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Multi-Target Antidiabetic Potentials of *Xylocarpus mekongensis*: In Vivo Efficacy, Enzyme Inhibition, and Molecular Docking

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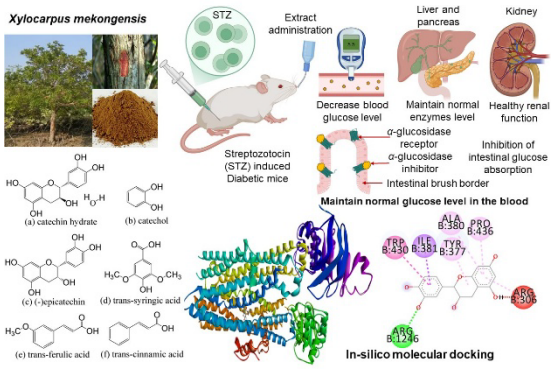
Abstract: ***Xylocarpus mekongensis*** Pierre (Meliaceae), locally known as "Poshur" is a mangrove plant traditionally used in South and Southeast Asia for the management of diabetes and related disorders. This study comprehensively evaluated the phytochemical composition, safety, antidiabetic efficacy, enzymatic inhibition, and in-silico molecular docking analysis of its ethanolic bark extract. HPLC-DAD profiling identified six major phenolic compounds — catechin hydrate, catechol, (–) epicatechin, syringic acid, *trans*-ferulic acid, and *trans*-cinnamic acid. Acute and subacute toxicity assessments in Swiss albino mice (following OECD guidelines) confirmed its safety up to 3000 mg/kg without any physiological or behavioral alterations. In the oral glucose tolerance test (OGTT), the extract significantly reduced blood glucose levels in a dose-dependent manner. In streptozotocin (STZ)-induced diabetic mice, daily oral administration of the extract (250 and 500 mg/kg) markedly reduced fasting blood glucose, restored body weight, and normalized hepatic, renal, and lipid biomarkers comparable to glibenclamide. Moreover. the extract also demonstrated potent α-glucosidase inhibitory activity (IC_{50} = 0.420 mg/mL), indicating delayed intestinal glucose absorption. Molecular docking revealed strong binding affinities of these compounds—particularly catechin hydrate and (–) epicatechin demonstrated strong binding affinities with key diabetic targets, including sulfonylurea receptor 1 (SUR1), peroxisome proliferator-activated receptor gamma (PPAR-γ), dipeptidyl peptidase-4 (DPP4), glucokinase, and AMP-activated protein kinase (AMPK), suggesting multi-targeted modulation of insulin secretion, sensitivity, and glucose utilization. These findings provide the first comprehensive mechanistic validation of the traditional use of *X. mekongensis* and highlight its polyphenolic constituents as promising natural leads for developing multi-target antidiabetic therapeutics.



Keywords: *Xylocarpus mekongensis*, phenolic compounds, diabetes, in-silico molecular docking

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1 Introduction

Diabetes mellitus is a metabolic disorder characterized by persistent hyperglycemia resulting from impaired insulin secretion from pancreatic ß-cells, insulin resistance, or both[1, 2]. It profoundly affects carbohydrate, lipid, and protein metabolism and remains one of the major causes of morbidity and mortality worldwide. According to global health estimates, 422 million people are struggling with diabetes, and most of them belong to developing states. WHO data states that the rate of mortality for diabetes each year is nearly 1.5 million cases as of 2019, with this number projected to rise dramatically in the coming decades[3, 4]. Chronic hyperglycemia contributes to a cascade of metabolic dysfunctions, leading to complications such as nephropathy, neuropathy, cardiovascular disorders, and hepatic impairment, ultimately resulting in multi-organ damage and metabolic imbalance[5-7]. Although currently available oral hypoglycemic drugs, including sulfonylureas, biguanides, and enzyme inhibitors, are clinically effective, their long-term use is often limited by adverse effects, high cost, and reduced efficacy over time[8-10]. Consequently, there is growing interest in identifying safer, plant-derived alternatives for diabetes management[11, 12]. Medicinal plants have historically served as vital sources of antidiabetic agents like metformin, was derived from the plant Galega officinalis[13]. The World Health Organization (WHO) emphasizes the scientific validation of traditional medicinal plants as potential sources of novel hypoglycemic agents due to their affordability, biocompatibility, and minimal side-effect profiles[14]. Numerous phytoconstituents such as glycosides, flavonoids, alkaloids, terpenoids, and carotenoids have been reported to exert significant antidiabetic activity through diverse molecular pathways[15-17].

Xylocarpus mekongensis Pierre (family Meliaceae), locally known as "Poshur" is a mangrove species widely distributed in the coastal and estuarine ecosystems of Southeast Asia, including the Sundarbans of Bangladesh[18]. Traditionally, various parts of this plant have been used as an astringent tonic and for the treatment of ailments such as fever, dysentery, inflammation, urinary disorders, abdominal complications, and, notably, diabetes[19, 20]. The plants contain secondary metabolites, including terpenoids, alkaloids, flavonoids, and limonoids, which are known to possess antioxidant and antihyperglycemic properties[21, 22]. However, despite its extensive traditional use, there is a paucity of systematic pharmacological and mechanistic studies validating its antidiabetic potential.

Given the ethnopharmacological relevance and secondary metabolites richness in *X. mekongensis*, the present study was designed to identify the phytoconstituents and comprehensively elucidate its antidiabetic potential using integrated in vivo and in-silico approaches. Phytochemical profiling and HPLC–DAD were conducted to identify and quantify major bioactive polyphenolic compounds in *X. mekongensis* bark extract. The study evaluated the safety and effects on glucose tolerance using oral glucose tolerance test (OGTT) and streptozotocin (STZ)-induced diabetic mice model first time. Streptozotocin selectively destroys pancreatic ß-cells, leading to insulin deficiency, persistent hyperglycemia, and oxidative stress—thereby mimicking the pathophysiological conditions of diabetes mellitus. Restoration of glycemic balance and normalization of metabolic biomarkers such as hepatic transaminases [serum glutamic pyruvic transaminase (SGPT or ALT) and serum glutamic oxaloacetic transaminase (SGOT or AST)], alkaline phosphatase (ALP), renal indices (creatinine and urea), and serum lipid parameters are critical indicators of recovery from diabetic complications. Furthermore, its α-glucosidase inhibitory activity was assessed to elucidate its role in postprandial glucose regulation. To delineate molecular mechanisms, computational docking studies were performed against key diabetes-related protein targets, including sulfonylurea receptor 1 (SUR1) - which regulates insulin secretion via K^+-ATP channel closure[23]; peroxisome proliferator-activated receptor-γ (PPAR-γ) - a nuclear receptor enhancing insulin sensitivity[24]; (dipeptidyl peptidase-4 (DPP-4) - which degrades incretin hormones[25]; (glucokinase - a glucose sensor promoting glycogen synthesis[26]; and AMP-activated protein kinase (AMPK) - a central metabolic regulator enhancing glucose uptake and fatty acid oxidation[27]. This integrated framework bridges traditional medicinal knowledge with modern pharmacological and computational validation, aiming to elucidate the mechanistic basis of the antidiabetic activity of *X. mekongensis* and to identify its bioactive phenolic constituents as potential multi-target agents for the management of diabetes mellitus.

2 Experimental Procedures

2.1 Botanical specimen collection and extract preparation

Xylocarpus mekongensis bark was collected from the Southeast region of Bangladesh. The plant material was taxonomically identified by experts at the Bangladesh National Herbarium, Mirpur, Dhaka-1216, where a voucher specimen (**DACB 43584**) was deposited for future reference. The bark was thoroughly cleaned, shade-dried, and pulverized into coarse powder. The powdered bark was extracted with ethanol using a maceration technique at room temperature (sample-to-solvent ratio 1:5, w/v) in a sealed jar. The crude extract was filtered, and the solvent was removed under reduced pressure at 40 °C using a rotary evaporator (Büchi Rotavapor, Switzerland). The dried extract was stored at 3 °C in airtight vials until further phytochemical and pharmacological investigations.

2.2 Experimental animals

Swiss albino young male mice (5–6 weeks old, body weight 22–28 g) were used in the experiments. Animals were housed under controlled environmental conditions(temperature 24–27 °C, relative humidity 55 ± 5 %, and a 12 h light/dark cycle) and had ad libitum access to a standard pellet diet (providing balanced carbohydrates, proteins, fats, and dietary fiber to support normal growth and health) and water. Prior to the experiments, the mice- were acclimatized for one week before experimentation in the Pharmacology Laboratory, Discipline of Pharmacy, Khulna University, Bangladesh. All experimental protocols were approved by the Animal Ethics Committee of Khulna University (**Approval No.: KUAEC-2018/06/11**) and conducted in accordance with institutional and national guidelines for the care and use of laboratory animals.

2.3 Chemicals and reagents

All experiments were performed using analytical-grade chemicals and reagents. Streptozotocin (STZ) was purchased from Sigma-Aldrich (St. Louis, MO, USA). The standard antidiabetic drug glibenclamide was obtained from Square Pharmaceuticals Ltd. (Dhaka, Bangladesh). Commercial diagnostic kits for biochemical parameters, including lipid profile, serum glutamate pyruvate transaminase (SGPT), serum glutamate oxaloacetate transaminase (SGOT), bilirubin, creatinine, and urea, were procured from Human Gesellschaft für Biochemica und Diagnostica mbH (Max-Planck-Ring 21, 65205 Wiesbaden, Germany). All solvents, including ethanol and chloroform, were of analytical or HPLC grade and were purchased from Loba Chemie (Mumbai, India) and Sigma-Aldrich (St. Louis, MO, USA).

2.4 Phytochemical profiling

Preliminary phytochemical analysis *X. mekongensis* bark extract was performed following standard qualitative protocols[28]. The presence of major secondary metabolites, including alkaloids, flavonoids, phenolics, saponins, tannins, and terpenoids, was investigated. Comprehensive test procedures for phytochemical groups identification are described in the Supplementary Information (SI).

2.5 Quantification of polyphenolic compounds

High-Performance Liquid Chromatography with Diode Array Detection (HPLC-DAD) was employed to identify and quantify the compounds present in the *X. mekongensis*. The measurement was conducted on a Shimadzu LC-20A system (Shimadzu, Japan) equipped with dual solvent pumps, an autosampler, a column oven, and a photodiode array detector controlled by LabSolution software following the established method with minor modifications[29]. Separation was achieved on a Luna C18 column (250 × 4.6 mm, 5 µm; Phenomenex, USA) maintained at 33 °C. The mobile phase consisted of solvent A (1 % acetic acid in acetonitrile) and solvent B (1 % acetic acid in water) under a programmed gradient elution. Detection was carried out at 270 nm, and compounds were identified and quantified by comparing their retention times and UV spectra with those of authentic standards.

2.6 Acute toxicity test

The acute oral toxicity of the *X. mekongensis* was evaluated following the OECD guideline 425 with minor modifications[30]. Healthy Swiss albino mice were randomly divided into six groups (n = 6 per group). The control (group-I) received distilled water, whereas the test groups (XM-250, XM-500, XM-1000, XM-2000, and XM-3000 to Group-VI) were administered the extract at graded doses of 250, 500, 1000, 2000, and 3000 mg/kg body weight, via oral gavage. Before dosing, all animals were individually weighed to ensure accurate dose calculations. Following administration by oral gavage, the animals were carefully monitored during the initial 30 minutes, observed periodically over the subsequent 24 hours, and thereafter assessed daily for 28 consecutive days to detect any behavioral changes, physical abnormalities, or signs of mortality.

2.7 Sub-acute toxicity test

The sub-acute toxicity assessment of the *X. mekongensis* was conducted following the procedure described by Dev et al. with minor modifications[31]. Twelve Swiss albino mice were randomly divided into two groups: Group-I (control) and a test group (XM-500) (n = 6 per group). The control group received 2 % Tween-80 as the vehicle, while the test group was administered the extract orally at a dose of 500 mg/kg body weight once daily for 28 consecutive days. Throughout the experimental period, all animals were closely observed for signs of behavioral abnormalities, physiological changes, and mortality. At the end of the treatment period, measured their body weight, and then animals were anesthetized to death using chloroform, and blood samples were collected in heparinized tubes from the cervical vein with a slight modification of the method. The collected blood was centrifuged at 3000 rpm for 10 minutes to obtain serum. The serum

samples were analyzed for biochemical parameters to evaluate hepatic functions (SGPT, SGOT, and ALP and bilirubin) and renal (Creatinine, Urea).

2.8 Oral glucose tolerance test (OGTT)

The oral glucose tolerance test (OGTT) was conducted following the method described by Joy et al. with slight modifications[32]. Twenty-four healthy mice were randomly divided into four groups (n = 6 per group). Group I served as the control and received % cellulose Group II (GLI) received the standard drug glibenclamide (10 mg/kg, b. wt.); Groups III and IV were administered *X. mekongensis* at doses of 250 mg/kg and 500 mg/kg body weight, respectively and denoted as (XM-250 and XM-500). After 30 minutes of treatment, mice were given an oral glucose load (2 g/kg body weight). Blood glucose levels were determined at 0, 30, 60, and 120 minutes post-glucose administration by collecting venous blood samples from the tail vein using sterile needle pricks. Glucose concentrations were measured using a commercial glucometer (Accu-Chek, USA).

2.9 Treatment protocol in STZ-induced diabetic mice

Experimental diabetes was induced by a single intraperitoneal injection of streptozotocin (STZ, 120 mg/kg in 0.9 % NaCl). After 72 h, mice with blood glucose levels >10 mM were considered diabetic mice[33]. Group I (control), the mice received 2 % cellulose (CMC) in water. Diabetic mice were allocated into four groups (n = 6 per group) as follows: Group II (STZ); Group III (STZ+GLI), diabetic mice treated with glibenclamide (10 mg/kg, orally) for 28 days; Group IV and Group V (STZ+XM-250 and STZ+XM-500) diabetic mice treated with *X. mekongensis* at the dose of 250 and 500 mg/kg respectively, orally for 28 days. *X. mekongensis* was suspended in 2 % CMC in pure water and each mouse received 0.5 mL freshly prepared suspension. Treatments continued for 28 days. Body weight and fasting blood glucose were recorded weekly (days 7, 14, and 28) by collecting the blood from the mice's tails with sterile needle pricks. At the end of 28 days, the mice were anesthetized using chloroform, and blood samples were collected from the cervical vein in heparinized tubes for biochemical analysis[34].

2.10 Estimation of blood serum biochemical enzymes

Blood samples (1 mL) were centrifuged at ~1,500 × g for 15 minutes at 2–4 °C. After centrifugation, the supernatant serum was carefully separated from the cellular components and stored at −20 °C until further analysis. The collected serum was subsequently used for biochemical assays to evaluate hepatic and renal functions. The hepatic biomarkers included serum glutamic pyruvic transaminase (SGPT), serum glutamic oxaloacetic transaminase (SGOT), alkaline phosphatase (ALP), and total bilirubin. The renal function was assessed by measuring serum creatinine and urea levels. Additionally, lipid profile parameters, including total cholesterol (TC), triglycerides (TG), and high-density lipoprotein (HDL), were determined following established methods (60). All biochemical estimations were performed using standard enzymatic colorimetric methods with commercial diagnostic kits (LiquiUV, HUMAN GmbH, Germany).

2.11 α- glucosidase enzyme inhibition activity

The α-glucosidase inhibitory activity of the *X. mekongensis* was determined following the method of Rauscher et al. with slight modifications[35]. The assay was based on the enzymatic hydrolysis of *p*-nitrophenyl-α-D-glucopyranoside (pNPG) by α-glucosidase, releasing *p*-nitrophenol, a yellow chromophore quantified spectrophotometrically at 405 nm. Various concentrations of *X. mekongensis* extract and acarbose were prepared. Subsequently, a mixture of potassium phosphate buffer, α-gluco-sidase enzyme, and *p*-nitrophenyl glucopyranoside was combined with the extract and standard. The reaction was stopped by the addition of a sodium carbonate solution. Absorbance was measured using a Thermo Scientific Multiskan Go microplate reader. Control wells received 10 µL of DMSO in place of the extract, while acarbose was used as the reference standard inhibitor. All assays were performed in triplicate. The percentage inhibition was calculated, and the inhibitory concentration required to reduce enzyme activity by 50 % (IC_{50}) was derived from the dose–response curve plotted between percentage inhibition and extract concentration.

2.12 In-silico molecular docking studies

2.12.1 Ligand preparation

The plant phytochemicals identified through HPLC, along with the reference drug glibenclamide, were retrieved from the PubChem database[36]. The ligands were energy-minimized and geometry-optimized using Avogadro v1.2.0 with the Universal Force Field (UFF). The optimized structures were saved in Protein Data Bank (.pdb) format for docking studies.

2.12.2 Protein preparation

The three-dimensional crystal structures of the sulfonylurea receptor 1 (SUR1; PDB ID: 5YW7), peroxisome

proliferator-activated receptor gamma (PPAR-γ; PDB ID: 2XKW), dipeptidyl peptidase-4 (DPP4; PDB ID: 6BIE), glucokinase (PDB ID: 1V4S) and AMP-activated protein kinase (AMPK; PDB ID: 4CFE) were obtained from the Protein Data Bank[37-39]. The receptors were processed to remove impure molecules and non-essential ligands using PyMOL v2.0 (Schrödinger, LLC) and further energy-minimized using Swiss-PdbViewer v4.1.

2.12.3 Molecular docking and visualization

Docking simulations were carried out using AutoDock Vina implemented in PyRx 0.8[40]. Both ligands (identified compounds and glibenclamide) and protein receptors were imported into PyRx and defined appropriately as "ligand" or "macromolecule." Grid boxes were generated to cover the active site residues: The best docking poses were selected based on binding affinity (lowest binding energy scores). The docked ligand–receptor complexes were further visualized and analyzed in Discovery Studio Visualizer v4.5 (BIOVIA, Dassault Systemes) to identify hydrogen bonding, hydrophobic, and electrostatic (amino acid) interactions

2.13 Statistical analysis

Data are presented as mean ± standard error of mean (SEM). Statistical analyses were conducted using one-way analysis of variance (ANOVA), followed by Tukey's post hoc test to determine statistically significant differences among the experimental groups (SPSS software, IBM Corporation, New York, USA; version 16.0). A statistically significant level of probability was defined as $^{\#}p < 0.05$, $*p < 0.01$, $**p < 0.001$, $***p < 0.0001$, and ns is equal to nonsignificant. The figures were drawn using OriginLab.

3 Results

3.1 Phytochemical profiling and quantification of polyphenolic compounds

Phytochemical screening of the *X. mekongensis* bark extract revealed the presence of reducing sugar, tannins, flavonoids, alkaloids, glycosides, steroids, terpenoids, gums and acidic compounds, while Xanthoproteins were absent (**Table S1**). These secondary metabolites are widely recognized for their pharmacological activities[41,42]. In particular, phenolic compounds have been extensively reported to exert antioxidant and antidiabetic effects by modulating endocrine responses[43]. In HPLC-DAD analysis, the chromatogram profile revealed six distinct peaks corresponding to catechin hydrate, catechol, (–) epicatechin, syringic acid, *trans*-ferulic acid, and *trans*-cinnamic acid (**Fig. S1**), identified by comparison of their retention times and UV spectra with authentic reference standards (**Fig. S2**). Among these, catechin hydrate and (–) epicatechin were found in higher abundance (**Table S2**). The chemical structures of these identified compounds are presented in **Fig. 1**. These compounds are known to possess free radical–scavenging[44], enzyme-inhibitory[45], and insulin-sensitizing activities[46], which collectively may contribute to the extract's observed pharmacological activity.

3.2 Safety study (acute and sub-acute toxicity) of the extract

Acute toxicity evaluation following OECD guidelines demonstrated no mortality, behavioral changes, or signs of toxicity up to a dose of 3000 mg/kg body weight. All treated animals appeared healthy, with normal grooming behavior (**Table S4**), and body weight progression comparable to the control group (**Fig. S3**). Similarly, subacute toxicity testing (28 days, 500 mg/kg) showed no significant alterations in behavioral change or body weight (**Fig. S4**). Hepatic enzymes (SGPT, SGOT, ALP, bilirubin) (**Figs. 2a-2d**) and renal function markers (creatinine, urea) (**Figs. 2e**, **2f**) remained within normal physiological limits. These findings establish the safety margin of *X. mekongensis* extract and support its suitability for prolonged pharmacological use.

3.3 Oral glucose tolerance test (OGTT)

The hypoglycemic effect of the *X. mekongensis* was initially assessed using the oral glucose tolerance test in mice. Administration of the extract produced a marked and dose-dependent improvement in glucose tolerance compared to the control group (**Fig. 3a**). In glucose-loaded mice, blood glucose peaked at 30 min in the control group (12.04 ± 1.03 mmol/L), while significantly lower values were recorded in the XM-250 (10.7 ± 0.38 mmol/L), XM-500 (10.5 ± 1.01 mmol/L), and glibenclamide-treated groups (9.5 ± 0.27 mmol/L). At 90 min post-glucose load, blood glucose levels declined sharply in the treated groups relative to the control, indicating enhanced glucose clearance. By 120 min, the XM-500 group showed glucose levels (6.3 ± 0.39 mmol/L) closely matching those of the glibenclamide-treated group (5.6 ± 0.50 mmol/L). These findings demonstrate that *X. mekongensis* facilitates more efficient glucose utilization and maintains glycemic stability, suggesting improved peripheral glucose uptake or enhanced insulin sensitivity. Given that glucose tolerance is a primary indicator of ß-cell responsiveness and peripheral insulin action[47], the observed improvement implies that *X. mekongensis* extract enhances both insulin-mediated and non–insulin-dependent glucose disposal mechanisms.

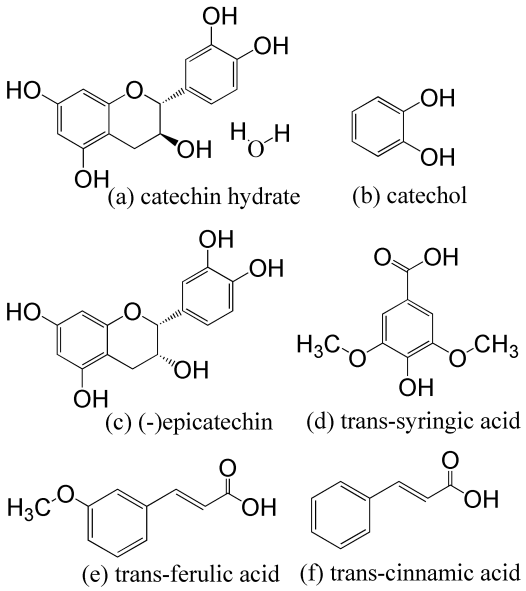

Fig. 1 Chemical structures of major bioactive polyphenolic compounds identified in the ethanolic bark extract of *Xylocarpus mekongensis* through HPLC analysis, along with the quantification of their respective contents. (a) Catechin hydrate, (b) Catechol, (c) (–) Epicatechin, (d) Syringic acid, (e) *trans*-Ferulic acid, and (f) *trans*-Cinnamic acid.

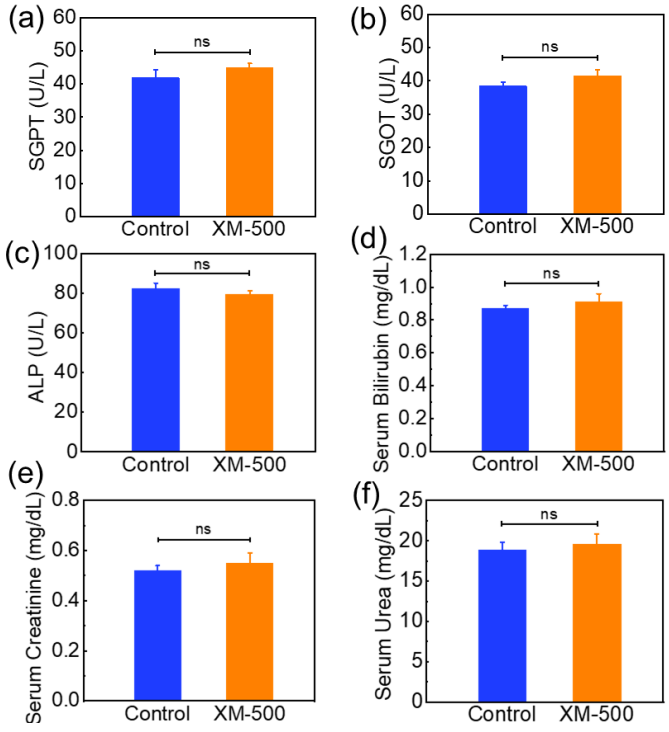

Fig. 2 Evaluation of the safety profile of *Xylocarpus mekongensis* bark extract. Effects of the extract on liver function markers: (a) serum glutamate pyruvate transaminase (SGPT), (b) serum glutamate oxaloacetate transaminase (SGOT), (c) alkaline phosphatase (ALP), and (d) serum bilirubin; and kidney function markers: (e) serum creatinine and (f) serum urea. Data are expressed as mean ± standard error of the mean (SEM), n = 6. XM: *Xylocarpus mekongensis*; ns: not significant; SGPT: serum glutamate pyruvate transaminase; SGOT: serum glutamate oxaloacetate transaminase; ALP: alkaline phosphatase.

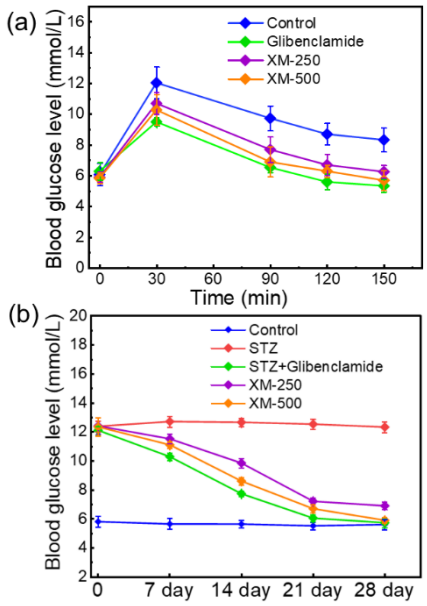

Fig. 3 Evaluation of the anti-diabetic efficacy of *Xylocarpus mekongensis* bark extract. a) Blood glucose levels at different time points following oral glucose administration during the oral glucose tolerance test (OGTT). (b) Changes in fasting blood glucose levels measured on 0, 7, 14, 21, and 28 days in streptozotocin (STZ)-induced diabetic mice. Data are expressed as mean ± standard error of the mean (SEM), n = 6. XM*: Xylocarpus mekongensis*; STZ: streptozotocin; glibenclamide was used as the standard drug.

3.4 Antidiabetic activity in streptozotocin (STZ)-induced diabetic mice

Based on the promising OGTT results, *X. mekongensis* was further evaluated in a streptozotocin (STZ)-induced diabetic model, which mimics diabetes by selectively destroying pancreatic ß-cells, leading to insulin deficiency and sustained hyperglycemia[48, 49]. STZ-treated mice exhibited a significant decline in body weight compared to the normal control group (21.52 ± 0.47 g vs. 32.1 ± 0.65 g), reflecting catabolic changes associated with chronic hyperglycemia (**Fig. S5**). After 28 days of treatment, mice receiving *X. mekongensis* extract demonstrated significant restoration of body weight in a dose-dependent manner (STZ+XM-250: 31.3 ± 0.39 g; STZ+XM-500: 31.0 ± 0.80 g), comparable to glibenclamide (29.9 ± 0.90 g). This suggests attenuation of protein catabolism and improved metabolic efficiency. Serial monitoring of fasting blood glucose levels further substantiated the antihyperglycemic effect (**Fig. 3b**). The untreated diabetic group maintained persistently elevated glucose levels (12.31 ± 0.37 mmol/L) throughout the study, while extract-treated groups showed progressive glycemic normalization. By day 28, glucose concentrations in the XM-500 group (5.90 ± 0.19 mmol/L) were statistically indistinguishable from those in the glibenclamide-treated mice (5.73 ± 0.32 mmol/L) and near physiological levels observed in normal controls (5.84 ± 0.25 mmol/L). These results demonstrate that prolonged oral administration of *X. mekongensis* bark extract significantly improves glycemic control and body weight in diabetic mice. The observed effects were comparable to the standard antidiabetic drug, glibenclamide. The antihyperglycemic activity of *X. mekongensis* may be attributed, at least in part, to its ability to inhibit α-glucosidase, an intestinal enzyme responsible for carbohydrate hydrolysis[50]. This inhibition delays glucose absorption from the intestinal brush border, thereby reducing postprandial glucose spikes and contributing to overall glycemic control.

3.4.1 Effects on hepatic enzymes

Diabetes-induced hepatic dysfunction was evident from the elevated serum levels of SGPT, SGOT, ALP, and bilirubin in STZ-diabetic mice (**Figs. 4a-4d**). Administration of *X. mekongensis* extract significantly attenuated the elevated hepatic enzyme levels induced by diabetes, bringing hepatic enzyme levels closer to those observed in the control group. Both XM-250 and XM-500 doses showed notable hepatoprotective effects in comparison with the standard drug. . Notably, SGPT, SGOT, ALP, and bilirubin levels were reduced from 81.84 ± 4.23 U/L and 65.3 ± 4.32 U/L, 137.2 ± 7.07 U/L, and 1.7 ± 0.09 mg/dL in diabetic control to 45.1 ± 2.43 U/L and 41.3 ± 2.74 U/L, 39.2 ± 2.5 U/L, and 82.7 ± 5.99 U/L, respectively, in the STZ+XM-500 group. The normalization of liver enzyme levels suggests reduced hepatocellular injury and improved metabolic regulation, likely mediated by the antioxidant polyphenols within the extract. These compounds can

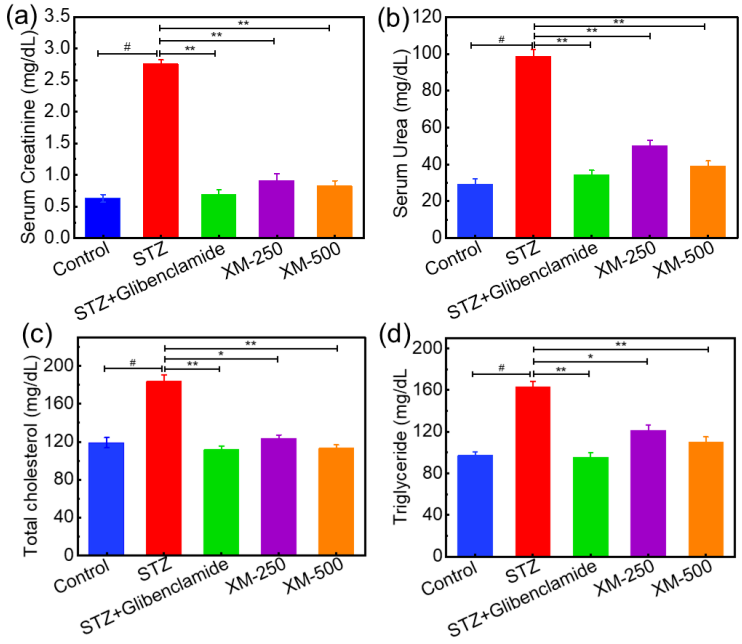

Fig. 4 Effect of *Xylocarpus mekongensis* bark extract on liver function parameters in streptozotocin (STZ)-induced diabetic mice. (a) Serum glutamate pyruvate transaminase (SGPT), (b) Serum glutamate oxaloacetate transaminase (SGOT), (c) alkaline phosphatase (ALP), and (d) serum bilirubin levels. Data are presented as mean ± standard error of the mean (SEM), $^{\#}p < 0.05$ versus control group; $^{*}p < 0.01$, and $^{**}p < 0.001$ versus STZ group (Post Hoc Tukey's test). XM: *Xylocarpus mekongensis*; STZ: streptozotocin; SGPT: serum glutamate pyruvate transaminase; SGOT: serum glutamate oxaloacetate transaminase; ALP: alkaline phosphatase.

scavenge reactive oxygen species generated during hyperglycemia, preserving cellular integrity and hepatic enzyme balance[51, 52].

3.4.2 Effect on renal and lipid profile enzymes

Hyperglycemia-induced oxidative stress and protein glycation often lead to renal and lipid metabolism impairment. In the diabetic control group, serum creatinine, urea, total cholesterol, and triglyceride levels were markedly elevated compared to the control (**Figs. 5a-5d**). *X. mekongensis* extract significantly improved renal function markers (urea, creatinine) and corrected lipid abnormalities associated with diabetes. Both treatment doses showed restorative effects comparable to the standard drug. Although slightly greater improvements were observed at the higher dose for certain parameters, the overall data do not provide convincing evidence of a clear dose-dependent effect. For instance, creatinine and urea levels decreased from 2.75 ± 0.07 mg/dL and 98.72 ± 2.98 mg/dL in diabetic mice to 0.82 ± 0.09 mg/dL and 39.2 ± 2.72 mg/dL in the XM-500 group, respectively. Similarly, total cholesterol and triglycerides were reduced to near-normal values (113 ± 3.74 mg/dL and 109.5 ± 5.52 mg/dL). These improvements indicate that *X. mekongensis* not only exerts hypoglycemic action but also mitigates diabetic dyslipidemia and nephrotoxicity, reflecting systemic metabolic protection. Such multifaceted benefits may be attributed to its antioxidant constituents and enzymatic activity[53], which together contribute to its overall antidiabetic potential.

3.5 α-Glucosidase enzyme inhibitory activity

To elucidate the possible mechanism underlying the antihyperglycemic effect of *X. mekongensis*, an in vitro α-glucosidase inhibition assay was conducted. The *X. mekongensis* bark extract inhibited α-glucosidase in a concentration-dependent manner with an IC_{50} value of 0.420 mg/mL, comparable to acarbose (IC_{50} = 0.342 mg/mL) (**Fig. 6a**). Inhibitors of α-glucosidase are known to delay the enzymatic hydrolysis of carbohydrates in the small intestine, thereby reducing postprandial glucose absorption and mitigating hyperglycemia in diabetic conditions[54, 55]. The assay utilized *p*-nitrophenyl-α-D-glucopyranoside (pNPG) as a substrate, which, upon enzymatic hydrolysis, releases *p*-nitrophenol detectable at 405 nm (**Fig. 6b**). A schematic representation (**Fig. 6c**) illustrates the inhibition mechanism: under physiological

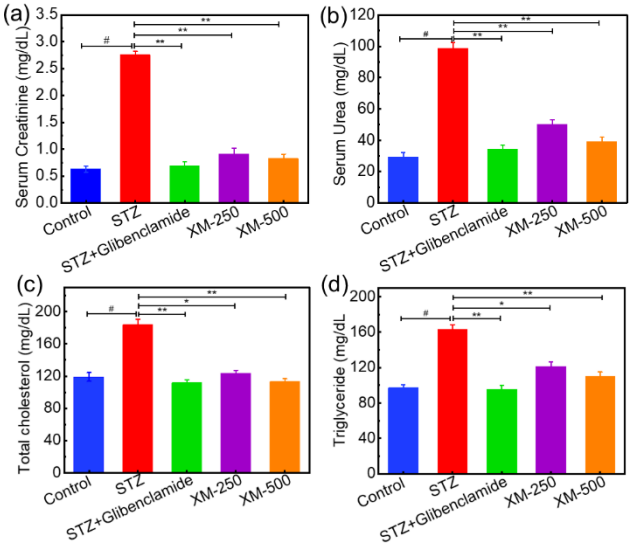

Fig. 5 Effect of *Xylocarpus mekongensis* bark extract on kidney function and lipid profile parameters in streptozotocin (STZ)-induced diabetic mice. (a) Serum creatinine, (b) serum urea, (c) total cholesterol, and (d) triglyceride levels. Data are expressed as mean ± standard error of the mean (SEM), $^{\#}p < 0.05$ versus control group; $^{*}p < 0.01$, and $^{**}p < 0.001$ versus STZ group (Post Hoc Tukey's test). XM: *Xylocarpus mekongensis*; STZ: streptozotocin.

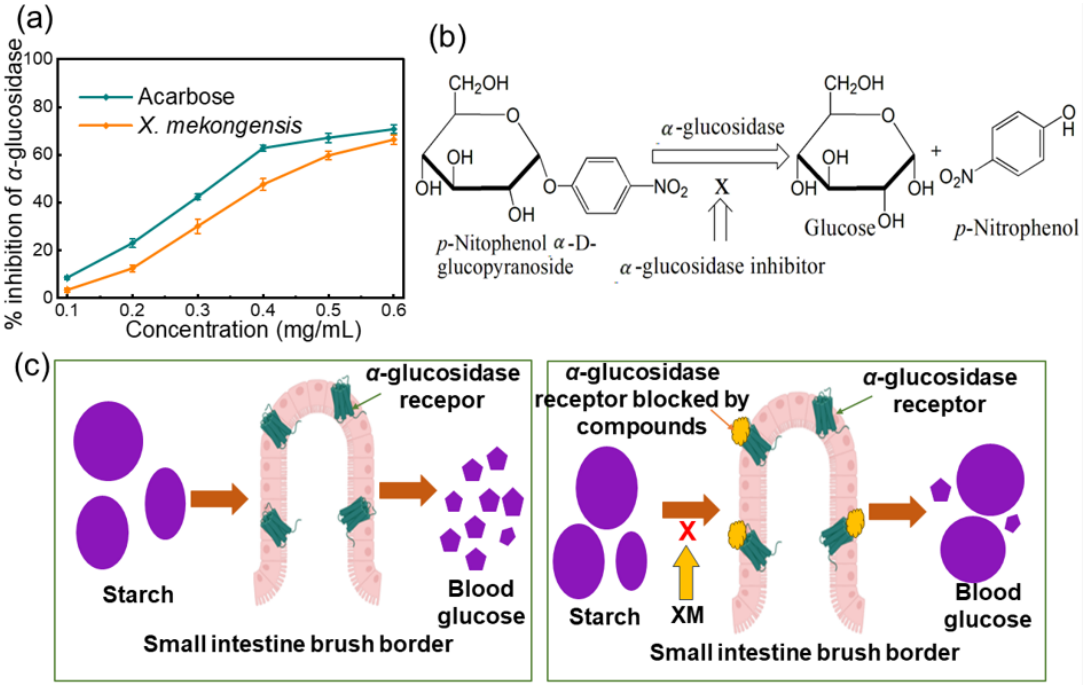

Fig. 6 α-Glucosidase inhibitory activity of *Xylocarpus mekongensis* bark extract. (a) Dose-dependent inhibition of α-glucosidase by XM compared with the standard acarbose, (b) Schematic representation of the α-glucosidase inhibition mechanism, where p-nitrophenyl-α-D-glucopyranoside (pNPG) is hydrolyzed by α-glucosidase to release p-nitrophenol and glucose. The inhibitor (XM) blocks this enzymatic hydrolysis, resulting in reduced glucose release. (c) Illustrative comparison showing normal glucose absorbed by α-glucosidase through small intestinal cell wall (left) and glucose absorption inhibition through small intestinal cell wall due to inhibition of α-glucosidase receptor by the presence of compounds from *X. mekongensis* (right), highlighting reduced glucose absorption.

conditions, α-glucosidase catalyzes carbohydrate breakdown into glucose, which is subsequently absorbed through the intestinal brush border.

3.6 In-silico molecular docking and mechanistic insights of polyphenolic compounds

The in-silico molecular docking analysis provided further mechanistic insights into the multi-targeted antidiabetic action of the phenolic constituents. Catechin hydrate and (–) epicatechin exhibited the strongest binding affinities across five key diabetic target proteins: sulfonylurea receptor 1 (SUR1; PDB ID: 5YW7), peroxisome proliferator-activated receptor-γ (PPAR-γ; PDB ID: 2XKW), dipeptidyl peptidase-4 (DPP-4; PDB ID: 6B1E), glucokinase (PDB ID: 1V4S), and AMP-activated protein kinase (AMPK; PDB ID: 4CFE). The reference drug glibenclamide was used for comparison. Among the identified compounds (ligands), catechin hydrate exhibited the strongest binding affinities across all targets (**Fig. 7**) with docking scores ranging from –6.9 to –8.9 kcal/mol, as well as (–) epicatechin also showed very good binding affinity (–6.3 to –9.2 kcal/mol) with selected protein molecules (**Fig. 8**) that are comparable to glibenclamide (**Fig. S6**). However, other phenolic compounds-catechol, syringic acid, *trans*-ferulic acid, and *trans*-cinnamic acid-also demonstrated moderate-to-good docking interactions. The docking scores and their interacting amino acids are summarized in **Table S5**.

4 Discussion

The present study provides integrated experimental and computational evidence supporting the antidiabetic potential of *X. mekongensis* by integrating phytochemical profiling, in vivo antidiabetic evaluation, enzyme inhibition assays, and molecular docking analyses. The significant improvement in fasting blood glucose levels and glucose tolerance observed in streptozotocin-induced diabetic mice indicates that *X. mekongensis* extract exerts a robust antihyperglycemic effect. α-Glucosidase plays a pivotal role in the terminal step of carbohydrate digestion by catalyzing the hydrolysis of oligosaccharides into absorbable glucose. Inhibition of this enzyme delays intestinal glucose absorption, thereby attenuating postprandial hyperglycemia. The α-glucosidase inhibitory activity of the extract, which was comparable to that of acarbose, provides mechanistic support for the improved glycemic control observed in vivo. The inhibitory potential can be attributed to the presence of polyphenolic compounds- particularly catechin hydrate, (–) epicatechin, catechol, syringic acid, *trans*-ferulic acid, and *trans*-cinnamic acid, identified via HPLC–DAD analysis. In addition, comprehensive GC–MS profiling revealed the presence of nineteen major phytoconstituents in *X. mekongensis* (**Table S3**). The predominant compounds included catechin hydrate [(2*R-trans*)-2-(3,4-dihydroxyphenyl)-3,4-dihydro-2H-1-benzopyran-3,5,7-triol monohydrate], (–) epicatechin [(2*R*,3*R*)-2-(3,4-dihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol], and syringic acid (4-hydroxy-3,5-dimethoxybenzoic acid). These compounds are well documented in the literature for their antioxidant and antidiabetic activities, supporting the pharmacological relevance of the extract. These compounds are known to interact with the catalytic site of α-glucosidase through hydrogen bonding and hydrophobic interactions[56, 57]. Polyphenols can occupy the enzyme's active pocket, thereby preventing substrate binding, and also may exert inhibitory effects by forming non-covalent complexes with the enzyme due to their multiple hydroxyl groups[58]. The extract's α-glucosidase inhibitory capacity aligns with its in vivo hypoglycemic effect, indicating that reduced postprandial glucose absorption is a key contributing mechanism. Furthermore, molecular docking studies have shown that these same polyphenols also exhibit strong binding affinities with major antidiabetic protein targets.

Molecular docking analysis further supports a multi-target mechanism underlying the antidiabetic activity of *X. mekongensis*. Catechin hydrate and (–) epicatechin showed strong binding affinities to SUR1 (–8.9 and –8.5 kcal/mol, respectively), interacting with critical residues ARG B1246, TRP B430, ILE B381, PRO B436, ALA A380, ASN B437, ARG B306, TYR B377 and ARG B306, ALA B380, TRP B430, ILE B381, PHE B433, PRO B436, TYR B377, SER B376, respectively. These sites are mostly similar to those occupied by glibenclamide (–8.9 kcal/mol). SUR1 protein molecule forms part of the ATP-sensitive potassium (K-ATP) channel complex on pancreatic ß-cells; its inhibition leads to membrane depolarization, Ca^{2+} influx, and subsequent insulin release[59,60]. Catechol (–5.3 kcal/mol), syringic acid (–5.6 kcal/mol), *trans*-ferulic acid (–6.3 kcal/mol), and *trans*-cinnamic acid (–6.3 kcal/mol) also demonstrated favorable interactions (**Figs. S7-S10**), suggesting they may stabilize or support SUR1 modulation, collectively contributing to enhanced insulin secretion. The results highlight the strong binding affinity and diverse interaction modes of these compounds within the active sites of the targeted proteins, which support their potential role in glucose metabolism regulation. PPAR-γ, a nuclear receptor crucial for insulin sensitivity and adipocyte differentiation[61], exhibited strong interactions with (–) epicatechin (–8.4 kcal/mol) and catechin hydrate (–8.0 kcal/mol). These compounds formed hydrogen bonds with residues GLY B284, ARG B288, SER B342, GLU B291, and PHE B264, implying potential agonistic modulation similar to thiazolidinedione-class drugs. Other phenolics, including *trans*-ferulic acid (–6.5 kcal/mol) and *trans*-cinnamic acid (–6.3 kcal/mol), showed moderate affinities, which may further enhance insulin responsiveness and glucose uptake in peripheral tissues. DPP-4

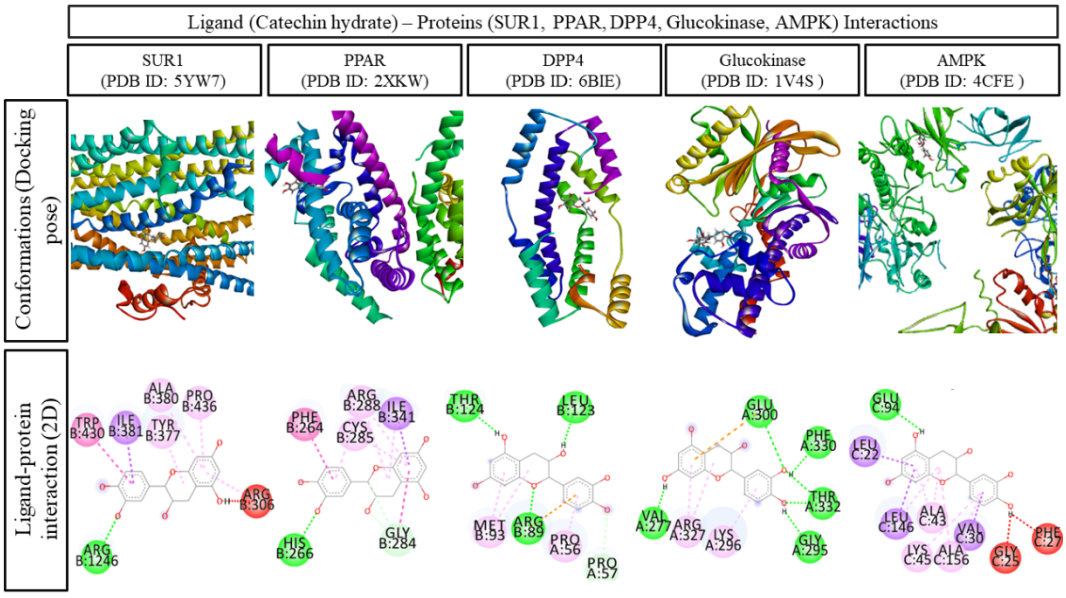

Fig. 7 In-silico molecular docking interactions of catechin hydrate (PubChem ID: 107957) with key receptor proteins involved in anti-diabetic activity. The figure illustrates the binding interactions of catechin hydrate with (a) SUR1 (PDB ID: 5YW7), (b) PPAR (PDB ID: 2XKW), (c) DPP4 (PDB ID: 6BIE), (d) Glucokinase (PDB ID: 1V4S), and (e) AMPK (PDB ID: 4CFE). The upper panel presents the three-dimensional (3D) ligand–protein docking complexes, while the lower panel shows the corresponding two-dimensional (2D) interaction maps. Color codes represent the interaction types: green: conventional hydrogen bond; light green: carbon-hydrogen bond; red: unfavorable acceptor/donor; pink: π-π T-shaped interaction; orange: π-cation interaction; and light pink: π-alkyl interaction.

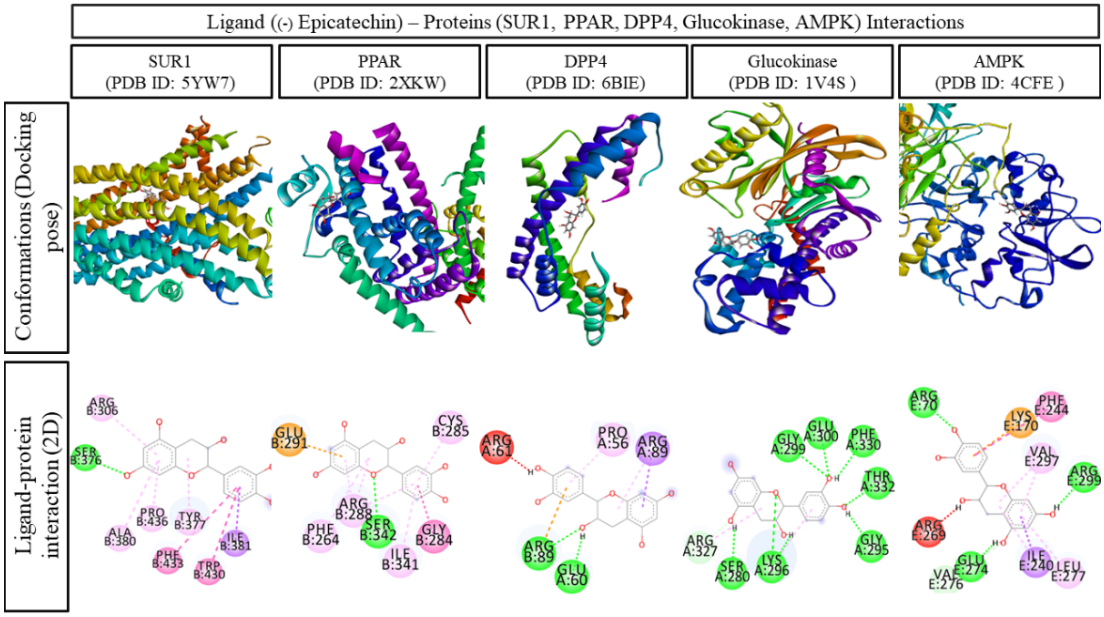

Fig. 8 In-silico molecular docking interactions of (−) epicatechin (PubChem ID: 72276) with receptor proteins implicated in anti-diabetic activity: SUR1 (PDB ID: 5YW7), PPAR (PDB ID: 2XKW), DPP4 (PDB ID: 6BIE), Glucokinase (PDB ID: 1V4S), and AMPK (PDB ID: 4CFE). The upper panel depicts the 3D conformations of the ligand–protein complexes, while the lower panel presents the corresponding 2D interaction profiles. Color codes indicate specific interaction types: green: conventional hydrogen bond; light green: carbon–hydrogen bond; red: unfavorable acceptor/donor interaction; pink: π–π T-shaped interaction; orange: π–π-cation interaction; and light pink: π–π-alkyl interaction.

inhibitors prolong the activity of incretin hormones, thereby improving postprandial insulin release[62]. Catechin hydrate (–6.4 kcal/mol) and (–) epicatechin (–6.8 kcal/mol) exhibited favorable docking at the DPP-4 active site, forming hydrogen bonds with ARG B89, THR B124, LEU B123, PRO A56, and MET B93. Catechol, syringic acid, and *trans*-ferulic acid (–5.0 to –5.2 kcal/mol) also demonstrated moderate DPP-4 inhibition potential, suggesting that the extract may exert natural incretin-enhancing activity via DPP-4 inhibition. Glucokinase acts as a glucose sensor, catalyzing the phosphorylation of glucose to glucose-6-phosphate in pancreatic ß-cells and hepatocytes61). Catechin hydrate (–6.9 kcal/mol) and (–) epicatechin (–7.0 kcal/mol) formed stable interactions with residues ARG A327, PHE A338, GLU A300, THR A332, SER A281, and VAL A277, supporting potential glucokinase activation. Other compounds, including *trans*-ferulic acid and *trans*-cinnamic acid (–6.2 to –6.7 kcal/mol), also exhibited notable affinity, suggesting a cooperative mechanism that enhances glucose utilization and glycogen synthesis. AMPK is a central metabolic regulator that enhances glucose uptake, fatty acid oxidation, and energy homeostasis[63,64]. (–) Epicatechin showed the strongest overall interaction with AMPK (–9.2 kcal/mol), closely followed by catechin hydrate (–8.8 kcal/mol), forming bonds with residues GLU C94, GLY C25, PHE C27, VAL C30, LYS C45, ALA C156, and LEU C146. These interactions suggest direct AMPK activation, which enhances insulin sensitivity and reduces hepatic glucose production[65]. *Trans*-ferulic and *trans*-cinnamic acids also exhibited moderate affinity (–6.5 and –6.6 kcal/mol), possibly supporting AMPK-dependent glucose regulation. Collectively, the molecular docking results reveal that the polyphenolic constituents of *X. mekongensis* can interact with multiple diabetic target proteins simultaneously. Catechin hydrate and (–) epicatechin emerged as the most promising bioactive molecules, showing binding energies comparable to glibenclamide and favorable hydrogen bonding within active sites. 3D ligand–protein interaction diagrams for catechin hydrate and (–) epicatechin, the most active compounds, are illustrated in (**Figs. S11** and **S12**). In addition, the contributions of catechol, syringic acid, *trans*-ferulic acid, and *trans*-cinnamic acid cannot be discounted, as they may synergistically reinforce the anti-diabetic effect through moderate binding and auxiliary modulation of these targets. This multi-targeted molecular interaction supports the in vivo findings that *X. mekongensis* extract reduces diabetes and improves metabolic enzymes through complementary molecular pathways.

5 Conclusion

The present study provides comprehensive experimental and computational evidence that *X. mekongensis* is a promising natural therapeutic agent for diabetes management. Phytochemical screening and HPLC–DAD profiling confirmed the presence of multiple bioactive phenolic compounds, notably catechin hydrate, and (–) epicatechin, and *trans*-cinnamic acid, improved glucose tolerance, restored body weight, and normalized hepatic, renal, and lipid biomarkers. In vitro α-glucosidase inhibition further confirmed its role in modulating postprandial hyperglycemia. The in-silico molecular docking analysis revealed that the polyphenolic compounds—particularly catechin hydrate and (–) epicatechin—demonstrated strong binding affinities with multiple diabetic targets (SUR1, PPAR-γ, DPP-4, glucokinase, and AMPK). These interactions suggest a multi-target synergistic mechanism involving enhanced insulin secretion, improved insulin sensitivity, increased glucose utilization, and inhibition of intestinal glucose absorption. Further pharmacokinetic and molecular mechanism investigations are warranted to develop *X. mekongensis*-derived bioactive compounds as potential natural leads for the treatment of diabetes mellitus.

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Ethical Approval

All the experimental protocols were approved by the Animal Ethics Committee of Khulna University (**Approval No.: KUAEC-2028/06/11**) and conducted in accordance with the institutional and international guidelines for care and use of experimental animals.

Conflict of Interest

All the authors declare no conflict of interest.

Suppoting Information

Additional data for phytoconstituents screening, HPLC spectra, safety study, STZ-induced anti-diabetic activity, and in-silico molecular docking analysis. These materials are available free of charge via the internet at doi: 10.57342/ess25270.

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