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Acacetin Interacts with Glycolytic Enzymes and Inhibits Diabetes

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Abstract

Diabetes mellitus, a chronic metabolic disorder, has been a global health concern with rising prevalence. The search for novel therapeutic agents, especially from natural sources, remains a priority. Acacetin, a flavonoid found in various plants, has shown potential in various biological activities. However, its role in diabetes management, particularly its interaction with glycolytic enzymes, has been less explored. This study aimed to investigate the interaction of acacetin with glycolytic enzymes and its potential as a therapeutic agent for diabetes management. A comprehensive molecular docking analysis was employed to explore the binding affinity of acacetin to glycolytic enzymes, including hexokinase, phosphofructokinase, and pyruvate kinase. The study utilized advanced computational tools and techniques to simulate the interaction dynamics. The binding energy, interaction sites, and stability of the acacetin-enzyme complex were evaluated. Acacetin exhibited significant binding affinity towards all three glycolytic enzymes, with notable stability in the enzyme active sites. The binding energies indicated a strong interaction, suggesting potential inhibitory effects on the enzymes. The interaction was characterized by both hydrogen bonding and hydrophobic interactions, contributing to the stability of the complexes. The molecular docking analysis suggests that acacetin interacts effectively with key glycolytic enzymes, potentially inhibiting their activity. This interaction could impede the glycolytic pathway, which is crucial in diabetes pathophysiology. Therefore, acacetin emerges as a promising candidate for diabetes management, warranting further in-vitro and in-vivo studies to explore its therapeutic potential and mechanism of action.

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Introduction

Diabetes mellitus, a chronic metabolic disorder, is characterized by impaired insulin function or insulin resistance, leading to aberrant glucose metabolism, affecting millions worldwide [1]. With an increased prevalence and the associated complications, there is a growing need for innovative and effective therapeutic strategies. Insulin resistance is a hallmark of diabetes, and glycolytic enzymes have been implicated in its development. Several studies have investigated the relationship between glycolytic enzymes and insulin resistance in diabetes.

Glycolysis, the metabolic pathway that converts glucose into pyruvate, plays a significant role in the development and progression of diabetes. Several studies have investigated the activity of glycolytic enzymes in individuals with type 1and type 2 diabetes. Altered activities of glycolytic enzymes, such as hexokinase, phosphofructokinase, aldolase and lactate dehydrogenase, have been observed in diabetic patients [2]. Study proposed that hexokinase-2 linked glycolytic overload and unscheduled glycolysis may contributed to insulin resistance and the development of vascular complications of diabetes [3]. These alterations can impact the rate of glycolysis and subsequent energy production. Research has also highlighted the potential implications of glycolytic enzymes levels in diabetic nephropathy. Increased levels of glycolytic enzymes, such as pyruvate kinase M2 and enolase 1, have been observed in individuals with diabetic nephropathy, suggesting a potential link between glycolysis and diabetic kidney disease [4]. Furthermore, targeting key metabolic and regulatory enzymes to enhance glycolysis has been proposed as a viable approach for the treatment of diabetes [5]. The study found that almost all glycolytic enzymes were upregulated in diabetic islets, and glycolytic glucose metabolism was reduced in pancreatic beta-cells, contributing to insulin resistance [6]. However, the specific roles of glycolytic enzymes in the development of diabetic atherosclerosis and impaired mitochondrial metabolism in diabetic beta cells are still being elucidated [7,8]. The study investigates the binding affinity of acacetin with glycolytic enzymes and its potential to inhibit diabetes. In summary, this introduction sets the stage for a comprehensive exploration of acacetin's interaction with glycolytic enzymes such as hexokinase, Phosphoglucose isomerase, Phosphofructokinase, fructose- bisphosphate aldolase, triosephosphate isomerase, Glyceraldehyde 3-phosphate dehydrogenase, Phosphoglycerate kinase, Phosphoglycerate mutase, Enolase, and Pyruvate kinase through molecular docking analysis, emphasizing its potential as a novel and promising therapeutic agent for inhibiting diabetes. The article concludes that acacetin has the potential to inhibit diabetes through its interaction with glycolytic enzymes.

Materials and Methods

Preparation of Ligand

The Acacetin [CID: 5280442] 3D chemical structure was downloaded from PubChem database. The chemical structure was downloaded in SDF file format, then it is converted into PDB file format by using the online translator. Ultimately the ligand format was changed by using Auto Dock Tool for the further analysis.

Preparation of Receptors

Three-dimensional coordinates of hexokinase [P08237], Phosphoglucose isomerase [P06744], Phosphofructokinase [P08237], fructose- bisphosphate aldolase [P04075], triosephosphate isomerase

[P60174], Glyceraldehyde 3-phosphate dehydrogenase [P04406], Phosphoglycerate kinase [P00558], Phosphoglycerate mutase [P18669], Enolase [P13929], and Pyruvate kinase [P30613] were retrieved from Uniprot Protein Data Bank. The auto dock tool is used to create the receptor molecule, after which the protein molecules are given Kollman charges and the missing atoms and polar hydrogen are inserted. Finally, the file format was changed to PDBQT format for further analysis.

Docking

The process of docking molecules using Auto Dock Tools involves several steps. First, the Auto Grid strategy generates three-dimensional grid boxes to assess the binding energies on the coordinates of macromolecules. Grid maps representing the whole ligand at the actual docking target site are then generated using Auto Grid. The complete ligand is lodged in the binding site, which is eventually surrounded by cubic grids. The graphical user interface of Auto Dock, version 4.2.6, provided by MGL Tools is used to design the Auto Dock atom kinds. One of the most effective docking techniques readily available in Auto Dock, the Lamarckian genetic algorithm, was used [9]. The binding free energy and the ideal fit of a ligand conformation in the macromolecular structure are calculated and assessed using Auto Dock. This can be beneficial for understanding the nature of the binding as well as for creating more effective drug possibilities [10].

Results

The molecular docking study was performed to elucidate the interaction between Acacetin and Glycolytic enzymes. The binding energy, a critical indicator of the ligand-protein interaction strength, was computed using Auto dock.

Docking Result of Acacetin with Hexokinase

In our study, we investigated the interaction of the flavonoid Acacetin with the enzyme Hexokinase. Utilizing computational docking techniques, we determined the binding affinity and characterized the molecular interactions within the active site of the enzyme.

Binding Energy: The binding of Acacetin to Hexokinase was observed with a significant binding energy of -7.53 kcal/mol (Table 1). This high binding energy indicates a strong interaction between Acacetin and the Hexokinase enzyme, suggesting a stable complex formation. Active Site Interactions: Analysis of the enzyme-ligand complex revealed that Acacetin interacts predominantly with the following amino acid residues in the active site of Hexokinase: PHE-90, TYR-112, ASP-113, THR-114, GLU-116, VAL-119, and HIS-120 (Figure 1). These interactions are crucial for the stability of the bound complex.

Key Interactions

Hydrogen Bonding: Two hydrogen bonds were identified as critical for the binding of Acacetin. These include hydrogen bonds with PHE-90 and ASP-113. The presence of these hydrogen bonds plays a significant role in stabilizing the Acacetin-Hexokinase complex. Other Interactions: In addition to hydrogen bonding, hydrophobic and electrostatic interactions contribute to the binding affinity. Notably, residues TYR-112, THR-114, GLU-116, VAL-119, and HIS-120 are involved in forming hydrophobic interactions, further stabilizing the complex.

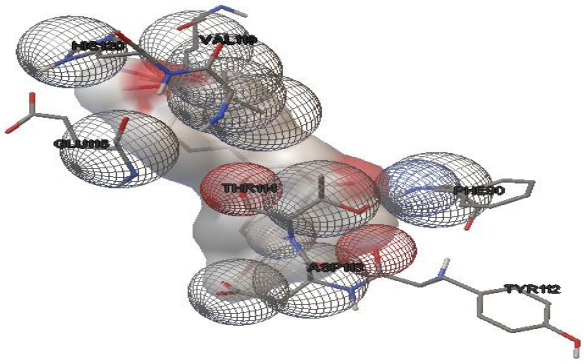

Figure 1. Schematic Representation of Hexokinase with Acacetin.

Docking Result of Acacetin with Phosphoglucose Isomerase

Binding Energy Acacetin with Phosphoglucose Isomerase

The molecular docking analysis of Acacetin with Phosphoglucose Isomerase [PGI] revealed a significant interaction, evidenced by a binding energy of -6.84 kcal/mol (Table 1). This value indicates a strong and stable binding affinity between the ligand, Acacetin, and the protein. Such a negative binding energy is often suggestive of spontaneous binding and potential inhibitory effects on the protein's activity.

Binding Pocket Composition

Further analysis of the docking pose demonstrated that Acacetin fits snugly within the binding pocket of Phosphoglucose Isomerase. This pocket is formed by a series of critical amino acid residues, which play a pivotal role in stabilizing the ligand-protein complex. Notably, the interaction involves key residues including GLY-383, ASP-341, PRO-408, THR-411, HIS-420, HIS-421, LEU-424, GLN-412 and LEU-481 (Figure 2).

Key Binding Interactions

The nature of these interactions includes hydrophobic contacts. HIS-420, LEU-424, HIS-421, and LEU-481 contribute to the formation of a hydrophobic environment, facilitating the binding of Acacetin. The involvement of PRO-408 and GLY-383 also adds to the stability of the interaction, although their specific roles may require further investigation. These findings suggest that Acacetin has a strong affinity for Phosphoglucose Isomerase, with the potential to influence its activity. This interaction might underpin the observed biological effects of Acacetin in diabetes management, providing a molecular basis for its therapeutic potential.

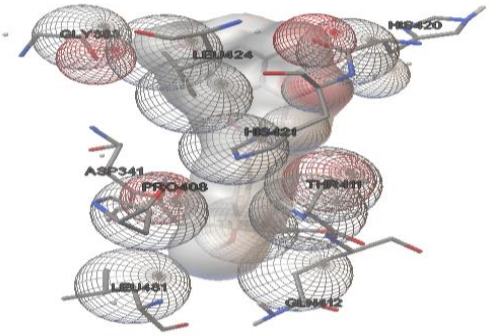

Figure 2. Schematic Representation of Phosphoglucose Isomerase with Acacetin

Docking Analysis of Acacetin with Phosphofructokinase

Binding Energy of Acacetin with Phosphofructokinase

In our molecular docking study, acacetin was analysed for its binding affinity with the enzyme phosphofructokinase, a key regulator in the glycolytic pathway. Among the glycolytic enzymes studied, acacetin displayed the second highest binding affinity towards phosphofructokinase, with a notable binding energy of -7.48 kcal/mol (Table 1). This high binding energy suggests a strong and stable interaction between acacetin and phosphofructokinase, potentially implicating significant inhibitory effects on the enzyme's activity.

Binding Pocket Composition and Key Binding Interaction

The docking analysis revealed a specific and intricate interaction pattern within the binding pocket of phosphofructokinase. Acacetin primarily interacts with several crucial amino acid residues, including TRP-227, VAL-228, LYS-233, PRO-234, PRO-235, ASP-236, ARG-246, TYR-385 and LYS-386 (Figure 3). These interactions are characterized by a combination of hydrophobic contacts and hydrogen bonds, contributing to the stability and specificity of the ligand-enzyme complex. Notably, two hydrogen bonds were observed, involving the residues VAL-228 and TYR-385. These hydrogen bonds play a critical role in stabilizing the interaction, further supporting the high binding affinity of acacetin with phosphofructokinase. The presence of these interactions in the binding pocket, which is crucial for the enzyme's catalytic activity, highlights the potential of acacetin as a strong inhibitor of phosphofructokinase. The results from our docking study suggest that acacetin may exert its antidiabetic effects, at least in part, by targeting and inhibiting phosphofructokinase, thereby impeding the glycolytic pathway which is central to glucose metabolism in diabetes.

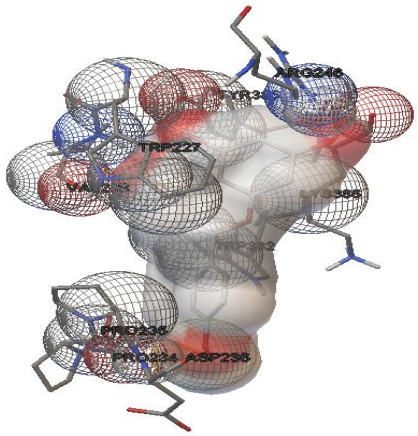

Figure 3. Schematic Representation of Phosphofructokinase with Acacetin

Docking Results of Acacetin with Fructose-Bisphosphate Aldolase

Binding Energy of Acacetin with Fructose-Bisphosphate Aldolase

The docking results revealed a significant binding affinity between acacetin and fructose-bisphosphate aldolase, with a calculated binding energy of -6.56 kcal/mol (Table 1). This value indicates a strong and favourable interaction between the ligand and the protein, suggesting that acacetin could effectively bind and potentially inhibit the activity of fructose-bisphosphate aldolase.

Binding Pocket and Interaction Analysis

The binding pocket of fructose-bisphosphate aldolase for acacetin comprises a set of amino acid residues that engage in interactions with the ligand. These residues include PRO-192, GLY-236, HIS-237, CYS-239, GLN-241, LYS-242, PHE-243, GLY-272 and GLN-274 (Figure 4). Notably, a hydrogen bond was observed between the 1-hydroxyl group of acacetin and the side chain of PHE-243, which is critical for the stability of the ligand-enzyme complex.

The interactions within the binding pocket are predominantly hydrophobic, with notable contributions from residues such as PHE-243, CYS-239, and HIS-237. These interactions are complemented by hydrogen bonding and electrostatic interactions, which further stabilize the acacetin-enzyme complex.

The molecular docking analysis indicates a strong and specific interaction between acacetin and fructose-bisphosphate aldolase, primarily facilitated by hydrophobic interactions and a key hydrogen bond. The favourable binding energy suggests that acacetin is a promising candidate for further investigation as a potential inhibitor of fructose-bisphosphate aldolase, with implications for diabetes treatment.

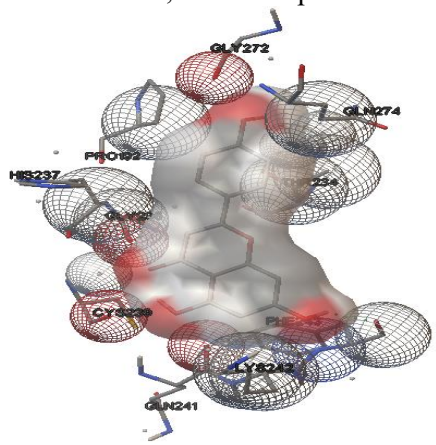

Figure 4. Schematic Representation of Fructose- Bisphosphate Aldolase with Acacetin

Docking Results of Acacetin with Triosephosphate Isomerase

The molecular docking study revealed a significant interaction between acacetin and triosephosphate isomerase. The binding energy of this interaction was found to be -6.92 kcal/mol (Table 1), indicating a strong and stable binding affinity of acacetin towards the enzyme. This high negative value suggests a spontaneous and energetically favorable interaction, which is critical in the context of potential inhibitory effects. The analysis of the docking pose highlighted several key interactions between acacetin and specific amino acid residues in the active site of triosephosphate isomerase. The binding involved both hydrogen bonding and hydrophobic interactions, which contribute to the stability and specificity of the complex. Notably, acacetin formed hydrogen bonds with GLU-77, ARG-95, ARG-98, PHE-102, GLU-104, SER-105 and LEU-106 (Figure 5). Among these, the interactions with GLU-77 and GLU-104 are particularly noteworthy due to their potential roles in the enzyme's catalytic mechanism.

The engagement of GLU-77 and GLU-104 in hydrogen bonding with acacetin could be significant, as these residues are crucial for the catalytic activity of triosephosphate isomerase. The involvement of these residues suggests that acacetin may exert its inhibitory effect by interfering with the catalytic process of the enzyme, which is a vital aspect of its potential as a therapeutic agent in diabetes management.

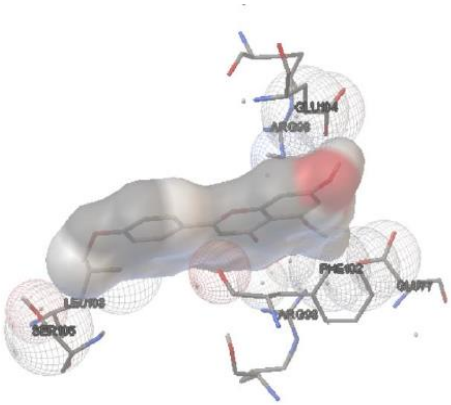

Figure 5. Schematic Representation of Triosephosphate Isomerase with Acacetin

Docking Results of Acacetin with Glyceraldehyde 3-Phosphate Dehydrogenase

Binding Energy of Acacetin with Glyceraldehyde 3-phosphate Dehydrogenase

The results showed that Acacetin binds to GAPDH with a binding energy of -7.27 kcal/mol (Table 1). This significant negative value suggests a strong and spontaneous interaction between Acacetin and the active site of GAPDH, indicative of potential inhibitory effects.

Binding Pocket and Key Binding Interaction Analysis

The analysis of the binding pocket revealed that Acacetin interacts with several key residues within GAPDH. The binding interaction is characterized by the involvement of multiple amino acids, including GLN-204, PRO-238, VAL-240, THR-237, ALA-238 and ASN-239(Figure 6). Notably, two hydrogen bonds were observed in the interaction, contributing to the stability and specificity of the ligand-enzyme complex. These hydrogen bonds were formed between Acacetin and the residues GLN-204 and ASN-239.

This specific interaction pattern within the active site of GAPDH suggests that Acacetin fits snugly into the binding pocket, primarily through hydrophobic interactions and hydrogen bonding. The involvement of these key residues in the binding interaction is crucial as it may affect the enzymatic activity of GAPDH, which is a pivotal enzyme in the glycolytic pathway. The docking results, therefore, provide a molecular basis for the potential inhibitory action of Acacetin on GAPDH, offering insights into its mechanism of action as a potential antidiabetic agent.

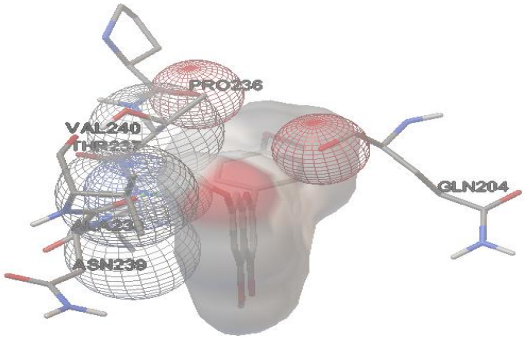

Figure 6. Schematic Representation of Glyceraldehyde 3-Phosphate Dehydrogenase with Acacetin

Docking Result of Phosphoglycerate Kinase with Acacetin

Binding Energy and Docking Results for Acacetin with Phosphoglycerate Kinase

The molecular docking analysis revealed a significant interaction between acacetin and phosphoglycerate kinase. The computed binding energy for this complex was found to be -6.9 kcal/mol (Table 1), indicating a strong and favourable interaction between the ligand and the protein. This high binding affinity suggests that acacetin could effectively inhibit the function of phosphoglycerate kinase, which plays a crucial role in the glycolytic pathway.

Binding Pocket and Key Binding Interaction Analysis

In-depth analysis of the docking pose showed that acacetin binds within a specific pocket of phosphoglycerate kinase, involving several key amino acid residues. The binding pocket is composed of ASN-25, PRO-27, MET-28, LYS-74, TYR-75, LEU-83, LYS-215, GLY-378 and 3PG-1420 (Figure 7). Notably, the ligand forms a hydrogen bond with ASN-25, which is a critical interaction contributing to the stability and specificity of the ligand-protein complex. Additionally, 3-phosphoglycerate [3PG-1420] is also located within the binding site, suggesting a competitive inhibition mechanism.

The interaction profile is characterized by a mix of hydrophobic interactions and hydrogen bonding. The hydrophobic contacts involve residues such as MET-28, LYS-74, TYR-75, and LEU-83, which help to stabilize the ligand within the binding pocket. On the other hand, the hydrogen bond with ASN-25 provides specificity to the binding, reinforcing the potential inhibitory action of acacetin on phosphoglycerate kinase.

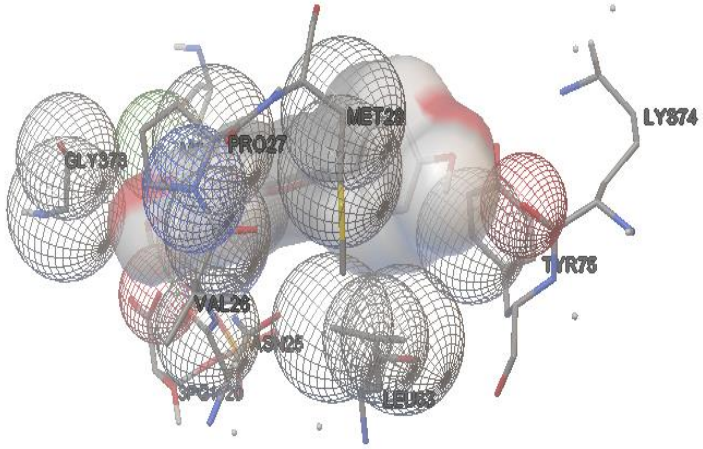

Figure 7. Schematic Representation of Phosphoglycerate Kinase with Acacetin

Docking Result of Phosphoglycerate Mutase with Acacetin

Binding Energy for Acacetin with Phosphoglycerate Mutase

In our molecular docking study, acacetin exhibited a notable affinity towards phosphoglycerate mutase, a key enzyme in key glycolytic pathway. The binding energy was computed to be -6.38 kcal/mol (Table 1), indicating a stable and significant interaction between the ligand and the protein.

Binding Pocket Composition

The analysis identified a specific binding pocket on phosphoglycerate mutase, comprising amino acid residues that interact directly with acacetin. These residues are TRP-85, ARG-86, ASP-148, GLN-149, PRO-151, SER-152, CYS-153, ASP-158 and ARG-162 (figure 8). The arrangement of these residues

forms a conductive environment for the binding of acacetin, suggesting a potential inhibitory effect on the enzyme's activity.

Key Binding Interactions

Among these amino acids, ASP-158 plays a crucial role, forming a hydrogen bond with acacetin. This interaction is particularly significant as it likely contributes to the stabilization of the ligand within binding site. The presence of both polar [like ASP-158] and non-polar [like TRP-85 and PRO-151] residues in the binding pocket indicates a complex interaction scenario, where hydrogen bonding and hydrophobic interactions collectively enhance the binding affinity.

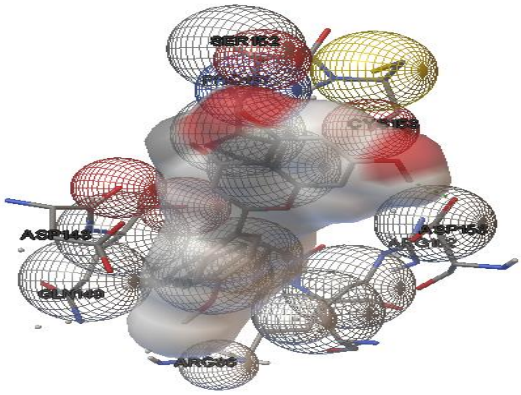

Figure 8. Schematic Representation of Phosphoglycerate Mutase with Acacetin

Docking Results of Acacetin with Enolase

Binding Energy of Acacetin with Enolase

The docking results are particularly insightful for understanding the potential inhibitory effects of acacetin on enolase, which could have implications for diabetes treatment. The docking study revealed a significant binding affinity between acacetin and enolase, with a computed binding energy of -6.62 kcal/mol (Table 1). This value indicates a strong and potentially favourable interaction between the ligand and the protein, suggesting that acacetin could effectively inhibit the activity of enolase.

Binding Pocket and Key Interactions

The analysis identified a specific binding pocket on enolase comprising several amino acids: ALA-123, ALA-124, LYS-120, VAL-128, PRO-129, LEU-130, TYR-131, GLN-409, ARG-412, ILE-413 and ALA-416 (Figure 9). Notably, acacetin was found to form hydrogen bonds with two residues, namely VAL-128 and LYS-120. These interactions are crucial as they likely contribute to the stability and specificity of the ligand-enzyme binding. The presence of hydrogen bonds, along with the hydrophobic interactions involving other residues in the binding pocket, further supports the potential inhibitory role of acacetin on enolase activity.

These findings provide a molecular basis for the potential use of acacetin as an inhibitor of enolase, which could have significant therapeutic implications in the management of diabetes. Further experimental validation is required to confirm these computational predictions and to fully understand the mechanism of action of acacetin in the context of diabetes treatment.

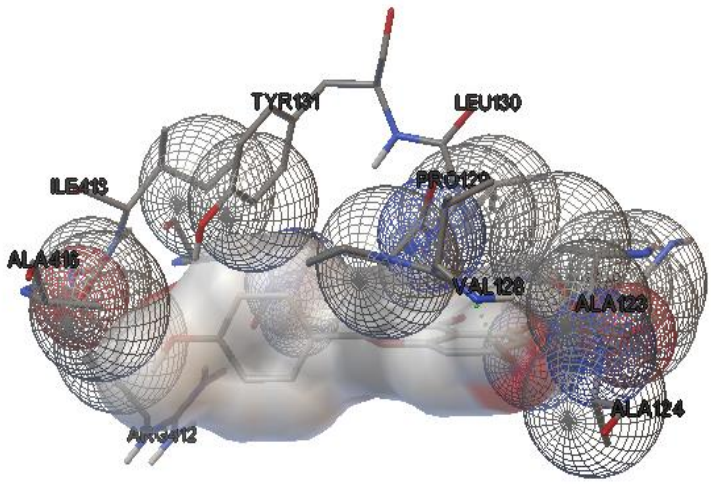

Figure 9. Schematic Representation of Enolase with Acacetin

Docking Results of Acacetin with Pyruvate Kinase

Binding Energy of Acacetin with Pyruvate Kinase

In our molecular docking study, acacetin was analysed for its binding affinity with the enzyme pyruvate kinase, a key regulator in the glycolytic pathway. Among the glycolytic enzymes studied, acacetin displayed the highest binding affinity towards pyruvate kinase, with a notable binding energy of -8.74 kcal/mol (Table 1). This high binding energy suggests a strong and stable interaction between acacetin and pyruvate kinase, potentially implicating significant inhibitory effects on the enzyme's activity.

Binding Pocket Composition and Key Binding Interaction

The docking analysis revealed a specific and intricate interaction pattern within the binding pocket of pyruvate kinase. Acacetin primarily interacts with several crucial amino acid residues, including SER-57, ALA-84, ALA-85, SER-87, ARG-426, GLU-429, ALA-430, HIS-434, PRO-489, ARG-490, VAL-493, ARG-510, GLY-511 (Figure 10). These interactions are characterized by a combination of hydrophobic contacts and hydrogen bonds, contributing to the stability and specificity of the ligand-enzyme complex.

Notably, two hydrogen bonds were observed, involving the residues ALA-84 and ARG-490. These hydrogen bonds play a critical role in stabilizing the interaction, further supporting the high binding affinity of acacetin with pyruvate kinase. The presence of these interactions in the binding pocket, which is crucial for the enzyme's catalytic activity, highlights the potential of acacetin as a strong inhibitor of pyruvate kinase.

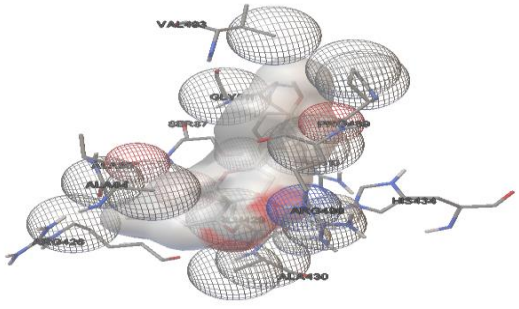

Figure 10. Schematic Representation of Pyruvate Kinase with Acacetin

Table 1. Contains the Binding Energy, Amino Acid Interaction and Bond Formation between Acacetin and the Glycolytic Enzymes.

S.No	Target molecules	Compound	Binding energy	Amino acid interacted	Bond formed
1.	Hexokinase	Acacetin	-7.53	PHE-90, TYR-112, ASP-113, THR-114, GLU-116, VAL-119, HIS-120	2-H, PHE-90, ASP-113
2.	Phosphoglucose isomerase	Acacetin	-6.84	GLY-383, ASP-341, PRO-408, THR-411, HIS-420, HIS-421, LEU-424, GLN-412, LEU-481	--
3.	Phosphofructokinase	Acacetin	-7.48	TRP-227, VAL-228, LYS-233, PRO-234, PRO-235, ASP-236, ARG-246, TYR-385, LYS-386	2-H, VAL-228, TYR-385
4.	Fructose-bisphosphate aldolase	Acacetin	-6.56	PRO-192, GLY-236, HIS-237, CYS-239, GLN-241, LYS-242, PHE-243, GLY-272, GLN-274	1-H, PHE-243
5.	Triosephosphate isomerase	Acacetin	-6.92	GLU-77, ARG-95, ARG-98, PHE-102, GLU-104, SER-105, LEU-106	2-H, GLU-77, GLU-104
6.	Glyceraldehyde 3-phosphate dehydrogenase	Acacetin	-7.27	GLN-204, PRO-238, VAL-240, THR-237, ALA-238, ASN-239	2-H, GLN-204, ASN-239
7.	Phosphoglycerate kinase	Acacetin	-6.9	ASN-25, PRO-27, MET-28, LYS-74, TYR-75, LEU-83, LYS-215, GLY-378, 3PG-1420	1-H, ASN-25
8.	Phosphoglycerate mutase	Acacetin	-6.38	TRP-85, ARG-86, ASP-148, GLN-149, PRO-151, SER-152, CYS-153, ASP-158, ARG-162	1-H, ASP-158
9.	Enolase	Acacetin	-6.62	ALA-123, ALA-124, LYS-120, VAL-128, PRO-129, LEU-130, TYR-131, GLN-409, ARG-412, ILE-413, ALA-416	2-H, LYS-120, VAL-128
10.	Pyruvate kinase	Acacetin	-8.74	SER-57, ALA-84, ALA-85, SER-87, ARG-426, GLU-429, ALA-430, HIS-434, PRO-489, ARG-490, VAL-493, ARG-510, GLY-511	2-H, ALA-84, ARG-490

Discussion

Hexokinase is an enzyme that plays a crucial role in glucose metabolism. Recent studies suggest that hexokinase-2 [HK2] is linked to glycolytic overload and unscheduled glycolysis, which are drivers of insulin resistance and the development of vascular complications of diabetes [3,11]. HK2-linked glycolytic overload explains tissue-specific pathogenesis in diabetes linked to vascular complications and contributes to pathogenesis

in ischemia-reperfusion injury [11]. HK2 is also linked to diabetic retinopathy and neuropathy, partial knockdown of HK2 in mice improved glucose tolerance in the late stage [3].

Fructose-1,6-bisphosphate aldolase [FBA] is an enzyme that catalyses the fourth step of glycolysis and has been found to play a role in diabetes. Research has shown that FBA depletion can lead to the promotion of hepatocellular carcinogenesis through activating insulin receptor signaling and lipogenesis [12]. Additionally, a study demonstrated that FBA injection induced anti-inflammatory Th2 immune response, resulting in attenuated inflammation of pancreatic islets and thus ameliorating type I diabetes. Furthermore, FBA has been reported to possess numerous non-glycolytic functions, indicating its involvement in various physiological processes [13].

Triosephosphate isomerase [TPI] is an enzyme involved in the glycolytic pathway, which is central to glucose metabolism. While the specific role of TPI in diabetes development and progression is not fully elucidated, some studies have suggested its potential relevance. For instance, TPI deficiency has been associated with increased methylglyoxal and advanced glycation end product [AGE] formation, which are implicated in the vascular complications of diabetes mellitus [14]. Additionally, plasma levels of TPI1, a protein isoform of TPI, have been found to decrease in type 2 diabetes cases [15]. These findings hint at a potential link between TPI and glucose metabolism in the context of diabetes.

Glyceraldehyde-3-phosphate dehydrogenase [GAPDH] is an enzyme that plays a crucial role in glycolysis, a process that generates energy in the form of ATP [16]. The role of GAPDH in diabetes development and progression has been extensively studied, particularly in the context of diabetic retinopathy, a chronic complication of diabetes that affects the eyes. Key findings related to the role of GAPDH in diabetes include: GAPDH activity is an independent modifier of methylglyoxal levels in diabetes, which are toxic compounds that can cause damage to proteins, lipids, and nucleic acids [17]. GAPDH plays a significant role in the development of diabetic retinopathy and its progression after cessation of hyperglycemia. Mitochondrial superoxide levels are elevated in the retina in diabetes, and manganese superoxide dismutase overexpression prevents the development of retinopathy. Superoxide inhibits GAPDH, which activates major pathways implicated in diabetic complications, including advanced glycation end products [AGEs], protein kinase C, and the hexosamine pathway [18]. In diabetic retinopathy, GAPDH levels are reduced in the retina and remain compromised even after good glycemic control is reinstituted [19]. Inhibition of GAPDH increases the levels of glycolytic metabolite glyceraldehyde-3-phosphate, which activates major pathways implicated in diabetes complications, including AGEs formation, PKC activation, and the hexosamine pathway [18].

Enolase, a glycolytic enzyme that catalyses the inter-conversion of 2-phosphoglycerate to phosphoenolpyruvate, has been associated with the development of type 2 diabetes mellitus and its comorbidities. In an experimental murine model, inhibition of enolase-1 [ENO-1] reduced blood glucose concentration, LDL cholesterol levels, cardiac hypertrophy, and liver fibrosis [20]. Additionally, the relationship between neuron-specific enolase [NSE] and diabetic peripheral neuropathy has been studied, suggesting a potential link between NSE and the development of clinical diabetic peripheral neuropathy [21]. These findings indicate that enolase, particularly ENO-1 and NSE, may play a role in the development and progression of type 2 diabetes and its associated complications.

Pyruvate kinase [PK] plays a significant role in diabetes development and progression. Research has shown that the M2 isoform of pyruvate kinase is involved in various aspects of diabetes, including diabetic retinopathy and diabetic nephropathy. Activation of pyruvate kinase M2 [PKM2] has been associated with the protection against the progression of diabetic glomerular pathology and mitochondrial dysfunction [22,23]. Additionally, PKM2 activation may protect against diabetic retinopathy. Ammaji et al., studies have suggested that PKM2 could serve as a new therapeutic target for diabetes-related complications [22]. The role of pyruvate kinase in diabetes is linked to its impact on glucose metabolism and glycolysis. PKM2 activation can influence glucose oxidation, insulin activity, and glycolytic flux, which are relevant to the pathogenesis of diabetes [23,24]. Moreover, PKM2 has been proposed as a potential biomarker for the early detection of diabetes-induced nephropathy [25]. In summary, pyruvate kinase, particularly the M2 isoform, is involved in the pathophysiology of diabetes, including its impact on glucose metabolism, diabetic retinopathy, and diabetic nephropathy. The activation of PKM2 appears to play a protective role against the progression of diabetes-related complications.

Conclusion

In conclusion, the molecular docking analysis of acacetin with glycolytic enzymes presents compelling evidence for its potential as a diabetes inhibitor. The high binding affinity observed in silico warrants further experimental validation to establish acacetin as a promising anti-diabetic agent. This brief highlights the importance of molecular docking studies in the early stages of drug discovery and sets the stage for future research aimed at harnessing the therapeutic potential of acacetin in the fight against diabetes. While molecular docking analysis provides valuable insights, challenges such as in vivo validation and clinical trials remain. Robust preclinical studies, including animal models of diabetes, are essential to validate the anti-diabetic efficacy of acacetin. Additionally, human clinical trials will be crucial to assess safety, efficacy and dosage considerations before acacetin can be considered a viable therapeutic option for diabetes management.

Conflict of Interest

The author hereby declares that there is no conflict of interest.

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