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Research Article

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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 also 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 results as 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, integrative therapies highlighting both its efficacy and safety considerations.

Keywords: UDP-Glucuronate Decarboxylase 1, Autodock Vina, Mcule Database, Polydatin, Cancer Therapies.

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 cellular signaling capacity. UGDH is notably upregulated in various tumors, including glioblastoma, 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 (also known as Piceid), a natural polyphenol known for its low toxicity and anti-tumor effects [7]. Additionally, Polydatin exhibits anti-inflammatory effects by inhibiting the production of inflammatory mediators and reducing oxidative stress [8,9]. These properties make it a promising candidate for the management of various inflammatory conditions [8,9].

The short communication focused on the potential role of Polydatin in cancer research using the Molecular Docking method. Molecular Docking is a powerful computational technique used in the field of molecular modeling and drug discovery [10-13].

By employing Molecular Docking, researchers can predict the preferred orientation and conformation of a molecule (such as Polydatin/piceid) when bound to a receptor involved in cancer pathways[10]. This allows for the exploration of potential interactions between Polydatian and target proteins associated with cancer, providing insights into its therapeutic potential in cancer treatments and related inflammations

2. Material and Methods

UDP-glucuronic acid decarboxylase 1 was performed by Mcule Database by Autodock Vina [10.11].

-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

The research uncovered a significant Binding energy of around -10 kcal/mol between Polydatin and the UXS1 target, demonstrating a robust and advantageous binding interaction. This discovery implies that Polydatin has promising prospects in cancer research, providing valuable insights into its capacity to interact with and potentially regulate the activity of UXS.

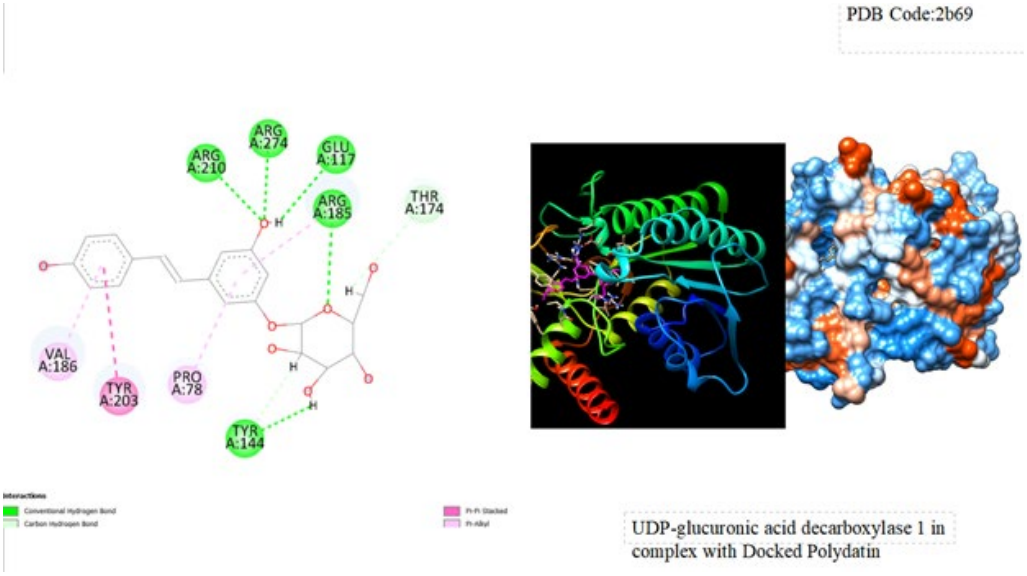

Figure 1: Displays the docking outcomes of Crystal Structure of Human UDP-glucoronic acid decarboxylase in conjunction with Polydatin -10 kcal/mol within the Ligand Binding Site, as analyzed by Autodock Vina through the Mcule Database. On the left side, 2D diagrams illustrate the residue interactions between the protein and Polydatin. Meanwhile, the right side exhibits the Ligand Binding Site of the protein, highlighting the specific location of Polydatin.

Compounds	AMES toxicity	Max. tolerated dose(human) (logmg/kg/day)	hERG I inhibitor	hERG I 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

Table 1: Shows the Comparison of Predicted Toxicity Parameters with Polydatin Through pKCSM Server

4. 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 (UDP-Glucuronate Decarboxylase-1), 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].

The novelty of this study aimed to investigate the potential of Polydatin, a natural polyphenol known for its low toxicity and anti-tumor effects [7], as well as its anti-inflammatory properties [8,9], through the utilization of Molecular Docking methods : Molecular docking (MD) is a computational method employed in drug research and molecular biology to anticipate the optimal arrangement of one molecule concerning another when they're connected to create a stable complex[10-13].

In this study, molecular docking (MD) simulations analyzed using Autodock Vina via the Mcule Database [12] were employed to forecast the binding interactions between Polydatin and UDP-Glucuronate Decarboxylase-1 (UXS), providing insights into potential therapeutic applications. The docking results (refer to Fig. 1) revealed an outstanding binding energy score of approximately -10 kcal/mol for Polydatin with the UXS target, indicating its potential role in cancer research. Furthermore, we assessed the toxicity parameters of this natural compound using the pKCSM Server [13].

Literature reviews corroborate that Polydatin exhibits lower toxicity compared to other natural compounds or drugs [14]. As depicted in Table 1, Polydatin exhibited excellent biological properties, including a high maximum tolerated dose (human) of 0.569 log mg/kg/day and low toxicity properties with theoretical Oral Rat Acute Toxicity (LD50) of 2.516 (mol/kg) and theoretical Oral Rat Chronic Toxicity (LOAEL) of 4.473 log mg/kg_bw/day.

5. 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 researchs, 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 with related inflammations, integrative therapeutic strategies

Limitations

There is not a limitation of the study

Funding

No funding was received for this research.

Conflict of Interest

No conflict of interest

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