Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 9, No. 2, 1482-1492
2025
Publisher: Learning Gate
DOI: 10.55214/25768484.v9i2.4795

Antioxidative stress activity of phloroglucinol as a protector against pancreas cell damage in diabetes: In silico and in vivo study

Renny Novi Puspitasari[1,2], Rochmah Kurnijasanti[3], Reny I'tishom[4], Mohammad Rais Mustafa[5], Sri Agus Sudjarwo[3*]
[1]Doctoral Program of Medical Science, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.
[2]Department of Pharmacology, Faculty of Medicine, Universitas Nahdlatul Ulama, Surabaya, Indonesia.
[3]Department of Pharmacology, Faculty of Veterinary Medicine, Airlangga University, Surabaya, Indonesia; ags158@yahoo.com (S.A.S.).
[4]Department of Medical Biology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia.
[5]Department of Pharmacology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia.

Abstract: Diabetes is a metabolic disease characterized by hyperglycemia, which can increase oxidative stress and induce pancreatic cell damage. The study's objective was to investigate the in silico and in vivo anti-oxidative stress activity of phloroglucinol as a protector against streptozotocin-induced pancreatic cell damage in mice. Molecular docking of phloroglucinol on the target proteins of the nuclear factor erythroid 2–related factor 2 (Nrf2), superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (Cat) was conducted in the in silico study. In rat pancreatic cells stimulated with streptozotocin, in vivo research was conducted to prove the anti-oxidative stress activity of phloroglucinol as a protector against pancreatic cell damage. It was histologically analyzed using hematoxylin and eosin staining. Additionally, blood glucose levels were measured. In the in silico evaluation, phloroglucinol exhibited higher binding energy against Nrf2 (ΔG affinity = -3.8 kcal/mol), SOD (ΔG affinity = -4.2 kcal/mol), GPx (ΔG affinity = -4.1 kcal/mol), and catalase (ΔG affinity = -5.3 kcal/mol). In the in vivo investigation, STZ treatment resulted in morphological abnormalities, pancreatic cell necrosis, and increased blood glucose levels. However, the administration of phloroglucinol prevented the necrosis of pancreatic cells and decreased blood glucose levels. This study shows that phloroglucinol can protect pancreatic cells from oxidative damage through its antioxidant properties, such as SOD, GPx, and catalase. Phloroglucinol exhibited higher binding energy against Nrf2, SOD, GPx, and catalase.

Keywords: *Antioxidant, Diabetes, In silico, In vivo, Pancreas, Phloroglucinol.*

1. Introduction

Diabetes mellitus (DM) is a chronic endocrine disease with significant morbidity and mortality rates due to impaired secretion or function of insulin in the body, which can cause increased blood glucose levels (hyperglycemia) in the body. Chronic hyperglycemia can lead to complications of diabetes, such as the destruction of the insulin-producing β cells in the pancreas, resulting in little or no insulin production, which can lead to type 1 diabetes [1-3].

Hyperglycemia can increase ROS (H_2O_2, O_2-, OH- and decrease antioxidants (SOD, GPx, and Cat) are thought to be linked to oxidative stress, which is a significant factor in diabetic complications [4-6]. Researchers widely use Streptozotocin to create diabetes models in mice because of its relationship with elevated ROS formation and reduced antioxidant production which can cause oxidative damage to pancreatic β cells [7-9]. Increased reactive oxygen species (ROS) formation during oxidative stress

History: Received: 12 December 2024; Revised: 17 January 2025; Accepted: 20 January 2025; Published: 15 February 2025
* Correspondence: ags158@yahoo.com

triggers NRF2, which in turn boosts the expression of SOD, GPx, and Cat, enhancing the antioxidant capacity of the cell. Nrf2 regulates the expression of genes involved in the production of antioxidant enzymes, such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (Cat). These enzymes help reduce oxidative stress by neutralizing free radicals and protecting cells from damage. Molecular docking can be used to evaluate the binding affinity of phloroglucinol to SOD and GPx [9-11]. This study can provide insight into how strongly phloroglucinol can bind to these enzymes and potentially modulate their activities. Molecular docking between phloroglucinol, superoxide dismutase (SOD), and glutathione peroxidase (GPx) is an interesting area of research because phloroglucinol is known to have antioxidant properties. Molecular docking predicts the low-energy conformation of the small molecule at the protein's binding site, which helps determine the binding process and affinity of small molecules to a protein. Receptor grid creation, molecular docking, ADME-Tox Screening, MM/GBSA, target retrieval from a PDB database, ligand library preparation, and building from an online database are some of the techniques employed. A computational method was used for the study to identify potential treatment possibilities and understand the biological mechanisms underlying protein-ligand interactions [12, 13].

Natural antioxidants have been employed extensively in the development of techniques to lessen oxidative damage to pancreatic cells to minimize pancreatic cell damage in diabetes complications [2, 7, 14]. Numerous studies have shown that utilizing certain exogenous antioxidants can prevent the majority of diabetic problems caused by oxidative stress[15-17]. Phloroglucinol is also reported to have antioxidant properties[16, 17]. The pharmacological activities of phloroglucinol compounds include antiviral, antibacterial, diabetes prevention, anti-allergic, antioxidant, and antiapoptotic properties [18-20]. This investigation aims to examine in silico and in vivo study of the anti-oxidative stress activity of phloroglucinol as a protector against Streptozotocin-induced pancreas cell damage in mice

2. Methods

2.1. In Silico Study the Effect of Antioxidant of Phloroglucinol

2.1.1. Ligand Preparation for Docking

A test compound is a compound obtained from the compound profile results. Table 1 shows the 3D structure from the PubChem database. (https://pubchem.ncbi.nlm.nih.gov/). The compound was prepared by optimizing its conformation using the Open Babel 2.3.1 plugin integrated into the Protein Data Bank (.pdb) file integrated with PyRx 0.9 software. The optimal conformation provides flexibility in the ligand structure.

2.1.2. ADME Test

ADME test is used to determine the pharmacokinetic and toxicity properties of a ligand compound. ADME is absorption, distribution, metabolism, and excretion, which are important in drug safety assessment. ADME analysis was performed by copying the canonical SMILES of the ligand compounds on the Swiss ADME website, which provided information on pharmacokinetic aspects.

2.1.3. Preparation of Receptors (Target Proteins) for Docking

The protein structures used in the test are the protein structures of NrF2, SOD, Cat, GPx. The protein structures were accessed from the Protein Data Bank (PDB) (https://www.rcsb.org/) and UniProt (https://www.uniprot.org/) along with their respective IDs. Biovia Discovery Studio 2019 software is used to remove contaminant molecules in proteins.

2.1.4. Screening Docking

Molecular docking was performed using Auto Dock Vina, which was integrated into PyRx 0.8 software. The docking performed is a blind docking to predict ligand interactions in protein regions. The stability of the interaction between protein and ligand is indicated by the binding affinity value. The lower the binding affinity value, the more stable the protein-ligand interaction.

Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 9, No. 2: 1482-1492, 2025
DOI: 10.55214/25768484.v9i2.4795

2.1.5. Molecular Docking Visualization

Water content was removed to produce NrF_2, CAT, SOD, and GPx. The proteins were separated from the ligands. The ligand then binds partial charges and hydrogens. Discovery Studio 2019 software was used for 3D and 2D visualization. 3D structures are shown to provide an overview of ligand-protein interactions. 3D visualization of protein-ligand interactions is performed using 2D visualization of protein-ligand interactions.

2.1.6. Analysis of Molecular Docking Results

The docking results were visualized using Biovia Discovery Studio 2019 software. The chemical interactions between the displayed ligands (phloroglucinol) and target proteins (Nrf2, SOD, CAT, Gpx) are hydrophobic, electrostatic interactions, and hydrogen bonds. The more hydrogen bonds produced, the more stable the interaction. The bond energy value (ΔG bond) is used as a parameter in the docking process. The binding energy value between the ligand and the receptor is the inverse of the affinity value. The lower the energy value, the higher the affinity, and vice versa.

2.2. In Vivo Study of the Effect of Phloroglucinol as Protector of Pancreas Cell Damage and Reduced Blood Glucose on Diabetic Mice

2.2.1. Ethical Approval

The care, use, and treatment of experimental animals in the research have been approved by the Animal Ethics Committee of the Faculty of Veterinary Medicine, Airlangga University, Surabaya, Indonesia (No2.KEH.058.04.2023)

2.2.2. Experimental animals

Healthy male mice (weight 25–30g) were obtained from Pharma Veterinary Center, Surabaya, Indonesia, and used for the study. Mice were kept in plastic cages indoors with standard conditions: temperature 22 ± 2°C, humidity 55–60%, light period 12 hours light/12 hours dark. The mice were fed with normal mouse chow and water as much as they wanted. All mice were adapted for 1 week before the study.

2.2.3. Diabetic model mice

Overnight fasted mice were injected with a single dose of streptozotocin (60 mg/kg body weight, intraperitoneally) in citrate buffer (0.1 M, pH 4.5). 72 hours after the STZ injection, blood glucose levels were measured with a glucometer. Mice were used for research if they had blood glucose levels above 250 mg/dl.

.

2.2.4. Experimental design

The study consisted of five groups (8 mice per group): control group (mice were given distilled water orally), diabetes mellitus group (mice were injected with STZ 150 mg/kg BW intraperitoneally), and phloroglucinol group (mice were injected with STZ 150 mg/kg BW intraperitoneally and given phloroglucinol 100 mg/kg and 200 mg/kg orally). Mice were given phloroglucinol once daily for 28 days, starting after 3 days. On the 29th day, blood was taken by puncturing the tail vein, and blood glucose levels were measured using a digital glucometer (Accu-Chek, Roche, Germany). Furthermore, mice were euthanized with ketamine (60 mg/kg BW) and xylazine (7.5 mg/kg BW) intraperitoneally, and then the pancreas was taken from each mouse for histopathological examination with hematoxylin and eosin staining.

2.2.5. Blood glucose analysis

Examination of blood sugar levels in mice, Previously the mice were fasted for 10 hours, then blood was taken from the lateral vein of the tail and dripped as much as 1 drop on the glucometer stick that

Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 9, No. 2: 1482-1492, 2025
DOI: 10.55214/25768484.v9i2.4795

had been attached to the glucometer ®Gluco Dr. After 10 seconds the blood glucose level results will appear on the screen.

2.2.6. Histopathological Examination

Mice pancreas was collected fixed in 10% buffered formalin and embedded in paraffin. Hematoxylin and eosin were used to stain pancreatic tissue sectioned at a thickness of 5 µm. Under a microscope, the sections were inspected to look for signs of cellular damage, such as the number of pancreatic cells and the extent of damage to the islets of Langerhans.

2.2.7. Statistical Analysis.

The research data were analyzed using a one-way analysis of variance (ANOVA), followed by Tukey's post hoc test. The results of the analysis are shown as mean ± SEM, which is considered significantly different at <0.05.

3. Results

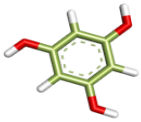
3.1. In silico study the Effect of Antioxidant of Phloroglucinol

The results of observation on phloroglucinol chemical compounds obtained from literature and downloaded through the Pubchem website were used to determine the prediction of affinity for four target proteins Nrf2, SOD, Catalase, GPx in silico by molecular docking method.

3.1.1. Ligand Preparation (Phloroglucinol) For Docking

Phloroglucinol as a test ligand can be seen in Figure 1 which consists of the compound name, CID, and the website source where the compound was obtained. 3D view of compounds using atomic coloring and in stick figure form. The C atom is green, the O atom is red, and the H atom is white (Table 1).

Table 1.
Ligand, CID, Reference, 3D structure.

Ligan	CID	Reference	3 Dimensional
Phloroglucinol	359	PubChem	

3.1.2. ADME Test

The following are the results of the ADME test of the ligand compound. The parameters used include absorption and distribution. In addition, metabolic parameters are measured from the inhibition ability that targets phase 1 that occurs in CYP450. This is because CYP is involved in 90% of the metabolism of enzymatic reactions. In this parameter, metabolism is shown in the category "yes" or "no" as an inhibitor of the CYP450 family.

Phloroglucinol meets the criteria for absorption and metabolism because they have high GIA and are not an inhibitor of P-gp and CYP450. Glycoprotein P (P-gp) is an ATP-binding cassette (ABC) transporter in the cell membrane and acts as a barrier to the excretion of toxins within the cell. These two compounds are not characterized as substrates or inhibitors of P-gp, so they are considered to have therapeutic potential. (Table 2)

Table 2.
Results of compound absorption prediction.

Compound	GIA	BBB	P-gp	CYP450					
				1A2	2C19	2C9	2D6	3A4	Kp
Phloroglucinol	High	Yes	No	No	No	No	No	Yes	-6,96

Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 9, No. 2: 1482-1492, 2025
DOI: 10.55214/25768484.v9i2.4795

GIA (Gastrointestinal Absorption); BBB (Blood Brain Barrier); P-gp (P-glycoprotein substrate); cytochrome 450 (CYP450) = 1A2, 2C19, 2C9, 3A4; Log Kp (skin penetration, cm/s)

3.1.3. Target Protein for Docking

Table 3 shows a list of proteins used in this study (Nrf2, SOD, CAT, GPx) .

Table 3.
Protein, protein ID, and reference.

Protein	Protein ID	Reference
Nrf2	7X5E	RCSB PDB
SOD	6SPI	RCSB PDB
GPx	2F8A	RCSB PDB
CAT	8SGV	RCSB PDB

Figure 1 shows the 3D structure of the protein is shown as ribbons with secondary structure coloring. Green color represents a coiled-coil structure, red color represents a helical structure, white color represents ring structure and light blue color represents beta-sheet structure.

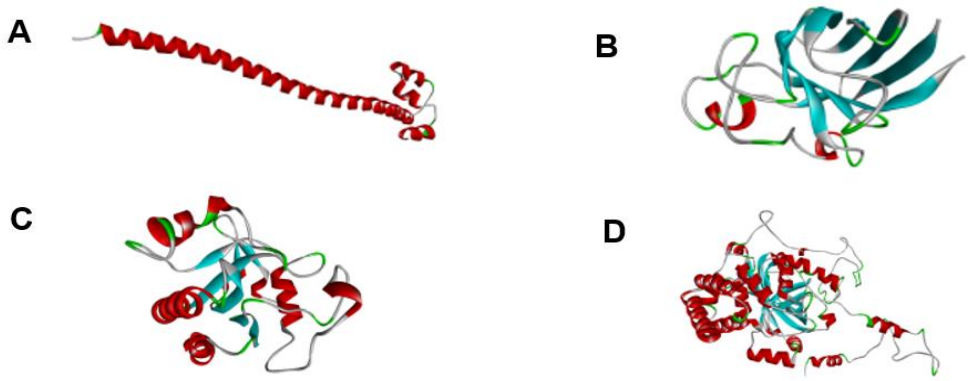


Figure 1.
3D structure of target proteins: Nrf2 (A); SOD (B); GPx (C); CAT (D).

3.1.4. Visualization and analysis of Molecular docking

Docking results show the binding affinity values and the type of chemical bond formed. The energy required to form a protein-ligand bond can be seen in the binding affinity. The smaller the binding affinity value, the easier it is for the ligand to bind to the protein and the greater its potential to affect the protein. The docking results between proteins and compounds produce binding affinity values as shown in Table 4.

The docking results show that each protein receptor mostly has more efficient inhibition indicated by low binding affinity values. The stability and turnover of cellular protein activity are greatly influenced by hydrogen bonds.

Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 9, No. 2: 1482-1492, 2025
DOI: 10.55214/25768484.v9i2.4795

Table 4.
Binding affinity and interaction of phloroglucinol-protein results.

Protein	Binding affinity	Bond category	Bond type	Residue
Nrf2	-3,8	Hidrofobik	Pi-Alkyl	Arg499, Arg502
SOD	-4,2	Hydrogen	Konvensional	His80
			Pi-donor	His63
		Hidrofobik	Pi-Pi Stacked	His80
			Pi-Pi T-shaped	His63
			Pi-Alkyl	Pro62, Lys136
GPx	-4,1	Hydrogen	Konvensional	Glu111
		Elektrostatik	Pi-kation	His121
			Pi-anion	Glu111
		Hidrofobik	Pi-pi T-shaped	His121
			Pi-alkyl	Ala19, Arg20, Cys113
CAT	-5,3	Hidrofobik	Pi-pi t-shaped	Tyr358

Ligand-protein linkages are produced by the interaction of phloroglucinol molecules with NRF2, SOD, GPx and catalase. Phloroglucinol interact with NRF2 using hidrofobic bond at Arg499, Arg502(ΔG affinity = -3,8 kcal/mol); with SOD using hydrogen and hydrofobik bond at HIS80, HIS63,HIS80, his63, Pto62 and Lys136 (ΔG affinity = -4.2 kcal/mol); GPX using hydrogen, elektrostatik and hydrofobik bond at Glu111, His121, Glu111, His121 , Ala19, Arg20, Cys113 (ΔG affinity = -4.1 kcal/mol); CAT hydrofobik bond at Tyr358 (ΔG affinity = -5.3 kcal/mol). Based on these results, phloroglucinol has the most stable bond with catalase because it has the lowest bond, -5.3kcal/mol.

Normal drug discovery begins with the determination of the ligand binding site. As seen in Figure 2 and Figure 3, the interaction between phloroglucinol and the protein is shown in 2D and 3D.

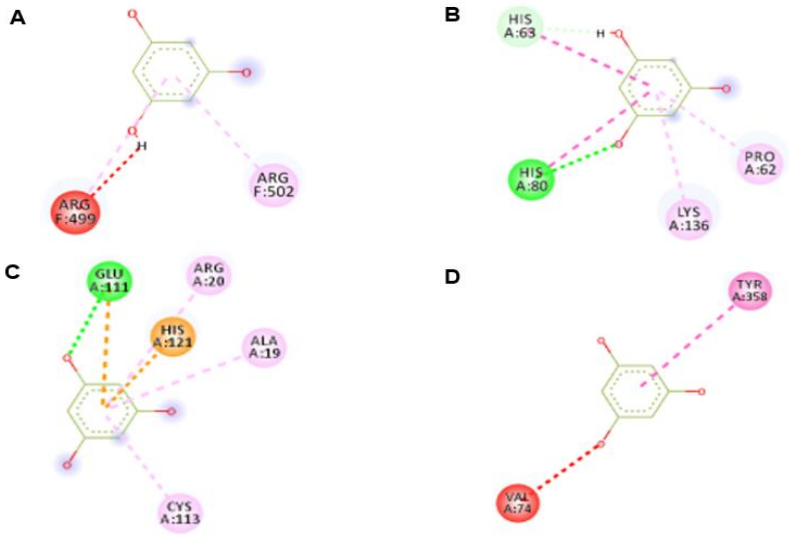


Figure 2.
2D structure of target interacts phloroglucinol with proteins: Nrf2 (A); SOD (B); GPx (C); CAT (D).

Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 9, No. 2: 1482-1492, 2025
DOI: 10.55214/25768484.v9i2.4795

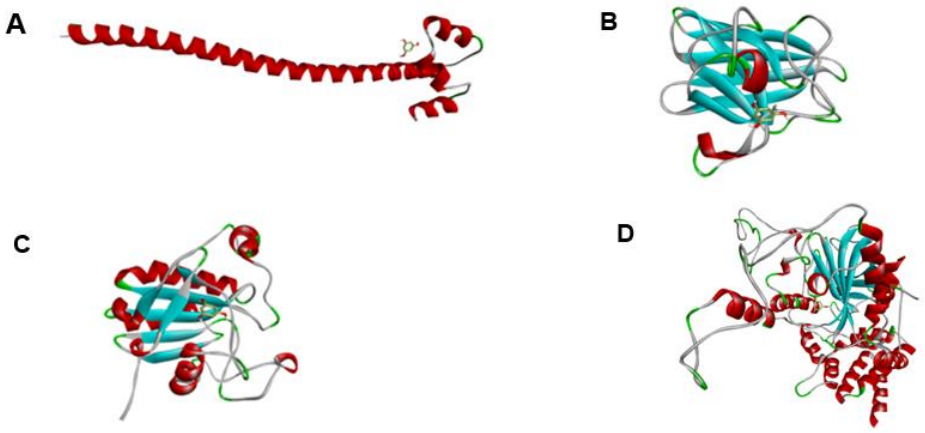


Figure 3.
3D structure of target interact phloroglucinol with proteins: Nrf2 (A); SOD (B); GPx (C); CAT (D).

3.2. In Vivo Study of the Phloroglucinol Protective Effect on Pancreas Cells Damage of Diabetic Mice

3.2.1. The Effect of Phloroglucinol on Blood Glucose of Diabetic Mice

Glucose dramatically increased in STZ-induced animals as compared to healthy control mice, according to the glucometer findings. In the meantime, blood Glucose levels were lower in diabetic mice treated with phloroglucinol than in diabetic mice (Figure 5).

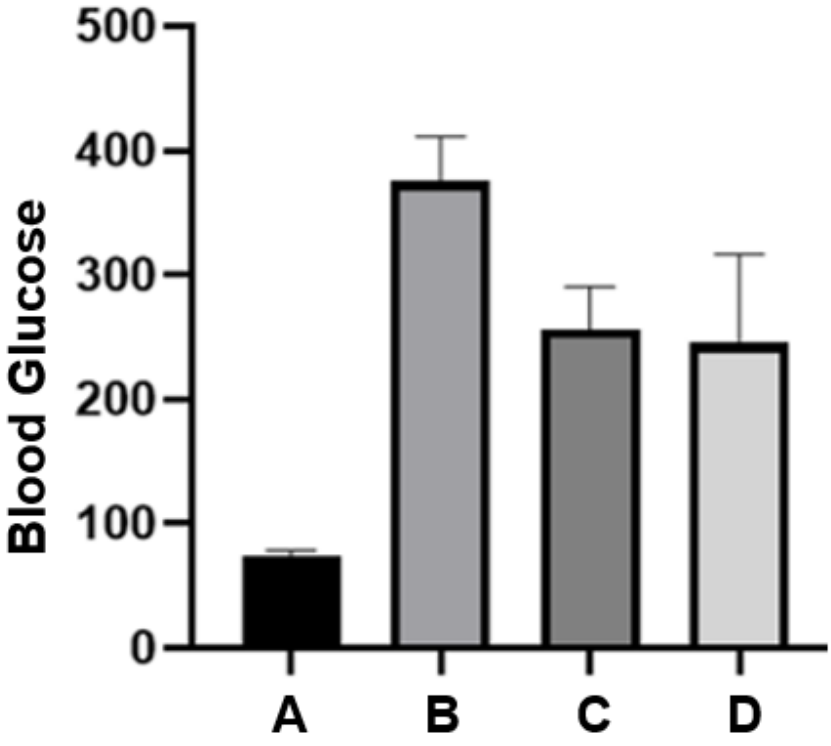


Figure 4.
The effect of Phloroglucinol on blood glucose levels in diabetic mice. Control group (A); Diabetic group (B); Phloroglucinol group at a dose of 100 mg/Kg BW (C), and a dose of 200 mg/Kg BW (D).

Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 9, No. 2: 1482-1492, 2025
DOI: 10.55214/25768484.v9i2.4795

3.3. The Effect of Phloroglucinol on the Histopathologic Pancreas of Diabetic Mice

To prove the effect of phloroglucinol administration, a histopathological examination of the pancreas of diabetic mice induced by streptozotocin. Light microscopic examination showed that the healthy control group showed normal pancreatic structure and circular islets of Langerhans containing β-cells. Administration of streptozotocin can cause pancreatic morphological irregularities and a reduction in pancreas cells. Treatment with Phloroglucinol can inhibit pancreatic damage and they show an increase in the size of the islets of Langerhans and their number of β-cells.

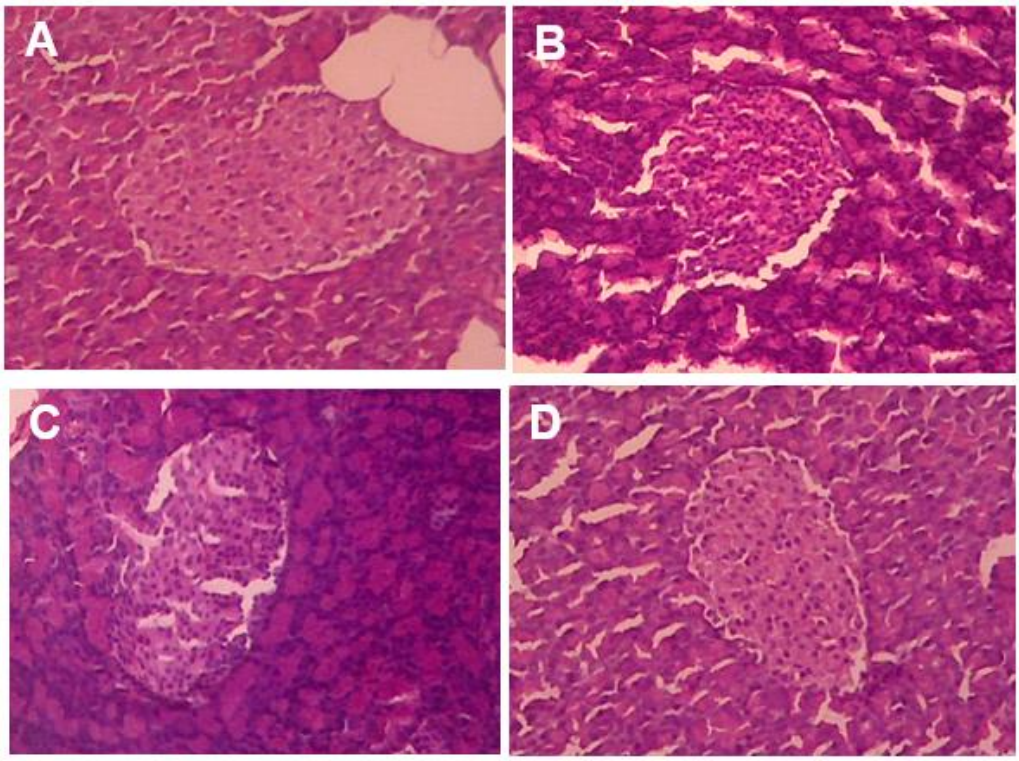


Figure 5.
Photomicrographs of the pancreases from all groups of rats as stained by hematoxylin and eosin (H &E) stain: represents control (A) and they show normally sized, circular islets of Langerhans containing β-cells; diabetic mice (B) and shows obvious shrinkage in the islets of Langerhans; and diabetic mice treated with phloroglucinol at a dose 100 mg/kg BB (C) and at dose 200 mg/kg (D). Magnification. 400×

4. Discussion

Molecular docking is a widely recognized method in drug discovery used to investigate the binding interactions of ligands with target proteins. This approach allows for rapid and accurate prediction of phloroglucinol activity, as reflected by the docking score [12, 13]. This study contributes to the discovery of new compounds while deepening our understanding of the pharmacological activity of natural compounds under therapeutic conditions. This study demonstrated that phloroglucinol effectively binds antioxidant enzymes such as SOD, GPx, and catalase. The binding interactions are characterized by significant binding energies, measured at -10.2310 kcal/mol and -9.0518 kcal/mol, respectively. In silico analysis in this study predicted favourable binding affinities of phloroglucinol with key target protein residues, achieving high docking scores against Nrf2, SOD, GPx, and catalase. This computational method provides a valuable platform for predicting and understanding biological phenomena, optimizing experimental designs, and significantly reducing the time and costs associated

Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 9, No. 2: 1482-1492, 2025
DOI: 10.55214/25768484.v9i2.4795

with laboratory research. In addition, integrating in silico and in vivo approaches allows researchers to combine the predictive power of computational models with the biological relevance of experimental studies. This synergy facilitates a deeper understanding of biological processes and accelerates the path to novel drug discovery and development [12, 13]. This study provides a systematic comparative evaluation of the potential of phloroglucinol to protect the pancreas under STZ-induced oxidative stress. In addition, NRF2 is an important transcription factor that regulates the expression of antioxidant enzymes such as SOD, GPx and Catalase in response to oxidative stress, which play a major role in cellular defence mechanisms against oxidative damage by neutralizing free radicals. Studies have shown that activation of NRF2 can increase the production of antioxidant enzymes, which protect cells from oxidative stress. NRF2 activators are being explored as potential preventive or therapeutic agents for conditions such as diabetic complications, cancer, and neurological disorders, all of which are exacerbated by oxidative stress [4, 9, 11]. It has confirmed that NRF2 regulates the expression of antioxidant enzymes, including CAT, GPx, and glutathione reductase (GRx), which can further protect cells from oxidative damage. . Antioxidant enzymes play an important role in reducing oxidative stress, and their expression is regulated by NRF2 through transcription. Among these enzymes, superoxide dismutase (SOD) catalyzes the conversion of superoxide radicals to oxygen and hydrogen peroxide. Superoxide, a highly reactive oxygen species, can damage tissues and cells; SOD neutralizes it, thereby protecting cells from oxidative stress [4, 21]. Catalase (CAT) completes this process by splitting hydrogen peroxide into water and oxygen, further preventing oxidative damage. Glutathione peroxidase (GPx) utilizes reduced glutathione (GSH) to catalyze the reduction of hydrogen peroxide and organic hydroperoxides, neutralizing reactive oxygen species and protecting cells from oxidative damage. Studies have shown that activation of NRF2 can increase the production of antioxidant enzymes such as SOD, CAT, GPx, and GRx, underscoring the potential of NRF2 as a therapeutic target for oxidative stress-related complications in diabetes [5, 7, 9].

Animal models of diabetes are commonly established using streptozotocin (STZ), a compound widely utilized in diabetes research. STZ induces hyperglycemia, leading to increased production of reactive oxygen species (ROS). The excessive accumulation of ROS triggers oxidative stress, which causes the oxidation of lipids, proteins, and DNA, ultimately resulting in pancreatic cell damage and elevated blood glucose levels [6, 7, 22].

Recent research highlights that phloroglucinol interacts with key amino acid residues, demonstrating high binding energy and favourable docking scores with antioxidant proteins. The docking scores for phloroglucinol with Nrf2, SOD, GPx, and catalase were -3.8, -4.2, -4.1, and -5.3 kcal/mol, respectively. These interactions include hydrophobic bonds with Nrf2 and catalase, hydrogen and hydrophobic bonds with SOD, and hydrogen, electrostatic, and hydrophobic bonds with GPx. Such interactions suggest that phloroglucinol may act as an effective antioxidant. Nrf2 plays a crucial role in oxidative stress defence by regulating cellular antioxidants. However, oxidative stress can inhibit the induction of genes encoding antioxidants, reducing the synthesis of endogenous antioxidants such as SOD, GPx, and catalase. Hyperglycemia is associated with decreased activity and expression of Nrf2. Studies show that STZ-induced oxidative stress disrupts the Keap1-Cul3 ubiquitination mechanism, damages Keap1 cysteines, and accelerates Nrf2 degradation via the 26S proteasome, leading to a short Nrf2 half-life and reduced Nrf2 production [4, 11].

Phloroglucinol has been identified as a highly effective DPPH free radical scavenger. Its antioxidant and anti-inflammatory properties have been demonstrated in various medical conditions, where it suppresses cell apoptosis and mitigates oxidative damage [16, 17, 20]. In vivo studies reveal that phloroglucinol minimizes damage to the pancreatic islets of Langerhans in STZ-induced diabetic mice and significantly reduces serum glucose levels. Furthermore, phloroglucinol lowers blood glucose levels by inhibiting hepatic gluconeogenesis [17, 23]. These findings underscore the potential of phloroglucinol as a therapeutic agent in managing diabetes and reducing its associated oxidative stress and complications

Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 9, No. 2: 1482-1492, 2025
DOI: 10.55214/25768484.v9i2.4795

5. Conclusion

Phloroglucinol, a ligand with robust hydrogen bonding capabilities, has demonstrated a strong affinity for essential antioxidant proteins, including Nrf2, SOD, GPx, and catalase. These interactions emphasize its critical role in mitigating oxidative stress, suggesting its effectiveness in protecting the pancreatic islets of Langerhans from damage. Furthermore, phloroglucinol significantly lowered blood glucose levels in streptozotocin (STZ)-induced diabetic rats. These findings underscore its potential as a promising therapeutic agent for diabetes management and the reduction of associated diabetic complications.

Transparency:

The authors confirm that the manuscript is an honest, accurate, and transparent account of the study; that no vital features of the study have been omitted; and that any discrepancies from the study as planned have been explained. This study followed all ethical practices during writing.

References

[1] S. Shimsa, N. P. P. Soumya, S. Mondal, and S. Mini, "Syringic acid affords antioxidant protection in the pancreas of type 2 diabetic rats," *Bioactive Compounds in Health and Disease-Online ISSN: 2574-0334; Print ISSN: 2769-2426*, vol. 6, no. 2, pp. 13-25, 2023. https://doi.org/10.31989/bchd.v6i2.1061

[2] S. Putta and K. Silakabattini, "Protective Effect of Tylophora indica against streptozotocin induced pancreatic and liver dysfunction in Wistar rats," *Biomedical and Pharmacology Journal*, vol. 13, no. 4, pp. 1755-1763, 2020.

[3] R. Al-Hussan, N. A. Albadr, G. M. Alshammari, S. A. Almasri, and M. A. Yahya, "Phloretamide prevent hepatic and pancreatic damage in diabetic male rats by modulating Nrf2 and NF-κB," *Nutrients*, vol. 15, no. 6, p. 1456, 2023.

[4] G. Wardani, J. Nugraha, R. Kurnijasanti, M. R. Mustafa, and S. A. Sudjarwo, "Molecular mechanism of fucoidan nanoparticles as protector on endothelial cell dysfunction in diabetic rats' aortas," *Nutrients*, vol. 15, no. 3, p. 568, 2023. https://doi.org/10.3390/nu15030568

[5] R. Kurnijasanti, G. Wardani, M. R. Mustafa, and S. A. Sudjarwo, "Protective mechanism pathway of Swietenia macrophylla extract nanoparticles against cardiac cell damage in diabetic rats," *Pharmaceuticals*, vol. 16, no. 7, p. 973, 2023. https://doi.org/10.3390/ph16070973

[6] C. A. Pieme *et al.*, "Relationship between hyperglycemia, antioxidant capacity and some enzymatic and non-enzymatic antioxidants in African patients with type 2 diabetes," *BMC Research Notes*, vol. 10, no. 1, pp. 1-7, 2017. https://doi.org/10.1186/s13104-017-2463-6

[7] O. Ertik, B. B. Bayrak, G. Sener, and R. Yanardag, "Melatonin improves liver and pancreatic tissue injuries in diabetic rats: Role on antioxidant enzymes," *Journal of Diabetes & Metabolic Disorders*, vol. 22, no. 1, pp. 591-602, 2023. https://doi.org/10.1007/s40200-022-01179-w

[8] I. N. Tyurenkov *et al.*, "Pancreatic β-cell protective effect of novel GABA derivatives in rats with type 2 diabetes," *Research Results in Pharmacology*, vol. 9, no. 3, pp. 59-70, 2023.

[9] A. Začiragić *et al.*, "The protective effects of vitamin D3 on histopathology of pancreas and liver in streptozotocin-induced diabetic rats," *Journal of Research in Pharmacy*, vol. 26, no. 2, pp. 325-333, 2022. https://doi.org/10.29228/jrp.130

[10] R. Kurnijasanti, G. Wardani, M. R. Mustafa, and S. A. Sudjarwo, "Protecting mechanism of Swietenia macrophylla ethanol extract nanoparticle on streptozotocin induced renal damage in rat," *Open Veterinary Journal*, vol. 13, no. 12, pp. 1623-1630, 2023. https://doi.org/10.5455/ovj.2023.v13.i12.12

[11] L. Zhang *et al.*, "New perspectives on the therapeutic potential of quercetin in non-communicable diseases: Targeting Nrf2 to counteract oxidative stress and inflammation," *Journal of Pharmaceutical Analysis*, vol. 14, no. 6, p. 100930, 2024. https://doi.org/10.1016/j.jpha.2023.12.020

[12] T. T. Fasooto *et al.*, "In-silico and in-vivo comparative evaluation of the cardioprotective potential of Yellow turmeric and White turmeric in Mn-induced cardiac oxidative stress," *Pharmacological Research-Modern Chinese Medicine*, vol. 10, p. 100399, 2024. https://doi.org/10.1016/j.prmcm.2024.100399

[13] C. Lauritano, E. Montuori, G. DeFalco, and S. Carrella, "In silico methodologies to improve antioxidants' characterization from marine organisms," *Antioxidants*, vol. 12, p. 710, 2023.

[14] N. Eguchi, N. D. Vaziri, D. C. Dafoe, and H. Ichii, "The role of oxidative stress in pancreatic β cell dysfunction in diabetes," *International Journal of Molecular Sciences*, vol. 22, no. 4, p. 1509, 2021. https://doi.org/10.3390/ijms22041509

[15] M. Ghasemi-Dehnoo, H. Amini-Khoei, Z. Lorigooini, and M. Rafieian-Kopaei, "Oxidative stress and antioxidants in diabetes mellitus," *Asian Pacific Journal of Tropical Medicine*, vol. 13, no. 10, pp. 431-438, 2020. https://doi.org/10.4103/1995-7645.291036

[16] K. Drygalski, E. Fereniec, A. Zalewska, A. Krętowski, M. Żendzian-Piotrowska, and M. Maciejczyk, "Phloroglucinol prevents albumin glycation as well as diminishes ROS production, glycooxidative damage, nitrosative stress and inflammation in hepatocytes treated with high glucose," *Biomedicine & Pharmacotherapy*, vol. 142, p. 111958, 2021. https://doi.org/10.1016/j.biopha.2021.111958

[17] K. Drygalski *et al.*, "Phloroglucinol strengthens the antioxidant barrier and reduces oxidative/nitrosative stress in nonalcoholic fatty liver disease (NAFLD)," *Oxidative Medicine and Cellular Longevity*, vol. 2021, no. 1, p. 8872702, 2021. https://doi.org/10.1155/2021/8872702

[18] G. Peron *et al.*, "Antiviral and antibacterial properties of phloroglucinols: a review on naturally occurring and (semi) synthetic derivatives with potential therapeutic interest," *Critical Reviews in Biotechnology*, vol. 44, no. 2, pp. 319-336, 2024. https://doi.org/10.1080/07388551.2022.2160695

[19] H. Bridi, G. de Carvalho Meirelles, and G. L. von Poser, "Structural diversity and biological activities of phloroglucinol derivatives from Hypericum species," *Phytochemistry*, vol. 155, pp. 203-232, 2018. https://doi.org/10.1016/j.phytochem.2018.08.002

[20] R.-K. Kim, N. Uddin, J.-W. Hyun, C. Kim, Y. Suh, and S.-J. Lee, "Novel anticancer activity of phloroglucinol against breast cancer stem-like cells," *Toxicology and Applied Pharmacology*, vol. 286, no. 3, pp. 143-150, 2015. https://doi.org/10.1016/j.taap.2015.03.026

[21] P. González, P. Lozano, G. Ros, and F. Solano, "Hyperglycemia and oxidative stress: An integral, updated and critical overview of their metabolic interconnections," *International Journal of Molecular Sciences*, vol. 24, no. 11, p. 9352, 2023. https://doi.org/10.3390/ijms24119352

[22] L. Dilworth, A. Facey, and F. Omoruyi, "Diabetes mellitus and its metabolic complications: The role of adipose tissues," *International Journal of Molecular Sciences*, vol. 22, no. 14, p. 7644, 2021. https://doi.org/10.3390/ijms22147644

[23] J.-Y. Yoon, H. Choi, and H.-S. Jun, "The effect of phloroglucinol, a component of Ecklonia cava extract, on hepatic glucose production," *Marine Drugs*, vol. 15, no. 4, p. 106, 2017. https://doi.org/10.3390/md15040106

Edelweiss Applied Science and Technology
ISSN: 2576-8484
Vol. 9, No. 2: 1482-1492, 2025
DOI: 10.55214/25768484.v9i2.4795