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Molecular Docking Study of Anti-diabetic Xanthones from *Garcinia Xanthochymus*

Sathya Babu[1,2†]

Abstract

Diabetes mellitus has become a major growing public health problem worldwide. More than 90% of all diabetes cases are classified as type 2 diabetes (T2D), which is also known as non-insulin dependent diabetes. Protein tyrosine phosphatase 1B (PTP1B) plays an important role in the negative regulation of insulin signal transduction pathway and has emerged as novel therapeutic strategy for the treatment of type 2 diabetes. PTP1B inhibitors enhance the sensibility of insulin receptor (IR) and have favorable curing effect for insulin resistance-related diseases. Recently twelve anti-diabetic xanthones were isolated from the bark of *Garcinia xanthochymus.* Hence, in the present study, molecular docking was carried out for these twelve xanthones. The objective of this work is to study the interaction of the newly isolated xanthones with PTP1B. The docking results showed that xanthones have good interactions and has better docking score with PTP1B and suggest LYS120 and ASP181 are the important residues involved in interaction between PTP1B enzyme and the xanthones.

Keywords: Diabetes Mellitus, *Garcinia xanthochymus*, Molecular Docking.

1. Introduction

Diabetes mellitus (DM), commonly referred to as diabetes, is a group of metabolic disorders in which there are high blood sugar levels over a prolonged period[1]. Diabetes mellitus has become a major growing public health problem worldwide. It is estimated that there will be a greatest increases in the diabetes patients especially in the developing countries such as Africa, Asia and South America[2]. More than 90% of all diabetes cases are classified as type 2 diabetes (T2D) which is also known as non-insulin dependent diabetes. Type 2 DM begins with insulin resistance, a condition in which cells fail to respond to insulin properly. Here as the disease progresses a lack of insulin may also develop. The most common cause of T2D is excessive body weight and not enough exercise[3]. T2D is characterized by insulin resistance and b-cells dysfunction, resulting in postprandial hyperglycemia[4,5]. Protein-tyrosine phosphatase 1B (PTP1B) is localized to the cytoplasmic face of the endoplasmic reticulum and is expressed ubiquitously, including in the classical insulin-targeted tissues such as liver, muscle and fat[6]. This enzyme catalyzes the dephosphorylation of the activated insulin receptor, and thus negatively regulates the insulin signal transduction. PTP1B is a negative regulator of the leptin and insulin signaling pathways. The important roles of PTP1B related to obesity and diabetes were confirmed by a deletion of PTP1B gene in mice[7]. Inhibition of PTP1B can reduce the resistant state and has emerged as an attractive promising therapeutic target for the treatment of T2D[8-10]. There are no clinically approved PTP1B inhibitors. Thus, demand of new PTP1B inhibitors is still urgent. However, targeting PTP1B for drug discovery is challenging because of the highly conserved and positively charged active-site pocket.

Molecular docking plays an important role in drug designing by placing a ligand molecule into the binding site of the target molecule[11] and is demonstrated in the following studies[12-14]. The present work aimed at the *in silico* docking of PTP1B against anti diabetic xanthones isolated from the bark of *Garcinia xanthochymus*. The aim of this study is to study the interaction of the newly isolated xanthones with PTP1B enzyme

[1]Department of Bioinformatics, School of Bioengineering, SRM University, Kattankulathur, Chennai 603203, India
[2]Department of Genetic Engineering, School of Bioengineering, SRM University, Kattankulathur, Chennai 603203, India

[†]Corresponding author : sathyainfo26@gmail.com
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through molecular docking approach. Docking program implemented in SYBYL called Surflex dock[15] was used to predict favorable receptor–ligand complex with reasonable accuracy and speed. The docked complex is then visualized using pymol software[16].

2. Materials and Methods

2.1. Protein Preparation

In the present study, the X-ray crystal structure of PTP1B complexed with (3'-(1,1-dioxido-4-oxo-1,2,5-thiadiazolidin-2-yl)-4'-methyl-[1,1'-biphenyl]-4-yl)acetamide (2.1Å) was downloaded from PDB database (5T19) and the protein structure was prepared using protein preparation tool in biopolymer module of SYBYL. During protein preparation, water molecules and metal ions present in the crystal structure were removed and subsequently hydrogen atoms and charges such as Gasteiger Huckel charges were added to the protein structure. Finally, energy minimization of protein was performed for 100 steps utilizing Powell method, Gasteiger Huckel charge and Tripos force field.

2.2. Ligand Preparation

The twelve xanthones obtained from the bark of *Garcinia xanthochymus*[17] were drawn using sketch molecule function in SYBYLX2.0. The energy minimization of the molecules was performed using Tripos force field and Gasteiger Huckel charge. The structure of the xanthones used in this study is shown in Fig. 1.

2.3. Molecular Docking

Twelve xanthones which are proved to have anti-diabetic activity were taken for molecular docking. Surflex dock module of SYBYL was utilized to perform molecular docking in this study. The docking algorithm in

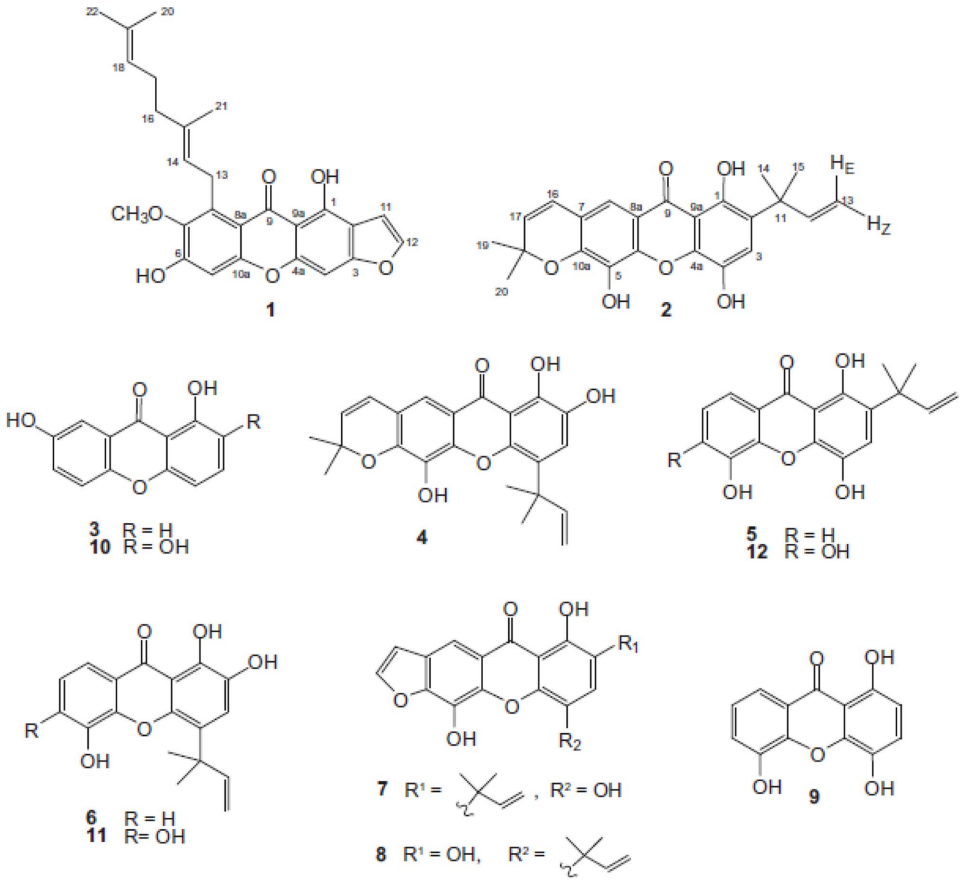

Fig. 1. Chemical structure of Anti-diabetic xanthones from Garcinia xanthochymus.

surflex dock uses an idealized active site called protomol[18] which is the representation of intended binding site to which the ligand molecules were docked. The extent of a protomol was determined by two parameters, namely threshold and bloat. Since the active site of the protein was not determined previously, the automatic mode was used for generation of protomol. Surflex dock uses an empirical scoring function which takes into account several terms, including hydrophobic, polar, repulsive, entropic and solvation and the docking scores are expressed in terms of $-\log_{10} K_d$ units, where K_d represents a dissociation constant of a ligand[19].

3. Results and Discussion

To study the interaction of newly isolated xanthones, molecular docking was performed using Surflex dock module.

3.1. Molecular Docking

Molecular docking was performed for twelve xanthones. For each compound 20 different conformations was generated and the best conformation was chosen based on surflex score and interaction with the residues. The docking score and H-bond forming residues for all the molecules are tabulated in Table 1. The compound number 8 (5.41) and 11 (5.31) showed higher docking score compared to others. Compound number 9 has lower docking score of 3.38 but have more H-bond interacting residues (GLN262, LYS120, ARG221, SER216) compared to other compounds. We observed that LYS120 and ASP181 play a major role in interaction of these xathones with the protein PTP1B. GLN262 and GLU115 also have interaction with few compounds. The interaction of xanthones with PTP1B was depicted in Fig. 2. The docking results authenticates that LYS120 and ASP181 were the most important residues and all these compounds have good interaction which

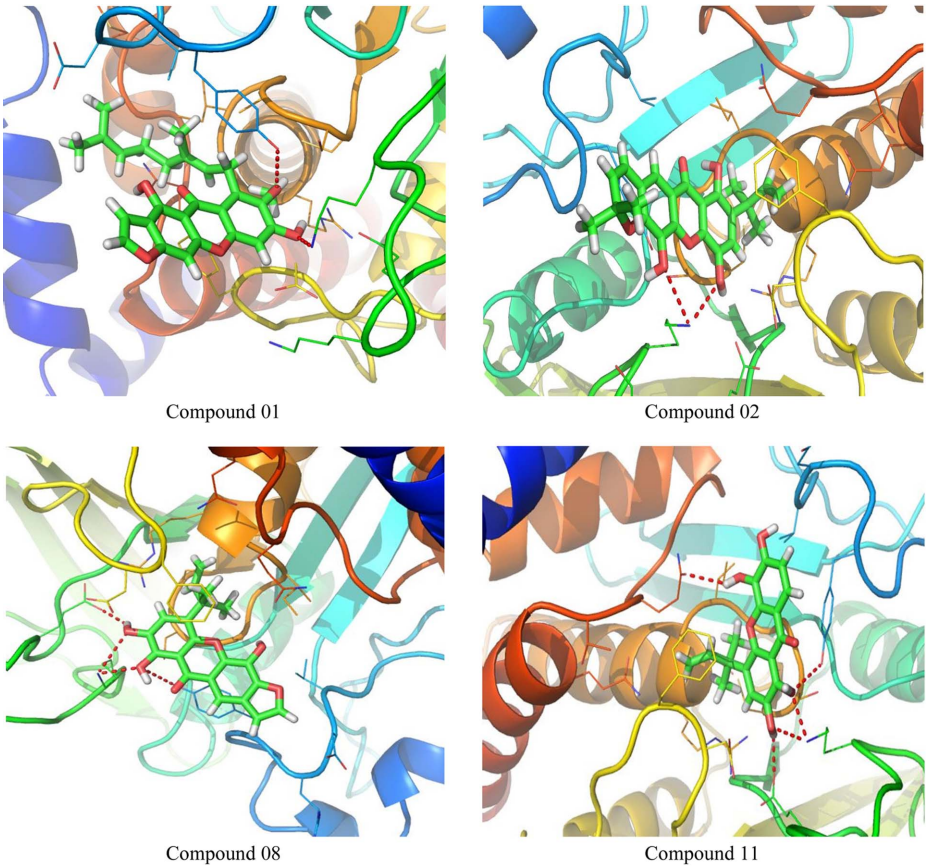

Fig. 2. Interaction between PTP1B and xanthones from *Garcinia xanthochymus*.

Table 1. Docking scores and H-bond forming residues formed between HBV and inhibitors

Compound	Docking score	Interacting residues
1	4.92	LYS120
2	4.80	LYS120
3	4.56	GLU115, LYS120
4	4.80	ASP181, LYS120, GLN262
5	4.82	LYS120, ASP181
6	4.85	LYS120, ASP181
7	4.68	LYS120, ASP181
8	5.41	GLU115, LYS120
9	3.38	GLN262, LYS120, ARG221, SER216
10	4.11	GLY220, ARG221,
11	5.31	GLN262, LYS120, GLU115
12	4.78	LYS120

validates these compounds can be used as anti-diabetic drugs.

4. Conclusion

In silico docking study of twelve xanthones isolated from *Garcinia xanthochymus* with PTP1B demonstrates that these compounds docked well into the binding site of PTP1B. This study also clearly indicated the all these compounds have similar kind of interaction into the binding site. This study offered valuable information on these xanthones for seeking anti-diaabetic drug for type II diabetes.

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