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Teratogenicity of D-allulose

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ABSTRACT

The objective of this study was to evaluate whether D-allulose has teratogenic effects on rats. A prenatal developmental toxicity test was conducted in SD rats in compliance with modified OECD guidelines test number 414, prenatal developmental toxicity study. Pregnant female rats received repeated doses of 1250, 2500, or 5000 mg/kg body weight D-allulose, or a vehicle control by gavage on GD 6–15. On GD 20, one day prior to the expected day of delivery, pregnant rats were weighed and anesthetized, and laparotomized to remove the uterine and its content were weighed. Fetuses were examined macroscopically for any soft tissue and skeletal changes. The evaluation indicators included general sign observation, body weight, food consumption, animal death, corpora lutea, numbers of embryonic or fetal deaths, and viable fetuses including live birth rate, fetal resorption rate, and stillbirth rate, as well as sex, body weights, and skeletal and soft tissue alterations of fetuses. No treatment-related abnormalities were observed in prenatal developmental toxicity and fetal malformation parameters, indicating that D-allulose had no teratogenic effects on pregnant rats and fetuses. From the findings of this prenatal developmental toxicity study, the NOAEL of D-allulose was estimated to be 5000 mg/kg/day in pregnant SD rats.

1. Introduction

Rare sugars are defined as monosaccharides and their derivatives that exist in nature but only in limited quantities. D-allulose (also known as D-psicose or D-ribo-2-hexulose), a natural rare sugar found in natural and commercial sources, is an epimer of D-fructose at the C-3 position [10,12,13,4]. It originated from processed cane and beet molasses. D-allulose can be found naturally in wheat, *Itea* plants, processed cane, and beet molasses as well as in fruit juice, seasoning sauces, and other food stuffs. It can be also found in commercial carbohydrate or agricultural products at an extremely low level [13]. The level of D-allulose found in foods varies from 0.5 mg/100 g (coffee) to 130.6 mg/100 g (Worcester sauce).

D-allulose can be produced chemically or via microbial fermentation. Chemical methods include the use of molybdate ion catalyst with D-fructose, synthesis from 1,2,4,5-di-*o*-isopropylidene-*β*-D-fructopyranose, and the boiling of ethanol and triethylamine with D-allulose. However, these chemical methods are insufficient for large-scale production. A biological method consisting of D-tagatose 3-spimerase and D-fructose can be used to improve the mass production of D-allulose [4,5]. Additionally, D-allulose can be produced by a heat treatment of the fructose in the high-sugar food products [13,17].

D-allulose can be used ideally as a sugar substitute for sucrose. It has 70% of the sweetness of sucrose, high solubility, clean taste, smooth texture, desirable mouthfeel, no calories, and low glycemic response. It can improve the gelling characteristics and flavor. Additionally, it can improve the foaming properties of the egg white proteins and the quality of butter cookies [5,13].

The safety of D-allulose has been proven through an acute toxicity, 90-day subchronic toxicity, and a chronic toxicity study as well as mutagenicity and genotoxicity studies in rats [2]. According to the previous study [2], D-allulose produced from *Microbacterium folirum* did not cause any important compound-related toxicities, resulting in 5000 mg/kg body weight (bw)/day no-observed-adverse-effect level (NOAEL). Although one generation reproduction toxicity study indicated that D-allulose did not exert reproductive toxicity [8], no teratogenicity study data are available up to date. This study is the first to present the prenatal developmental toxicity or teratogenicity of D-allulose in Sprague-Dawley (SD) rats.

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2. Materials and methods

2.1. Materials

D-allulose (purity, >98%; Lot No.SPS180716) was provided by Samyang Corporation, Republic of Korea. It was manufactured from an aqueous solution of fructose via enzymatic epimerization using *M. foliorum* SYG27B–MF, a non–GMO strain [2].

2.2. Animals

SD rats (100 females, 60 males) and rat production feed were provided by Jie Si Jie Laboratory Animal Co. Ltd (Shanghai, China). Rats were housed at room temperature (22.5–24.5 °C) and at a relative humidity of 53.2–62.8%. The animals were quarantined for 8 days, and the health status was observed and recorded daily. After the quarantine period, male and female rats were housed together at a ratio of 1:1 for the longest 5 days. The day that vaginal plug or sperm in the vagina was found was indicated as gestation day 0 (GD0). The rats observed with vaginal plug or sperm were randomly assigned to each group (20 females/group), weighed, and numbered. Pregnant rats were kept in individual cages to ensure sufficient reproduction feed and drinking water. The animals were allowed to have free access to solid diets and sterilized drinking water. All rat maintenance and experimental procedures were approved by the Institutional Animal Care and Use Committee of Ningbo entry-exit inspection and quarantine bureau technical center of the People's Republic of China(Approval no. 2009001), and proceeded in compliance with the National food safety standards teratogenicity test of People's Republic of China (GB 15193.14–2015), which refers to the Economic Co-operation and Development (OECD) guidelines 414, prenatal developmental toxicity study, adopted at 2001 [15].

2.3. Study design and parameters evaluated

Rats received either 1250, 2500, 5000 mg/kg body weight (bw) D-allulose, or the vehicle (distilled water) on gestation days 6–15 through intragastric administration. The test samples were prepared by dissolving 62.5, 125 and 250 g samples, respectively in 500 mL sterile water. Rats received test samples by gavage once a day with the volume of 10 mL per kg body weight to the final doses of 1250, 2500, and 5000 mg/kg bw, respectively.

The animals were observed at least once daily during the exposure period to record any clinical effects including mortality, moribundity, behavioral changes. The animals were weighed once daily at every 3 days during the gestational period from GD0 to GD18.

On the GD 20, one day prior to the expected day of delivery, the pregnant rats were weighed and anesthetized, and laparotomized to remove the uteri. At the time of termination or death during the study, the dams were examined macroscopically for any structural abnormalities. Evaluation of the dams during caesarean section and subsequent fetal analyses were conducted preferably without knowledge of treatment group in order to minimize bias.

Developmental endpoints evaluated were corpora lutea number, implantation number, number and percent of live and dead fetuses, and fetal resorption rate. For live fetuses, parameters evaluated were as followings: sex ratio, body weight, body length, tail length, malformation rates on external, visceral, and skeletal alterations. Live fetuses were divided into two groups according to odd and even numbers. The even numbered fetuses were fixed with Bouin's solution to check the visceral development situation while the odd numbered fetuses were fixed with 95% ethanol to examine the skeleton after hyalinizing and dyeing [6].

2.4. Statistical analysis

All data are given as mean ± standard deviation. Non-parametric data were tested via Kruskal-Wallis analysis of variance (ANOVA) followed by a Mann-Whitney U test where appropriate, while a one-way ANOVA was used to test parametric data. When significant differences were detected, a multiple comparisons test was performed based on the Dunnett method. Incidence data, including clinical signs and histopathologic findings, were compared by via Fisher's exact probability test. Statistical significance was indicated as $p < 0.05$ (*).

3. Results

3.1. Maternal toxicity

Among 20 rats observed with vaginal plug or sperm for each group, pregnancies were confirmed to 17, 20, 17, and 18 rats for the vehicle control, 1250, 2500, and 5000 mg/kg bw dose group, respectively. The rats, which were found pseudopregnant, were excluded from the evaluation of prenatal developmental toxicity (3, 3, 2 for the vehicle control, 2500, and 5000 mg/kg bw dose group, respectively). Therefore, these rats with pregnancy confirmed became the dams for evaluating prenatal developmental toxicity of D-allulose administration. No animal death was found during the test period. No significant differences in body weight were reported among the groups at each gestational day (GD0, GD6, GD9, GD12, GD15, GD18, and GD20, Table 1). In addition, no treatment-related abnormalities were observed in clinical signs such as mortality, moribundity, and behavioral changes.'.

3.2. Embryo-fetal toxicity

No statistically significant differences among the three D-allulose administration groups and the vehicle control group were observed for various embryo toxicity indicators including corpus luteum number and implantation number (Table 2). Concerning on the fetal development parameters, there were no significant differences in live fetuses number, fetal body length, fetal tail length, and body weight among the D-allulose administration groups and the vehicle control group. Number of live fetuses was 249, 306, 266, and 248 for the vehicle control, 1250, 2500, and 5000 mg/kg bw dose groups, respectively. In addition, both the absorbed fetuses number and the fetal resorption rate were not significantly different among the these four groups.

3.3. Fetal malformations or alterations

No external alterations were observed with the all live fetuses for the 4 groups (data not shown). In detail, encephalocele, hydrocephalus, or exencephalia of fetal head was not observed, and no exophthalmos or tongue thrust was found for the vehicle and the D-allulose administration groups.

Regarding on trunk or limb anomalies, these four groups did not demonstrate any umbilical hernia, limb flexion abnormality, dactylion, or ectrodactyly. In addition, no visceral malformations were observed for the vehicle and the D-allulose administration groups.

Table 1
Body weights of pregnant rats for prenatal development toxicity study.

Gestational day	D-allulose administration Dose (mg/kg body weight)			
	0 (N = 17)	1250 (N = 20)	2500 (N = 17)	5000 (N = 18)
0	282.5 ± 23.3	286.0 ± 17.4	274.8 ± 20.8	279.4 ± 18.2
6	333.1 ± 28.6	329.0 ± 22.3	317.6 ± 24.7	321.9 ± 18.6
9	338.5 ± 26.6	338.4 ± 22.9	332.7 ± 24.9	331.0 ± 22.8
12	358.6 ± 29.7	354.7 ± 23.5	352.5 ± 24.6	346.6 ± 23.2
15	379.9 ± 33.4	372.2 ± 21.3	376.6 ± 29.0	367.8 ± 24.5
18	419.0 ± 35.4	419.3 ± 28.0	428.8 ± 36.2	407.5 ± 26.9
20	450.6 ± 46.3	459.7 ± 29.4	462.5 ± 34.3	441.4 ± 34.7

No statistically significant differences were noted among the groups when analyzed by the Anova or Dunnett test.

Table 2
Effects of D-allulose administration on embryo or fetal development[a].

Examination indicators (per litter unless noted otherwise)	D-allulose administration Dose (mg/kg body weight)			
	0	1250	2500	5000
Number of corpora lutea	15.1 ± 2.1	15.7 ± 2.0	15.9 ± 2.2	14.1 ± 2.7
Number of implantations	14.8 ± 2.7	15.4 ± 1.9	15.7 ± 2.1	14.1 ± 2.6
Live fetuses				
Number of live fetuses	14.6 ± 2.7	15.3 ± 2.0	15.6 ± 2.1	13.8 ± 2.7
Body length (mm)	36.0 ± 2.1	36.1 ± 1.6	35.9 ± 1.8	36.0 ± 1.9
Tail length (mm)	11.5 ± 1.0	11.5 ± 1.0	11.4 ± 1.0	11.4 ± 1.0
Body weight (g)	4.3 ± 0.5	4.4 ± 0.4	4.3 ± 0.4	4.4 ± 0.4
Sex ratio (female:male)	0.89	1.01	1.09	1.10
Resorbed fetuses				
Total number of corpora lutea	257	314	270	253
Total number of litters	4	1	1	3
Total number of resorbed fetuses	5	1	1	5
Fetal resorption rate (%)[b)]	2.0	0.3	0.4	2.0

No statistically significant differences were noted among the groups when analyzed by the Anova or Dunnett method.

[a] Examination indicators were enumerated on 17, 20, 17, and 18 dams with pregnancy confirmed for 0, 1250, 2500, and 5000 mg/kg body weight group, respectively.

[b]) Fetal resorption rate was calculated through dividing the total number of resorbed fetuses by the total number of corpora lutea.

Approximately one-half of each litter was examined for skeletal alterations, in that 120, 150, 129, and 120 fetuses from 17, 20, 17, and 18 litters of the vehicle control, 1250, 2500, and 5000 mg/kg bw dose groups, respectively. Skull osteolysis, interparietal bone imperfect, interparietal bone deficiency, occipital bone imperfect, and occipital bone deficiency were examined for skull alteration. In addition, oligodactyly was checked for phalanges malformation. Ribs were examined for incidence of wavy rib, shortened rib, rib fracture, rib absence, and extra rib. Sternum deficiency and sternum fusion were also examined. Except two cases of sternum deficiency in 2 litters each from the 2500 and 5000 mg/kg dose groups and 1 case sternum deficiency in 1 litter from the vehicle control group, no other skeletal alterations were found among the live fetuses from the 4 groups (Table 3). Since the sternum deficiency was also found in the control group and is considered a relatively common spontaneous observation, the sternum deficiencies in the D-allulose administration groups were not included as a skeleton malfunction in principle.

4. Discussion

This study demonstrated that D-allulose at daily doses up to 5000 mg/kg bw did not exhibit teratogenic effects in pregnant SD rats. No adverse effects including body weight gains or animal death were observed. No significant changes were noted in fetal embryo development such as appearance, visceral, and skeletal malformations. Results from this study support the previous findings [8] that D-allulose did not exert reproductive toxicity. In a one-generation reproductive toxicity study which was conducted in compliance with OECD Test Guideline 415 [16], no D-allulose treatment-related abnormalities were observed in precoital time, copulation index, fertility index (male), or pregnancy index (male) between groups [8]. Relative to the vehicle control, there was also no effect of D-allulose treatment on pregnancy rates, implantation, pregnancy length, gender ratios, viability indexes, lactation indexes, prenatal death rates, the number of live young at time of birth, organ weights and indexes and necropsy or histopathological examination parameters. In the F1 offspring, the body weights of pups born to

Table 3
Effects of D-allulose administration on fetal skeletal alterations[a].

Examination Indicators	Dose Groups (mg/kg bw)			
	0	1250	2500	5000
Skull				
Skull osteolysis	0/0[b)]	0/0	0/0	0/0
Interparietal bone imperfect	0/0	0/0	0/0	0/0
Interparietal bone deficiency	0/0	0/0	0/0	0/0
Occipital bone imperfect	0/0	0/0	0/0	0/0
Occipital bone deficiency	0/0	0/0	0/0	0/0
Sternum				
Sternum deficiency	1/1	0/0	2/2	2/2
Sternum fusion	0/0	0/0	0/0	0/0
Rib				
Wavy rib	0/0	0/0	0/0	0/0
Shortened rib	0/0	0/0	0/0	0/0
Rib fracture	0/0	0/0	0/0	0/0
Absence of rib	0/0	0/0	0/0	0/0
Extra rib	0/0	0/0	0/0	0/0
Phalanges				
Oligodactyly	0/0	0/0	0/0	0/0

No statistically significant differences were noted among the groups when analyzed by the Anova or Dunnett test.

[a] Skeletal alterations were examined on 120, 150, 129, and 120 fetuses from 17, 20, 17, and 18 litters of the vehicle control, 1250, 2500, and 5000 mg/kg bw dose groups, respectively.

[b]) Number of fetuses with the alteration /number of litters with the alteration.

parents administered D-allulose (500, 1000, and 2000 mg/kg bw) were slightly higher on days 1–9 postnatally relative to controls ($P < 0.05$), however after day 9 these effects were no longer evident. Thus, the NOAEL was placed at 2000 mg/kg for parent animals and their offspring.

No adverse effects of D-allulose observed in the reproductive toxicity study [8] are considered partially due to the fact that D-allulose is rapidly excreted into urine in both humans and rats [9,20]. With intravenous administration, approximately 98% was excreted into the urine via the bloodstream without significant changes within 6–7 h in rats [21]. In a mass balance study with eight healthy adult males receiving a single dose of 15 g allulose and 776 nCi of ^{14}C(U)-allulose (in an aqueous solution) after a light breakfast, allulose was recovered in plasma at 80.3% of total radioactivity, and the peak plasma concentration occurred within 1 h of administration [19]. Within 48 h, majority of the radiotracer was eliminated via urine and feces, and the urine was the major route of elimination (81.47%). This study confirmed the findings by Matsuo et al. [9], which reported that the estimated intestinal absorption was 66.2–80% in humans receiving 0.35 g D-allulose/kg bw and that the absorbed D-allulose was not metabolized into energy. Erythritol, whose metabolic pathway and energy value are similar to those of D-allulose, also did not show any reproductive toxicity or teratogenicity [14]. Erythritol is rapidly absorbed and excreted into urine. No treatment-related abnormalities in reproductive performance or fertility of the parents and development of the offspring were reported with erythritol doses up to 10% (or 16 g/kg bw/day) in diet, up to 8 g/kg bw/day administered by gavage, and up to 3 g/kg bw/day by intravenous injection [14]. Teratology studies demonstrated that erythritol doses of up to 10% in diet had no reproductive, embryotoxic, fetotoxic, or teratogenic effects [14]. Both D-allulose and erythritol have an energy value of approximately 0.2 kcal/g. The LD_{50} values of the two compounds are comparable; 15.8–16.3 g/kg for D-allulose and 15.3 g/kg for erythritol [11,23]. An oral embryotoxicity and teratogenicity study of another monosaccharide D-ribose with female albino Wistar rats demonstrated the NOAEL of 5% in diet, corresponding to an average daily intake between 3.64 and 4.61 g/kg bw was not embryotoxic or teratogenic [7]. Maltitol was not teratogenic; however, the fetus weights were decreased by all dose levels and the highest dose (4 g/kg body weight) caused growth retardation in bone marrow cells of SD rats [3].

Another factor contributing to the non-adverse effects of D-allulose is that it is an ordinary carbohydrate. Like other carbohydrates, the LD_{50} of D-allulose was found to be 15.8 or 16.3 g/kg [11]. The LD_{50} values of D-fructose and D-glucose were 14.7 and 25.8 g/kg bw, respectively [18]. The substance whose LD_{50} value of over 15 g/kg bw is categorized into 'relatively harmless' [1]. In a 90-day subchronic study, the NOAEL of D-allulose was determined to be 5000 mg/kg/day, the highest dose tested, for both sexes in Sprague-Dawley (SD) rats [2]. In a chronic study, no D-allulose treatment-related abnormalities were reported from Male Wistar rats receiving diets containing 3% D-allulose (corresponding to 1.28 g/kg bw/day) for 12–18 months [22]. Toxicological studies of erythritol also found that it was well tolerated without mutagenicity and carcinogenicity [14].

5. Conclusion

Based on the observations and analyses in these studies, it is concluded that D-allulose is not teratogenic, which is comparable to other monosaccharides and sugar alcohols. Because no prenatal developmental toxicities were found in the highest dose group (5000 mg/kg bw), the NOAEL value for the teratogenicity study was estimated to be 5000 mg/kg/day in pregnant rats.

CRediT authorship contribution statement

Soonok Sa: Conceptualization, Methodology, Data curation, Validation. **Yunji Seol**, **Albert W. Lee**: Writing – original draft, Validation. **Yong Heo, Hye-jung Kim** : Writing – review & editing, **Chong Jin Park:** Funding acquisition, Project administration, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Conflict of Interest

The authors report that Soonok Sa, Hye-jung Kim, and Chong Jin Park are employed by Samyang Corporation, the sponsor of the study. Other authors declare no conflicts of interest.

References

[1] T. Altug, Introduction to Toxicology and Food, CRC Press, Boca Raton, Florida, 2003.
[2] M. An, J. Lee, Y. Park, C. Park, H. Kim, 90-Day repeated oral toxicity test of D-allulose produced from *Microbacterium foliorum*, Regul. Toxicol. Pharmacol. 109 (2019), 104485.
[3] S. Canimoglu, E. Rencuzogullari, The genotoxic and teratogenic effects of maltitol in rats, Toxicol. Ind. Health. 29 (2013) 935–943.
[4] S. Chattopadhyay, U. Raychaudhuri, R. Chakraborty, Artificial sweeteners – a review, J. Food Sci. Technol. 51 (2014) 611–621.
[5] M.Y. Chung, D.K. Oh, K.W. Lee, Hypoglycemic health benefits of D-psicose, J. Agric. Food Chem 60 (2012) 863–869.
[6] A.T. Farag, T.A. Karkour, A.E. Okazy, Developmental toxicity of orally administered technical dimethoate in rats, Birth Defects Res 77 (2006) 40–46.
[7] J.C. Griffiths, J.F. Borzelleca, J.S. Cyr, Lack of oral embryotoxicity/teratogenicity with D-ribose in Wistar rats, Food Chem. Toxicol. 45 (2007) 388–395.
[8] H. Kim, C. Park, S. Sa, I. Case, C. Li, Y. Gao, H. Wang, J. Tian, A study of D-allulose-associated reproductive toxicity in rats, Food Chem. Toxicol. 131 (2019), 110548.
[9] T. Matsuo, T. Tanaka, M. Hashiguchi, K. Izumori, H. Suzuki, Metabolic effects of D-psicose in rats: studies on faecal and urinary excretion and caecal fermentation, Asia Pac. J. Clin. Nutr. 12 (2003) 225–231.
[10] T. Matsuo, H. Suzuki, M. Hashiguchi, K. Izumori, D-psicose is a rare sugar that provides no energy to growing rats, J. Nutr. Sci. Vitaminol. ((Tokyo)). 48 (2002) 77–80.
[11] T. Matsuo, T. Tanaka, M. Hashiguchi, K. Izumori, H. Suzuki, Effects of oral acute administration and subchronic feeding of several levels of D-psicose in rats, J. Nutr. Sci. Vitaminol. ((Tokyo)). 48 (2002) 512–516.
[12] A.D. Mooradian, M. Smith, M. Tokuda, The role of artificial and natural sweeteners in reducing the consumption of table sugar: A narrative review, Clin. Nutr. ESPEN. 18 (2017) 1–8.
[13] W. Mu, W. Zhang, Y. Feng, B. Jiang, L. Zhou, Recent advances on applications and biotechnological production of D-psicose, Appl. Microbiol. Biotechnol. 94 (2012) 1461–1467.
[14] I.C. Munro, W.O. Berndt, J.F. Borzelleca, G. Flamm, B.S. Lynch, E. Kennepohl, E. A. Bär, J. Modderman, Erythritol: an interpretive summary of biochemical, metabolic, toxicological and clinical data, Food Chem. Toxicol 36 (1998) 1139–1174.
[15] OECD (Organisation for Economic Cooperation and Development), 2001, Guidelines for Testing of Chemicals, No. 414 "Pre-natal Developmental Toxicity". Available at ⟨https://ntp.niehs.nih.gov/iccvam/suppdocs/feddocs/oecd/oecd_gl414.pdf⟩.
[16] OECD, Guidelines for Testing of Chemicals, No. 415, "One-generation Reproduction Toxicity Study" (1983) 1–8.
[17] H. Oshima, I. Kumura, K. Izumori, Psicose contents in various food products and its origin, Food Sci. Technol. Res. 12 (2006) 137–143.
[18] N.I. Sax, Dangerous Properties of Industrial Materials, Van Nostrand Reinhold Company, Inc,, New York, 1984.
[19] Tate and Lyle. 2015. Citizen Petition Regarding Nutrition Labeling of Allulose, a Very Low Calorie Sugar, submitted by Tate and Lyle to the US Food and Drug Administration. April 14, 2015. Docket No. FDA-2015-P-1201. Available at: ⟨https://beta.regulations.gov/document/ FDA-2015-P-1201–0001⟩.
[20] I. Tsukamoto, A. Hossain, F. Yamaguchi, Y. Hirata, Y. Dong, K. Kamitori, L. Sui, M. Nonaka, M. Ueno, K. Nishimoto, H. Suda, K. Morimoto, T. Shimonishi, M. Saito, T. Song, R. Konishi, M. Tokuda, Intestinal absorption, organ distribution, and urinary excretion of the rare sugar D-psicose, Drug Des. Devel. Ther 8 (2014) 1955–1964.
[21] R.L. Whistler, P.P. Singh, W.C. Lake, D-Psicose metabolism in the rat, Carbohydr. Res. 34 (1974) 200–202.
[22] K. Yagi, T. Matsuo, The study on long-term toxicity of d-psicose in rats, J. Clin. Biochem. Nutr 45 (2009) 271–277.
[23] Yamamoto, H., Tateishi, T., Sadamasu, K., Kosuge, M., Takahashi, K., Nakano, S., Kasai, Y. 1987. Acute Intraveneous, Subcutaneous and Oral Toxicity Study With NIK-242 in Rats. Division of Toxicology, Omiya Research Laboratory, Nikken Chemicals Co, Ltd, Japan (Internal Report).