Communication

Amentoflavone: Exploring Potential Therapeutic Applications for Diabetes Mellitus

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Amentoflavone: Exploring Potential Therapeutic Applications for Diabetes Mellitus

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Abstract: Diabetes mellitus is acknowledged as a significant contributor to severe complications. The present work has explorated the potential role amentoflavone as an aldose reductase inhibitor through Docking Simulations. From these results this compound has shown excellent results with this enzyme with a high binding energy of -11 kcal/mol. If amentoflavone,a natural biflavonoid, proves effective in inhibiting aldose reductase, it could hold therapeutic promise for managing diabetic complications. However, it's crucial to emphasize that while computational studies offer valuable insights, experimental validation is essential to confirm the actual inhibitory effects and to establish the safety and efficacy of amentoflavone for this purpose. Further research and clinical studies are warranted to fully understand and harness the potential therapeutic benefits of amentoflavone in the context of diabetes.

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1. Introduction

Diabetes mellitus is recognized as a major cause of serious complications, including blindness, painful neuropathy, heart disease, and kidney failure[1,2]. One of the theories that tries to explain the mechanisms underlying these complications is linked to the stimulation of glucose metabolism through the polyol pathway. This pathway involves an enzyme present in critical tissues such as the eye (cornea, retina, lens), the kidney and the myelin sheath. Since these tissues are often involved in diabetes-related complications, it is hypothesized that the polyol pathway may contribute to the occurrence of these problems. This brief study, the focus was on examining the role of the enzyme aldose reductase through a computational approach. The investigation centered around the interaction of aldose reductase with a natural substance known as Amentoflavone. Amentoflavone is a biflavonoid, characterized by bis-apigenin coupling at 8 and 3′ positions, or 3′,8″-biapigenin. This compound is naturally found in various plants, including Ginkgo biloba[6]. The focus of this study was investigated the role of Aldose reductase because it is involved with Diabetes[5].

General speaking this enzyme facilitates the NADPH-dependent transformation of glucose into sorbitol, marking the initial stage in the polyol pathway of glucose metabolism. Consequently, the polyol pathway results in the conversion of glucose to fructose, accompanied by the proportional consumption of NADPH and the generation of NADH[7]. Under normal glucose conditions, only a small portion is routed through the polyol pathway, while the majority undergoes phosphorylation by hexokinase. The resulting glucose-6-phosphate is then used as a substrate for glycolysis or pentose phosphate metabolism. However, in the presence of chronic hyperglycemia in diabetic patients, glucose flux through the polyol pathway increases significantly, accounting for up to 33% of total glucose utilization in some tissues. Aldose reductase is thought to be responsible for diabetic complications involving multiple organs, given the elevation of glucose concentrations in diabetics. Despite the development of several aldose reductase inhibitors as potential drugs, most of them have been unsuccessful, although some, such as epalerestat, are commercially available in various countries[3–5]. Numerous aldose reductase inhibitors have been developed as potential drugs, but most have faced setbacks in clinical trials. Despite these challenges, a few, like epalerestat, have

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successfully reached commercial availability in various countries[8].The ongoing quest to understand and mitigate the impact of the polyol pathway in diabetic complications remains a focal point in diabetes research and drug development.

This study aims to explore the interaction between the anti-cancer compound Amentoflavone [9] and the enzyme Aldose Reductase using Molecular Docking simulations [10] with the Mcule Database[11]. The primary objectives include assessing the binding capacity of Amentoflavone with Aldose Reductase and identifying the specific types of bond interactions between the compound and the enzyme.Through this computational approach, the research seeks to provide insights into the molecular-level interactions, potentially shedding light on the inhibitory effects of Amentoflavone on Aldose Reductase. Understanding the nature of the binding and the involved bond interactions is crucial for unraveling the mechanisms that may contribute to the anti-cancer properties of Amentoflavone, opening avenues for further exploration and potential therapeutic applications. It's important to note that while Molecular Docking simulations offer valuable predictions, experimental validation is essential to confirm the actual binding dynamics and the potential utility of Amentoflavone in targeting Aldose Reductase for anti-cancer purposes.

2. Material and Methods

Aldose reductase target was taken by Protein Data Bank (PDB Code: 1pwm) and was prepared by Mcule Database[11], before to perform Docking analysis [10] in the Ligand Binding Site pocked of this enzyme. Binding site center Coordinates: X(17,0837),Y (-7,8034) Z(16,5386).

3. Results and Discussion

Under normal glucose conditions, a small portion of glucose follows glycolysis, while the majority undergoes phosphorylation. In diabetes, up to 33% of glucose fluxes through the polyol pathway, contributing to complications[3–5]. Aldose reductase, converting glucose to sorbitol, is pivotal, yet clinical success with inhibitors is limited. The study employed Molecular Docking[10], utilizing the Mcule Database[11], to investigate Amentoflavone's potential as an aldose reductase inhibitor in diabetes. This computational approach aimed to unveil Amentoflavone's inhibitory effects, enhancing understanding of the polyol pathway's role in diabetic complications. The primary objectives include assessing the binding capacity of Amentoflavone with Aldose Reductase and identifying the specific types of bond interactions between the compound and the enzyme. Through this computational approach, the research seeks to provide insights into the molecular-level interactions, potentially shedding light on the inhibitory effects of Amentoflavone on Aldose Reductase. Understanding the nature of the binding and the involved bond interactions is crucial for unraveling the mechanisms that may contribute to the anti-cancer properties of Amentoflavone, opening avenues for further exploration and potential therapeutic applications. The main results were shown in the below Figure 1 of the protein, highlighting the specific location of Amentoflavone.

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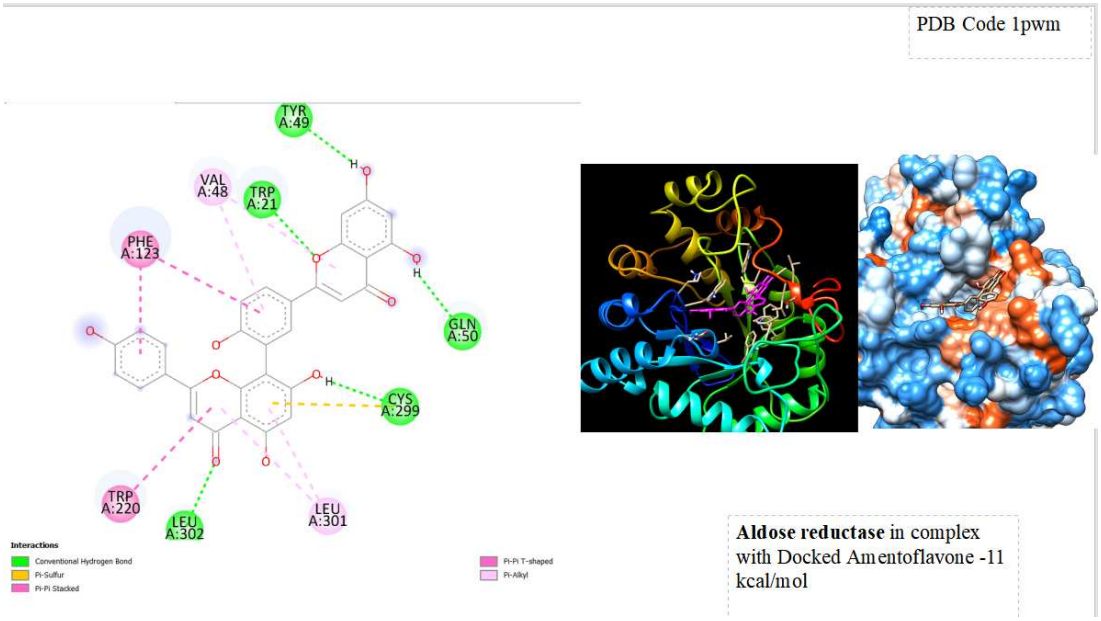

Figure 1. Displays the docking outcomes of Aldose reductase in conjunction with Amentoflavone within the Ligand Binding Site, as analyzed by Autodock Vina through the Mcule Database. On the left side, 2D diagrams illustrate the residue interactions between the protein and Amentoflavone. Meanwhile, the right side exhibits the Ligand Binding Site.

4. Conclusion

This work focused on the investigation of amentoflavone as an aldose reductase inhibitor was investigated due to the enzyme's role in the polyol pathway and its implications in diabetic complications. Amentoflavone, a natural biflavonoid, has undergone computational studies, notably Molecular Docking, revealing promising interactions with aldose reductase. These simulations predict favorable binding modes and strengths between amentoflavone and aldose reductase, suggesting potential inhibitory effects on the enzyme's activity.However, it's crucial to emphasize that while computational studies offer valuable insights, experimental validation is essential to confirm the actual inhibitory effects and to establish the safety and efficacy of amentoflavone for this purpose. Further research and clinical studies are warranted to fully understand and harness the potential therapeutic benefits of amentoflavone in the context of diabetes.

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