# *In Silico* Docking of Dibutyl Phthalate Isolated from *Ventilago maderaspatana* for the Treatment of Diabetes Mellitus

**Karuppannan Periyasamy and Saravanan Kaliyaperumal**

**Abstract - In the present study, molecular docking of ligand dibutyl phthalate was performed by autodock ver. 4.0 with diabetic targets such as insulin receptor tyrosine kinase, glucokinase and aldose reductase. The ligand, dibutyl phthalate effectively bound with the three targets *viz*.,, insulin receptor tyrosine kinase, glucokinase and aldose reductase. Target insulin receptor tyrosine kinase showed the minimum binding energy (-8.46 kcal/mol) at tenth run with RMSD value of 67.98 compared to glucokinase (-6.51 kcal/mol at eighth run) and aldose reductase (-7.28 kcal/mol at sixth run). Thus, the bioactive compound dibutyl phthalate may be used as the drug candidate for the treatment of diabetes mellitus after clinical validation.**

**Key words - Diabetes mellitus, diabetic targets, ligand dibutyl phthalate, molecular docking and binding energy.**

## 1. INTRODUCTION

DIABETES MELLITUS is a chronic metabolic disorder caused due to insulin deficiency or insulin resistance. In Type 1 diabetes autoimmune destruction of the beta cells of pancreas leads to insulin deficiency. Type 2 diabetes involves insulin resistance or decreased insulin secretion. Insulin is essential for maintaining blood glucose and regulating carbohydrate metabolism. In developing countries including India, the prevalence of diabetes mellitus and the numbers are increasing at an alarming rate. India alone has more than 40 million diabetic individuals which represent nearly 20% of the total populations (Hoskote and Joshi, 2008).

Insulin receptor (IR) is a tetrameric protein consisting of two extracellular alpha subunits and two transmembrane beta subunits (Goldfine, 1987). The binding of insulin to alpha subunit of IR causes conformational changes in the receptor leading to the activation of tyrosine kinase beta subunit. The activated IR has the ability to autophosphorylate and phosphorylate intracellular substrates that are essential for initiating other cellular responses of insulin (Kahn and White, **1988;** Kahn, 1994; White, 1998).

These events lead to the activation of downstream signaling molecules that participate in the insulin signaling pathway (Thies, *et al.,* 1990). Insulin signaling, including activation of IR tyrosine kinase activity, is impaired in most patients with diabetes mellitus. This resistance to insulin then leads to hyperglycemia and other metabolic abnormalities of the disease (Moller and Flier, 1991; Virkamaki *et al.,* 1999).

Aldose reductase inhibitors can play a significant role in preventing diabetic complications. The discovery of 3D structure of aldose reductase helped to conduct molecular modeling techniques and thus will be useful for insight into the structure of enzyme bound inhibitor (Shuichi, 2002).

GK displays sigmoidal kinetics and its activity is not altered significantly by physiological concentrations of G6P (Postic *et al.,* 2001), however small changes in GK concentration are significant as they have an impact on the rate of glucose stimulated insulin secretion as well as the rate of glucose metabolism. GK also has a significant role in glucose utilization and glycogen synthesis (Postic *et al.,* 2001) and GK activity increases and decreases parallel to changes in blood glucose levels within the physiological range.

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There are several synthetic medicines are available for the management of diabetes. However, they have no permanent cure and they cause unwanted side effects, and they are not easy access to the middle class people due to high cost. Therefore, treatment of diabetes without any side effects is still a challenge to the medical system.

Bioactive compounds from plants play a vital role in the treatment of diabetes. Hence, the bioactive compounds from plants that augment activities of these three targets would be useful in the treatment of diabetes mellitus. Molecular docking is the technique employed for predicting and analyzing the interactions between protein receptors and ligands. It provides most detailed possible view of drug receptor interactions and also has created a new rational approach to drug design (Bothara *et al.*, 1991). Therefore, the present study was carried out to evaluate whether the bioactive compounds isolated from leaf ethyl acetate extract *Ventilago maderspatana* (Rhamnaceae) is a good ligand for the treatment of diabetes mellitus.

## 2. MATERIALS AND METHODOLOGY

### 2.1. Protein Preparation for Docking

The 3D structure of insulin receptor protein (PDB ID: 1IR3), glucokinase (PDB ID: 1V4S) and aldose reductase (PDB ID: 1US0) were downloaded from Protein Data Bank (PDB) (http: //www.pdb.org/pdb/home/home.do) given in figure 1. Before initiating the docking simulations, all non-protein molecules and non polar hydrogen bonds from targets were removed. The protein optimization and energy minimization of target protein was done by using SPDBV (Swiss-PDB Viewer) software. Structure of target proteins was slightly modified by adding polar hydrogen. Docking studies were done by using Autodock Ver. 4.0.

### 2.2. Ligand Preparation for Docking

The ligands dibutyl phthalate was isolated from leaf extract of *V. madraspatana* and 2D and3D sturcutre of ligands was given in figure 1. The structure of ligands was sketched using Chemsketch software and optimized using "Prepare Ligands" in the AutoDock 4.0 for docking studies. Before docking study, the molecular properties of drug candidate were checked using the software http://molsoft.com/mprop/. Then the optimized ligand molecule was docked into refined insulin receptor protein target using AutoDock Version 4.0.

### 2.3. Molecular Docking

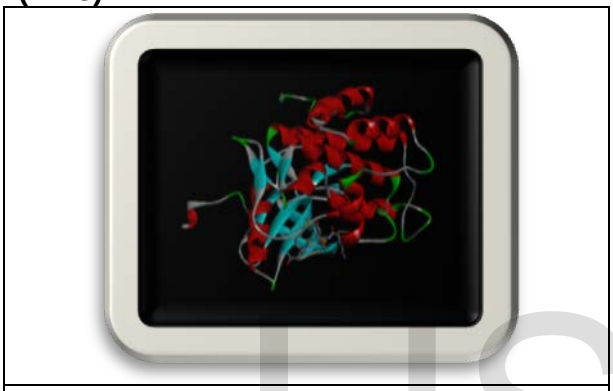
Auto Dock is an automatic docking tool. It is designed to predict how small molecules, such as substrates, bind to a receptor of known 3D structures. A graphical user interface called Auto Dock Tools or ADT was utilized to generate grids, calculate the dock score and evaluate the Conformers. AutoDock 4.0 was used to predict the ligands bound structurally with targets insulin receptor protein (1IR3), glucokinase (PDB ID: 1V4S) and aldose reductase (PDB ID: 1US0) and evaluate the biding energy of ligand and targets by scoring function. The search algorithm was based on the Lamarckian genetic algorithm and the results were analyzed using binding energy. Binding energy was calculated by Van der Waals interactions, H bond and electrostatic interactions. The docking result was visualized and analyzed using the software UCSF CHIMERA.

## 3. OBSERVATION AND RESULT

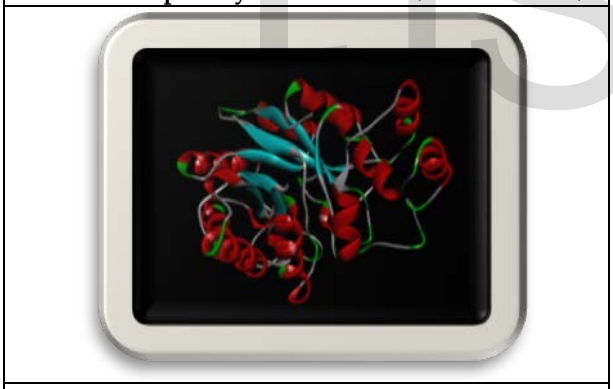
*In silico* models have potential use in the discovery and optimization of novel molecules, with affinity to the target, clarification of absorption, distribution, metabolism, excretion and toxicity properties as well as physiochemical characterization (Ekins, 2007). Molecular docking study was conducted for the evaluation of promising drug candidate for the treatment of diabetes mellitus. Ligand dibutyl phthalate from leaf extract of *V. Maderaspatana* was selected as ligand for docking stufy with target proteins insulin receptor tyrosine kinase (PDB ID: 1IR3), aldose reductase (PDB ID: 1US0) and glucokinase (PDB ID: 1V4S) (Figure 1). Docking of ligand dibutyl phthalate with target insulin receptor tyrosine kinase showed the minimum binding energy (-8.46 kcal/mol) in tenth run with RMSD value 67.98 followed by aldose reductase (-7.28 kcal/mol) in sixth run with RMSD value 12.76 and glucokinase (-6.51 kcal/mol) in eight run with RMSD value 61.78 (Table. 1 and Figure 2). Ligand dibutyl phthalate was effectively bound with all three target proteins with highest minimum binding energy. However, target insulin receptor tyrosine kinase was effectively bound with ligand dibutyl phthalate with minimum energy (-8.46 kcal/mol) than other two targets.

Docking is an important in the study of protein ligand interaction properties such as binding energy, geometry complementarity, electron distribution, hydrogen bond donor acceptor, hydrophobicity and polarizability. Thus molecular docking contributed a major role in the drug discovery in the identification of innovative small molecular scaffold, exhibiting the important properties with selectivity for the target (Krovat, 2005).

**Figure 1. Stucture Of Target Protein Insulin Receptor Tyrosine Kinase (1IR3)**



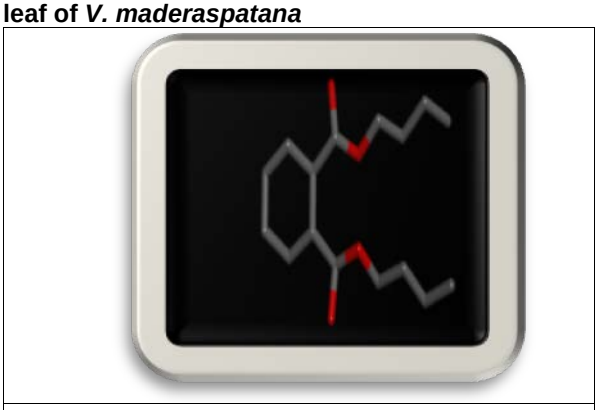
**Insulin receptor Tyrosine Kinase (PDB ID: 1IR3)**



**Aldose Reductase (PDB ID: 1US0)**

**Glucokinase (PDB ID: 1V4S)**

**Figure 2. 3D structure of Ligand Isolated from leaf of *V. maderaspatana***

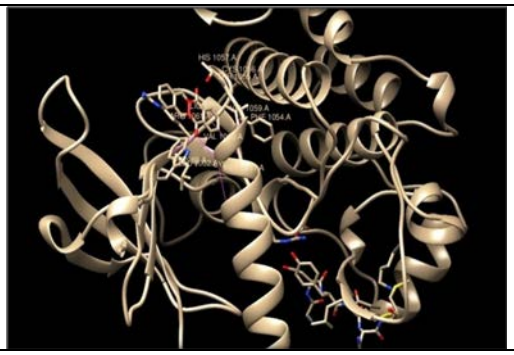


**Dibutyl Phthalate**

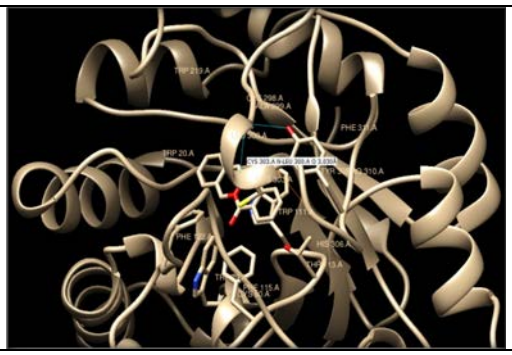
**Table 1. Docking results of ligand dibutyl phthalate from leaf extract of *V. maderaspatan* with three different targets of diabetes mellitus.**

| S. No | Name of the Ligands | Run | Binding energy (kcal/mol) | RMSD Value | Rank |
|---|---|---|---|---|---|
| **1** | Insulin receptor tyrosine kinase (1IR3) | 10 | -8.46 | 67.98 | 1 |
| **2** | Aldose reductase (1US0) | 6 | -7.28 | 12.76 | 2 |
| **3** | Glucokinase (1V4S) | 8 | -6.51 | 61.78 | 3 |

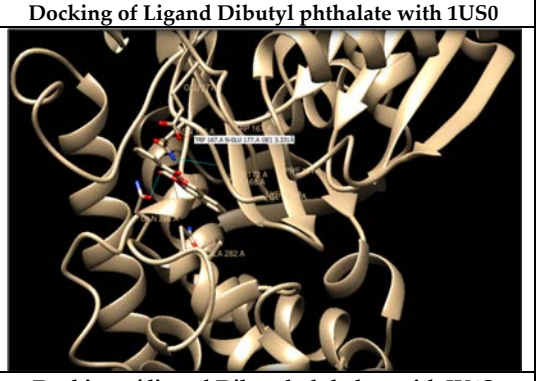
**Figure 3. Docking results of ligand dibutyl phthalate with three different targets of diabetes mellitus**



**Docking of Ligand Dibutyl phthalate with 1IR3**



**Docking of Ligand Dibutyl phthalate with 1US0**



**Docking of ligand Dibutyl phthalate with IV4S**

## 4. CONCLUSION

The ligand dibutyl phthalate was effectively bound with three targets with minimum binding energy. Among 3 targets, insulin receptor tyrosine kinase was effectively bound with ligand with minimum binding energy (-8.46kcal/mol). Hence the ligand dibutyl phthalate can be activated insulin receptor tyrosine kinase and it can be used as the alternative target for the treatment of diabetes mellitus.

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