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Stingless Honeybee's Rare Sugar and PCSK9–LDLR Interaction–A New Hope for Hormone-Dependent Breast Cancer Patients: An In-Silico Study

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Abstract

Hypercholesterolemia is a lipid disorder characterized by elevated levels of low-density lipoprotein (LDL), commonly known as "bad" cholesterol. This condition is a significant risk factor in the development and progression of hormone-dependent breast cancer, as well as in the emergence of resistance to hormonal therapy. One of the key regulators of cholesterol metabolism is the proprotein convertase subtilisin/kexin type-9 (PCSK9) protein, which facilitates the degradation of the LDL receptor (LDLR) after binding to it. The reduction of LDL receptors leads to increased circulating LDL cholesterol levels, thereby exacerbating hypercholesterolemia. Recent studies suggest that targeting the PCSK9-LDLR interaction, often referred to as the PCSK9-LDLR axis, may provide a promising strategy for managing hypercholesterolemia while also mitigating the progression of hormone-dependent breast tumors. Small-molecule inhibitors that disrupt this interaction have emerged as potential therapeutic agents in both cardiovascular and cancer research. Notably, docking studies have now identified trehalulose, a rare and non-toxic sugar present in the honey produced by stingless honeybees, as a potential candidate for lowering LDL cholesterol levels. By enhancing LDL clearance, trehalulose could offer significant benefits to breast cancer patients globally, presenting a novel and natural approach to cholesterol management and cancer prevention.

Keywords: Hypercholesterolemia, hormone-dependent breast cancer, PCSK9, LDLR, stingless honeybee, trehalulose, bad cholesterol

INTRODUCTION

Substantial research data have proven that hypercholesterolemia is a risk factor. Hypercholesterolemia plays a key role in hormone-dependent breast cancers. Elevated levels of low-density lipoprotein cholesterol (LDL-C) and very-low-density lipoprotein cholesterol (VLDL-C) have been shown to promote breast cancer. Researchers have observed fatty crystals in tumor samples and have established a connection between cholesterol and cancer [1–9].

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PCSK9 binds to LDLR, and the complex formed therein ensures the degradation of LDLR. This reduced the LDLR levels and decreased the amount of LDL-C removed from the blood. Increased blood levels of LDL-C lead to hypercholesterolemia. Familial hypercholesterolemia is caused by mutations in PCSK9 and leads to an increase in bad cholesterol levels, causing heart attacks at a very early stage. Monoclonal antibodies were designed to inhibit PCSK9 but are very expensive for the poorest sections of society. A new strategy that focuses on the protein-protein interface between PCSK9 and LDLR and attempts to design small-

molecule inhibitors that severely affect the interaction has attracted considerable interest worldwide. Previous research has shown that Pseurotin A, a fungal metabolite, reduces LDLR from degradation. Although a step forward, it is necessary to discover simple inhibitors of the interaction between PCSK9 and LDLR [9–17].

Trehalulose is a rare sugar in the honey of stingless bees and is a ketose analog of trehalose. Its low glycemic index helps manage type-2 diabetes and helps improve the control of blood glucose levels and insulin sensitivity. It is also known that foods with a low glycemic index reduce food intake due to increased levels of leptin.

With this background of the significance of the strategy for inhibiting the binding activity of PCSK9 with LDLR, a successful attempt was made to screen for a potential inhibitor molecule, trehalulose, based on molecular docking studies focusing on the interface of PCSK9 with LDLR.

MATERIALS AND METHODS

Atomic-level interactions between the ligand molecule, trehalulose, and the PCSK9 were performed using Schrödinger's bioluminescent, BIOVIA Discovery Studio, and Desmond simulation software.

RESULTS AND DISCUSSION

Interaction of Trehalulose at the Interface of PCSK9 and LDLR

Trehalulose [$C_{21}H_{22}O_{11}$; (3*S*, 4*R*, 5*R*) - 3,4,5,6-tetrahydroxy-1-[(2*S*,3*R*,4*S*,5*S*,6*R*)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxyhexan-2-one] belongs to the glycosyl glycoside family (Figure 1) [11].

Molecular docking studies were performed using Trehalulose and the PCSK9-LDLR complex file 3gcw from the protein data bank (PDB) database [12]. The docking score was -6.725 with the molecular mechanics/generalized born surface area (MMGBSA) value computed as -43.70. The interaction of trehalulose with the mutated PCSK9 obtained from the complex file 3gcw is shown in Figure 2.

The salient features of the docking studies included the presence of five hydrogen bonding interactions of the hydroxyl group of trehalulose with the residual amino acids of PCSK9, namely, Lys 222, Asp 374, Tyr 306, Ser 305, and two H-bonds with Ser 381 from the carbonyl group. The interaction with Asp 374 was the most important. The amino Asp 374 of PCSk9 docks with His 306 of the epidermal growth factor-like repeat A (EGF-A) domain of the LDLR receptor.

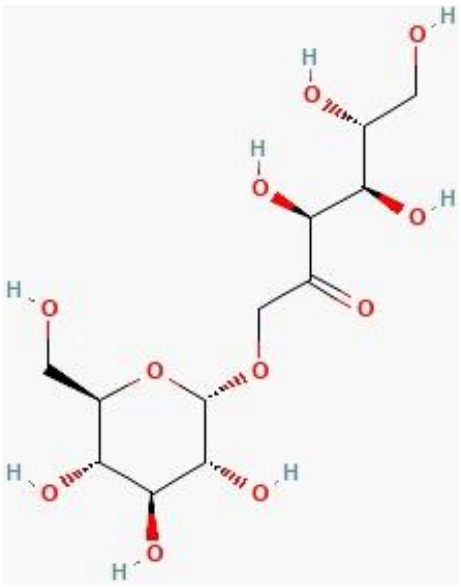

Figure 1. Chemical structure of trehalulose.

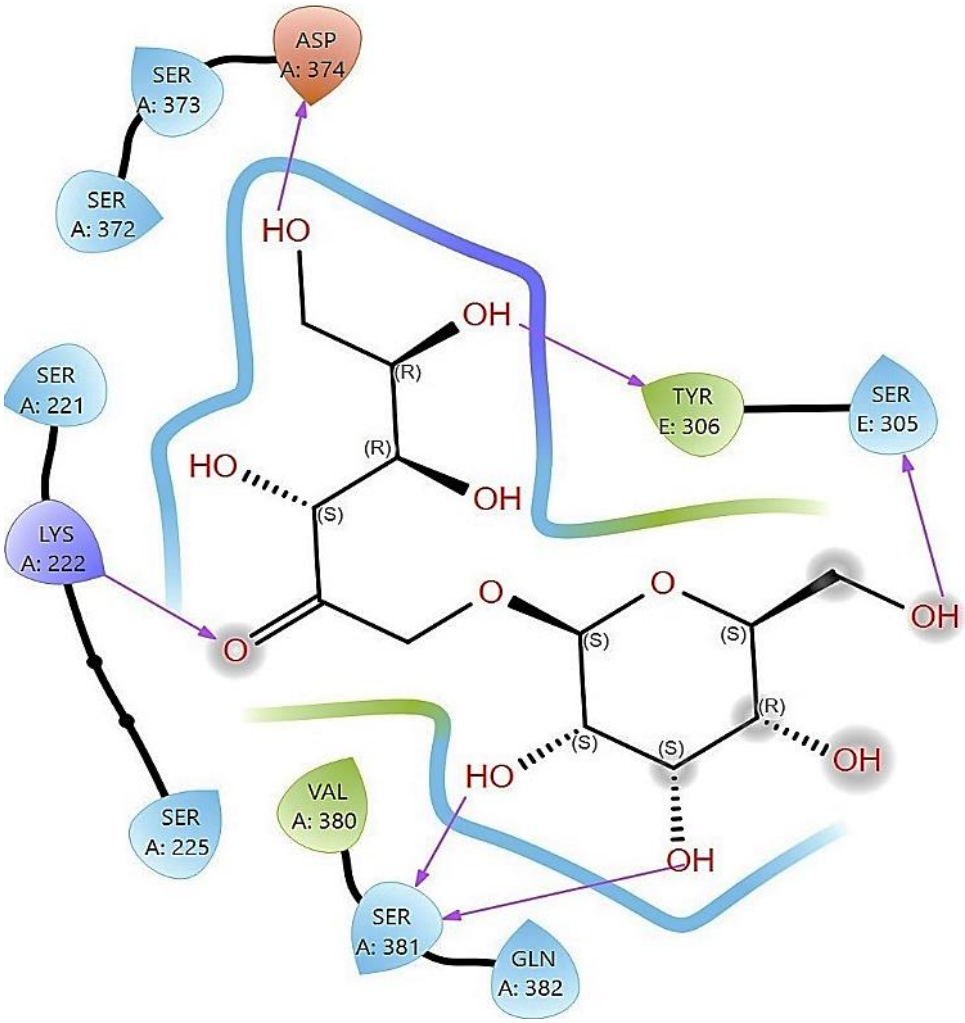

Figure 2. Docking structure of trehalulose showing the interactions with amino acid residues of PCSK9.

Mutation in LDLR, which affects the replacement of His 306 with Tyr 306, increases the affinity of PCSK9 multifold, leading to accelerated degradation of LDLR. Hence, blocking Asp 374 using small molecules is crucial [13]. Pseurotin A also achieved the same effect, although this is not shown here in Figure 2.

The bond lengths of the interactions between trehalulose and PCSK9 are shown in Figure 3. The H-bond with ASP 374 is approximately 2.26Å, and it was predicted to be stable enough to survive Molecular Dynamics simulations. Similar docking studies with PCSK9 have been conducted using a stable vitamin C glycoside from crabapples. Analysis of the results indicated the absence of any interaction with ASP 374 during the docking stage, as shown in Figure 4.

Molecular dynamics (MD) simulations were conducted on the trehalulose-PCSK9 complex to evaluate its stability over a period of 100 ns. The results indicated that the system remained stable throughout the simulation. Notably, the interaction between trehalulose and ASP 374 persisted for approximately 37% of the total simulation time, suggesting a significant and sustained interaction. An adequate number of water molecules was incorporated into the simulation to ensure an accurate assessment of the stability of the system. Interestingly, although several hydrogen bonds observed during the initial docking phase were no longer present, new hydrogen bonds were formed during the MD simulation. However, these newly formed hydrogen bonds exhibited shorter interaction durations than those identified during the docking stage.

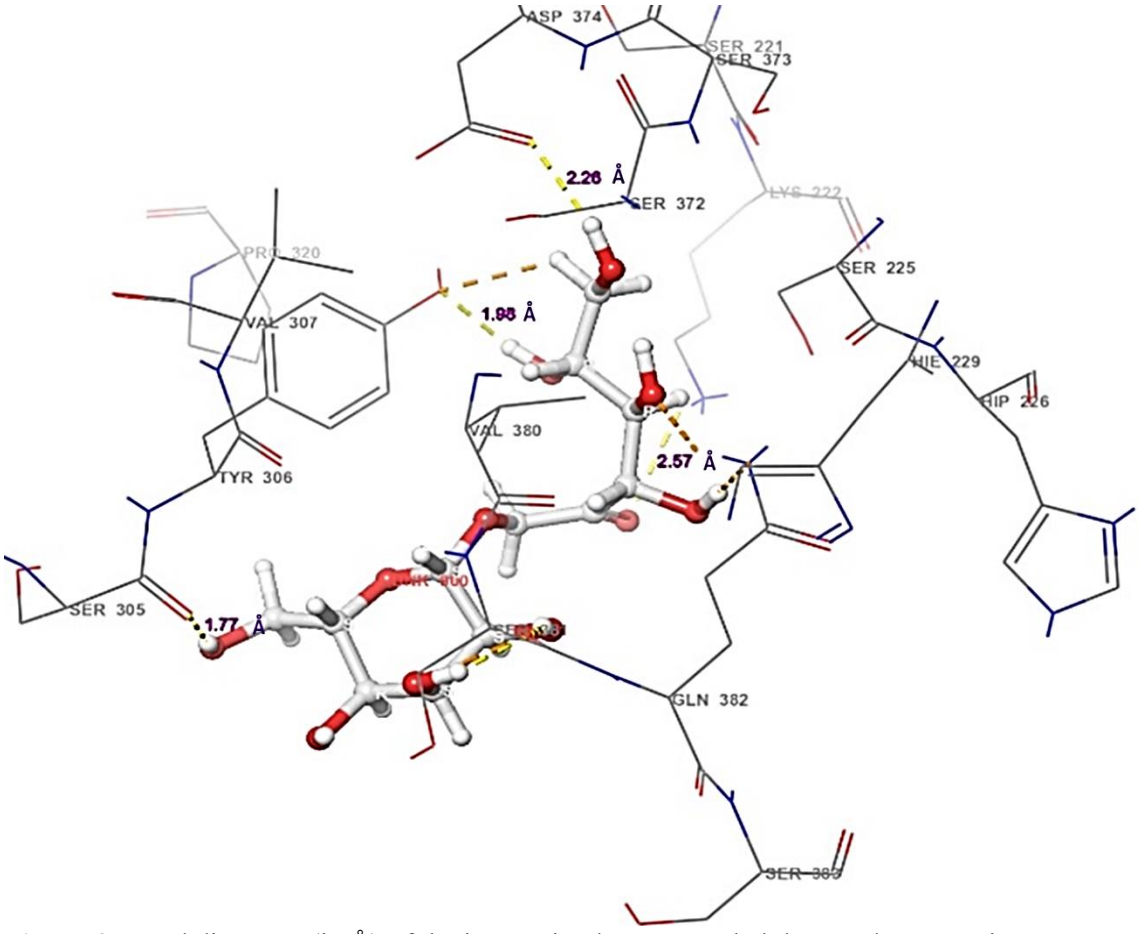

Figure 3. Bond distances (in Å) of the interaction between trehalulose and Proprotein Convertase Subtilisin/Kexin (PCSK).

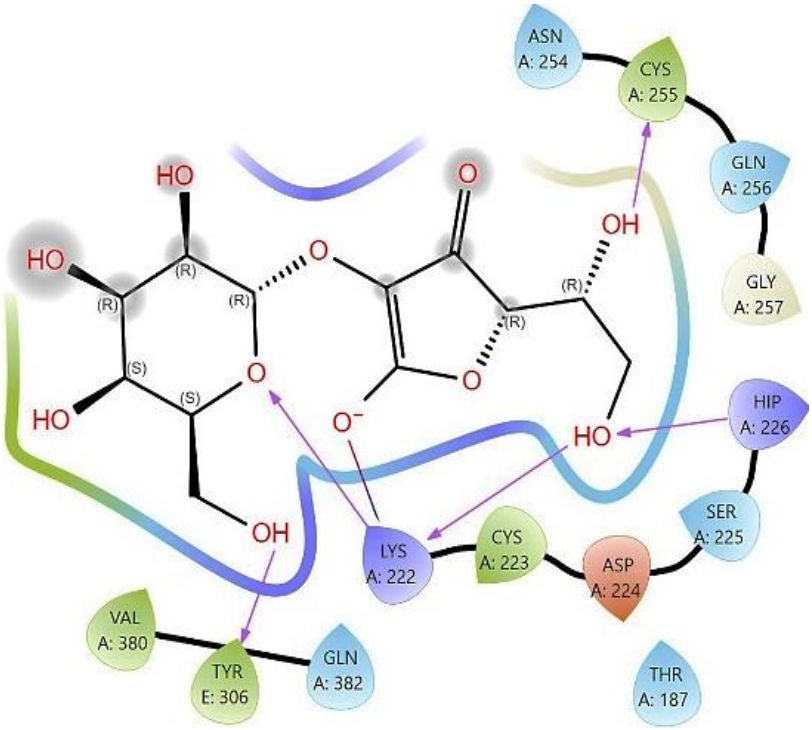

Figure 4. Docking structure of the interaction of stable vitamin C glycoside with PCSK9.

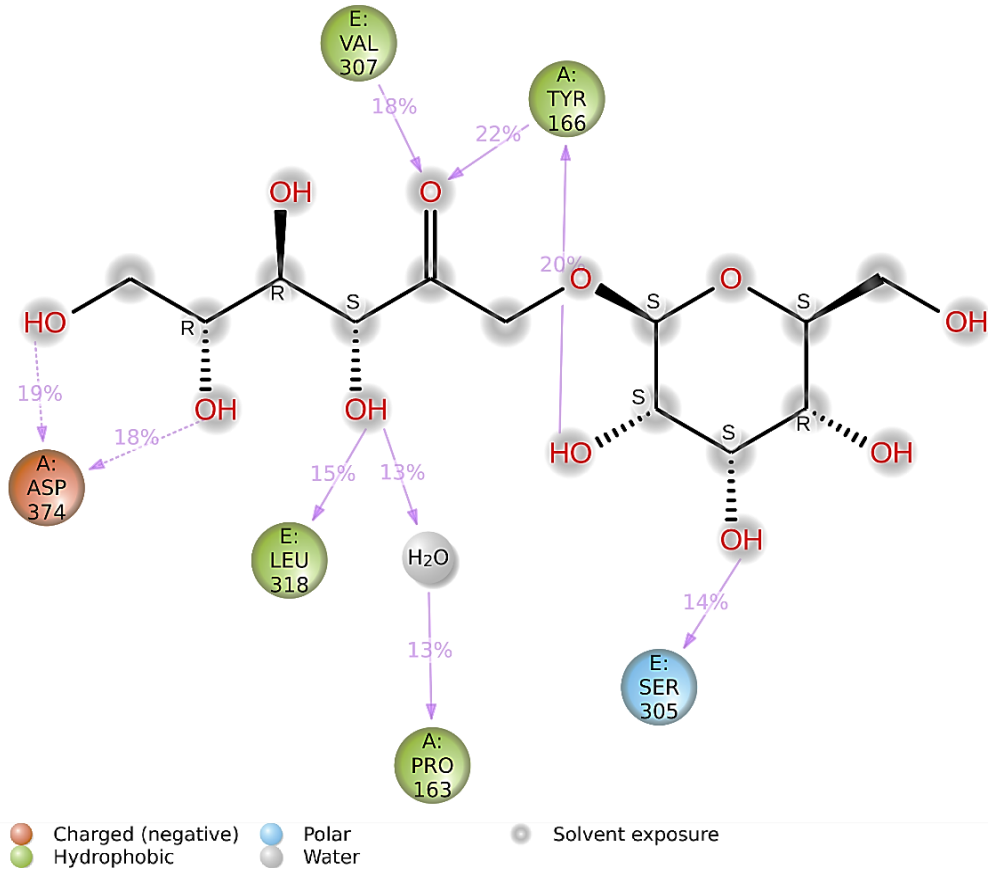

Figure 5. Molecular dynamics simulations were also performed on the trehalulose-PCSK9 complex.

Despite these fluctuations, the critical hydrogen bond with ASP 374 remained intact in a substantial portion of the simulation, reinforcing the potential significance of this interaction. Figure 5 provides a visual representation of this interaction, highlighting the stability and behavior of the Trehalulose-PCSK9 complex over time.

CONCLUSION

Inhibition of the interaction between PCSK9 and LDLR is essential to suppress the advancement of hormone-dependent breast cancers and to help treat hypercholesterolemia. For the first time, the potential of trehalulose, a non-toxic molecule produced by the stingless honeybee, has been reported to interact with PCSk9 through docking studies.

In vitro and in vivo studies on trehalulose as a therapeutic molecule are expected to result in a breakthrough towards alleviation of the suffering of breast cancer patients worldwide and help maintain a healthy heart.

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