Communication

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Polydatin in Cancer Research: Molecular Docking with UXS1 and Safety Profile Evaluation

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Abstract: Polydatin, a polyphenolic compound sourced from various natural origins, has garnered attention due to its potential anti-tumor properties and low toxicity. This research utilized Molecular Docking methods to investigate the molecular interactions between Polydatin and the Crystal Structure of Human UDP-glucuronic acid decarboxylase (UXS1), aiming to uncover the mechanisms contributing to its anti-tumor effects. The study revealed a substantial binding energy value of approximately -10 kcal/mol for the Polydatin-UXS1 interaction, indicating a robust and favorable binding. This suggests that Polydatin holds significant promise in cancer research, offering insights into its ability to interact with and potentially modulate the activity of UXS1. Moreover, the additional step of predicting toxicity properties using the pKCSM server provides valuable insights into the safety profiles of polydatin (or piceid). From these results, the parameters for polydatin: —Max. tolerated dose (human),- Oral Rat Acute Toxicity (LD50), and - Oral Rat Chronic Toxicity (LOAEL)—suggest a favorable safety profile.These findings position Polydatin as a compelling candidate for further exploration in cancer research, highlighting both its efficacy and safety considerations.

Keywords: UDP-Glucuronate Decarboxylase 1; Autodock Vina; Mcule Database; polydatin

1. Introduction

UXS1 (UDP-Glucuronate Decarboxylase 1) is a gene encodes an enzyme located in the perinuclear Golgi that facilitates the production of UDP-xylose, a crucial component in the synthesis of glycosaminoglycans (GAGs) on proteoglycans. These GAG chains become covalently attached to proteoglycans, playing a pivotal role in signaling pathways during the process of development [1,2].

UXS plays a key role in the biosynthesis of the polysaccharide xylose (Xyl), an important component of many cellular structures, including glycosaminoglycans [3]. This enzyme is part of the short-chain dehydrogenase/reductase (SDR) superfamily. The SDR superfamily is a large group of enzymes that share structural similarities and are involved in a diverse range of biological processes, including the metabolism of various compounds [4].

According studies conducted by Michelle Patricia Cicchini et al. 2023 aimed to validate UXS1 as a synthetic lethal target in UGDH-high cancers. In vitro and in vivo knockout experiments using CRISPR technology were conducted across lung carcinoma cell lines. Their findings suggested that dysregulation of metabolites occurs due to high UGDH expression when UXS1 knockout disrupts the conversion of UDP-glucuronic acid (UDP-GA) to UDP-xylose (UDP-X), leading to a synthetic lethal effect on cell growth [5]. In addition, the work published by Doshi et al., 2023 reported that UXS1 plays a crucial role in preventing the excessive accumulation of UDP-glucuronic acid (UDPGA), a product of UGDH (UDP-glucuronate dehydrogenase). Beyond simply eliminating UDPGA, UXS1 also exerts control over its production through negative feedback regulation on UGDH. The surplus UDPGA disrupts Golgi morphology and function, impeding the trafficking of surface receptors like EGFR (epidermal growth factor) to the plasma membrane and diminishing

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cellular signaling capacity. UGDH is notably upregulated in various tumors, including lung adenocarcinomas, with increased expression observed during chemoresistance. Consequently, tumor cells exhibit a selective dependence on UXS1 for detoxifying UDPGA, revealing a potential vulnerability in tumors characterized by elevated UGDH levels.

The primary objective of this communication was to investigate the potential role of Polydatin, a natural polyphenol known for its low toxicity and anti-tumor effects [7], through the application of Molecular Docking methods [8]. Molecular Docking is a computational technique used to predict the binding interactions between small molecules [9], like Polydatin, and specific target proteins, providing insights into potential therapeutic applications.

2. Material and Methods

UDP-glucuronic acid decarboxylase 1 was performed by Mcule Database [10] by Autodock Vina [11].

-UDP-glucuronic acid decarboxylase was taked by Protein Data Bank (PDB Code: 2b69,UXS1_HUMAN); Grid box Coordinates of Binding site center X(50,6115), Y(20,838) Z(23,3764).

3. Results and Discussion

Two recent studies, one led by Michelle Patricia Cicchini et al. in 2023 [5] and another by Doshi et al. in 2023 [6], focused on validating UXS1 as a synthetic lethal target in UGDH-high cancers. The studies conducted in vitro and in vivo knockout experiments using CRISPR technology in lung carcinoma cell lines. The findings indicated that dysregulation of metabolites results from high UGDH expression when UXS1 knockout disrupts the conversion of UDP-glucuronic acid (UDP-GA) to UDP-xylose (UDP-X), leading to a synthetic lethal effect on cell growth [5]. Additionally, the work by Doshi et al. highlighted UXS1's crucial role in preventing the excessive accumulation of UDP-glucuronic acid (UDPGA), a UGDH product. UXS1 not only eliminates UDPGA but also regulates its production through negative feedback on UGDH. The surplus UDPGA disrupts Golgi morphology and function, impacting surface receptor trafficking and reducing cellular signaling in tumors with elevated UGDH levels [6].

This communication aimed to explore the potential of Polydatin [7], a natural polyphenol recognized for low toxicity and anti-tumor effects, through Molecular Docking methods. Molecular Docking, a computational technique [8,9], helps predict the binding interactions between Polydatin and specific target proteins, offering insights into potential therapeutic applications.

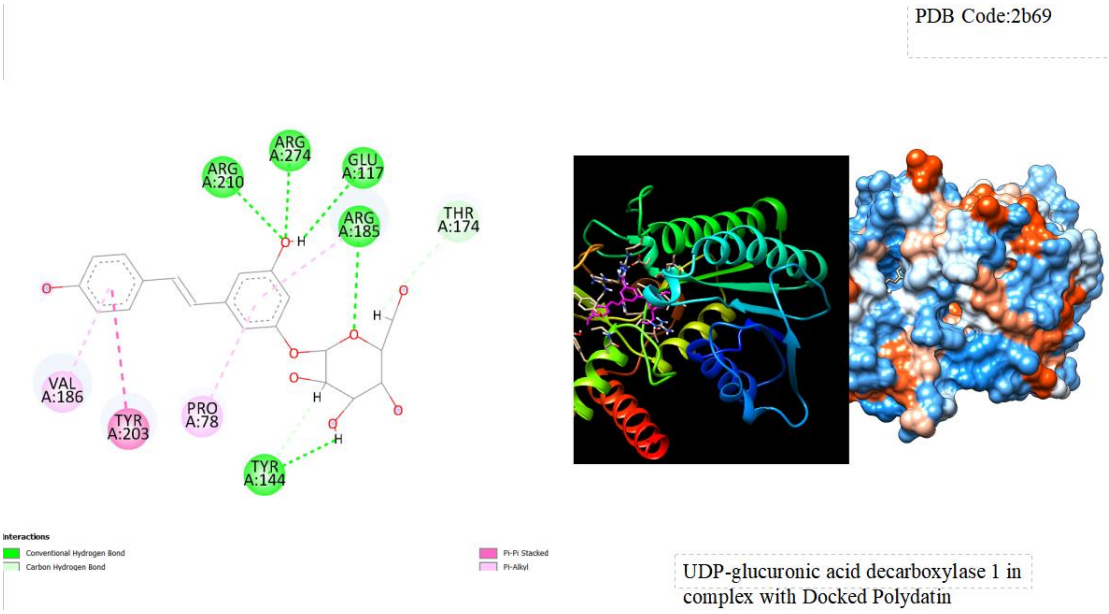

Figure 1. displays the docking outcomes of Crystal Structure of Human UDP-glucoronic acid decarboxylase in conjunction with Polydatin within the Ligand Binding Site, as analyzed by

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Autodock Vina through the Mcule Database. On the left side, 2D diagrams illustrate the residue interactions between the protein and Polydatin. Meanwhile, the right side exhibits the Ligand Binding Site of the protein, highlighting the specific location of Polydatin.

Table 1. shows the comparison of predicted toxicity parameters with Polydatin through pKCSM Server.

Compounds	AMES toxicity	Max. tolerated dose(human) (logmg/kg/day)	hERG I inhibitor	hERG II inhibitor	Oral Rat Acute Toxicity (LD50) (mol/kg)	Oral Rat Chronic Toxicity (LOAEL) (log mg/kg_bw/day)	Hepatotoxicity
Polydatin	no	0.569	no	no	2.516	4.473	no

4. Conclusion

Polydatin, a polyphenolic compound derived from diverse natural sources, has attracted interest due to its promising anti-tumor properties coupled with minimal toxicity. In this study utilizing Molecular Docking methods, we sought to unravel the molecular interactions between Polydatin and the Crystal Structure of Human UDP-glucuronic acid decarboxylase (UXS1), shedding light on the mechanisms contributing to its anti-tumor effects. The study revealed a notable binding energy value of approximately -10 kcal/mol between Polydatin and the target UXS1, indicating a strong and favorable binding interaction. This finding suggests that Polydatin holds significant potential in the realm of cancer research, offering insights into its ability to interact with and potentially modulate the activity of UXS1. The study's emphasis on molecular docking provides a computational perspective on the favorable binding between Polydatin and UXS1, supporting its consideration as a candidate for further exploration in cancer therapeutic strategies.

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