Research Article

Network Based Approach in the Establishment of the Relationship between Type 2 Diabetes Mellitus and Its Complications at the Molecular Level Coupled with Molecular Docking Mechanism

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Diabetes mellitus (DM) is one of the major metabolic disorders that is currently threatening the world. DM is seen associated with obesity and diabetic retinopathy (DR). In the present paper we tried to evaluate the relationship between the three ailments at the gene level and further performed the molecular docking to identify the common drug for all the three diseases. We have adopted several software programs such as Phenopedia, VennViewer, and CDOCKER to accomplish the objective. Our results revealed six genes that commonly associated and are involved in the signalling pathway. Furthermore, evaluation of common gene association from the selected set of genes projected the presence of SIRT1 in all the three ailments. Therefore, we targeted protein 4KXQ which was produced from the gene SIRT1 and challenged it with eight phytochemicals, adopting the CDOCKER. C1 compound has displayed highest -COCKER energy and -COCKER interaction energy of 43.6905 and 43.3953, respectively. Therefore, this compound is regarded as the most potential lead molecule.

1. Introduction

Globally, type 2 diabetes mellitus (T2DM) is one of the leading causes of death and it is estimated that over 70% of the population effected with T2DM are in the developing countries, China leading the world with 92.4 million [1, 2]. Once a patient is diagnosed with T2DM, lento develops the other diseases. It is generally noted that the T2DM patients are obese; however, the molecular association that exists between them is far from clear. Statistical data show an alarming figure, with 34% of the US adults being obese [3] and it may soon increase by 21% in another three decades [4]. It is well evidenced that obese men are more prone to develop T2DM than obese women at the ratio of 11.2 : 10. Nevertheless, it has to be noted that several patients with unrestrained weight again are not likely to develop T2DM, which warrants the need for understanding their relationship at the molecular level [3]. Another complication, which is seen associated with T2DM, is the diabetic retinopathy (DR) gradually causing visual impairment leading to blindness [5]. Recent reports evidently state the relationship between the BMI and DR [6]. Generally, BMI is considered as a determinant factor for obesity [7]. Wei et al. [8] also reported association between them at the genetic level. It is, hence, extremely essential to identify the relationship that exists between all the three diseases, majorly focusing on which disease is the initiator of the other two, and further to identify a common drug that could be a potential lead for all the diseases. To achieve this we have depended upon the system biology, which gives freedom in evaluating the biological system at the gene level. Additionally, this paper also makes an effort to identify the common genes and protein involved with the three ailments.

The objective of the present paper is to identify the genes representing the individual diseases and, further, the common genes involved and later to perform molecular docking to determine an effective drug molecule.
2. Materials and Methods

2.1. Identification of the Common Genes. To identify the common genes, we have employed Phenopedia [9], Public Healthy Genomics Knowledge Base (V1.0), to search for the genes responsible of the diseases and, consequently, the genes responsible for the three ailments were identified. Later, they were imported onto the pathway linkers [10] to understand the significant common genes associated with all the three diseases, which are precisely involved in the signalling pathways.

Furthermore, in order to understand the disease-gene relationship, we relied on VennViewer, provided with the Comparative Toxicogenomics Databases, which has an ability to develop the Venn diagrams pertaining to three genes, diseases, or chemicals. For the present investigation, we worked with three diseases.

2.2. Protein Ligand Docking. In order to identify the candidate drug molecules, it is very essential to perform the protein ligand docking, modelling technique used to predict the orientation, and the position of the ligand upon docking.
Table 1: Ligand name and structure.

| Ligand name | Structure |
|-------------|-----------|
| C1          | ![Structure of C1](image1) |
| C2          | ![Structure of C2](image2) |
| C3          | ![Structure of C3](image3) |
| C4          | ![Structure of C4](image4) |
| C5          | ![Structure of C5](image5) |
| C6          | ![Structure of C6](image6) |

Table 1: Continued.

| Ligand name | Structure |
|-------------|-----------|
| C7          | ![Structure of C7](image7) |
| C8          | ![Structure of C8](image8) |

Figure 3: Docking of the cocrystal represented in magenta. Blue indicates the docked pose.

Figure 4: Protein ligand docking. Green dashed lines represent the hydrogen bond interactions.

2.3. Protein Selection and Preparation. The protein selection for the present investigation is one of the most crucial aspects. Since we aim at identifying the protein from the common gene, we relied upon 4KXQ, a protein produced from the gene.
SIRT1 with the resolution of 1.85 Å and is known as NAD-dependent protein deacetylase which envisages developing a common drug for all the three diseases.

The selected protein was prepared prior to the docking studies by correcting the chemistry of the missing hydrogens and the unfilled valence atoms. Thereafter, the protein was subjected to energy minimization by applying the CHARMM force field until a satisfactory gradient tolerance was obtained.

### 2.4. Ligand Preparation

A total of eight natural compounds were chosen to challenge against the protein target molecule. These compounds were drawn on Marvin Sketch and their corresponding 3D structures were generated on the DS. CHARMM force field was applied as a measure to minimize the ligand molecules. The importance of choosing the natural compounds is to further formulate and translate them into nutraceuticals, Table 1.

### 3. Results and Discussions

#### 3.1. Identification of the Common Genes

Phenopedia was employed to identify the genes associated with obesity, diabetes mellitus, and diabetic retinopathy, respectively. A systematic search was conducted providing the disease names as a query. Consequently, SIRT1, MC4R, and VEGFA were determined for diabetes mellitus, type 2, obesity, and diabetic retinopathy, respectively.

Later, they were assessed for the common genes on pathway linkers that have an ability to link proteins to the signalling pathways. A total of 48 proteins were found to be associated; nevertheless, only six proteins were seen interacting with all the three genes. In addition, all the six proteins were involved in the signalling pathways and the nonsignalling proteins were ignored, Figure 1.

Alternatively, we tried to evaluate the gene that is involved in all the three disorders and in this pursuit, we adopted the VennViewer [11] available on Comparative Toxicogenomics Database (CTD) facilitating the three genes of interest as inputs. Following which, the results were generated pronouncing SIRT1 to be involved with all the three diseases, Figure 2. Additionally, we have identified two other genes, ICAM1 and SOD1, that were seen involved with the three diseases.

#### 3.2. Active Site Identification

Active site was identified based upon the co-crystal and all the amino acids around the co-crystals were taken into consideration. Furthermore, the co-crystal docking was performed to ascertain the active site and an
Table 2: CDOCKER scores.

| Compound name | -CDOCKER energy | -CDOCKER interaction |
|---------------|----------------|----------------------|
| C1            | 43.6905        | 46.3953              |
| C2            | 43.594         | 46.2159              |
| C3            | 43.4827        | 45.9837              |
| C4            | 41.0953        | 43.8479              |
| C5            | 39.5149        | 45.9837              |
| C6            | 38.0443        | 41.3656              |
| C7            | 37.9135        | 41.3597              |
| C8            | 37.8977        | 41.12                |
| C9            | 37.8849        | 41.0074              |
| C10           | 36.7593        | 40.0819              |
| C11           | 34.1467        | 30.8196              |
| C12           | 34.0604        | 30.898               |
| C13           | 33.9507        | 30.5325              |
| C14           | 33.8314        | 30.5452              |
| C15           | 33.7333        | 30.2313              |
| C16           | 33.6998        | 30.4529              |
| C17           | 33.6256        | 30.2404              |
| C18           | 33.3807        | 29.9087              |
| C19           | 33.3558        | 29.9264              |
| C20           | 33.3249        | 29.8632              |
| C21           | 16.1116        | 43.6807              |
| C22           | 15.345         | 45.089               |
| C23           | 13.6468        | 43.0185              |
| C24           | 11.3233        | 33.3176              |
| C25           | 11.117         | 29.8403              |
| C26           | 10.8676        | 39.7459              |
| C27           | 10.6943        | 36.1858              |
| C28           | 6.76306        | 39.212               |
| C29           | 6.74011        | 29.1499              |
| C30           | 6.5533         | 28.9768              |
| C31           | 6.37705        | 26.9035              |
| C32           | 6.2874         | 27.1806              |
| C33           | 6.10317        | 27.0072              |
| C34           | 5.97667        | 26.6726              |
| C35           | 5.92624        | 27.6206              |
| C36           | 5.92438        | 26.961               |
| C37           | 5.89596        | 26.796               |
| C38           | 5.85111        | 26.9232              |
| C39           | 5.82535        | 30.565               |
| C40           | 5.72081        | 26.7008              |
| C41           | 5.42032        | 42.1491              |
| C42           | 5.2531         | 32.1618              |
| C43           | 4.22422        | 40.4729              |
| C44           | 3.15406        | 40.3832              |
| C45           | 2.38138        | 36.5095              |
| C46           | 2.31672        | 38.5722              |
| C47           | 2.27477        | 36.9574              |
| C48           | 1.9534         | 36.4364              |
| C49           | 1.49815        | 36.2616              |
| C50           | 1.18856        | 38.0515              |

Table 2: Continued.

| Compound name | -CDOCKER energy | -CDOCKER interaction |
|---------------|----------------|----------------------|
| C51           | 0.420181       | 22.2711              |
| C52           | 0.183442       | 23.049               |
| C53           | 0.0514005      | 48.6528              |
| C54           | -1.0173        | 26.8177              |
| C55           | -1.88654       | 45.5105              |
| C56           | -2.08119       | 47.319               |
| C57           | -2.33309       | 48.7866              |
| C58           | -2.40939       | 41.621               |
| C59           | -3.58299       | 42.0705              |
| C60           | -4.44257       | 41.6539              |
| C61           | -4.72479       | 41.9058              |
| C62           | -4.92736       | 45.634               |
| C63           | -5.16567       | 44.7624              |
| C64           | -6.0176        | 39.6754              |
| C65           | -6.11149       | 39.7136              |
| C66           | -7.27294       | 42.9186              |
| C67           | -13.8456       | 32.8447              |
| C68           | -16.8805       | 32.324               |
| C69           | -19.8347       | 37.0598              |
| C70           | -19.8904       | 32.4273              |

acceptable RMSD of 0.9 was obtained projecting that our docking parameters are valid ones, Figure 3.

3.3. Molecular Docking Mechanism. Molecular docking was performed adopting the CDOCKER, which depends on CHARMm-based force field. Subsequently, diverse poses are generated adopting the random rigid body rotation and simulate annealing. In order to initiate this mechanism, all the default parameters were considered allowing the generation of 10 poses for every ligand. The docking estimation was performed by the -CDOCKER energy, which was calculated, based upon the internal ligand strain energy and receptor-ligand interaction energy. Additionally, -CDOCKER interaction signifies the energy of the nonbonded interaction that exists between the protein and the ligand. In both the cases, it has to be noted that greater -CDOCKER energy and -CDOCKER interaction energy value implies greater favourable binding between the protein and the ligand.

As mentioned above, eight naturally available phytochemicals were challenged with the protein target. Seven ligands have displayed an efficient docking with the generation of 10 conformers each; however, one ligand failed to dock. The representative dock results are displayed in Table 2. Among the docked ligands, C1 displayed higher -CDOCKER energy and -CDOCKER interaction energy value-making itself the potential leading molecule for the three common diseases. Furthermore, the protein ligand complex was assessed for the hydrogen bond interaction followed by the binding mode analysis. Delineating on the interactions reveals that the residues, ASN465, SER442, and ARG274, have participated in the hydrogen bond formation, Figure 4, while the amino
acid ARG466 participated by Vander Walls interaction and ASP272 and GLU467 interacted by the Pi-anion and ARG274 with Pi-alkyl bonds, respectively, Figure 5. Regardless of the binding energies projected by the ligands, they all obeyed the same pattern of binding mode as with the cocrystal.

4. Discussion

It has been a long subject of debate regarding the diabetes mellitus type 2 and its associated complication [12]. However, nothing concrete has yet been established. In the present paper, we have successfully evaluated the common genes associated with the three diseases. These findings could lead the researchers towards unfolding the mystery behind the diabetes complications. In the event of identifying the common genes associated among the three selected genes, our results determine SIRT1 to be the link gene, a gene which was chosen for diabetes mellitus. Therefore, it can be deduced that diabetes mellitus can influence the manifestation of obesity and diabetic retinopathy. Furthermore, our study centralizes on the identification of a common nutraceutical for all the three ailments. Accordingly, we have preferred the protein 4KXQ, a protein produced from the gene SIRT1. We have further evidenced the presence of SIRT1 in DM, obesity, and DR [13–15]. Following this, we challenged the selected protein with eight natural compounds or the phytochemicals. Natural compounds offer a host of applications such as low cost, wider availability, and low side effects which are a few to mention. Additionally, they can be supplemented through diet. Amongst all the ligand molecules, CI emerged as the best ligand demonstrating a highest -CDOCKER interaction value of 46.3953 and its corresponding -CDOCKER energy of 43.6905, respectively.

In summary, our results signify being of greater scientific usefulness in finding the most prominent results in combating the diabetes complications.

Competing Interests

The authors declare that they have no competing interests.

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