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*Original Research Article*

# Impact of some Bioactive Compounds of Flavonoid-Rich Fraction of *Monodora tenuifolia*, Benth on Glucose Concentration and Certain Proteins Associated with Glucose Metabolism using Molecular Docking Approach

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ABSTRACT

Hyperglycemia is a hallmark of diabetes mellitus, known to be a metabolic disorder caused by excess blood glucose due to lack of insulin secretion, or cellular insensitivity to insulin or damage to pancreatic β-cell. This study focused on the potential of flavonoid-rich fraction of *M. tenuifolia* seeds (FRFMTS) to reducing plasma glucose concentration in diabetic rats and determine the molecular interaction of some phytochemicals in FRRMTS against certain proteins associated with diabetes mellitus. The plant sample was pulverized and extracted at 1g in 5 ml of 80% v/v ethanol to obtain hydro-ethanol extract subjected to solvent-solvent fractionation to obtain the FRFMTS used for HPLC screening. Seven (7) groups of male Wistar rats containing six (6) rats each were used. The groups were normal control, 25 mg/kg FRFMTS, 50 mg/kg FRFMTS, diabetic control, diabetic rats + 25 mg/kg FRFMTS, diabetic rats + 50 mg/kg FRFMTS and diabetic rats + metformin (6.67 mg/kg). A glucose oxidase kit was used to determine blood glucose concentrations, while the molecular interactions with some target proteins were docked using the extra precision (XP) algorithm. The results revealed a significant increase in the plasma glucose of diabetic control group in comparison to normal control group. Diabetic rats treated with 25 mg/kg FRFMTS, 50 mg/kg FRFMTS and metformin showed that glucose concentrations significantly reduced compared to diabetic control group. The molecular docking model revealed highest binding affinity of quercetin to acetyl-CoA carboxylase, glucose-1-transporter, glycogen synthase kinase 3β, glucagon-like peptide 1 and insulin receptor kinase. This study suggests that FRFMTS possesses glucose lowering ability and quercetin present in FRFMTS binds effectively to proteins linked to diabetes and could elicit antihyperglycemic effect.

***Keywords:*** Hyperglycemia, Glucose metabolism, Diabetes mellitus, Molecular docking, *Monodora tenuifolia*

## Introduction

Diabetes mellitus is well known with chronic hyperglycemia and abnormalities in carbohydrate, fat, and protein metabolism. Diabetes mellitus is a metabolic illness that is absolutely characterized with lack of insulin production due to damage in the pancreatic β-cells of langerhans, decrease in insulin activity or insensitivity of cells of organs to recognize insulin present in the blood.[1] Diabetes mellitus causes significant morbidity, mortality and diabetic complications such as cardiovascular disease, retinopathy, ulceration, nephropathy, and peripheral nerve damage.[2]

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Certain factors predispose individuals to the development of diabetes mellitus such as obesity, sedentary lifestyles, genetic predisposition, lack of exercise, old age and bad diets. Report from International Diabetes Federation (IDF) showed that about 537 million of adult humans from the age of 20 to 79 years had diabetes mellitus in 2017. According to IDF, the number of persons suffering from diabetes mellitus may increase to 643 million by the year 2030, and probably to 783 million persons by the year 2045.[3] Studies have shown that diabetes is a silent killer whereby in every two persons suffering from diabetes, one remains undiagnosed, and 6.7 million people are said to have died of diabetes annually. Larger percent of adults are living with diabetes and comprise three in every four adults in under developed nations[4]. Meo *et al.*[5] asserted that type 2 diabetes mellitus (T2DM) epidemics is rising at a faster rate in many regions of the world, irrespective of gender, regions, and level of socioeconomic development. Their report emphasized the rising trend of T2DM in the male folk as a serious global burden among men. Especially given the recent discovery that the burden is rapidly increasing in lower-income countries, the high rate of type 2 diabetes continues to rise globally and shows no indications of slowing down. Insulin and expensive oral medications are the cornerstones of the current diabetes management strategy, which is failing. Lowering the blood glucose levels may not be sufficient or effectively reduce the all-cause mortality of diabetic patients.[6] Despite the increasing incidence of T2DM and significant advancements in scientific and clinical research, a permanent cure for diabetes does not

yet exist. Therefore, there is a need for an apt, cost-effective, and side-effect-free approach in mitigating the burden of diabetic disease. The research of the pathophysiology of diabetes mellitus in an appropriate animal model has become one of the traditional ways towards the development of viable treatment strategies for the potential cure of the disease,[7] and due to fewer side effects of medicinal plants with lower cost, herbal formulations become preferred over synthetic medications to lessen the negative effects of diabetes and its subsequent complications.[8] Species of plants that possess bioactive phytochemicals, which can be used therapeutically for medicinal purposes to ameliorate various ailments, serve as active ingredients for drug productions in pharmaceutical companies, are known as medicinal plants. The leaves, stem, root, and flower of these plants all contain variable amounts of bioactive substances that can be utilized as natural remedies for illnesses or as raw materials to make effective medications.[9]

According to research on medicinal plants by Uritu *et al.*[10] medicinal plants are used as safe, inexpensive, sustainable, and medically effective sources of bioactive secondary metabolites in traditional medicine. Medicinal plants are widely used for therapeutic purposes, including anti-inflammatory, anti-diabetic, cardioprotective, anthelmintic, anti-obesity, anti-hypertensive, and anti-cancer activities.[11] Many pharmaceutical companies utilize active ingredients derived from plants as raw materials to create synthetic medications that treat illnesses. Plants naturally produce phytochemicals, which are bioactive molecules with non-nutritional uses such as protecting plants against environmental threats like pollution, stress, wind-attack, drought, plant predators, UV rays, and pathogenic attacks Hasanuzzaman *et al.*[12] and Nyamai *et al.*[13]. They can also attract pollinating insects and be used for fragrance and decoration. The medicinal properties of these chemicals, which can prevent or treat ailments, benefit both humans and animals.

*Monodora tenuifolia* is a plant species with a lengthy ethnobotanical history; it is commonly used as a vermifuge and to treat toothaches, diarrhea, dermatitis, and migraines. The seeds of *Monodora tenuifolia* are utilized in food industry as condiments and to enhance the aroma of meals due to their sweet aroma and delightful taste.[14,15] Additionally, the seeds are employed in natural remedies for skin ailments in Southern Nigeria.[16,17] In addition to examining the molecular interactions of certain phytochemicals in FRFMTS against specific proteins involved in glucose metabolism, the current study further aimed to determine whether the FRFMTS could reduce plasma glucose levels in diabetic rats.

## Materials and Methods

*Reagents and Chemicals*

Ethanol, n-hexane, and ethylacetate were purchased from Fisher Scientific U.K, Merck KGaA, Germany, and Guandang Guanghan Chemical, China, respectively. $H_2SO_{4(aq)}$, D-fructose and $HCl_{(aq)}$ were bought from Mumbai, India. STZ was bought from Sigma Aldrich Co. Spruce Street, St. Louis, USA. Monosodium dihydrogen phosphate and disodium hydrogen phosphate were purchased from Guandong, China.

*Sample collection and processing*

The mature and ripe fruits of *Monodora tenuifolia* Benth were gathered from the Botanical Garden at Obafemi Awolowo University (OAU), Ile-Ife, Nigeria (7.5174º N, 4.5228º E) between March to June 2021. The plant sample was identified by a taxonomist, Mr. G.A. Ademoriyo and deposited at IFE Herbarium in the Department of Botany, Faculty of Science, Obafemi Awolowo University (OAU) with identification number (IFE-17,979) as reported in Nzekwe *et al.*[18]

The method described by Akinwunmi and Oyedapo,[19] was used to obtain the hydro-ethanol extract of the *M. tenuifolia* seeds. It involved soaking the dry marcerated residue in a 1:5 (w/v) 80% (v/v) hydro-ethanol mixture for 48 hours, stirring occasionally. The dried macerated residue weighed 1.5 kg. After being decanted, the supernatant was extracted once again using the same solvent, and this process was repeated until the supernatant had lost all of its color. A rotary evaporator was used to concentrate the supernatant at 40°C. Hydro-ethanolic extract obtained was dissolved in 1:5 (w/v) hot distilled water and refluxed in 1% (v/v) $H_2SO_4$ at 1:4 v/v and filtered. According to Bala *et al.*[20], the filtrate was combined with 1:4 v/v ethyl acetate to create the ethyl acetate fraction, which was further concentrated and used as the flavonoid-rich fraction of *M. tenuifolia* seeds (FRFMTS).

*High-Performance Liquid Chromatography (HPLC) analysis*

FRFMTS obtained was chromatographically and separated into distinct flavonoids using a capillary column and standard techniques. A chromatogram with a particular peak region and peak profile was generated following the initial introduction of the different standard analytes into the HPLC. An aliquot of the FRFMTS solution was then added to the HPLC in order to get a peak area that matched the standard.

The concentration of flavonoids in the sample was determined as:

$$Conc.(mg)of\ flavonoids = peak\ area\ of\ M.tenuifolia \times \frac{standard\ conc.}{\text{peak area of standard}}$$

*Animal Care and Induction of diabetes mellitus*

Forty-two (42) male Wistar rats were purchased for this study. They rats weighed 150–250 g and acclimatized in the animal house for 7 days at the Department of Biochemistry, Adeleke University. These animals were kept under natural 12-hour light/dark cycle with typical humidity and temperature levels. The rats were divided into seven (7) groups and each group consist of six (6) rats. Ethical clearance was obtained from Adeleke University Ethical Committee and reference number was given as AUERC/FOS/BCH/04. A solution of streptozotocin (STZ, 40 mg/kg) was prepared according to the method explained in Nzekwe *et al.*[18] and 1 ml was injected intraperitoneally into the rats based on the groupings to induce diabetes mellitus according to Wilson and Islam,[21], which involved initial administration of fructose solution 10% (w/v) in drinking water for a period of two weeks. Following the induction, the rats were given 72 hours to stabilize while an Acu-check glucometer was used to confirm diabetes in the rats. Any rat with blood sugar level of ≥ 250 mg/dl was considered to be diabetic. In order to determine the consistency of the diabetic state, the diabetic rats were subsequently observed for 21 days without medication. The glucose levels were measured at regular intervals of 7 days.

*Study design*

As indicated above, the rats grouped into seven (7) of six (6) rats.
Group one (1): Normal control rats
Group two (2): Non-diabetic rats given 25 mg/kg FRFMTS
Group three (3): Non-diabetic rats given 50 mg/kg FRFMTS
Group four (4): Diabetic control rats
Group five (5): Diabetic rats given 25 mg/kg FRFMTS
Group six (6): Diabetic rats given 50 mg/kg FRFMTS
Group seven (7): Diabetic rats given 6.67 mg/kg Metformin

Rats were given a single daily dosage of conventional medications (metformin, 6.67 mg/kg), then 25 mg/kg FRFMTS and 50 mg/kg FRFMTS according to their groupings for 21 days using the Momoh *et al.*[22] approach. The rats were given a single dose (1 ml) of the extract and metformin daily according to their groupings for 14 days while the control groups received water *ad-libitum*. After an overnight fast and under diethyl-ether anesthesia, the rats were sacrificed after the 14-day experiment according to the protocol outlined by Akinwunmi and Oyedapo.[23] Blood samples were obtained by vein puncture into fluoride oxalate and lithium heparin anticoagulant-coated vials under ice for determination of glucose concentrations.

*Determination of plasma glucose concentration*

The concentration of fasting plasma glucose was determined using spectrophotometer according to the method of glucose oxidase as described in the Randox kit manufacturer's manual. 0.1M phosphate buffer, pH 7.0, 11M phenol, 1.5 kU/l glucose oxidase, 0.77 mM 4-aminophenazone and 1.5 kU/l peroxidase were all components of the assay reagent. To create the working reagent for the glucose assay, the regents were produced in 500 ml of the buffer. A glucose standard of 150 mg/dl was prepared and calibrated with certified glucose (D-

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glucose) in 6-fold different concentrations. The glucose assay was conducted by pipetting the plasma samples into the corresponding labelled test tubes together with 20 $\mu$l of the standard glucose solution included in the kit pack. Each of the test tubes was set up and added with 1.0 ml of the Randox kit prepared reagent, then heated for 30 min at 37 °C in a water bath. The absorbance of the final solution was measured at 546 nm and the graph of absorbance wavelength against the standard concentration was plotted and result expressed in mg/dl of glucose standard.

*Molecular docking*

The three-dimensional (3D) structures of acetyl CoA carboxylase 1, insulin receptor kinase, glucose-1-transporter, glycogen synthase kinase 3 beta, and glucagon-like peptide 1 were obtained from the Protein Data Bank (https://www.rcsb.org/) using the structure data format (SDF) in the PubChem database (https://pubchem.ncbi.nlm. nih.gov/). They were assigned PDB IDs 5VEW, 1IR3, 4PYP, 1Q5K, and 1W96, respectively. The model energy score (e-model), which includes the glide score, the non-bonded interaction energy, and the excess internal energy of the produced ligand conformation, was used to select the best-docked structure for each ligand. Three-dimensional (3D) structures of acetyl CoA carboxylase 1, insulin receptor kinase, glucose-1-transporter, glycogen synthase kinase 3 beta, and glucagon-like peptide 1 were obtained from the protein databank (https://www.rcsb.org/) using the structure data format (SDF) in the PubChem database (https://pubchem.ncbi.nlm. nih.gov/). These were coded with PDB IDs 5VEW, 1IR3, 4PYP, 1Q5K, and 1W96, respectively.[24]

The model energy score (e-model), which included the glide score, the non-bonded interaction energy, and the excess internal energy of the produced ligand conformation, was used to select the best-docked structure for each ligand.[25]

*Statistical analysis*

The data were presented in triplicates as mean ± SEM. The level of significant was obtained using GraphPad Prism version 7 to establish statistical significance using One-Way Analysis of Variance (ANOVA). The Duncan's multiple comparison method was used to compare between diabetic control rats and treated diabetic rats at $p<0.05$.

## Results and Discussion

*HPLC identification phytochemicals in FRFMTS*

Since the beginning of time, medicinal plants have been utilized as a source of medicine in all societies.[26] Medicinal plants are the basis of traditional medicines because of their compatibility with the human body, increased cultural acceptability globally, and decreased adverse effects and are today considered to be beneficial.[27] The presence of phytochemicals in medicinal plants has been the basis of their medicinal values, according to Merecz-Sadowska *et al.*[28] Since various phytochemical components have distinct roles in the treatment of various diseases, they have a wide range of therapeutic indications against neurodegenerative, inflammatory and cancerous diseases.

Antioxidant properties of flavonoids, flavones, phenolic acid, or flavanones have been linked to the treatment of oxidative stress-generated diseases like diabetes mellitus, hypertension, neurodegenerative disorders, and cardiovascular diseases.[29] The HPLC peak chromatogram analysis of flavonoids revealed the presence of different flavonoids in FRFMTS which were methylgallate, thymol, methyleugenol, eugenol, eucalyptol, catechin, epicatechin, Beta-sitosterol, stigmasterol, terpecurcumin, quercetin, kaempferol, rutin, rhamnocitrin, carvacrol, melicarpinone, annonamine, methylsarpagine and ixoside as shown in Figure 1 and Table 1.

*Effect of FRFMTS on glucose concentration in the plasma*

The lack of insulin secretion due to damage in the pancreatic β-cells of Langerhans, decreased insulin activity, or insensitivity of organ cells to recognize insulin present in the blood, which offsets persistent insulin resistance, leads to type 2 diabetes.[30]

**Table 1:** Retention time, peak area, peak height and concentration of the flavonoids obtained from HPLC

| Component | Retention | Area | Height | Conc. analytes (mg/g extract) |
|---|---|---|---|---|
| MethylGallate | 1.266 | 1319.7430 | 35.630 | 0.917 |
| Thymol | 2.750 | 2648.9885 | 25.740 | 1.84 |
| Methyl Eugenol | 4.450 | 799.5065 | 13.324 | 0.56 |
| Eugenol | 5.466 | 353.3530 | 8.655 | 0.25 |
| Eucalyptol | 6.483 | 241.1495 | 7.065 | 0.17 |
| Catechin | 7.033 | 50.8605 | 5.831 | 0.035 |
| Epicatechin | 7.333 | 81.9950 | 5.385 | 0.057 |
| Beta-Sitosterol | 7.950 | 102.3055 | 5.087 | 0.071 |
| Stigmasterol | 8.816 | 51.5560 | 5.194 | 0.036 |
| Terpecurcumin | 9.350 | 53.9795 | 2.782 | 0.038 |
| Quercetin | 11.050 | 8719.2635 | 154.960 | 6.06 |
| Kaempferol | 12.166 | 2915.1055 | 56.785 | 2.03 |
| Rutin | 13.700 | 1335.6985 | 29.027 | 0.93 |
| Rhamnocitrin | 14.816 | 175.3440 | 0.439 | 0.12 |
| Carvacrol | 15.716 | 164.7435 | 6.464 | 0.11 |
| Melicarpinone | 16.250 | 103.2780 | 5.271 | 0.072 |
| Annonamine | 16.850 | 51.7795 | 4.887 | 0.036 |
| MethylSarpagine | 17.616 | 581.3260 | 8.544 | 0.404 |
| Ixoside | 18.500 | 58.5210 | 9.773 | 0.041 |

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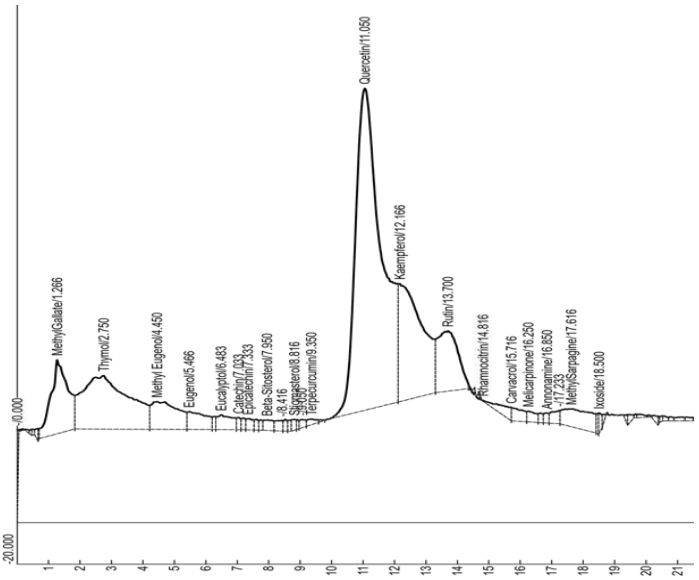


**Figure 1:** HPLC peak representation of flavonoids present in FRFMTS

Figure 2 illustrates the plasma glucose concentration in diabetic rats. In the comparison of non-diabetic control group with the diabetic control group, the blood glucose was significantly higher ($p < 0.05$) in the diabetic control group. Non-diabetic rats treated with 25 mg/kg bwt FRFMTS and 50 mg/kg bwt FRFMTS showed no significant difference ($p < 0.05$) in plasma glucose concentrations compared to the normal control rats. In contrast, the diabetic control group exhibited elevated plasma glucose levels, indicating that diabetes mellitus ensued. The outcomes of the present study revealed that groups treated with 50 mg/kg bwt of FRFMTS and metformin demonstrated significant decrease in plasma glucose concentrations compared to the diabetic control group. In contrast, diabetic rats treated with 25 mg/kg bwt FRFMTS did not exhibit significant decrease in glucose concentration, supporting the study conducted by Airaodion *et al.*[31] that investigated the effect of pawpaw leaf extract on alloxan-induced diabetes mellitus. In their work, the animals treated with different dosages of C. papaya leaf extract had their fasting blood sugar significantly reduced compared to the diabetic control group (negative control group). The results of this study also correlate with the findings of Omoboyowa *et al.*[32] that showed that 50 mg/kg and 100 mg/kg of the ethyl acetate extract of *Spondias mombin* administered to diabetic rats positively influenced the pathological alterations in the pancreas, thereby causing a significant reduction in glucose concentration under diabetic conditions, ameliorating the effects of pathological complications linked to diabetes mellitus.

*Molecular docking interaction of three HPLC-identified flavonoids against five selected proteins implicated in diabetes mellitus*

The docking scores of methylgallate, quercetin and kaempferol docked against acetyl-CoA carboxylase, glycogen synthase kinase 3β, glucagon-like peptide 1, glucose-1-transporter and insulin receptor kinase are shown in Table 2, 3 and 4.

The docking scores showed the binding affinity of different flavonoid compounds with proteins associated with glucose metabolism. The quercetin had the following binding affinity with acetyl-CoA carboxylase (-9.177 kcal/mol), glycogen synthase kinase 3β (-8.811 kcal/mol), glucagon-like peptide 1 (-6.296 kcal/mol), Glucose-1-transporter (-10.982 kcal/mol) and insulin receptor kinase (-8.026 kcal/mol); kaempferol had the binding affinity with Acetyl-CoA carboxylase (-6.877 kcal/mol), glycogen synthase kinase 3β (-8.805 kcal/mol), glucagon-like peptide 1 (-3.113 kcal/mol), glucose-1-transporter (-7.204 kcal/mol) and Insulin receptor kinase (-9.117 kcal/mol) and methylgallate had the binding affinity with acetyl-CoA carboxylase (-3.126 kcal/mol), glycogen synthase kinase 3β (-8.313 kcal/mol), glucagon-like peptide 1 (-5.496 kcal/mol), Glucose-1-transporter (-5.678 kcal/mol) and insulin receptor kinase (-7.397 kcal/mol). The present results agree with the work of Hadi *et al.*[33] which revealed that molecular docking of *N. cordifolia* compounds against targeted proteins associated with of T2DM such as INSR (5e1s), CDK2 (6gue), SMAD3 (1mjs), EGFR (1m17), IGF1 (5u8q), BRAF (3og7), and AKT1(4ekl) showed effectiveness in treating T2DM. According to their research, one of the substances found in *N. cordifolia*, ellagic acid, demonstrated more precise docking results for every target protein. When the ligands and proteins interacted, hydrogen bonds were created as a result of the compounds' extremely high binding affinity. The strength of the binding energy is mostly determined by these hydrogen bonds; the more hydrogen bonds between the ligand and the protein, the higher the bond affinity.

The amino acids residues that quercetin bound to were acetyl-CoA carboxylase (Gly 396, Pro 389), glycogen synthase kinase 3β (Lys 183, Asp 200, Ile 62, Val 135), glucagon-like peptide 1 (Asn 407, Asn 406, Leu 401, Lys 351, Thr 355), glucose-1-transporter (Asn 411, Gln 161, Phe 379, Asn 317) and insulin receptor kinase (Met 1079, Gln 1004); kaempferol bound to amino acids residues in acetyl-CoA carboxylase (Phe 510, Trp 487, Arg 76), glycogen synthase kinase 3β (Val 135, Pro 136), glucagon-like peptide 1 (nil), glucose-1-transporter (Phe 26, Asn 415, Asn 411, Glu 380) and insulin receptor kinase (Lys 1030, Glu 2077, Met 1079) and methylgallate bound to amino acid residues in acetyl-CoA carboxylase (Pro 389, Asn 485), glycogen synthase kinase 3β (Val 135), glucagon-like peptide 1 (Asn 406, Asn 407, Ser 352), glucose-1-transporter (Gln 283, Glu 380) and insulin receptor kinase (Arg 1136, Lys 1030). The quercetin interacted more with the studied proteins.

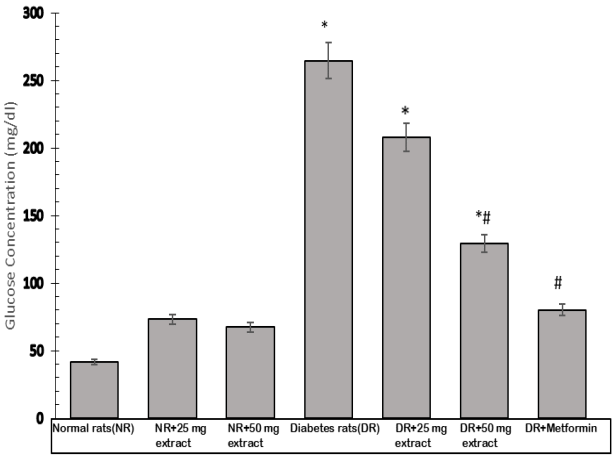


**Figure 2:** Effect of FRFMTS on glucose concentration in the plasma of diabetic rats

Data is shown as mean ± SEM

(#) denotes significantly different from the diabetes normal rats at $p < 0.05$.

(*) denotes significantly different at $p < 0.05$ compared to the normal rats

Molecular docking is a tool protein studies that predicts the binding interactions and intermolecular framework between ligand molecules and proteins, thereby plays a very vital role in drug discovery.[34] Glucagon-like peptide-1 (GLP-1) is a protein that promotes proliferation of beta-cells while inhibiting programmed cell death. It also, promotes reduction in glucagon secretion, induces satiety and improves glucose up take by organs of the body.[35] In this study, quercetin and methylgallate expressed significant binding affinity to GLP-1 (Figure 3) while kaempferol did not show any binding affinity as there was non-existence of hydrogen bonding with GLP-1.

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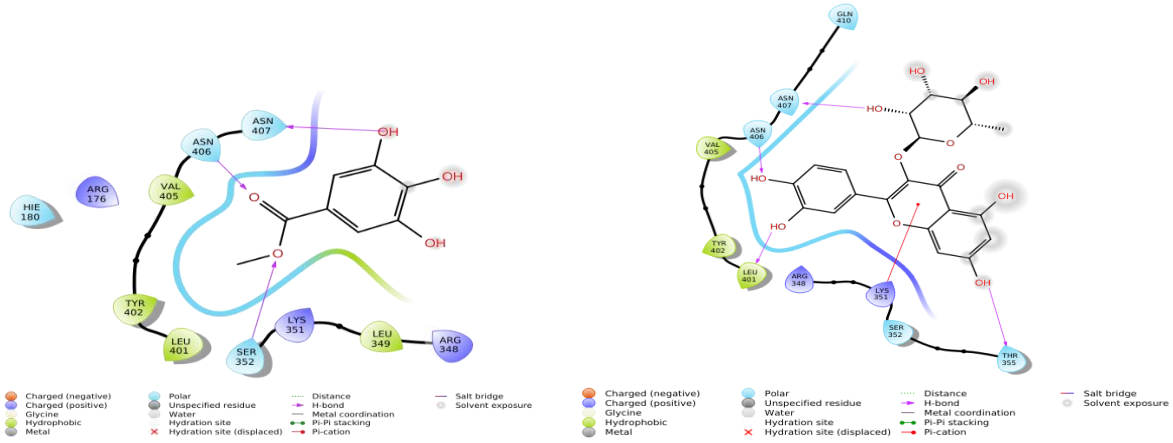
**Table 2:** Amino acid residues of acetyl-CoA carboxylase and glycogen synthase kinase 3β binding pockets that interacted with the phytochemicals

**(a) Acetyl-CoA carboxylase**

| Compounds | Docking scores | Molecular interactions | Number of H-bonds | Number of O-bonds |
|---|---|---|---|---|
| Quercetin | -9.177 | Gly 396, Pro 389 | 2 | 0 |
| Kaempferol | -6.877 | Phe 510, Trp 487, Arg 76 | 2 | 1 |
| Methylgallate | -3.126 | Pro 389, Asn 485 | 2 | 0 |

**(b) Glycogen synthase kinase 3β**

| Compounds | Docking scores | Molecular interactions | Number of H-bonds | Number of O-bonds |
|---|---|---|---|---|
| Quercetin | -8.811 | Lys 183, Asp 200, Ile 62, Val 135 | 4 | 0 |
| Kaempferol | -8.805 | Val 135, Pro 136 | 2 | 0 |
| Methylgallate | -8.313 | Val 135 | 1 | 0 |




**(A)** **(B)**

**Figure 3:** Interaction of phytochemicals (A) kaempferol (B) methylgallate (C) quercetin with amino acid residues of glucagon-like peptide 1

**Table 3:** Amino acid residues in the glucagon-like peptide 1 and glucose-1 transporter binding pockets that interacted with the phytochemicals

**(a) Glucagon-like peptide 1**

| Compounds | Docking scores | Molecular interactions | Number of H-bonds | Number of O-bonds |
|---|---|---|---|---|
| Quercetin | -6.296 | Asn 407, Asn 406, Leu 401, Lys 351, Thr 355 | 4 | 1 |
| Kaempferol | -3.113 | - | - | - |
| Methylgallate | -7.397 | Asn 406, Asn 407, Ser 352 | 2 | 1 |

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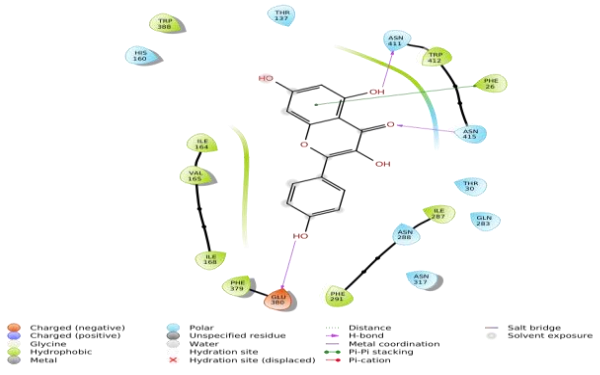
**(b) Glucose-1 transporter**

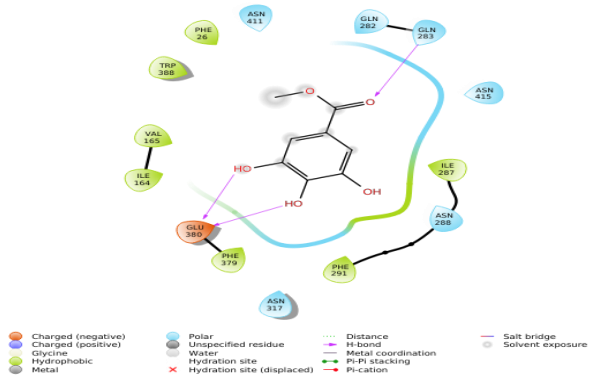
| Compounds | Docking scores | Molecular interactions | Number of H-bonds | Number of O-bonds |
|---|---|---|---|---|
| Quercetin | -10.982 | Asn 411, Glu 161, Phe 379, Asn 317 | 4 | 1 |
| Kaempferol | -7.204 | Phe 26, Asn 415, Asn 411, Glu 380 | 3 | 1 |
| Methylgallate | -5.678 | Glu 283, Glu 380 | 2 | 1 |

This may predict the capacity of FRFMTS to stimulate glucagon-like peptide-1 activity, enhancing the cellular uptake of glucose for glycogen biosynthesis and prevent glucagon secretion.

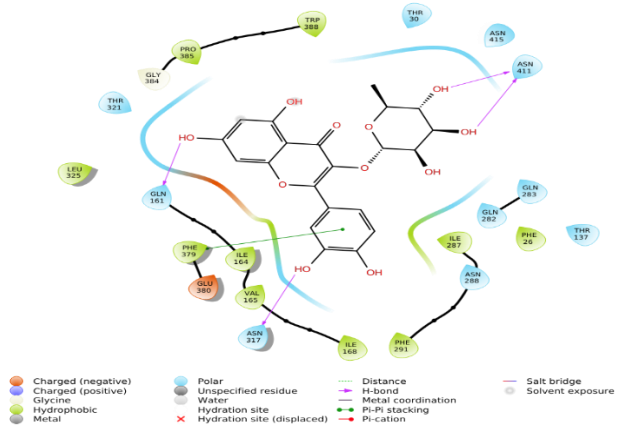
The primary energy source for the mammalian cells that are carried by the membrane-bound proteins' facilitative diffusion is glucose. The most prevalent glucose transporter, glucose-1-transporter, is primarily in charge of cellular uptake of glucose into erythrocytes and blood-brain barrier endothelial cells.[36] The binding of methylgallate and quercetin to glucagon-like peptide-1 through Asn 406, Asn 407, Ser 352 and Asn 407, Asn 406, Leu 401, Lys 351, Thr 355 respectively (Figure 4) could facilitate optimum uptake of glucose from circulation into the cells of the body, mostly the brain cells.




**(A)**




**(B)**




**(C)**

**Figure 4:** Interaction of phytochemicals (A) kaempferol (B) methylgallate (C) quercetin with amino acid residues of glucose-1-transporter

The insulin receptor (IR) and its intrinsic tyrosine kinase activity, which is triggered by ligand interaction, mediate these actions at the cellular level. Figure 5 shows how quercetin at amino acids (Met 1079, Gln 1004), kaempferol (Lys 1030, Glu 2077, Met 1079), and methylgallate (Arg 1136, Lys 1030) could modulate insulin receptors to improve the uptake of glucose into organ cells. To carry out its traditional metabolic and mitogenic functions, insulin uses the insulin receptor (IR) site, which is abundant in tyrosine, methionine, glutamate, glutamine, and lysine.[37] In this study, the binding of quercetin, kaempferol and methylgallate to methionine, glutamate and glutamine present in the active site could allow for adequate binding of insulin to the insulin receptor. Quercetin, kaempferol and methylgallate have a direct effect on modulating the GSK-3β at varying amino acid residues such as lysine, aspartate, isoleucine, valine and proline through hydrogen bonding as shown in Figure 6. Studies have proven that pharmacological intervention in inhibiting GSK-3β activity has become a vital technique or approach in management of T2DM.[38]

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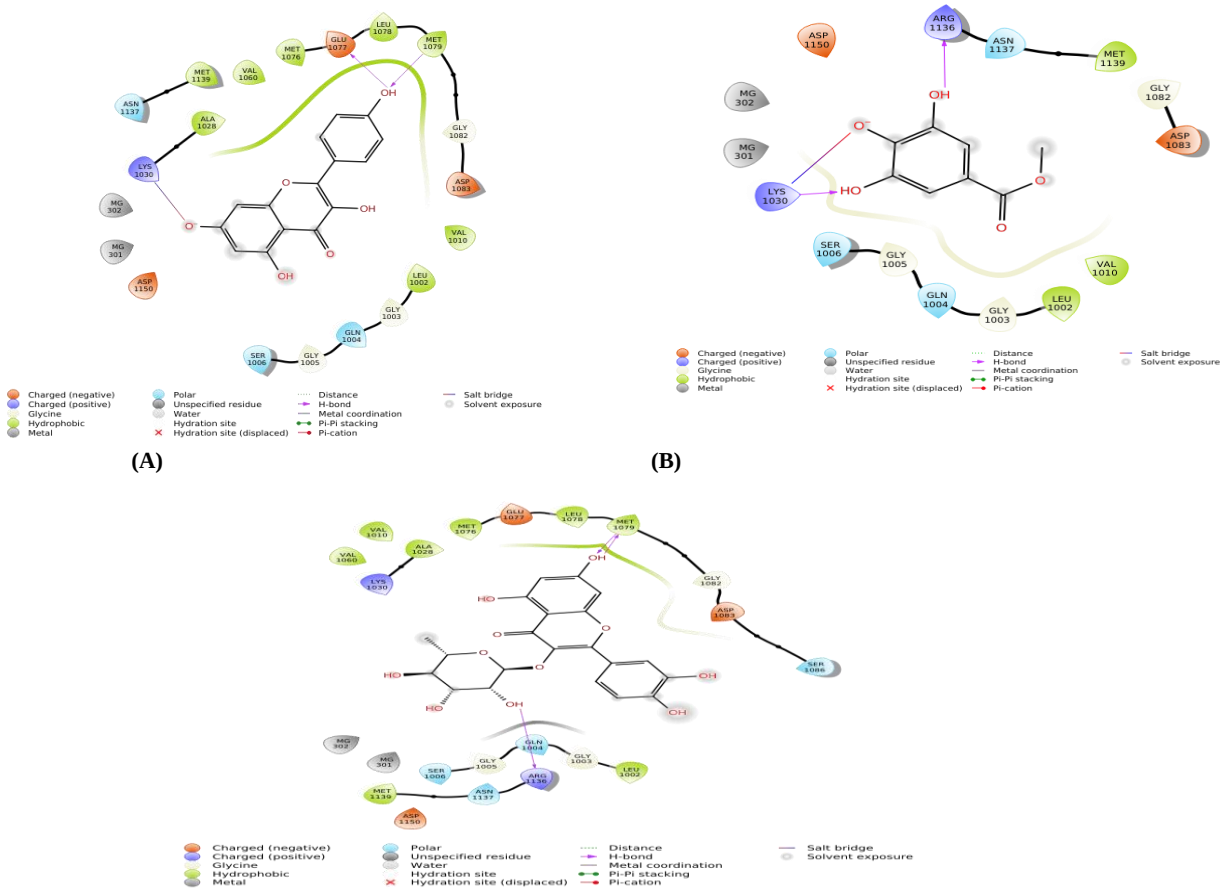
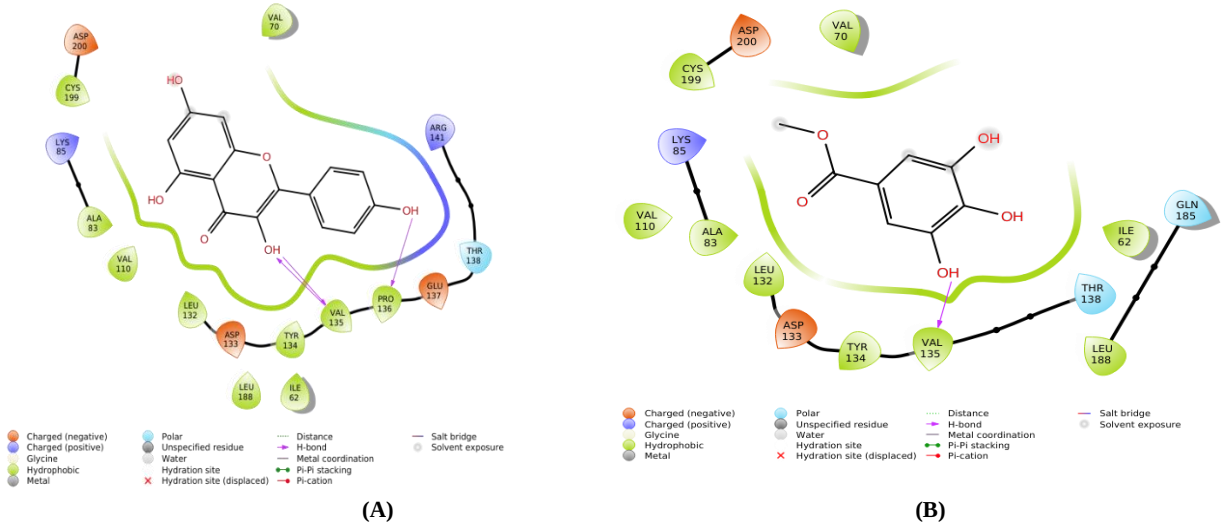



**Figure 5**: Interaction of phytochemicals (A) kaempferol (B) methylgallate (C) quercetin with amino acid residues of insulin receptor kinase



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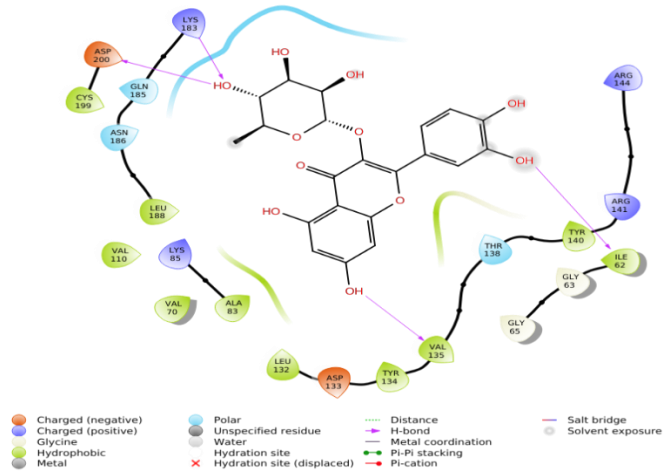


**(C)**

**Figure 6:** Interaction of phytochemicals (A) kaempferol (B) methylgallate (C) quercetin with amino acid residues of glycogen synthase kinase 3β

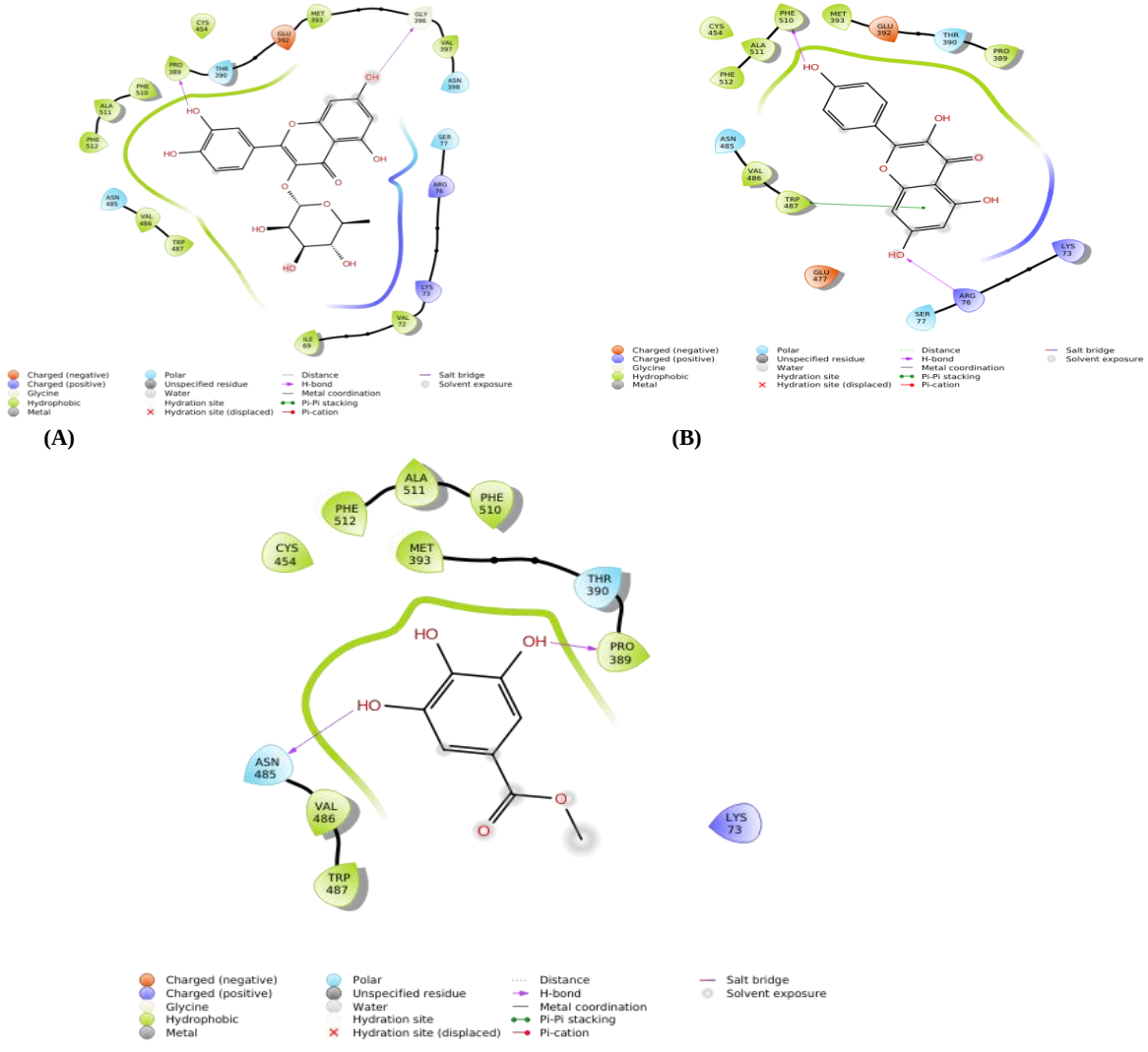


**Figure 7:** Interaction of phytochemicals (A) kaempferol (B) methylgallate (C) quercetin with amino acid residues of acetyl CoA carboxylase 1

GSK-3 is a serine and threonine kinase enzyme which is involved in a number of cellular activities like regulation of cell signaling, cell proliferation, glucose metabolism, insulin sensitivity and cellular transport. Phosphorylation of this enzyme will cause the enzyme to be modified and lack the ability to regulate glucose metabolism through enhancing insulin sensitivity and cellular transport of glucose.

**Table 4:** Amino acid residues in the insulin receptor kinase binding pockets that interacted with phytochemicals

| Compounds | Docking scores | Molecular interactions | Number of H-bonds | Number of O-bonds |
|---|---|---|---|---|
| Quercetin | -8.026 | Met 1079, Gln 1004 | 2 | 0 |
| Kaempferol | -9.557 | Lys 1030, Glu 2077, Met 1079 | 2 | 1 |
| Methylgallate | -7.397 | Arg 1136, Lys 1030 | 2 | 1 |

## Conclusion

This study shows that FRFMTS possesses the ability to reduce glucose level thereby ameliorating hyperglycemia. Bioactive compounds such as quercetin, rutin, catechin, thymol, eugenol, kaempferol, methylgallate and several others that are found in FRFMTS may be responsible for its therapeutic effects against diabetes mellitus. The study also revealed good molecular interactions of quercetin, kaempferol and methylgallate in FRFMTS with some proteins involved in glucose metabolism with quercetin having the highest binding affinity for acetyl-CoA carboxylase, glycogen synthase kinase 3$\beta$, glucagon-like peptide 1, glucose-1-transporter and insulin receptor kinase. The unique interaction of bioactive compounds from medicinal plants with enzymes and proteins involved in carbohydrate metabolism opens to the molecular approach disease diagnosis, precision medicine and the development of targeted therapies to treat diabetes mellitus.

## Conflict of Interest

The authors declare no conflict of interest.

## Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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