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Identification of PTPN1B inhibitors from *Momordica charantia* and their enrichment analysis

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ABSTRACT

Background: PTPN1B is identified to play a prime role in a negative role in the insulin signaling pathway which can be inhibited and could contribute to the enhancement of insulin function. **Objective:** The present study aimed to identify PTPN 1B inhibitors from *Momordica charantia* and perform gene set enrichment analysis of regulated protein molecules. **Methods:** The phytoconstituents present in *Momordica charantia* were identified and queried for PTPN1B inhibitors. Druglikeness score, side effects and gene expression were predicted for each compound. A docking study was performed to predict the binding affinity with PTPN1B receptor; later the binding affinities were compared. Kyoto Encyclopedia of Genes and Genomes pathway analysis was performed for the regulated genes to identify the modulated pathways. **Results:** Among the forty-four identified compounds present in *Momordica charantia* thirty-three compounds were found to inhibit PTPN 1B. Momordin I possessed the highest binding affinity with PTPN1B. Cytokine-cytokine receptor pathway was predicted to modulate the most amounts of protein molecules in diabetes mellitus. The side effects of these compounds were also estimated and only three compounds showed side effects when Pa≥0.7. **Conclusion:** The present study indicates that PTPN 1B inhibitors from *Momordica charantia* have their anti-diabetic action due to their action on multiple protein molecules and the synergistic effect can be confirmed by future investigations.

Keywords: Diabetes, Docking, *Momordica charantia*, PTPN1B inhibitors

INTRODUCTION

Type 2 Diabetes Mellitus is a polygenic condition which is characterized by hyperglycemia resulting from insulin resistance [1]. This is also due to a defect in insulin signaling pathways in which PTPN1B has a major contribution. Further, inhibition of this protein is a well-known approach in the management of type 2 Diabetes Mellitus [2]. Likewise, the current pharmacotherapy of Type 2 Diabetes Mellitus includes synthetic oral hypoglycaemic agents which are associated with multiple side effects [3] suggesting the requirement of identification of new drug molecules in the treatment of diabetes mellitus with minimum side effects. The newer trend of drug discovery involves the use of *in-silico* studies including molecular docking and network pharmacology [3]. Further, these *in-silico* studies provide an overview of the characteristic of the drug molecule with the target and their probable interaction. Further, better characteristics of the drug with respect to its target can be predicted using gene set enrichment analysis [4].

Momordica charantia, also known as bitter melon (Karela) is being popularly used to treat sweet urea (Diabetes) from ancient times. It is a popular medicine for the treatment of diabetes in the population among Asia, South America, India and East Africa [5]. *Momordica charantia* has good anti-diabetic effects as it protects the pancreatic β-cells through the down-regulation of MAPKs and NF-κB in MIN6N8 cells. *Momordica charantia* also modulates the stress-activated protein kinase/c-Jun N-terminal kinase (SAPK/JNK), p38, and p44/42, and the activity of NF-κB [6]. Management of diabetes is better with the concept of the synergistic effect of compound over multiple targets rather than focusing on single compound-protein interaction [7]. Hence, this study was designed to identify the PTPN1B inhibitors from the compounds present in *Momordica charantia* by using drug-gene set enrichment analysis and network pharmacology to assess the synergistic effect.

MATERIALS AND METHODS

Mining of phytoconstituents and their targets

The lists of compounds were obtained from Published literature and their canonical SMILES, molecular weight, and molecular formula were obtained from PubChem database (https://www.rcsb.org) [8].

The targets were identified by using SwissTargetPrediction [9] by querying the Canonical SMILES obtained from the PubChem database. The compounds inhibiting PTPN1B were identified and recorded and based upon the top 25 results from the database the compounds were retrieved.

Druglikeness and side effect(s) of phytoconstituents

The druglikeness and side effect of the phytoconstituents was predicted by querying the retrieved Canonical SMILES in MolSoft [10] (http://molsoft.com/mprop/) and ADVERPred [11] respectively. The Pa>0.7 was considered to be experimentally expressed side effects.

Prediction of gene expression profiles and Enrichment analysis

Gene expression profile of phytoconstituents was identified by DIGEP-Pred [12]. Canonical SMILES were used to identify the protein molecules which either upregulated or downregulated at a probable activity of 0.5. The protein interaction was identified through STRING [13] and the pathways involved in diabetes were identified using the Kyoto Encyclopaedia of Genes and genomes (KEGG) pathway database (https://www.genome.jp/kegg/) [14, 15] and published literature.

Network construction

Cytoscape 3.7 [16] was used to construct the network between compounds, target proteins and pathways and the command "Network analyzer" was used to analyze the network based on edge count. The map node size was set from "Low values to small sizes" and map color from "Low values to bright colors" based on edge count for both settings.

Docking studies

The pdb formats of the compounds present in *Momordica charantia* were retrieved from the Pub Chem database. MMFF94 forcefield [17] was used to minimize the energy of the ligand molecule to obtain ten different confirmations. The confirmations scoring the lowest energy were chosen as the ligand molecule. The X-ray crystallographic structure of protein tyrosine phosphatase nonreceptor 1B (PDB:2NT7) was obtained from the RCSB protein databank [18] and hetero atoms were removed using Discovery studio [19]. The docking study was carried out using autodock 4.0 [20]. After the completion of docking the pose having the lowest binding energy was chosen and then ligand-protein interaction was visualized in Discovery Studio 2019.

RESULTS

Bio actives and targets

Forty-four compounds were identified from (*Momordica charantia*); among them, thirty-three compounds were predicted to inhibit PTPN1B. The PubChem CID, molecular formula and Canonical SMILES of these compounds are summarized in Table 1.

Druglikeness and probable side effects

Among thirty-three phytoconstituents, fourteen compounds were predicted to have a positive druglikeness score. Among them, momordenol was predicted to have the highest druglikeness score i.e. 1.07. Table 2 summarizes the molecular weight, number of hydrogen bond donor, acceptor, Log P and Log S and druglikeness score of individual phytoconstituents. Similarly, among thirty-three phytoconstituents only 3 compounds i.e. beta-cryptoxanthin, D-galacturonic acid and zeaxanthin were predicted to possess side effects at the probability of Pa>0.7. Table 3 summarizes the probable activity of predicted side effects of each compound.

Enrichment analysis and pathway analysis

The probable gene expressed proteins of PTPN1B inhibitors were identified in SwissTargetPrediction and analysis in STRING; identified 17 pathways to be involved in diabetes mellitus. Among them, Cytokine-cytokine receptor interaction was predicted to be primarily modulated with the highest number of gene count i.e. 10. Table 4 summarizes the probable modulated genes and their respective pathways involved in the diabetic pathogenesis. Similarly, Figure 1 represents the pathway- protein interaction modulated by phytoconstituents of (*Momordica charantia*). Assessment of phytoconstituent-protein interaction identified lauric acid to be primarily involved to target the highest number of proteins. Similarly, CCL2 was predicted to be majorly targeted by the maximum number of phytoconstituents. The network of phytoconstituents and protein/gene is represented in Figure 2.

***In silico* molecular docking**

Docking study was performed using Autodock 4.0 with a grid box as a center to the ligand. momordin-I showed the best binding affinity i.e. -9.5 Kcal/mol. The ligand and target cloud have been represented in figure 3 along with the 2D structure showing the different types of bonds. Table 5 summarizes the binding energy, Number of hydrogen bonds and hydrogen bond residues of each phytoconstituent with PTPN1B.

DISCUSSION

The present study aimed to identify PTPN1B inhibitors from (*Momordica charantia*) and identify if these compounds are involved in the modulation of multiple pathways in the pathogenesis of Diabetes Mellitus. To evaluate this hypothesis we utilized system biology tools in which targets of phytoconstituents were queried in the STRING database to evaluate the protein-protein interaction followed by docking analysis to evaluate PTPN1B inhibitors as explained by a previous study [21].

The prediction is based on the principle that "*similar compounds target similar proteins*". Hence, this study utilizes the docking study for the prediction of phytoconstituents from *M. charantia* as a target for PTPN1B inhibitors. On analyzing the data for probable side effects it was found that among the 33 compounds only 3 compounds i.e. beta-Cryptoxanthin, D-galacturonic acid and zeaxanthin were predicted to have side effects as myocardial infarction, Nephrotoxicity and Myocardial infarction respectively. The compounds were screened to have probable side effects if they have Pa≥ 0.7.D- galacturonic acid has the highest probable side effect. The druglikeness score gives us the information if the molecule can behave like a drug if administered orally. Hence, the druglikeness score helps to compare the bioavailability of the compounds [22] which was also screened in the present study.

It is known that single drug molecules can upregulate or downregulate a number of proteins. The concept of "one drug one protein and one therapeutic activity" is associated with multiple limitations. It is better to estimate on the basis of a single molecule to act on multiple proteins [23]. The compounds in this study were predicted to regulate multiple protein molecules at a probable activity of 0.5 in which the compounds from *M. charantia* were found to regulate 17 pathways involved in Diabetes Mellitus.

The network constructed identified that Cytokine-cytokine receptor interaction pathways being majorly modulated and are also confirmed by KEGG pathway analysis as it has the highest number of gene count which can contribute to DM. The proteins modulated by cytokine-cytokine receptor pathway were found to be TNFRSF1A, LEP, CCL4, CCL3, GH1, IL6R, FLT1, NGFR, CCL2 and IFNG. The results indicate that CCL2 promotes monocyte recruitment by acting on both locally and remotely and that of expression of CCL2 by insulin-producing cells can lead to insulitis and islet destruction [24]. From the network obtained from phytoconstituent-protein interaction, we get to know that lauric acid modulates by targeting the most number of

protein molecules and CCL2 were known to be most targeted by a number of phytoconstituents.

A docking study provides a better idea of how the compound (ligand) may bind with the desired receptor[25]. If the compound has a good binding affinity with the receptor to show pharmacological action clinically, this study may add weightage to preclinical studies and may provide confirmation of therapeutic response. Docking study was performed on the compounds and the results show that momordin I have the highest binding affinity with PTPN1B, this further indicates that the anti-diabetic effect of (*Momordica charantia*) may be due to momordin I [26].

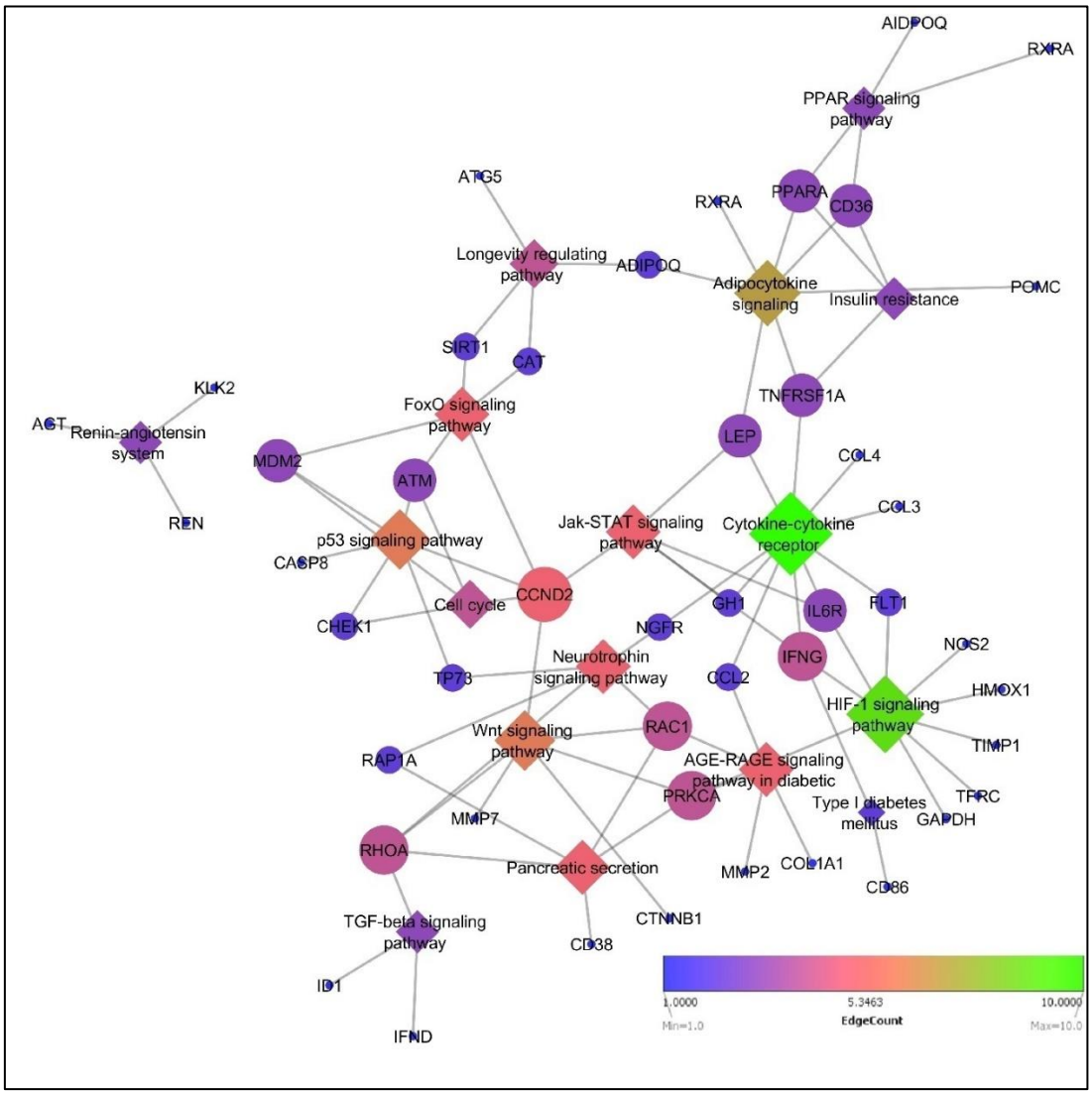

Figure 1: Pathway-protein interaction

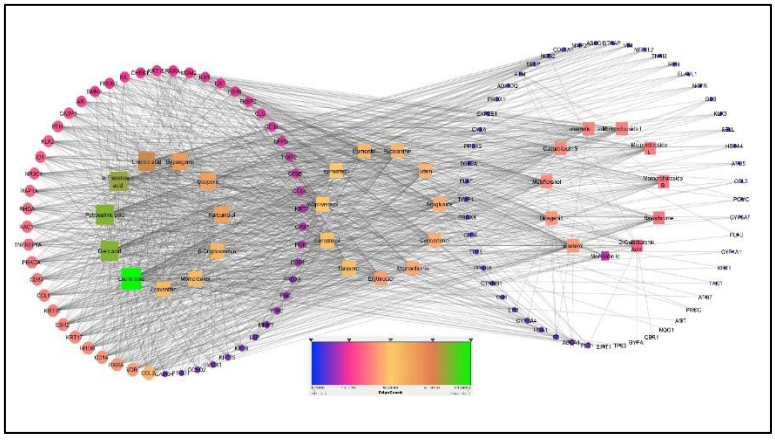

Figure 2: Compound-Gene interaction

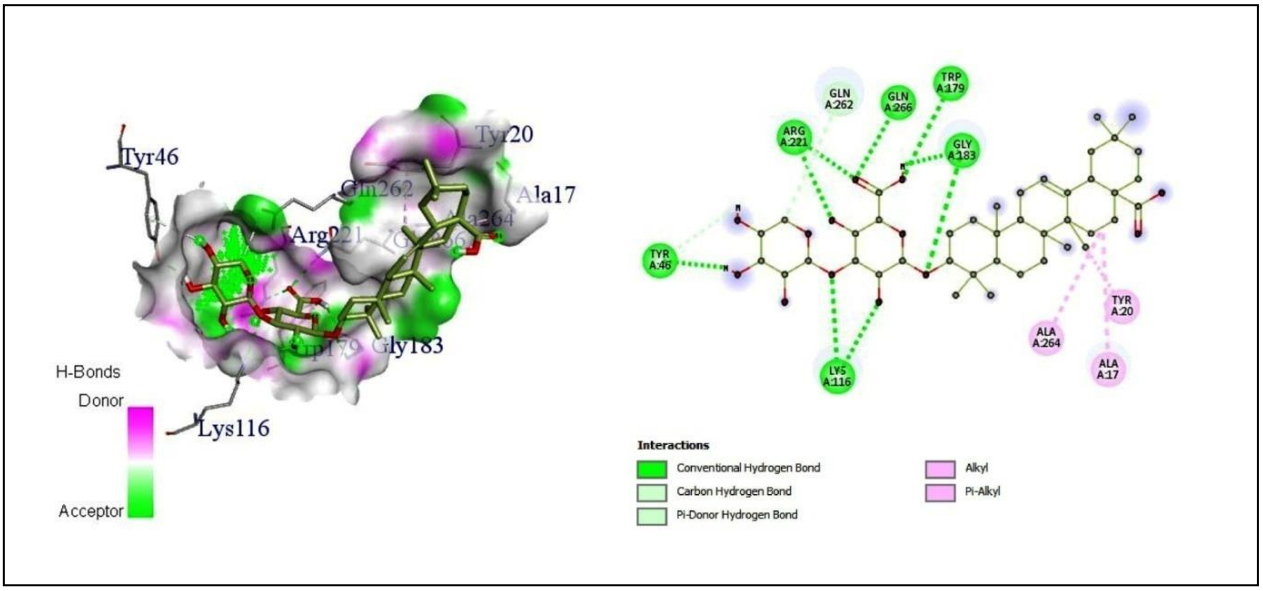

Figure 3: Interaction of momordin-I with PTPN1B

Table 1: Name of compound, PubChem CID, Molecular formula, Molecular weight and SMILES

SNo	compounds	PubChem CID	Molecular formula	SMILES
1.	alpha-Eleostearic acid	5281115	$C_{18}H_{30}O_2$	CCCCC=CC=CC=CCCCCCCCC(=O)O
2.	alpha-Spinasterol	5281331	$C_{29}H_{48}O$	CCC(C=CC(C)C1CCC2C1(CCC3C2=CCC4C3(CCC(C4)O)C)C)C(C)C
3.	beta-Cryptoxanthin	5281235	$C_{40}H_{56}O$	CC1=C(C(CCC1)(C)C)C=CC(=CC=CC(=CC=CC=C(C)C=CC=C(C)C=CC2=C(CC(CC2(C)C)O)C)C)C
4.	Cucurbitacin S	119287	$C_{30}H_{42}O_6$	CC1C2C(CC3(C2(CC(=O)C4(C3CC=C5C4C=C(C(=O)C5(C)C)O)C)C)C)OC(CC1=O)C(C)(C)O
5.	Cycloartenol	92110	$C_{30}H_{50}O$	CC(CCC=C(C)C)C1CCC2(C1(CCC34C2CCC5C3(C4)CCC(C5(C)C)O)C)C
6.	D-Galacturonic Acid	439215	$C_6H_{10}O_7$	C1(C(C(OC(C1O)O)C(=O)O)O)O
7.	Diosgenin	99474	$C_{27}H_{42}O_3$	CC1CCC2(C(C3C(O2)CC4C3(CCC5C4CC=C6C5(CCC(C6)O)C)C)C)OC1
8.	elasterol	15599640	$C_{29}H_{46}O$	CCC(CCC(C)C1=CCC2C1(CCC3C2=CCC4C3(CCC(C4)O)C)C)C(=C)C
9.	Erythrodiol	101761	$C_{30}H_{50}O_2$	CC1(CCC2(CCC3(C(=CCC4C3(CCC5C4(CCC(C5(C)C)O)C)C)C2C1)C)CO)C
10.	Flavochrome	10127727	$C_{40}H_{56}O$	CC1=CCCC(C1C=CC(=CC=CC(=CC=CC=C(C)C=CC=C(C)C2C=C3C(CCCC3(O2)C)(C)C)C)C)(C)C
11.	Gypsogenin	92825	$C_{30}H_{46}O_4$	CC1(CCC2(CCC3(C(=CCC4C3(CCC5C4(CCC(C5(C)C=O)O)C)C)C2C1)C)C(=O)O)C
12.	Karounidiol	159490	$C_{30}H_{48}O_2$	CC1(C(CCC2(C1CC=C3C2=CCC4(C3(CCC5(C4CC(CC5)(C)CO)C)C)C)C)O)C
13.	lanosterol	246983	$C_{30}H_{50}O$	CC(CCC=C(C)C)C1CCC2(C1(CCC3=C2CCC4C3(CCC(C4(C)C)O)C)C)C
14.	lauric acid	3893	$C_{12}H_{24}O_2$	CCCCCCCCCCCC(=O)O
15.	Linoleic acid	5280450	$C_{18}H_{32}O_2$	CCCCCC=CCC=CCCCCCCCC(=O)O
16.	Linolenic acid	5280934	$C_{18}H_{30}O_2$	CCC=CCC=CCC=CCCCCCCCC(=O)O
17.	lutein	5281243	$C_{40}H_{56}O_2$	CC1=C(C(CC(C1)O)(C)C)C=CC(=CC=CC(=CC=CC=C(C)C=CC=C(C)C=CC2C(=CC(CC2(C)C)O)C)C)C
18.	lycopene	446925	$C_{40}H_{56}$	CC(=CCCC(=CC=CC(=CC=CC(=CC=CC=C(C)C=CC=C(C)C=CC=C(C)CCC=C(C)C)C)C)C)C
19.	Momorcharaside B	131828	$C_{36}H_{62}O_{10}$	CC(C1CCC2(C1(CCC3(C2CC=C4C3CCC(C4(C)C)OC5C(C(C(C(O5)CO)O)O)O)C)C)C)C(C(C(C(C)(C)C)O)O)O)O
20.	Momordenol	85724901	$C_{29}H_{46}O_2$	CCC(CCC(C)C1C(=O)C=C2C1(CCC3C2CC=C4C3(CCC(C4)O)C)C)C(C)C
21.	Momordicinin	14526924	$C_{30}H_{46}O_2$	CC1CCC23CCC4(C5(CCC6C(C(=O)CCC6(C5C=CC4(C2C1C)OC3)C)(C)C)C)C
22.	Momordicoside I	71717036	$C_{36}H_{58}O_8$	CC(CC=CC(C)(C)O)C1CCC2(C1(CCC34C2C=CC5(C3CCC(C5(C)C)OC6C(C(C(C(O6)CO)O)O)O)O)OC4)C)C

2 3.	Momordicoside L	101743788	$C_{36}H_{58}O_9$	CC(CC=CC(C)(C)O)C1CCC2(C1(CCC3(C2C(C=C4C3CCC(C4(C)C)O)OC5C(C(C(C(O5)CO)O)O)O)C=O)C)C
2 4.	Momordin Ic	176596	$C_{41}H_{64}O_{13}$	CC1(CCC2(CCC3(C(=CCC4C3(CCC5C4(CCC(C5(C)C)OC6C(C(C(C(O6)C(=O)O)O)OC7C(C(C(CO7)O)O)O)O)C)C2C1)C)C(=O)O)C
2 5.	Momordol	71308241	$C_{26}H_{48}O_5$	CCC1C(=O)C=CC(C1(C)CCCC(C)CCC(C)C(CC(C(CC)CO)O)O)(C)O
2 6.	multiflorenol	12312990	$C_{30}H_{50}O$	CC1(CCC2(CCC3(C4=CCC5C(C(CCC5(C4CCC3(C2C1)C)C)O)(C)C)C)C)C
2 7.	oleanolic acid	10494	$C_{30}H_{48}O_3$	CC1(CCC2(CCC3(C(=CCC4C3(CCC5C4(CCC(C5(C)C)O)C)C)C2C1)C)C(=O)O)C
2 8.	oleic acid	445639	$C_{18}H_{34}O_2$	CCCCCCCCC=CCCCCCCCC(=O)O
2 9.	Petroselinic acid	5281125	$C_{18}H_{34}O_2$	CCCCCCCCCCCC=CCCCCC(=O)O
3 0.	Rubixanthin	5281252	$C_{40}H_{56}O$	CC1=C(C(CC(C1)O)(C)C)C=CC(=CC=CC(=CC=CC=C(C)C=CC=C(C)C=CC=C(C)CCC=C(C)C)C)C
3 1.	Sitogluside	5742590	$C_{35}H_{60}O_6$	CCC(CCC(C)C1CCC2C1(CCC3C2CC=C4C3(CCC(C4)OC5C(C(C(C(O5)CO)O)O)O)C)C)C(C)C
3 2.	Taraxerol	92097	$C_{30}H_{50}O$	CC1(CCC2(CC=C3C4(CCC5C(C(CCC5(C4CCC3(C2C1)C)C)O)(C)C)C)C)C
3 3.	Zeaxanthin	5280899	$C_{40}H_{56}O_2$	CC1=C(C(CC(C1)O)(C)C)C=CC(=CC=CC(=CC=CC=C(C)C=CC=C(C)C=CC2=C(CC(CC2(C)C)O)C)C)C

Table 2: Drug likeness score of Phytoconstituents

Compound Name	Molecular formula	Molecular weight	Number of HBA	Number of HBD	MolLog P	Drug-likeness model score
alpha-Eleostearic acid	C18H30O2	278.22	2	1	6.49	-0.08
alpha-Spinasterol	C29H48O	412.37	1	1	9.06	0.06
beta-Cryptoxanthin	C40H56O	552.43	1	1	12.25	0.99
Cucurbitacin S	C30H42O6	498.3	6	2	4.53	-0.25
Cycloartenol	C30H50O	426.39	1	1	9.22	-0.31
D-Galacturonic Acid	C6H10O7	194.04	7	5	-3.01	-0.3
Diosgenin	C27H42O3	414.31	3	1	6.39	-0.04
elasterol	C29H46O	410.35	1	1	9.48	0.52
Erythrodiol	C30H50O2	442.38	2	2	8.05	-0.13
flavochrome	C40H56O	552.43	1	0	13.07	-0.19
Gypsogenin	C30H46O4	470.34	4	2	6.44	0.33
Karounidiol	C30H48O2	440.37	2	2	7.73	-0.26
Lanosterol	C30H50O	426.39	1	1	9.47	0.52
Lauric acid	C12H24O2	200.18	2	1	4.73	-0.33
Linoleic acid	C18H32O2	280.24	2	1	6.73	-0.08
Linolenic acid	C18H30O2	278.22	2	1	6.31	0.36
lutein	C40H56O2	568.43	2	2	11.07	-0.33
lycopene	C40H56	536.44	0	0	14.28	-1.04
Momorcharaside B	C36H62O10	654.43	10	8	3.13	0.18
Momordenol	C29H46O2	426.35	2	1	8.31	1.07
Momordicinin	C30H46O2	438.35	2	0	7.22	0.38
Momordicoside I	C36H58O8	618.41	8	5	4.67	-0.41
Momordicoside L	C36H58O9	634.41	9	6	3.55	0.15
Momordin Ic	C41H64O13	764.43	13	7	3.8	0.78
Momordol	C26H48O5	440.35	5	4	5.67	-0.52
Multiflorenol	C30H50O	426.39	1	1	9.17	-0.35
Oleanolic acid	C30H48O3	456.36	3	2	7.8	0.37
Oleic acid	C18H34O2	282.26	2	1	7.15	-0.08
Petroselinic acid	C18H34O2	282.26	2	1	7.15	-0.08
Rubixanthin	C40H56O	552.43	1	1	12.69	0.15
Sitogluside	C35H60O6	576.44	6	4	7.13	0.51
Taraxerol	C30H50O	426.39	1	1	9.07	-0.91
Zeaxanthin	C40H56O2	568.43	2	2	11.09	-0.18

Table 3: Side effect of compounds

S No	compounds	Side effect	Pa	Pi
1.	beta-Cryptoxanthin	Myocardial infarction	0.700	0.012
2.	D-Galacturonic Acid	Nephrotoxicity	0.850	0.008
3.	Zeaxanthin	Myocardial infarction	0.711	0.010

Table 4: Enrichment analysis of phytoconstituents

KEGG pathway	Description pathway	Count in gene set	Gene codes
hsa04066	HIF-1 signaling pathway	9	IL6R,IFNG,NOS2,TIMP1,HMOX1,TFRC,FLT1,PRKCA,GAPDH
hsa04920	Adipocytokine signaling pathway	7	TNFRSF1A,CD36,LEP,PPARA,POMC,ADIPOQ,RXRA
hsa04060	Cytokine-cytokine receptor interaction	10	IL6R,GH1,CCL4,CCL3,IFNG,LEP,CCL2,TNFRSF1A,FLT1,NGFR
hsa04115	p53 signaling pathway	6	CASP8,CCND2,MDM2, CHEK1, ATM,TP73
hsa04310	Wnt signaling pathway	6	MMP7,RHOA,RAC1,PRKCA,CTNNB1,CCND2
hsa04972	Pancreatic secretion	5	CD38,RAP1A,RHOA,RAC1,PRKCA
hsa04933	AGE-RAGE signaling pathway in diabetic complications	5	CCL2,MMP2,COL1A1,RAC1,PRKCA
hsa04614	Renin-angiotensin system	3	AGT,REN,KLK2
hsa04722	Neurotrophin signaling pathway	5	RAP1A,RHOA,RAC1,NGFR,TP73
hsa03320	PPAR signaling pathway	4	CD36,PPARA,AIDPOQR,XRA
hsa04068	FoxO signaling pathway	5	CAT,SIRT1,MDM2,ATM,CCND2
hsa04211	Longevity regulating pathway	4	ADIPOQ,CAT,ATG5,SIRT1
hsa04630	Jak-STAT signaling pathway	5	IL6R,GH1,IFNG,LEP,CCND2
hsa04110	Cell cycle	4	CCND2,MDM2,CHEK1,ATM
hsa04350	TGF-beta signaling pathway	3	RHOA,IFND,ID1
hsa04940	Type I diabetes mellitus	2	IFNG,CD86
hsa04931	Insulin resistance	3	CD36,PPARA,TNFRSF1A

Table 5: Binding affinity of phytoconstituents with PTPN1B along with Hydrogen bond interactions

Ligand	Binding Affinity (kcal/mol)	Number of hydrogen bonds	Hydrogen bond residues
Cucurbitacin S	-7.9	2	THRA:177,GLNA:127
Cycloartenol	-7.9	NA	NA
D Galacturonic Acid	-6.2	2	LYSA:116,ARGA:221
Diosgenin	-8.3	NA	NA
Erythrodiol	-8.4	2	ASNA:162,ASPA:137
Gypsogenin	-8.3	1	ASNA:162
Karounidiol	-7.6	1	SERA:28
Lanosterol	-8.6	NA	NA
Lauric acid	-5.7	NA	NA
Linoleic acid	-5.8	1	LYSA:197
Linolenic acid	-6	4	GLUA:200,LYSA:197,ASNA:193
Momorcharaside B	-7.1	4	ASNA:90, ASPA137,GLUA:132GLNA:127
Momordenol	-7.5	NA	NA
Momordicinin	-8.8	2	LYSA:120,TYRA:46
Momordicoside I	-8.5	1	SERA:205
Momordicoside L	-7	5	GLNA:123,ARGA156,GLNA:127,GLUA147

Momordin I	-9.5	9	TYRA:46,ARGA:221, GLNA:266, TRPA:179, GLYA:183, LYSA:116
Momordol	-6.4	2	LYSA:197,ASNA:193
Multiflorenol	-8.4	1	ARGA:238
Oleic acid	-5.6	NA	NA
Petroselinic acid	-5.5	2	LYSA:197, ASNA:193
Rubixanthin	-8.4	NA	NA
Sitogluside	-7.6	NA	NA
Taraxerol	-8	1	GLUA:76
Zeaxanthin	-8.6	NA	NA
alpha-Eleostearic acid	-6.3	1	GLUA: 276
alpha-Spinasterol	-7.9	NA	NA
beta-Cryptoxanthin	-8.9	NA	NA
elasterol	-7.5	1	ALAA:189
flavochrome	-8.3	NA	NA
lutein	-8.4	NA	NA
lycopene	-7.4	NA	NA
oleanolic	-8.6	1	ASNA:162

CONCLUSION

The present study identified momordin I from *M. charantia* to play a prime role in the management of diabetes mellitus. Further, it adds scientific literature to provide an additional mechanism of action for the management of diabetes mellitus. However, the findings of the present study are only based on the computer simulations which need to be validated by using experimental protocols.

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Conflict of Interest

Nil

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