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D-ALLOSE: A RARE SUGAR TO SWEETEN CANCER CELLS

D-ALOSA: UN AZÚCAR POCO FRECUENTE PARA ENDULZAR A LAS CÉLULAS CANCEROSAS

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ABSTRACT

D-Allose is considered a rare sugar with potential to regulate glucose metabolism. In this review of the literature, scientific evidence is presented to support the role of D-Allose as an antiproliferative inhibitor of a variety of cancers by principally up-regulating the Thioredoxin-Interacting Protein. Due to the multiple chemical and enzymatic ways to produce D-Allose and its safety; this low-calorie sugar could be proposed as an ingredient for functional foods for cancer under chemotherapy treatment.

Keywords: D-allose, D-glucose, metabolism, anti-cancer agent, reactive oxygen species

RESUMEN

D-Alosa es considerado un azúcar poco frecuente en la naturaleza, con un potencial para regular el metabolismo de la glucosa. En esta revisión de la literatura, se presenta evidencia científica para sostener el papel de D-Alosa como un inhibidor de tipo antiproliferativo de una variedad de cánceres, principalmente por su efecto sobre la expresión de la proteína que interactúa con la tioredoxina. Considerando las múltiples formas químicas y enzimáticas de producir D-Alosa y su seguridad; este azúcar de baja caloría, podría ser propuesto como un ingrediente en alimentos funcionales, para pacientes con cáncer bajo tratamiento quimioterapéutico.

Palabras clave: D-alose, D-glucosa, metabolismo, anticancerígeno, especies de oxígeno reactivas

INTRODUCTION

Cancer is a worldwide disease that estimated 19.3 million new cancer cases in 2020 and is expected to be 28.4 million cases in 2040 (Sung et al., 2021). Cancer cells develop molecular strategies to keep growing and adapting to several conditions, such as nutrient deprivation and low oxygen conditions (Zhang et al., 2022). One of the major cancer cell adaptations is the rewiring metabolic network to increase glucose absorption needed for pyruvate and lactate production in an anaerobic microenvironment for cell growth (Hönigova et al., 2022). For that reason, many scientific research groups have dedicated their efforts to discover treatments to target this adaptive metabolic strategy of cancer cells.

Rare sugars are defined as mono- and disaccharides that are rarely found in nature. Recently, a lot of attention has been dedicated to this type of sugars since they have shown beneficial effects for glycemic control and weight loss (Ahmed et al., 2022). Among them, D-allose has been shown to have antioxidant properties (Ishihara et al., 2011) and to regulate glucose metabolism (Pratt et al., 1994). In addition, experiments have been performed to study the effect of D-Allose on cancer. Here, a mini-review of the literature about the D-Allose effect on cancer cells is presented.

D-Allose

D-Allose was discovered present in the leaves of African shrub *Protea rubropilosa* as a 6-O-cinnamyl glycoside (Perold et al., 1973). Later, its presence has been detected in *Veronica filiformis* (Chari et al., 1981), Mentzelia (Jensen et al., 1981) and the leaves of *Solanum tuberosum* (Weckwerth et al., 2004). More recently, D-Allose has been isolated from the seagrass *Halodule pinifolia* (Ragupathi Raja Kannan et al., 2012) and the leaves of the Euphorbiaceae *Acalypha hispida* (Sithara et al., 2017). Interestingly, D-Allose has also been detected in human umbilical cord blood (Hashimoto et al., 2013) but no physiological functions of this sugar in the fetal development have been studied yet.

D-Allose has a molecular weight of 180.16 g/mol with a 128°C melting point and a $C_6H_{12}O_6$ molecular formula (Figure 1A). This rare aldohexose has a high solubility in water and is insoluble in alcohol.

Chemical and enzymatic methods have been developed to increase the production of D-Allose. According to the Izumori strategy, the inexpensive D-fructose can be modified to D-allulose by epimerization, and then converted to D-Allose using ketose 3-epimerase (EC 5.1.3.31) (Izumori, 2006). Currently, several bacterial enzymes have been identified for D-Allose production, such as L-rhamnose isomerase (EC 5.3.1.14), D-ribose-5-phosphate isomerase (EC 5.3.1.6), D-galactose-6-phosphate isomerase (EC 5.3.1.26) and glucose-6-phosphate isomerase (EC 5.3.1.9) as reviewed in Chen et al. (2018).

Absorption and metabolism of D-Allose

Enterocytes absorb mono-carbohydrates via the sugar transporters SGLT-1 and GLUT-5. In a recent study, the mechanism of D-Allose intestinal absorption was evaluated (Kishida et al., 2021). Adult male rats were orally administered with D-Allose with or without the SGLT-1 inhibitor, KGA-2727 after a 16 h fasting period.

The SGLT-1 inhibitor prevented oral D-Allose from being absorbed into the plasma while increasing GLUT-5 expression with a high-fructose diet did not promote D-Allose absorption. Thus, D-Allose intestinal absorption is mostly regulated by SGLT-1 cotransporter (Kishida et al., 2021).

After 24 h of oral administration of D-Allose (8 g/kg body weight), the presence of this rare sugar is found in urine and stools (91 % and 3 %, respectively) in rats (Iga & Matsuo, 2010). Also, this study showed that there was a sharp decrease of D-Allose in the gastric content 1 to 3 h after its ingestion. Then, absorbed D-allose in blood is rapidly excreted in the urine (Iga & Matsuo, 2010).

D-allose as anti-cancer agent

Cancer cells rewire their metabolic pathways to support their growth through the process of glycolysis, despite the lower ATP obtained compared to mitochondrial oxidative catabolism. In order to achieve the required amounts of ATP, cancer cells increase the uptake of glucose by changing the expression of glucose transporters (Szablewski, 2022).

As aforementioned, D-Allose is absorbed via SGLT-1 but not GLUT-5 (Kishida et al., 2021). Since there is strong evidence that several cancers over-express SGLT-1 (Köpsell, 2017), it could be inferred that cancer cells could avidly uptake absorbed D-Allose. Therefore, D-Allose within cancer cells could regulate their metabolic pathways possibly leading to inhibition of growth.

Thus, D-Allose could be considered a tumor inhibitor molecule. In line with this notion, experiments have been performed to demonstrate the anticancer effect of D-Allose. By using the MTT assay to measure proliferation and several cell lines, it was shown that D-Allose inhibited the growth of human hepatocellular carcinoma HuH-7 and HepG2 cells, human ovarian cancer cells OVCAR3, and human cervical carcinoma HeLa cells in a dose-dependent manner (Sui et al., 2005). Hoshikawa et al. (2010), also demonstrated this *in vitro* growth inhibitory effect of D-Allose on oral squamous cell carcinoma cell lines (Ca9–22, HSC-3, HSC-4, SAS, and KON). Notably, D-Allose significantly reduced the tumor growth of the squamous cell carcinoma cell line HSC-3 in a xenograft assay in athymic nude mice (Hoshikawa et al., 2010). Mechanistically, it has been suggested that D-Allose up-regulates Thioredoxin-Interacting Protein (TXNIP) (Yamaguchi et al., 2008; Hoshikawa et al., 2010; Indo et al., 2014; Noguchi et al., 2016; Tohi et al., 2022) that represses the transcription of the glucose transporter GLUT-1 and therefore promotes its protein downregulation (Noguchi et al., 2016).

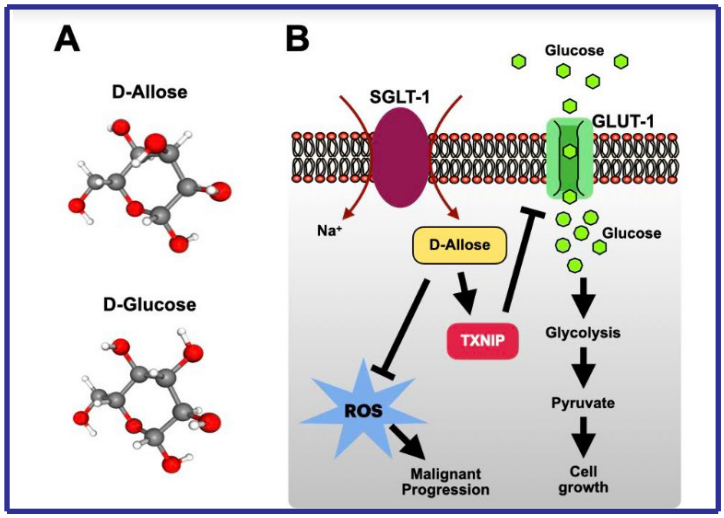
Since GLUT-1 is over-expressed and predominant in several tumor types (Pliszka & Szablewski, 2021), it is relevant to search for molecules that could decrease its expression in cancer cells. Noteworthy, TXNIP is frequently underexpressed in most cancers (Jia et al., 2019) and regulates energy metabolism (Alhawiti et al., 2017).

In addition to regulating glucose metabolism in cancer cells, D-Allose may offer other anticancer properties. Naha et al. (2008), demonstrated that D-Allose promoted

mitochondria-dependent apoptosis of hormone-refractory prostate cancer cell lines in a dose - and time - dependent manner without affecting normal prostatic epithelial cells (Naha et al., 2008). Several studies have also proposed that D-Allose can enhance the effects of chemotherapeutic drugs on cancer cells. Thus, 50 mM D-Allose (but no D-Psicose) and 0.5 µg/mL 5-fluorouracil co-treatment synergistically reduced the cell viability of the hepatocellular carcinoma cell line HuH-7 (Yamaguchi et al., 2008). In another study, D-Allose improved the *in vitro* cytotoxic effect and *in vivo* tumor growth inhibition of docetaxel on the tongue carcinoma HSC3 cell line (Indo et al., 2014). Another well-known metabolic disturbance in cancer is the increased production and accumulation of reactive oxygen species (ROS) (Figure 1B). ROS in cancer cells can induce gene mutations and activate pro-oncogenic signaling causing the promotion of carcinogenesis and malignant progression (Luo et al., 2022). Interestingly, it has been demonstrated that D-Allose can preclude mitochondrial ROS production stimulated by D-glucose in neuroblastoma cells. In addition, D-Allose inhibited the ATP production triggered by D-glucose. Thus, D-Allose could also reduce intracellular ROS production (Ishihara et al., 2011).

FIGURE 1

D-Allose as an anticancer molecule



(A) Comparison of D-Allose and D-Glucose structures. Chemical structural 3D models of both hexoses were obtained from PubChem website (Kim et al., 2021). Gray, red and white spheres represent carbon, oxygen and hydrogen molecules, respectively. (B) Proposed model of D-Allose effect on cancer cells. D-Allose may enter cancer cells via the sodium-glucose cotransporter-1 (SGLT-1) causing the up-regulation of Thioredoxin-Interacting Protein (TXNIP). In turn, TXNIP blocks glucose absorption via the down-regulation of the glucose transporter-1 (GLUT-1). Additionally, D-Allose may decrease reactive oxygen species (ROS) production, reducing the positive effect of ROS on promoting malignant progression.

D-allose in foods

The toxicity of D-Allose has been previously tested (Iga et al., 2010). An acute toxicity assay determined the D-Allose LD_{50} as 20.5 g/Kg by oral administration to rats. In addition, this study showed that 6-month sub-chronic administration of D-Allose up to 3 % in rodent food caused no major differences in serum and hematological markers compared to the control group (Iga et al., 2010). Therefore, D-Allose is considered a non-toxic monosaccharide with a great potential to be included in the functional food industry due to its ultra-low caloric value (Mooradian et al., 2017). Nevertheless, appropriate clinical trials are still required to guarantee the safety of foods containing D-Allose.

CONCLUSION

- Many studies have proven that D-Allose can interfere with cancer metabolism and tumor growth. Thus, this rare sugar has the potential to be used as a cotreatment with well-defined anticancer drugs and could be used to elaborate functional foods directed to cancer patients.

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