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## Authors' Affiliation:

<sup>1</sup>The Nicolaus Copernicus Municipal Polyclinical Hospital in Olsztyn, ul. Niepodległości 44, 10-045 Olsztyn, Poland

<sup>2</sup>Provincial Complex Hospital named after Jędrzej Śniadecki in Białystok, ul. M. Curie-Skłodowskiej 26, 15-950 Białystok, Poland

<sup>3</sup>University Clinical Hospital in Białystok, ul. M. Curie-Skłodowskiej 26, 15-276 Białystok, Poland

## \*Corresponding author:

Aleksandra Rusak-Sobolewska,  
The Nicolaus Copernicus Municipal Polyclinical Hospital in Olsztyn,  
ul. Niepodległości 44, 10-045 Olsztyn, Poland,  
ORCID: 0009-0006-7366-3368  
E-mail: [olarusak008@gmail.com](mailto:olarusak008@gmail.com)

## ORCID List:

|                             |                     |
|-----------------------------|---------------------|
| Aleksandra Rusak-Sobolewska | 0009-0006-7366-3368 |
| Gabriela Krych              | 0009-0005-6873-5358 |
| Joanna Oklińska             | 0009-0001-5779-0539 |
| Michał Skóra                | 0009-0001-5137-9490 |
| Klaudia Jadczyk             | 0000-0002-2214-8319 |
| Bartłomiej Kazimierski      | 0009-0007-4480-5440 |
| Weronika Gniado             | 0009-0002-5676-3456 |
| Dawid Mądry                 | 0009-0003-5948-4548 |

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# D-Allulose, a promising sweetener in the fight against type 2 diabetes - review of recent studies

**Aleksandra Rusak-Sobolewska<sup>1\*</sup>, Gabriela Krych<sup>2</sup>, Joanna Oklińska<sup>2</sup>, Michał Skóra<sup>2</sup>, Klaudia Jadczyk<sup>3</sup>, Bartłomiej Kazimierski<sup>2</sup>, Weronika Gniado<sup>2</sup>, Dawid Mądry<sup>2</sup>**

## ABSTRACT

Diabetes is a common disease associated with high levels of glucose in the body due to poor insulin function or secretion, and it has significant health implications worldwide. Diabetes can be managed through the use of drugs, insulin, and dietary modifications to achieve normoglycemia. D-Allulose is a low-calorie sugar substitute that is showing promise. The current research work discusses the characteristics, metabolism, and effects of D-Allulose on the metabolism of sugars. D-Allulose possesses an impressive ability to induce hypoglycemic action. It has been proven to lower postprandial glucose in patients with diabetes and improve glycemic state for long periods. Moreover, D-Allulose may potentially reduce tissue insulin resistance and decrease the progression of diabetic nephropathy. The ways D-Allulose affects the body are associated with competition of D-Allulose and glucose for their intestinal transporters, inhibition of intestinal enzymes and hormones activation. From a safety standpoint, D-Allulose does not demonstrate adverse events. Despite current technological problems in the production process, further development of bacterial epimerase technology suggests that large-scale production of D-Allulose can become possible in the near future.

**Keywords:** diabetes mellitus, d-allulose, glycemia, dpsicode

## 1. INTRODUCTION

Diabetes is a metabolic disorder characterized by an impairment in insulin action or secretion, resulting in chronic hyperglycemia, which is an elevated level of glucose in the bloodstream (Deshpande et al., 2008). The disease can cause very serious complications involving the functioning of different organs such as the heart, kidney, blood vessels, eyes, and nerves (Tomic et al., 2022). In an epidemiological context, diabetes is one of the greatest problems that current medicine faces today. Research utilizing serial glucose tolerance tests indicates that the annual prevalence of diabetes among European populations is approximately 7 cases per 1,000 individuals each year. Additionally, according to worldwide statistics, there is a disturbing pattern showing that the number of people with diabetes will grow from 382 million people or 8.3% of adults in 2013 to 592 million people or 10.1% by 2035 (Forouhi et al., 2014). To combat this growing health crisis, one key management

strategy for diabetes is to maintain normoglycemia—normal blood glucose levels—through a combination of pharmacological interventions, such as diabetes medications and insulin therapy, as well as dietary modifications, particularly reducing consumption of high-sugar products (Melmer and Laimer, 2016). One of the molecules that has attracted interest as a possible replacement for sugar is D-Allulose or D-Psicose. This molecule is increasingly considered as a possible sugar replacement due to the presence of several beneficial characteristics. In contrast to other carbohydrates, this monosaccharide is low in calories and does not have any influence on glucose concentration considerably; thus, it might be useful for diabetics (Matsuo et al., 2002). Due to the specific properties of D-Allulose, it can have an effect on sugar metabolism which, in turn, can provide some health benefits to people with diabetes. The objective of this paper is to conduct a review of the recent studies regarding the effect of D-Allulose on sugar metabolism.

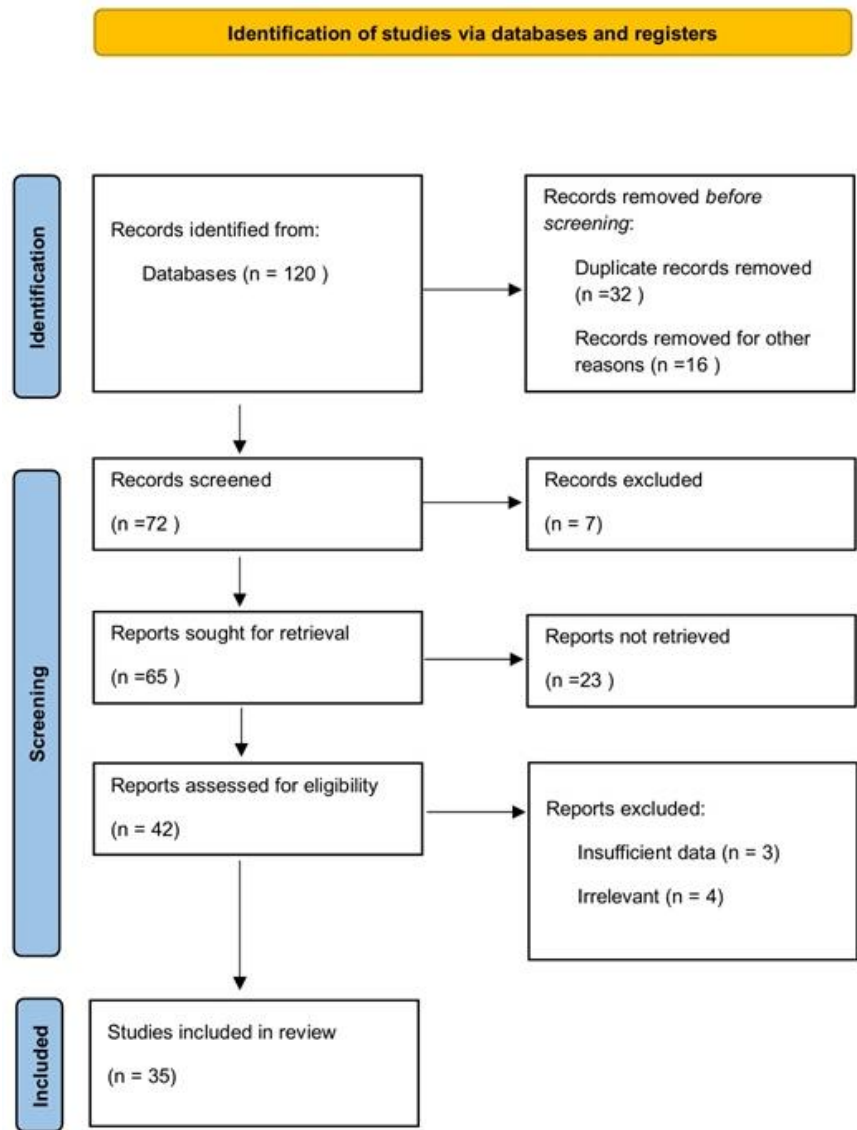


Figure 1. PRISMA CONSORT chart

## 2. REVIEW METHODS

This research was done through an extensive literature review of available scientific literature from several credible databases like PubMed, Mendeley, Google Scholar, and WHO guidelines. Some of the most important search terms used during the literature review include "D-Allulose," "Diabetes," "D-psicose," "D-Allulose Safety," and "D-Allulose Characteristics." Only those articles written in English and available online were considered for this literature review, and the emphasis has been on post-2024 studies to have an up-to-date understanding of the latest clinically relevant research. Older literature was also taken into consideration for historical reasons

and to give basic knowledge about the topic. This paper will be written by following the PRISMA guidelines for literature reviews (Figure 1). Through this paper, we aim to highlight the potential implications and applications of D-Allulose in diabetes management and its effects on metabolic processes.

### 3. RESULTS AND DISCUSSION

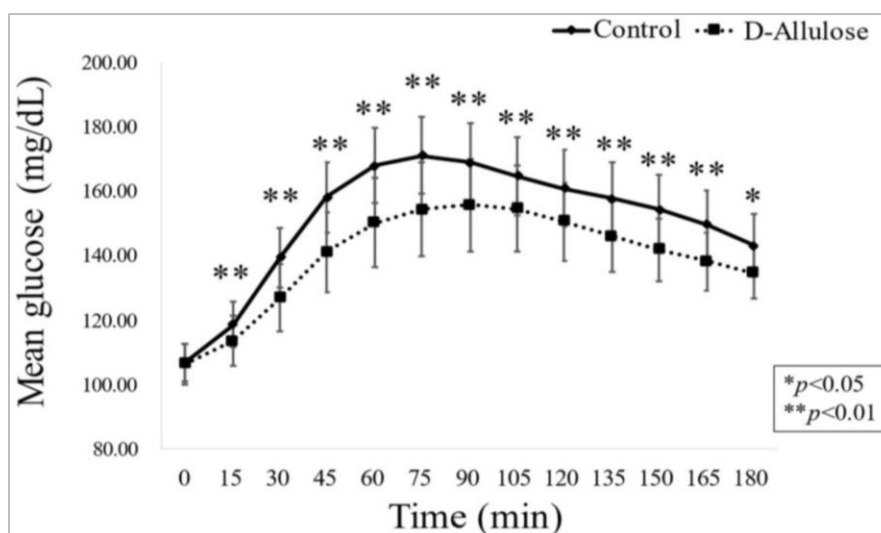
#### Characteristics of D-Allulose and its metabolism

The D-allulose sugar is also referred to as D-Psicose sugar and has a distinct property of being a rare six-carbon sugar that is an epimer at position C3 of the fructose (Chan et al., 2012). This sugar has a characteristic of being crystalline in nature and is white in color and odorless (Wang et al., 2022). One of the most significant attributes of D-allulose is its almost negligible caloric content; it boasts an energy value of just 0.2 kilocalories per gram—only 5% of the caloric value found in sucrose (table sugar)—while still delivering approximately 70% of the sweetness of sugar (Chung et al., 2012). D-allulose is absorbed efficiently from the gastrointestinal tract into the bloodstream following ingestion. Surprisingly, almost all of this sugar (approximately 99%) gets excreted through the kidney function, implying that the sugar does not go through much metabolism inside the body, making it ideal for use as a low-calorie sweetener (Tsukamoto et al., 2014).

D-allulose is present in many traditional foods; however, in very small quantities and does not have any effect on diet (Oshima et al., 2006). This limitation has led researchers to explore the use of bacterial epimerases—enzymes that can convert D-fructose into D-allulose—as a viable pathway for the industrial production of D-allulose. Such advancements could facilitate the creation of D-allulose on a large scale, making it more accessible and affordable for consumers and manufacturers alike (Tan et al., 2023).

#### Hypoglycemic effect of D-Allulose

A prospective, randomized, single-blind clinical trial was conducted to investigate the effects of D-allulose on postprandial glucose levels in patients diagnosed with diabetes mellitus type In this study, participants consumed 8.5 grams of D-allulose per meal. Compared to the control group, volunteers in the study group who consumed meals rich in D-allulose exhibited lower postprandial blood glucose concentrations. (Figure 2). More precisely, the average difference in the peaks of the postprandial blood sugar concentrations (in mg/dl) for the studied subjects versus those of the control group was 18 mg/dl lower, and the p value was lower than 0.001, meaning that the effect is highly significant (Fukunaga et al., 2023). This rather impressive hypoglycemic effect remained stable for all meals taken by the subjects throughout the experiment, which speaks in favor on D-allulose's possible use in the nutrition of diabetic patients. In general, research of D-allulose can provide information not only about its metabolism but also about its useful application.



**Figure 2.** Mean glucose level curves for all meals during the intake period of each diabetic diet group.

There has been a meta-analysis undertaken by Yuma et al., in 2023 who used eight random controlled trials in establishing the impact of D-Allulose in glycemic management. The study established a statistically significant decline in blood glucose after the intake

of 5g and 10g of D-Allulose together with food. In addition, there was another detailed study carried out for 8 weeks, which targeted overweight and obese subjects as well as diabetic individuals. The study indicated the improvement in glycemic control through decrease in key markers compared to base line measures. There were decreases in HbA1C of  $-0.20 \pm 0.47$  (p-Value 0.041) and HOMA-IR of  $-0.87 \pm 1.57$  (p-Value 0.009). Apart from this, other studies showed that the obesity parameters improved among the participants. The recorded changes included a decrease in body weight of  $-0.77 \pm 1.36$  (p-value 0.008), a reduction in Body Mass Index (BMI) of  $-0.29 \pm 0.52$  (p-value 0.009), and a reduction in waist circumference by  $-1.31 \pm 2.04$  cm (p-Value 0.003). Notably, the researchers pointed out that the amount of calories and nutritional content in the diet of participants did not change throughout the research, making sure that the changes noted in weight and obesity parameters could be attributed directly to the supplementation of D-Allulose only and not to any changes in the diet (Tak et al., 2023).

Researchers suppose that the noted decrease in body weight and parameters associated with obesity could possibly act synergically with the hypoglycemic effects of D-Allulose and thus assist in preventing or managing diabetes mellitus (Boles et al., 2017). Moreover, D-Allulose has been examined in the participants suffering from Type 2 Diabetes Mellitus (T2DM) during the fasting month of Ramadan. In the retrospective trial conducted by Salimah Japar et al., the participants took 8.5 g of D-Allulose daily for five days, just before their evening Iftar meal. The results of the study showed a significant suppressive effect on glucose spikes after meal consumption compared to the five-day control period (Japar et al., 2022). This indicates that the hypoglycemic properties of D-Allulose can be applicable for other demographics than Asian one as was proved earlier.

### **D-Allulose reduces tissue insulin resistance**

Insulin resistance is otherwise known as an impaired response of the body's tissues to insulin (Kahn et al., 2014). As a result, it leads to hyperglycemia, hyperlipidemia, obesity and hypertension (Guo et al., 2014). Chronic consumption of high-calorie sugars, among other things, can lead to its development. In animal tests, it has been shown that a diet containing D-Allulose can improve tissue sensitivity to insulin (Natsume et al., 2021; Gou et al., 2021). The ability of D-allulose to enhance IFN- $\gamma$  signaling and alleviate macrophage dysfunction is suspected to be related to the reduction of tissue insulin resistance (Bae et al., 2023). It is known that macrophages play a key role in obesity-induced inflammation, and the production of insulin resistance, which are key factors responsible for the occurrence of t.2 diabetes (Li et al., 2022). Another mechanism with a proven effect that promotes the production of insulin resistance, which is also affected by D-Allulose, is the impairment of mitochondrial function manifested by reduced energy expenditure and impaired oxidative phosphorylation (Højlund et al., 2008; Krako et al., 2021). Studies prove that with the use of Allulose in patients, the normal process of mitochondrial energy expenditure and mitochondrial translation is restored (Bae et al., 2023).

### **D-Allulose slows the development of diabetic nephropathy**

Apart from effects on insulin resistance, D-Allulose has shown promise in slowing the progression of diabetic nephropathy, a serious kidney complication arising from diabetes. A pivotal study conducted by Niibo et al., (2022) used diabetic animal models to evaluate the nephroprotective effects of D-Allulose. In this study, diabetic rats ingested an aqueous solution containing 3% D-Allulose. Histological examinations of their kidneys revealed a significant reduction in the proliferation of mesangial cells—an indicator of diabetic nephropathy—when compared to the control group that did not receive D-Allulose. In the group receiving this therapy, there were reduced inflammatory markers with IL-6 levels being reduced by 19.2% and TNF- $\alpha$  levels being reduced by 34%. This effect of reducing inflammation indicates that D-Allulose not only helps improve glycemic control but is also protective against renal dysfunction due to the anti-inflammatory properties.

### **Mechanisms of action**

While the exact mechanisms by which D-Allulose lowers glycemia are still being studied, several hypotheses have emerged. A crucial aspect of its function appears to involve competition with glucose at the GLUT2 transporter in the intestinal epithelial cells (Hishiike et al., 2013). Such competitive inhibition could result in a decrease in glucose uptake, which will eventually bring down the postprandial blood glucose concentration. Similarly, there is also competitive inhibition of fructose by the GLUT5 transporter (Kishida et al., 2019). Moreover, D-allulose inhibits intestinal  $\alpha$ -glucosidase—an important enzyme in sugar digestion—by suppressing the response in animal models (Matsuo et al., 2009).

Studies demonstrate that oral intake of D-allulose promotes the secretion of glucagon-like peptide-1 (GLP-1). This hormone plays an important role in metabolism and appetite regulation. This increase in GLP-1 secretion is significantly greater than that observed

with oral glucose consumption (Hayakawa et al., 2018). The stimulatory effect of D-Allulose on GLP-1 secretion resembles the administration of GLP-1 analogs, which are used therapeutically to reduce appetite and improve glycemic control (Iwasaki et al., 2018). Additionally, recent findings have shown that D-Allulose inhibits the phosphorylation of insulin receptor substrate tyrosine (IRS)-1 and reduces the expression of the GLUT4 glucose transporter in muscle tissue, leading to stabilization of glycemic parameters. In conclusion, The above discussions reveal that the wide-ranging impacts of D-Allulose do not only limit to the fact that it is a calorie sugar but also in terms of improving insulin sensitivity and delaying the onset of diabetic complications, amongst other factors (Lee et al., 2022).

Safety of administration

Several studies have shown that D-allulose is safe for human consumption. For example, a well-designed double-blind clinical trial assessed the impact of one-time dose of 25 g of D-allulose and concluded that there were no side effects observed on the part of the subjects (Teyssseire et al., 2023). The metabolic pathway of D-allulose shows that the substance is mainly excreted in the urine; more precisely, 99% of the consumed substance is eliminated by the body. A little accumulation of the substance in the liver was detected; however, this is minimal, and after taking D-allulose continuously for seven days, only 1% of the initial dose remained in the body. Importantly, D-allulose, similar to fructose, does not cross the blood-brain barrier and, therefore, cannot accumulate in the brain (Tsukamoto et al., 2014). Furthermore, there have been no findings regarding teratogenic effects through research conducted on animals (Sa et al., 2022). A randomized, double-blind study lasting a total of 48 weeks was conducted, in which volunteers received 5 g and 15 g of D-allulose. No clinically significant adverse effects were observed compared to the control group. Comprehensive evaluations of the physical health of subjects, as well as various renal parameters— including blood urea nitrogen, creatinine levels, uric acid concentrations, urine specific gravity, urinary microalbumin, and urinary pH—remained within normal ranges. Additionally, the participants demonstrated positive changes in biliary enzymes such as alkaline phosphatase (ALP) and gamma-glutamyl transferase (GGTP), along with liver enzymes, including aspartate aminotransferase (AST) and alanine aminotransferase (ALT) (Tanaka et al., 2020).

Influence on gut microbiota

The development of type 2 diabetes is associated with a decreased abundance of probiotic bacteria that produce sodium butyrate. The latter is well-known for its role in enhancing the intestinal wall permeability and regulating appetite and lipid metabolism; it can also boost the work of the immune system. As studies show, sodium butyrate increased cellular sensitivity to insulin by modulating pancreatic beta cells through the mechanism of FFAR2/3 activation and the GLP-1 signaling pathway. In 2025, there appeared a scientific publication about the effect of consumption of d-allulose on the abundance of probiotic bacteria in the intestines (Adolphus et al., 2025). The production was studied in vitro and in vivo. The investigation enrolled a total of 12 volunteers—half with type 2 diabetes and half with normoglycemia. It was estimated that, with a daily intake of 5–20 g, approximately 80% of this sugar is metabolized in the upper gastrointestinal tract, while the remaining 20% undergoes direct metabolism in the intestine.

In the course of taking a daily dose of d-allulose, an increased number of bacteria belonging to the genus Anaerostipes hadrus and unknown species of the family Lachnospiraceae was noted within 48 hours, along with increased levels of sodium butyrate within 6-24 hours in both healthy and diabetic individuals. Regarding fermentative processes in the distal gastrointestinal tract, d-allulose decreased local pH and increased the production of gases and short-chain fatty acids (SCFAs). In contrast, it did not affect levels of branched-chain fatty acids (BCFAs), lactic acid, or valeric acid. According to existing information, the aforementioned research is pioneering in nature, hence the need for further validation and replication of its findings. The key findings are summarized in Table 1. However, the findings are optimistic and indicate an advantageous impact on metabolic health among healthy subjects and those diagnosed with diabetes. Considering its low calorie content, high intake of the sugar does not pose a risk of obesity in cases where the patients are obese.

Table 1. Summary of key findings

| Aspect           | Key findings                                                                                |
|------------------|---------------------------------------------------------------------------------------------|
| Characteristics  | D-allulose is a rare sugar with only 0.2 kcal/g and about 70% of the sweetness of sucrose.  |
| Metabolism       | Rapidly absorbed, but ~99% is excreted in urine, resulting in minimal metabolism.           |
| Glycemic control | Significantly reduces postprandial blood glucose and improves long-term glycemic control (↓ |

|                               |                                                                                                                                                                                   |
|-------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                               | HbA1c).                                                                                                                                                                           |
| <b>Insulin resistance</b>     | Improves <b>insulin sensitivity</b> by reducing inflammation and restoring mitochondrial function.                                                                                |
| <b>Body weight</b>            | Promotes modest reductions in <b>body weight, BMI, and waist circumference</b> without dietary changes.                                                                           |
| <b>Diabetic complications</b> | May <b>slow the progression of diabetic nephropathy</b> through anti-inflammatory effects.                                                                                        |
| <b>Mechanisms of action</b>   | Inhibits intestinal glucose absorption (GLUT2/GLUT5), suppresses $\alpha$ -glucosidase, and increases <b>GLP-1 secretion</b> .                                                    |
| <b>Safety</b>                 | Well tolerated in clinical studies, with <b>no significant adverse effects</b> during short- and long-term use.                                                                   |
| <b>Gut microbiota</b>         | May increase <b>butyrate-producing bacteria</b> and short-chain fatty acid production, supporting metabolic health.                                                               |
| <b>Overall conclusion</b>     | D-allulose is a <b>safe, low-calorie sweetener</b> with promising benefits for <b>glycemic control, insulin sensitivity, weight management, and diabetes prevention/support</b> . |

#### 4. CONCLUSION

Changes in the way people live around the world, including more sedentary lifestyles and changes in eating habits, have made life difficult for today's medicine. The major problem facing modern medicine is the growing incidence of type 2 diabetes mellitus (T2DM), which now affects millions worldwide. The rising prevalence of this chronic condition not only poses serious health risks, such as cardiovascular disease and neuropathy, but it also incurs substantial social and economic costs. Therefore, it is imperative to explore innovative strategies that can effectively combat T2DM, mitigate its ever-increasing complications, and ultimately reduce the burden on healthcare systems. Out of numerous possible treatment options, one may name D-allulose as a promising alternative because of its special characteristics. As one of the rare sugars, this sugar substitute can decrease postprandial levels of glucose, which might be useful for patients with T2DM. Also, D-allulose helps with weight loss and improves various in different metabolic parameters related to obesity. Such unique characteristics of the substance suggest its potential for being a functional sweetener, which will match the requirements of patients with diabetes and also help with additional benefits in their treatment. Nowadays, research shows that D-allulose does not have any serious negative effects on the health of the patient when it is used in recommended amounts.

The main obstacle with using this substance is that currently, the industry cannot produce D-allulose in the amounts that are needed for further inclusion in food products. Such problem deprives many people at risk of developing diabetes or people suffering from it from using D-allulose. However, there are very high hopes for the future in this aspect. Advances in our understanding of bacterial D-pep classes (DPEases), combined with innovative molecular engineering techniques and alternative production methods, suggest that efficient and cost-effective production could be within reach. If successful, these developments could lead to greater availability of D-allulose. Not only would this make it easier for people to include this drug in their diets, but it would also serve as an important tool for people who have been having problems with managing their diabetes and other metabolic conditions.

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#### Authors' Contributions

Conceptualization, supervision, and project administration: Aleksandra Rusak-Sobolewska, Gabriela Krych, Joanna Oklińska

Methodology: Michał Skóra, Klaudia Jadczyk

Software, validation, formal analysis, investigation, resources, writing original draft preparation: Weronika Gniado, Bartłomiej Kazimierski, Dawid Mądry.

Writing review, editing, and visualization: Aleksandra Rusak-Sobolewska, Gabriela Krych.

All authors have read and agreed with the published version of the manuscript.

#### Informed consent

Not applicable.

**Ethical approval**

Not applicable. This article does not contain any studies with human participants or animals performed by any of the authors.

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**Conflict of interest**

The authors declare that they have no conflicts of interest, competing financial interests or personal relationships that could have influenced the work reported in this paper.

**Data and materials availability**

All data associated with this study will be available based on the reasonable request to corresponding author.

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