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Original Article

IN SILICO MOLECULAR DOCKING AND PHARMACOKINETIC PREDICTION OF GALLIC ACID DERIVATIVES AS PPAR-γ AGONISTS

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ABSTRACT

Objective: To perform molecular docking and pharmacokinetic prediction of gallic acid derivatives as Peroxisome proliferator-activated receptors-γ (PPAR-γ) agonist for the treatment of diabetes.

Methods: Molecular docking study on gallic acid and different derivatives of gallic acid was performed using GOLD v5.2 software. In addition to this, all the derivatives were analysed for drug likeliness, Lipinski's rule and ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties using online tools like admet SAR, Molinspiration and Medchem designer.

Results: Molecular docking studies reveals that SSP-12, SSP-13 and SSP-40 demonstrated significant binding to the PPAR-γ receptor with good Gold score fitness (73.11, 69.86 and 75.51 respectively) and relative ligand energy (-8.26,-8.33 and-7.82, respectively) as compared to standard drugs i.e. rosiglitazone and pioglitazone, (64.10 and 66.72) and (-4.30 and-2.47) respectively.

Conclusion: The final results of molecular docking along with information gathered from pharmacokinetic parameters of gallic acid derivatives may be utilised further for the development of newer PPAR-γ agonists having anti-diabetic potential with better pharmacokinetic and pharmacodynamic profile.

Keywords: Diabetes, Gallic acid, *In silico* designing, Molecular docking, PPAR-γ

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INTRODUCTION

Diabetes mellitus is a leading endocrine disorder and approximately 7% people of the world's total population are suffering from this chronic disorder [1]. It is a chronic disorder which not only affects the carbohydrate metabolism but also alters lipid and protein metabolism on the long term and may lead to microvascular as well as macrovascular complications that are more fatal than the primary diabetic state, and all credit goes to diabetic oxidative stress [2]. These vascular complications alter the physiological functions of vital organs, causing an increase in morbidity state and ultimately reduced the quality of life [1, 3]. The commonly prescribed therapeutic drugs for the treatment of diabetes includes oral hypoglycemic agents and insulin therapy, which have limitations in their own way. This indicates the need for the development of newer agents with reduced adverse events [4].

Peroxisome proliferator-activated receptors (PPAR) are the nuclear receptors, present in three different isoforms; PPAR-α, PPAR-β and PPAR–γ. PPARs are expressed in different tissues where catabolism of fatty acid takes place, i.e. liver, white and brown adipose tissues, heart, kidney and skeletal muscles, but white and brown adipose tissues contain a greater expression of PPAR-γ. Upon activation by fatty acids and fatty acid-derived eicosanoids, PPARs form heterodimers with retinoid-X-receptors (RXRs). These PPAR-RXR heterodimers bind with the precise sequence termed as a Peroxisome Proliferator-Response Element (PPRE) and ultimately activate or suppress the transcription of specific target genes [5]. Numerous synthetic ligands are identified for PPAR-γ agonistic activity and are widely used for the treatment of type-II diabetes mellitus as they restore the insulin sensitivity. This insulin sensitising property is attributed to direct effect on adipose tissues to improve fatty acid metabolism and also improve glucose utilisation in skeletal muscles and hepatocytes [6, 7].

PPAR-γ agonist promotes adipogenesis and accelerates adipocytes differentiation by promoting the uptake of Free Fatty Acid (FFA) in subcutaneous adipose tissues. An agonist of PPAR-γ decreases circulating FFA through improved uptake of FFA and thereby decreases associated insulin resistance. Transcription of glucose transporter GLUT-4 also improved by PPAR-γ agonist treatment improves the glucose uptake into skeletal muscles and hepatic cells [8]. In addition to this, PPAR-γ agonist also improves the adiponectin level with decreased level of inflammatory cytokine TNF-α and all these together improve the insulin sensitivity [9, 10]. Although PPAR-γ agonists, viz. rosiglitazone and pioglitazone, are well tolerated, use related incidences of cardiovascular complications are well known. Patients are having a history of heart failure, edema and anaemia are advised to take glitazones with cautious and required hepatic function test to monitor the toxicity [11]. To overcome or minimise the adverse effects related to cardiovascular events, it is crucial to search for new potent ligands having a favourable pharmacological profile.

Gallic acid (3,4,5-trihydroxy benzoic acid) is tannin, mainly obtained from *Emblica Officinalis* and many other plants by hydrolysis of gallo-tannins with sulfuric acid. Gallic acid contains two functional groups in the same molecule, i.e. carboxylic acid group and hydroxyl groups, which can produce different ester derivatives [12]. Gallic acid obtained from *E. Officinalis* showed good anti-diabetic activity in animal models of type two diabetes and showed up-regulation of the PPAR-γ and GLUT-4 expression in 3T3-L1 pre-adipocytes [13]. In spite of this, molecular docking study also suggested safety of the gallic acid [14]. We have designed different gallic acid derivatives for PPAR-γ agonistic activity in order to obtain good anti-diabetic activity.

Structure-based drug designing (SBDD) is an important tool for development of new molecules using X-ray crystal structure of a protein from protein data bank. In molecular modelling techniques, drug-receptor complex stability, exact binding mode and interaction of the ligand with amino acids of the protein molecule can be visualised using docking methodology. Various software is available to carry out docking simulations, i.e. GOLD, Molegro Virtual Docker,

Autodock, FlexX, Schrödinger and many more. In this study, GOLD v5.2 was utilised to study the interaction of gallic acid derivatives with PPAR-γ receptor (PDB id-4EMA).

MATERIALS AND METHODS

Software utilized

GOLD (Version 5.2 CCDC, Cambridge, UK) was used for docking study. Sketch function and Tripos force field of SYBYL-X 1.2 (Tripos Ltd.) were accessed for drawing structures and energy minimization, respectively. Several online servers, viz. admet SAR, Molinspiration and Medchem designer were accessed to predict various molecular properties, toxicity and bioactivity of the designed gallic acid derivatives. (www. lmmd. ecust. edu. cn, accessed on 12th march 2015 for prediction of ADMET properties, www. molinspiration. com, accessed on 12th march 2015 to extrapolate drug likeliness and bioactivity score and www. simulations-plus. com accessed on 13th march 2015 for molecular property predictions).

Docking methodology

The X-Ray crystallographic structure of PPAR-γ protein, co-crystallized with rosiglitazone (PDB ID 4EMA), was derived from the RCSB Protein Data Bank (PDB, www. rcsb. org/pdb, accessed on 15th march 2015) and utilised for further docking study. In the further communication, the PDB id 4EMA represents the crystal structure of the PPAR-γ receptor.

The genetic algorithm in GOLD (version 5.2, CCDC, Cambridge, UK), computer based program installed in 3.3 GHz Intel Core i3 processor and 2 GB RAM, having windows 7 Professional as an operating system, was utilised to perform automated docking studies to predict the protein-ligand interaction as described earlier [15]. The algorithm had been previously validated. It includes protein and ligand preparation followed by docking algorithm. Initially, all the water molecules, metals and ligands were removed from PDB protein and were loaded in the Hermes module of GOLD and subsequently hydrogen atoms were added. The active site chain was selected, and the binding site was identified by co-crystallized ligand interaction with the protein. In the docking methodology, each ligand was kept as a flexible while amino acid in protein was held rigid. All the selected gallic acid derivatives under the study were docked into the binding site of the active chain of 4EMA using GOLD. The GOLD program uses a genetic algorithm to explore the full range of ligand conformational flexibility and the rotational flexibility of selected receptor hydrogens. In the docking process, a maximum number of 10 diversified conformations were taken into consideration and the conformer having highest binding score was utilised for further analysis. The Gold score is a function of molecular mechanics like S (hb_ext), S(vdw_ext), S(hb_int) and S(int). Gold score, relative ligand energy and possible amino acid interaction of top five selected derivatives are shown in table 1. The fitness score obtained from the GOLD, can be obtained from the below equation:

$$\text{Fitness} = S(hb_{ext}) + 1.375 \times S(Vdw_{ext}) + S(hb_{int}) + 1.000 \times S(Vdw_{int})$$

Where, S(hb_ext) and S(Vdw_ext) represent the protein-ligand H-bond score and van der Waals scores, respectively. S (hb_int) reveals the Fitness based upon intracellular H-bonds while S (Vdw_int) represent intramolecular strain within the ligand.

Ligand preparation

The ligand compound designed using sketch function of SYBYL-X 1.2 (Tripos) and energy minimization was simultaneously done using the Tripos force field in SYBYL-X 1.2. Ligand preparation includes the addition of gasteiger-huckel charges, polar hydrogen and keeping rotatable bond then energy minimised confirmation of all the designed derivatives of gallic acid saved in. mol^2 format and all the ligands were coded by SSP.

Protein preparation

PPAR-γ protein co-crystalized with rosiglitazone was obtained from RCSB Protein Data Bank at a resolution of 2.55 Å and refined by subtracting water molecules and the addition of hydrogen bond and gasteiger-huckel charges. The structure of PPAR-γ is composed of two polypeptide chains with 275 amino acids. The protein was refined by an assortment of the active site, identification of the active binding site and extraction of co-crystallized rosiglitazone from the active site. The Gold scoring and ranking was used as an outcome of molecular screening.

Validation

To validate docking protocol, co-crystallized ligand rosiglitazone was utilised. During protein preparation, co-crystallized rosiglitazone was extracted from 4EMA and the extracted ligand was re-docked into the active site of the refined protein. Validation was performed by computing the RMSD value by overlying the structures of co-crystallized ligand and re-docked ligand.

Prediction of ADMET properties for the designed derivatives

Drugs were withdrawn at the different stages of the clinical trials and from the market during the post-marketing surveillance (phase 4) owing to have poor ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties and adverse events which are directly or indirectly associated with the molecular structure of the drugs. Therefore, *in silico* prediction of ADMET properties plays an important role during the lead identification and optimisations.

Admet SAR is a free online server used to predict ADMET properties like human intestinal absorption, BBB^+ penetration, $CACO^{-2}$ permeability, biodegradability, AMES toxicity, carcinogenicity, rat acute toxicity, etc. The ADMET properties of gallic acid derivatives were estimated using admetSAR online database (www. lmmd. ecust. edu. cn, accessed on 12th march 2015 to predict ADMET properties). It provides inclusive data for different entities linked with known ADMET profiles [16].

Bioactivity score prediction

Bioactivity of different gallic acid derivatives can be checked by calculating the activity score of GPCR ligand, ion channel modulator, nuclear receptor ligand, kinase inhibitor, a protease inhibitor, enzyme inhibitor [17]. All these parameters were obtained using an online server database, molinspiration drug likeliness (www. molinspiration. com), and calculated drug likeliness scores of gallic acid derivatives were compared with the standard drug rosiglitazone.

Molecular properties prediction

Lipinski's rule of five (RO5) was used to evaluate drug likeness and/or to determine if a chemical compound with a certain pharmacological or biological activity has properties that would make it an orally active drug like moiety for humans. Essential molecular properties such as molecular weight, hydrogen bond donor, hydrogen bond acceptor, log*P* of different gallic acid derivatives were calculated using Medchem Designer (www. simulations-plus. com).

RESULTS AND DISCUSSION

In the present study, initially, a set of 72 compounds with the different substitution in core gallic acid moiety were evaluated through GOLD molecular docking against PPAR-γ (4EMA).

All the ligands of gallic acid derivatives were engendered (supplied in supplementary data fig. S1) while Chemical structure of standard drugs, gallic acid and top six selected compounds shown in fig. 1. And energy minimization was attained by SYBYL. The GOLD module was validated for docking protocol.

The RMSD value was found to be 0.985 and the superimposed structure was shown in the fig. 2. From the 72 ligands used for docking, 41 derivatives were found to have a higher Gold fitness score as compared to gallic acid i.e. 44.30 and were utilised for the further study. The results were analysed in terms of Gold scores and relative ligand energy which are ranging from 46.32 to 95.50 and -33.05 to -0.007 Kcal/Mol, respectively.

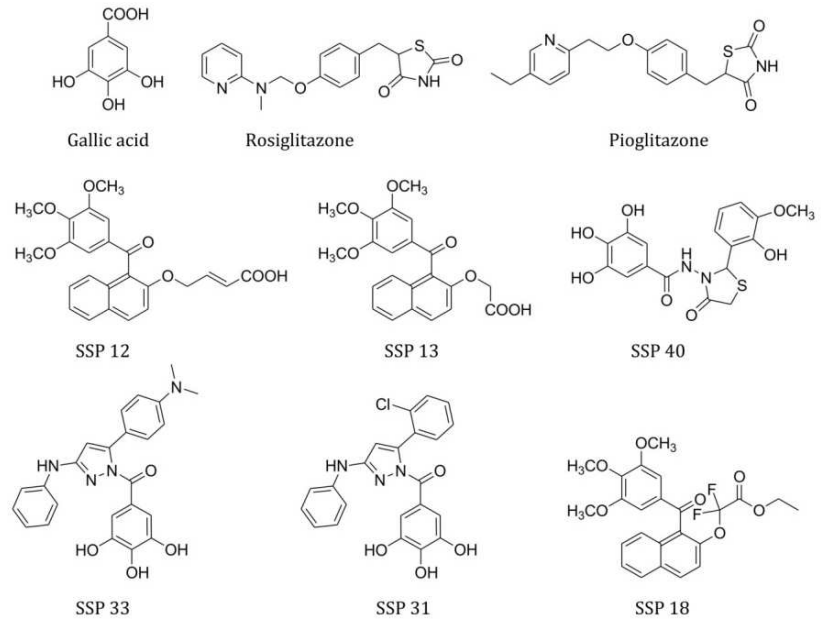

Fig. 1: Chemical structure of standard drugs, gallic acid and top six selected compounds

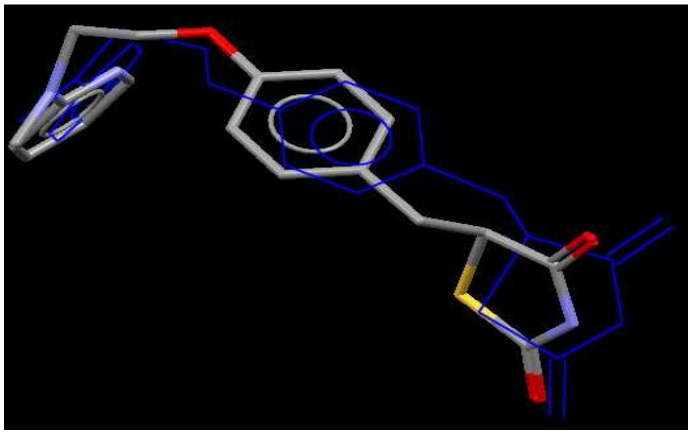

Fig. 2: Re-docked rosiglitazone blue superimposed with co-crystallized ligand (Rosiglitazone) in the PPAR-γ (4EMA)

Structure-functional relationship of gallic acid and other derivatives of gallic acid were gaged to predict the biological activity using 4EMA, acquired from Protein Data Bank. For documentation of biological interaction with protein, docking scoring function was utilised. Binding pattern of gallic acid and different derivatives of gallic acid was found to be varied with the molecular conformation of the ligand. PPAR-γ standard ligand rosiglitazone showed H-bond interaction with amino acid residues of Ser289 and His449 with 64.10 Gold fitness score and -2.47 relative ligand energy, while pioglitazone interacted with Phe282 and Ser289 amino acid residue. On the other side, the gallic acid interaction was observed with Phe282, Gln286, Ser289 and Tyr327 with best fitness score of 44.30 and -5.69 relative ligand energy which is shown in fig. 3.

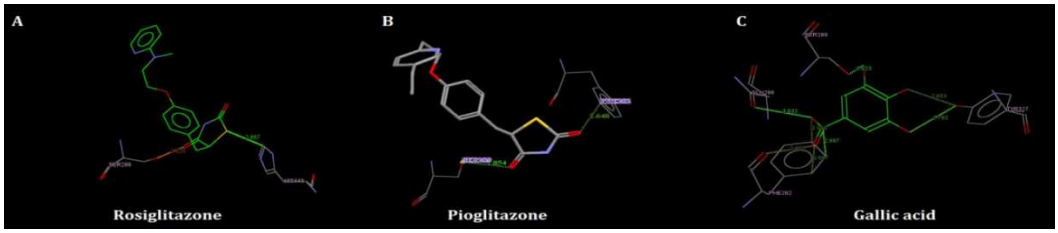

Fig. 3: Hydrogen bond interactions of A) Rosiglitazone, B) Pioglitazone and C) Gallic acid with amino acid residues of PPAR-γ (4EMA)

The previous pharmacophore study showed that hydrophobic pocket of PPAR-γ comprises of mainly five amino acid residues, to wit Gln286, Ser289, His323, His449 and Tyr473, responsible for hydrogen bond formation during the interaction. Besides of this, Arg280, Ile281, Gly284, Arg288, Ile341 and Glu343, amino acid residues of PPAR-γ, form a hydrophobic pocket, responsible for

direct or indirect hydrophobic interactions. The linker between the polar head and hydrophobic tail also plays an important role in binding of the ligand with PPAR-γ [18]. The compounds were selected based upon the number of interactions with active amino acids enlisted in the earlier pharmacophore.

However, few derivatives of gallic acid like SSP-12 and SSP-13 showed a higher Gold score, 73.11 and 69.86 respectively. The interaction of SSP-12 was noticed with five amino acids of 4EMA protein, three of which are from the pharmacophore described by Sohn *et al.* i.e. Ser289, His323 and Tyr473, whereas SSP-13 showed binding pattern with different five amino acids (Phe282, Ser289, Tyr473, His449, Cys285); three of which are from the pharmacophore as shown in fig. 4 [18]. Other derivatives viz. SSP-40, SSP-33 and SSP-31 also showed a higher Gold fitness score through interaction with additional amino acids as compared to standard rosiglitazone and pioglitazone, while derivatives showing subordinate Gold fitness were excluded from the study (supplied in supplementary data table S1). These docking results with 4EMA revealed that the designed molecules, containing gallic acid moiety, interact with PPAR-γ protein active site.

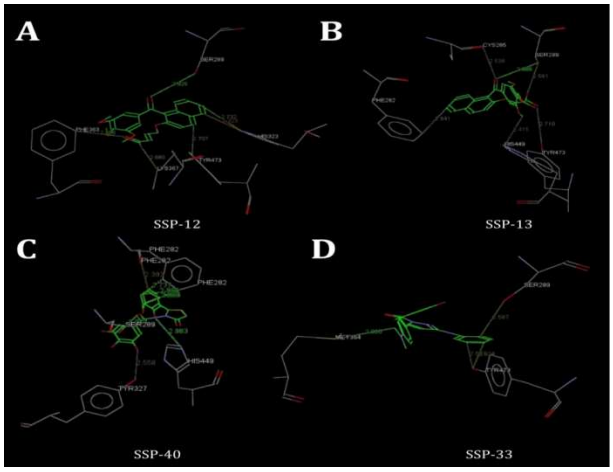

Fig. 4: Hydrogen bond interactions of A) SSP-12, B) SSP-13C) SSP-40 and D) SSP-33 with PPAR-γ amino acid residues (4EMA)

Table 1: Docking results and predicted Lipinski's rule of five for top five selected gallic acid analogues

Molecules	Best Gold Score Fitness	Relative Ligand Energy Kcal/Mol	Hydrogen Bond Interaction	Lipinski Properties				T PSA
				Hydrogen Bond Donner	Hydrogen Bond Acceptor	Molecular Weight (g/Mol)	AlogP	
Rosiglitazone	64.10	-2.47	Ser 289, His 449	1	6	343.40	2.31	71.53
Pioglitazone	66.72	-4.30	Phe 282, Ser 289	1	5	356.44	2.31	68.29
Gallic Acid	44.30	-5.69	Phe 282, Gln 286, Ser 289, Tyr 327	4	5	170.12	0.68	97.99
SSP-12	73.11	-8.26	Ser 289, Lys 367, His 323, Tyr 473, Phe 363	1	7	422.43	3.50	91.29
SSP-13	69.86	-8.33	Phe 282, Ser 289, Tyr 473, His 449, Cys 285	1	7	396.39	2.99	91.29
SSP-40	75.51	-7.82	Ser 289, His 449, Phe 282, Tyr 327	5	9	392.38	1.35	139.56
SSP-33	73.81	-10.92	Met 364, Tyr 473, Ser 289	4	8	430.46	4.13	110.85
SSP-31	73.47	-10.44	Gln 286, Cys 285, Met 364, Ser 289	4	7	421.84	4.74	107.61

Critical observation of the binding interaction of standard rosiglitazone and pioglitazone with 4EMA showed that rosiglitazone interacted via H-bond with two amino acids of the residue, i.e. Ser289 and His449 of the protein while pioglitazone showed two different interactions; Pi-Pi interaction withPhe282 and H-bonding with amino acid residue Ser289 (fig. 3). The binding data of two standard molecules and different derivatives of the gallic acid suggested that H-bond interaction is the most common amongst all the molecules (table 1). Anti-diabetic property of the rosiglitazone and pioglitazone in association with binding interaction with 4EMA denote that the gallic acid and designed analogues of the gallic acid could be efficiently utilised for the control of hyperglycemia inpatient of diabetes. It is interesting to note that standard compounds, viz. rosiglitazone and pioglitazone, gallic acid and many of the gallic acid derivatives have a common binding site either at Phe282 or at Ser289 of the 4MEA protein. All the molecules share some features as described earlier pharmacophore [18].

The molecular descriptors of the different gallic acid derivatives were evaluated for Lipinski's rule of five, and all the mentioned derivatives have a molecular weight in the range of 200-500 except two molecules, i.e. SSP-16 and SSP-17. Molecular weight is an important aspect with respect to the medicinal action because as the molecular weight increases beyond the certain limit, the surface area of the compound also increases correspondingly and this ultimately affects the penetrability of the compound [19].

Lipophilicity (log P value) and Topological Polar Surface Area (TPSA) are the two major factors which affect the permeability of the compounds and ultimately determine oral bioavailability [20]. TPSA was obtained as a calculation of the total surface areas occupied by oxygen and nitrogen atoms and hydrogen attached to these molecules. This points out the direct relation of the potential of hydrogen bonding with the TPSA value of the compound. The Log P value of all compounds was analysed by Medchem designer and was found to be less than 5 (table 1). The compounds having ≤ 140 Å TPSA value and rotational bonds of ≤ 10, is more likely to have good bioavailability because rotational bonds give flexibility to the compound and flexible compound can easily interact with specific rigid binding areas [21]. Remarkably, almost all the derivatives showed good numbers of rotational bonds and TPSA value within limits.

Along with the permeability, drug solubility is a critical parameter which affects the pharmacokinetic and pharmacodynamics profile of the drug, starting from the site of administration, absorption into systemic circulation, movement in the blood and excretion. ADMET of the compounds were calculated using online dataset admet SAR [16]. Different permeability i.e. Blood Brain Barrier (BBB) penetration, Human Intestinal Absorption (HIA), Caco2 cell permeability, renal organic cation transport and AMES toxicity test were calculated (data are shown in supplementary table S3). The cytochrome enzymes are mainly involved in the drug metabolism for elimination and/or biotransformation. Major drug-drug interactions are reported due to activation or inhibition of the CYP enzymes and therefore co-administration of the drug might get accumulated to toxic level due to inhibition of CYP enzymes or rapidly excreted due to activation of CYP microsomal enzymes [22]. In the medical field, P-glycoproteins are the major reason for drug resistance or making the cell less susceptible to the drugs. P-glycoprotein mainly involved in the efflux and activation of P-glycoprotein would increase the efflux of the drug and creates drug concentration below the minimal required concentration which may lead to therapeutic failure [23]. Almost all the derivatives of gallic acid, except a few, did not show interaction with P-glycoprotein (shown in supplementary data, table S4). Tumorogic or carcinogenic potential also have a direct or indirect correlation with the molecular properties of the compounds. Carcinogenicity, oral toxicity and acute dose toxicity in rat (LD_{50}) were summarised in supplementary data, table S5. Based on the obtained data from admet SAR, all the derivatives of gallic

acid may be able to pass through the human intestine barrier and can be absorbed from the intestine. The majority of the designed derivatives of gallic acid did not show any toxicity and mutagenicity. The currently available drugs mainly act through interaction with different GPCR ligands, ion channels, nuclear receptors or different kind of enzymes, viz. kinase, protease, etc. and interaction of chemicals with these biomolecules indicate their drug likeliness. All the derivatives of gallic acid were screened for drug likeliness using Molinspiration online tool, and data of top five derivatives are shown in table 2. The molecules having a positive biological value (more than 0.00) are supposed to have good biological activity, the value in between-0.50 to 0.00 are recognised as a mild to moderate active while compounds having biological scoreless than-0.50 are considered to be biologically inactive [24].

Table 2: Predicted biological interaction for top five selected gallic acid analogue, (GPCR-G Protein-Coupled Receptor; CYP-Cytochrome P family; HERG-Human Ether-à-go-go-Related Gene)

Molecules	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor	P-Glycoprotein substrate	CYP450 3A4 inhibitors	CYP450 2D6 inhibitors	CYP Inhibitory promiscuity*	HERG Inhibition
Rosiglitazone	-0.04	-0.89	-0.86	0.11	-0.31	-0.34	0.612	0.567	0.725	0.691*	0.916
Pioglitazone	0.25	-0.51	-0.71	0.64	-0.09	0.05	0.635	0.603	0.808	0.886*	0.934
Gallic Acid	-0.77	-0.26	-0.88	-0.52	-0.94	-0.17	0.663	0.842	0.969	0.931	0.982
SSP-12	0.06	-0.06	0.06	0.32	0.04	0.13	0.575†	0.689	0.657	0.516	0.963
SSP-13	0.07	-0.12	0.01	0.29	0.00	0.11	0.523†	0.844	0.884	0.871	0.969
SSP-40	-0.01	-0.05	0.13	0.13	-0.12	0.09	0.5442	0.850	0.880	0.742	0.995
SSP-33	-0.06	-0.26	0.26	-0.07	-0.18	-0.07	0.539†	0.704	0.862	0.736	0.993
SSP-31	-0.27	-0.30	-0.16	-0.22	-0.34	-0.09	0.688	0.581	0.876	0.500*	0.991
							†substrate	Non inhibitor	Non inhibitor	*high CYP inhibitory promiscuity	Weak inhibitors

In the present study, all the compounds were docked against 4EMA which is a nuclear receptor; hence they should possess significant activity with the nuclear receptor. The results revealed that the derivatives were biologically active and can produce pharmacological action through interaction with the nuclear receptor. All the study compounds showed good biological score except gallic acid and four other derivatives. Although gallic acid did not show the good biological score for nuclear receptors (-0.52), experimental data obtained from western blot showed good biological activity with PPAR-γ (4EMA) in 3T3-L1 pre-adipocytes (supplied in supplementary data fig. S6). However, few derivatives i.e. SSP-11, SSP-12, SSP-13, SSP-17, SSP-18, SSP-19, SSP-23, SSP-39, SSP-40 showed identical or higher biological score than that of standard rosiglitazone (biological score 0.11). SSP-33, SSP-35 and few other derivatives showed a good biological score for Kinase inhibition, which may modulate disease state by an alteration in the signal cascading pathway and may consider as a promising lead for development of the other drugs.

CONCLUSION

In order to achieve efficient treatment for diabetes, development of novel compounds with potential biological activity and minimal or no adverse events, is an exigent need. In the current study, to visualise drug interaction study, gallic acid and numerous derivatives of gallic acid were successfully docked onto the PPAR-γ protein, responsible protein for insulin sensitization, and the fitness scores of the designed compounds were calculated using GOLD 5.2. Although, different derivatives of gallic acid showed different interaction with 4EMA with respect to H-bonding and π-interaction, Gold fitness score support the hypothesis that gallic acid and various derivatives of gallic acid may have substantial anti-diabetic property through up-regulation of PPAR-γ. From the study, it is concluded that gallic acid could be a lead molecule for the development of the novel anti-diabetic agents and in the future, the gallic acid analogues hold immense potential to develop a competent therapy for diabetes. However, further molecular biology study on cell culture and/or animal study will help to address the potential biological activity of the gallic acid derivatives with PPAR-γ.

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CONFLICT OF INTERESTS

The authors declare that are no conflict of interest pertaining to this manuscript

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