Research Journal of Pharmaceutical, Biological and Chemical Sciences

Bioinformatics Based Study on *Curcumin* Pharmacophore and its Suitability as Natural Remedy for Diabetes.

Yedavelli Sarang Reddy, Madhuri Girdhar, Anand Mohan, Vishnu Mohan, and Neeta Raj Sharma*.

School of Biotechnology and Biosciences, Lovely Professional University, Phagwara, Punjab, India.

ABSTRACT

The present study was aimed to design, evaluation and screening of potent ligand for binding with peroxisome proliferators-activated receptor (PPAR) gamma. Curcumin and some of its herbal congeners were taken into consideration to evaluate their anti diabetic and binding affinity to PPAR gamma. Most of these herbal compounds have also earlier been known for their potent binding affinity as compared to other known drugs. The binding affinity of curcumin at binding sites of PPAR was compared with that of 'Pioglitazone' a known drug and it was found that curcumin may act as potent regulator of PPAR gamma. The Pharmacophore and docking based study establishes these herbal compounds on comparative levels with synthetic drugs along with added benefits of less side effects considering adsorption, distribution, metabolism, elimination and toxicity (ADMET) properties for diabetes. Further with the help of Chemdraw 10.0, T.E.S.T and Argus Lab 13, modified compound structures were obtained and their binding capability with the binding site is studied. The curcumin derivative compounds namely Mod 2 and 3 were found to be the best derivatives having negligible mutagenicity and also high binding capability among all Mod compounds.
Keywords: Diabetes, Peroxisome proliferators-activated receptor, Curcumin, Pioglitazone, ADMET

*Corresponding author

INTRODUCTION

Diabetes is a chronic disorder in metabolism of carbohydrates, proteins, and fat due to absolute or relative deficiency of insulin secretion with/without varying degree of insulin resistance [1, 2]. Also, it may be defined as a disease where the body either produces little insulin/ceases to produce insulin, or becomes progressively resistant to its action [3]. It has now become an epidemic with a worldwide incidence of 5% in the general population. As it is evident from the available studies that most of the food we eat is broken down into simple sugar called glucose. This glucose is the main source of fuel to get energy for the body. After digestion, the glucose reaches our blood stream where it is available for body cells to utilize for energy, but insulin is needed for the glucose to get into cells. Insulin is a hormone secreted by the pancreas to transport glucose from blood into different cells of the body. If the pancreas does not produce enough insulin or the produced insulin does not work properly, the glucose cannot enter the body cells so it stays in the blood cells, which makes the blood sugar level high. Diabetes is initially characterized by a loss of glucose homeostasis. The major effects of insulin on glucose, fatty acid, and amino acid metabolism and on ion flux are initiated by the attachment of the insulin molecule to a specific insulin receptor on the cell surface. This hormone receptor interaction is reversible, and the insulin molecule is not chemically altered during this contact. The hormone receptor complex is then internalized by an endocytotic mechanism. Insulin molecule eventually is metabolized, and the insulin receptor is recycled into the membrane for re usage [4,5]. The normal blood glucose level is 80 mg/dl on fasting and up to 160 mg/d in the postprandial state. Sugars between 6.1 and 7.0 mmol/L (110 and 125 mg/dL) are considered to have impaired fasting glucose and patients with plasma glucose at or above 140 mg/dL or 7.8 mmol/L two hours after a 75 g oral glucose load are considered to have impaired glucose tolerance.

There are above 800 medicinal plants reported to be with antidiabetic potential. Ethnopharmacological surveys indicate that more than 1200 plants are used in traditional medicine for their alleged hypoglycemic activity [6]. Ancient literature indicates that diabetes was fairly well conceived in ancient India. Its earliest reference (1000 BC in the Ayurvedic literature) is found in mythological form where it is said to have originated by eating Havisha [7], a special food, which used to be offered at the times of yagna organized by Dakshaprajapati.

Curcumin present in turmeric is a part of Havisha which occurs naturally in the roots of the herb *Curcumin longa* (Turmeric) and is isolated by steam distillation. Essential oil of C.longa yields ranging between 1.3 & 5.5 % oil, in addition it contain Tumerone, free acids, cineol, Borneol, Zingerone, Phellandrene, and 3-4% curcumin [7].

Some herbs have also been known to facilitate the regeneration process of ß-cells and in overcoming resistance. In addition, some herbs are also revealed to show antioxidant activity and cholesterol-lowering action. The management of type 2 diabetes mellitus (NIDDM) is possible with the drugs that can lower the blood sugar level in one hand and restore the liver glycogen level on the other [8]. There is no such drug which posses both of these properties. However, the hypoglycemic effect of some herbal extracts have been confirmed in human and animal models of type 2 diabetes and conventional drugs have been derived from the active constituents of these medicinal herbs. Metformin, a less toxic biguanides and potent oral glucose-lowering agent, was developed from *Galega officianalis* and used to treat diabetes [9]. Out of dozens of oral medications for diabetes, only one medication (metformin) is approved for use in children and it has been originated from herbs.

Potential of curcumin as antidiabetic agent is studied, whose chemical structure is analysed with respect to conventional synthetic drugs for diabetes where pharmacophore of these drugs are compared with curcumin. The macromolecule structure of peroxisome proliferators-activated receptor (PPAR) gamma was obtained from PDB having micro molecule Pioglitazone bounded to its site and flexible docking was carried out utilizing these binding sites and also further binding analysis was carried out referring the existing literature [10]. ADMET properties of curcumin was compared with synthetic drugs.

MATERIAL AND METHODS

The chemical structure of curcumin was obtained from pubchem with SID 12626 its chemical structure was analysed by PyMol.
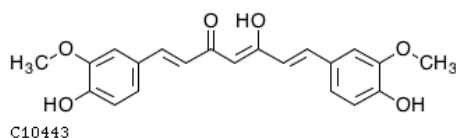

Figure: 1 Structural representation of Curcumin (Pubchem SID 12626)

Thiazolidinediones drugs in drug bank were given 5 hits namely Pioglitazone, Rosiglitazone, Troglitazone, Repaglinide, Nateglinide with accession number DB01132 (APRD00653), DB00412 (APRD00403), DB00197 (APRD00488), B00912 (APRD00439), DB00731 (APRD00593) respectively. The structure were downloaded in mol format and were analyzed using PyMol. Above mentioned drugs selectively stimulate nuclear receptor peroxisome proliferators-activated receptor gamma (PPAR-gamma). They modulate the transcription of the insulin-sensitive genes involved in the control of glucose and lipid metabolism in the lipidic muscular tissues and in the liver. Various derivatives and modifications are carried out from the basic structure of curcumin as drug design model wherein quantitative structural analysis, toxicity and mutagenic properties of these drugs are studied using a T.E.S.T software procured from United States Environmental Protection Agency (http://www.epa.gov/nrmrl/std/qsar/install.exe). Flexible docking was performed.

The binding sites and related energy output were utilized in analysis and establishment of curcumin as a potential herbal antidiabetic agent. The binding site of "Peroxisome Proliferator-Activated Receptor Gamma" was obtained from Protein Data Bank (PDB).

RESULTS AND DISCUSSION

The computational analysis of Curcumin with chemically synthesised five drug molecules have shown that they have a similar pharmacophore structure that can be used as an antidiabetic drug. These five drug molecules were aligned with curcumin molecule using PyMol. The pharmacophore structure of drug molecules is attained and is represented as below.
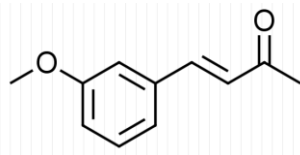
Figure 2: Pharmacophore of five synthetic drugs (Chem Doodle 5.0.1)

Using pharmacophore structure, modified curcumin molecule has shown the binding affinity with PPAR-Gamma which has resulted proposed structure of drug that seems far more superior than curcumin. The SMILES (Simplified Molecular Input Line Entry Specification) format of this pharmacophore was obtained with the help of Symyx draw and was used to validate its structure by researching in Drug bank that gave the perfect hit of all five drug molecules. The alignment results of five drug molecules along with executive RMS value are shown in Table 1.

Table 1: Comparison of RMS values of five drug molecules

Name of molecule	Executive RMS	No of atoms aligned
Pioglitazone (Fig:3)	1.901	20
Rosiglitazone (Fig:5)	2.505	20
Troglitazone (Fig:7)	3.773	25
Repaglinide (Fig:6)	1.897	21
Nateglinide (Fig:4)	3.206	24

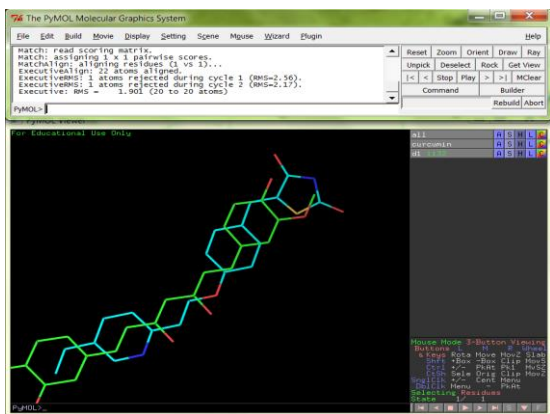*If Zero RMS value is considered as a perfect match

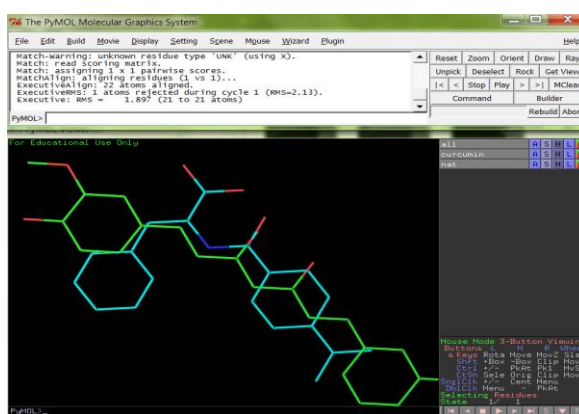Figure 3: Curcumin (green) and Pioglitazone (blue)

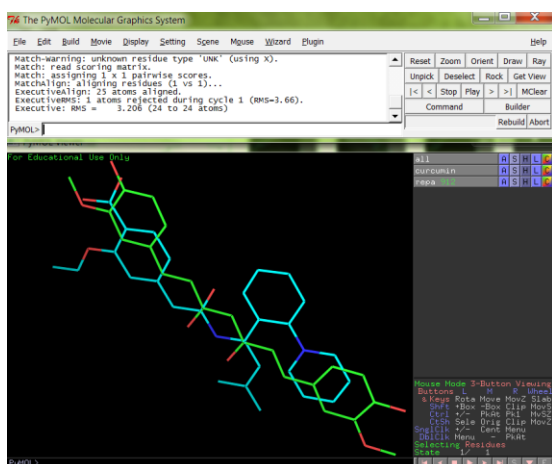Figure 4: Curcumin (green) and Nateglinide (blue)
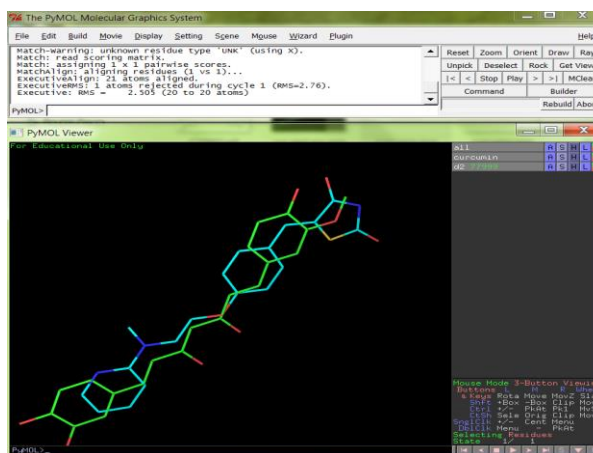

Figure 5: Curcumin (Green) and Rosiglitazone (blue)

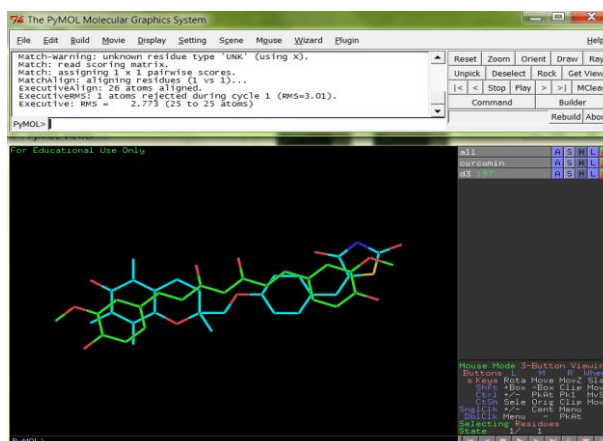Figure 6: Curcumin (Green) and Repaglinide (Blue)

Figure 7: Curcumin (Green) and Troglitazone (Blue)

The binding Energy of Pioglitazone at the binding sites of 1475 and 1478 was found to be -10.88 kcal/mol and -10.96 kcal/mol respectively. The binding analysis of Curcumin through Argus Lab (www.arguslab.com) has shown that Curcumin also has binding potential at site number 1475 with binding energy of -6.65 kcal/mol (pose 1) when compared to -5.82kcal/mol (pose 2) have shown greater binding energy which shows binding of molecule in pose 1 is easier. The same when performed at site 1478 has shown binding energy of -5.23 kcal/mol (pose 1) when observed with pose 2 that is 5.07kcal/mol and the bound structure are represented below respectively.
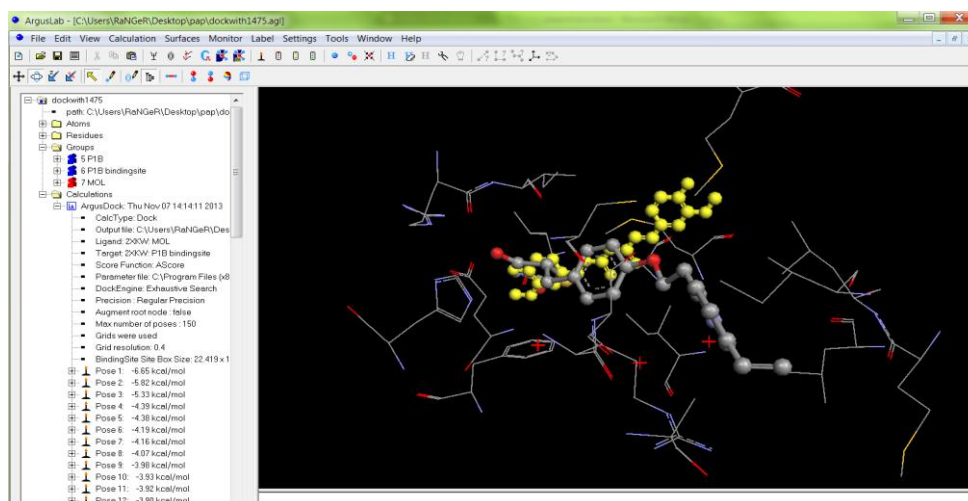
Figure 8: Binding of Curcumin(Yellow) at binding site of Pioglitazone(Grey) at site 1475(pose 1) (Binding Energy -6.65 Kcal/mol)
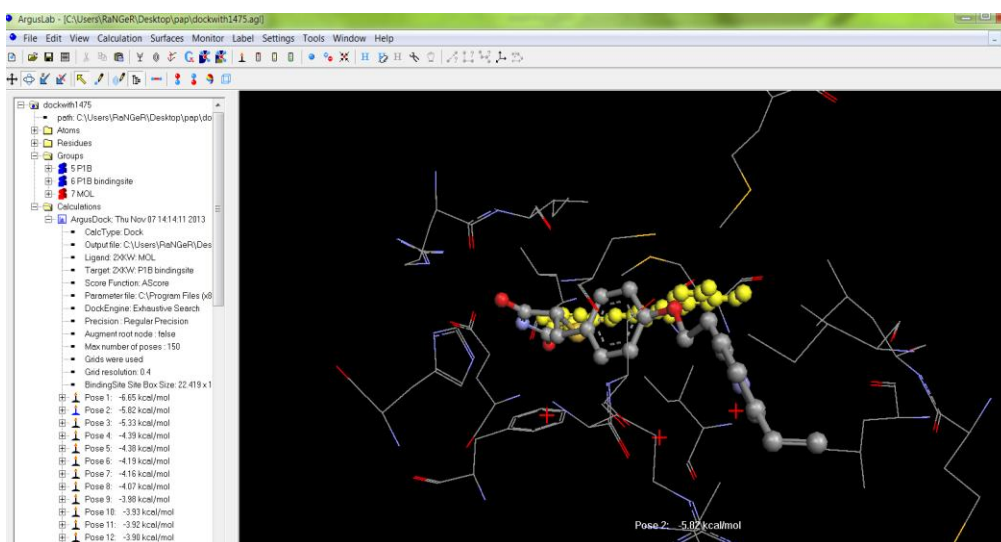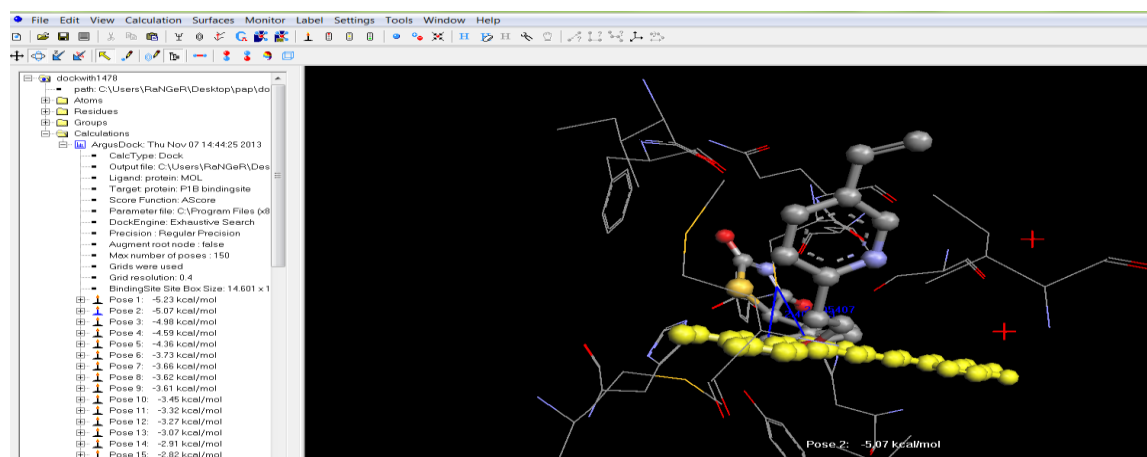

Figure 9: Binding of Curcumin(Yellow) at binding site of Pioglitazone (Grey) at site 1475 (pose 2) (Binding Energy -5.82 Kcal/mol)
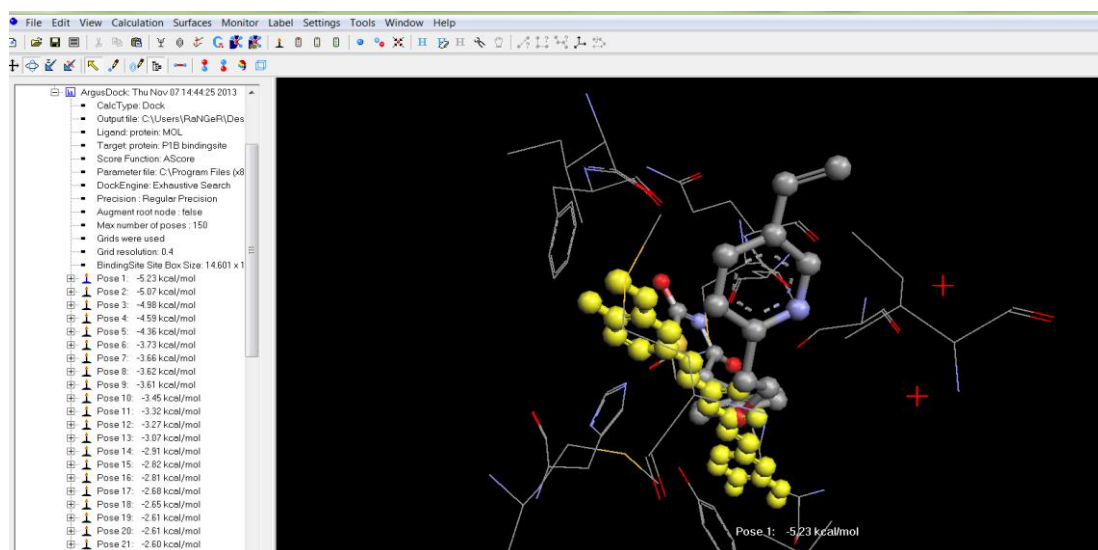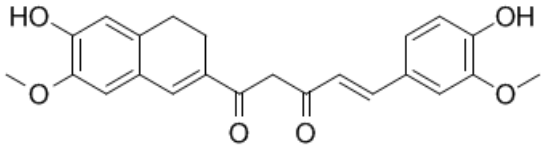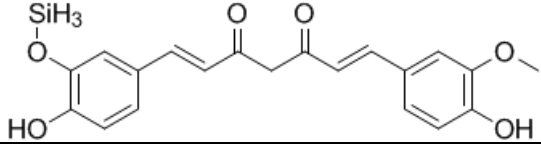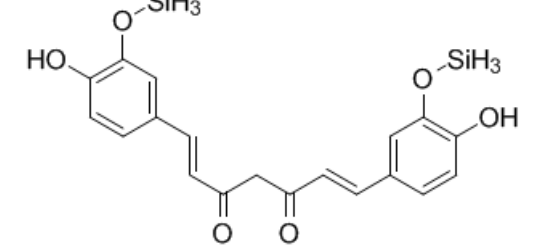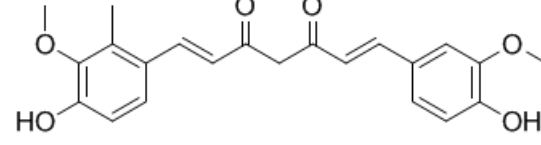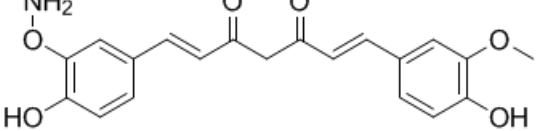
Figure 10: Binding of curcumin(Yellow) at binding site of Pioglitazone(Grey) at site 1478 (pose 1) (Binding Energy -5.23 Kcal/mol)
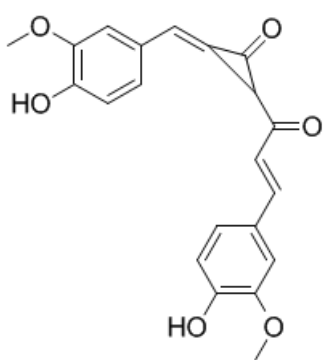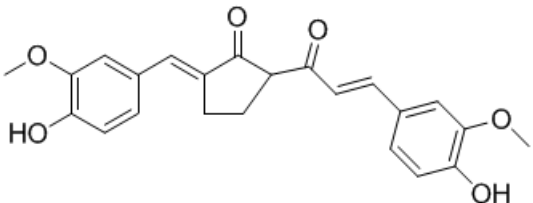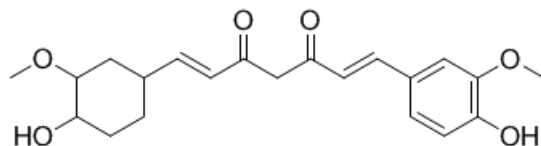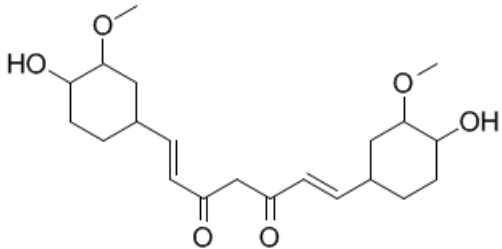
Figure 11: Binding of curcumin(Yellow) at binding site of Pioglitazone(Grey) at site 1478 (pose 2) (Binding Energy -5.07 Kcal/mol)

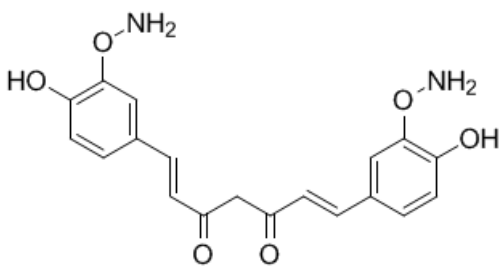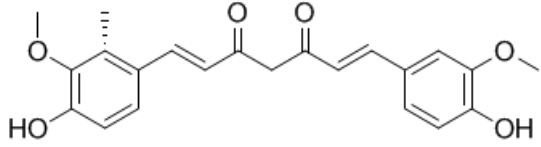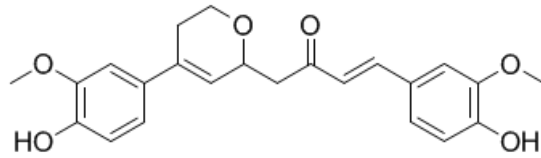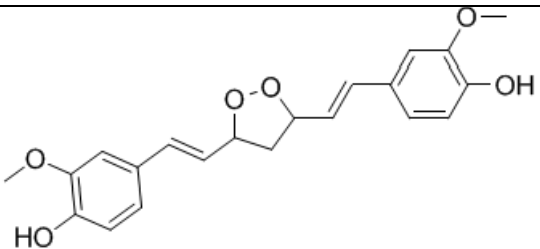The structure of modified curcumin compounds and their IUPAC names are given below in the Table 2.

Serial Number	Given Name	Structure	IUPAC name
1	Mod 1		(E)-5-(4-hydroxy-3-methoxyphenyl)-1-(6-hydroxy-7-methoxy-3,4-dihydronaphthalen-2-yl)pent-4-ene-1,3-dione
2	Mod 2		(1E,6E)-1-(4-hydroxy-3-(silyloxy)phenyl)-7-(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione
3	Mod 3		(1E,6E)-1,7-bis(4-hydroxy-3-(silyloxy)phenyl)hepta-1,6-diene-3,5-dione
4	Mod 4		(1E,6E)-1-(4-hydroxy-3-methoxy-2-methylphenyl)-7-(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione
5	Mod 5		(1E,6E)-1-(3-(aminooxy)-4-hydroxyphenyl)-7-(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione

6	Mod 6		(1E,6E)-1,7-bis(3-(aminooxy)-4-hydroxyphenyl)hepta-1,6-diene-3,5-dione
7	Mod 7		(1E,6E)-1-(4-hydroxy-3-methoxy-2-methylphenyl)-7-(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione
8	Mod 8		(E)-4-(4-hydroxy-3-methoxyphenyl)-1-(4-(4-hydroxy-3-methoxyphenyl)-5,6-dihydro-2H-pyran-2-yl)but-3-en-2-one
9	Mod 9		4,4'-(1E,1'E)-2,2'-(1,2-dioxolane-3,5-diyl)bis(ethene-2,1-diyl)bis(2-methoxyphenol)
10	Mod 10		(E)-2-(4-hydroxy-3-methoxybenzylidene)-3-((E)-3-(4-hydroxy-3-methoxyphenyl)acryloyl)cyclopropanone
11	Mod 11		(E)-2-(4-hydroxy-3-methoxybenzylidene)-5-((E)-3-(4-hydroxy-3-methoxyphenyl)acryloyl)cyclopentanone
12	Mod 12		(1E,6E)-1-(4-hydroxy-3-methoxycyclohexyl)-7-(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione

| 13 | Mod 13 | | (1E,6E)-1,7-bis(4-hydroxy-3-methoxycyclohexyl)hepta-1,6-diene-3,5-dione |

Table 2: Thirteen derived compounds with their structure and IUPAC names

Further analysis of the derived compounds has shown that the binding energy can be increased and further results of these 13 derived compounds have shown below with their RMS values and binding scores at positions 1475 and 1478 respectively.

S.No	Compound Name	RMS Values	Binding Energy value at 1475 (kcal/mol)	Binding Energy value at 1478 (kcal/mol)
1	Mod1	0.386	-7.84	-6.42
2	Mod2	0.006	-7.09	-7.59
3	Mod 3	1.398	-8.49	-7.80
4	Mod4	0.006	-5.81	-5.17
5	Mod5	0.386	-7.88	-7.60
6	Mod6	1.398	-9.31	-7.46
7	Mod7	0.006	-6.00	-5.17
8	Mod8	0.005	-7.21	-6.24
9	Mod9	0.381	-7.78	-6.90
10	Mod10	1.507	-7.78	-7.30
11	Mod11	0.236	-4.97	-4.95
12	Mod12	0.973	-4.95	-5.63
13	Mod13	2.192	-8.78	-7.78

Table 3: Modified Curcumin compounds with RMS values and binding energies at position 1475 and 1478.

The analysis of Pioglitazone synthetic drugs and 13 derivatives of curcumin, was done and values were compared with respect to mutagenicity, bio-accumulation factor and oral rat LD 50 have been shown in the Table 4, using T.E.S.T. software. Considering the values, Mod 1 and Mod 2 curcumin derivatives were found with antidiabetic potential and can be explored further in wet lab to authenticate the results.

S.No	Compound Name	Oral Rat LD 50 (mg/kg)	Bio-Accumulation	Mutagenicity
1	Curcumin	1515.0	17.20	-Ve (0.09)
2	Pioglitazone	1281.55	11.49	-Ve (0.17)
3	Rosiglitazone	1124.86	12.31	-Ve (0.22)
4	Troglitazone	708.37	14.75	-Ve (0.10)
5	Nateglinide	9134.25	4.32	-Ve (0.03)
6	Repaglinide	433.46	11.54	-Ve (0.30)
7	Mod1	1338.16	13.62	-Ve (0.02)
8	Mod2	N/A	N/A	-Ve (0.04)
9	Mod3	N/A	N/A	-Ve (0.16)
10	Mod4	879.94	19.97	-Ve (0.11)
11	Mod5	924.70	N/A	+Ve (0.66)
12	Mod6	1090.60	N/A	+Ve (1.08)
13	Mod7	879.94	19.97	-Ve (0.11)
14	Mod8	1616.17	15.90	-Ve (0.02)
15	Mod9	3806.45	17.59	-Ve (0.03)
16	Mod10	686.99	13.13	-Ve (0.18)
17	Mod11	602.02	20.03	-Ve (0.02)
18	Mod12	517.09	5.00	-Ve (0.03)
19	Mod13	272.46	3.06	-Ve (0.09)

Table 4: Five synthetic drugs, curcumin and 13 derivatives of curcumin comparative values of oral rat LD 50, bio-accumulation, and mutagenicity

CONCLUSION

As per this preliminary study on curcumin and its derivatives, it is learned that curcumin may act as potent regulator of peroxisome proliferators-activated receptor (PPAR) gamma than known drug Pioglitazone. Earlier studies also revealed that natural herbal compounds have exceptionally high binding affinity for PPAR gamma, and can regulate this receptor for peroxisomal beta-oxidation pathway of fatty acids. Curcumin has been found as a competent compound when compared to that of pioglitazone. Present study also supports that consumption of herbal spices may reduce the risk of diabetes by regulating acyl-CoA oxidase gene and hence PPAR gamma complex. Further structural optimization of these curcumin derivative compounds could open the way for improved modalities for regulation of peroxisomal beta-oxidation pathway of fatty acids to manage/cure diabetes. Chemdraw 10.0, T.E.S.T and Argus Lab were utilized for obtaining 13 modified compound structures and their binding capability with the binding site was obtained. The Mod 3 and Mod 6 were the best compounds showing highest activity for binding. Further analysis of all compounds shows that Mod 6 was having mutagenic activity which was deduced by T.E.S.T software. Mod 2 and Mod 3 compounds were found as the best compound having negligible mutagenicity and also high binding capability among all Mod compounds. These compounds can be explored further for chemical derivatization of curcumin followed by clinical trials for the treatment of diabetes.

ACKNOWLEDGEMENT

REFERENCES

[1]   Barar FSK. 2000. Essentials of Pharmacotherapeutics. 3rd ed. S.Chand and Company Ltd: New Delhi.
[2]   Devlin MT. 1997. Text book of Bio Chemistry. 4th edn. Wileyliss Inc: New York.
[3]   Ranjan C, Ramanujam R. Curr Sci 2002;83: 1533- 38.
[4]   Edwin E, Sheeja E, Gupta VB, Jain DC. Express Pharma Review 20061: 41-2.
[5]   Andrew JK. 2000. Diabetes. Churchill living stone: New York.
[6]   Kesari AN, Kesari S, Santosh KS, Rajesh KG, Geeta W. J Ethnopharmacol 2007;112(2): 305-11.
[7]   Latha M, Pari L. Clin Exp Pharmacol Physiol 2003;30(1-2): 38-43.
[8]   Shrabana C, Tuhin KB, Begum R, Liaquat A, Mosihuzzaman M, et al. J Ethnopharmacol 2003;84: 41-6.
[9]   Daniel SF, Norman RF. Environ Health Perspect 2001;109: 69-75.
[10]   Singh DB, Gupta MK, Kesharwani RK, Misra K. Netw Model Anal Health Inform Bioinforma 2013;2: 13–27.