Special Article

Rare sugars and their health effects in humans: a systematic review and narrative synthesis of the evidence from human trials

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Context: *Rare sugars are monosaccharides and disaccharides (found in small quantities in nature) that have slight differences in their chemical structure compared with traditional sugars. Little is known about their unique physiological and cardiometabolic effects in humans.* ***Objective:*** *The objective of this study was to conduct a systematic review and synthesis of controlled intervention studies of rare sugars in humans, using PRISMA guidelines.* ***Data Sources:*** *MEDLINE and EMBASE were searched through October 1, 2020. Studies included both post-prandial (acute) and longer-term (≥1 week duration) human feeding studies that examined the effect of rare sugars (including allulose, arabinose, tagatose, trehalose, and isomaltulose) on cardiometabolic and physiological risk factors.* ***Data extraction:*** *In all, 50 studies in humans focusing on the 5 selected rare sugars were found. A narrative synthesis of the selected literature was conducted, without formal quality assessment or quantitative synthesis.* ***Data synthesis:*** *The narrative summary included the food source of each rare sugar, its effect in humans, and the possible mechanism of effect. Overall, these rare sugars were found to offer both short- and long-term benefits for glycemic control and weight loss, with effects differing between healthy individuals, overweight/obese individuals, and those with type 2 diabetes. Most studies were of small size and there was a lack of large randomized controlled trials that could confirm the beneficial effects of these rare sugars.* ***Conclusion:*** *Rare sugars could offer an opportunity for commercialization as an alternative sweetener, especially for those who are at high cardiometabolic risk.*
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INTRODUCTION

As rates of obesity and type 2 diabetes continue to rise globally, the role of excess sugars in the diet has become a focus of intense concern.[1] Most of the attention has centered on the adverse health effects of the common sugars – fructose, sucrose, and high-fructose corn syrup (HFCS).[2] Rare sugars, defined as "monosaccharides and their derivatives that are present in limited quantities in nature", have received comparatively far less attention.[3] These sugars, which can be found in small amounts in a variety of food sources (including honey, certain fruits and vegetables, and grains), may present as unique alternative sweeteners with both caloric and metabolic benefits.[2,3] Over 40 different types of rare sugars have been identified as having subtle differences in their chemical structure compared with traditional sugars.[2] Consumption of rare sugars as a sweetener alternative has demonstrated several beneficial physiologic and cardiometabolic effects, including improved glycemic response and weight loss in in vitro and animal models. Whether these findings translate to humans and have clinical relevance is unclear.[4,5] However, evidence of the health effects of rare sugars in humans has begun to accrue for a number of rare sugars, including allulose (psicose), tagatose, isomaltulose (palatinose), L-arabinose, and trehalose. The aim of this review was to provide a systematic summary of the current literature on these rare sugars regarding their physiological and cardiometabolic effects in humans, discuss the possible mechanism for their effects, and highlight their food sources, while also identifying current gaps in the literature on rare sugars.

METHODS

The study followed a systematic search and narrative review methodology.[6] A systematic search was conducted according to the Cochrane Handbook for Systematic Reviews of Interventions[7] and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta- Analyses (PRISMA) guidelines.[8] The systematic search was followed by a narrative synthesis of the selected literature, without formal quality assessment or quantitative synthesis. The study protocol was registered as an OSF Registration (osf.io/fw43d) under the following identification number: 10.17605/OSF.IO/FW43D.

Search and selection

MEDLINE and EMBASE were searched through October 1, 2020 for eligible trials. Electronic searches were supplemented with manual searches of references from included studies. Appendix A shows the detailed search strategy. Studies included were randomized, non-randomized, and uncontrolled human feeding trials that examined rare sugars (including allulose, L-arabinose, D-tagatose, trehalose, or isomaltulose) and reported on cardiometabolic and physiological risk factors. Both post-prandial (acute) studies and longer-term (≥1 week duration) studies were included. The PICOS (population, intervention, outcome, study design) criteria are provided in Table 1. In all, 882 records were identified through searching MEDLINE and EMBASE. Following removal of duplicates, and after completing a full-text review of the studies identified, 50 studies were eligible for inclusion in this review.

Table 1 **PICOS criteria for inclusion of studies**

Parameter	Criterion
Population	Adult humans from all health backgrounds
Intervention	Rare sugars (allulose, L-arabinose, D-tagatose, trehalose, or isomaltulose)
Comparison	Common sugars (sucrose, glucose, maltose, or fructose) Another rare sugar No sugar
Outcomes	Cardiometabolic and physiological risk factors
Study design	Acute (post-prandial studies) trials Longer-term (≥1 week duration) trials *Included randomized, non-randomized, and uncontrolled human feeding trials*

Allulose

Table 2[9–39] gives the study characteristics for all the included studies on rare sugars. A total of 5 acute and 7 longer-term human studies reported results for allulose and cardiometabolic risk factors. Table 3[2,37,40–55] gives the chemical and physiological characteristics of rare sugars. Allulose is a monosaccharide found in small amounts in maple syrup, dried fruit, and brown sugar. It is a C-3 epimer of fructose that has about two-thirds of the sweetness of sucrose but a minimal caloric content (0.2 kcal/g).[40,56] About 70% of allulose is absorbed in the small intestine into the bloodstream (within 1 h) but is excreted intact in urine (within 24 h), while the other 30% is transported to the large intestine, where it is not fermented and thus is excreted intact (within 48 h).[57] Acute and longer-term randomized controlled trials have examined the effect of allulose consumption on plasma glucose and insulin release, and weight loss, showing benefit in both healthy populations and in individuals with type 2 diabetes.

Table 4[3,9–22,25–28,30,32,34–37,40,41,58–61] describes the effects of rare sugars in human studies. Kimura et al, in an acute single-bolus randomized controlled trial with healthy participants, examined the effects of

Table 2 **Study characteristics**

Study, year	Participants	Setting	Mean age, years (SD or range)	Mean BMI, kg/m^2 (SD)	Design	Feeding control	Randomization	Rare sugar dose (g)	Intervention or control	Follow-up	Funding sources	Main findings
Allulose (acute)												
Braunstein et al (2018)[60]	25 H (13 M, 12 F)	OP, Canada	37 (16)	24.7 (3.5)	Crossover	Supp	Yes			120 min	A, I	No effect on plasma iAUC or secondary markers of postprandial blood glucose regulation
Intervention								5	5 g allulose + 75 g OGTT			
Intervention								10	10 g allulose + 75 g OGTT			
Control									75 g OGTT			
Iida et al (2008)[59]	20 H (11 M, 9 F)	OP, Japan	28.2 (6.3)	20.7 (1.8)	Crossover	Supp	Yes			120 min	NR	Suppressed glucose and insulin levels in a dose-dependent manner ($P < 0.05$)
Intervention								2.5	2.5 g allulose + 75 g OMTT			
Intervention								5	5 g allulose + 75 g OMTT			
Intervention								7.5	7.5 g allulose + 75 g OMTT			
Control									75 g OMTT			
Kimura et al (2011)[58]	13 H (5 M, 8 F)	OP, Japan	35.7 (7.6)	20.9 (2.5)	Crossover	Supp	Yes	5		240 min	NR	Reduction in plasma glucose and increase in fat energy expenditure following test meals ($P < 0.05$)
Intervention									5 g allulose (in 150 mL water) at 30 min prior to MTT			
Control									10 g aspartame (in 150 mL water) at 30 min prior to MTT			
Noronha et al (2018)[40]	24 T2DM (12 M, 12 F)	OP, Canada	66 (5.9)	27 (3.4)	Crossover	Supp	Yes			120 min	A, I	Reduction in plasma glucose iAUC at 10 g of allulose ($P < 0.05$)
Intervention								5	5 g allulose + 75 g OGTT			
Intervention								10	10 g allulose + 75 g OGTT			
Control									75 g OGTT			
Allulose (longer term)												
Han et al (2018)[56]		OP, Korea	(20–40)		Parallel	Supp	Yes			12 wk	A	Reduction in body fat percentage and fat mass at 8 g/d and 14 g/d of allulose ($P < 0.05$)
Intervention	40 OW/OB (20 M, 20 F)			27.45 (3.21)				8	8 g/d of allulose in a 30 mL grapefruit flavored noncarbonated beverage			
Intervention	41 OW/OB (22 M, 19 F)			26.79 (2.47)				14	14 g/d of allulose in a 30 mL grapefruit flavored noncarbonated beverage			
Control	40 OW/OB (17 M, 23 F)			26.83 (2.81)					0.024 g/d of sucralose in a 30 mL grapefruit flavored noncarbonated beverage			
Hayashi et al (2010)[10]		OP, Japan			Parallel	Supp	Yes	15		12 wk	I	No effect on plasma glucose or insulin levels
Intervention	8 H (4 M, 4 F)		33.4 (3.5)	21.3 (2.2)					15 g/d allulose in water			
Control	9 (4 M, 5 F)		34.6 (4)	21.5 (3)					15 g/d glucose in water			
Hayashi et al (2014)[3]		OP, Japan			Parallel	Supp	Yes	1.8		12 wk	I	Reduction in body weight, fat mass, and waist circumference with consumption of the rare sugar syrup ($P < 0.01$)
Intervention	17 OW/OB (8 M, 9 F)		41.7 (11.5)	25.6 (2.5)					30 g/d of a rare sugar syrup containing 6% allulose			
Control	17 OW/OB (9 M, 8 F)		42.4 (10.7)	25.4 (2.5)					28 g/d of high-fructose corn syrup			
Tanaka et al (2019)[9]												
Intervention	18 borderline T2DM/ T2DM (9 M, 9 F)	OP, Japan	57.9 (7.4)	27.5 (5.5)	Open study	Supp	N/A	15	5 g allulose consumed with each meal	12 wk	I	Increased body fat percentage with allulose consumption ($P < 0.05$)
Control									None			
L-arabinose (acute)												
Krog-Mikkelsen et al (2011)[13]	15 H (15 M, 0 F)	OP, Denmark	25 (3.2)	22.8 (2.1)	Crossover	Supp	Yes			180 min	I	Reduced glucose and insulin peak with L-arabinose consumption ($P < 0.05$)
Intervention								1	1 g L-arabinose + 75 g sucrose in 300 mL water			
Intervention								2	2 g L-arabinose + 75 g sucrose in 300 mL water			

(continued)

Table 2 **Continued**

Study, year	Participants	Setting	Mean age, years (SD or range)	Mean BMI, kg/m^2 (SD)	Design	Feeding control	Randomization	Rare sugar dose (g)	Intervention or control	Follow-up	Funding sources	Main findings
Intervention								3	3 g L-arabinose + 75 g sucrose in 300 mL water			
Control									75 g sucrose in 300 mL water			
Shibanuma et al (2011)[11]	21 H (18 M, 3 F)	OP, Japan	NR	NR	Crossover	Supp	No			120 min	NR	Reduction in blood glucose levels at 120 min following L-arabinose consumption ($P < 0.05$)
Intervention								2	2 g L-arabinose + 40 g sucrose dissolved in 108 g deionized water			
Control									40 g sucrose in a 150 g sucrose solution			
Halschou Jensen et al (2018)[38]	17 H (17 M, 0 F)	OP, Denmark	22.5 (2.6)	22 (1.22)	Crossover	Supp	Yes			5 h	I	No change in peak plasma glucose or glucose iAUC
Intervention								2.5 or 2.9	Breakfast and lunch meals supplemented with 5% arabinose by weight			
Intervention								4.9 or 5.9	Breakfast and lunch meals supplemented with 10% arabinose by weight			
Control									Breakfast and lunch meals			
L-arabinose (longer term)												
Yang et al (2013)[12]												
Intervention	30 MetS (20 M, 10 F)	OP, China	49.9 (9.9)	NR	Open study	Supp	N/A	40 or 45	20 g twice daily or 15 g thrice daily of L-arabinose	6 mo	I	Reduction in waist circumference ($P < 0.01$), total cholesterol ($P < 0.05$), and fasting glucose ($P < 0.01$)
Control									None			
D-tagatose (acute)												
Buemann et al (2000)[39]	20 H (20 M, 0 F)	OP, Denmark	25.7 (4)	24 (2.2)	Parallel	Supp	NR	29		13 h	I	Reduced appetite and intake at dinner ($P < 0.05$)
Intervention									29 g tagatose added to a continental breakfast			
Control									29 g sucrose added to a continental breakfast			
Kwak et al (2013)[15]	52 H (27 M, 25 F)	OP, Korea	35.8 (10.5)	23.7 (3.9)	Crossover	Supp	Yes	5		120 min	A	Reduction in post-test meal glucose iAUC ($P < 0.05$)
Intervention									5 g tagatose sweetened drink + MTT			
Control									Placebo sweetened (erythritol + 0.004 g sucralose) drink + MTT			
Kwak et al (2013)[15]	33 pre-diabetes/ T2DM (18 M, 15 F)	OP, Korea	57.2 (9.8)	25 (2.6)	Crossover	Supp	Yes	5		120 min	A	Reduction in post-test meal glucose iAUC ($P < 0.05$)
Intervention									5 g tagatose-sweetened drink + MTT			
Control									Placebo sweetened (erythritol + 0.004 g sucralose) drink + MTT			
Wu et al (2012)[14]	10 H (7 M, 3 F)	OP, Australia	28.8 (12.6)	25.5 (4.7)	Crossover	Supp	Yes			240 min	NR	Reduced glucose iAUC, serum insulin levels, and slower gastric emptying following the test meal ($P < 0.05$)
Intervention								16	40 g tagatose and isomaltulose mixture dissolved in 400 mL water			
Control									60 g sucralose dissolved in 400 mL water			
D-tagatose (longer term)												
Boesch et al (2001)[16]	12 H (12 M, 0 F)	OP, Switzerland	(21–30)	<25	Crossover	Supp	No			4 wk	NR	No change in body weight
Intervention								45	15 g tagatose added to 3 meals daily			
Control									15 g sucrose added to 3 meals daily			
Buemann et al (1998)[17]	8 H (3 M, 5 F)	OP, Denmark	26.2 (2.8)	NR	Crossover	Supp	Yes					No change in body weight
Intervention								30	30 g/d tagatose given in a slice of cake	2 wk	A, I	
Control									30 g/d sucrose given in a slice of cake			
Donner et al (2010)[19]	8 T2DM (4 M, 4 F)	OP, USA	50.7 (10.9)	36.7 (5.1)	Open study	Supp	N/A			12 mo	I	Reduction in body weight ($P < 0.05$) and nonsignificant reduction in glycosylated
Intervention								45	15 g tagatose taken with food 3 times/ day			

(continued)

Table 2 **Continued**

Study, year	Participants	Setting	Mean age, years (SD or range)	Mean BMI, kg/m^2 (SD)	Design	Feeding control	Randomization	Rare sugar dose (g)	Intervention or control	Follow-up	Funding sources	Main findings
												hemoglobin with tagatose consumption
Control									None			
Ensor et al (2015)[20]	356 T2DM	OP, India & USA	51.7 (10.4)	28.3	Parallel	Supp	Yes			40 wk	A, I	Reduction in body weight ($P < 0.05$) and nonsignificant reduction in glycosylated hemoglobin with tagatose consumption
Intervention								45	15 g tagatose dissolved in 125–250 mL of water 3 times/day			
Control									1.5 g Splenda dissolved in 125–250 mL of water 3 times/day			
Saunders et al (1999)[18]	8 H (4 M, 4 F)	OP, USA	43.6 (5.1)	NR	Parallel	Supp	Yes			8 wk	NR	No change in blood glucose levels, lipid levels, or uric acid levels
Intervention								75	25 g tagatose added to 3 meals daily			
Control									25 g sucrose added to 3 meals daily			
Saunders et al (1999)[18]	8 T2DM (4 M, 4 F)	OP, USA	53.8 (11.9)	NR	Parallel	Supp	Yes			8 wk	NR	No change in blood glucose levels, lipid levels, or uric acid levels
Intervention								75	25 g tagatose added to 3 meals daily			
Control									No sugar supplementation			
Trehalose-acute												
Maki et al (2009)[22]	23 OB (23 M, 0 F)	OP, USA	49.8 (10.9)	34.9 (0.7)	Crossover	Supp	Yes			120 min	I	Lower rise in plasma glucose and insulin levels ($P < 0.05$)
Intervention								75	75 g trehalose in a 414 mL beverage			
Control									75 g glucose in a 414 mL beverage			
van Can et al (2012)[21]	10 OW (6 M, 4 F)	OP, Netherlands	56 (8)	30.8 (4.9)	Crossover	Supp	Yes			3 h	I	Lower rise in plasma glucose ($P < 0.01$) and insulin levels ($P < 0.05$)
Intervention								75	75 g trehalose dissolved in 400 mL water			
Control									75g glucose dissolved in 400 mL water			
Trehalose (longer term)												
Kaplon et al (2016)[25]	32 H (15 M, 17 F)	OP, USA		NR	Parallel	Supp	Yes			12 wk	A	No change in body weight, lipid levels, or blood pressure
Intervention	15 H (7 M, 8 F)		64 (7.7)					100	100 g trehalose mixed with 355 mL of water daily			
Control	17 H (8 M, 9 F)		63 (8.2)						100 g maltose mixed with 355 mL of water daily			
Mizote et al (2016)[23]	34 MetS (33 M, 1 F)	OP, Japan			Parallel	Supp	NR			12 wk	NR	Reduction in fasting plasma glucose levels in individuals who had greater trunk fat with trehalose consumption ($P < 0.05$)
Intervention	17 MetS (17 M, 0 F)		47.9 (7.7)	26.4 (2.8)				9.9	3.3 g trehalose added to meals and dissolved in drinks 3 times/day			
Control	17 MetS (16 M, 1 F)		47.2 (6)	26.2 (2.6)					3.3 g sucrose added to meals and dissolved in drinks 3 times/day			
Yoshizane et al (2020)[24]	50 H (20 M, 30 F)	OP, Japan	43.7 (8.4)	22.4 (3.3)	Parallel	Supp	Yes			12 wk	NR	Plasma glucose levels 2 h after an OGTT closer to fasting plasma glucose levels with trehalose consumption ($P < 0.05$)
Intervention								3.3	3.3 g trehalose added to meals and dissolved in drinks			
Control									3.3 g sucrose added to meals and dissolved in drinks			
Isomaltulose (acute)												
Ang et al (2014)[29]	11 T2DM (5 M, 6 F)	OP, Germany	53.7 (8.3)	31.6 (4.3)	Crossover	Supp	Yes			240 min	NR	Reduced plasma glucose and insulin levels ($P < 0.05$)
Intervention								1 g/kg BW	1 g/kg BW of isomaltulose			
Control									1 g/kg BW of sucrose			
Arai et al (2005)[31]	7 H (7 M, 0 F)	OP, Japan	31.6 (1.3)	23 (2.6)	Crossover	Supp	Yes			240 min	A	Reduction in plasma glucose levels at a second meal following isomaltulose beverage consumption ($P < 0.05$)
Intervention								NR	Beverage containing 55.7% isomaltulose			
Control									Beverage containing 97.2% dextrin			
Henry et al (2017)[28]	20 H (20 M, 0 F)	OP, Singapore	23.8 (1.8)	24.4 (3.1)	Crossover	Supp	Yes			24 h	A	Lower 24 h glucose iAUC ($P < 0.01$) as well as reduced glucose variability with isomaltulose ($P < 0.001$)
Intervention								NR	Breakfast, lunch, and afternoon snack supplemented with isomaltulose			

(continued)

Table 2 **Continued**

Study, year	Participants	Setting	Mean age, years (SD or range)	Mean BMI, kg/m^2 (SD)	Design	Feeding control	Randomization	Rare sugar dose (g)	Intervention or control	Follow-up	Funding sources	Main findings
Control									Breakfast, lunch, and afternoon snack supplemented with sucrose			
Kendall et al (2018)[26]	77 H (18 M, 59 F)	OP, New Zealand	21.9 (5.6)	23.7 (3.6)	Crossover	Supp	Yes			120 min	A	Reduction in blood glucose levels at 60 min following isomaltulose consumption ($P < 0.001$)
Intervention								73.2	Trifle containing 73.2 g isomaltulose			
Control									Trifle containing 73.2 g sucrose			
Maeda et al (2013)[32]	10 H (10 M, 0 F)	OP, Japan	46.6 (7.7)	21.1 (1.6)	Parallel	Supp	NR			180 min	A	Reduction in postprandial plasma insulin and glucose levels following isomaltulose consumption ($P < 0.05$)
Intervention								50	50 g isomaltulose dissolved in 300 mL distilled water			
Control									50 g sucrose dissolved in 300 mL distilled water			
Sridonpai et al (2016)[30]	11 T2DM	OP, Thailand	49.6 (5.7)	27.8 (2)	Crossover	Supp	Yes			240 min	NR	Nonsignificant reduction in plasma glucose levels 30 min–60 min following isomaltulose consumption
Intervention								NR	Breakfast supplemented with isomaltulose			
Control									Breakfast supplemented with sucrose			
Suklaew et al (2014)[27]	12 OB (12 M, 0 F)	OP, Thailand	25.9 (6.6)	25.7 (0.3)	Crossover	Supp	Yes			480 min	A	Reduction in blood glucose iAUC following isomaltulose consumption ($P < 0.05$)
Intervention								40	40 g isomaltulose dissolved in 300 mL beverage + high-fat breakfast			
Control									40 g sucrose dissolved in 300 mL beverage + high-fat breakfast			
Isomaltulose (longer term)												
Brunner et al (2012)[36]	101 T2DM (66 M, 35 F)	OP, Germany			Parallel	Supp	Yes			12 wk	I	No difference in HbA1c levels
Intervention	52 T2DM (34 M, 18 F)		60.6 (7.5)	29.9 (4.2)				50	50 g isomaltulose given in biscuits, toffees, milk drinks, and soft drinks			
Control	49 T2DM (32 M, 17 F)		60.5 (8.7)	32.3 (4.5)					50 g sucrose given in biscuits, toffees, milk drinks, and soft drinks			
Holub et al (2009)[37]	20 hyperlipidemic (8 M, 12 F)	OP, Germany	48.2 (21–61)	32.5	Crossover	Met	Yes			4 wk	I	No difference in HbA1c levels
Intervention								50	50 g isomaltulose given in sweet foods and drinks			
Control									50 g sucrose given in sweet foods and drinks			
Lightowler et al (2019)[33]	50 OW/OB	OP, UK	40.7 (11.7)	29.4 (2.7)	Parallel	Supp	Yes			12 wk	I	Reduction in weight ($P < 0.001$) and fat mass ($P < 0.01$) with isomaltulose consumption
Intervention								40	40 g isomaltulose + energy-restricted diet			
Control									40 g sucrose + energy-restricted diet			
Mateo-Gallego et al (2019)[34]	43 prediabetes/ T2DM (27 M, 16 F)	OP, Spain		NR	Parallel	Supp	Yes			10 wk	A	Reduction in HOMA-IR and insulin levels with isomaltulose consumption ($P < 0.05$)
Intervention	21 prediabetes/ T2DM (12 M, 9 F)		55.9 (6)					16.5	Alcohol-free beer supplemented with 16.5 g isomaltulose			
Control	22 prediabetes/ T2DM (15 M, 7 F)		55.7 (8.7)						Alcohol-free beer supplemented with 5.28 g dextrin			
Okuno et al (2010)[35]	50 H (10 M, 40 F)	OP, Japan			Parallel	Supp	Yes			12 wk	NR	Reduction in HOMA-IR with isomaltulose consumption ($P < 0.01$)
Intervention	25 H (5 M, 20 F)		52.2 (8.6)	23 (2.9)				40	40 g isomaltulose given in sugar sticks, jelly, and drinks			
Control	25 H (5 M, 20 F)		53.2 (9.4)	22.7 (2.8)					40 g sucrose given in sugar sticks, jelly, and drinks			

Data represents mean ± SD, unless otherwise stated. *Abbreviations:* A, agency; F, female; H, healthy; I, industry; M, male; Met, metabolic; MetS, metabolic syndrome; MTT, meal tolerance test; N/A, not applicable; NR, not reported; OB, obese; OGTT, oral glucose tolerance test; OMTT, oral maltodextrin tolerance test; OP, outpatient; OW, overweight; Supp, supplemented; T2DM, type 2 diabetes mellitus.

Table 3 **Chemical and physiological characteristics of rare sugars**

Rare sugar	Structure	Caloric content (kcal/g)	Sweetness (compared with sucrose)	Glycemic index	Gut enzymes and metabolic fate
Allulose	Monosaccharide *(C-3 epimer of fructose)*	0.2[40]	70%[41]	ND	Transported via GLUT5 in the enterocyte and further transported using GLUT2 (same as fructose)[49]
L-arabinose	Monosaccharide *(aldopentose)*	0[50]	~50%[51]	ND	Inhibited sucrase activity[2]
D-tagatose	Monosaccharide *(C-4 epimer of fructose)*	(~1.5–3)[43]	92%[42]	3[52]	Transported via GLUT5 in the enterocyte, metabolized via glycolytic pathway (same as fructose),[2] fermented in the colon[53]
Trehalose	Dissacharide *(2 glucose molecules in an α1,1-glycosidic linkage)*	4[44]	~50%[45]	ND	Trehalose broken down by trehalase in the small intestine into 2 glucose molecules, which are then absorbed[54]
Isomaltulose (palatinose)	Disaccharide *(glucose and fructose in an α1-6 glycosidic bond)*	4[46]	50%[47]	32[52]	Completely but slowly digested by isomaltase[37]
Kojibiose	Disaccharide *(2 glucose molecules connected by an α1-2 glycosidic bond)*	ND	ND	ND	ND
Sorbose	Monosaccharide *(Ketose)*	ND	70%[48]	ND	ND
D-allose	Monosaccharide *(C-3 epimer of glucose)*	ND	80%[48]	ND	Downregulated GLUT1 expression[55]

consumption of 5 g allulose, compared with that of 10 mg of aspartame, administered as preloads, on the postprandial glycemic response to a test meal consisting of rice and hamburger steak. They showed a reduction in plasma glucose at 90 minutes following the test meal.[58] Furthermore, ingestion of allulose as a preload resulted in an increase in fat energy expenditure (but a decrease in carbohydrate energy expenditure) at 90 minutes in response to the test meal compared with ingestion of the test meal alone, demonstrating a possible weight-loss effect.[58] Iida et al demonstrated that, in healthy individuals, 5 g and 7.5 g of allulose consumed as preloads prior to 75 g of maltodextrin suppressed glucose levels in a dose-dependent manner compared with consumption of the maltodextrin.[59] Braunstein et al, however, found no effect of 5 g or 10 g of allulose on the postprandial plasma glucose response to a 75 g oral glucose tolerance test (OGTT) in a healthy population. However, the results did reach statistical significance in sensitivity analyses when the results were analyzed according to the assigned placebo (as opposed to the pooled placebo), and the magnitude of effect (25% reduction) was similar to that seen in the earlier trials by Kimura et al and Iida et al.[60] Noronha et al showed an effect of the same interventions in individuals with type 2 diabetes. Ingestion of 10 g of allulose together with a 75 g OGTT resulted in both a lower plasma glucose iAUC and plasma glucose absolute mean compared with a control of water, while a dose of 5 g of allulose had a borderline significant effect.[40] A systematic review and meta-analysis of acute feeding trials in people with and without diabetes showed that a small dose of allulose (<30 g) reduced the postprandial iAUC glucose response to the oral glucose load by 10%, while there was an indication of a nonsignificant improvement in iAUC insulin.[62] These randomized controlled trials demonstrate that small doses of allulose can lead to modest improvement in the postprandial glycemic response to co-ingested carbohydrate.

Longer-term randomized controlled trials show a benefit of allulose on adiposity and glycemic control, though the effect has not been consistently shown.[3,41] Hayashi et al compared consumption of a beverage sweetened with a rare sugar syrup (containing 6% allulose) daily for 12 weeks with that of a caloric-equivalent beverage sweetened with HFCS, and showed a reduction in body weight, fat mass, and waist circumference in the rare sugar syrup group in obese individuals.[3] In addition to allulose, this rare sugar solution also contained glucose, fructose, mannose, sorbose, and other oligosaccharides, making it difficult to attribute the effect entirely to the allulose content.[3] It should be noted, however, that the oligosaccharide content of the rare sugar syrup was similar to that of the HFCS

Table 4 **Rare sugars and their effects in human studies**

Rare sugar	Health-related effects			Side effects
	Healthy individuals	Obese/overweight individuals	Individuals with type 2 diabetes/ borderline type 2 diabetes	
Allulose	Acute: -reduced plasma glucose post-test meal[58,59] -no effect on plasma glucose[60] -increased FEE, decreased CEE[58] Longer term: -reduced BF[41]	Long term: -Reduced BW[3] -Reduced fat mass[3]	Acute: -Reduced glucose iAUC[40] Longer term: -No effect on plasma glucose or insulin[10] -Increased BF[9]	Diarrhea, abdominal pain, distension[41]
L-arabinose	Acute -reduced insulin and glucose peak post-test meal[11,13]	Longer term -reduced WC[12] -reduced TC[12] -reduced fasting plasma glucose[12]		Nausea, abdominal pain, diarrhea[12,13]
D-tagatose	Acute -appetite suppression[61] -lower glucose iAUC[14] Longer term -no effect on BW[16,17] -no effect on plasms glucose levels[18]		Acute -reduced glucose iAUC[15] Longer term -reduced BW[19,20]	Nausea, diarrhea, flatulence, bloating[61,18–20]
Trehalose	Longer term -no effect on BW[25]	Acute -reduced rise in plasma glucose and insulin levels post–test meal[21,22] (3)		Bloating, flatulence, diarrhea[22,25]
Isomaltulose (palatinose)	Acute -reduced plasma glucose post–test meal[26,28,32] Longer term -reduced HOMA-IR[35]	Acute -reduced plasma glucose post–test meal[27] Longer term -reduced BW[33]	Acute -reduced plasma glucose post–test meal[30] Longer term -no effect on BW[34] -reduced HOMA-IR[34] -no effect on HbA1c levels[36,37]	Diarrhea, nausea, constipation[34]

Abbreviations: BF: body fat; BW: body weight; CEE: carbohydrate energy expenditure; FEE: fat energy expenditure; HbA1c: hemoglobin A1c; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance; iAUC: incremental area under the curve; TC: total cholesterol; WC: waist circumference.

Table 5 **Rare sugars and their FDA, Health Canada, and EFSA designations**

Rare sugar	FDA designation	FDA intended use	Health Canada Designation	EFSA designation
Allulose	GRAS Notice 693	Bakery products, beverages, confectionaries, dairy products, sugar substitute, etc.	ND	N.D.
L-arabinose	GRAS Notice 782	Bakery products, baking mixes, condiments, confectionaries, dairy products, snack foods, etc.	ND	N.D.
D-tagatose	ND	ND	ND	Novel food
Trehalose	GRAS Notice 912	Bakery products, frozen desserts, dairy-based foods and toppings, hard and soft confectionery, etc.	Novel food	Novel food

Abbreviations: EFSA, European Food Safety Authority; FDA, Food and Drug Administration; GRAS, generally recognized as safe; ND not described.

intervention. Han et al assessed the effect of two allulose drinks of low (8 g) and high (14 g) dose compared with a 0.024 g sucralose beverage consumed daily for 12 weeks in healthy participants and found a reduction in body fat percentage and fat mass with both allulose drinks; the high dose additionally reduced total subcutaneous fat.[41] Conversely, Tanaka et al found that 15 g/day for 12 weeks of allulose supplementation led to an increase in body fat percentage in 18 diabetic or borderline diabetic participants.[9] This study lacked a control, and the change in body fat was ascribed by the authors to the additional calories provided by the allulose and the foods with which it was consumed.[9]

In a longer-term randomized controlled trial examining specifically allulose, Hayashi et al demonstrated that 5 g of allulose (compared with 5 g of glucose) 3 times a day for 12 weeks in 17 borderline diabetic participants resulted in no difference in either plasma glucose or insulin levels.[10] A systematic review and meta-analysis of controlled feeding trials of healthy and overweight/obese patients, assessing the effect of small dose of allulose on glycemic markers, did not demonstrate a benefit on hemoglobin A1c (HbA1c) or fasting insulin, though there was a small beneficial effect on fasting glucose.[63] In assessing the effect of allulose on cardiometabolic outcomes, Tanaka et al determined that consumption of either 5 g or 15 g of allulose for 48 weeks led to no changes in total cholesterol or LDL cholesterol in 82 hypercholesteremic males and females.[64] No side effects were observed. Han et al explored gastrointestinal tolerance to allulose in healthy participants and noted symptoms of severe diarrhea only in doses above 0.5 g/kg body weight. When a dose of 0.5 g/kg body weight of allulose was compared with the same dose of sugar, participants reported increased abdominal pain, distention, and diarrhea. Doses below this threshold, however, were not associated with an increase in the measured gastrointestinal outcomes, indicating that the average individual could consume roughly up to 0.5 g/kg body weight of allulose in a single dose without side effects.[41]

In summary, clinical studies show that both the short- and longer-term effects of allulose ingestion may lead to improvement in glycemic outcomes, with possible downstream benefit on body weight and body fat. It is hypothesized that allulose may competitively inhibit movement of glucose into the portal circulation, sharing the same glucose transporter, thereby reducing absorption of glucose in the small intestine.[40] Additionally, allulose may also increase hepatic glucose uptake, therefore encouraging glycogen synthesis, reducing glucose output from the liver, and reducing glucose plasma levels.[40] The beneficial effect on glycemic outcomes could also be due to a "catalytic" effect, whereby the small doses of fructose and its epimers may increase the rate-limiting glucokinase activity, leading to a subsequent increase in hepatic glucose metabolism.[65] In a recent guidance to the industry, the Food and Drug Administration (FDA) concluded, based upon scientific evidence, that allulose is virtually unmetabolized in the human body and thus allowed manufacturers to use a very low 0.4 calories per gram (kcal/g) for allulose. The FDA also concluded that, while allulose is a carbohydrate, based upon its chemical definition, it can be excluded from the "Total Sugars" and "Added Sugars" in a Nutrition Facts label because it is not metabolized, has almost no caloric value, and does not promote dental caries (see Table 5 for regulatory designations for rare sugars).[57] Overall, as allulose is generally regarded as safe by the FDA, it could prove to be a viable sweetener alternative to sucrose, given its demonstrated physiological and cardiometabolic properties.[57]

L-arabinose

Results from a total of three acute studies and one longer-term human study on L-arabinose and cardiometabolic risk factors have been reported (Table 2). L-arabinose is a monosaccharide and aldopentose found naturally in certain plant cell walls, including many grains and plant gums. It has half the sweetness of sucrose and has been shown in animals to be less metabolizable compared with glucose. With no caloric value, most of the studies examining consumption of L-arabinose in humans are acute post-prandial studies, and they demonstrate a benefit on glycemic control in healthy individuals. All acute trials examining the effect of L-arabinose in humans were conducted using a randomized controlled crossover design. Krog-Mikkelson et al showed that a number of doses of L-arabinose reduced insulin and glucose peak in healthy males when given prior to a test meal, compared with sucrose. In a similar study design, Shibanuma et al 2010 also found that, in both males and females, consumption of 2 g of L-arabinose before a 40 g sucrose test beverage led to reduced blood glucose levels at 2 hours compared with a control of water.[11] However, Halschou-Jensen et al were unable to confirm this effect and found that a breakfast meal supplemented with L-arabinose resulted in no changes in the peak plasma glucose or glucose iAUC compared with a sucrose-supplemented meal in healthy participants.

Yang et al examined the longer-term effect of L-arabinose supplementation in individuals with metabolic syndrome who consumed 40 g–45 g L-arabinose (dissolved in water) daily for 6 months with no alteration in lifestyle habits.[12] This intervention resulted in a reduction in waist circumference, total cholesterol, and fasting glucose, showing an overall benefit in participants with metabolic syndrome.[12] However, since this study lacked a control arm and participants were all diagnosed with metabolic syndrome, it is difficult to extend these results to a larger population. Regardless, the study results promise a novel approach to reducing cardiometabolic risk factors in persons suffering with metabolic syndrome.

No study has specifically examined the side effects of arabinose consumption, though they may occur: the abovementioned study by Krog-Mikkelsen et al showed that out of 15 participants, one experienced mild nausea after 1 g of arabinose, one experienced mild diarrhea after 2 g of arabinose, and another experienced a severe stomach ache and diarrhea after 2 g of arabinose.[13] Yang et al also noted that, with doses of either 40 or 45 g daily, 13 out of the 30 participants had mild nausea and diarrhea following treatment.[12] A study that specifically examined the gastrointestinal tolerance of arabinose would be helpful in determining arabinose's side effects and also the maximum recommended dose.

The mechanism by which L-arabinose affects glucose and insulin release in humans is unknown, but in rodent studies it has been shown to inhibit the brush border enzyme sucrose, which can reduce glucose absorption.[2] Further high-quality studies in humans will be needed to confirm its acute effects and help us to better understand the long-term effects of regular L-arabinose consumption on cardiometabolic outcomes.

D-tagatose

Table 2 shows the study characteristics of 4 acute and 6 longer-term human studies that have reported results for D-tagatose consumption and cardiometabolic risk factors. D-tagatose, a monosaccharide, is a C-4 epimer of D-fructose that is found primarily in whey milk protein and is 92% as sweet as sucrose.[42] While it has been used as a low-calorie sweetener alternative in milk and yogurt, there is a debate about its exact calorie content, with values ranging from 1.5 kcal/g to 3 kcal/g.[42,43] Multiple longer-term studies examining the effects of D-tagatose on body weight and blood glucose show a mild benefit.

Randomized acute controlled trials show a benefit for D-tagatose for both glucose and appetite control. In a crossover study, Wu et al demonstrated that in 10 healthy participants a beverage of 40 g D-tagatose and isomaltulose (palatinose), rather than a sucralose beverage, consumed prior to a test meal led to reduced glucose iAUC and serum insulin levels, and slower gastric emptying following the test meal.[14] Buemann et al, using a parallel study design, determined that giving 29 g of D-tagatose in a breakfast meal resulted in reduced appetite and decreased food intake at dinner on the same day in 19 healthy individuals, thus possibly acting as an appetite suppressant.[61] Similarly, Kwak et al conducted an acute cross-over trial in individuals with prediabetes or newly diagnosed type 2 diabetes who were given 5 g of D-tagatose compared with a combination of sucralose plus erythritol. The post–test meal glucose iAUC was reduced with tagatose compared with the control, indicating a benefit in the plasma glucose response.[15]

In longer-term studies in healthy individuals, D-tagatose was equivocal in showing benefit. Buemann et al (2 weeks, 8 individuals) and Boesch et al (4 weeks, 12 individuals) both showed no change in body weight with daily ingestion of 30 g and 45 g of D-tagatose, respectively, in a randomized controlled crossover trial.[16,17] The direction of effect still indicated a possible benefit; it is possible that the effect is small and can only be shown by a different dose or longer duration. In a

randomized controlled parallel trial, Saunders et al similarly examined the effect of 75 g of D-tagatose compared with sucrose daily for 8 weeks in 8 healthy individuals, but saw no change in any of the measured cardiometabolic outcomes, with included blood glucose levels, lipid levels, and uric acid levels.[18]

Compared with healthy individuals, the benefit in patients with type 2 diabetes was clearer. In two studies in patients with type 2 diabetes, both Donner et al (8 participants) and Ensor et al (112 participants) demonstrated that the ingestion of D-tagatose resulted in weight loss in a dose- and time-dependent manner.[19,20] Specifically, Donner et al showed that 45 g/d of D-tagatose for 12 months led to mean reduction of 3.1 kg in an uncontrolled trial, while Ensor et al confirmed this effect with a mean reduction of 5.1 kg in body weight with 45 g/d of D-tagatose for 12 months in a randomized controlled parallel trial.[19,20] Both studies also showed a non-significant reduction in HbA1C, indicating a possible benefit for blood glucose control in individuals with type 2 diabetes.[19,20]

Donner et al also noted that all 8 participants had mild gastrointestinal symptoms (including diarrhea, nausea, and flatulence) during the first 2 weeks of D-tagatose supplementation, but these effects subsided for the remainder of the 6 month trial period.[19] Ensor et al reported mild to moderately severe adverse effects, mostly due to gastrointestinal intolerance, with a 5% withdrawal rate due to adverse effects.[20] Boesch et al similarly reported diarrhea-like effects and increased bloating in 7 of the 12 participants during the tagatose phase of the study.[16] This was also seen by Saunders et al, in whose study the majority of participants experienced diarrhea and flatulence.[18] Lastly, in a study looking specifically at gastrointestinal tolerance of D-tagatose, Buemann et al determined that approximately 30 g of D-tagatose resulted in diarrhea in approximately 30% of participants, and nausea in approximately 15% of participants, with all individuals reporting flatulence during the 15 day study period.[61] As such, D-tagatose appears to have poor gastrointestinal tolerance at a range of doses, but the effects subside over time.

D-tagatose is known to inhibit the enzymes sucrase and maltase, resulting in reduced absorption of dietary disaccharides, which in turn can increase satiety, potentially explaining the observation of weight loss in human studies.[66] D-tagatose also promotes hepatic glycogen synthase and prevents glycogen breakdown, resulting in an increase in glycogen production, leading to reduced plasma glucose levels.[66] This mechanism, along with the evidence from the trials discussed, demonstrates that D-tagatose shows promise as an alternative sweetener, especially in individuals with type 2 diabetes.

Trehalose

Table 2 gives the study characteristics for all the included studies on trehalose: 2 acute and 3 longer-term human studies reported results for trehalose and cardiometabolic risk factors. Trehalose, a disaccharide of 2 glucose molecules with an α1,1-glycosidic linkage, is found in yeast, honey, shrimp, insects (for which it is the primary circulating form of energy), and some plants.[67] It is half as sweet as sucrose, but has the same caloric content.

Trehalose, in acute randomized controlled crossover studies, has been shown to reduce blood glucose levels.[44,45] Both van Can et al and Maki et al demonstrated that, in overweight adults, consumption of trehalose prior to a test meal led to a lower plasma glucose and attenuated insulin rise when compared with a glucose control.[21,22] Longer-term parallel controlled studies also show a benefit, but only in individuals with impaired glucose tolerance. Mizote et al determined that 10 g/d of trehalose compared with sucrose for 12 weeks in individuals with metabolic syndrome resulted in a reduction in the fasting plasma glucose levels, but this was limited to those individuals who had greater trunk fat.[23] Furthermore, when participants were stratified by body weight, individuals on the higher end of body weight also saw a reduction in waist circumference and systolic blood pressure.[23] Yoshizane et al similarly showed that, in healthy individuals, consumption of 3.3 g of trehalose for 12 weeks led to plasma glucose levels 2 hours after an OGTT being closer to fasting plasma glucose levels, compared with consumption of sucrose, indicating a benefit in lowering postprandial glucose levels.[24] Conversely, Kaplon et al compared 100 g/d of trehalose with 100 g/d of maltose (2 glucose molecules with an α1,4-glycosidic linkage) for 12 weeks in healthy individuals and saw no difference in body weight, lipid levels, or blood pressure between the groups, indicating a lack of benefit in a healthy population compared with more common sugars.[25] However, short- and long-term glucose control measures (such as blood glucose or HbA1c levels) were not measured in this study.

Side effects of trehalose have not been well reported. Kaplon et al saw mild to moderate gastrointestinal discomfort, including bloating, flatulence, and diarrhea in 4 of its 15 patients, while Maki et al reported no adverse effects.[21,22,25] As such, future studies should also look at the side effects of trehalose at different doses.

Trehalose is metabolized by the brush border enzyme trehalase, which cleaves the 1,1-glycosidic linkage, leaving 2 glucose molecules.[22] Trehalase activity, however, is shown to be slower compared with that of other

disaccharidase enzymes, leading to reduced absorption of trehalose and therefore a blunted glucose and insulin response.[22] However, trehalose has considerably fewer clinical trials compared with the other rare sugars discussed, and as such needs more long-term clinical and mechanistic studies to substantiate its use as a low-calorie alternative sweetener.

Isomaltulose (palatinose)

A total of 7 acute and 5 longer-term human studies reported results for isomaltulose and cardiometabolic risk factors, as shown in Table 2. Isomaltulose, a more intensely studied rare sugar also known as palatinose, is a disaccharide of glucose and fructose linked together by an α1-6 glycosidic bond.[46] Naturally found in small amounts in honey and cane sugar, isomaltulose has half the sweetness of sucrose.[46,47] While it does have the same caloric content as regular sugar, isomaltulose has been shown to improve the glycemic response in human studies, thus showing promise as an alternative sweetener.[46,68]

Acute randomized controlled crossover trials demonstrate a benefit for blood glucose and insulin levels from isomaltulose consumption. In an acute trial with 77 healthy adults, Kendall et al demonstrated that consumption of a trifle containing 72.3 g of isomaltulose, compared with one with the same amount of sucrose, led to a reduction in blood glucose levels at 60 minutes following the test meal, with no difference in mean satiety.[26] Suklaew et al showed a reduction in glucose iAUC following a meal supplemented with isomaltulose, compared with sucrose, in 12 obese males.[27] In a 24 hour study examining supplementation of isomaltulose against sucrose, Henry et al determined that low–glycemic index meals supplemented with isomaltulose led to a lower 24 h glucose iAUC as well as reduced glucose variability over the study period in 20 healthy adults.[28] This effect was also confirmed in individuals with type 2 diabetes by Ang et al, who demonstrated that ingestion of 1 g per kg of body weight of isomaltulose compared with sucrose resulted in reduced plasma glucose and insulin concentrations.[29] A similar effect was found by Sridonpai et al in individuals with type 2 diabetes, in which an isomaltulose-based breakfast reduced plasma glucose levels 30 to 60 minutes following consumption, compared with a sucrose-based breakfast.[30] This effect was carried forward to the next meal, when a standard lunch was given to both groups: those who had an isomaltulose-based breakfast still demonstrated lower plasma glucose levels following the second meal.[30] Arai et al confirmed a second-meal effect in 7 healthy males, with plasma glucose and insulin levels remaining low at lunch, following a test breakfast containing isomaltulose.[31] Finally, Maeda et al demonstrated that ingestion of 50 g of isomaltulose, compared with 50 g of sucrose, resulted in lower postprandial plasma insulin and glucose levels in 10 healthy males in a parallel controlled trial.[32] Overall, isomaltulose shows a benefit in lowering plasma glucose levels acutely compared with sucrose in both healthy participants and in patients with type 2 diabetes, and appears to have an additional second-meal effect.

Longer-term randomized controlled parallel studies also demonstrate a beneficial effect of isomaltulose on cardiometabolic outcomes in both healthy participants and in those at high cardiometabolic risk. In obese and overweight individuals, comparing the intake of 40 g/d isomaltulose with that of sucrose in a calorie-restricted diet, Lightowler et al demonstrated weight loss and reduction in fat mass in the isomaltulose group when given for 12 weeks.[33] Mateo-Gallego et al, on the other hand, did not see any additional effect of isomaltulose on weight loss in a population with type 2 diabetes by administering alcohol-free beer with or without isomaltulose plus maltodextrin for 10 weeks.[34] There was, however, a reduction in both Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) and insulin levels in the isomaltulose group but not in the regular alcohol-free beer group, indicating a possible benefit for insulin resistance.[34] Okuno et al further confirmed the benefit of isomaltulose for insulin response, because they showed that 40 g/d of a 50/50 isomaltulose and sucrose mix compared with 40 g/d of pure sucrose resulted in a significantly reduced HOMA-IR in healthy adults.[35] However, 2 studies, both looking at the effect of 50 g of isomaltulose on glycosylated hemoglobin levels compared with sucrose for either 4 or 12 weeks, found that isomaltulose did not lower HbA1c levels in a patients with type 2 diabetes, nor did it affect hyperlipidaemia.[36,37] The authors hypothesize that the dose provided was not enough to determine a true difference between the effects of isomaltulose and sucrose, suggesting further research is needed on the effects of different doses on HbA1c levels.[36,37]

Few studies saw any significant side effects of isomaltulose consumption, with only Mateo-Gallego et al reporting that a few participants experienced abdominal discomfort, nausea, diarrhea, and constipation.[34] To better understand the maximum tolerable dose of isomaltulose, however, future studies should examine gastrointestinal responses in a dose-dependent manner.

While the exact mechanism of how isomaltulose exerts its effect on plasma glucose and insulin levels has yet to be elucidated, Keyhani-Nejad et al determined that ingestion of isomaltulose (compared with sucrose) resulted in reduced gastric inhibitory polypeptide but increased glucagon-like peptide 1, explaining the

improved metabolic profile seen in many studies.[69] Overall, while in the literature there is a lack of isomaltulose's effect on body weight, there appears to be an improvement in insulin resistance in several studies, and therefore it may be of some benefit to individuals with type 2 diabetes, though more research is warranted.

Less-studied rare sugars

While there are numerous rare sugars that have yet to be studied in detail, there are a few that show potential in nonhuman studies (cell culture or animal studies). These include kojibiose, sorbose, and allose. Kojibiose, a glucose disaccharide connected by an α1-2 glycosidic bond, is found in honey in small amounts.[70] When examined in vitro in conditions mimicking the upper gastro-intestinal tract and small intestine, kojibiose demonstrated resistance to hydrolysis and was only cleaved by α-glycosidases, and then at a very slow rate.[70] This delayed digestion might explain the reduced absorption of glucose and may confer a benefit in managing blood glucose levels.[70] In addition, kojibiose has been shown to be a significant substrate for gut microbiota, creating a beneficial short-chain fatty acid profile, which makes kojibiose a prebiotic.[70,71] However, kojibiose has yet to be studied in clinical trials; thus, these possible benefits can only be hypothesized for humans.

Similarly, sorbose is a keto monosaccharide with structural similarity to fructose and 70% of the sweetness of table sugar.[48] It has been well studied in animal models: in long-term studies in rats, sorbose consumption for 2 weeks, compared with sucrose, led to decreased food intake and a reduction in body weight.[72] Furthermore, acute studies in rats have also demonstrated that sorbose, compared with sucrose, resulted in reduced glucose and insulin levels 30 minutes following ingestion, and the authors identified inhibition of sucrase as a possible mechanism for this result.[72] Currently, research is needed to identify sorbose's food sources, its effects in humans, its mechanism of action, and its potential as an alternative sweetener.

Lastly, D-allose, a C-3 epimer of glucose, is 80% as sweet as sucrose and, although its exact caloric content is unknown, it is estimated to be very low in calories.[48] While these properties would make D-allose ideal as a low-calorie sweetener, its cardiometabolic effects are not well known, with research instead focusing on its anti-cancer and anti-tumor properties.[73] Shown to inhibit proliferation of carcinoma cells and display strong antioxidant characteristics, D-allose shows benefit in overall inflammation and treatment of disease.[73] Future clinical trials should, however, also investigate allose as a replacement for sucrose, and its subsequent cardiometabolic effects. Overall, the current literature contains very little information on these rare sugars, in particular whether these sugars would be beneficial as alternative sweeteners, thus providing future areas of research on rare sugars.

Conclusion

Rare sugars, specifically allulose, L-arabinose, D-tagatose, trehalose, and isomaltulose, are exciting in that they may become alternative sweeteners that will offer many physiological and cardiometabolic benefits, ranging from weight loss to improving glycemic control and reducing insulin resistance. Many of these rare sugars need high-quality randomized clinical trials in a larger number of participants coming from a greater variety of health backgrounds, to substantiate many of their benefits. Indeed, for allulose, which has been studied fairly extensively, manufacturers can now state a very low caloric content for it and can also exclude it from "Total sugars" and "Added Sugars" on the Nutrition and Supplemental Facts label in the USA, as per FDA guidance.[57] Further data elucidating the mechanism of the beneficial effects of these rare sugars is also needed. Given that future research may confirm the safety and benefit of these rare sugars for use as alternative sweeteners, commercialization of these rare sugars could be of great value in helping mitigate the risk associated with diseases such as obesity and type 2 diabetes.

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SUPPORTING INFORMATION

The following Supporting Information is available through the online version of this article at the publisher's website.

Table S1 **Search term strategy to identify the effects of rare sugars in human studies**

Figure S1 **Flow of the literature**

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