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In silico Comparative Molecular Docking Study and Analysis of Glycyrrhizin from *Abrus precatorius* (L.) against Antidiabetic Activity

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Authors' contributions

This work was carried out in collaboration between both authors. Author AJ is involved in secondary metabolite isolation and extraction of pure compound. Authors AJ and PPG designed the study, protocol and performed exercises; the literature survey was carried out by both the authors, wrote the protocol and wrote the first draft of the manuscript. As author PPG being an expert in bioinformatics and cheminformatics the In-silico molecular docking was carried out by him and results were analysed by both the authors. Authors AJ and PPG has read and approved the final manuscript.

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ABSTRACT

Aim: To test and evaluate the anti–diabetic potential using binding energy and pharmacological interaction of glycyrrhizin using *In-silico* molecular interaction strategy against Pioglitazone, Roziglitazone and Miglitol.
Study Design: *In-silico* molecular docking study and analysis of anti-diabetic compounds.
Place and Duration: Department of Biotechnology and Bioinformatics, D Y Patil University, Navi Mumbai, Maharashtra, India between April 2014 and August 2014.
Methodology: The ligands were sketched using Chemsketch and optimized using UFF. Active sites were considered from the crystallized structure of selected complexes Pdb-id: 2XKW, 1FM6 and 3L4W. Molecular docking simulation study is carried out in IGemDock using Genetic algorithm and Pharmacological interactions with binding energies were calculated.

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Results: In the present study, we investigated the anti-diabetic potential of glycyrrhizin by evaluating the *in-silico* binding ability and pharmacophoric interactions of this compound to known inhibitors (Pioglitazone, Roziglitazone and Miglitol). Glycyrrhizin displayed better binding affinity against PPAR gamma and Alpha amylase receptor protein with respect to their inhibitors. Since glycyrrhizin shows a good binding affinity, it holds great promise for use in the treatment of diabetic complications. Results of the docking simulations of glycyrrhizin demonstrated negative binding energies (-123.242 kcal/mol for PPAR gamma against Pioglitazone, -105.847 kcal/mol for PPAR gamma against Roziglitazone and -98.415 kcal/mol for Alpha amylase against Miglitol), which indicated a higher affinity and tighter binding capacity of glycyrrhizin for the active site of the enzyme.

Conclusion: The study finding indicates the potential of glycyrrhizin for the management and treatment of diabetes and diabetes-associated complications. Further specific study in wet lab and a parallel *in-silico* methodology can provide supportive evidence for glycyrrhizin to be use as a suitable alternative in management of diabetes.

Keywords: Glycyrrhizin; molecular docking; Abrus precatorius (L.); antidiabetic.

ABBREVIATION

MM: Molecular Mechanic; ImpTor: Improper Torsion.

1. INTRODUCTION

Diabetes mellitus is a metabolic disorder and is characterized by chronic hyperglycemia accompanied by disturbances of carbohydrate, fat and protein metabolism resulting defects in insulin secretion, insulin action, or both. It is affecting 10% of the population worldwide [1]. The frequency of the diabetes will escalate worldwide, with a major impact on the population of developing countries [2]. The Current studies in India indicate that there is an alarming rise in prevalence of diabetes which has gone beyond epidemic form to a pandemic form [3]. Presently India has got the largest number of diabetics and is being called as diabetic capital of the world [4].

Diabetes is associated with premature mortality. Heterogeneity within the diabetic syndrome results in two types of D*iabetes mellitus*: Type I, insulin-dependent *Diabetes mellitus* and Type II, noninsulin-dependent *Diabetes mellitus*. Type 1 diabetes is caused by the autoimmune destruction of the β-cells of the pancreatic islets, whereas type 2 diabetes results from both impaired insulin secretion and resistance to the action of insulin. Type 2 *Diabetes mellitus* is the more common type and frequently presents with minimal or no symptoms referable to the metabolic aberrations of diabetes. Patients with NIDDM are not dependent on insulin for prevention of ketonuria and are not prone to ketosis. The typical chronic associations and complications of diabetes are macroangiopathy, microangiopathy, neuropathy, and cataracts. There are many commercially anti-diabetic medications available. Metformin is generally recommended as a first line treatment in diabetic condition whereas other classes of medications includes sulfonylureas, nonsulfonylurea secretagogue, *Alpha glucosidase* inhibitors, thiazolidinedione, glucagon-like peptide-1 analog, and *Dipeptidyl peptidase* - 4 inhibitors [5,6]. Roziglitazone, a thiazolidinedione, has not been found to improve long term outcomes even though it improves blood sugar levels [7]. Moreover it is associated with increased rates of heart disease and death [8]. Metformin should not be used in those with severe kidney or liver problems [9]. Injections of insulin may either be added to oral medication or used alone [8].

Traditionally medicinal plants with various active principles and properties have been used since ancient times by physicians and laymen to treat a great variety of human diseases such as diabetes, coronary heart disease and cancer. The beneficial multiple activities like manipulating carbohydrate metabolism by various mechanism, preventing and restoring integrity and function of β-cells, insulin-releasing activity, improving glucose uptake and utilization and the antioxidant properties present in medicinal plants offer exciting opportunity to develop them in to novel therapeutics. The multi factorial pathogenecity of diabetes demands multimodal therapeutic approach. Thus, future therapeutic strategies require the combination of various types of multiple agents. Therefore, plant based herbal drugs and botanicals with free radical scavenging activity are emerging as the primary components of holistic approaches to diabetes

management [10,11]. Hence, present study aims to explore the *in silico* testing of glycyrrhizin which can be an efficient alternative natural source with antidiabetic properties.

The plant *Abrus precatorius* Linn popularly known as Rosary pea, jequirity bean belong to the family leguminosae (*Fabaceae*) is mostly found throughout India. The seeds are reported to be the deadly poisonous but it has also been reported that the toxic form of abrin gets transformed to mitogenic form upon long refrigerated storage. Generally the seeds of *Abrus precatorius* are of two types one is scarlet with black spot and the other variety is pure white and traditionally used against leucoderma, wounds, alopecia, asthma, tubercular glands, leprosy, fever, ulcer and tumor [12,13]. The seed extract have also been shown to possess other pharmacologic properties due to presence of glycyrrhizin (Fig. 1). It was shown to have antifertility effect [14], ureterotonic effect [15], antidiarrhoeal effect [16], antidiabetic [17], arthritis [18] and antimicrobial [19] activity.

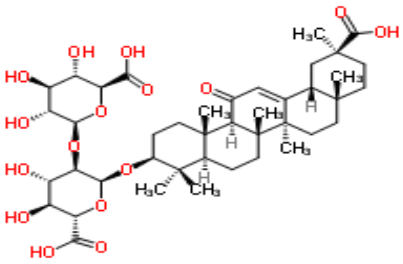

Fig. 1. Glycyrrhizin (3β)-30-Hydroxy-11,30-dioxoolean-12-en-3-yl 2-O-β-D-glucopyranuronosyl-α-D-glucopyranosiduronic acid)

Glycyrrhizin is an important phytoconstituent of licorice which is widely used in the pharmaceutical and food industry. As the roots and leaves of *Abrus precatorius* contain glycyrrhizin, it can be used as an alternative source. In spite of extensive research work undertaken with cultures of *Glycyrrhiza glabra*, the glycyrrhizin production remains elusive. Therefore, *Abrus precatorius* cultures can be serve as substitute for isolation of Glycyrrhin. Out of the many compounds tested for their potential in anti-diabetic activity, glycyrrhizin has gathered much interest due to their high hypoglycemic activities.

The benefit of using Licorice or Gunja versus other herbal medication or conventional Western medicine is that there is very little interaction with liver enzymes that metabolize drugs. Amongst these enzymes are CYP3A4 and CYP2D6 are main enzymes. Pandit et al. [20] used enzyme assays on a standard licorice extract, and found that the interaction from a standardized extract was less than a standard inhibitor. Furthermore, when the pure compound of glycyrrhizin was compared with the plant extract, the interaction potential of pure compound with liver enzyme was less than the extract. Thus, *Abrus* may be an attractive choice for those using multiple herbal or conventional medicines to limit any possible drug-drug or drug-herb interaction.

2. MATERIALS AND METHODS

2.1 Antidiabetic Drugs

Thiazolidinedione (TZDs) are a pharmacological insulin-sensitizing class of compounds that are high-affinity ligands for PPAR-γ and widely used for treatment of type 2 diabetes [21].

2.1.1 Pioglitazone

Pioglitazone is used for the treatment of diabetes mellitus type 2. Pioglitazone selectively stimulates nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR-gamma) [21,22].

2.1.2 Roziglitazone

Rosiglitazone is an antidiabetic drug in the thiazolidinedione class of drugs. It works as an insulin sensitizer, by binding to the PPAR gamma [21,22].

2.1.3 Miglitol

Miglitol is an oral anti-diabetic drug and is primarily used in diabetes mellitus type 2 for establishing greater glycemic control by preventing the digestion of carbohydrates (such as disaccharides, oligosaccharides, and polysaccharides) into monosaccharides which can be absorbed by the body. Miglitol inhibits glycoside hydrolase enzymes called Alpha-glucosidases. Since Miglitol works by preventing digestion of carbohydrates. Hence, it lowers the degree of postprandial hyperglycemia [23-26].

2.2 Preparations of Ligand and Receptor Protein

The selected ligands were sketched using Chemsketch and transformed into the 3D

structure, intermolecular interactions of these ligands were optimized to attain a local minimum energy structure using Universal force fields (UFF) [27,28]. Considering the three available inhibitors for type 2 diabetes the indigenous docked complex of Pioglitazone PPAR gamma Pdb-id - 2XKW, Roziglitazone PPAR gamma Pdb-id – 1FM6 and Miglitol with Alpha-amylase Pdb-id- 3L4W, the 3D-crystallographic structures were considered [29-31].

2.3 Active Site

The default active site were considered of docked complexes, Amino acid within 10 A by considering the ligand of interest in center.

2.4 Molecular Docking

Molecular interactions play a key role in all biological reactions. Drugs are either mimicking or mitigating the effect of natural ligands binding to the receptor by exerting the pharmacological reactions. Computational methods are used to identify and understand this mode of binding, interacting and orientation of ligands into the active site to their receptors which is called as Molecular Docking [32]. It is an attempt to find out the optimal binding between different a set of molecules: a receptor and a ligand. Genetic Algorithm (GA) based approach were used with the following parameters Population size = 200; Generations = 70 and number of solutions =3 in iGEM dock [33]. Pharmacological points and interaction are the key features in drug binding ability and in formation of a stable complex. Hence, in the present study, Glycyrhizin binding affinity was compared with the indegenious inhibitors of PPAR gamma and alpha amylase i.e. Pioglitazone, Roziglitazone and Miglitol to validate the pharmacological interactions between them.

3. RESULTS

The technique implemented for predicting and generating a stable conformation to detect all possible interactions between protein receptors and ligands, is now an essential phase in drug discovery and development area. In spite a variety of treatment and course of therapy for diabetes it is the third leading cause of death, and demand for newer and safer molecules. The optimization of ligands was significantly changes the conformations of ligands with respect to its energies Table 1 shows the release of constraints and its final energy level.

Thiazolidinedione derivative Pioglitazone and Roziglitazone showed binding interactions with their indigenous receptor PPAR gamma and Miglitol with Alpha amylase respectively. As in the present study we have shown a comparative molecular interaction study of Glycyrhizin against to Pioglitazone, Roziglitazone and Miglitol with their indigenous receptor. Glycyrhizin forms a more stable complex with PPAR gamma and Alpha amylase with respect to their indigenous inhibitors (Table 2).

Table 1. Ligand optimized energy using Universal force field (UFF)

	Pioglitazone		**Roziglitazone**		**Miglitol**		**Glycyrhizin**	
	Initial Energy	**Final Energy**	**Initial Energy**	**Final Energy**	**Initial Energy**	**Final Energy**	**Initial Energy**	**Final Energy**
MM Bond	0.39	0.004	0.38	0.005	0.004	0.002	1.15	0.025
MM Angle	0.06	0.058	0.065	0.062	0.01	0.0035	2.14	0.05
MM Dihedral	0.03	0.031	0.031	0.031	0.0040	0.0003	0.13	0.10
MM ImpTor	0.00	0.00	0.00	0.00	0.036	0.013	0.008	0.0065
MM vdW	0.18	0.036	0.23	0.042	0.016	0.018	1332.29	0.11
MM Coulomb	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Total Energy	0.67 au	0.13a.u.	0.71 au	0.142a.u.	0.075	0.039a.u.	1335.73a.u.	0.30 a.u.
Total Energy in Kcal/mol	425.45 kcal/mol	82.18 kcal/mol	448.90 kcal/mol	89.13 kcal/mol	47.30905230 kcal/mol	24.64 kcal/mol	838189.15 kcal/mol	193.65 kcal/mol

Table 2. Molecular interaction energy

Receptor (Pdb-id)	Ligand	Total Energy	VDW	H Bond	Elec
2XKW	Pioglitazone	-97.7625	-81.8006	-15.9619	0
(PPAR gamma)	Glycyrhizin	-123.242	-95.0611	-27.7449	-0.43564
1FM6	Roziglitazone	-104.191	-90.7277	-13.4633	0
(PPAR gamma)	Glycyrhizin	-105.847	-77.8287	-25.4678	-2.55088
3L4W	Miglitol	-84.5834	-62.0384	-22.545	0
(Alpha amylase)	Glycyrhizin	-98.4157	-70.4054	-28.0103	0

3.1 Mining of Pharmacological Interactions

Pioglitazone with indigenous receptor PPAR gamma (Pdb-id: 2XKW): (Figs. 2a, 2a1 and 2a2)

Hydrogen bond interaction:

ARG-288; GLU-291; GLU-295; ILE-325; ILE-326; SER-342 and GLU-343

Vanderwaal Interaction:

ILE-281; GLY-284; CYS-285; PHE-287; ARG-288; ARG-288; GLU-291; MET-329; LEU-330; ILE-341; SER-342 and GLU-343.

Glycyrhizin with PPAR gamma (Pdb-id: 2XKW): (Figs. 2b, 2b1 and 2b2)

Hydrogen bond interaction:

ILE-281; CYS-285; ARG-288; GLU-291; GLU-295; ILE-325; ILE-326; SER-342; GLU-343 and GLU-343

Vanderwaal Interaction:

ILE-281; GLY-284; CYS-285; PHE-287; ARG-288; GLU-291; LEU-330; ILE-341; SER-342; and GLU-343;

Roziglitazone with indigenous receptor (Pdb-id: 1FM6): (Figs. 3.a, 3.a1 and 3.a2)

Hydrogen bond interaction:

LEU-228; LEU-270; GLN-271; GLU-272; GLN-283; GLU-343; SER-464 and HIS-466.

Vanderwaal interactions:

GLN-271; ILE-281; GLN-283; GLY-284; PHE-287; ARG-288; LEU-340; ILE-341; GLU-343; and MET-348.

Glycyrhizin with PPAR gamma (Pdb-id: 1FM6): (Figs. 3b, 3b1 and 3b2)

Electrostatic interaction:

HIS-466

Hydrogen bond interactions:

LEU-228; LEU-270; GLN-271; GLU-272; GLN-283; GLU-343; SER-464 and HIS-466 .

Vanderwaal interactions:

GLN-271; ILE-281; GLN-283; GLY-284; PHE-287; ARG-288; LEU-340; ILE-341; GLU-343; MET-348; SER-464; LEU-465 and HIS-466

Miglitol with indigenous receptor Alpha amylase (Pdb-id: 3L4W): (Figs. 4a, 4a1 and 4a2)

Hydrogen bond interactions:

ASP-327; ARG-334; ASP-336; GLU-404; ASP-443; MET-444; SER-448; ASN-449; ARG-526; ASP-542 and HIS-600

Vanderwaal interactions:

TYR-299; ASP-327; ASP-336; PRO-367; GLU-404; VAL-405; TRP-406; ASP-443; SER-448; ASN-449; TRP-539; ASP-542 and PHE-575

Glycyrhizin with Alpha amylase (Pdb-id: 3L4W): (Figs. 4b, 4b1 and 4b2)

Hydrogen bond interactions:

ARG-334; ASP-336; GLU-404; ASP-443; MET-444; SER-448; ASN-449; ARG-526; ASP-542 and HIS-600.

Vanderwaal Interactions:

TYR-299; ASP-327; ASP-336; PRO-367; GLU-404; VAL-405; TRP-406; ASP-443; SER-448 and ASN-449

3.1.1 Pioglitazone–PPAR gamma complex

Figure describes the most stable conformation of Pioglitazone interacting with Hydrogen bond donator and acceptor group (Fig. 2a) in the hydrophobic cavity of its indigenous receptor PPAR gamma (Fig. 2a1). Fig. 2a2 represents the 2 dimensional orientation of Pioglitazone interaction with selective amino acids.

3.1.2 Glycyrhizin – PPAR gamma complex

Figure describes the most stable conformation of Glycyrhizin interacting with Hydrogen bond donator and acceptor group (Fig. 2b) in the hydrophobic cavity of PPAR gamma (Fig. 2b1). Fig. 2b2 represents the 2 dimensional orientation of Glycyrhizin interaction with selective amino acids.

3.1.3 Roziglitazone – PPAR gamma complex

Figure describes the most stable conformation of Roziglitazone interacting with Hydrogen bond donator and acceptor group (Fig. 3a) in the hydrophobic cavity of its indigenous receptor PPAR gamma (Fig: 3a1). Fig: 3a2: represents the 2 dimensional orientation of Roziglitazone interaction with selective amino acids.

3.1.4 Glycyrhizin – PPAR gamma complex

Figure describes the most stable conformation of Glycyrhizin interacting with Hydrogen bond donator and acceptor group (Fig. 3b) in the hydrophobic cavity of PPAR gamma (Fig. 3b1). Fig. 3b2 represents the 2 dimensional orientation of Glycyrhizin interaction with selective amino acids.

3.1.5 Miglitol – Alpha amylase complex

Figure describes the most stable conformation of Miglitol interacting with Hydrogen bond donator and acceptor group (Fig. 4a) in the hydrophobic cavity of its indigenous receptor Alpha amylase (Fig. 4a1). Fig. 4a2 represents the 2 dimensional orientation of Miglitol interaction with selective amino acids.

3.1.6 Glycyrhizin – Alpha amylase complex

Figure describes the most stable conformation of Glycyrhizin interacting with Hydrogen bond donator and acceptor group (Fig. 4b) in the hydrophobic cavity of alpha amylase (Fig. 4b1). Fig. 4b2 represents the 2 dimensional orientation of Glycyrhizin and interaction with selective amino acids.

To compare the results in listed diagram one can refer Fig. 5.0 as a hydrophobic, H-bond and residual interaction index.

4. DISCUSSION

As prior to the advent of defined antidiabetic drugs the treatment of various diseases including diabetes was dependent of number of herbs and plant metabolites. Over a period of time Abrus precatorius (Gunja) is one of the extensively used medicinal plant. Where glycyrrhizin, is founded to be the major constituent of Gunja root and has long been studied for its medicinal acctivity. Takii et al. [34] in his work have cleared the antidiabetic effect of glycyrrhizin in genetically diabetic KK-A^{y} mice.

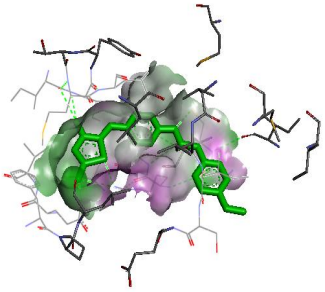

Fig. 2a: Pioglitazone with indigenous receptor PPAR gamma (Pdb-id: 2XKW), hydrophobic interaction

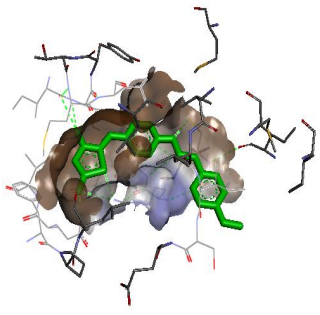

Fig. 2a1: Pioglitazone with indigenous receptor PPAR gamma (Pdb-id: 2XKW), H-Bonds interaction

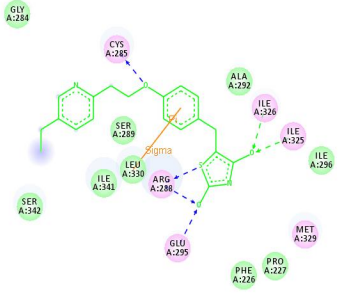

Fig. 2a2: Pioglitazone with indigenous receptor PPAR gamma (Pdb-id: 2XKW), residue interaction

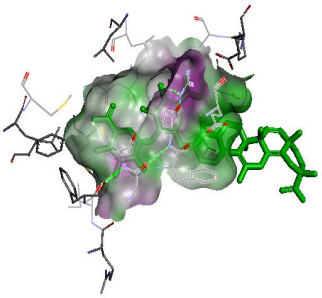

Fig. 2b: Glycyrhizin with PPAR gamma (Pdb-id: 2XKW), hydrophobic interaction

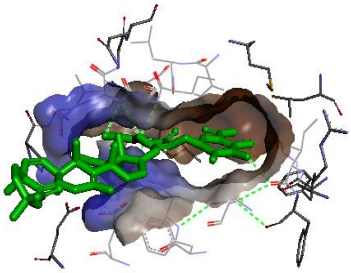

Fig. 2b1: Glycyrhizin with PPAR gamma (Pdb-id: 2XKW), H-Bonds interaction

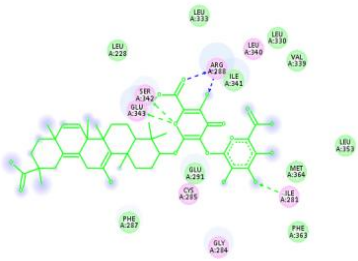

Fig. 2b2: Glycyrhizin with PPAR gamma (Pdb-id: 2XKW), residue interaction

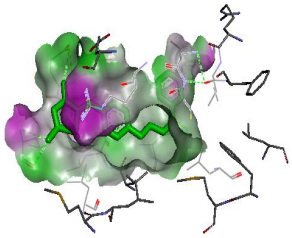

Fig. 3a: Roziglitazone with indigenous receptor (Pdb-id: 1FM6), hydrophobic interaction

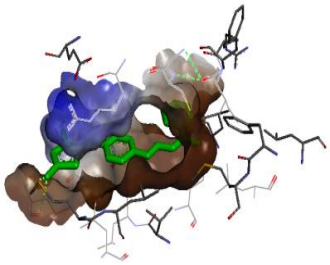

Fig. 3a1: Roziglitazone with indigenous receptor (Pdb-id: 1FM6), H-Bonds interaction

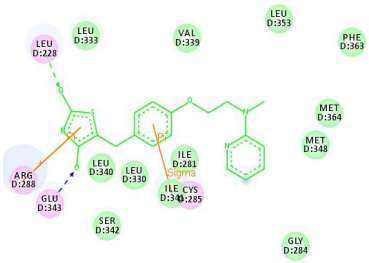

Fig. 3a2: Roziglitazone with indigenous receptor (Pdb-id: 1FM6), residue interaction

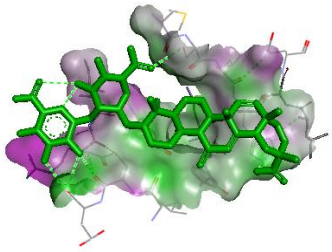

Fig. 3b: Glycyrhizin with PPAR gamma (Pdb-id: 1FM6), hydrophobic interaction

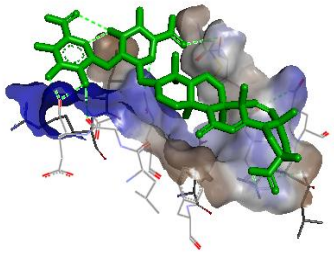

Fig. 3b1: Glycyrhizin with PPAR gamma (Pdb-id: 1FM6), H-Bonds interaction

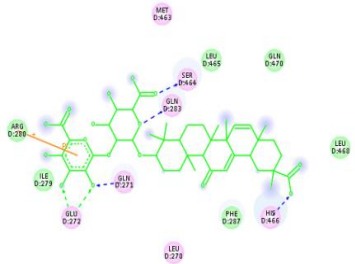

Fig. 3b2: Glycyrhizin with PPAR gamma (Pdb-id: 1FM6), residue interaction

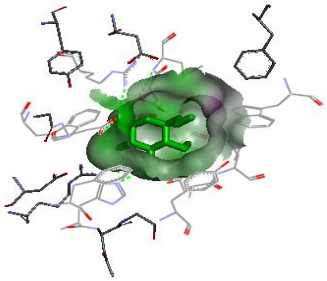

Fig. 4a: Miglitol with indigenous receptor Alpha amylase (Pdb-id: 3L4W), hydrophobic interaction

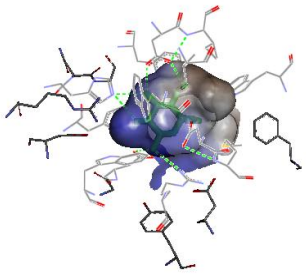

Fig. 4a1: Miglitol with indigenous receptor Alpha amylase (Pdb-id: 3L4W), H-Bonds interaction

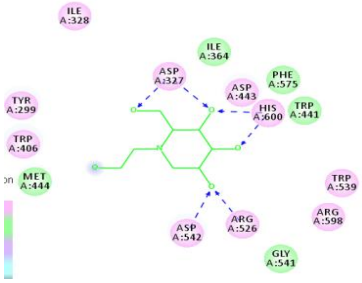

Fig. 4a2: Miglitol with indigenous receptor Alpha amylase (Pdb-id: 3L4W), residue interaction

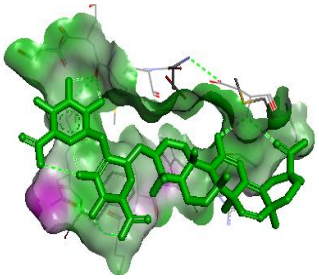

Fig. 4b: Glycyrhizin with Alpha amylase (Pdb-id: 3L4W), hydrophobic interaction

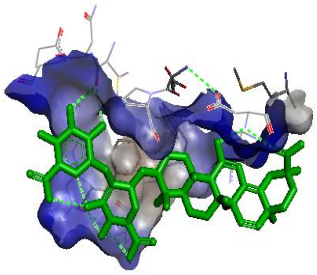

Fig. 4b1: Glycyrhizin with Alpha amylase (Pdb-id: 3L4W), H-Bonds interaction

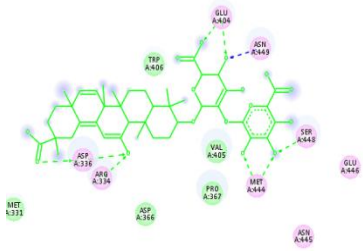

Fig. 4b2: Glycyrhizin with Alpha amylase (Pdb-id: 3L4W), residue interaction

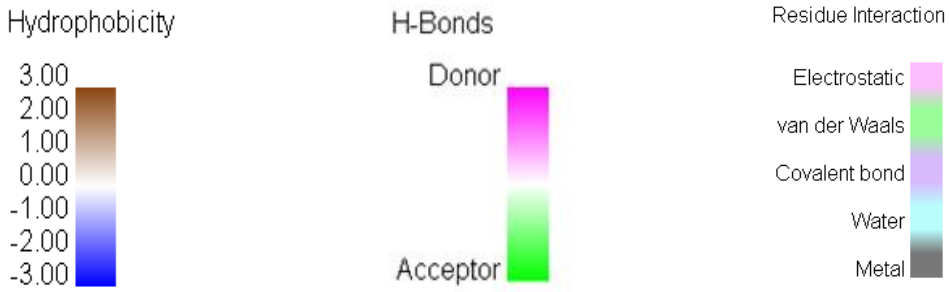

Fig. 5.0. Hydrophoboicity, H-Bonds and Residue interaction scale

Recent research have reported the healing effect of glycyrrhizin 10 or its metabolite, 18β-glycyrrhetinic acid in streptozotocin-induced type 1 diabetes mellitus in rat model [35–38]. The upregulated expression of total P_{14}ARγP has been reported in different tissues of normal rats after the treatment of glycyrrhizin [39]. Eu et al. [40] have also reported that glycyrrhizin increases insulin sensitivity in high fat diet-induced obese rats. Inspite of wet lab techniques Yang et al reported the docking calculation of glycyrrhizin and proved the correlation between anticancer activities and EGFR inhibitory activities [41]. Dyah et al. [42] has explained that betulin could be a potential inhibitor to alpha amylase. Where betulin-alpha amylase complex model is evaluated with Vanderwaal, hydrogen bond interactions and pharmacological interactions. In the current research study binding efficiency of Glycyrrhizin over Pioglitazone, Roziglitazone and Miglitol has significantly increased which can be clearly depicted by Vanderwaal bonding energy (VDW), Hydrogen bonding energy and Electrostatic energy (Table 2). The increase in binding energy signals a constructive path for Glycyrrhizin can be use as a potential anti diabetic molecule over a current and existing drug. Therefore, it is suggested that glycyrhhizin is highly active compound which shows antioxidant, antitumor activity and studied as well as reported as an anti diabetic. This further warrants SAR and QSAR studies on this particular compound to identify the optimum activity of glycyrrhizin.

5. CONCLUSION

The present comparative swot depicts the binding efficiency of Glycyrrhizin with respect to the Pioglitazone, Roziglitazone and Miglitol to their respective receptor protein. Comparing the pharmacological interaction and amino acid residue from PPAR gamma and Alpha amylase involved with the Pioglitazone, Roziglitazone and Miglitol, were very much similar with respect to Glycyrrhizin (3.1 Mining of Pharmacological interactions). The present swot highlights the better binding feature on both receptor protein PPAR gamma and Alpha amylase which can be further continue with parallel dry lab (SAR and QSAR) and wet lab (synthesis and biological evaluation) studies and analysis will be an optimum validation process in the screening and identification of most promising lead compound to a particular receptor.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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