Figure 1.Biovia discovery studio structural analysis of Proteins (A-AMP:Activatedprotein Kinase, B-C-Reactive Prorein (CRP), C-Protein tyrosine phosphatase, D - Glutamine fructose-6-phosphate amidotransferase(Ash color) with receptor resveratrol aldehyde (green).

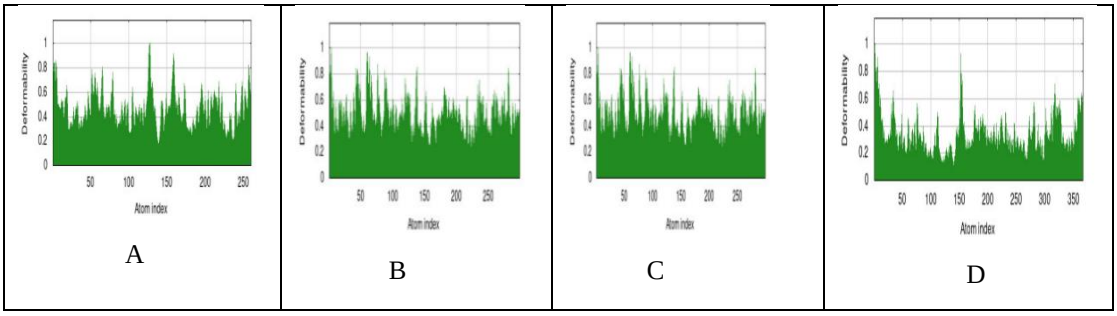

Figure 2. Deformability of four proteins (A-AMP:Activatedprotein Kinase, B-C-Reactive Prorein (CRP), C-Protein tyrosine phosphatase, D - Glutamine fructose-6-phosphate amidotransferaseA,B,C,D) upons binding with Resveratrol aldehyde.

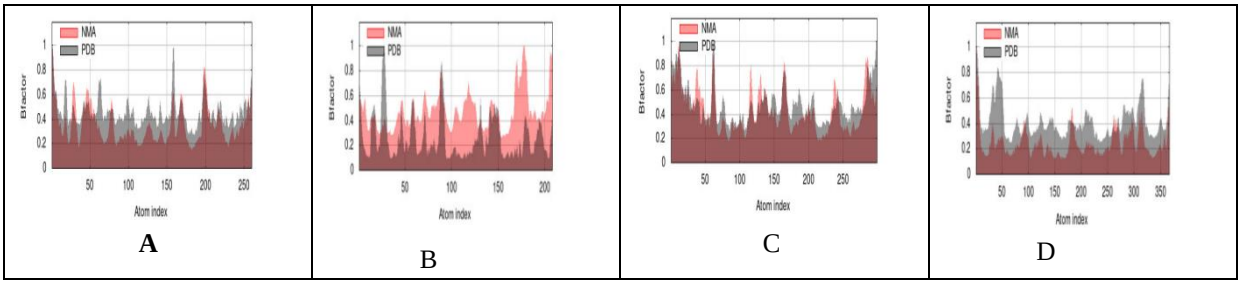

Figure 3.B-factor of proteins upon binding (A-AMP:Activatedprotein Kinase, B-C-Reactive Prorein (CRP), C-Protein tyrosine phosphatase, D - Glutamine fructose-6-phosphate amidotransferase) with resveratrol aldehyde.

Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(4), 490-503 | ISSN:2251-6727

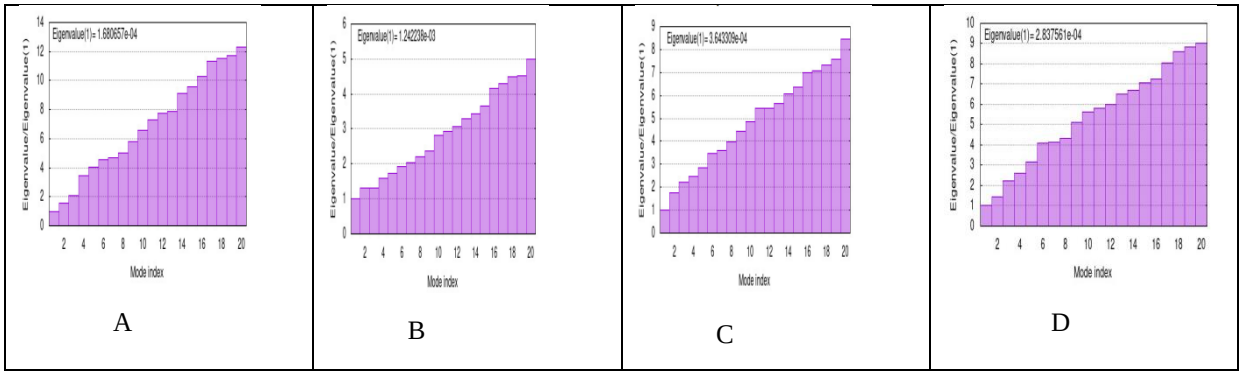

Figure 4. Eigenvalues of the docked complex of Proteins (A-AMP:Activatedprotein Kinase, B-C-Reactive Prorein (CRP), C-Protein tyrosine phosphatase, D - Glutamine fructose-6-phosphate amidotransferase)with resveratrol aldehyde.

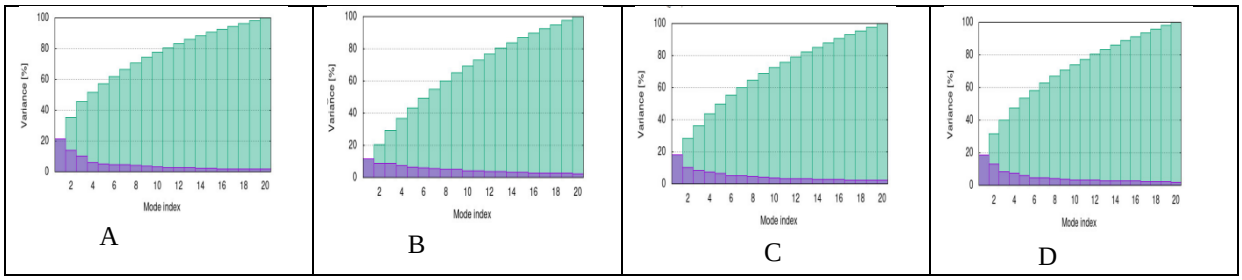

Figure 5.Variance of the docked complex of proteins (A-AMP:Activatedprotein Kinase, B-C-Reactive Prorein (CRP), C-Protein tyrosine phosphatase, D - Glutamine fructose-6-phosphate amidotransferase and resveratrol aldehyde. Variance.blue and green, respectively, showed individual and cumulative variances.

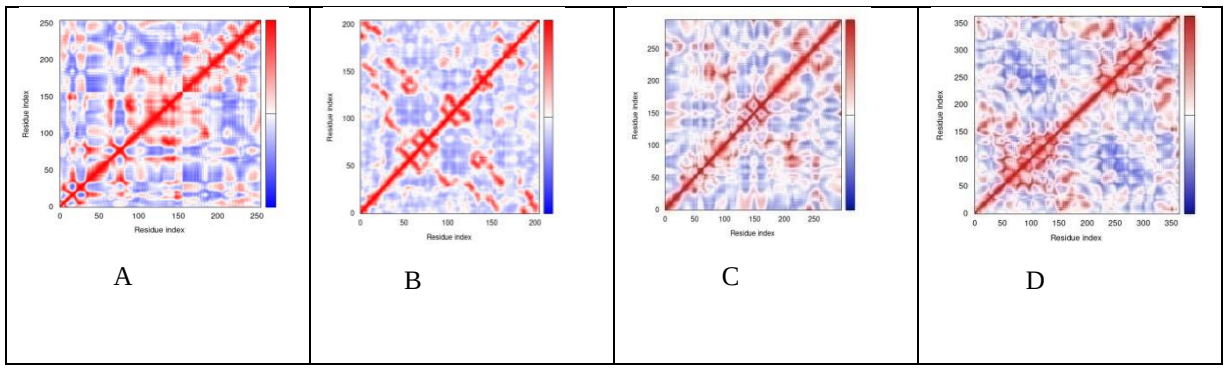

Figure 6. Covariance map of the docked complex of proteins (A-AMP:Activatedprotein Kinase, B-C-Reactive Prorein (CRP), C-Protein tyrosine phosphatase, D - Glutamine fructose-6-phosphate amidotransferase and resveratrol aldehyde. Variance Red, white and blue, respectively, shows correlated, uncorrelated, and anti-correlated motions.

Journal of Chemical Health Risks

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JCHR (2024) 14(4), 490-503 | ISSN:2251-6727

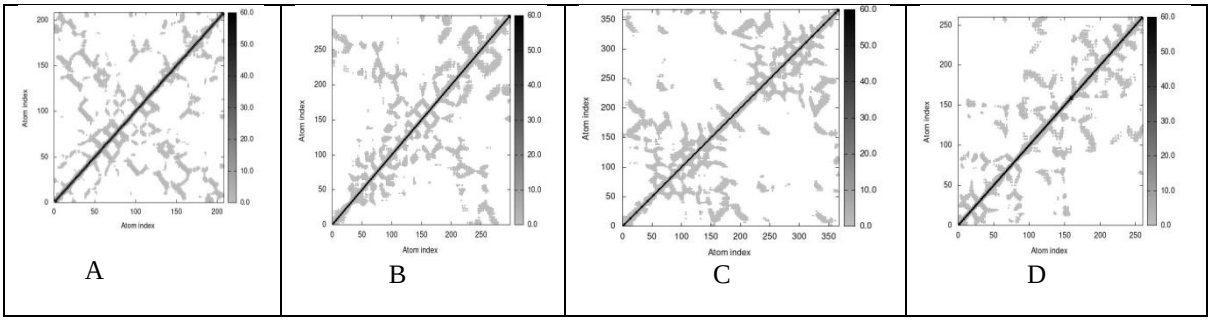

Figure 7. Elastic network: Each dot in the graph represents one spring between the corresponding pair of atoms. Dots are colored .