DERLEME REVIEW
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Prebiotic Effect of D-Allulose (D-Psicose): Traditional Review

D-Allulozun (D-Psikoz) Prebiyotik Etkisi: Geleneksel Derleme

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ABSTRACT Healthy nutrition is to consume the nutrients that people need in an adequate and balanced way according to their requirement. Also, it is also crucial to consume biologically active compounds and phytochemicals which are not nutrients but have a beneficial effect. Many vegetables and fruits contain prebiotics, which are dietary compounds that are contained in the carbohydrate structure and have a beneficial effect. Prebiotics are used and converted into short-chain fatty acids by probiotic bacteria, as well as improving sensory properties like taste and smell. D-allulose is a simple carbohydrate defined as a natural sweetener with no energy (0.2 kcal/g). The effects of regulating energy metabolism and health effects have been investigated in recent years. Because of its resistance to digestive enzymes, it was thought that it might have prebiotic effects and researches on this subject have also begun. Studies have shown that D-allulose is used by certain probiotic bacteria and increases short-chain fatty acids. Therefore, it has been shown to have prebiotic effects. However, the number of studies using it as a prebiotic is very few. As a result, further research into the health effects of prebiotics in combination with various foods is needed.

Keywords: D-allulose; D-psicose; prebiotic; functional food

ÖZET Sağlıklı beslenme, kişinin gereksinimlerine göre besin ögelerini yeterli ve dengeli olarak tüketmesidir. Bunun yanında, besin ögesi olmayan ancak sağlıklı etki gösteren biyolojik aktif bileşiklerin ve fitokimyasalların alınması da önemlidir. Prebiyotikler birçok sebze ve meyvede karbonhidrat yapısında bulunan ve önemli sağlık etkileri gösteren fonksiyonel besin bileşimleri olarak kabul edilmektedir. Prebiyotikler, tat ve koku gibi duyusal özellikleri geliştirmenin yanında probiyotik bakteriler tarafından kullanılmakta ve kısa zincirli yağ asitlerine dönüşmektedir. D-alluloz, enerji içermeyen (0,2 kkal/g) doğal tatlandırıcı olarak tanımlanan bir basit karbonhidrattır. Enerji metabolizmasını düzenleyen etkileri ile son yıllarda sağlık etkileri araştırılmaya başlamıştır. Sindirim enzimlerine direnç göstermesinden dolayı prebiyotik etkileri olabileceği düşünülmüş ve bu konuda da araştırmalar başlamıştır. Yapılan çalışmalarda, D-allulozun bazı probiyotik bakteriler tarafından kullanıldığı ve kısa zincirli yağ asitlerini artırdığı belirtilmiş, bu nedenle de prebiyotik etkilerinin olduğu gösterilmiştir. Ancak prebiyotik olarak kullanıldığı çalışmaların sayısı oldukça azdır. Bu nedenle farklı besinlerle prebiyotik olarak kullanıldığında, sağlık üzerine göstereceği etkiler ile ilgili daha fazla çalışmaya ihtiyaç vardır.

Anahtar Kelimeler: D-alluloz; D-psikoz; prebiyotik; fonksiyonel besin

Today, to reach the quality of a long and healthy life, it is recommended that healthy nutrition should be a lifestyle with the nutritional awareness of the society and individuals. The basis for the protection, improvement and development of the health of the society and the individual throughout life should be adequate and balanced nutrition.[1] In addition to satisfying hunger and meeting the need for nutrients, foods are consumed today for the prevention and treatment of diseases associated with nutrition.[2] The word "functional foods" was coined in the 1980s to describe foods that contain components that have significant physical effects.[3]

The terms "foods for a healthy life" in Japan, "special nutritional foods and dietary foods" in the European Union and Canada, "healthy foods" in China all refer to functional foods.[4] Functional foods can be found naturally in foods, as well as foods that have been fortified with compounds that have a beneficial impact on health or foods that have had harmful components decreased or eliminated.[5] Adding compounds including phenolic substances, antioxidants, dietary

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pulp, oligosaccharides, prebiotics, probiotics, certain vitamins or minerals, and plant sterols to different foods provides functionality at the same time.[6]

Prebiotics are carbohydrates that can be fermented selectively by moving from the small intestine to the colon without being digested, making them available to probiotic bacteria but not to other bacteria throughout the gut.[7] Prebiotics in the human diet include galactooligosaccharides, fructooligosaccharides, maltooligosaccharides, resistant starch, inulin (and inulin hydrolyzates), and lactulose.[8] Many foods, such as onion, garlic, chicory, asparagus, artichoke, leek, banana, and tomato, contain oligosaccharides, which are classified as combinations of sugar with different polymerization degrees.[9] The key end components of carbohydrate metabolism, short-chain fatty acids, such as acetic acid, propionic acid, and butyric acid, are used as an energy source, especially by the host organism.[10] Prebiotics can be made in three ways: Isolation from plant sources, microbiological production, or enzymatic synthesis.[11,12]

Synbiotics, which are probiotics and prebiotics combined, are present in a variety of foods, including yogurt, cheese, and certain fermented products, and have been shown to help with diseases including dyslipidemia, non-alcoholic fatty liver, and obesity.[13-16] The discovery and development of new synbiotics, with their promising results in disease prevention and treatment, benefit both consumer health and the food industry's growth. In recent years, D-allulose has been used as a prebiotic in the development of new synbiotic products to avoid excessive fat accumulation in the body and to control diet-induced obesity.[17] We investigated the effects of D-allulose as a prebiotic in the food industry, as well as its beneficial effects on carbohydrate and fat metabolism and high antioxidant properties.

OVERVIEW OF D-ALLULOSE

D-allulose, also known as D-Psicose, is the C-3 epimer of fructose and is classified as 'rare sugars' because it is rarely found in nature.[18] A very small amount of D-allulose can be produced from the hydrolysis of sugar cane and sugar beet.[19] In addition, enzymatic and non-enzymatic fructose hydrolysis, ion (molybdenum) catalysis from fructopyranose, and D-Psicose 3-epimerase enzyme from certain bacteria are also examples.[20-22] Catalysis may also be used to obtain it. In the United States of America, commercially obtained D-allulose has begun to be used.[23] As compared to sucrose, D-allulose has 95 percent less energy (0.2 kcal/g) and 70 percent less relative sweetness.[24] The US Food and Drug Administration approved D-allulose, which has also been used as a dietary supplement, in 2014, and it was widely accepted as safe.[25] (GRAS Notification Number: GRN 418).[26]

D-allulose has anti-hyperglycemic, anti-hyperlipidemic, anti-inflammatory, and neuroprotective properties.[27-29] Furthermore, due to its scavenging function and therapeutic effects against atherosclerosis, reactive oxygen species is a pharmaceutical in clinical applications such as the treatment of D-allulose, obesity, diabetes, hypertension, and atherosclerotic diseases.[30,31]

Since it contains relatively little energy and is considered a natural sweetener, D-allulose has been viewed as a new area of research for the food industry.[32] D-allulose, which produces a more crunchy structure in confectionery when used as a sucrose replacement, also has a higher antioxidant effect.[33] When sucrose was used as a pudding replacement, it was discovered that it had higher breaking strength and viscoelasticity than sucrose.[34] It has also been documented that when compared to sucrose and fructose, it produces a more balanced form in egg whites.[35] Another research discovered that formulations containing D-allulose had less starch-induced retrogradation.[36] D-allulose also plays a role in improving the gelling properties of food, enhancing its taste, and reducing the amount of oxidation that occurs during meals.[37,38]

D-allulose is used in soft drinks, ice cream, dairy products, salty meals (soups, sauces, salads, and pickles), drugs as a gelling agent, baking products, and other foods, in addition to its energy-saving properties. It is used as a thickening agent and stabilizing agent in cakes made of bread, biscuits and rye flour.[39] Because of these properties, it was hypothesized that they may have an effect on meat production, and research into this field has begun.[32]

USE OF D-ALLULOSE AS A PREBIOTIC

To regulate lipid and carbohydrate metabolism and obesity, D-allulose can be used as a prebiotic in synbiotics.[40] Owing to its strong gastrointestinal resistance, gelling reaction, and stronger Maillard reaction, D-allulose has more beneficial effects than other substitute sugars.[41-43] According to Sharma et al., the conversion of sugar cane molasses to D-fructose by the enzyme dextran sucrase and D-fructose to D-allulose by the enzyme epimerase is a C atom donor for the formation of *Leuconostoc mesenteroides*, and the bioprocessed portion becomes a prebiotic and functionally effective product.[44] Sharma et al. also investigated into the prebiotic effect of D-allulose on banana pseudostem extracts and found that D-allulose obtained by biotransformation of banana fiber extracts can be used as a functional fruit juice.[45] D-allulose suppresses the acid released by lactic acid bacteria, D-allulose added soy yogurt significantly increases the number of lactic acid bacteria, and has better sensory properties than other sugar products, according to a study investigating the impact of D-allulose on soy yoghurt fermentation.[46] Lactic acid bacteriae suppress excess acid production in the first stage of fermentation without disrupting their probiotic activities, according to a study using D-allulose as a prebiotic source in dairy products. It has been reported that D-allulose may be useful in the development of new dairy products, especially with probiotic strains such as *Lactococcus lactis* H61.[47]

In a study conducted in a diet-induced obese experimental animal model, the synbiotic effects of *Lactobacillus sakei* LS03 and *Leuconostoc kimchii* GJ2 probiotic bacteria and D-allulose were investigated, and it was revealed that the synbiotic mixture of these two probiotics and D-allulose was the most effective model in suppressing obesity and obesity-related complications. In diet-induced obese mouse models, synbiotic products containing D-allulose have been shown to be more efficient than probiotic use alone in controlling lipid metabolism.[48] Short-chain fatty acids formed as a result of a complex interaction between diet and intestinal microbiota are thought to have therapeutic potential in the treatment of diet-induced obesity by controlling energy balance.[49,50] A study found that a D-allulose-rich diet boosts the development of short-chain fatty acids as compared to a high-fat diet. D-allulose has also been shown to increase the presence of *Coprococcus*, which produces butyrate and propionate, as well as *Lactobacillus*, which maintains intestinal integrity.[51]

CONCLUSION

Prebiotics are carbohydrate substances that cannot be digested by human digestive enzymes and increase the function of some beneficial bacterial groups selectively. Probiotic bacteriae use prebiotics to generate short-chain fatty acids in the intestine. The use of D-allulose has increased in recent years in research on simple carbohydrates known as rare sugars. Studies have shown that D-allulose, a C-3 epimeric carbohydrate of fructose that is rarely found in nature, has regulatory effects on energy metabolism. Due to these consequences, D-allulose, which has received a lot of attention in the food industry, was thought to have prebiotic properties due to its resistance to digestive enzymes, and scientific studies proved it. When used as a sugar substitute, it is also considered to maintain the rheological properties of foods. Such positive effects of D-allulose give rise to the possibility of acquiring new functional nutrients as a result of mixing this carbohydrate with foods in a novel way, and show promising results in order to benefit from the potential positive effects on obesity and find solutions to society's health problems in this direction.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

All authors contributed equally while this study preparing.

REFERENCES

1. T.C. Ministry of Health [Internet]. [Cited: 17 January 2021]. Turkey Nutritional Guidelines. Ankara. 2016. Available from: [Link]
2. Lange KW. Movement and nutrition in health and disease. MNHD. 2017;1. [Crossref]
3. Grajek W, Olejnik A, Sip A. Probiotics, prebiotics and antioxidants as functional foods. Acta Biochim Pol. 2005;52(3):665-71. [Crossref] [PubMed]
4. Patel D, Dufour Y, Domigan N. Functional food and nutraceutical registration processes in Japan and China: a diffusion of innovation perspective. J Pharm Pharm Sci. 2008;11(4):1-11. [Crossref] [PubMed]
5. Raghuveer C, Tandon R. Consumption of functional food and our health concerns. Pak J Physiol. 2009;5(1):76-83. [Link]
6. Hasler CM, Brown AC; American Dietetic Association. Position of the American Dietetic Association: functional foods. J Am Diet Assoc. 2009;109(4):735-46. [Crossref] [PubMed]
7. Khafaga AF, Abd El-Hack ME, Taha AE, Elnesr SS, Alagawany M. The potential modulatory role of herbal additives against Cd toxicity in human, animal, and poultry: A review. Environ Sci Pollut Res Int. 2019; 26(5):4588-604. [Crossref] [PubMed]
8. Al-Sheraji SH, Ismail A, Manap MY, Mustafa S, Yusof RM, Hassan FA. Prebiotics as functional foods: A review. J Funct Foods. 2013; 5(4):1542-53. [Crossref]
9. Sarkar S. Functional foods as self-care and complementary medicine. NFS. 2007;37(3): 160-7. [Crossref]
10. Ashaolu TJ, Ashaolu JO, Adeyeye SAO. Fermentation of prebiotics by human colonic microbiota in vitro and short-chain fatty acids production: a critical review. J Appl Microbiol. 2021;130(3):677-87. [Crossref] [PubMed]
11. Crittenden RA, Playne M. Production, properties and applications of food-grade oligosaccharides. Trends Food Sci Tech. 1996;7(11):353-61. [Crossref]
12. Gulewicz P, Ciesiołka D, Frias J, Vidal-Valverde C, Frejnagel S, Trojanowska K, et al. Simple method of isolation and purification of alpha-galactosides from legumes. J Agric Food Chem. 2000;48(8):3120-3. [Crossref] [PubMed]
13. Marteau P, Boutron-Ruault MC. Nutritional advantages of probiotics and prebiotics. Br J Nutr. 2002;87 Suppl 2:S153-7. [Crossref] [PubMed]
14. Umeki M, Oue K, Mochizuki S, Shirai Y, Sakai K. Effect of Lactobacillus rhamnosus KY-3 and cellobiose as synbiotics on lipid metabolism in rats. J Nutr Sci Vitaminol (Tokyo). 2004; 50(5):330-4. [Crossref] [PubMed]
15. Upadhyay N, Moudgal V. Probiotics: A review. JCOM. 2012;19(2):76-84. [Link]
16. Yoo JY, Kim SS. Probiotics and prebiotics: Present status and future perspectives on metabolic disorders. Nutrients. 2016;8(3):173. [Crossref] [PubMed] [PMC]
17. Patel SN, Kaushal G, Singh SP. A Novel d-Allulose 3-Epimerase Gene from the Meta genome of a Thermal Aquatic Habitat and d-Allulose Production by Bacillus subtilis Whole-Cell Catalysis. Appl Environ Microbiol. 2020; 86(5):e02605-19. [Crossref] [PubMed] [PMC]
18. Granström TB, Takata G, Tokuda M, Izumori K. Izumoring: a novel and complete strategy for bioproduction of rare sugars. J Biosci Bioeng. 2004;97(2):89-94. [Crossref] [PubMed]
19. Thacker J, Toyoda Y. Lung and heart-lung transplantation at University of Pittsburgh: 1982-2009. Clin Transpl. 2009:179-95. [PubMed]
20. Oshima H, Kimura I, Izumori K. Psicose contents in various food products and its origin. Food Sci Technol Res. 2006;12(2):137-43. [Crossref]
21. He W, Jiang B, Mu W, Zhang T. Production of d-Allulose with d-Psicose 3-Epimerase Expressed and Displayed on the Surface of Bacillus subtilis Spores. J Agric Food Chem. 2016;64(38):7201-7. [Crossref] [PubMed]
22. Park CS, Kim T, Hong SH, Shin KC, Kim KR, Oh DK. D-Allulose Production from D-Fructose by Permeabilized Recombinant Cells of Corynebacterium glutamicum Cells Expressing D-Allulose 3-Epimerase Flavonifractor plautii. PLoS One. 2016;11(7):e0160044. [Crossref] [PubMed] [PMC]
23. Newsweek [Internet]. © 2020 NEWSWEEK DIGITAL LLC [Cited: 17 December 2020]. The search for perfect sugar substitute. 2016. Available from: [Link]
24. Chung YM, Hyun Lee J, Youl Kim D, Hwang SH, Hong YH, Kim SB, et al. Dietary D-psicose reduced visceral fat mass in high-fat diet-induced obese rats. J Food Sci. 2012;77(2): H53-8. [Crossref] [PubMed]
25. Mu W, Zhang W, Feng Y, Jiang B, Zhou L. Recent advances on applications and biotechnological production of D-psicose. Appl Microbiol Biotechnol. 2012;94(6):1461-7. [Crossref] [PubMed]
26. Hossain A, Yamaguchi F, Matsuo T, Tsukamoto I, Toyoda Y, Ogawa M, et al. Rare sugar D-allulose: Potential role and therapeutic monitoring in maintaining obesity and type 2 diabetes mellitus. Pharmacol Ther. 2015; 155:49-59. [Crossref] [PubMed]
27. Moller DE, Berger JP. Role of PPARs in the regulation of obesity-related insulin sensitivity and inflammation. Int J Obes Relat Metab Disord. 2003;27 Suppl 3:S17-21. [Crossref] [PubMed]
28. Hayashi N, Iida T, Yamada T, Okuma K, Takehara I, Yamamoto T, et al. Study on the postprandial blood glucose suppression effect of D-psicose in borderline diabetes and the safety of long-term ingestion by normal human subjects. Biosci Biotechnol Biochem. 2010; 74(3):510-9. [Crossref] [PubMed]
29. Takata MK, Yamaguchi F, Nakanose K, Watanabe Y, Hatano N, Tsukamoto I, et al. Neuroprotective effect of D-psicose on 6-hydroxydopamine-induced apoptosis in rat pheochromocytoma (PC12) cells. J Biosci Bioeng. 2005;100(5):511-6. [Crossref] [PubMed]
30. Suna S, Yamaguchi F, Kimura S, Tokuda M, Jitsunari F. Preventive effect of D-psicose, one of rare ketohexoses, on di-(2-ethylhexyl) phthalate (DEHP)-induced testicular injury in rat. Toxicol Lett. 2007;173(2):107-17. [Crossref] [PubMed]
31. Murao K, Yu X, Cao WM, Imachi H, Chen K, Muraoka T, et al. D-Psicose inhibits the expression of MCP-1 induced by high-glucose stimulation in HUVECs. Life Sci. 2007;81(7): 592-9. [Crossref] [PubMed]
32. Hadipernata M, Ogawa M, Hayakawa S. Effect of d-allulose on rheological properties of chicken breast sausage. Poult Sci. 2016; 95(9):2120-8. [Crossref] [PubMed]
33. O'Charoen S, Hayakawa S, Matsumoto Y, Ogawa M. Effect of D-psicose used as sucrose replacer on the characteristics of meringue. J Food Sci. 2014;79(12):E2463-9. [Crossref] [PubMed]
34. Sun Y, Hayakawa S, Jiang H, Ogawa M, Izumori K. Rheological characteristics of heat-induced custard pudding gels with high antioxidative activity. Biosci Biotechnol Bioc hem. 2006;70(12):2859-67. [Crossref] [PubMed]
35. Sun Y, Hayakawa S, Ogawa M, Fukada K, Izumori K. Influence of a rare sugar, d-Psicose, on the physicochemical and functional properties of an aerated food system containing egg albumen. J Agric Food Chem. 2008; 56(12):4789-96. [Crossref] [PubMed]
36. Ilhan E, Pocan P, Ogawa M, Oztop MH. Role of 'D-allulose' in a starch based composite gel matrix. Carbohydr Polym. 2020;228:115373. [Crossref] [PubMed]

37. Oshima H, Kimura I, Kitakubo Y, Hayakawa S, Izumori K. Factors affecting psicose formation in food products during cooking. Food Sci Technol Res. 2014;20(2):423-30. [Crossref]

38. Zeng Y, Zhang H, Guan Y, Zhang L, Sun Y. Comparative study on the effects of d-psicose and d-fructose in the Maillard reaction with β-lactoglobulin. Food Sci Biotechnol 2013;22(2): 341-6. [Crossref]

39. Jiang S, Xiao W, Zhu X, Yang P, Zheng Z, Lu S, et al. Review on D-Allulose: In vivo Metabolism, Catalytic Mechanism, Engineering Strain Construction, Bio-Production Technology. Front Bioeng Biotechnol. 2020;8:26. [Crossref] [PubMed] [PMC]

40. Do GY, Kwon EY, Kim YJ, Han Y, Kim SB, Kim YH, et al. Supplementation of non-dairy crea mer-enriched high-fat diet with D-allulose ameliorated blood glucose and body fat accumulation in C57BL/6J mice. App Sci. 2019; 9(13): 2750. [Crossref]

41. Han Y, Choi BR, Kim SY, Kim SB, Kim YH, Kwon EY, et al. Gastrointestinal tolerance of d-allulose in healthy and young adults. A non-randomized controlled trial. Nutrients. 2018; 10(12):2010. [Crossref] [PubMed] [PMC]

42. O'Charoen S, Hayakawa S, Ogawa M. Food properties of egg white protein modified by rare ketohexoses through Maillard reaction. Int J Food Sci Technol. 2015;50(1):194-202. [Crossref]

43. Sun Y, Hayakawa S, Izumori K. Modification of ovalbumin with a rare ketohexose through the Maillard reaction: effect on protein structure and gel properties. J Agric Food Chem. 2004;52(5):1293-9. [Crossref] [PubMed]

44. Sharma M, Patel SN, Lata K, Singh U, Krishania M, Sangwan RS, et al. A novel approach of integrated bioprocessing of cane molasses for production of prebiotic and functional bioproducts. Bioresour Technol. 2016;219:311-8. [Crossref] [PubMed]

45. Sharma M, Patel SN, Sangwan RS, Singh SP. Biotransformation of banana pseudostem extract into a functional juice containing value added biomolecules of potential health benefits. IJEB. 2017;55:453-562. [Link]

46. Kim HJ, Han MJ. The fermentation characteristics of soy yogurt with different content of d-allulose and sucrose fermented by lactic acid bacteria from Kimchi. Food Sci Biotechnol. 2019;28(4):1155-61. [Crossref] [PubMed] [PMC]

47. Kimoto-Nira H, Moriya N, Hayakawa S, Kuramasu K, Ohmori H, Yamasaki S, et al. Effects of rare sugar D-allulose on acid production and probiotic activities of dairy lactic acid bacteria. J Dairy Sci. 2017;100(7):5936-44. [Crossref] [PubMed]

48. Choi BR, Kwon EY, Kim HJ, Choi MS. Role of Synbiotics Containing d-Allulose in the Alteration of Body Fat and Hepatic Lipids in Diet-Induced Obese Mice. Nutrients. 2018;10(11): 1797. [Crossref] [PubMed] [PMC]

49. Li X, Shimizu Y, Kimura I. Gut microbial metabolite short-chain fatty acids and obesity. Biosci Microbiota Food Health. 2017;36(4): 135-40. [Crossref] [PubMed] [PMC]

50. Sánchez B, Delgado S, Blanco-Míguez A, Lourenço A, Gueimonde M, Margolles A. Probiotics, gut microbiota, and their influence on host health and disease. Mol Nutr Food Res. 2017;61(1). [Crossref] [PubMed]

51. Han Y, Park H, Choi BR, Ji Y, Kwon EY, Choi MS. Alteration of Microbiome Profile by D-Allulose in Amelioration of High-Fat-Diet-Induced Obesity in Mice. Nutrients. 2020; 12(2):352. [Crossref] [PubMed] [PMC]