ACS OMEGA

http://pubs.acs.org/journal/acsodf

Article

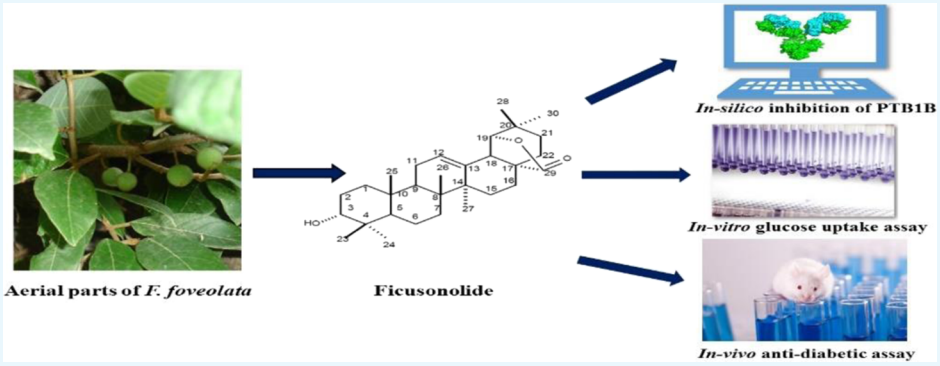
Antidiabetic Activity of Ficusonolide, a Triterpene Lactone from *Ficus foveolata* (Wall. ex Miq.): *In Vitro*, *In Vivo*, and *In Silico* Approaches

Ala Ud Din, Maria Khan, Muhammad Zahir Shah, Abdur Rauf,* Umer Rashid, Anees Ahmed Khalil, Khair Zaman, Yahya S. Al-Awthan, Mohammed A. Al-Duais, Omar Bahattab, Adil A.H. Mujawah, and Naveed Muhammad

Cite This: *ACS Omega* 2021, 6, 27351−27357

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



ABSTRACT: Diabetes is a chronic condition which is locally managed through the stem of *Ficus foveolata*. To find the exact chemical constituent responsible for this activity, a triterpene lactone (ficusonolide) isolated from *F. foveolata* was studied for antidiabetic potential through the *in vitro* antidiabetic paradigm employing L-6 cells and an *in vivo* antidiabetic assay against non-insulin-dependent rats. The results on glucose uptake in the L-6 cell line indicated that ficusonolide has enhanced the uptake of glucose by 53.27% over control at a dose of 100 μg/mL, while at doses of 50 and 25 μg/mL, the glucose uptake was enhanced by 22.42 and 14.34%, respectively. The extract of *F. foveolata* (100 mg/kg) and ficusonolide (50 mg/kg) demonstrated a significant ($p < 0.001$) decline in streptozotocin-induced hyperglycemia of diabetic rats. Ficusonolide displayed conspicuous inhibitory activity against the molecular docking studies with proteins such as dipeptidyl peptidase-IV (DPP-IV), protein tyrosine phosphatase 1B (PTP-1B), α-glucosidase, and α-amylase subjected to molecular targets. Detailed computational and structural insights affirmed promising interactions between target proteins and ficusonolide. In conclusion, the plant and its isolated compound have significant antidiabetic activity with a possible mechanism of interaction with DPP-IV, PTP-1B, α-glucosidase, and α-amylase.

1. INTRODUCTION

Diabetes mellitus (DM) refers to a heterogeneous metabolic disorder that results due to the insufficient secretion of insulin, lack of insulin action, or both and consequently results in high levels of blood glucose with disruption of carbohydrates, lipids, and protein metabolism. There has been a global concern regarding the increase in the occurrence of type 2 DM (T2DM), which is a chronic disorder affecting metabolism, resulting from the inability of body to use insulin properly. According to a research in 2010, 285 million people were estimated to have DM. The chances of this data are expected to become twice in the coming 20 years.[1] One of the main categories of T2DM is insulin-resistant T2DM, in which body tissues fail to respond to insulin to counterbalance the insulin contention.[2] Insulin-resistant T2DM is of key concern owing to the fact that it has been linked to complexities such as cardiovascular abnormalities.[3] Though the preliminary treatment for insulin-resistant T2DM comprises an appropriate diet along with proper exercises, patients suffering from DM who cannot be treated with the above-mentioned only are prescribed with medicines such as thiazolidine derivatives, gliptins, sulfonylureas, and biguanides.[4,5] However, the application of such drugs is delimited due to side effects and non-responders. Therefore, there is an urge to develop more

Received: August 7, 2021
Accepted: September 21, 2021
Published: October 5, 2021

effective ways to cure T2DM. One of such methods is the treatment of T2DM by inhibiting protein-tyrosine phosphatase 1B.

PTP1B is a notable integral membrane enzyme and an essential factor in insulin-resistant diabetes (T2DM). It regulates the insulin-signaling pathway negatively by hydrolyzing the phosphor tyrosine on the insulin receptor, which inactivates the receptor. Oversecretion of PTB1B provides the way to cause T2DM.[6,7] This enzyme (PTB1B) has been a potential target for drugs meant to treat T2DM and obesity. Moreover, leptin and insulin activities have been advocated to be raised by these inhibitors and work as effective therapeutics for T2DM. *In vivo* PTP1B inhibition causes increase in both insulin and leptin levels, which results in normalization of glucose in blood.[8] Furthermore, protein-tyrosine inhibitory activities have been explored broadly.[9] Due to their novel mode of action, these inhibitory substances have gained appreciable attention for their curative properties and are under consideration to develop new pharmaceuticals. Although some of these are in the process of clinical trial, till date none of them are available for clinical applications. Therefore, the treatment of T2DM can be achieved by inhibiting PTP1B, and it can prove to be a milestone in discovering drugs.[6,10] This has lead researchers all around the globe to discover novel PTP1B inhibitors from natural products as well as synthetic pathways.

The family Moraceae (mulberry) consists of about 40 genera, the Ficus genus (fig genus) is one of them. It comprises about 800 species which inhabit the wetlands of the tropical region.[11] Although *Ficus* species are employed in Ayurveda as well as Traditional Chinese Medicine (TCM), their medicinal uses started from the Middle East.[12] Various parts of the species including root, leaf, stem, fruit, and pigments are known to possess antidiabetic, anticancer, and anti-inflammatory properties.[13] Many bioactive compounds have been isolated. The bioassay-guided phytochemical studies of these plants have resulted in the isolation of secondary metabolites of medicinal importance such as phenanthroindolizidine alkaloids, flavonoids, coumarins, triterpenoids, different triacylglycerols, and various volatile organic compounds.[13−17] *Ficus foveolata* is an evergreen wild climber shrub found at high altitude in the northern parts of Pakistan. The plant was collected from the district of Buner of Pakistan where it is known as "baatanzar" in local terms. Various parts including leaves, stem, roots, fruits, and latex are being used as antidiabetic drugs in folk medicine in the area of collection; however, the literature survey revealed little previous phytochemical investigations.[18] Regardless of the useful capabilities of *F. foveolata*, no proper work has been done to develop antidiabetic drugs using compounds isolated from the said plant via molecular docking simulation. Bioassay-guided studies on the crude extract of *F. foveolata* stem led to the isolation of a new cytotoxic compound, ficusonolide (Figure 1);[18] herein, we report the *in vitro*, *in vivo* antidiabetic potential and *in silico* PTP1B inhibitory activity of ficusonolide, isolated from *Ficus foveolata* (family Moraceae). Due to the lack of phytochemical studies on the interaction of PTP1B and ficusonolide, we have proposed an advance way to establish ficusonolide as a potential antidiabetic contender via its molecular docking foresights.

2. RESULTS

2.1. *In Vitro* Studies. The results of the *in vitro* glucose uptake assay in the L-6 cell line are presented in Table 1 and Figure 2. The results indicate that ficusonolide has enhanced the uptake of glucose by 53.27% over control at a dose of 100 μg/mL, while at doses of 50 and 25 μg/mL, the glucose uptake was enhanced by 22.42 and 14.34%, respectively. The glucose uptake was also compared to the standard injectable antidiabetic drug insulin and the oral antidiabetic standard drug metformin. Insulin enhanced the glucose uptake by 146.71% (at 1 IU/mL) and metformin elevated it by 76.24% (at 100 μg/mL) over the control.

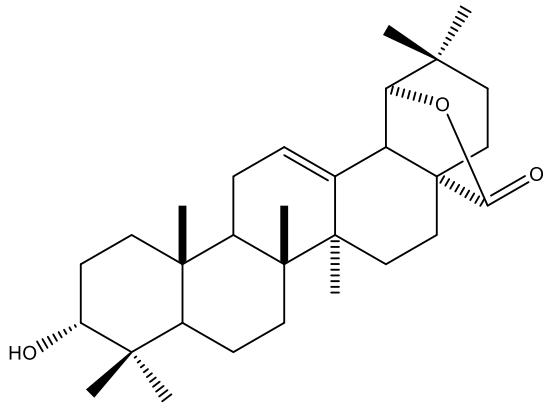


Figure 1. Chemical structure of ficusonolide.

Table 1. Effect of Ficusonolide on Glucose Uptake in the L-6 Cell Line

treatment	dose	% glucose uptake compared to control
10% Tween 80	10 mL/kg	
ficusonolide	100 μg/mL	53.27 ± 0.42
	50 μg/mL	22.42 ± 0.37
	25 μg/mL	14.34 ± 0.53
insulin	1 IU/mL	146.71 ± 0.32
metformin	100 μg/mL	76.24 ± 0.42
insulin + metformin (100 μg/ml)	1 IU/mL + 100 μg/mL	151.69 ± 0.42

2.2. *In Vivo* Studies. The administration of an extract of *F. foveolata* (100 mg/kg) and ficusonolide (50 mg/kg) demonstrated a significant ($p < 0.001$) decline in the hyperglycemia of diabetic rats during an acute time period of 7 h as compared to the control group, confirming the antidiabetic potential of the compound as well as the plant extract (Table 2).

2.3. Multitarget Molecular Docking Investigation. We have performed docking simulations in the active sites of DPP-IV, protein tyrosine PTP-1B, α-amylase, and homology-modeled α-glucosidase. For docking simulations, the MOE 2016 software package was used.

After the energy minimization of the selected proteins, we defined the active sites and the active site residues by two methods: (i) centroid of co-crystallized ligands of each and (ii) identification of catalytic amino acids *via* dummy atoms using the site finder tool implemented in MOE (in the case of α-glucosidase). After the identification of the binding site, a comprehensive docking protocol validation was carried out by using the re-dock method. Native co-crystallized of the ligands in their respective processed enzymes, and the resulting root mean-square deviation (rmsd) was computed.

The structures of all the native co-crystallized ligands were extracted and redocked into the active sites of their respective

https://doi.org/10.1021/acsomega.1c04230
ACS Omega 2021, 6, 27351−27357

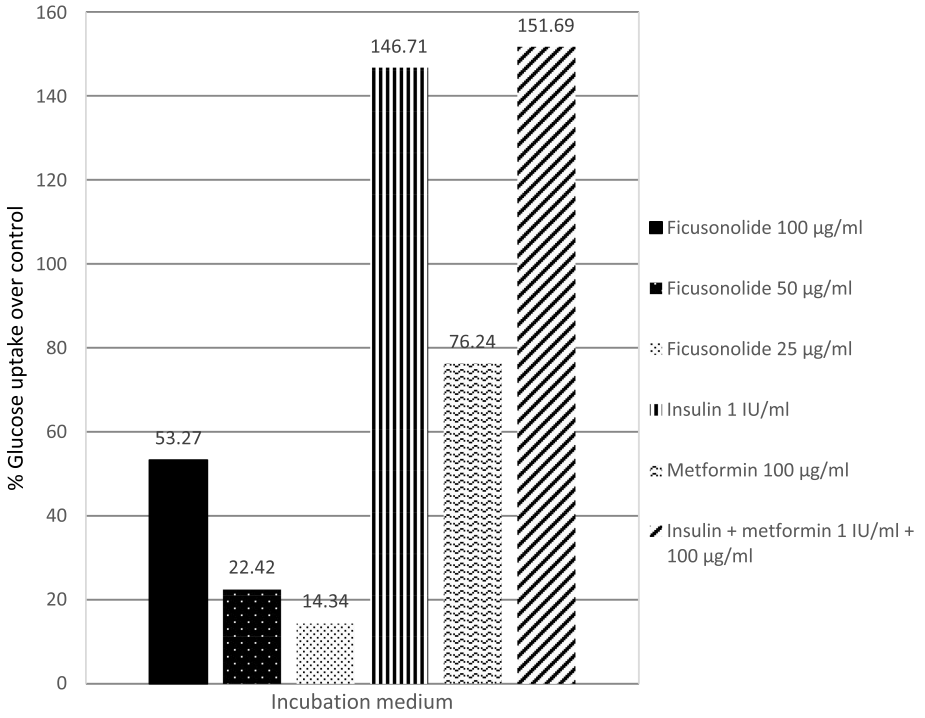


Figure 2. Effect of ficusonolide on glucose uptake in the L-6 cell line.

Table 2. Percent Variation of Blood Glucose Level in Streptozotocin−Nicotinamide-Induced Hyperglycemic Rats with *F. foveolata* Extract and Ficusonolide

		% variation of glucose level ± SEM (mg/dL)				
sample	dose (mg/kg)	0 h	1st h	3rd h	5th h	7th h
vehicle (control)	10 mL/kg	0	9.10 ± 11.02	−1.69 ± 5.09	−0.51 ± 5.11	−5.65 ± 6.08
glibenclamide	5	0	−20.50 ± 8.17[a]	−36.34 ± 7.55[a]	−37.48 ± 7.16[a]	−43.65 ± 10.0[a]
plant extract	100	0	−20.40 ± 6.17[a]	−17.49 ± 3.09[a]	−26.38 ± 9.78[a]	−27.99 ± 6.70[a]
ficusonolide	50	0	−26.92 ± 5.7[a]	−14.1 ± 6.78[a]	−23.2 ± 9.9[a]	−21.92 ± 8.9[a]

[a]$P < 0.001$.

Table 3. Feasible Docking Parameters

		placement		refinement		
enzyme	PDB ID	method	scoring	method	scoring	rmsd (Å)
DPP-IV	2G63	triangle matcher	London dG	rigid receptor	GBVI/WAS dG	1.2
PTP-1B	1NNY	triangle matcher	ASE	rigid receptor	GBVI/WAS dG	0.89
α-Amylase	1OSE	triangle matcher	Affinity dG	rigid receptor	GBVI/WAS dG	1.4
α-Glucosidase	homology	triangle matcher	London dG	rigid receptor	GBVI/WAS dG	

processed proteins, and the rmsd was calculated. Default parameters (triangle matcher at the placement stage) and London dG (as the scoring function) were used. The final score was calculated with GBVI/WAS dG. Binding orientation (interactions with active site residues)/rmsd and binding energy of the redocked ligands and experimental ligands were compared. Further, we tried for other parameters (methods and scoring functions) at the placement and refinement stage to achieve the reasonable performance (rmsd < 2.0 Å). The reasonable parameters for initiating docking of ficusonolide are presented in Table 3.

The three-dimensional (3-D) structure of enzyme DPP-IV in complex with cyanopyrrolidine inhibitor-24b was retrieved from the Protein Data Bank (PDB ID = 2G63, Table 3). The 3-D interaction plot of the isolated compound showed three hydrogen bond interactions. Arg358 forms a bifurcated hydrogen bond interaction with carbonyl oxygen of the compound. Another hydrogen bond interaction was observed between the hydroxyl group and Glu205. Tyr666 forms the π-alkyl type of hydrophobic interactions (Figure 3a).

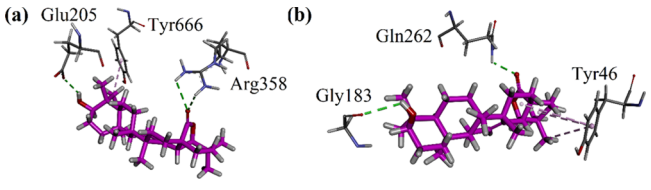


Figure 3. Close-up depiction of the lowest energy 3-D docking interaction plot of ficusonolide in the active site of (a) DPP-IV and (b) PTP-1B.

https://doi.org/10.1021/acsomega.1c04230
ACS Omega 2021, 6, 27351−27357

The 3-D structure of enzyme PTP-1B in complex with the catalytic inhibitor was retrieved from the Protein Data Bank (PDB ID = 1NNY). The 3-D interaction plot of the isolated compound showed two hydrogen bond interactions. The hydroxy group forms hydrogen bond interactions with Gly183, while the carbonyl oxygen forms hydrogen bond interactions with Gln262. Tyr46 forms π-alkyl type of hydrophobic interactions (Figure 3b). The computed binding energy for the isolated compound is −6.0220 kcal/mol.

Figure 4a,b illustrates the binding orientation plot of the isolated compound ficusonolide in the active site of α-amylase

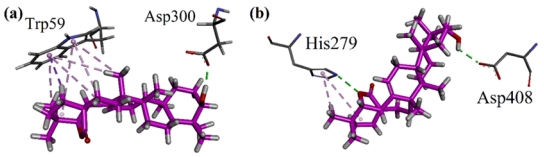


Figure 4. Close-up depiction of the lowest energy 3-D docking interaction plot of ficusonolide in the active site of (a) α-amylase and (b) α-glucosidase.

and α-glucosidase, respectively. In the active site of α-amylase, the isolated compound forms hydrogen bond interactions with Asp300. Moreover, the indole rings of Trp59 form π-σ and π-alkyl type of hydrophobic interactions (Figure 4a). The 3-D crystal structure of Baker's yeast (*Saccharomyces cerevisiae*) has not yet been reported. The phytoconstituents identified in this study were further docked in the active site of homology-modeled α-glucosidase from Baker's yeast. The 3-D interaction plot showed two hydrogen bond interactions with His279 and Asp408 (Figure 4b). The computed binding energy value is −6.2678 kcal/mol. The interaction plots of the standard drug (acarbose) in the active site of α-amylase and α-glucosidase are presented in the Supporting Information as Figures S1 and S2.

3. DISCUSSION

Traditionally, natural products are used for the treatment of various ailments. These natural products contain thousands of chemical constituents with multiple biological potentials and an agonist−antagonist relationship. These multiple constituents might be responsible to create various adverse effects. In addition to these facts, the need of new, safe, and effective drug candidates is also essential for various disorders. Therefore, the isolation and testing of these chemical constituents is the need of the day for targeted therapy as well as for the searching of new therapeutic agents.

In the current study, *F. foveolata* methanolic extract (stem) and ficusonolide were subjected for the antidiabetic potential using *in vitro* and *in vivo* experimental methods. The stem of *F. foveolata* is traditionally used as an antidiabetic drug. In the case of an *in vitro* study, the L-6 cell line was used, which induces the expression of an endogenous GLUT-4 transporter for the update of glucose. The induction of these transporters reduces the hyperglycemic condition. The tested compound induced the glucose uptake by 53% in our *in vitro* experiment. The methanolic extract and ficusonolide also demonstrated a significant effect in streptozotocin−nicotinamide-induced hyperglycemic rats. The STZ damages the beta cells of the pancreas and produces hypoinsulinemia; this insulin-deficient condition results in hyperglycemia. The significant antihyperglycemic effect indicting that the tested samples involve in the repairing of beta cells of pancreas thus restoring the normal insulin level, which is, diminish the hyperglycemic condition.

In order to explore the mechanism of the antidiabetic mechanism of the compound under study, we used a multitarget strategy and docked it into the binding sites of four molecular targets, namely, DPP-IV, protein tyrosine PTP-1B, α-amylase, and homology-modeled α-glucosidase. The current therapeutics to treat multifactorial diseases such as Alzheimer's disease, diabetes, and cancer demonstrate the need for multitarget designed ligands (MTDLs) that can target multiple enzymes associated with these disorders. A number of studies presented the identification of MTDLs by using in silico to treat these multifactorial diseases. Apart from the designed ligands, recent studies have shown that natural products can also be used for this strategy. Recently, Herrera-Calderon et al. reported in silico studies to identify carvacrol as a multipotent compound for the treatment of breast cancer.

Diabetes is also considered as a multifactorial disease. Hence, for the current study, we selected four molecular targets to explore the mechanism of the antidiabetic action of ficusonolide. A number of investigations have suggested that dipeptidyl peptidase-IV (DPP-IV), protein tyrosine phosphatase 1B (PTP-1B), α-amylase, and α-glucosidase can be targeted for type-II DM (DM-II) treatment. DPP-IV enzymes are present on the surface of most of the cell types. Inhibition of DPP-IV enzymes is considered as a new strategy for the design of new therapeutics.[19] α-Glucosidase and α-amylase are the major enzymes which are involved in the digestion of carbohydrates. Competitive inhibitors of these enzymes effectively delay and slow down the absorption of glucose and control the increase of blood sugar level. In a research, it has been concluded that inhibition of tyrosine phosphatase 1B (PTP1B) can serve as a novel target in the control of obesity and type 2 DM.[20]

In this study, ficusonolide was tested for the interaction with DPP-IV, PTP1B, α-glucosidase, and α-amylase. DPP-IV is also known as an adenosine deaminase complexing protein -II and plays a significant biological role in glucose metabolism. The DPP-IV antagonists actually block the action of this enzyme, which degrades the incretin hormone. The incretin hormone regulates the production of insulin and plays a significant role in the treatment or management of DM.[21] Our tested compound significantly blocked this protein, which indicates the antidiabetic potential of this chemical constituent. A significant computational interaction was also found between ficusonolide and PTP1B. The PTP1B inhibitors are a new resent approach for the treatment of DM-II and obesity. These proteins dephosphorylate the tyrosine residue of insulin receptors and thus block the insulin receptor intracellular signaling.[22] For docking, we used our previously constructed Baker's yeast α-glucosidase model.[23] There is another enzyme (α-glucosidase) which is the key enzyme for the degradation of starch into simple glucose molecules and promotes a hyperglycemic condition.[24] The inhibition of this enzyme is also helpful for the attenuation of hyperglycemic symptom.

In the current study, ficusonolide demonstrated an antagonistic reaction with α-glucosidase. The tested samples also blocked α-amylase, which also plays a significant role in glucose metabolism. The inhibition of this enzyme is also a good adjuvant in the treatment or management of DM.

The interaction plots of ficusonolide in the binding sites of all the studied targets revealed that it is one of the significant compounds to inhibit these target proteins/enzymes, and

https://doi.org/10.1021/acsomega.1c04230
ACS Omega 2021, 6, 27351−27357

therefore, it has the ability to modulate the multiple targets for the treatment of diabetes. Further study has been planned to investigate the *in vitro* inhibition potential against the targets.

4. MATERIALS AND METHODS

4.1. Plant Material. The stem of *F. foveolata* was obtained from Buner district, KPK Pakistan, in July 2007. Taxonomist Prof. Ambara Khan botanically identified it. Deposition of voucher specimen (Bot.15077) was done in the herbarium of the Department of Botany, University of Peshawar, Pakistan.

4.2. Chemicals and Reagents. Fetal bovine serum (FBS) and Dulbecco's modified Eagle's medium (DMEM) were obtained from Invitrogen USA and GIBCO USA, respectively. Trypsin phosphate versene glucose (TPVG) solution, metformin, glibenclamide, nicotinamide, streptozotocin, bovine serum albumin (BSA), insulin, $NaHPO_3$, $NaHCO_3$, $MgCl_2$, $CaCl_2$, KCl, and NaCl were bought from Sigma-Aldrich Co. (CA, USA). The glucose kit was purchased from Randox.

4.3. Extraction and Isolation. The shade-dried stem (13.00 kg) of title plat was extracted with 80% MeOH/H_2O for 2 weeks. The extract obtained was concentrated with the help of a rotary evaporator at low pressure in temperature, which afforded the crude extract (101 g). The crude extracted was partitioned to various polar and non-polar extracts. Amount the entire fraction the DCM fraction was subjected to HPLC, which afforded ficusonolide (99.97% pure). The chemical structure of the isolated compounds has been reported by our group.[18]

4.4. *In Vitro* Glucose Uptake Activity. *4.4.1. Preparation of L6 Cell Culture.* A layer of L-6 cells was placed in growth media prepared from DMEM, 10% FBS, 100 μg/mL of streptomycin, and100 IU/mL of penicillin at 36 °C provided with sufficient O_2 and 5% CO_2 in an incubator. TPVG solution was used to maintain the cells of the subconfluent layer in continuous passage by trypsinization.

4.4.2. Glucose Uptake Activity. The L-6 cells cultured on a six-well plate were placed in an incubator (5% CO_2) at 36 °C for a period of 48 h. The culture was revived with DMEM, consisting of 0.2% BSA after the formation of a semiconfluent monolayer and incubated again for 16 h at the same conditions. The cells were washed with KRP buffer, and the medium was discarded after 16 h. The cultured cells were then treated with ficusonolide and metformin along with 1 M glucose and further incubated for 30 min. The cells were washed (3×) using 1 mL of ice-cold KRP buffer to terminate glucose intake. For the estimation of glucose intake, the supernatant was collected. Later, the cells were lysed by repeated freezing and melting. Finally, glucose intake was estimated from the collected lysate. The uptake of glucose was estimated by the GOD-POD method.[25]

4.5. *In Vivo* Antidiabetic Activity. *4.5.1. Animals.* The research was carried out by using male Wistar rats having a body weight of about 250 g. Standard conditions were maintained in the laboratory with a 12/12 h day and night duration. The rats were provided with proper diet and water. Fasting rats were devoid of food only (not water) for a period of 16 h. All animal procedures were conducted in accordance with the Federal Regulations for Animal Experimentation and Care and approved by the Institutional Animal Care and Use Committee based on US National Institute for Health publication (no. 85e23, revised 1985).

4.5.2. Induction of T2DM. Citrate buffer with pH 4.5 was used to dissolve streptozotocin, while normal physiological saline solution was used for the dissolution of nicotinamide. Rats were fasted overnight, and a dose of 110 mg/kg nicitinamide was given to them. After 15 min, they were injected with 60 mg/kg of streptozotocin intra-peritoneally to induce T2DM. After 72 h, the raised glucose level in the plasma was determined by a commercial glucometer, confirming hyperglycemia. Antidiabetic evaluation was carried out with the rats whose blood glucose concentration was higher than 250 mg/dL.[26]

4.5.3. In Vivo Antidiabetic Assay. The hypoglycemic reference drug used was glibenclamide (5 mg/kg). The rats were divided into six groups (n = 8). A suspension of ficusonolide in 10% Tween 80 (50 mg/kg) and a suspension of the *F. foveolata* methanolic extract (100 mg/kg) were given orally to the rats. The rats of the control group were given 10% Tween 80. Blood samples were collected from the caudal vein at 0, 1, 3, 5, and 7 h after vehicle, sample, and drug administration. The blood glucose concentration was measured using a commercial glucometer. The percentage variation of blood glucose for each group was calculated in relation to the initial (0 h) level according to

$$\%\ \text{variation of glucose} = \frac{(G_x - G_0)}{G_0} \times 100$$

where G_0 is the initial glucose level and G_x is the glucose level at +1, +3, +5, and +7 h, respectively. All values were expressed as mean ± SEM.[27]

4.6. Molecular Docking Simulation. We performed docking studies of ficusonolide on various diabetes-related protein targets by using the Molecular Operating Environment (MOE 2016) software package.[28] The selected molecular targets are DPP-IV, PTP-1B, α-glucosidase, and α-amylase.

4.6.1. Protein Preparation. The 3-D crystal structures of PTP-1B, DPP-IV, and α-amylase were obtained from the Protein Data Bank (PBD) with accession code numbers 2G63, 1NNY, and 1OSE, respectively, while docking studies on α-glucosidase were performed by using our previously reported homology-modeled protein.[23,29,30] In the preparation of ligands and enzymes, docking studies were performed according to our previously reported methods.[23,29−31]

First of all, 3-D protonation of the downloaded enzyme was carried out at pH = 7, temperature = 300 K, and salt concentration 0.1 M. The MMFF94X force field was used for energy minimization. The active sites of the enzymes were determined (details in the Results section). The minimized enzyme structures were saved as .moe extension file.

4.6.2. Ligand Preparation. Structures of the ligands were drawn in the MOE window and were energy-minimized up to a gradient of 0.0001 using the MMFF94X force field.

4.6.3. Docking Procedure. After the preparation of enzymes, docking protocol validation was performed (details in the Results section), and the isolated compound was docked into the binding site of enzymes by using default parameters. Finally, lowest energy ligand−enzyme complexes were analyzed by using 2-D or 3-D interaction plots.

5. CONCLUSIONS

In the light of the above results, the triterpene lactone ficusonolide isolated from *F. foveolata* clearly enhances the uptake of glucose in *in vitro* conditions. It also possesses a

https://doi.org/10.1021/acsomega.1c04230
ACS Omega 2021, 6, 27351−27357

significant *in vivo* antidiabetic potential against non-insulin-dependent diabetic rat models. Additionally, it displays promising potential as a PTP1B inhibitor. Thus, it can be considered for developing better and new PTP1B inhibiting agents and used as a curative agent for the treatment of DM and associated complexities. The possible mode of action of ficusonolide revealed the inhibition of various diabetes-related protein targets such as DPP-IV, PTP-1B, α-glucosidase, and α-amylase. Detailed computational and structural insights affirmed promising interactions between target proteins and ficusonolide. The current study provides a strong scientific background to the folklore of *F. foveolata* stem as an antidiabetic drug.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c04230.

2-D interaction plot of the compounds' standard drug acarbose into the binding site of homology-modeled α-glucosidase (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Abdur Rauf − *Department of Chemistry, University of Swabi, Anbar 23430 Khyber Pakhtunkhwa, Pakistan;* orcid.org/0000-0003-2429-5491; Email: mashaljcs@yahoo.com

Authors

Ala Ud Din − *Department of Chemistry, Bacha Khan University Charsadda, Charsadda 24420 Khyber Pakhtunkhwa, Pakistan;* Present Address: Department of Chemistry, University of Buner, Buner, 17290, KP, Pakistan; orcid.org/0000-0001-6470-0952

Maria Khan − *Department of Chemistry, Bacha Khan University Charsadda, Charsadda 24420 Khyber Pakhtunkhwa, Pakistan*

Muhammad Zahir Shah − *Key Laboratory of Synthetic and Natural Fucntional Molecule, North West University, Xian 710127, P. R. China*

Umer Rashid − *Department of Chemistry, COMSATS University Islamabad, Abbottabad 22060, Pakistan;* orcid.org/0000-0002-2419-3172

Anees Ahmed Khalil − *University Institute of Diet and Nutritional Sciences, Faculty of Allied Health Sciences, The University of Lahore, 54590 Lahore, Pakistan*

Khair Zaman − *Department of Chemistry, Abdul Wali Khan University, Mardan 23200 Khyber Pakhtunkhwa, Pakistan*

Yahya S. Al-Awthan − *Department of Biology, Faculty of Science, University of Tabuk, Tabuk 71491, Saudi Arabia; Department of Biology, Faculty of Science, Ibb University, Ibb 70270, Yemen;* orcid.org/0000-0001-8738-8076

Mohammed A. Al-Duais − *Department of Biochemistry, Faculty of Science, University of Tabuk, Tabuk 71491, Saudi Arabia; Biochemistry Unit, Chemistry Department, Faculty of Science, Ibb University, Ibb 70270, Yeme*

Omar Bahattab − *Department of Biology, Faculty of Science, University of Tabuk, Tabuk 71491, Saudi Arabia*

Adil A.H. Mujawah − *Department of Chemistry, College of Science and Arts, Qassim University, Ar Rass 51921, Saudi Arabia*

Naveed Muhammad − *Department of Pharmacy, Abdul Wali Khan University, Mardan 23200 Khyber Pakhtunkhwa, Pakistan*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.1c04230

Author Contributions

Conceptualization, methodology, and validation: A.U.D., M.K., and M.Z.H.; formal analysis, investigation, and resources: A.R., U.R., A.A.K., and K.Z.; data curation: Y.S.A., M.A., and O.B.; and original draft preparation: A.A.H.M. and N.M. Both authors have read and agreed to the published version of the manuscript.

Funding

Higher Education Commission (HEC), Pakistan, supported this work under the International Research Support Initiation Program (IRSIP).

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We would like to extend our gratitude to Dr. Inam Ullah of Department of Pharmacy, University of Peshawar, for helping us with the antidiabetic activity.

■ REFERENCES

(1) Nazaruk, J.; Borzym-Kluczyk, M. The role of triterpenes in the management of diabetes mellitus and its complications. *Phytochem. Rev.* **2014**, *14*, 675−690.

(2) Turkoski, B. B. Diabetes and diabetes medications. *Orthop. Nurs.* **2006**, *25*, 227−231.

(3) Rader, D. J. Effect of insulin resistance, dyslipidemia, and intra-abdominal adiposity on the development of cardiovascular disease and diabetes mellitus. *Am. J. Med.* **2007**, *120*, S12−S18.

(4) Duez, H.; Cariou, B.; Staels, B. DPP-4 inhibitors in the treatment of type 2 diabetes. *Biochem. Pharmacol.* **2012**, *83*, 823−832.

(5) Inzucchi, S. E. Oral Antihyperglycemic Therapy for Type 2 Diabetes. *J. Am. Med. Assoc.* **2002**, *287*, 360−372.

(6) Elchebly, M.; Payette, P.; Michaliszyn, E.; Cromlish, W.; Collins, S.; Loy, A. L.; Normandin, D.; Cheng, A.; Himms-Hagen, J.; Chan, C. C.; Ramachandran, C.; Gresser, M. J.; Tremblay, M. L.; Kennedy, B. P. Increased insulin sensitivity and obesity resistance in mice lacking the protein tyrosine phosphatase-1B gene. *Sci* **1999**, *283*, 1544−1548.

(7) Kasibhatla, B.; Wos, J.; Peters, K. G. Targeting protein tyrosine phosphatase to enhance insulin action for the potential treatment of diabetes. *Curr. Opin. Invest. Drugs* **2007**, *8*, 805−813.

(8) Zinker, B. A.; Rondinone, C. M.; Trevillyan, J. M.; Gum, R. J.; Clampit, J. E.; Waring, J. F.; Xie, N.; Wilcox, D.; Jacobson, P.; Frost, L.; Kroeger, P. E.; Reilly, R. M.; Koterski, S.; Opgenorth, T. J.; Ulrich, R. G.; Crosby, S.; Butler, M.; Murray, S. F.; McKay, R. A.; Bhanot, S.; Monia, B. P.; Jirousek, M. R. PTP1B antisense oligonucleotide lowers PTP1B protein, normalizes blood glucose, and improves insulin sensitivity in diabetic mice. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 11357−11362.

(9) González-Rodríguez, Á.; Más-Gutierrez, J. A.; Mirasierra, M.; Fernandez-Pérez, A.; Lee, Y. J.; Ko, H. J.; Kim, J. K.; Romanos, E.; Carrascosa, J. M.; Ros, M.; Vallejo, M.; Rondinone, C. M.; Valverde, Á. M. Essential role of protein tyrosine phosphatase 1B in obesity-induced inflammation and peripheral insulin resistance during aging. *Aging Cell* **2012**, *11*, 284−296.

(10) Koren, S.; Fantus, I. G. Inhibition of the protein tyrosine phosphatase PTP1B: potential therapy for obesity, insulin resistance and type-2 diabetes mellitus. *Best Pract. Res., Clin. Endocrinol. Metab.* **2007**, *21*, 621−640.

(11) Woodland, D. W. *Comtemporary plants systematic*, 2nd ed.; Andrews University Press: Barrien Springs, MI, 1997.
(12) Kislev, M. E.; Hartmann, A.; Bar-Yosef, O. Early domesticated fig in the Jordan Valley. *Sci* **2006**, *312*, 1372−1374.
(13) Lansky, E. P.; Paavilainen, H. M.; Pawlus, A. D.; Newman, R. A. Ficus spp. (fig): Ethnobotany and potential as anticancer and anti-inflammatory agents. *J. Ethnopharmacol.* **2008**, *119*, 195−213.
(14) Ahmad, W.; Khan, A. Q.; Malik, A. Two triterpenes from the leaves of Ficus carica. *Planta Med.* **1998**, *54*, 481.
(15) Chiang, Y.-M.; Chang, J.-Y.; Kuo, C.-C.; Chang, C.-Y.; Kuo, Y.-H. Cytotoxic triterpenes from the aerial roots of Ficus microcarpa. *Phytochem* **2005**, *66*, 495.
(16) Teixeira, D. M.; Patão, R. F.; Coelho, A. V.; da Costa, C. T. Comparison between sample disruption methods and solid-liquid extraction (SLE) to extract phenolic compounds from Ficus carica leaves. *J. Chromatogr. A* **2006**, *1103*, 22−28.
(17) Din, A. U.; Uddin, G.; Hussain, N.; Khan, A.; Khan, I.; Shad, A. A.; Choudhary, M. I. Bioassay-guided isolation of new antitumor agent from Ficusfaveolata (Wall. ex Miq.). *J. Cancer Sci. Ther.* **2013**, *5*, 404−408.
(18) Kumar, V.; Sharma, K.; Ahmed, B.; Al-Abbasi, F. A.; Anwar, F.; Verma, A. Deconvoluting the dual hypoglycemic effect of wedelolactone isolated fromWedelia calendulacea: investigationviaexperimental validation and molecular docking. *RSC Adv.* **2018**, *8*, 18180−18196.
(19) Mechchate, H.; Es-Safi, I.; Bourhia, M.; Kyrylchuk, A.; El Moussaoui, A.; Conte, R.; Ullah, R.; Ezzeldin, E.; Mostafa, G. A.; Grafov, A.; Bekkari, H.; Bousta, D. In-Vivo Antidiabetic Activity and In-Silico Mode of Action of LC/MS-MS Identified Flavonoids in Oleaster Leaves. *Molecules* **2020**, *25*, 5073.
(20) Kennedy, B. P. Role of protein tyrosine phosphatase-1B in diabetes and obesity. *Biomed. Pharmacother.* **1999**, *53*, 466−470.
(21) Setyaningsih, E. P.; Saputri, F. C.; Mun'im, A. The Antidiabetic Effectivity of Indonesian Plants Extracts via DPP-IV Inhibitory Mechanism. *J. Young Pharm.* **2019**, *11*, 161−164.
(22) Zhang, C.-C.; Geng, C.-A.; Huang, X.-Y.; Zhang, X.-M.; Chen, J.-J. Antidiabetic Stilbenes from Peony Seeds with PTP1B, α-Glucosidase, and DPPIV Inhibitory Activities. *J. Agric. Food Chem.* **2019**, *67*, 6765−6772.
(23) Ali, M.; Ali, S.; Khan, M.; Rashid, U.; Ahmad, M.; Khan, A.; Al-Harrasi, A.; Ullah, F.; Latif, A. Synthesis, biological activities, and molecular docking studies of 2-mercaptobenzimidazole based derivatives. *Bioorg. Chem.* **2018**, *80*, 472−479.
(24) He, X.-F.; Chen, J.-J.; Huang, X.-Y.; Hu, J.; Zhang, X.-K.; Guo, Y.-Q.; Zhang, X.-M.; Geng, C.-A. The antidiabetic potency of Amomum tsao-ko and its active flavanols, as PTP1B selective and α-glucosidase dual inhibitors. *Ind. Crops Prod.* **2021**, *160*, 112908.
(25) Gupta, R. N.; Pareek, A.; Suthar, M.; Rathore, G. S.; Basniwal, P. K.; Jain, D. Study of glucose uptake activity of Helicteres isora Linn. fruits in L-6 cell lines. *Int. J. Diabetes Dev. Ctries.* **2009**, *29*, 170−173.
(26) Vianna, R.; Brault, A.; Martineau, L. C.; Couture, R.; Arnason, J. T.; Haddad, P. S. In VivoAnti-Diabetic Activity of the Ethanolic Crude Extract ofSorbus decoraC.K.Schneid. (Rosacea): A Medicinal Plant Used by Canadian James Bay Cree Nations to Treat Symptoms Related to Diabetes. *J. Evidence-Based Complementary Altern. Med.* **2011**, *2011*, 1−7.
(27) Gheibi, S.; Kashfi, K.; Ghasemi, A. A practical guide for induction of type-2 diabetes in rat: Incorporating a high-fat diet and streptozotocin. *Biomed Pharmacother* **2017**, *95*, 605−613.
(28) Molecular Operating Environment Chemical Computing Group ULC, 1010 Sherbooke St. West, Suite# 910, Montreal, QC, Canada, H3A 2R7, 2018.
(29) Nadeem, M.; Mumtaz, M. W.; Danish, M.; Rashid, U.; Mukhtar, H.; Irfan, A. Antidiabetic functionality of Vitex negundo L. leaves based on UHPLC-QTOF-MS/MS based bioactives profiling and molecular docking insights. *Ind. Crops Prod.* **2020**, *152*, 112445.
(30) Hussain, F.; Khan, Z.; Jan, M. S.; Ahmad, S.; Ahmad, A.; Rashid, U.; Ullah, F.; Ayaz, M.; Sadiq, A. Synthesis, in-vitro α-glucosidase inhibition, antioxidant, in-vivo antidiabetic and molecular docking studies of pyrrolidine-2,5-dione and thiazolidine-2,4-dione derivatives. *Bioorg. Chem.* **2019**, *91*, 103128.
(31) Studio, D. *Dassault Systemes BIOVIA, Discovery studio modelling environment, Release 4.5*; Accelrys Software Inc, 2015; pp 98−104.

https://doi.org/10.1021/acsomega.1c04230
ACS Omega 2021, 6, 27351−27357