7.1 Introduction

Network pharmacology is a novel concept that creates a molecular network by integrating multidisciplinary concepts of biology including Biochemistry, Bioinformatics, and Systems Biology[1]. The concept is based on multi targeting potentials of the effective drugs for therapeutic applications[2,3]. Several complex diseases occur because it involves the interactions of multiple genes as well as functional proteins[4]. In such cases, network pharmacology helps in detecting how and where in the disease network, one target inhibits or activates the disease phenotypes and assists in systematic characterization of the drug targets to reduce the challenges of drug discovery[5].

To determine the relation between the traditionally used antidiabetic plants of NE India and T2DM, the network pharmacology approach was used in the study. The network comprises of nodes and edges, where the nodes represent molecular species (compounds and proteins), and the edges specify intermolecular interactions connecting the nodes (compound– target or target– target interactions). Thus, the complex relationship between the compounds and their targets can be visualized. To achieve that, the "Compound– Target network" (CTN) was constructed after combining the predicted compounds and all relevant targets. In addition, the properties of the network were also analyzed. Cytoscape is an open source software to visualize the biomolecular interaction networks and biological pathways. It also helps in integrating these networks with annotations, gene expression profiles and other state of data and makes it a unified conceptual framework[6].

In the field of drug discovery, a new approach has been developed considering the integration of Network Biology and Polypharmacology. Due to the use of the principles of System Biology, it is also known as System Pharmacology. This new approach of drug discovery also helps in understanding the disease pathogenesis using system level approach and hence, it gives a better idea for developing new lead molecules and their targets without the limitations of a single target along with its side effects. It helps in finding the potent molecules present in the traditionally used medicinal plants which have supposedly more efficacies for the therapeutic targets as well as in their mechanism of action.

The northeast India is rich in medicinal plants and the traditional knowledge regulating their use as medicine for the treatment of different diseases is well known. With its vast and unique plant resources, this region of India has huge potential and possibilities in the field of drug discovery. Therefore, efforts can justifiably be focused on these plant species for identifying the much needed new potent molecules having antidiabetic activity. It may also be more effective in combination with the different molecules present in different plants, as has been used in the Traditional Chinese Medicine (TCM). Thus, in this study, on the basis of molecular docking and network analysis, some suitable compounds of polypharmacophoric nature were found out from some of the traditionally used antidiabetic plants and their therapeutic targets along with its molecular mechanism, for the treatment of T2DM. This research could lead to better opportunities in the near future for the development of effective lead molecules for monotherapy or combination therapy for betterment of T2DM treatment.

7.2 Materials and methods

7.2.1 Natural Product (NP) Library Development

A library of 505 natural products from plant sources, having well known ethnobotanical use for the treatment of diabetes, was collected form extensive literature survey. The compounds were sketched using MarvinSketch v6.0 and energetically optimized using CHARMM based force field at BIOVIA Discovery Studio v4.5. CHARMM based smart minimizer used 1500 steps of Steepest Descent followed by Conjugate Gradient algorithms with a convergence gradient of 0.001 kcal mol^{-1} [7]. Diverse conformation options were applied and 250 conformations were generated using BEST generation module of Discovery Studio (DS) by applying Poling Algorithm at an energy threshold of 15 kcal mol^{-1}. The principles of rigorous energy minimization in both torsional and Cartesian space are employed in this option, as it ensures the best coverage of conformational space by application of the poling algorithm[8,9]. Further, natural products library was used to study the ADMET properties such as Blood-brain barrier (BBB) permeability, Solubility, Human intestinal absorption (HIA), Oral Bioavailability and Hepatotoxicity[10,11,12]. Density Functional Theory based descriptor such as Highest Occupied Molecular Orbital Energy (HOMO) and Lowest Unoccupied Molecular

Orbital's (LUMO) are also annotated in order to reveal their reactivity to the target protein. A set of drug molecules from the Drug Bank was retrieved and 925 drugs were selected as reference to analysis the natural products library. Drug Library was also used to prepare similar to the NPs library for further analysis (Table 7.1).

Table 7.1: Molecular Descriptors of NPs and Drugs

Descriptor Variable	NPs (505 Molecules)				Drugs (925 Molecules)			
	Min	Max	Mean	Std. Dev.	Min	Max	Mean	Std. Dev.
*n*HBD	0	7	1.400	1.354	0	7	1.164	0.994
*n*HBA	0	12	3.228	2.168	0	9	3.489	1.465
MW	44.01	806.9 6	251.16	107.82	28.013	891.53	309.25	93.84 2
MFPSA	0	0.825	0.221	0.170	0	1	0.191	0.110
*n*Rotatable Bonds	0	16	2.815	2.926	0	21	4.290	2.947
*n*Rings	0	8	2.375	1.772	0	8	2.674	1.392
ALogP	4.408	6.967	2.632	2.128	-8.065	8.843	2.654	1.622
*n*Aromatic Rings	0	4	0.859	0.874	0	4	1.398	0.915

*n*HBD: Number of Hydrogen Bond Donor; *n*HBA: Number of Hydrogen Bond Acceptor; MW: Molecular Weight; ALogP: Water/Octanal Partition Coefficient; MFPSA:Molecular Fractional Polar Surface Area

7.2.2 Collection of T2DM Drug Targets

Twenty four proteins were selected on the basis of their association with insulin resistance and T2DM. The 3D structures of these proteins were retrieved from the Protein Data Bank (PDB) of Research Collaboratory for Structural Bioinformatics (RCSB) as presented in Table 7.2. All the structures were cleaned and optimized using Steepest Descent Algorithm (200 steps) at Protein Preparation module of DS v4.5. The potential ligand binding site of all the structures was further computed using the Edit and Built binding site tool of DS v4.5. The resolution of the protein targets were in the range of 1.55 to 3.0 Å.

Table 7.2: 24 target proteins involved in the pathogenesis of insulin resistance and T2DM pathway

Sl No.	Proteins	Code name	PDBID	Resolution (Å)	PM ID
1	Toll Like Receptor 4	TLR4	2Z65	2.7	[13]
2	Nuclear Factor κB P50	NFkBP50	1SVC	2.6	[14]
3	Protein Kinase C θ	PKC θ	1XJD	2.0	[15]
4	Peroxisome Proliferator-Activated Receptor γ	PPAR γ	2P4Y	2.25	[16]
5	Dipeptidyl Peptidase 4	DPP 4	1RWQ	2.2	[17]
6	Glucokinase	GK	1V4S	2.3	[18]
7	Cytochrome P450	CYP450	1W0E	2.8	[19]
8	Aldose reductase	AR	3RX3	1.95	[20]
9	Protein Tyrosine Phosphatase 1B	PTP1B	2F70	2.12	[21]
10	Phosphatase and Tensin Homolog	PTEN	1D5R	2.1	[22]
11	Glycogen synthase kinase 3β	GSK3B	1H8F	2.8	[23]
12	Peroxisome Proliferator-Activated Receptor α	PPARα	1I7G	2.2	[24]
13	Glycogen phophorylase	GP	1Z8D	2.3	[25]
14	Adenosine Monophosphate Activated Protein Kinase	AMPK	2V92	2.4	[26]
15	Glucagon Like Peptide-1	GLP-1	3IOL	2.1	[27]
16	Pyruvate dehydrogenase kinase	PDK	3D2R	2.03	[28]
17	Carbonic anhydrase 1	CA1	2FOY	1.55	[29]
18	Carbonic anhydrase 2	CA2	2VVB	1.66	[30]
19	Growth factor receptor-bound protein 2	GRB2	1IO6	-	[31]
20	Peroxisome Proliferator-Activated Receptor -δ	PPAR-δ	2ZNP	3.0	[32]
21	Insulin-like growth factor 1 receptor kinase	IGF-1R	1K3A	2.1	[33]
22	11-beta hydroxysteroid dehydrogenase 1	11β-HSD1	3PDJ	2.3	[34]
23	Estrogen receptor	ER	3ERT	1.9	[35]
24	Glucocorticoid receptor	GR	3K22	2.1	[36]

7.2.3 Chemical Space Analysis

Principal component analysis (PCA) is an orthogonal linear statistical transformation method which can transform the data into a new coordinate system in a three dimensional system. Principal component analysis (PCA) was conducted on the NPs by using the *Library Analysis module* of DS v4.5. In a PCA model, variance of the data which was maximized on the first coordinate was called first principal component and rest of variance maximized on the second coordinate, and so on[37,38]. Herein, the NPs library for Space analysis was used along with the drug library as reference.

7.2.4 Molecular Docking

In silico molecular docking analysis was performed using the LibDock docking algorithms of Discovery Studio (DS) v3.5 software. The LibDock algorithm is based on the Diller and Merz algorithm. The LibDock methodology was originally developed to handle the rapid docking analysis of combinatorial libraries of the compounds with the goal of prioritizing the selection of libraries rather than rank ordering the compounds themselves[39,40]. The four functional aspects of using this algorithm are conformation generation of the ligands, creation of a binding site image (hot spot identification), matching the binding site image and the ligand, and a final optimization stage and scoring. Docking was performed for all the 505 compounds against the entire Receptor model as shown in the Table 7.2. Docking result was analyzed based on the "LibDock" score. The compounds that obtained more than 100 LibDock score were further considered as selected for the Ligand-Protein Network analysis[41].

7.2.5 Network Pharmacology

Ligand-Target Networking analysis is a well established method to reveal the poly pharmacological phenomenon of natural products towards their disease targets. Herein, the docking score (LibDock Score) was used to develop the NPs-Target Network. The compounds with LibDock > 100 were subjected to develop the Network Pharmacology Modeling. The network comprised of nodes and edges where the nodes represent molecular species (compounds and proteins), and the edges specify intermolecular interactions connecting the nodes (compound– target

or target– target interactions). Thus, the complex relationships between the compounds and their targets can be developed. The "*NPs – Target network*" (NPsTN) was developed based on the combination of the predicted compounds and all the 24 drug targets (Table 7.1). In addition, the important parameters such as Degree, Stress, Betweenness Centrality, Closeness Centrality and Average Shortest Path Length were also computed to establish the *NPs – Target* networking relationship. In order to develop this relationship, the Cytoscape v3.3.0 was employed. Cytoscape software is used to visualize the biomolecular interaction networks and biological pathways. It also helps in integrating these networks with annotations, gene expression profiles and other state data and making it a unified conceptual framework[42]. The networking parameters were also analyzed using the Network Analyzer Plugin.

7.2.6 DFT Computation

Density Functional Theory (DFT) is a computational quantum mechanical modelling method to examine the electronic structure of matter and also to find out the orbital energy values of compounds[43]. Herein, the DFT computation was employed to determine the most effective compounds as a type 2 diabetes mellitus inhibitor. From the network analysis, the compounds having the degree ≥ 10were further subjected to DFT analysis. Frontier Orbital energy descriptor namely HOMO and LUMO were calculated for all the screened compounds by using B3LYP module of DS. Further, compounds with least band energy gap (LUMO-HOMO) were selected as suitable natural products with multi targeted Type 2 diabetes mellitus inhibitors.

7.3 Results

7.3.1 ADMET and Physicochemical property analysis

The pharmacokinetics properties of a molecule are carried out by ADMET study where absorption, distribution, metabolism, excretion and toxicity of the compound are investigated. To select the drug like compound from the entire dataset ADMET plot was prepared which is depicted in the Figure 7.1. Among all the 799 natural products, only 505 compounds satisfied all the criteria of ADMET

prediction. These 505 NPs were considered as drug like compounds and used for the further studies.

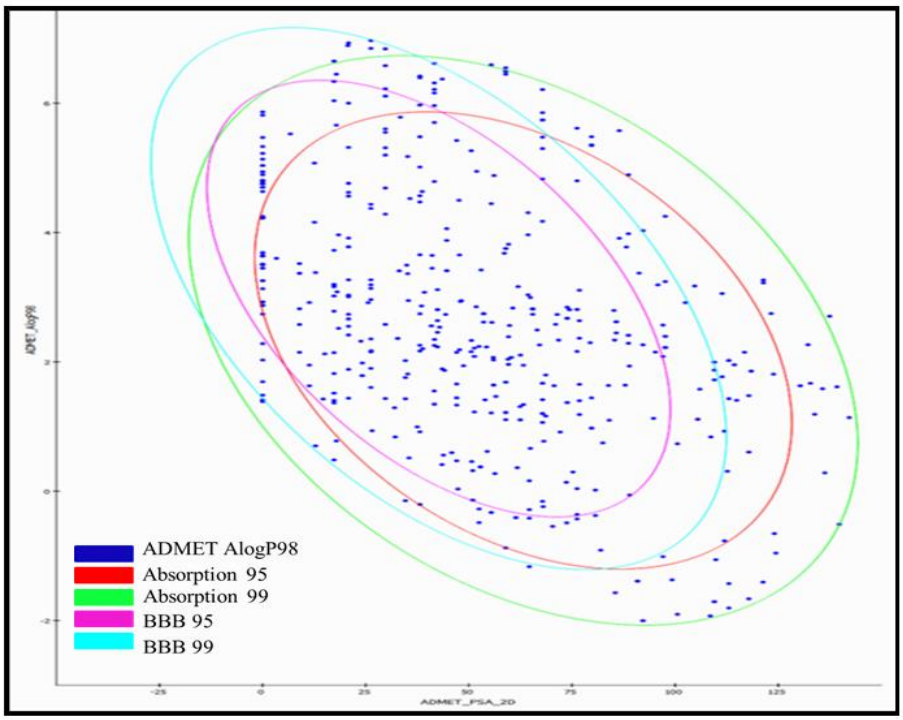

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Figure 7.1: ADMET plot of NPs Library.

To understand the biological activities including metabolism, toxicity, pharmacokinetics and pharmaceutical properties of a compound, the physicochemical properties are determined which depend on the structure of the compound. The physicochemical properties of the 505 natural products (with optimum ADME/Tox score) were predicted and compared with a set of 925 known drugs retrieved from the Drug Bank (Table7.1). From the study, it was found that most of the natural products obey the Lipinski's rules of five with mean H-bond donor < 5 and mean H-bond acceptor < 10. The average molecular weight of the natural products is less than 500 Da. Similarly, the mean value of ALogP was found to be less than 5. A similar set of results were obtained in the case of the Drug bank compounds. The *n*Rotatable Bonds was also determined and the mean value was found to be less than 10, suggesting that the compounds would have good oral bioavailability. The mean value of the *n*Rings and the *n*Aromatic Rings were also predicted for both the natural products Library and the Drug Library. Very close values were found between them as presented in the Table 7.1.

7.3.2 Principle Component analysis

The natural products and the Drug Library were further compared using the Principal Component analysis (PCA) to visualize the distribution in the chemical space. The 3D descriptors (Table 7.1) were used to develop the PCA Model. From the PCA analysis, it has been observed that the distribution of drug like natural products (Yellow Sphere) are similar to the 3D space occupied by the compounds retrieved from the Drug Bank database (Blue Sphere) indicating the presence of drug like properties in natural products.

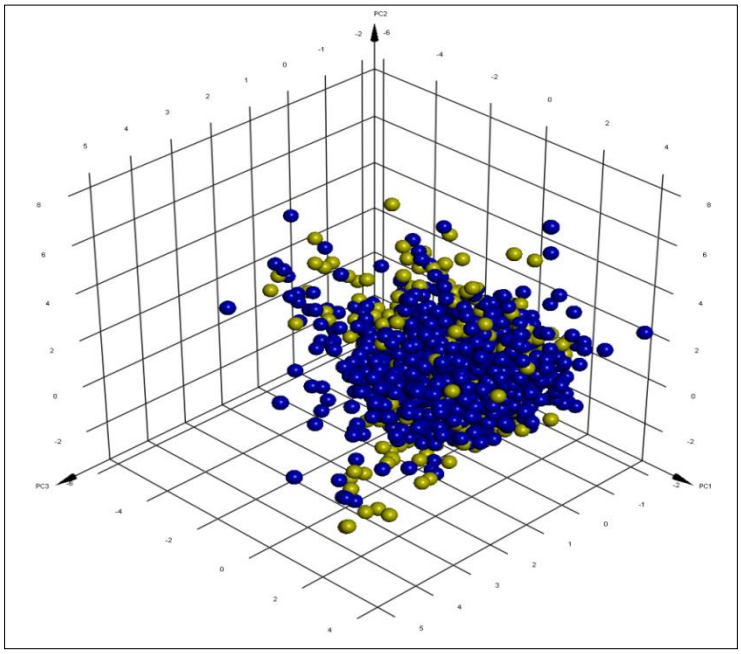


Figure 7.2: PCA Model of NPs (Yellow Sphere) and Drugs (Blue Sphere)

7.3.3 Molecular Docking Analysis

Docking is a suitable approach to understand the atomic level interactions of novel natural products to its specific targets[44]. In the current investigation, molecular docking was carried out for the entire 505 drugs like natural products, against 21 proteins that are associated with insulin resistance and T2DM. In this study, LibDock score 100 was used as the threshold limit to pick the best ligands for the prediction of active molecules to their targets. Aldose reductase was found to be the most potential drug target, where the highest numbers of natural products comprising of 141 compounds (27%) were docked with LibDock Score > 100 as presented in the Figure 7.3 followed by 11β-HSD1 (18%), AMPK (12.27%),

GR(11.48%), PPARγ (10.09%), PPARα (9.1%), ER (8.31%), CA2 (8.31%), GLP1 (5.94%), PTP1B (4.95%), PDK1 (4.75%), GK (4.75%), PKCθ (4.35%), PTEN (4.15%), IGF (2.97%), CYP450 (2.77%), CA1 (2.37%), TLR4 (1.78) and PPARδ (0.99%). A minimum of three natural products were found to be docked at LibDock value >100 with DPP4 and GSK3β receptor model with 0.59%. On the other hand no compound was docked with GRB2 with LibDock value more than equal to 100.

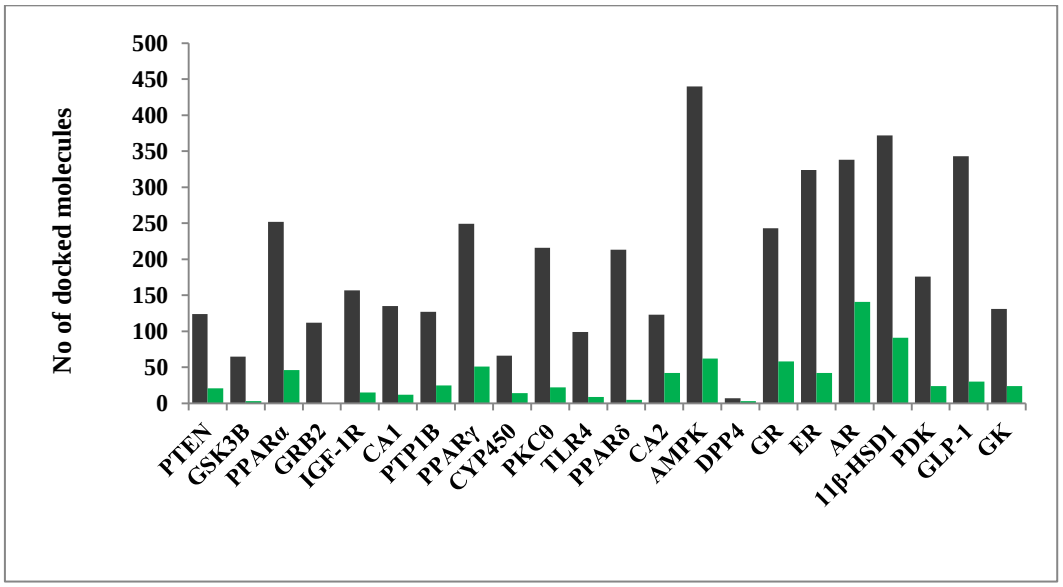


Figure 7.3: Bar diagram of the docking result. The black bars represent the total number of Compounds docked with various receptors; Green bars represent the number of compounds with LibDock > 100

7.3.4 NPs-Target Network Analysis

There are several complex diseases which involve the interactions of multiple genes as well as functional proteins[45]. In such cases, network pharmacology helps in solving how and where in the disease network, one target inhibits or activates the disease phenotypes, and assists in systematic characterization of drug targets to reduce the challenges of drug discovery[46]. To determine the relationship between compounds of the traditionally used antidiabetic plants of NE India to the disease, network pharmacology approach was used. Since several natural products have better binding affinity to the target proteins associated with insulin resistance and T2DM, natural products - target network (NTN) was developed on the basis of LibDock result using natural products - target binding data, and the Degree ≥10 was considered for the

further study. In NTN, a total of 188 compounds and 21 protein targets were used. The network comprised of 209 nodes and 736 edges with average degree of 7.04.

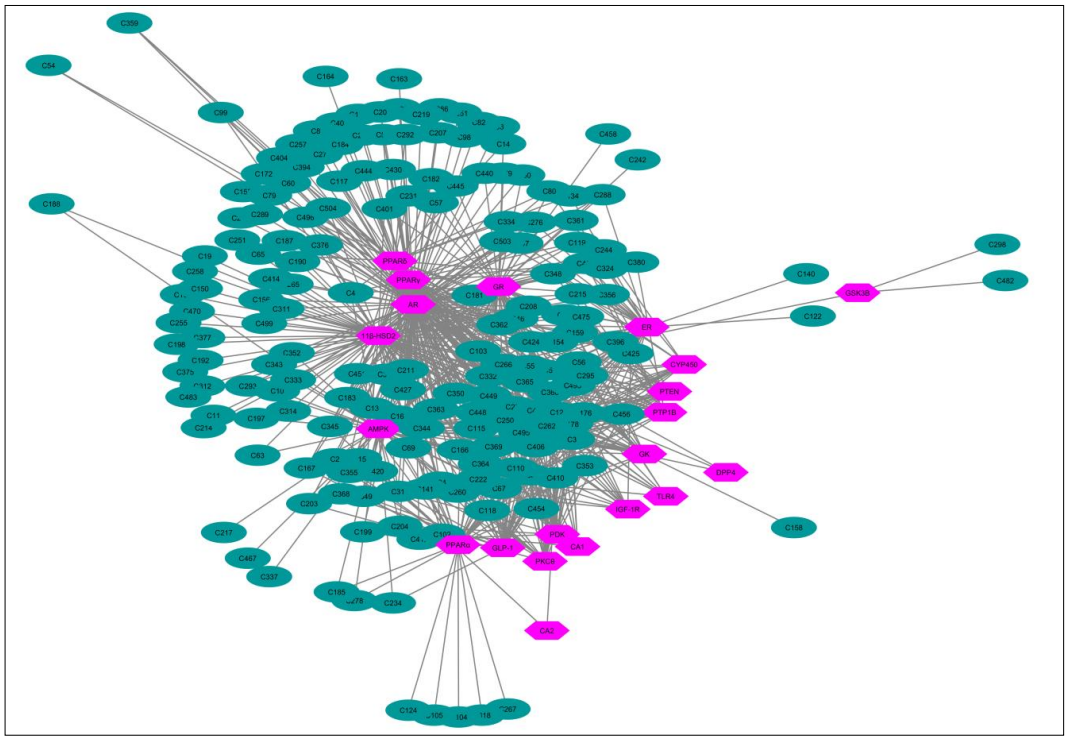


Figure 7.4: Natural Products - Target Network (NTN) between natural products with LibDock score >100 and their targets. The green coloured circles represent the natural products and the pink coloured hexagons represent the target proteins. The grey coloured edges represent the relation between the nodes.

From the network analysis it was revealed that 14 natural products can bind to minimum 10 different receptors at a time with good binding affinity (Table 7.3) where the compounds C262, C3, C171 and C176 can bind to18 different receptors with better binding affinity. Along with the degree, other important key parameters such as Betweenness Centrality, Closeness Centrality were also determined. Betweenness Centrality varied between 0.005 and 0.018 whereas the Closeness Centrality ranged from 0.513 to 0.465.

From the NTN analysis, of the 14 natural products targeting multiple target proteins, 4 compounds were found to have relationship with 18 numbers of targets out of 21 proteins used for the study. Compound C12 and C495 formed relationship network with 17 and 16 numbers of targets respectively and so on.

Table 7.3: Network topology of Natural Products and Target Network (NTN) with degree ≥ 10.

Compounds ID	Average Shortest Path Length	Betweenness Centrality	Closeness Centrality	Degree	Stress
C262	1.94711538	0.01459936	0.51358025	18	46944
C3	1.94711538	0.01802189	0.51358025	18	45792
C171	1.94711538	0.01459936	0.51358025	18	46944
C176	1.94711538	0.01788283	0.51358025	18	47172
C12	1.95673077	0.01374114	0.51105651	17	45254
C495	1.96634615	0.01221954	0.50855746	16	43310
C365	2.05288462	0.00787117	0.48711944	13	30284
C250	1.99519231	0.00965482	0.50120482	13	37558
C166	2.02403846	0.00855239	0.49406176	12	31790
C226	2.05288462	0.00735451	0.48711944	11	29030
C405	2.07211538	0.00622606	0.48259861	11	23680
C406	2.11057692	0.00524846	0.4738041	11	19712
C410	2.14903846	0.00989057	0.46532438	11	23260
C449	2.05288462	0.00675471	0.48711944	10	26636

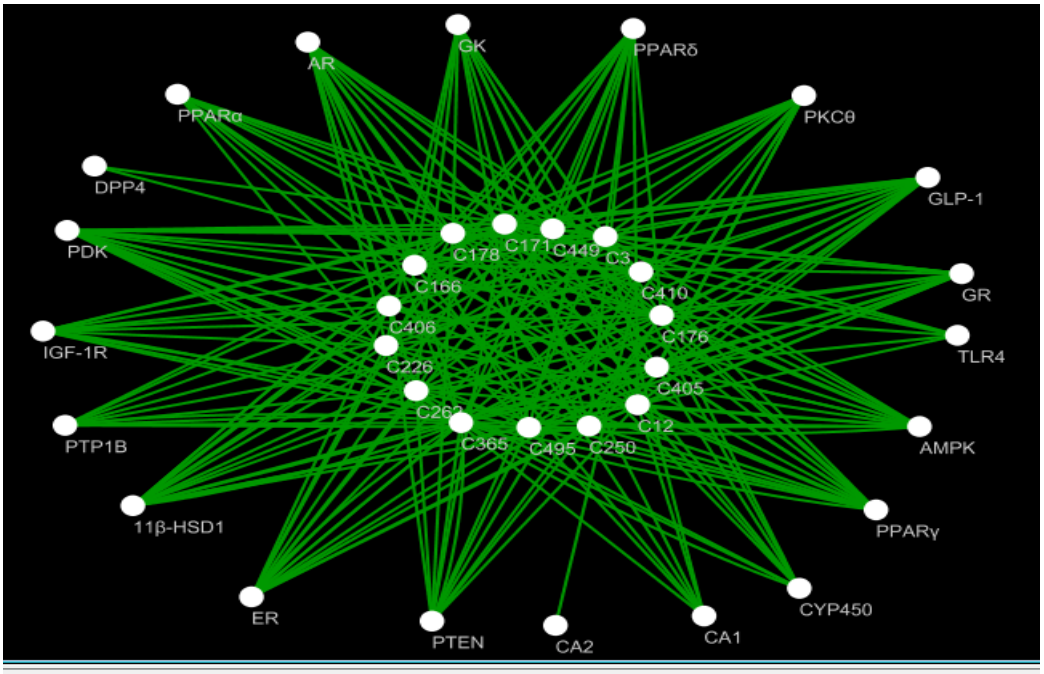


Figure 7.5: NPs- Target Network (NTN) between natural products with degree ≥ 10 and their targets. The yellow coloured circles represent the NPs and the light blue

coloured circles represent the target proteins. The deep blue coloured edges represent the relation between the nodes.

7.3.5 DFT Computation

A group of 14 numbers of natural products targeting more than 10 targets were subjected to DFT analysis to find out the efficient molecules in terms of their binding energy. DFT-based descriptors such as atomic charges, molecular orbital energies, frontier orbital densities, and atom-atom polarizabilities are very useful in predicting the reactivity of atoms in molecules[47]. The energy difference between HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) of a compound is known as HOMO-LUMO gap. The lower the HOMO-LUMO gap, the more reactive the molecules are considered, possessing lower kinetic stability. The reason for this is because it is energetically unfavorable to add electrons to a high-lying LUMO by extracting electrons from a low-lying HOMO, in order to form the activated complex of any potential reaction[48].

Table 7.4: Screened natural products with LUMO-HOMO orbital energy value

Compound ID	Compound Name	HOMO	LUMO	ΔE (LUMO-HOMO)
C405	Aurapten	-0.227	-0.058	0.169
C226	Gigantean	-0.193	-0.019	0.174
C365	Cannabichromene	-0.193	-0.013	0.179
C262	Eleostearic acid	-0.190	-0.010	0.220
C176	Marmesinin	-0.223	0.002	0.226
C171	Lonoleic Acid	-0.224	0.003	0.227
C3	Z_Z-4_16-octadecadien-1-ol Acetate	-0.226	0.008	0.234
C12	Vernolic acid	-0.233	0.005	0.239
C495	1-(14-methylhexadecanoyl) pyrrolidine	-0.229	0.038	0.268
C250	Ethyl hexadecanoate	-0.268	0.008	0.276

From the DFT study it was found that the compounds,*viz*, aurapten (C405), Gigantean (C226) and Cannabichromene (C365) have the lowest HOMO-LUMO gaps as a result of which these 3 compounds were more reactive for their targets with good binding affinity. The network property revealed that these 3 compounds

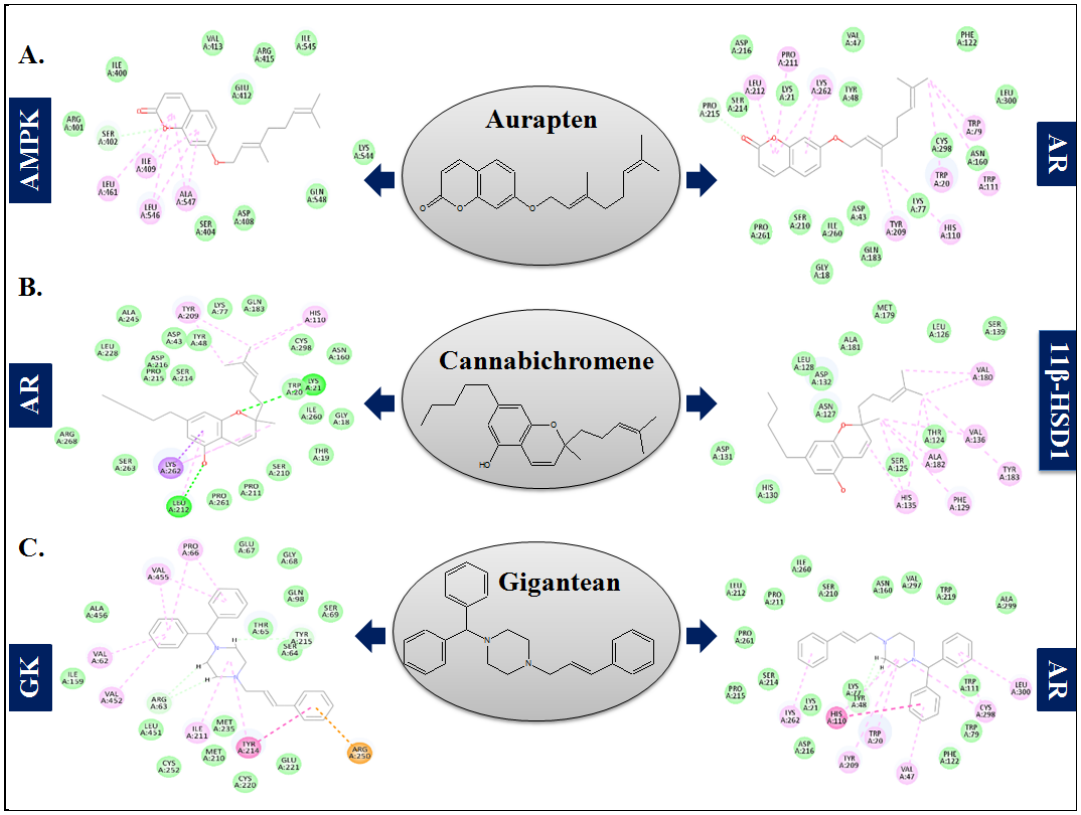
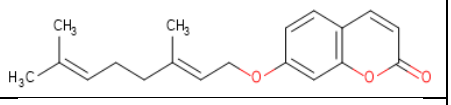
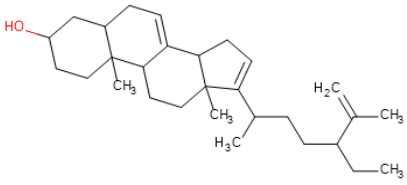
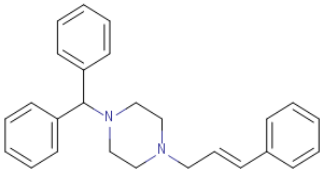


Figure 7.6: Docking view of best 3 compounds with receptors having highest binding affinity. Docking of Aurapten with AMPK and AR with LibDock score 115.788 and 140.027 respectively (A), Docking of Cannabichromene with AR and 11β-HSD1 with LibDock score 132.302 and 120.071 respectively (B), Docking of Gigantean with GK and AR with LibDock score 149.126 and 151.455 respectively (C)

can target multiple numbers of receptor proteins where cannabichromene showed its binding affinity to maximum 13 receptors associated with type 2 diabetes mellitus. Table 7.5 represents the 2D structures of the most potent ligands among all the compounds present in 25 antidiabetic plants used by various ethnic groups present in the north eastern part of India.

Table 7.5: 2D representation of potential natural products

Aurapten	
Cannabichromene	
Gigantean	

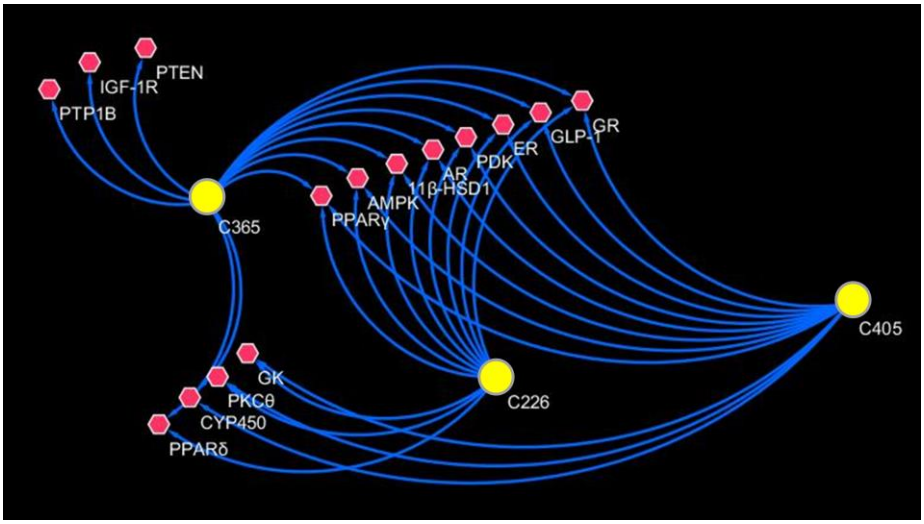


Figure 7.7: Natural Products - Target Network (NTN) between 3 potential natural products and their targets. The yellow coloured hexagons represent the natural products and the pink coloured hexagons represent the target proteins. The blue coloured edges represent the relation between the nodes.

7.4 Discussion

Although there are plenty of drugs currently available in the market, it has to be accepted that the traditional knowledge on the use of medicinal plants plays a vital role in the important discoveries in the field of drug development[49,50]. Due to their structural diversity, they provide a limitless source for developing new lead entities[51]. From 1981 to 2010, 1135 new drugs were approved by the US Food and Drug Administration (FDA) out of which 34% were of natural origin[52]. But

isolation of a single bioactive compound from the traditionally used plants sometimes may not be very effective for the treatment of disease. Herbal derived compounds acts synergistically or additively to exert its mechanism of action. Therefore, from the pharmacological point of view, the traditional preparation containing a mixture of compounds may have the potential to treat the complex disease like T2DM by targeting multiple therapeutically important proteins[53]. It is worth mentioning that the North East India is known for its diversity in the use of medicinal plants based on inherited knowledge by the different ethnic groups inhabiting in this area. The use of several plant based resources for the treatment of diabetes by different communities has been reported with few scientific validations, but a huge number of plants have not been documented yet. Since, different parts of these plants show their efficacy to T2DM treatment alone, a hypothesis was generated to mix these traditionally used antidiabetic plants of the NE India as a form of combination therapy which would be more effective. As all the compounds are not equally important for the disease targets, hence, finding out the active compounds from all these antidiabetic plants and their molecular targets with proper scientific validation would be helpful for decreasing the risk of having T2DM. In this study the network pharmacology based virtual screening of natural products has been studied for identifying the active principles for the treatment of insulin resistance and T2DM.

Network pharmacology based study helps in deciphering the underlying mechanism of biological system and helps in several aspects in drug discovery including target identification, lead discovery and optimization, mode of action and safety assessment[54]. From the NTN analysis, the best molecules having good affinity to multiple numbers of target proteins were further analyzed. Since the network was developed on the basis of LibDock study, a large scale interaction was obtained between natural products and the targets. Hence DFT calculation was performed considering the compounds having the degree more than 10 with maximum values of betweenness centrality. Degree is nothing but the number of neighbours of a node whereas betweenness represents the role of nodes in transmission of information in a network. So, Degree and betweenness centrality act as a primary parameters in evaluating the importance of the node in a

network[55]. From the DFT analysis, 3 best active compounds were obtained, *viz.* aurapten, gigantean and cannabichromene for their targets on the basis of their reactivity. These compounds were reported to be present in *Aegle marmelos (L) Corr Roxb*., *Calotropis gigantean (L) W Aiton.* and *Cannabis sativa Linn.* respectively[56,57]. Moreover, it has been reported that auraptene shows antidiabetic activity by modulating lipid metabolism through PPARα activation[58]. There is no report of cannabichromene and gigantean as anti hyperglycaemic agent. Rather the derivatives of cannabichromene reduce inflammation with its high anti-inflammatory effect[59]. Since inflammation is one of the responsible factors for developing insulin resistance cannabichromene may ameliorate insulin resistance by lowering the inflammation in the body[60].

From this study the probable multitargeting therapeutic choices are demonstrated for the treatment of insulin resistance and T2DM, based on network pharmacology and DFT based approach. The concoction of these compounds may reduce the risk of T2DM which may be validated after further *in vitro* and *in vivo* experiments.

References

1. Hopkins, A. L. Network pharmacology: the next paradigm in drug discovery, *Nature Chemical Biology* **4**(11), 682--690, 2008.
2. Hopkins, A. L. Network pharmacology, *Nature Biotechnology* **25**(10), 1110--1111, 2007.
3. Roth, B. L., et al. Magic shotguns versus magic bullets: selectively non-selective drugs for mood disorders and schizophrenia, *Nature Reviews Drug Discovery* **3**(4), 353--359, 2004.
4. Wu, X., et al. Network-based global inference of human disease genes, *Molecular Systems Biology* **4**, 1--11, 2008.
5. Zhang,G., et al. Network Pharmacology: A new approach for chinese herbal medicine research, *Evidence-Based Complementary and Alternative Medicine* **2013** (621423), 9 pages, 2013
6. Shannon,P., et al. Cytoscape: A software environment for integrated models of biomolecular interaction networks, *Genome Res.* **13**, 2498--2504, 2003.
7. John, S. S., et al. Development, evaluation and application of 3D QSAR pharmacophore model in the discovery of potential human renin inhibitors, *BMC Bioinformatics* **12**(14), 4, 2011.
8. Arooj, M. et al. 3D QSAR pharmacophore modeling, in silico screening, and density functional theory (DFT) approaches for identification of human chymase inhibitors, *Int J Mol Sci* **12**, 9236--64, 2011.
9. Niu, M. et al. Pharmacophore modeling and virtual screening for the discovery of new type 4 cAMP phosphodiesterase (PDE4) inhibitors, *PLoS One* **8**, 82360, 2013
10. Xia, X., et al. Classification of kinase inhibitors using a Bayesian model, *J Med Chem* **47** ,4463--70, 2004
11. Cheng, A., & Merz, K.M. Jr. Prediction of aqueous solubility of a diverse set of compounds using quantitative structure-property relationships,*J Med Chem* **46**, 3572--80, 2003.
12. Egan, W.J. & Lauri, G. Prediction of intestinal permeability, *Adv Drug Deliv Rev* **54**, 273--89, 2002.

13. Kim, H.M., et al. Crystal structure of the TLR4-MD-2 complex with bound endotoxin antagonist Eritoran, *Cell* **130**, 906--17, 2007.

14. Muller, C.W., et al. Structure of the NF-kappa B p50 homodimer bound to DNA, *Nature* **373**, 311--7, 1995.

15. Xu, Z.B., et al. Catalytic domain crystal structure of protein kinase C-theta (PKCtheta), *J Biol Chem* **279**, 50401--9, 2004.

16. Einstein, M., et al. The differential interactions of peroxisome proliferator-activated receptor gamma ligands with Tyr473 is a physical basis for their unique biological activities, *Mol Pharmacol* **73**, 62--74, 2008.

17. Peters, J.U., et al. Aminomethylpyrimidines as novel DPP-IV inhibitors: a 10(5)-fold activity increase by optimization of aromatic substituents, *Bioorg Med Chem Lett* **14**, 1491--3, 2004.

18. Kamata, K., et al. Structural basis for allosteric regulation of the monomeric allosteric enzyme human glucokinase, *Structure* **12**, 429--38, 2004.

19. Williams, P.A., et al. Crystal structures of human cytochrome P450 3A4 bound to metyrapone and progesterone, *Science* **305**, 683--6, 2004.

20. Zheng, X., et al. The molecular basis for inhibition of sulindac and its metabolites towards human aldose reductase, *FEBS Lett* **586**, 55-9, 2012.

21. Klopfenstein, S.R., et al. *1,2,3,4-Tetrahydroisoquinolinyl sulfamic acids as phosphatase PTP1B inhibitors*, *Bioorg Med Chem Lett* **16**, 1574--8, 2006.

22. Lee, J.O. et al., Crystal structure of the PTEN tumor suppressor: implications for its phosphoinositide phosphatase activity and membrane association, *Cell* **99**, 323-34, 1999.

23. Dajani, R., et al. Crystal structure of glycogen synthase kinase 3 beta: structural basis for phosphate-primed substrate specificity and autoinhibition, *Cell* **105**, 721--32, 2001.

24. Cronet, P., et al. Structure of the PPARalpha and -gamma ligand binding domain in complex with AZ 242; ligand selectivity and agonist activation in the PPAR family, *Structure* **9**,699--706, 2001.

25. Lukacs, C.M., et al. The crystal structure of human muscle glycogen phosphorylase a with bound glucose and AMP: an intermediate conformation with T-state and R-state features, *Proteins* **63**, 1123--6, 2006.

26. Xiao, B., et al. Structural basis for AMP binding to mammalian AMP-activated protein kinase,*Nature* **449**, 496--500, 2007.

27. Underwood, C.R., et al. Crystal structure of glucagon-like peptide-1 in complex with the extracellular domain of the glucagon-like peptide-1 receptor, *J Biol Chem* **285**, 723--30, 2010.

28. Wynn, R.M., et al. Pyruvate dehydrogenase kinase-4 structures reveal a metastable open conformation fostering robust core-free basal activity, *J Biol Chem* **283**, 25305--15, 2008.

29. Jude, K.M., et al. Ultrahigh resolution crystal structures of human carbonic anhydrases I and II complexed with "two-prong" inhibitors reveal the molecular basis of high affinity, *J Am Chem Soc* **128**, 3011--8, 2006.

30. Sjoblom, B., et al. Structural study of X-ray induced activation of carbonic anhydrase, *Proc Natl Acad Sci USA* **106**, 10609--13, 2009.

31. Kawasaki, M., et al. Solution Structure of the C-Terminal SH3 Domain of Grb2 Complexed with a Ligand Peptide: A Ligand Exchange Model of the SH3 Domain. (http://www.rcsb.org/pdb/explore.do?structureId=1io6)

32. Oyama, T., et al. Adaptability and selectivity of human peroxisome proliferator-activated receptor (PPAR) pan agonists revealed from crystal structures, *Acta Crystallogr D Biol Crystallogr* **65**, 786--95, 2009.

33. Favelyukis, S., et al. Structure and autoregulation of the insulin-like growth factor 1 receptor kinase, *Nat Struct Biol* **8**, 1058--63, 2001.

34. Sun, D., et al. Synthesis and optimization of novel 4,4-disubstituted cyclohexylbenzamide derivatives as potent 11beta-HSD1 inhibitors, *Bioorg Med Chem Lett* **21**, 405--10, 2011.

35. Shiau, A.K., et al. The structural basis of estrogen receptor/coactivator recognition and the antagonism of this interaction by tamoxifen, *Cell* **95**, 927--37, 1998.

36. Biggadike, K., et al. Design and x-ray crystal structures of high-potency nonsteroidal glucocorticoid agonists exploiting a novel binding site on the receptor, *Proc Natl Acad Sci USA* **106**, 18114--9, 2009.

37. Zhang, X., et al. Network pharmacology study on the mechanism of traditional Chinese medicine for upper respiratory tract infection, *Mol Biosyst* **10**, 2517--25, 2014.

38. Gu, J., et al. Use of natural products as chemical library for drug discovery and network pharmacology, *PLoS One* **8**, e62839, 2013.

39. Diller, K.M. & Jr., M. High throughput docking for library design and library prioritization, *Proteins* **43**, 113--24, 2001.

40. Rao, S.N., et al. Validation studies of the site-directed docking program LibDock, *J Chem Inf Model* **47**, 2159--71, 2007.

41. Jiang, L., et al. Virtual Screening and Molecular Dynamics Study of Potential Negative Allosteric Modulators of mGluR1 from Chinese Herbs, *Molecules* **20**, 12769--86, 2015.

42. Shannon, P., et al. Cytoscape: a software environment for integrated models of biomolecular interaction networks, *Genome Res* **13**, 2498--504, 2003.

43. Kavitha, R., et al. Pharmacophore modeling, virtual screening, molecular docking studies and density functional theory approaches to identify novel ketohexokinase (KHK) inhibitors, *Biosystems* **138**, 39--52, 2015.

44. Ma, D.L., et al. Molecular docking for virtual screening of natural product databases, *Chemical Science* **2**, 1656--1665, 2011.

45. Hopkins, A.L., Network pharmacology: the next paradigm in drug discovery, *Nat Chem Biol* **4**, 682--90, 2008.
46. Zhang, G.B., et al. Network pharmacology: a new approach for chinese herbal medicine research, *Evid Based Complement Alternat Med* **2013**, 621423, 2013.
47. Haruaki, T., Editorial: Current status and perspective on drug targets in tubercle bacilli and drug design of antituberculous agents based on structure-activity relationship, *Current pharmaceutical design* **20**(27), 4305--4306, 2013.
48. Aihara, J. C., Reduced HOMO-LUMO Gap as an Index of Kinetic Stability for Polycyclic Aromatic Hydrocarbons, *J. Phys. Chem. A* **103**, 7487--7495, 1999.
49. Ngo, L.T., et al. 21st century natural product research and drug development and traditional medicines, *Natural product reports* **30**(4), 584--592, 2013.
50. David, B., et al. The pharmaceutical industry and natural products: historical status and new trends, *Phytochem Rev* **14**, 299--315, 2015.
51. Vafa, A., & Heinrich, M. Natural products and drug discovery: a survey of stakeholders in industry and academia, *Frontiers in pharmacology* **6,** 2015.
52. Harvey, A.L., et al. The re-emergence of natural products for drug discovery in the genomics era, *Nature Reviews Drug Discovery* **14**, 111--129, 2015.
53. Gertsch, J. Botanical drugs, synergy, and network pharmacology: forth and back to intelligent mixtures, *Planta medica* **77**(11), 1086--1098, 2011.
54. Zhang, A., et al. Predicting new molecular targets for rhein using network pharmacology, *BMC Systems Biology* **6(**1), 20, 2012.
55. Gu, J., et al. Use of Natural Products as Chemical Library for Drug Discovery and Network Pharmacology, *PLOS One* **8**(4), 1--10, 2013.

56. Tehranipour, M., et al. Antidiabetic effect of *Cannabis sativa* extract in wister rat, International Journal of Chemical And Pharmaceutical Research, 1(6), 124--130,2012.
57. Devi, A.P., Plants used by Meitei Community of Manipur for the treatment of Diabetes, *Assam University Journal of science and Technology* **7**(1), 63--66, 2011.
58. Nobuyuki, T., et al. Auraptene regulates gene expression involved in lipid metabolism through PPARα activation in diabetic obese mice, *Molecular nutrition & food research* **55**(12), 1791--1797, 2011.
59. Turner, C. E., &Elsohly,M. A. Biological activity of cannabichromene, its homologs and isomers, *The Journal of Clinical Pharmacology* **21**(1), 283--291, 1981.
60. Luca, C., et al. Inflammation and insulin resistance, *FEBS Letters* **582**, 97--105, 2008.