Section A-Research paper

Possible insilico exploration of alpinia mutica and tradescantia spatheca for diabetes mellitus

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Abstract

Molecular docking is computed aided tool to predict the interaction between protein and ligand. Several herbs were used in diabetic mellitus. In the current research article two medicinal plants naming *Alpinia mutica* and Tradescantia *spatheca* are screened against 4 protein to determine its *In silico* anti-diabetic potential. Fourty two constituents from *Alpinia mutica* and nineteen constituents from *Tradescantia spatheca* screened against targets namely Glutamine: Fructose-6-Phosphate Amindotransferase (GFAT,PDB ID-2ZJ3), Tetrameric 11b-HSD(PDB ID-1XU7), Aleglitaar (PDB ID-3G9E), Human SIRT6 (PDB ID-3K35) and protein tyrosine phosphatase - 1B(PDB ID-4Y14) were assessed. Molecular docking studies were performed using tool Autodock vina, biovia discovery studio and open bable, Additionally the Swiss ADME were utilized for its pharmacokinetic prediction. The docking studies with the ligands shows great inhibitory effect; In *Alpinia mutica*; 1,7-diphenyl-3-hydroxy-6-heptene5-one(-9.0kcal/mol) has the highest binding energy with protein 3K35;bisabolol(-8.1kcal/mol) with 2ZJ3; Flavokwain (-8kcal/mol) with 1XU7;1,7-diphenyl-3-hydroxy-6-heptene5-one(-6.9kcal/mol) with 4Y14 and Flavokwain (-7.8kcal/mol) with 3G9E.In *Tradescantia spatheca*, rutin (-10.1 kcal/mol),(-9.4 kcal/mol)and (-8.7 kcal/mol) respectively shows highest effect with 1XU7,2ZJ3 and 3G9E;bracteonalide A(-9.1kcal/mol) shows highest binding energy with 4Y14.

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INTRODUCTION

Diabetes is a growing metabolic disorder caused by disrupted metabolism of sugar, proteins well as fat. [1-2] It causes many problems because of decreased insulin secretion or working action of insulin and affect people of all age group. [3] Diabetes in children is easily identified by symptoms

like excessive urine, polydipsia, blurring of vision, loss of weight etc.[4] According to International Diabetes Federation , 10% of the world population will be affected by diabetes mellitus and the patients of diabetes will increase from 135 million in year 1995 to 350 million in 2030. [2] The process of generating energy from carbohydrates is called glycolysis. [5] The process of glycolysis cannot function properly due to complications related to pancreas, leading to high blood sugar resulting in high urination, excessive thirst and high appetite. [6] Oral antidiabetc drugs are facing many problems and drugs are facing clinical trials like PTP1-b inhibitors with no avail. [7-9] Ayurvedic drugs are being used in curing various diseases because of their origin and no after effects. [5] WHO has listed more than 21,000 plants which have extensive properties found around the world, Out of these, 2500 species are in India, and 150 of these species are being used commercially. [5] 90% of the population in the rural areas of developing countries depend on herbal medicines for their primary healthcare. Diabetes mellitus has two types, Type 1 mainly occurs in kids, because of autoimmune mediated destruction of pancreatic cell islets causing complete lack of insulin. Type 2, mostly affects adults and elderly people, which is caused because of insulin resistance or atypical insulin secretion. [5]
In present research work we are trying to find new cures using molecular docking. *Alpinia mutica* and *Tradescantia spatheca* are the two drugs were selected to screen its anti-diabetic activity.

Alpinia *is* the largest genera of the Zingiberaceae family which has about two hundred and thirty herbs widely distributed in Asia. Alpinia has 9 species of plants in southern India.[11-12] *Alpinia mutica* is a rhizomatous, perennial and aromatic herb native to Peninsular Malaysia and Thailand. [13-14] .*Alpinia Mutica* has a place with the Tribe Alpinieae of Alpinioideae sub family under the Zingiberaceae group of Zingiberales order. *Alpinia mutica* consist of several phytoconstituents such as 5,6-dehydrokwain, Flavokwain, flavokavain B, pinocembrins and 1, 7-diphenyl-5-hydroxy-6-hepten-3-one. [15-17]*Alpinia Mutica* leaves oil consist of sesquiterpenes with β-sesquiphellandrene as major component, with different constituent of rhizome oil. The essential oils present are monoterpene in nature. [18] The Fruit Oils of *Alpinia Mutica* consist of a-pinene, camphene, b-pinene, Myrcene, α-phellandrene, 1, 8-cineole, β(Z)-ocimene, (E)-β-ocimene-terpinene, terpinolene, Linalool, α fenchol, Camphor, Isoborneol, borneolterpinen, α-terpineol, 3- phenyl-2butanone, Citronellol, Geraniol, Geranial, bornyl acetate, carvacrol, α-cubebene, Geranyl acetate, α- copaene, β-elemene, β caryophyllene, α-bergamotene, γ-elemene, α-humulene, β-farnesen, ar-curcumene, zingiberene, α-farnesene, β-bisabolene, β-sesquiphellandrene, (E)-nerolidol, caryophyllene oxide, abisabolol, (E, E)-farnesol, (E, E)-farnesyl acetate, docosane, tricosane, tetracosane, pentacosane . [19-22]

Tradescantia is commonly known as ‘Spiderwort’,or oyster plant. [23] It is the second largest genus of the Commelnaceae family. [24-25] It has been used to treat infections since old time. Tradescantia’s roots helps in GIT infections as well as kidney infections. [26] The phytoconstituents present in *Tradescantia spatheca* are (±)-tradescantin , Hydroxytyrosol

,protocatechuic acid , oresbiusin A , 2-hydroxy-3′,4′- dihydroxyacetophenone , Tradecantoside , (S)-2-hydroxy-3-(4′- hydroxyphenyl) propanoic acid , (R)-2-hydroxy-3-(4′- hydroxyphenyl) propanoic acid ,latifolicinin C, latifolicin A ,latifolicin B,(6S,9R)-roseoside,Kaempferol , (2R,3R)-2,3-dihydroxy-2-methylbutyrolactone, Bracteanolide, 4-(3′,4′-dihydroxyphenyl)furan2(5H)-one , Epigallocatechin , Rhoeonin ,Peltatoside, rutin , ferulic acid , vanillic acid , glycosylated vanillic acid , p-coumaric acid, chlorogenic acid. [25, 27]

MATERIAL AND METHODS

Molecular Docking

Molecular docking is a useful computational technique for determining the protein ligand interaction at a target site.

Software and Database

Autodock_vina version 4.2.6 (https://vina.scripps.edu) software approaches were used to predict the in-silico interaction between active compounds of *Alpinia mutica* and *Tradescantia spatheca* to screen its anti-diabetic potential using proteins 1XU7,3G9E,3K35,2ZJ3 and 4Y14 for *Alpinia mutica* and four proteins for *tradescantia spatheca* 1XU7, 3G9E, 2ZJ3, 4Y14. BIOVIA Discovery Studio was downloaded from https://discover.3ds.com/ for visualization. [28] Open bable 3.1.1 was downloaded from http://openbabel.organd used to convert SDF to PDB format. [29] The calculations were performed on Windows 10 operating system.

Selection of protein and preparation of its structure

Isomerase domain of human glucose: fructose-6-phosphate Amidotransferase (PDB ID: 2ZJ3) with Resolution 1.90 Å, R-value free 0.217 and R-value work 0.185 were selected; Structure of protein tyrosine phosphatase 1B complexed with inhibitor (PDB ID:4Y14) with resolution 1.9 Å,R value free 0.266 and R value work 0.166 were selected. Aleglitaar. A new potent, and balanced dual ppara/g agonist for the treatment of type II diabetes(PBD ID:3G9E) with resolution 2.30 Å, R-Value Free 0.262 and R-Value Work 0.200 were selected. Crystal Structure of the Interface Open Conformation of Tetrameric 11b-HSD (PDB ID:1XU7) with resolution 1.80 Å,R value free 0.217 and R-Value Work 0.197 were selected and Crystal Structure of Human SIRT6(PDB ID:3K35) with resolution 2.00 Å, R-Value Free 0.267 and R-Value Work: 0.202 were selected

Ligand Selection

42 phytoconstituets of *alpinia mutica* and 19 phytoconstituents of *tradescantia spatheca* screen against several proteins. The 2D and 3D structures of these ligands in SDF format were downloaded from https://pubchem.ncbi.nlm.nih.gov Ligand preparation was performed in open bable 3.1.1 (http://openbabel.org). [29]

Target and Ligand Optimization

In molecular docking, an optimization algorithm was utilized to find a suitable binding pose of a ligand against a protein target to show high binding affinity. This algorithm plays a dynamic role

in determining the docking accuracy. A suitable binding pose was determined with autodock vina (version 4.2.6) and visualized with the help of BIOVIA Discovery Studio. [28, 30]

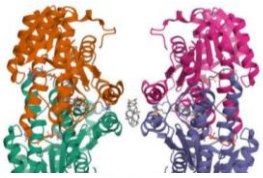
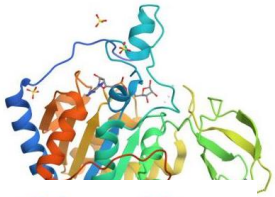
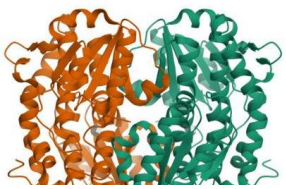
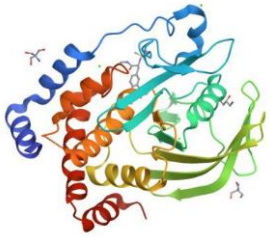
Analysis of Target Active Binding Sites

The active site of protein comprised of amino acids was determined by the CASTp tool (Computed Atlas for Surface Topography of Proteins) **(Table 1)** (http://sts.bioe.uic.edu). [31] interaction development of targeted protein PDB ID: 1XU7, PDB ID: 3G9E, PDB ID: 3K35, PDB ID: 2ZJ3 and PDB ID: 4Y14 was analysed with the help of BIOVIA Discovery Studio. After protein preparation, a single ligand is selected, and the receptor-ligand interaction is observed; the binding site and the expansion or SBD site sphere are edited. [32, 33]

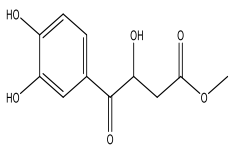
RESULTS AND DISCUSSION

The antidiabetic effects of several constituents of *Alpinia mutica* and *Tradescantia spatheca* using autodock vina were studied. Several protein structures were available for studying the antidiabetic effects of the phytoconstituents from *Alpinia mutica* and *Tradescantia spatheca* Finding suggested that potential interaction with the proteins and ligand for type 2 diabetes pathogenesis. Table no. 1 indicates the protein used in molecular docking study.

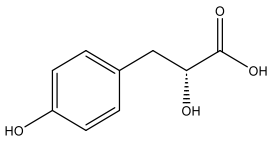
Table 1. 3D structure of 1XU7(a), 3G9E(b), 3K35(c), 2ZJ3(d) and 4Y14 (e) proteins

PDB ID	Name of protein	3D Structure
1XU7	Novel CDK-5 inhibitors - crystal structure of inhibitor EFQ with CDK-2	
3G9E	Aleglitaar. a new. potent, and balanced dual ppara/g agonist for the treatment of type II diabetes	
3K35	Crystal Structure of Human SIRT6	
2ZJ3	Isomerase domain of human glucose:fructose-6-phosphate amidotransferase	
4Y14	Structure of protein tyrosine phosphatase 1B complexed with inhibitor (PTP1B:CPT157633)	

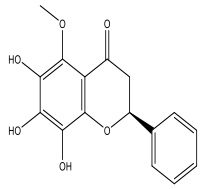
In this study ,we did literature study and we found out some suitable components that could show antidiabetic effect like flavokwain and 5,6 dehydrokwain from *alpinia mutica* and tradescantin and tradescantoside from *tradescantia spatheca* ,but to our surprise we found many different types of constituents which showed good binding affinity towards various proteins.



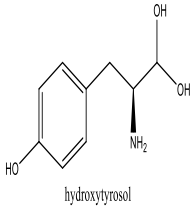
(±)-methyl-4-(3′,4′- dihydroxyphenyl)-3-hydroxy-4-oxobutanoate



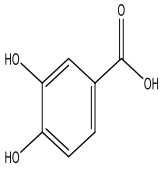
(R)-2-hydroxy-3-(4′-hydroxyphenyl) propanoic acid



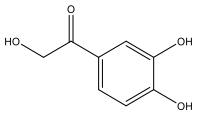
(2S)-6,7,8-trihydroxy-5-methoxy-2-phenyl-2,3-dihydrochromen-4-one



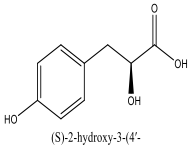
hydroxytyrosol



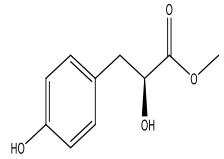
protocatechuic acid



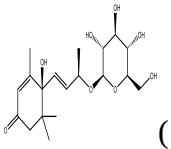
2-hydroxy-3′,4′-dihydroxyacetophenone



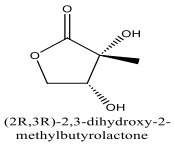
(S)-2-hydroxy-3-(4′-hydroxyphenyl) propanoic acid



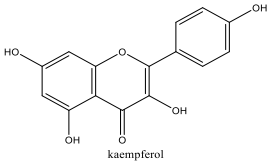
methyl (2S)-2-hydroxy-3-(4-hydroxyphenyl)propanoate



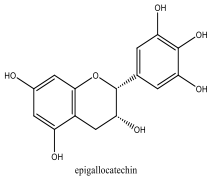
(6S, 9R)-roseoside



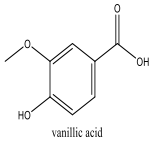
(2R,3R)-2,3-dihydroxy-2-methylbutyrolactone



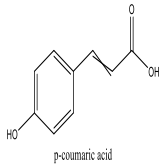
kaempferol



epigallocatechin



vanillic acid



p-coumaric acid

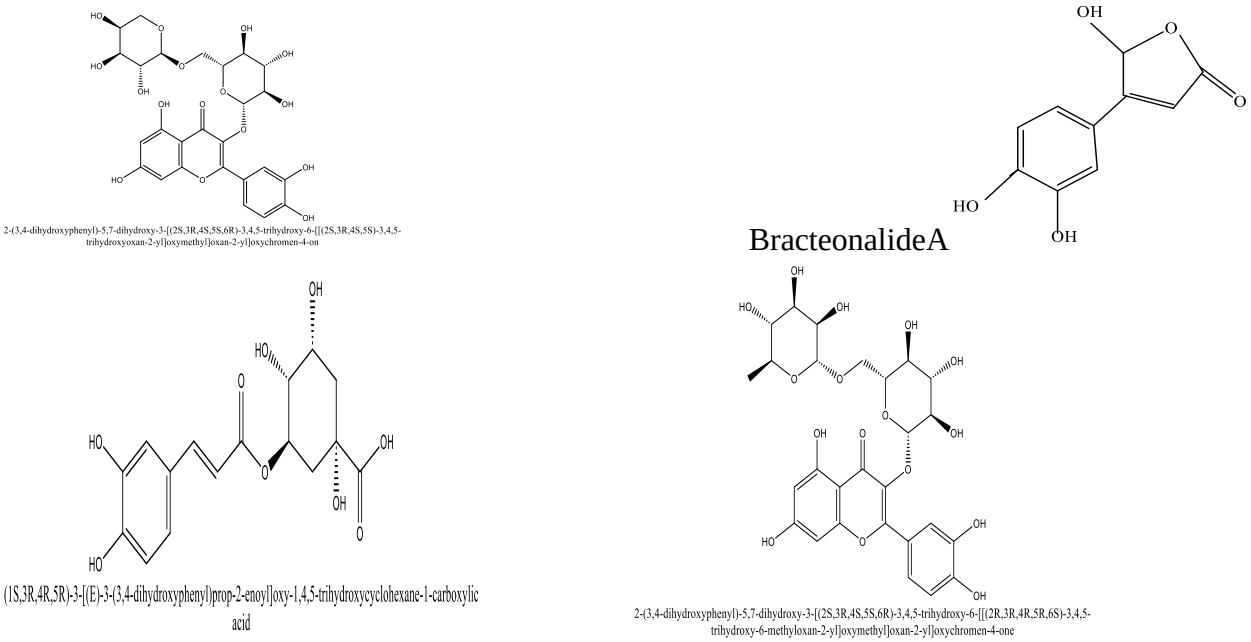
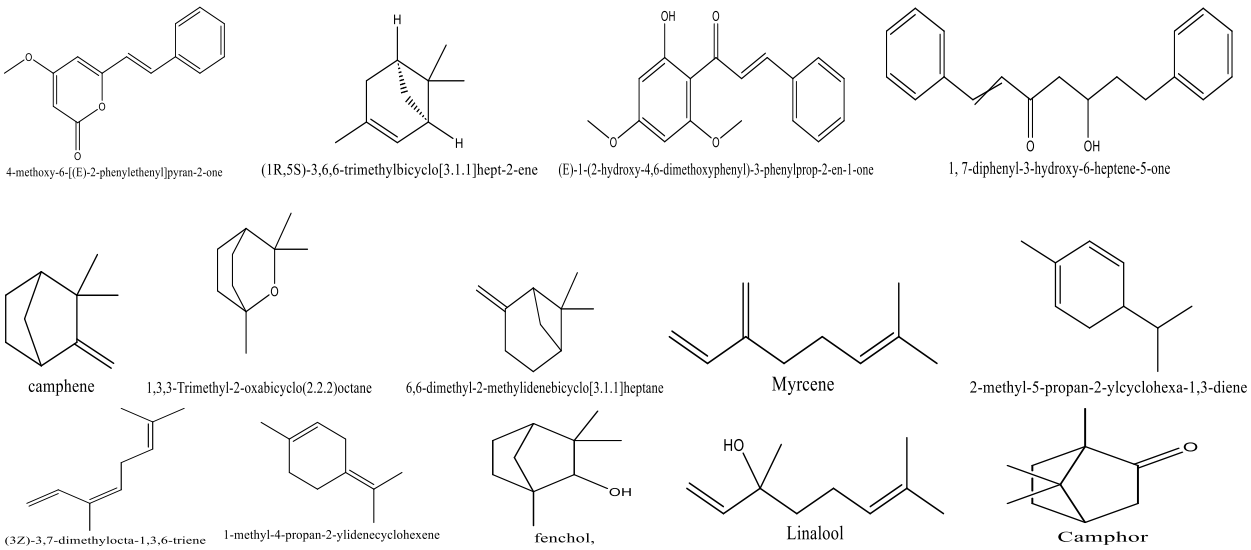


Fig 1- Chemical Structures of phytoconstituents present in *Tradescantia spatheca*



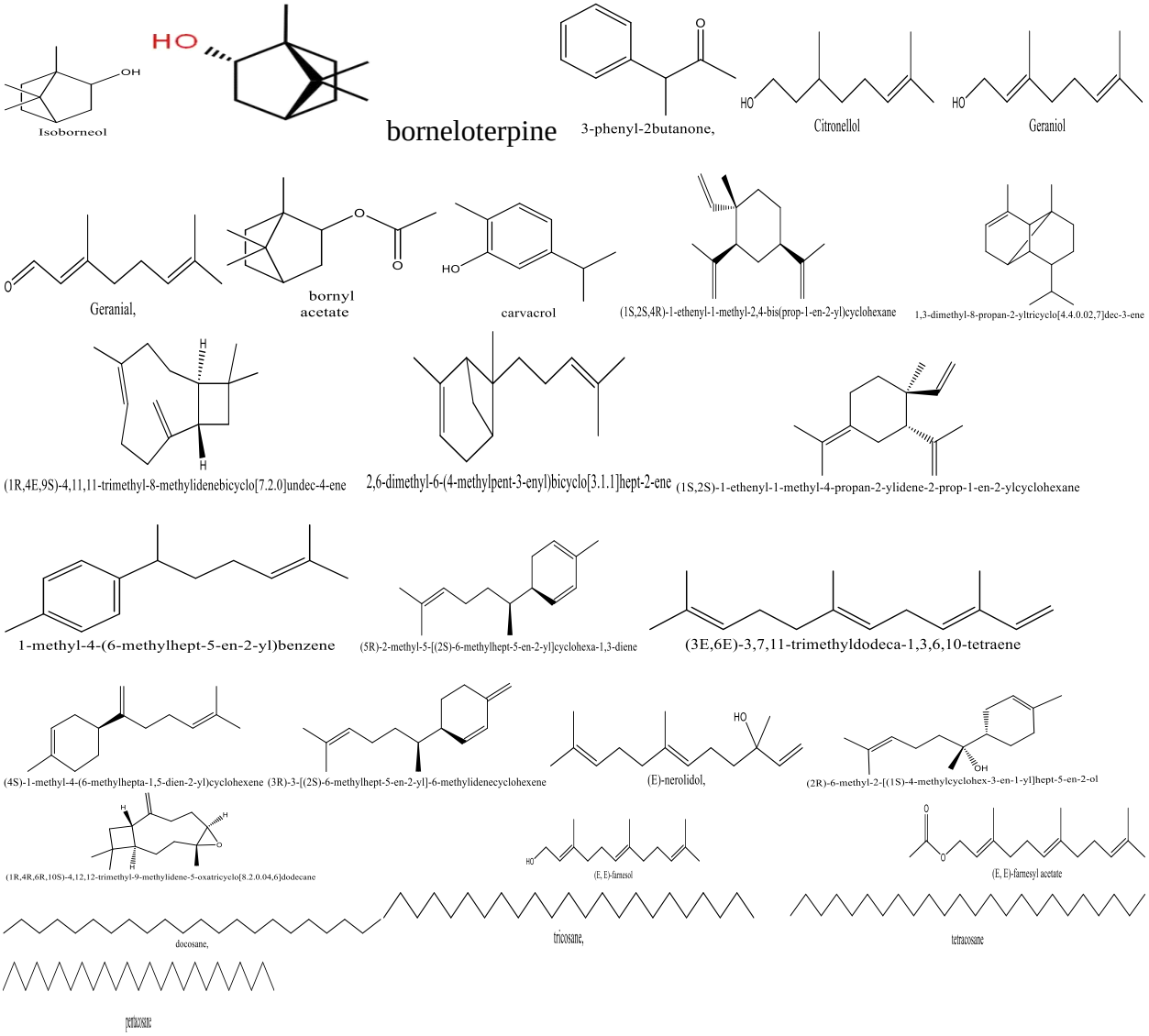


Fig 2- Chemical Structures of phytoconstituents present in *Alpinia mutica*

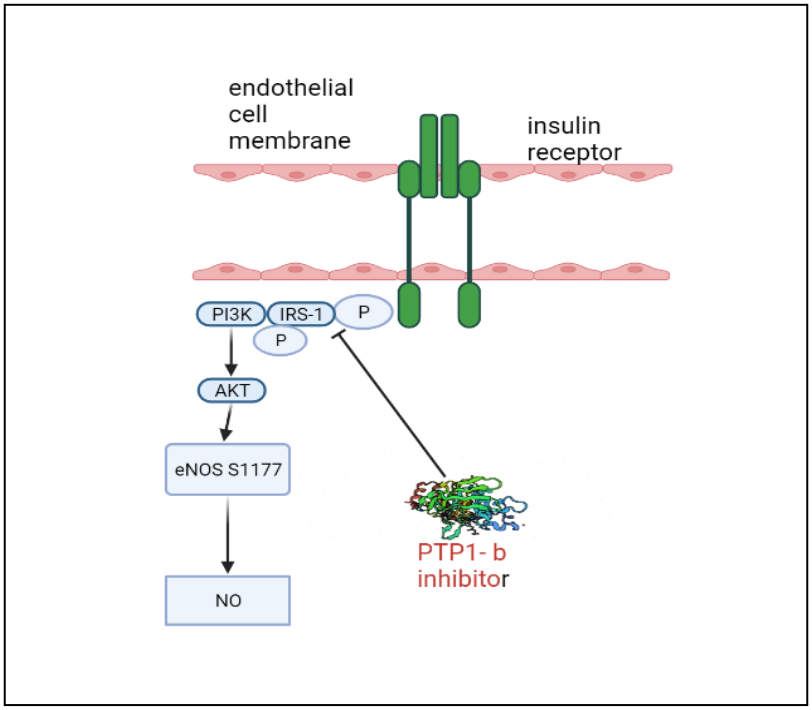


Fig3- Mechanism of PTP1b inhibitor (PDB ID:4Y14)

The protein 4Y14 showed the least interaction with the ligands and showed the most binding energy with 1,7-diphenyl-3-hydroxy-6-heptene5-one(-6.9kcal/mol). With 3G9E,The most binding energy was shown by Flavokwain(-7.8kcal/mol). In Tradescantia spatheca, rutin (-10.1 kcal/mol),(-9.4 kcal/mol)and (-8.7 kcal/mol) respectively shows highest effect with 1XU7,2ZJ3 and 3G9E;bracteonalide A(-9.1kcal/mol) shows highest binding energy with 4Y14. Our results show that there have been various constituents that can be researched further and this study can be used as a reference for further studies about which constituents can be used for studying on antidiabetic effects.

Table 2. Binding energy of different phytoconstituents *Tradescantia spatheca* against proteins

Targeted compound	**Binding Energy of protein (kcal/mol)(-ve values)**			
PDB ID	**1XU7**	**3G9E**	**4Y14**	**2ZJ3**
Tradescantin	6.8	6.5	6.3	7.2
Hydroxytyrosol	6.2	5.9	6.7	6.4

Protatecheuic acid	5.9	5.4	6.3	6.1
Orebiusina	9.1	7.9	6.9	8
Vanillic acid	6.2	5.4	6.5	6.2
2-hydroxy-3,4-dihydroxyacetophenone	6.1	5.6	6.5	6.6
(S)-2-hydroxy-3-(4_- hydroxyphenyl) propanoic acid	6.4	6.1	7.3	6.6
(R)-2-hydroxy-3-(4_- hydroxyphenyl) propanoic acid	6.7	6	7.2	6.9
Latifolicin c	6.2	6	7.1	6.3
{6s,9r)-roseoside	9	7.2	5.9	7.6
Kaempferol	9.1	7.9	7.5	7.7
(2r,3r)-2,3-dihydroxy-2-methylbutyrolactone	5.2	4.8	4.3	5.6
Epigallocatechin	9.4	7.5	6.5	7.6
Ferulic acid	6.7	6	7	6.8
P-coumaric acid	6.5	5.8	7.2	6.1
Pelatoside	7.7	8.4	8.1	7.6
Rutin	10.1	9.4	7	8.7
Chlorogenic acid	9	8	7.1	8.1
Bracteonalide a	7.7	7	9.1	8.4

Table 3. Binding energy of different phytoconstituents *Alpinia mutica* against proteins

Targeted compound	**Binding Energy of protein (kcal/mol)(-ve values)**

PDB ID	**1XU7**	**3K35**	**2ZJ3**	**3G9E**	**4Y14**
5,6 Dehydrokwain	7.2	8.2	7.3	7.6	6.3
Flavokwain	8	7.8	6	7.8	6.5
1,7-diphenyl-3-hydroxy-6-heptene5-one	7.1	9	6.4	6	6.9
a-Pinene	5.3	5.8	5.2	5.7	4.7
Camphene	5.5	4.7	5.2	5.7	4.5
b Pinene	5.3	5.6	5	5.9	4.6
Myrcene	5.2	5.2	4.2	5.4	5.8
alpha-Phelanderene	5.5	5.6	5	6.2	6.4
1,8 Cineole	5.5	4.6	5.5	5.5	4.5
(z)-beta-Ocimene	5.3	5.7	4.3	5.5	6
Terpinolene	5.6	5.8	5.2	5.9	6.4
fenchol	5.8	4.7	5.7	5.6	4.8
linalool	5.3	5.8	4.8	5.8	5.9
camphor	5.6	4.8	6.1	5.4	4.4
Isobernol	6	4.5	5.6	5.3	4.4
3-Phenylbutan-2-one	6	7.1	5.5	5.6	6.6
Citronellol	5.1	5.8	5	5.4	6.1
Geraniol	5.4	5.7	5	5.6	6.3
Gernial	5.2	6	5.1	5.5	6.4
Bornyl acetate	6.3	5.1	6.7	5	4.8
Carvacrol	5.8	6.6	5.8	6.4	4
alpha-Cubebene	7.4	7	6	6.8	6.2
Gernayl acetate	5.6	6.5	5.5	5.7	5.7

alpha-Copaene	7	6.2	6.4	6.7	5.9
beta Elemene	6.6	6.3	5.8	5.9	5
Caryophyllene	7.6	5.9	6.3	6.7	5.2
Bergamotene	6.3	6	5.4	6.4	5.5
Elemene	6.6	5.7	5.7	6.5	6.5
Curcumene	6.2	7.3	7.3	7.3	6.7
Zinzerbine	6.2	6.3	5.3	7.4	6.6
Fernesen	6.2	6.2	5.2	6.8	6.3
Bisabolene	6.4	6.7	5.4	7.3	6.4
Beta-sesquiphallandrene	6.3	7	5.3	7.4	6.7
Nerolidol	5.7	6.8	5.4	6.4	6.1
Caryophyllene oxide	7.5	6.3	6.8	6.5	6
Bisabolol	6.5	8.1	5.5	7.1	5.8
Farnesol	6.1	6.4	5	6.3	6.2
Farnesyl acetate	6.1	6.8	5.8	6.7	5.7
Docosane	5.5	6.5	5	6.1	4.4
Tricosane	5.5	6.3	4.6	6.3	4.8
Tetracosane	5.4	5.4	4.5	6.1	4.7
Pentacosane	5.7	5	5.1	6.2	4.3

Molecular docking of several phytoconstituents from *Alpinia mutica* screened against PDB ID-1XU7, 3G9E, 3K35, 2ZJ3 and 4Y14 while, four proteins naming 1XU7,3G9E,2ZJ3 and 4Y14 screened for *tradescantia spatheca* phytoconstituents. As we know the most negative the value of the binding energies better the interaction with the active site, it was observed that 1,7-diphenyl-3-hydroxy-6-heptene5-one(-9.0kcal/mol) has the highest binding energy with protein 3K35; While studying interactions with 2ZJ3, we found out that bisabolol(-8.1kcal/mol) has the highest binding energy. The protein 1XU7 shows the best interaction with Flavokwain(8kcal/mol).

CONCLUSION

Diabetes is a disease which is spread throughout the world, with very few drugs for treatment. Since last few years' herbal drugs were considered as suitable option for treatment. The present study scrutinizes the anti-diabetic potential of *Alpinia mutica* and *Tradescantia spatheca* utilizing *in silico* molecular docking approach. Several proteins were targeted to examine antidiabetic potential of phytoconstituents from *Alpinia mutica* and *Tradescantia spatheca*. Results indicate that shows considerable antidiabetic effects and can be further studied for a better understanding and new drug formation. Orebiusina, Kaempferol, Epigallocatechin, and rutin show the highest binding affinity from *Tradescantia spatheca* against PDB ID: 1XU7, PDB ID: 3G9E, PDB ID: 4Y14,PDB ID: 2ZJ3. In case of *Alpinia mutica* Flavokwain shows highest binding affinity towards PDB ID: 1XU7 and PDB ID: 3G9E, 1,7-diphenyl-3-hydroxy-6-heptene5-one shows highest binding affinity towards PDB ID:3K35and PDB ID: 4Y14. while 5,6 Dehydrokwain and Curcumene shows highest binding affinity against PDB ID: 2ZJ3. However, further studies on these phytoconstituents must establish a novel, safe and effective anti-diabetic drug.

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