ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Insilico Drug Target Identification and Potential Drug for Obesity - A Novel Drug Designing Approach

Krishnamoorthy P[1], Praveen Kumar PK[2], Jayalakshmi T[1] and Siva Ganesh M[1]

[1]School of Bio-engineering, Dept. of Bioinformatics, Bharath University, Chennai, Tamil Nadu, India.
[2]Assistant professor, S.V.C.E College, Sriperumbudur, Chennai, Tamil Nadu, India.

ABSTRACT

Accumulation of excess fat on the body is called as "obesity". A certain amount of body fat is necessary for strong energy, heat insulation, shock absorption and other functions. The normal amount of body fat is between 25-30 % in women and 18-23 % in men. Women with over 30% body fat and men with over 25% fat are considered obese. The calculation of body mass index (BMI) has also been used in the definition of obesity. The BMI equals a person's weight in kilograms (Kg) divided by their height in meters (m) squared. Since BMI describes body weight relative to height, it is strongly correlated with total body fat content in adults. Obesity is defined as having a body mass index of greater than 30.Lipoprotein lipase is an enzyme that hydrolyses lipids into two free fatty acids and one mono acyl glycerol molecule. The accumulation of this fat leads to obesity. So lipoprotein lipase plays an important role in obesity. So lipoprotein lipase used as a target protein for obesity. In our project to inhibit lipoprotein lipase activity we used drugs from plant and chemical sources. One drug is derived from drug bank (chemical source) and the other two drugs are derived from pubchem (herbal drugs). We compared and analyzed the activity of these drugs on lipoprotein lipase activity and we found the drug which best inhibits the lipoprotein lipase activity.The procedure includes following steps. They are as follows: Identification of target protein, Prediction of target structure, identification of ligands, docking of target with the ligands,finding the best drug which inhibits the target protein.

Key words: ligand, docking, prediction sites, protein.

Corresponding author

ISSN: 0975-8585

INTRODUCTION

Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have an adverse effect on health, leading to reduced life expectancy and/or increased health problems. Body mass index (BMI), a measurement which compares weight and height, defines people as overweight (pre-obese) when their BMI is between 25 kg/m^2 and 30 kg/m^2, and obese when it is greater than 30 kg/m^2[3].

Obesity increases the likelihood of various diseases, particularly heart disease, type 2 diabetes, breathing difficulties during sleep, certain types of cancer, and osteoarthritis. Obesity is most commonly caused by a combination of excessive dietary calories, lack of physical activity, and genetic susceptibility, although a few cases are caused primarily by genes, endocrine disorders, medications or psychiatric illness [6-7]. Evidence to support the view that some obese people eat little yet gain weight due to a slow metabolism is limited; on average obese people have a greater energy expenditure than their thin counterparts due to the energy required to maintain an increased body mass.

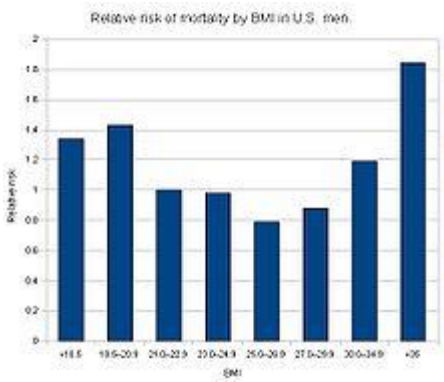
The primary treatment for obesity is dieting and physical exercise. To supplement this, or in case of failure, anti-obesity drugs may be taken to reduce appetite or inhibit fat absorption. In severe cases, surgery is performed or an intragastric balloon is placed to reduce stomach volume and/or bowel length, leading to earlier satiation and reduced ability to absorb nutrients from food.

Obesity is a leading preventable cause of death worldwide, with increasing prevalence in adults and children, and authorities view it as one of the most serious public health problems of the 21st century[1]. Obesity is stigmatized in the modern Western world, though it has been perceived as a symbol of wealth and fertility at other times in history, and still is in many parts of Africa.

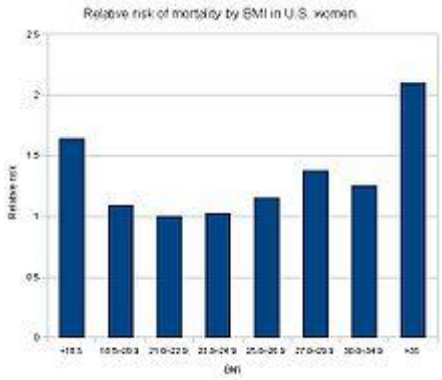
Mortality

Obesity is one of the leading preventable causes of death worldwide. Large-scale American and European studies have found that mortality risk is lowest at a BMI of 22.5–25 kg/m^2in non-smokers and at 24–27 kg/m^2 in current smokers, with risk increasing along with changes in either direction. A BMI above 32 has been associated with a doubled mortality rate among women over a 16-year period [5]. In the United States obesity is estimated to cause an excess 111,909 to 365,000 death per year, while 1 million (7.7%) of deaths in the European Union are attributed to excess weight. On average, obesity reduces life expectancy by six to seven years: a BMI of 30–35 reduces life expectancy by two to four years, while severe obesity (BMI > 40) reduces life expectancy by 10 years [8].

ISSN: 0975-8585



Relative risk of death for men in United States by BMI.



Relative risk of death for women in United States by BMI.

Morbidity

Obesity increases the risk of many physical and mental conditions. These comorbidities are most commonly shown in metabolic syndrome, a combination of medical disorders which includes: diabetes mellitus type 2, high blood pressure, high blood cholesterol, and high triglyceride levels [2].

Complications are either directly caused by obesity or indirectly related through mechanisms sharing a common cause such as a poor diet or a sedentary lifestyle. The strength of the link between obesity and specific conditions varies. One of the strongest is the link with type 2 diabetes. Excess body fat underlies 64% of cases of diabetes in men and 77% of cases in women [9-10].

MATERIALS AND METHODS

DATABASE USED

SWISS MODEL
PDB (PROTIEN DATA BANK)
PUBCHEM
SAVS
DRUG BANK
CASTp
Uniprot

TOOLS USED:

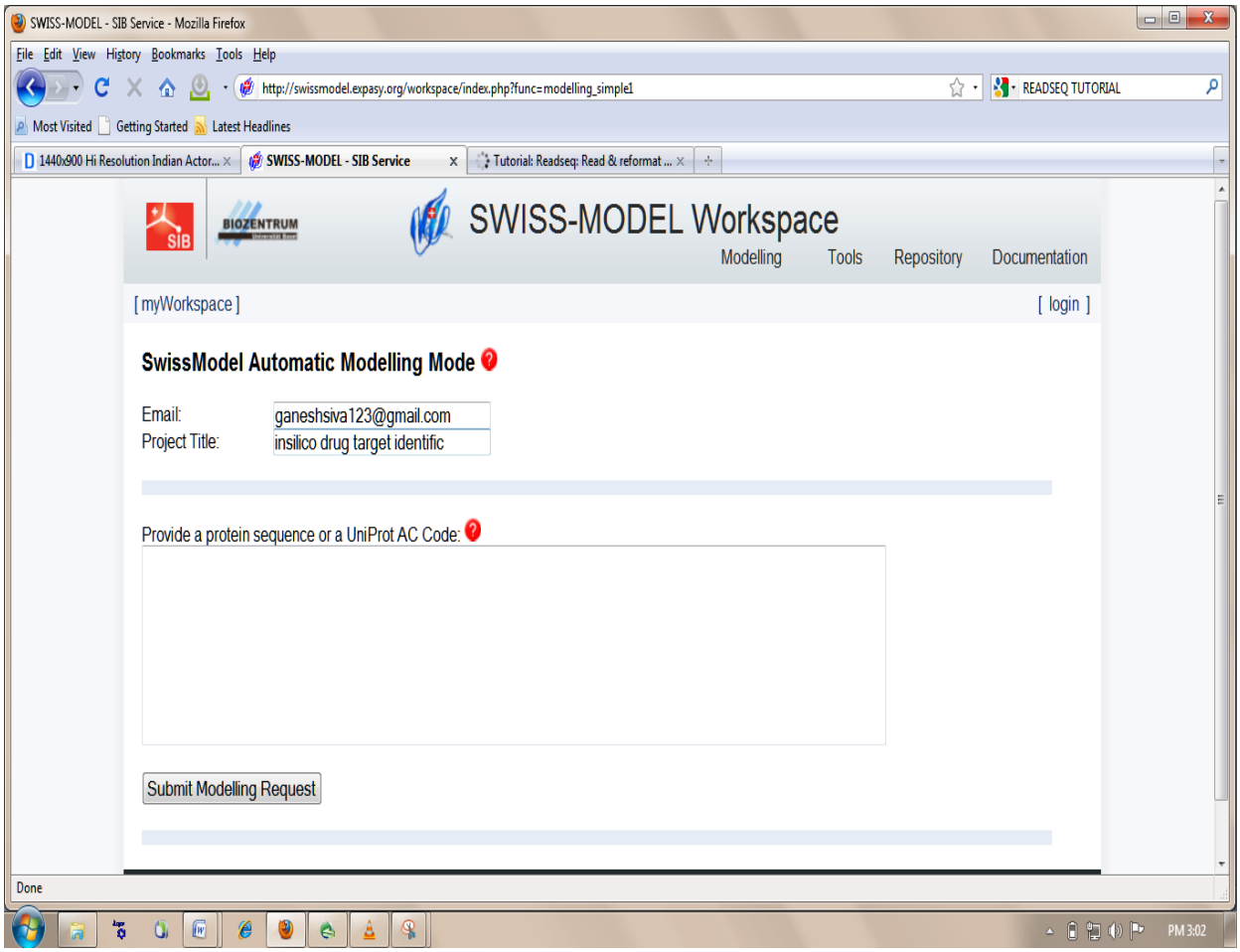
BLAST
Arguslab
Pymol

ISSN: 0975-8585

SIWSS MODEL

SWISS-MODEL is a fully automated protein structure homology-modeling server, accessible via the ExPASy web server, or from the program Deep View (Swiss Pdb-Viewer). The purpose of this server is to make Protein Modeling accessible to all biochemists and molecular biologists Worldwide [4]. The SWISS-MODEL Repository is a database of annotated three-dimensional comparative protein structure models generated by the fully automated homology-modelling pipeline SWISS-MODEL.

SWISS-MODEL is developed by the Protein Structure Bioinformatics group at the SIB - Swiss Institute of Bioinformatics and the Biozentrum University of Basel.



PROTIEN DATA BANK (PDB)

The Protein Data Bank (PDB) format provides a standard representation for macromolecular structure data derived from X-ray diffraction and NMR studies.

FINDING THE STRUCTUURE OF TARGET PROTEIN

The fasta sequence for the target protein (LPL) was retrieved from Uniprot and Swissprot databases. This is followed by doing alignment with template protein sequences in BLAST. In protein-BLAST submit the query sequence and do psi-BLAST, the similar

ISSN: 0975-8585

template sequences will be displayed from pdb. Choose the template which is most similar to target sequence (LPL).

The structure can be found using SWISSMODEL which works basing on homology modeling. Submit the query and template sequences to SWISSMODEL automated mode .the structure of query sequence will be retrieved from swissmodel, which can be downloaded in pdb format.

The structure obtained is validate d using SAVES an online tool .the structure is submitted to SAVES in pdb format and we will check for accuracy of the structure .if its accuracy is in between 75%-95% the structure is valid. We can view the structure using pymol.

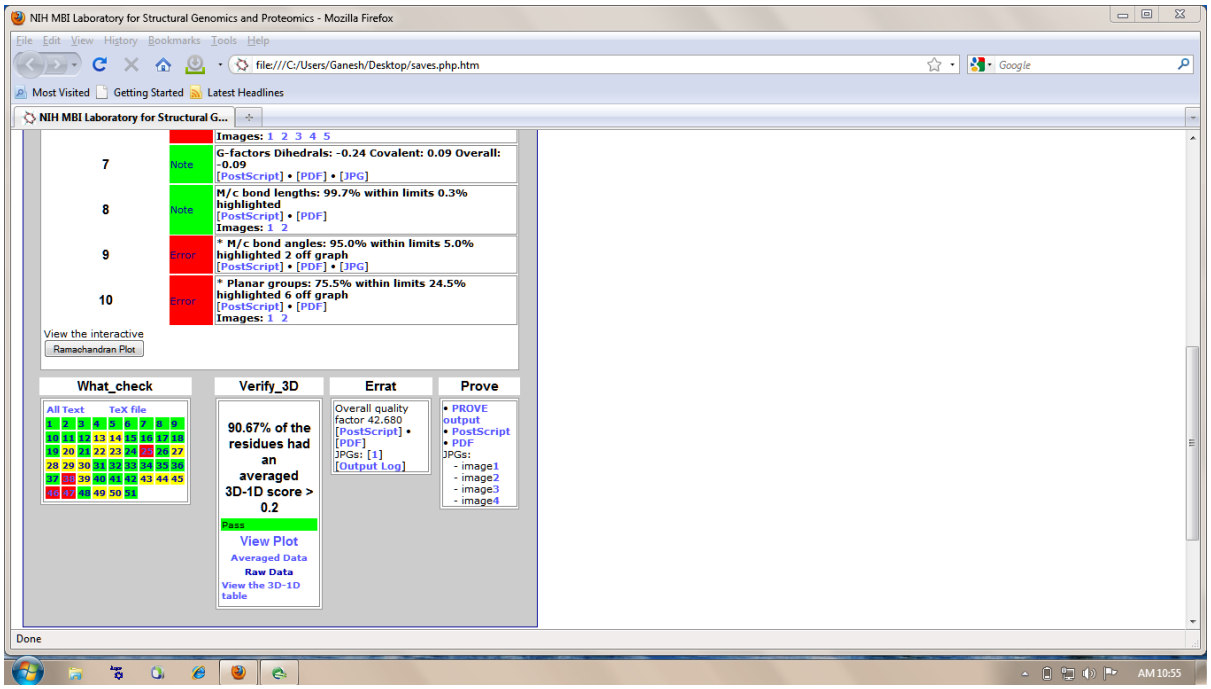


Figure shows saves results obtained for target protein.

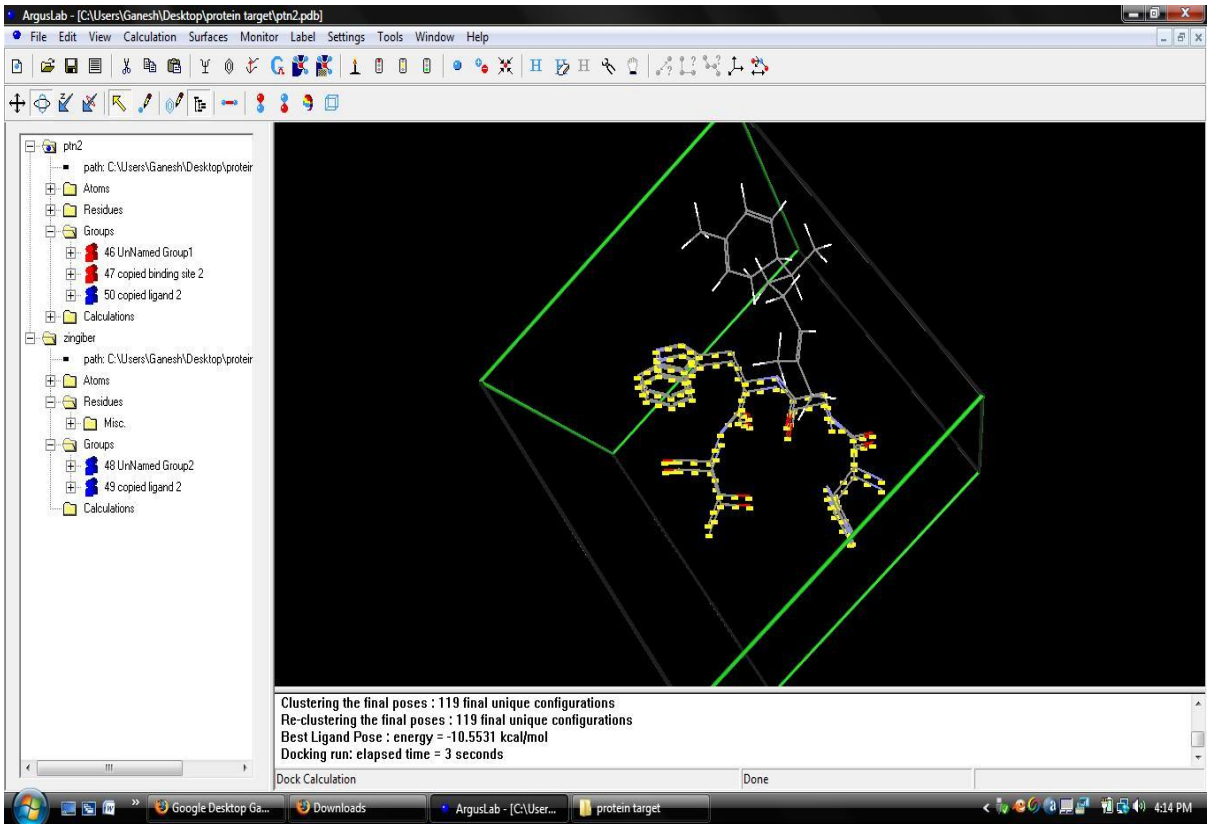
RESULTS AND DISCUSSION

The docking of the target protein lipoprotein lipase and the ligand molecules metformin, zingiberine and acanthophanax was carried out in Argus lab and the results docked complexes were analysed.

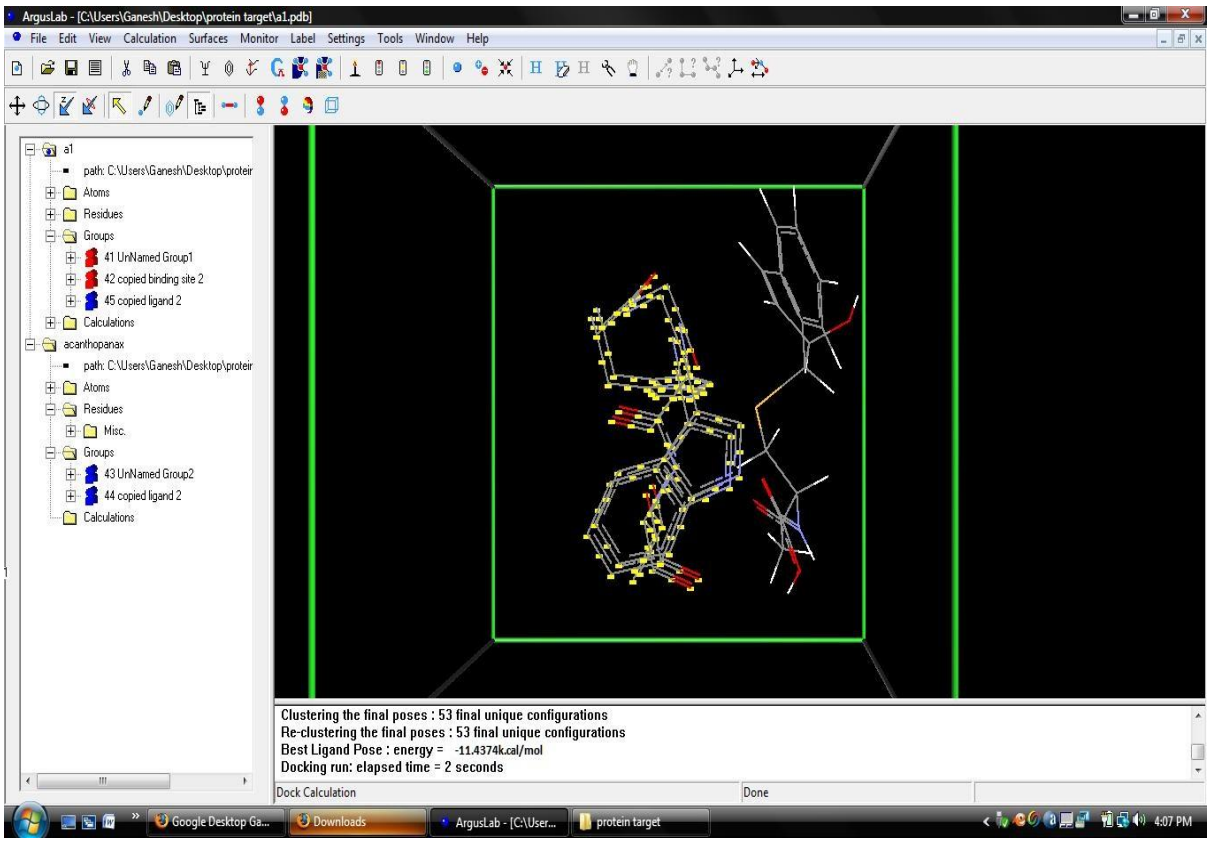
After docking, we obtained many conformations (represented as poses). The binding energy of the poses ranged from -11.4374kcal/mol to -7.97 kcal/mol. The best conformations are tabulated in the table below.

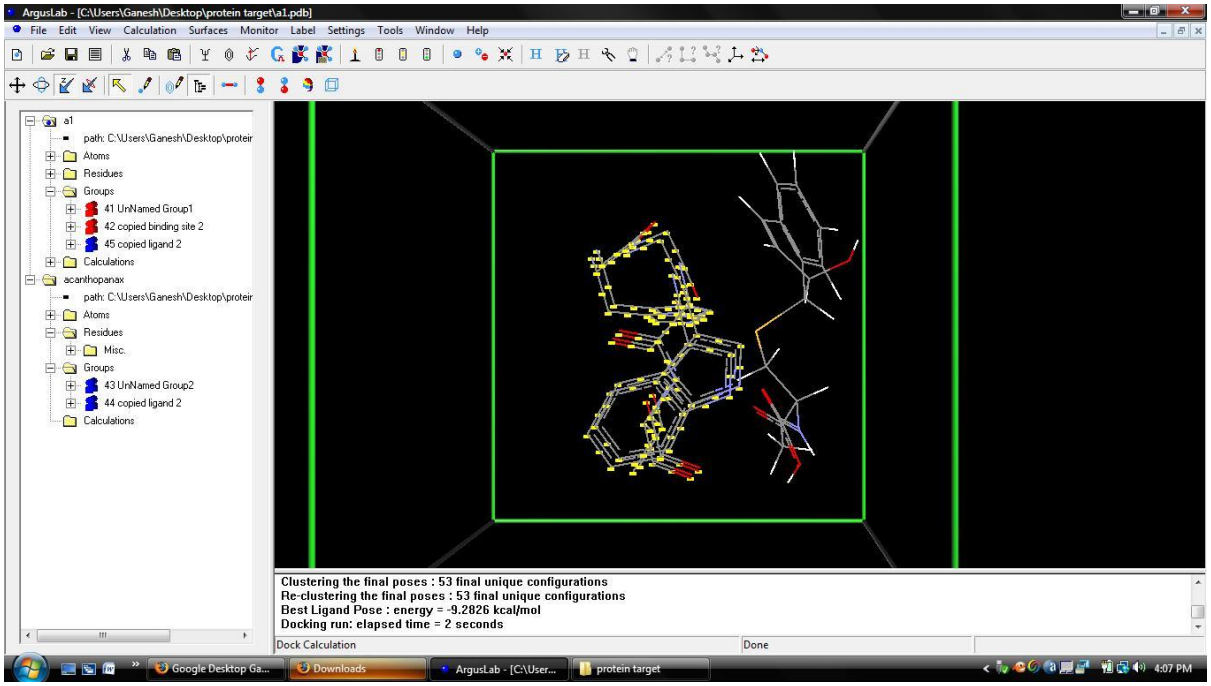
ISSN: 0975-8585

Poses	Energy
Pose 1	-11.4374 kcal/mol
Pose 2	-10.553kcal/mol
Pose 3	-9.2826kcal/mol
Pose 4	-7.86 kcal/mol



ISSN: 0975-8585





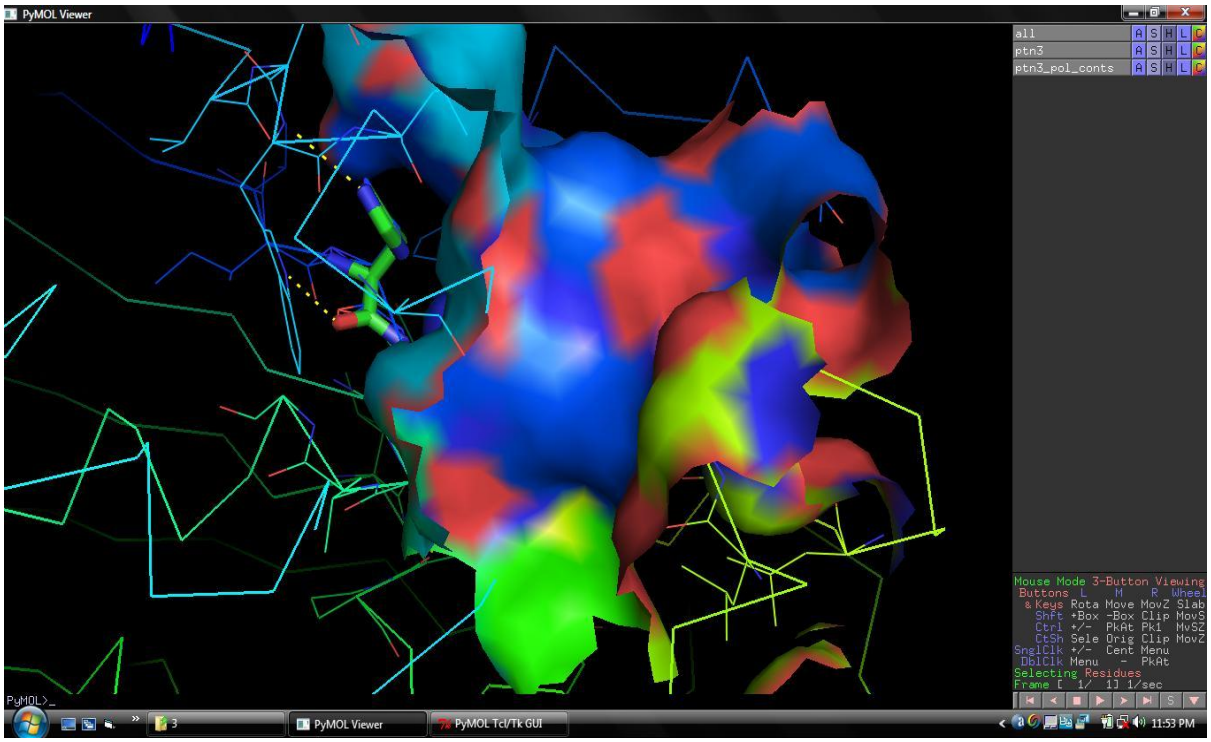
The above figures shows interactions between target and ligandcompounds

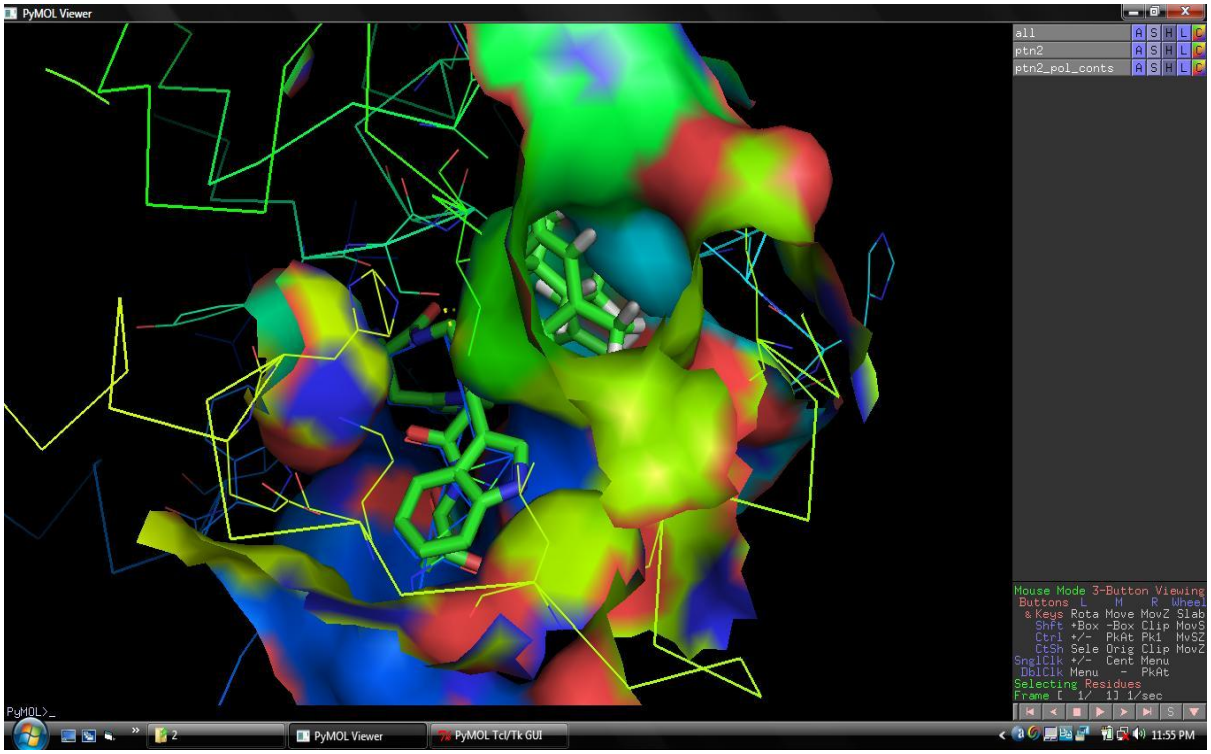
The first conformation with the binding energy -11.4374 kcal/mol is taken as the best complex.. The docked complex of the target protein and the ligand is shown in the

ISSN: 0975-8585

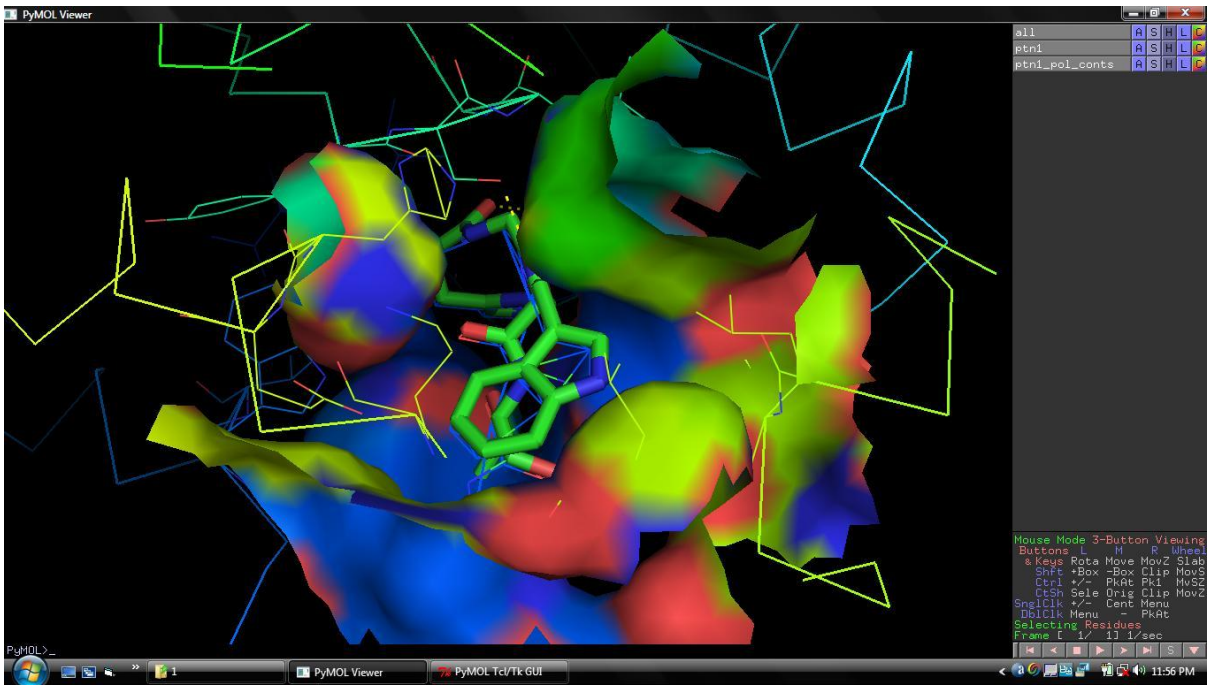
figure. A grid box of the resolutions 0.4 was formed surrounding the active site, which is essential for the binding of ligand to catalytic site of the target molecule.

The docked complex was transferred to Pymol for analysis of the interaction.





ISSN: 0975-8585



The above figures shows the pymol views of ligand and target interactions.

The interaction viewed in Pymol is shown in the above figure, with ligand represented in sticks, binding pocked of protein in lines.Thus, from the above theoretical studies, it is observed that the ligand metformin forms a good complex with the lipoprotein lipase protein, there by inhibiting the catalytic activity of the protein from causing obesity.

CONCLUSIONS

Lipoprotein lipase through its **lipid** hydrolysing activity causing the accumulation of free fatty acids in the body**,** they are an important cause of obesity. It has been evident that metformin drug has a greater affinity towards the binding site of lipoprotein lipase compared to zingiberine (plant protein) and acanthopanax (animal protein). Metformin drug had been taken from the drugbank database and the other proteins are taken by studying literatures from pubchem database.

The docking was done in arguslab. The energy values are found to be promising for the metformin drug compared to the other drugs. It has pose energy value of around -11.4374k.cal/mol. The plant compound has a pose energy value -10.5531k.cal/mol and the animal compound has the energy value -9.2826k.cal/mol. The docking analysis has shown that metformin has the maximum binding affinity compared to zingiberine and acanthopanax, there by inhibiting the activity of the protein (lipoprotein lipase). Thus the study aims at finding the potential ligand for the disease. The ligand is presented for further analysis involving inhibitor affinity and its pharmacophore binding.

REFERENCES

[1] Farese RV Jr, Yost TJ, Eckel RH. Metabolism 1991;40(2):214-6.
[2] Mead JR, Irvine SA, Ramji DP. J Mol Med 2002;80(12):753-69.

[3] PA Kern, JM Ong, B Saffari, and J Carty, 2001. Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA 90048.
[4] L Cominacini, U Garbin, A Davoli, M Campagnola, A De Santis, C Pasini, et al. Int J Obes Relat Metab Disord. 2000;24(1):93-100.
[5] International Journal of Obesity 2000;24:93-100.
[6] Nilsson-Ehle P. Int J Obes 1981;5(6):695-9.
[7] Coppack SW, Evans RD, Fisher RM, Frayn KN, Gibbons GF, Humphreys SM, Kirk ML, Potts JL, Hockaday TD. Metabolism 1992;41(3):264-72.
[8] Schwartz RS, Brunzell JD. Lancet 1978;1(8076):1230-1.
[9] Clin Invest 199; 95(5): 2111–2119