Puerarin as a Potential Drug Candidate for the Management of Type-2 Diabetes: Molecular Docking and Pharmacophore Modeling Studies

Oluwafemi Adeleke Ojo 1,2,*

1 Phytomedicine, Natural Products, Drug and Biochemical Toxicology Group, Department of Biochemistry, Landmark University, Omu Aran, PMB 1001, Kwara State, Nigeria
* Correspondence: oluwafemiadeleke08@gmail.com; Scopus Author ID 56415952100

Abstract: Traditional medicines have to turn out to be the most desired approach to lessen the damaging effects of type-2 diabetes and its stern problems as a result of minor effects and reduced cost. Lately, the anti-diabetic activity of Puerarin has been documented, but the mechanism of actions has not been elucidated. This study designed to assess the molecular relations obtainable between Puerarin, a compound isolated from *Pueraria lobata* and targeted receptors linked to Type 2 diabetes mellitus. These processes include the molecular modeling of Puerarin to 5 receptors: peroxisome proliferator-activated receptor - gamma (PPARγ), 11-β hydroxysteroid dehydrogenase type 1 (11-β HSD1), glutamine: fructose-6-phosphate amidotransferase (GFAT), protein-tyrosine phosphatase 1B (PTP1B) and mono-ADP-ribosyltransferase sirtuin-6 (SIRT6). Following the outcomes of docking of Puerarin with the five different receptor proteins, revealed that Puerarin is a potent inhibitor which binds well with the different receptors relevant to type-2 diabetes. The pharmacophore features also revealed hydrophobic interactions, hydrogen bond acceptors, and hydrogen bond donors. Hence, the results provided insights into the development of better Puerarin as a replacement to present diabetic management.

Keywords: Puerarin; type-2 diabetes; molecular docking; natural products; pharmacophore modeling.

1. Introduction

Diabetes mellitus (DM) is a metabolic condition designated by increase blood glucose concentrations occurring from a deficiency in the production of insulin, insulin action, or both [1]. Chronic damage in diabetes mellitus is related to increased oxidative or inflammatory activities of cytokines, coupled with continuous tissue assault resulting in austere complications [2].

Numerous efforts to discover the efficient cure for type 2 diabetes mellitus (T2DM) have been on the rise. Over the years, experts have strived not to employ only an oral anti-diabetic drug approach but also non-pharmacological methods. Although metformin and thiazolidinedione both have a good effect on insulin resistance, they cannot be extensively utilized as a result of their detrimental effects [3, 4].

Puerarin (PR), a bioactive component obtained from *Pueraria lobata* (Willd.), has been demonstrated to perform a harmonious healing effect in hepatocerebral and cardiovascular diseases [5]. Earlier findings specify that puerarin treatment adds to the diminishing of neuronal
degeneration in 6-OHDA-lesioned rats [6], the intervention of hepatoprotective effect against CCl4-induced hepatic fibrosis rats [7], and improvement of metabolic performance in chronic alcohol-induced liver damage rats [8], respectively. Puerarin has also been reported to many pharmacological activities like diabetic nephropathy [9], hypoglycemic effects [10], improve insulin resistance [11], anti-inflammatory [12], diabetic neuropathy [13]. The binding of Puerarin to human serum albumin was also reported by [14].

In light of these, there is no study signifying the affinity of Puerarin for T2DM. The receptor sites for T2DM documented by various experts till date are peroxisome proliferator-activated receptor - gamma (PPARγ), 11-β hydroxysteroid dehydrogenase type 1 (11-β HSD1), glutamine: fructose-6-phosphate amidotransferase (GFAT), protein-tyrosine phosphatase 1B (PTP1B) and mono-ADP-riboseyltransferase sirtuin-6 (SIRT6) and so forth [15].

Peroxisome proliferator-activated receptor - gamma (PPARγ) functions in insulin sensitization procedure and is a major therapeutic site of type-2 diabetic Mellitus. A known oral anti-diabetic drug, thiazolidinediones act by binding to the site of PPARγ, thus triggering the activation of insulin via glucose transporter 4 receptor (GLUT4) and synthesis of glycogen which results in upsurge insulin sensitivity and signaling [16]. 11β-HSD1 (11β-hydroxysteroid dehydrogenase type I) is an NADPH dependent enzyme significantly shown in key tissues comprising liver, skeletal, and adipose tissue. HSD11B1 decreases cortisone to the active hormone cortisol that triggers glucocorticoid receptors. Inhibition is an alluring site for the management of glucocorticoid-related disorders, specifically diabetes mellitus [17, 18]. Glutamine-fructose-6-phosphate amidotransferase (GFAT) is the primary and rate-committing enzyme of the hexosamine pathway. It regulates the influx of glucose and catalyzes the production of glucosamine 6-phosphate. The majority of glucose will access the Embden-Meyerhof pathway, with a little fraction moving into the hexosamine pathway. It controls the hexosamine pathway end products. Thus, GFAT is implicated as a healing target against T2DM [19]. Protein Tyrosine Phosphatase 1-Beta (PTP-1β) is found in major tissues that control the metabolism of glucose, for example, skeletal, liver, and adipose tissues. It negatively regulates insulin receptor tyrosine kinase. In recent years, researchers have drawn attention to PTP1B simply because of the role it played in attenuating insulin signaling and as a possible therapeutic site of type-2 diabetes. Sirtuin-6 or Mono-ADP ribosyltransferase-sirtuin-6 (SIRT6) is a stress-responsive protein deacetylase and mono-ADP ribosyltransferase enzyme programmed by the SIRT6 gene. SIRT6 roles in manifold pathways linked to aging, comprising DNA repair mechanism, telomere care, Embden-Meyerhof pathway, and inflammation. Favorably, the nonappearance of enzyme SIRT6 may result in markedly induction of blood sugar levels [20]. Hence, the objective of this study is to validate the anti-diabetic activity of Puerarin as a ligand for five targeted receptor proteins to measure its safety as a drug.

2. Materials and Methods

2.1. Receptor proteins.

The three-dimensional structures (3D) of PPARγ (PDB ID: 3VJI), 11-β hydroxysteroid dehydrogenase 1 (PDB ID: 3H6K), glutamine fructose 6-phosphate amidotransferase (PDB ID: 6SVO), protein-tyrosine phosphatase 1B (PDB ID: 1ECV) and SIRT6 (PDB ID: 6QCE) were gotten from protein data bank repository (www.rcsb.org).
2.2. Docking simulations.

To simulate binding affinity between the receptor proteins and Puerarin, the docking tool, AutoDock Vina (version 1.1.2) was used [21]. Puerarin structure was drawn using the ChemAxon suite (https://www.chemaxon.com). The structure was optimized for docking using Open Babel (http://openbabel.org). The grid settings and coordinates are listed in the table below (Table 1). Puerarin was docked into the active sites of the target proteins using AutoDock Vina. The procedure was carried out by considering the flexibility of the ligand such that all rotational bonds were set free, and the estimated binding energies for the best pose were recorded [22]. Pymol was used to analyze the ligand pose within the protein molecules, while Maestro was used to identifying the amino acid residues interacting with Puerarin.

| Protein target | Grid box setting | Coordinates |
|----------------|-----------------|-------------|
| 3VJI           | 0.375 (60 x 60 x 60) | X=-16.48, Y=21.01, Z=-11.88 |
| 3H6K           | 0.375 (60 x 60 x 60) | X=7.6, Y=-2.91, Z=19.15 |
| 6SVO           | 0.375 (60 x 60 x 60) | X=-3.21, Y=50.14, Z=-45.43 |
| 1ECV           | 0.375 (60 x 60 x 60) | X=9.82, Y=45.72, Z=19.65 |
| 6QCE           | 0.375 (60 x 60 x 60) | X=-24.87, Y=26.31, Z=18.01 |

2.3. E-pharmacophore model generation.

The ligand docked poses of all the fragments and their contributions in ligand binding were taken into account in this approach of model generation. The hypothesis was built by mapping energetic terms of Glide XP on pharmacophoric features. The structural and energy information present in between the protein and ligand molecule was used to compute these energetic terms. Consequently, a four featured model was generated, which consists of two hydrogen bond acceptors and two aromatic rings (AARRR).

3. Results and Discussion

3.1. 3D structure of the ligand and target proteins.

The 3D structure of the Puerarin was modeled and used as a target for docking simulation against 5 target proteins (Figure 1).

![Figure 1. 3D structure of the investigated compound (Puerarin).](https://biointerfaceresearch.com/)
The target proteins (peroxisome proliferator-activated receptor - gamma (PPARγ), 11-β hydroxysteroid dehydrogenase type 1 (11-β HSD1), glutamine: fructose-6-phosphate amidotransferase (GFAT), protein-tyrosine phosphatase 1B (PTP1B) and mono-ADP-ribosyltransferase sirtuin-6 (SIRT6)) (Figure 2) were downloaded from PubMed Chen and prepared for the docking using Maestro Molecular Modeling platform. Peroxisome proliferator-activated receptor - gamma (PPARγ) functions in insulin sensitization procedure and is a major therapeutic site of type-2 diabetes mellitus. A known oral anti-diabetic drug, thiazolidinediones act by binding to the site of PPARγ, thus triggering the activation of insulin via glucose transporter 4 receptor (GLUT4) and synthesis of glycogen which results in upsurge insulin sensitivity and signaling [16]. The molecular interaction of Pueraarin with receptor PPARγ reveals amino acid residues MET364, CYS285, ILE326, ALA292, LEU333, LEU330, and ILE341 that formed strong hydrophobic interactions and SER289 and SER342 forming polar contact with the compound. Similar amino acid interactions were seen in the potential (4Z, 12Z)-cyclopentadeca-4, 12-dienone from Grewia hirsute for treating type 2 diabetes [23].

Glucocorticoids are the powerful operating antagonist of action of insulin, thus, stimulate gluconeogenesis, possibly resulting in increased blood glucose levels. The entry of glucocorticoids to its receptors is controlled by 11β-HSD1 [24]. The molecular studies of Pueraarin with 11β-HSD1 reveals the binding energy -9.0 kcal/mol with co-crystallized ligand (33T) to be -10.6 kcal/mol. These interactions obviously indicate that Pueraarin fits very into the binding socket of 11β-HSD1. The amino acid residues involved in the interaction with Pueraarin include ILE121, ILE46, LEU126, VAL180, TYR180, ALA223, LEU217, ALA226, and VAL227. This statement is backed by an earlier report of [24].

Glutamine: fructose-6-phosphate amidotransferase (GFAT) catalyzes the first and rate-committing step in the generation of hexosamine end products. This enzyme is the main regulator in this pathway and thus performs a significant function in diabetic patients [25]. In this study, molecular docking of Pueraarin with GFAT revealed binding interaction of Pueraarin and formed hydrogen bonds with SER 337 and TYR32, while the interaction of the co-crystalized ligand with GFAT formed hydrogen bonds with THR376, VAL472, GLU561, SER421, GLN422 and SER423 which are the key interaction with GFAT. Comparable interactions were witnessed in (4Z, 12Z)-cyclopentadeca-4, 12-dienone interaction with GFAT [23].

Protein Tyrosine Phosphatase 1-Beta (PTP-1β) is found in major tissues that control the metabolism of glucose, for example, skeletal, liver, and adipose tissues. It negatively regulates insulin receptor tyrosine kinase. In recent years, researchers have drawn attention to PTP1B simply because of the role it played in attenuating insulin signaling and, as of recently, recognized as a possible therapeutic site of type-2 diabetes. Numerous studies have reported the implication of PTP1B in metabolism and negative regulation of the insulin signaling pathway [26]. The molecular docking studies revealed the interaction between Pueraarin and PTP1B formed hydrogen bonds with SER216 and GLN262.

Mono-ADP-ribosyltransferase sirtuin-6 (SIRT6) performs a significant role in the production of glucose and its metabolism. It controls pancreatic β-cell function, a vital organ for maintaining glucose concentration [27]. It also promotes glucose-activated insulin secretion and ATP production in pancreatic β-cells [28]. The molecular docking studies revealed the interaction between Pueraarin and SIRT6 formed hydrogen bonds with SER206 and THR205, though, the side chains of LEU186, ARG65 and ASN114 formed a hydrogen bond with the OH group of the co-crystallized ligands.
3.2. The binding energy of Puerarin to targeted receptors.

The molecular docking scores and binding affinity of Puerarin and co-crystallized ligand to target proteins produced negative values for free energy ranging from -5.2 to -10.6 Kcal/mol in the grid box, indicating high interaction with the binding pocket (Table 2).

| S/N | Target proteins | Ligands | Binding energy (Kcal/mol) |
|-----|-----------------|---------|--------------------------|
| 1   | PPAR gamma      | Puerarin| -7.2                     |
|     |                  | Co-crystallized ligand (J53) | -10.0 |
| 2   | 11-β HSD1       | Puerarin| -9.0                     |
|     |                  | Co-crystallized ligand (33T) | -10.6 |
| 3   | GFAT            | Puerarin| -7.8                     |
|     |                  | Co-crystallized ligand (HW2) | -6.0  |
| 4   | PTP1B           | Puerarin| -6.4                     |
|     |                  | Co-crystallized ligand (878) | -5.2  |
| 5   | SIRT6           | Puerarin| -8.6                     |
|     |                  | Co-crystallized ligand (HW2) | -8.3  |

Furthermore, the high binding affinity of the ligand to the receptors was displayed clearly by interaction analysis (Figures 3 and 4). Puerarin docking studies revealed the interaction with PPARγ residues (SER289, SER342, and ILE341). The backbones of ILE341 and side chains of SER289 and SER342 formed hydrogen bonds with the ligand hydroxyl groups (Figure 3). In addition, the interaction of the ligand with 11-β HSD1 residues shows (ASN119, THR220, THR124, and SER125). The side chain of ASN119 formed a hydrogen bond with the ligands OH groups (Figure 3). Also, the interaction of Puerarin with GFAT residues revealed (SER377, THR376, GLN422, SER423, SER474, TYR32).
Figure 3. Molecular interactions of Puerarin with the active site residues of four selected target receptor proteins.

Figure 4. Molecular interaction of the co-crystallized ligand with amino acid residues within the binding pocket of four targeted receptor proteins.
The side chains of SER377 and TYR37 formed hydrogen bonds with the OH groups of the ligand, though, VAL472, THR376, GLU561, SER421, GLN422, and SER423 formed hydrogen bonds with the OH group of the co-crystallized ligand (Figure 4). Furthermore, the interaction of the ligand with PTP1B residues shows (SER216, GLN262, and TYR46). The side chains of SER216 and GLN262 formed hydrogen bonds with the OH groups of the ligand. And the interaction of the ligand with SIRT6 residues shows (SER206, THR205) (Figure 3). Although the side chains of LEU186, ARG65, and ASN114 formed a hydrogen bond with the OH group of the co-crystallized ligands (Figure 4).

3.3. E-pharmacophore modeling.

As revealed by the ligand-protein complex, an energy-optimized pharmacophore model, AARRR was obtained. The generated e-pharmacophore model comprises three aromatic rings (R) and two hydrogen bond acceptors (A) (Figure 5). Pharmacophore analysis is a description step for docking studies that is whether the low or high binding score of ligand to proteins. It can be described as a group of steric and computerized attributes essential for maximal supramolecular relation with a precise site to activate its response [29]. It has developed as the main device in computational drug due to its potential to visualize enormous archives for powerful hits in a short time. Energy optimized pharmacophore (e-pharmacophore) simulations attempt to merge the stereo-electronic characteristics of the ligand with the dynamics of its interactions with the protein structure [30]. In the present study, an e-pharmacophore hypothesis AARRR was obtained. The generated e-pharmacophore simulations contain three aromatic rings (R) and two hydrogen bond acceptors (A). Puera rin reveals a fitness score of 1.440. The hypothesis AARRR was used as a 3D search inquiry to identify drugs with comparable pharmacophore features.

![Figure 5](https://doi.org/10.33263/BRIAC112.87518759)

**Figure 5.** Screening hypothesis is generated by a structure-based e-pharmacophore model consisting of two hydrogen bond acceptor (A) and three aromatic rings (R).

The compound puera rin possesses a fitness score of 1.440 (Table 3). Table 4 displays the feature score of the pharmacophore sites.

| S/N | Entry name | Vector score | Alignment score | Fitness score |
|-----|------------|--------------|-----------------|---------------|
| 1   | Puera rin  | 0.727        | 0.816           | 1.440         |
Table 4. Feature score of the pharmacophore sites.

| Protein target | No. of possible site | No. of accepted site | Hypotheses | Pharmacophore features with score |
|----------------|----------------------|----------------------|------------|----------------------------------|
| 6W63           | 6                    | 5                    | AARRR      | A3: -0.48, A4: -0.64, R9: -0.48, R10: -9.95, R11: -0.53 |

A, H-bond acceptor; R, aromatic ring

4. Conclusions

Puerarin docking studies with five targeted receptors revealed that it is a promising drug candidate that binds well with the receptors relevant to type-2 diabetes. Thus, if it can be examined for developing into an anti-diabetic drug.

Funding

This research received no external funding.

Acknowledgments

This research has no acknowledgment.

Conflicts of Interest

The authors declare no conflict of interest.

References

1. American Diabetes Association. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes. Diabetes Care 2018, 41(Suppl. 1), S13–S27.
2. Ojo, A.B.; Adanlawo, I.; Ojo, O.A. Ameliorative potentials of saponins from Helianthus annuus roots on hepatoprotective and some kidney function indices of alloxan-induced diabetic rats. Pharmacologyonline 2016, 3, 73–79.
3. Ojo, O.A.; Ajiboye, B.O.; Ojo, A.B.; Oyinloye, B.E.; Imiere O.D.; Adeyoun, O. Ameliorative potential of Blighia sapida K.D. Koenig bark against pancreatic β-cell dysfunction in alloxan-induced diabetic rats. Journal of Complementary and Integrative Medicine 2017, 14, https://doi.org/10.1515/jcim-2016-0145.
4. Ojo, O.A.; Afon, A.A.; Ojo, A.B.; Ajiboye, B.O.; Oyinloye, B.E.; Kappo, A.P. Inhibitory Effects of Solvent-Partitioned Fractions of Two Nigerian Herbs (Spondias mombin Linn. and Mangifera indica L.) on α-Amylase and α-Glucosidase. Antioxidants 2018, 7, https://doi.org/10.3390/antiox7060073.
5. Wong, K.H.; Li, G.Q.; Li, K.M.; Razmorski-Naumovski, V.; Chan, K. Kudzu root: traditional uses and potential medicinal benefits in diabetes and cardiovascular diseases. J Ethnopharmacol 2011, 134, 584-607, https://doi.org/10.1016/j.jep.2011.02.001.
6. Li, R.; Zheng, N.; Liang, T.; He, Q.; Xu, L. Puerarin attenuates neuronal degeneration and blocks oxidative stress to elicit a neuroprotective effect on substantia nigra injury in 6-OHDA-lesioned rats. Brain Research 2013, 1517, 28-35, https://doi.org/10.1016/j.brainres.2013.04.013.
7. Li, R.; Xu, L.; Liang, T.; Li, Y.; Zhang, S.; Duan, X. Puerarin mediates hepatoprotection against CCl4-induced hepatic fibrosis rats through attenuation of inflammation response and amelioration of metabolic function. Food and Chemical Toxicology 2013, 52, 69-75, https://doi.org/10.1016/j.fct.2012.10.059.
8. Chen, X.; Li, R.; Liang, T.; Zhang, K.; Gao, Y.; Xu, L. Puerarin improves metabolic function leading to hepatoprotective effects in chronic alcohol-induced liver injury in rats. Phytomedicine: International Journal of Phytotherapy and Phytopharmacology 2013, 20, 849-852, https://doi.org/10.1016/j.phymed.2013.04.001.
9. Zhong, Y.; Zhang, X.; Cai, X.; Wang, K.; Chen, Y.; Deng, Y. Puerarin attenuated early diabetic kidney injury through down-regulation of matrix metalloproteinase 9 in streptozotocin-induced diabetic rats. PloS one 2014, 9, e85690-e85690, https://doi.org/10.1371/journal.pone.0085690.
10. Wu, K.; Liang, T.; Duan, X.; Xu, L.; Zhang, K.; Li, R. Anti-diabetic effects of Puerarin, isolated from Pueraria lobata (Willd.), on streptozotocin-diabetic mice through promoting insulin expression and ameliorating metabolic function. Food and chemical toxicology: an international journal published for the British Industrial Biological Research Association 2013, 60, 341-347, https://doi.org/10.1016/j.fct.2013.07.077.
11. Zhang, W.; Liu, C.-Q.; Wang, P.-W.; Sun, S.-Y.; Su, W.-J.; Zhang, H.-J.; Li, X.-J.; Yang, S.-Y. Puerarin improves insulin resistance and modulates adipokine expression in rats fed a high-fat diet. European Journal of Pharmacology 2010, 649, 398-402, https://doi.org/10.1016/j.ejphar.2010.09.054.
12. Tu, Y.M.; Gong, C.X.; Ding, L.; Liu, X.Z.; Li, T.; Hu, F.F.; Wang, S.; Xiong, C.P.; Liang, S.D.; Xu, H. A high concentration of fatty acids induces TNF-α as well as NO release mediated by the P2X4 receptor, and the protective effects of Puerarin in RAW264.7 cells. *Food Funct* 2017, 8, 4336-4346, https://doi.org/10.1039/c7fo00544j.

13. Xue, B.; Wang, L.; Zhang, Z.; Wang, R.; Xia, X.-X.; Han, P.-P.; Cao, L.-J.; Liu, Y.-H.; Sun, L.-Q. Puerarin may protect against Schwann cell damage induced by glucose fluctuation. *Journal of Natural Medicines* 2017, 71, 472-481, https://doi.org/10.1007/s11418-016-1067-0.

14. He, Y.; Wang, Y.; Tang, L.; Liu, H.; Chen, W.; Zheng, Z.; Zou, G. Binding of Puerarin to human serum albumin: a spectroscopic analysis and molecular docking. *Journal of fluorescence* 2008, 18, 433-442, https://doi.org/10.1016/j.jfluc.2007.07.038.

15. Guttula, S.; Rao, A.A.; Sridhar, G.R.; Chakravarthy, M.S. Protein ligand interaction analysis an insilico potential drug target identification in diabetes mellitus and nephropathy. *Journal of Bioinformatics and Sequence Analysis* 2011, 3, 95–99.

16. Abbirami, E.; Selvakumar, M.; Dinesh Kumar, L.; Guna, R.; Sivasudha, T. Identification of Novel Drug Like Compounds from Momordica cymbalaria as PPAR-γ Agonists: A Molecular Docking Study. *Asian J Eng Appl Technol* 2019, 8(2), 71-74.

17. He, J.H.; Chen, L.X.; Li, H. Progress in the discovery of naturally occurring anti-diabetic drugs and in the identification of their molecular targets. *Fitoterapia* 2019, 134, 270 – 289.

18. Nguyen Vo, T.H.; Tran, N.; Nguyen, D.; Le, L. An in silico study on anti-diabetic activity of bioactive compounds in Euphorbia thymifolia Linn. *SpringerPlus* 2016, 5, https://doi.org/10.1186/s40064-016-2631-5.

19. Mostefauzi, L.; Mesli, F.; Merad, M.; Ghalem, S. Virtual screening of triazoles inhibitors of 11β-hydroxysteroid dehydrogenase enzymes using -adme - molecular docking, and molecular dynamics simulation studies. *J. Fundam. Appl. Sci* 2020, 12(2), 713-727.

20. Singh, P.; Singh, V.K.; Singh, A.K. Molecular docking analysis of candidate compounds derived from medicinal plants with type 2 diabetes mellitus targets. *Bioinformation* 2019, 15(3), 179-188, https://doi.org/10.6026/97320630015179.

21. Ojo, O.A.; Afon, A.A.; Ojo, A.B.; Ajiboye, B.O.; Okesola, M.A.; Aruleba, R.T.; Adekiya, T.A.; Oyinloye, B.E. Spondias mombim L. (Anacardiaceae): Chemical fingerprints, inhibitory activities, and molecular docking of key enzymes relevant to erectile dysfunction and Alzheimer’s diseases. *Journal of Food Biochemistry* 2019, 43, https://doi.org/10.1111/jfbc.12772.

22. Ojo, O.A.; Ojo, A.B.; Taiwo, O.A.; Oluba, O.M. Novel Coronavirus (SARS-CoV-2) Main Protease: Molecular docking of Puerarin as a Potential inhibitor. PREPRINT (Version 1). *Research Square* 2020, https://doi.org/10.21203/rs.3.rs-37794/v1.

23. Natarajan, A.; Sugumar, S.; Bitragunta, S.; Balasubramanyan, N. Molecular docking studies of (4Z, 12Z)-cyclopentadeca-4, 12-dienone from Grewia hirsuta with some targets related to type 2 diabetes. *BMC complementary and alternative medicine* 2015, 15, 73-73, https://doi.org/10.1186/s12906-015-0588-5.

24. Böhme, T.; Engel, C.K.; Farjot, G.; Güssregen, S.; Haack, T.; Tschan, G.; Ritter, K. 1,1-Dioxo-5,6-dihydropyrazine-4,1,2-oxathiazines, a novel class of 11β-HSD1 inhibitors for the treatment of diabetes. *Bioorg Med Chem Lett* 2013, 23, 4685-4691, https://doi.org/10.1016/j.bmcl.2013.05.102.

25. Szymura, S.J.; Zaemes, J.P.; Allison, D.F.; Clift, S.H.; D’Innocenzi, J.M.; Gray, L.G.; McKenna, B.D.; Morris, B.B.; Bekiranov, S.; LeGallo, R.D.; Jones, D.R.; Mayo, M.W. NF-κB upregulates glutamine-fructose-6-phosphate transaminase 2 to promote migration in non-small cell lung cancer. *Cell Commun Signal* 2019, 17, 24, https://doi.org/10.1186/s12964-019-0335-5, https://doi.org/10.1186/s12964-019-0335-5.

26. Hidalgo-Figueroa, S.; Estrada-Soto, S.; Ramírez-Espinosa, J.J.; Paoli, P.; Lori, G.; León-Rivera, I.; Navarrete-Vázquez, G. Synthesis and evaluation of thiazolidine-2,4-dione/benzazole derivatives as inhibitors of protein tyrosine phosphatase 1B (PTP-1B): antihyperglycemic activity with molecular docking study. *Biomedicine & Pharmacotherapy* 2018, 107, 1302–1310, https://doi.org/10.1016/j.biopha.2018.08.124.

27. Demir, I.E.; Ceyhan, G.O.; Friess, H. Epigenomic therapies: the potential of targeting SIRT6 for the treatment of pancreatic cancer. *Expert Opinion on Therapeutic Targets* 2017, 21, 1-3, https://doi.org/10.1080/14782222.2017.1265507.

28. Xiong, X.; Sun, X.; Wang, Q.; Qian, X.; Zhang, Y.; Pan, X.; Dong, X.C. SIRT6 protects against palmitate-induced pancreatic β-cell dysfunction and apoptosis. *J Endocrinol* 2016, 231, 159-165, https://doi.org/10.1530/JOE-16-0317.

29. Proekt, A.; Hemmings, H.C. Jr. Mechanisms of Drug Action. In: *Pharmacology and Physiology for Anesthesia: Foundations and Clinical Application*. Hemmings, H.C.J.; Egan, T.D. (eds) 2nd edn. Elsevier Inc, 2019, pp. 2-19.

30. Muthusamy, K.; Singh, K.D.; Chinnasamy, S.; Nagamani, S.; Krishnasamy, G.; Thiagarajan, C.; Premkumar, P.; Anusuyadevi, M. High throughput virtual screening and E-pharmacophore filtering in the discovery of new BACE-1 inhibitors. *Interdisciplinary Sciences: Computational Life Sciences* 2013, 5, 119-126, https://doi.org/10.1007/s12539-013-0157-x.