Narrative Review

INSIGHTS INTO *IN VIVO* GLYCEMIC REGULATIONS BY RESISTANT STARCH IN RODENT MODELS

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ABSTRACT

Over the years, resistant starch (RS) rich diet has gained numerous attention due to its health benefits in terms of improving glucose response in healthy or diabetic subjects. This review compiles *in vivo* studies done over the past 10 years related to the antidiabetic effects of RS prepared in different forms and from different sources; tested specifically in either non-diabetic or diabetic rodents. Few attempts have been made to improve the RS content through several methods including processing techniques, chemical modifications, mixture combinations or cooking methods for glycaemic control. In principle, RS exerts its postprandial blood glucose levels effects through different modes of action particularly in the gastrointestinal tract by inhibiting starch-digesting enzymes activity which ultimately delays carbohydrate digestion and decreases glucose absorption. In addition to *in vitro* studies, the glucose-lowering effects by different sources of RS were also further tested and confirmed in vivo using numerous test systems including healthy, diabetic and diabetic-induced rodents. This review has shown the beneficial effects of several types of RS in terms of managing postprandial blood glucose levels and glucose regulation in non-diabetic and diabetic rodent models. RS improved pancreatic β-cell islets content, density and functions, which may contribute to the glucose homeostasis in diabetes. The findings based on *in vivo* studies in rodents may justify further research on different types of RS to be replicated in the suggested animal models or carried out in human trials for diabetes management.

KEYWORDS: Antidiabetic, Glucose-lowering, Glycaemic, Resistant Starch, Type 2 Diabetes

INTRODUCTION

Type 2 diabetes (T2D) is a metabolic disease associated with hyperglycaemia due to diminished insulin secretion by the β-cell islets and insulin resistance in target tissues, resulting in decreased glucose peripheral utilisation and improved hepatic glucose output (1,2). Primary prevention and early treatment are crucial to prevent macrovascular and microvascular complications (3). Lifestyle modifications in combination with medications have been shown to be important in the prevention and delay of complications (4).

The beneficial effects of resistant starch (RS), an indigestible starch, have been investigated related to blood glucose regulation which is one of the main therapeutic targets in diabetic patients (5). Resistant starches are categorised into five types; RSI (Physically inaccessible starch: coarsely ground or whole-kernel grains), RSII (Granular starch with the B- or C-polymorphism: high amylose maize starch, raw potato, raw banana starch), RSIII (Retrograded starch: cooked and cooled starchy food), RSIV (Chemically modified starches: crossed-linked starch and octenyl succinate starch) and RSV (Amylose-lipid complex: stearic acid-complexed high-amylose starch) (6). RS can be categorised as one of the five types (RSI-V), some of which occur naturally in foods and are incorporated into food products, produced or modified commercially (7).

The higher the RS content in the food, the slower the digestion rate in the intestine and thus, the lower the glycemic index (GI) values, which indicate the ability of food to raise the blood sugar level after it is consumed. There are several factors affecting the GI of a food such as cooking method and duration, age, activity and digestive system health (8) as well as the structure of amylose and amylopectin. Low GI foods prevent blood glucose and insulin secretion from spiking after meals (9).

In principle, RS resists digestion in the small intestine and then is fermented by microbes in the colon which prevents a glucose spike and thus reduces postprandial glucose (7). The underlying mechanisms behind the low glycaemic response by RS mainly involve the inhibition of the starch digesting enzyme, α-amylase which delays carbohydrate digestion and reduces glucose absorption (10). Dietary RS might improve human health by altering the gastrointestinal tract function, mainly in adults at risk for developing diabetes (11). Therefore, several *in vitro* investigations have been performed to measure the inhibitory effects of α-amylase (12,13) and α-glucosidase (14) to understand the mechanisms of blood glucose-lowering in response to RS content in the gastrointestinal tract. To further confirm the *in vitro* results, *in vivo* experiments were performed using several models of T2D rodents which have similar diabetic characteristics to humans with impaired insulin secretion by the pancreas and decreased insulin sensitivity in the target tissues.

Besides *in vivo* studies, past reviews on meta-analysis and systematic reviews have compiled research done on the efficacy of consuming RS in humans (15-18). However, a compilation of pre-clinical experiments, particularly in vivo comparing the effects of RS in different diabetic animal models has not been done. Since diabetic animal models possess similar characteristics to diabetic humans in terms of impaired insulin secretion and resistance, any pre-clinical data obtained is valuable to determine if further confirmation needs to be carried out in humans. Thus, this review aims to compile pre-clinical studies to establish the importance of the glucose-lowering effects of RS in rodents in improving diabetic conditions and delaying complications which may be potentially further confirmed with clinical trials.

MATERIALS AND METHODS

Search Strategy

Original articles were searched based on three databases (PubMed, ScienceDirect and Scopus) from the year 2011 to 2021 to ensure all RS types were selected within the duration of 10 years. The keywords “diabetes” and “resistant starch” were selected to ensure only relevant articles were being generated. Publications with available abstracts were reviewed and limited to studies published in English language only. Only publications related to in vivo studies in rodents were included. Review articles, letter to editors and articles with no full access were excluded. Duplicate articles were eliminated. All investigators were involved in searching, screening and selection of articles.

RESULTS

Figure 1 shows the PRISMA flowchart used for the selection of articles. A total of 330 articles were generated from three different search engines: Scopus,

ScienceDirect and Pubmed. A refined search found only 56 articles were relevant to *in vivo* studies and related to the search terms. Further assessment based on the full text availability, peer-reviewed articles and library collection access resulted in only 19 full articles, which were included in this review.

Table 1 depicts the antidiabetic effects of several types of RS using different types of animal models and with different treatment duration affecting the glucose, insulin and hormone regulations. The RS types used were different in all studies which include native/modified gayam starch (19), germinated brown rice-based flour (20), sprouted/fermented/toasted quinoa flour (21), native starch, pyrodextrin, enzymatically resistant maltodextrin (ERM) (22), arrowroot, kidney beans flour and modified cassava flour (Mocaf) (23), Coleus tuberosus fluor/ crackers (24), corn starch, the high-quality premium rice Koshihikari and ae mutant rice cultivar KOY (9), dietary RS (HAM-RS2) (25), low maltodextrine/high starch, Hi-Maize, Fiberysm (26), glucidex (GLU), gelatinized corn starch (S), enzymatically modified starch (EMS) or RS (27), AIN-93G diet consisting of either 10% RS or 20% RS (HRS) (28), Wx/ae and Koshihikari rice (29), RS diet with 30% RS (30), cornstarch (31), sago analog rice, modification of sago analog rice with flour (32), high amylose maize (33), HA2 transgenic rice or regular Wild type in an indica rice cultivar (34) and different oat forms (35).

The animal models used as test systems in the experiments include healthy non-diabetic, diabetic and diabetic-induced rats or mice with varying stages of insulin resistance and β-cell defect. The healthy rats used include Wistar (21,22) and Sprague Dawley (19,33,35) rats whereas the animal model of spontaneously T2D includes the non-obese Goto kakizaki rat (GK) (30) and obese Zucker diabetic fatty (ZDF) (27,34) and lean Zucker diabetic rats (28). The diabetic-induced rats or mice with intraperitoneal injections of Streptozotocin (19,23,25,31,33,35,36) or Alloxan (24) were also used in several studies by either fully or partially destroying the pancreatic β-cells islets to mimic the T2D characteristic. Non-diabetic mice such as C57BL/6 (9,25), germ-free C3H mice (26) and spontaneously non-insulin-dependent diabetes mellitus mice Nagoya-Shibata-Yasuda (NSY/Hos) (29), mild glucose intolerance glucagon-like peptide-1 receptor (GLP-1R) knockout (KO) mice (25) were used to understand the effects of RS. Blood glucose, insulin and hormones were measured to understand the mechanisms involved. To understand the effects on the glucose regulations, treatments were given between 4 to 24 weeks in rodents.

DISCUSSION

This review compiled research studies done over the last 10 years on antidiabetic effects using different forms and types of RS tested in different pathophysiological features of rodent models. The results showed that in response to different types of RS given to the diabetic and healthy rodents, the blood glucose level was found to be decreased and genes associated with glucose regulation were expressed. The shortest treatment duration given for 4 weeks to rodents showed significant blood glucose lowering effects (19,20,23,32,33,34). This indicates the potential of RS in managing blood glucose, which may help in diabetes management.

For many years, animal models have been used for the characterisation and exploration of disease pathophysiology, target identification as well as studies on the assessment of novel therapeutic agents and in vivo experiments (37). Glucose tolerance test was performed in several studies by giving glucose load, followed by blood glucose measurement at different time points from 0 to 120 minutes. Glucose tolerance tests are often performed after an overnight fast to determine whether there is glucose intolerance or insulin insensitivity (38). Other parameters were also measured such as HbA1c, serum insulin, pancreatic islets content and β-cell function (HOMA-β) which indicates the effects of RS treatment in diabetes.

Glucose tolerance test was compared in mice fed with saccharose, glucose and germinated brown rice (GBR) (non-modified and enzymatically modified) starches. After 4 weeks, lower blood glucose reduction in the modified GBR starches was observed as compared to the non-modified GBR. The highest blood glucose level was at 120 min for GBR starches compared to other treatments. They also showed that modified GBR flour could maintain a low glycaemic index in diabetic mice (20).

Modified gayam starch fed to streptozotocin-induced diabetic Sprague Dawley rats showed the lowest blood glucose level after 4-weeks treatment followed by native gayam and the control group. Besides the hypoglycaemic effect, gayam starch-modified also exhibited the highest short-chain fatty acids (SCFA) content, which revealed the potential to be developed as a functional food (19). SCFA which is generated by

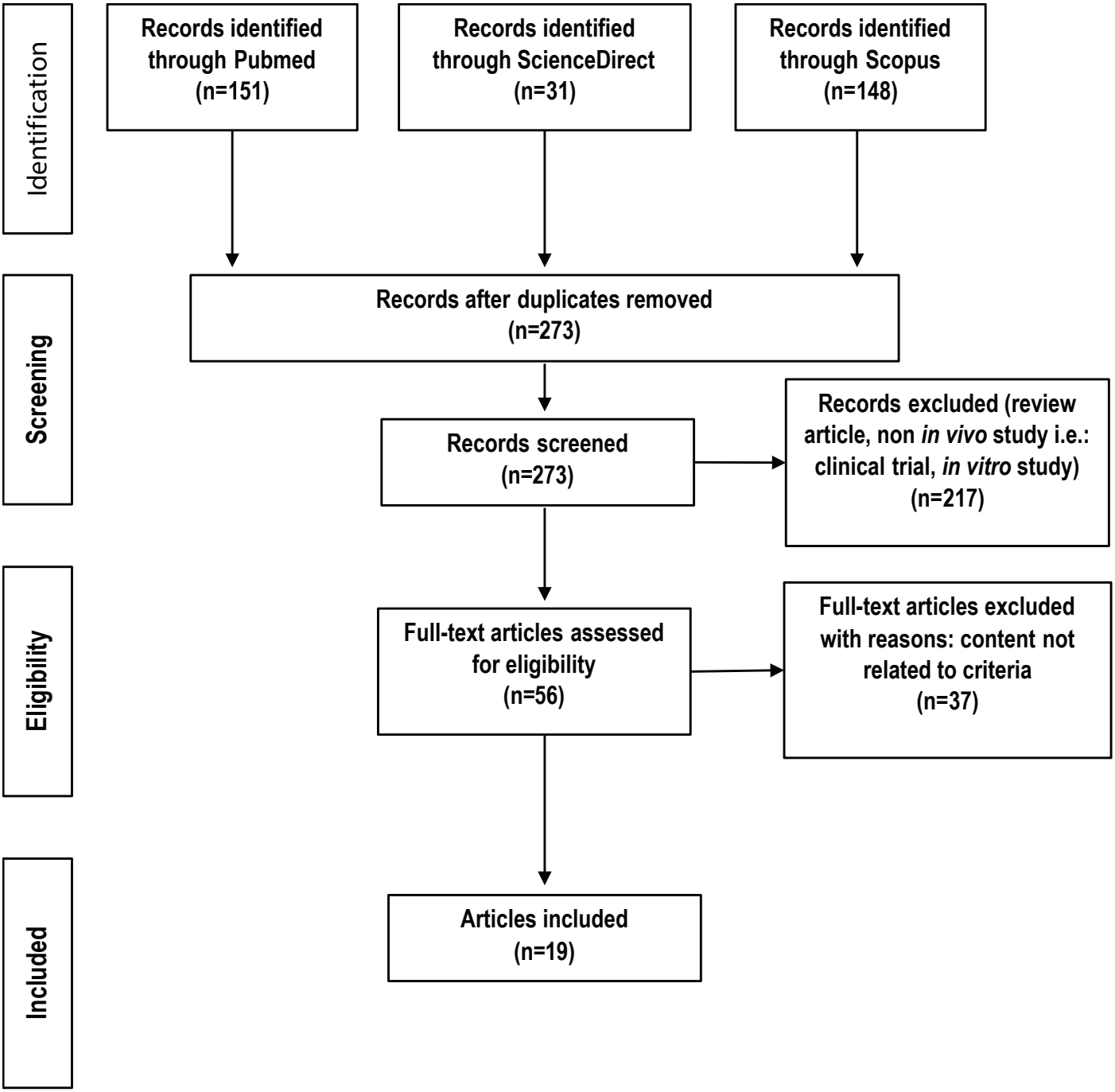

Figure 1: PRISMA flow diagram on the selection of articles.

Table 1. The antidiabetic effects of several types of RS using different types of animal models and different treatment duration.

No	Ref	Objectives	Samples/Treatment Groups	Duration	Animal Model	Blood Glucose and Insulin	Other Parameters	Conclusions
1	(20)	To investigate the effects of maltogenic amylase (Mase) on Modified GBR-based flour 5(MGBRF) and bioactive compounds (BCs) release with possible health benefits on normal and diabetic mice.	Starch was modified with four levels of Mase and spray-dried (0, 133, 266 and 399 U Mase/g flour).	4-week	Swiss strain and diabetic mice, aged 6–8 week, 25–30g body weight.	Glucose content (mg/dL), 120 min for OGTT GBR base flour nonmodified:272.7 ± 65.52 GBR base flour modified by MAse:146.78 ± 30.44 Glucose: 147.67 ± 14.54 Sucrose: 202.54 ± 9.35	Glycaemic Index Week 0 NS:7.67 ± 3.89 MA:7.13 ± 0.97 T2D-NS: 22.8 ± 0.26 T2D-MA: 23.63 ± 4.48 T2D-NS-M: 32.57 ± 1.27 T2S-MA-M:27.2 ± 2.7 Week 4 NS:6.57 ± 1.52 MA:6.1 ± 0.26 T2D-NS: 26.37 ± 1.5 T2D-MA: 22.1 ± 2.34 T2D-NS-M: 20.1 ± 2.31 T2S-MA-M:14.37 ± 1.36	BCs released considerably couple with the changes in starch properties caused by Mase enhanced the effectiveness of this product to diabetes.
2	(19)	To evaluate the antidiabetic properties (blood glucose and short chain fatty acids (SCFA) levels) of modified gayam starch *in vivo.*	I-DM: standard diet AIN 93 M II-NGS: native gayam starch diet III-MGS: modified gayam starch by autoclaving-cooling for three cycles diet.	4-week	Diabetic Sprague Dawley rats induced diabetic with streptozotocin-nicotinamide (STZ-NA).	Blood glucose (mg/dL) Week 0 DM:260.34 NGS:261.09 MGS:258.21 Week 4 DM:279.06 NGS:129.08 MGS:98.84	Total Short-chain fatty acid (mmol/L) DM:21.38 NGS:55.45 MGS:99.61	Feeding on high RS modified gayam starch revealed an antidiabetic potential as evidenced by reduced blood glucose and increased SCFA caecum levels. The gayam starch modified exhibited the most hypoglycaemic activity and SCFA content, so it had potential prospect to be developed as functional food.

3	(36)	To assess the effects of insufficient GPR109a signalling, via genetic deletion of GPR109a, on the development of renal injury in diabetic nephropathy.	Control diet or an isocaloric high-fibre diet (12.5% RS).	24-week	Male mice homozygous for deletion of the GPR109a receptor (Gpr109a−/−), diabetes was induced at 6 week of age by five daily intraperitoneal injections of STZ (55 mg/kg) in sodium citrate buffer.			12.5% RS supplementation did not protect from renal injury in diabetic nephropathy.
4	(35)	To compare the beneficial effects of several oats and to investigate the correlations between the key phylotypes of gut microbiota and type 2 diabetes (T2D) indexes and inflammation indexes in high-fat diet induced T2D rats.	I-BCD II-HFD III-HFD+WO IV-HFD+ORS V-HFD+OG WO, whole oat foods; OG, oat β-glucan; ORS, oat resistant starch; BCD, basic chow diet; HFD, high-fat diet.	9-week	Male Sprague-Dawley rats (4 weeks old, 105 ± 10 g body weight), diabetic induced by high-fat diet and STZ injection (30 mg/kg body weight)	HFD group showed remarkably increased levels of FBG, OGTT, AUC of OGTT, FPI, HOMA-IR, and HbA1c, while remarkably decreased levels of HOMA-β and C-peptide comparing with BCD group. After 9 weeks of dietary intervention, all the three oat products significantly decreased the levels of FBG, OGTT, AUC of OGTT, HOMA-IR, and HbA1c, while significantly increased the level of C-peptide. WO and OG also showed significant improvement in HOMA-β. Among the three oat products, WO exited better effects than ORS and OG.		WO exhibited better effects on ameliorating insulin resistance and glucose tolerance than OG and ORS ($p < 0.05$).

5	(21)	To measure food intake, blood glucose and lipid levels, and accumulation of epididymal adipose tissue in rats fed diets supplemented with quinoa.	I- (A, standard) II-(B, with high glucose levels, 31.5%) III- (C, with 31.5% glucose and 15% toasted quinoa flour) IV-(D, with 31.5% glucose and 15% sprouted and toasted quinoa flour)	47 days	Wistar rats, aged 56 days, 233.27 ± 27.2g body weight.	Initial blood glucose (mg/dl) A-77.4 B-72.0 C-81.75 D-77.66 E-81.5 F-80.3 Final blood glucose (mg/dl) A-78.0 B-79.4 C-69.6 D-69.58 E-73.83 F-75 Postprandial blood glucose (mg/dl) A-142.86 B-140.88 C-135.47 D- nil E-135.8 F-132.12		Quinoa reduced GI, reduce blood glucose levels and lipid levels, food intake and the accumulation of epididymal adipose tissue in Wistar rats
6	(22)	To identify the effects of modified banana starch on glycaemic control and blood pressure in rats fed with high sucrose diet (HSD).	20 rats received a high sucrose diet (HSD) and 5 were fed a normal diet and purified water (PW) for 12 weeks. At the end of week 8, the rats fed with HSD were divided into four groups;	12- week	Wistar rats	Starch treatments reduced glucose, insulin, HOMA-IR, and blood pressure (BP) in comparison with PC. Glucose AUC (0-120 min) was also decreased after starch treatments with respect to PC		NS and its modified products exerted beneficial effects on glycaemic control, lipid metabolism, and BP in obese rats fed HSD. Although the modified starches presented lower resistance to digestion than NS, their expected properties were maintained.

			I-positive control (PC) II- native starch (NS) III-pyrodextrin (PI) IV-enzymatically resistant maltodextrin (ERM). The negative control (NC) comprised the five rats fed PW.					
7	(23)	To confirm hypoglycaemic property of rice made from mocaf (fermented cassava flour), arrowroot and kidney beans.	Mocaf, arrowroot flour and kidney beans flour. I-H: Healthy rats+AIN 93M II-DM: Diabetes+AIN 93M III-C4: Diabetes+rice IV-AR: Diabetes+analog rice	4-week	Male white Wistar rats, induced diabetic with STZ-NA aged 2-3 months old, 200-250g body weight.	Blood glucose level (%) Week 0 H: 77.03 ± 1.32 DM: 207.63 ± 4.04 C4: 210.5 ± 5.41 AR: 215.07 ± 8.6 Week 4 H: 79.12 ± 1.10 DM: 210.98 ± 3.82 C4: 170.69 ± 2.72 AR: 96.62 ± 2.92	Total Short-chain fatty acid (mmol/L) H:44.14 ± 9.58 DM:36.45 ± 3.56 C4: 50.76 ±12.36 AR:53.96 ± 4.76 Langerhans islets number H:9.80 ± 5.81 DM:3.8 ± 2.77 C4: 6.8 ±1.78 AR:10.6 ± 3.56	RS and dietary fibre was responsible to glucose reduction effect by analog rice diet through SCFA as RS fermentation product in colon.
8	(32)	To investigate the hypolipidaemic effect of rice analog derived from ago and red bean flour in STZ-NA induced diabetic rat model.	I-(control): AIN96M (STD) II-standard dietary food (STDD) III-mentik wangi rice diet (MWRD) IV-sago analog rice (SARD) V-sago analog rice with 10% red bean flour (SARKBD).	4-week	Wistar rats aged 2-3 months with 200-250 g body weight.	HOMA-IR STD: 0.79±0.56 STDD: 9.13±3.31 MWRD: 5.61±0.81 SARD: 1.96±0.27 SARKBD: 2.3±0.8	Langerhans islets range STD:(8.4 ±3.98 to 23.20 ± 11.65) STDD:(4.6±1.95 to 6.4 ± 2.88) MWRD:(7.4±5.13 to 16.8 ± 7.16) SARD:(10.0±6.82 to 27.2 ± 13.97) SARKBD:(11.8±7.63 to 33.6±16.92)	SARD and SARKBD treatment could reduce the insulin resistance and increase the number of pancreatic β-cells.

9	(24)	To identify the effects of *Coleus tuberosus* crackers in lipid and glucose profiles.	Four treatments I-normal mice (NM): AIN 93 diet II-diabetic mice (DM): AIN 93 diet III-diabetic mice: Coleus tuberosus flour diet (DMF) IV-diabetic mice: Coleus tuberosus crackers rich in RS type 3.(DMC)	28 days	Wistar type white mice, 110-150 g body weight, intraperitoneal injection of alloxan (125 mg/kg)	Blood glucose (mg/dl) Day 0 NM: 65.24 ± 3.08 DM: 217.56 ± 6.75 DMF: 215.5 ± 7.85 DMC: 213.26 ± 2.7 Day 28 NM: 66.36 ± 2.85 DM: 217.02 ± 5.2 DMF: 121.43 ± 5.91 DMC: 108.99 ± 3.52		The raw materials which are rich in resistant starch type 3, *Coleus tuberosus* flour and crackers can potentially be consumed as a functional food to improve lipid profiles and glucose in diabetes mellitus condition.
10	(9)	To develop a novel product that inhibited both Aβ protein production and the abrupt increase in postprandial BGLs using super-hard brown rice bread blended with black rice bran (SRBBB).	I-Rice bread of 100% KOY brown rice flour II-Rice bread of 94.6% KOY brown rice flour mixed with 5.4% OKM rice brown (SRBBB) III-Commercial feed (MF) diet IV-Commercial feed (MF) diet mixed with 0.02% ferulic acid.	12-week	C57BL/6 mice, 24 week old.	KOY brown rice bread showed significant lower Aβ40 in blood than ordinary rodent diet after feeding aged mice.		Some metabolic benefits exerted by dietary RS, especially improvements in insulin levels, occur independently of the microbiota and could involve alterations in the bile acid cycle and adipose tissue immune modulation.

11	(26)	To determine the effects of RS when added to a Western diet on host metabolism in mice with and without a microbiota.	LFD (D12450K) and a customized WD (45% kcal from fat and 17% kcal from sucrose with low maltodextrine/high starch compared to D12451) where part of the corn starch was replaced by either 10% RS type 2 or 10% RS type 4.	8-week	C57BL/6 mice, 24 week old. Germ-free C3H mice and C57BL/6 (B6) mice.	Feeding a RS4-supplemented WD significantly decreased plasma insulin levels in CVZ mice. Feeding RS4 significantly improved the index of insulin resistance independently of the gut microbiota; feeding RS2 showed a similar trend.		Some metabolic benefits exerted by dietary RS, especially improvements in insulin levels, occur independently of the microbiota and could involve alterations in the bile acid cycle and adipose tissue immune modulation.
12	(27)	To study if waxy maize modified enzymatically with an increased degree of branching delayed the onset of diabetes in male Zucker diabetic fatty (ZDF) rats.	Experimental diets containing 52.95% starch I- gelatinized corn starch (S) II- glucidex (GLU) III-RS IV-enzymatically modified starch (EMS).	9-week	Male Zucker diabetic fatty (ZDF) rats, aged 5 weeks.	Plasma glucose was significantly lower in rats fed with S and RS diets (13.5 mmol/L) compared to rats fed with GLU and EMS diets (17.0 -18.9 mmol/L). Rats fed RS had lower HbA1c level (4.9%) than rats fed with S, GLU, and EMS (5.6-6.1%).		EMS did not delay the progression of diabetes in ZDF rats. No signs of diabetes was observed in rats fed with RS.
13	(28)	To identify the potential mechanisms of dietary RS type 2 in preventing proteinuria and promoting vitamin D balance in type 2 diabetic (T2D) rats.	Lean Control (LC) group;Lean Zucker rats fed with AIN-93G control diet containing 550 g/kg of corn starch. Zucker diabetic fatty rats were treated with I- AIN-93G control diet containing 550 g/kg of corn starch (DC)	6-week	Lean Zucker rats and Zucker diabetic fatty rats.	RS had significant effect on blood glucose and HbA1c. Adiponectin was 77% higher in HRS-fed compared to DC-fed rats.		

			II- AIN-93G diet containing 275 g/kg of corn starch and 275 g/kg of HAM (MRS) II- AIN-93G diet in which corn starch was replaced by 550 g/kg of HAM (HRS).					
14	(25)	To identify if sitagliptin and RS have a synergistic interaction in the GLP-1 induction.	Mice was given Sitagliptin (0.4g/100g diet) and tested with different dosages of dietary RS (HAM-RS2) at (0, 15, or 28g/100g diet).	11-week	Male C57BL/6 (WT) mice (7-weeks old), injected intraperitoneally with 40 mg/kg STZ. In another study part, male GLP-1R Knockout (KO) mice was used.	Improved glucose metabolism in WT mice but not in KO mice. The result suggests that the effect in glucose metabolism is dependent on GLP-1R, and clearance of plasma GLP-1 is dependent on the receptor.		The effect of sitagliptin was partly improved by RS.
15	(33)	To compare genome-wide analyses in liver tissues of STZ-induced diabetic rats in response to RS treatment using an oligonucleotide microarray.	RS, from high amylose maize (Hi-maize™)	4-week	Healthy male Sprague–Dawley rats (non-diabetic), 190 ± 10 g body weight. Diabetic induced with intravenous injection of STZ (45 mg/ kg).	Several genes related to glucose metabolism in the Local Gene Network were differently expressed in response to RS treatment; Phka1, Hk2, Gckr, Gck,Aldob,G6pc,Pygm, Ppp1r3a, Gapdh, Akr1b1, Pklr,Eno2 and Pck1.		RS activated the glucose metabolism process and resulted in blood glucose reduction.

16	(31)	To determine if treating high-amylose maize in STZ-treated rats may prevent the megalin and Dab2 function. The effects on urinary excretion of vitamin D, 25-hydroxycholecalciferol (25D3) and vitamin D-binding protein (DBP) functions were also evaluated.	I-Control-treated rats which were given standard semipurified diet (AIN-93G) with commercial corn starch II-STZ-treated rats which were given the AIN-93G diet III-STZ-treated rats which were given RS diet and amylose maize (RS).	5-week	Male Sprague-Dawley (Harlan) rats (body weight: 100–130 g). STZ-injected [60 mg/kg body weight whereas control rats were injected with vehicle (10 mmol/L citrate buffer, pH 4.5).	Blood glucose (mg/dL) 2-week Control: 209 ± 26 Diabetic: 613 ± 23 Diabetic+RS:438 ± 39 5-week Control: 249±13 Diabetic: 591±93 Diabetic+RS:574±59		Blood glucose levels were decreased in Diabetic+RS rats than in Diabetic rats at 2-week but no significant difference was observed at 5-week.
17	(29)	To examine the effects of wx/ae and Koshihikari brown on glucose and lipid metabolism.	Wx/ae and Koshihikari rice.	10-week	Type 2 diabetic NSY/Hos mice, aged 6 weeks.	The blood glucose (fasting) was significantly lower, glycaemic status and the pathological score for glycosuria was better in the wx/ae group compared to the Koshihikari group.		wx/ae brown rice intake improved plasma lipid level and glycaemic status.
18	(34)	To identify if high-amylose rice improves animal health in normal and diabetic rats	HA2 transgenic rice or regular Wild type (WT rice (SBE), SBEI and SBEIIb, in an indica rice cultivar.	4-week	Male Zucker diabetic fatty rats and Sprague Dawley.	Plasma glucose (mM) in Sprague Dawley rats HA2:6.59±1.04 WT:5.87±0.32 Zucker diabetic fatty rats (ZDF, T2D) fed with HA2 rice starch showed reduced plasma glucose levels compared to WT rice-fed rat.		High-amylose rice, HA2 improved glucose response in T2D. However, no significant difference was observed in normal SD rats or type-1 diabetic rats.

19	(30)	To confirm if dietary-RS may improve insulin sensitivity and pancreatic β cell mass in a type 2 diabetes rats.	I- GK (EC): fed with energy control diet. The equal energy density control (EC) diet with 100% amylopectin corn-starch II-GK (RS): fed with resistant starch diet with 30% (w/w) type 2 resistant starch (Hi-Maize® corn-starch containing 60% amylose. Wistar rats (genetic control}: fed with the equal energy density control (EC) diet with 100% amylopectin corn starch.	10-week	GK rats, aged 5 weeks and 80–100 g body weight and Wistar rat.	Pups produced from GK rats- RS fed showed lower fasting glucose, improved pancreatic insulin content compared with pups from GK rats- EC diet fed. No significant difference was observed in fasting serum insulin concentration, β cell density, 2 h glucose and insulin sensitivity (HOMA-IR) between the 2 groups.	Pancreatic Islets: GK had lower islets followed by non-diabetic Wistar rats. GK-EC rats showed the least. Pancreatic insulin content No significant difference between GK rats-RS fed and GK rats EC-fed. The β cell relative densities Between groups. Wistar rats: 0.758±0.24% GK-EC rats 0.301±0.09% GK-RS rat, 0.56±0.13% Islets shape, size and morphology GK-EC rats: the large islets displayed irregular capsules, disrupted configuration. Wistar rats: clearly boundary and homogeneously stained β cells.	Dietary RS has the potential in treating diabetes and help to improve outcomes of pregnancy complications by diabetes.

the gut microbiota modulates host energy and glucose metabolism affecting energy, insulin release and appetite. An imbalance in SCFAs influences the pathogenesis of both T2D and type 1 diabetes (T1D) (39).

In another study, an isocaloric high-fibre diet consisting of 12.5% RS (control diet) given for 24 weeks to diabetic-induced mice with streptozotocin injections showed that supplementation with RS had no protection against renal injury in diabetic nephropathy (36). Different types of oats such as oat resistant starch (ORS), whole oat (WO) and oat β-glucan (OG) improved inflammation, insulin resistance and gut microbiota in diabetic male Sprague-Dawley rats, induced by streptozotocin injection and high-fat diet. These findings highlight the importance of consuming oat products for human health (35).

Using Wistar, a non-diabetic rat model, a study showed that the food consumption, accumulation of epididymal adipose tissue, blood glucose and lipid levels were decreased after 47 days in rats fed diets supplemented with quinoa which may help in several disease risk preventions including diabetes (21). Native starch and its modified products given to obese Wistar rats receiving a high sucrose diet showed beneficial effects in terms of glycaemic control, lipid metabolism and blood pressure. Starch treatments for 12 weeks significantly reduced glucose, insulin, HOMA-IR, and blood pressure in comparison with positive control (PC). The area under the glucose curve AUC (0-120 min) was significantly decreased after starch treatments with respect to PC (22).

Wahjiningsih et al. reported that after 4-weeks treatment with analog rice (AR), the diabetic-treated rats showed the lowest blood glucose level with a higher level of total short-chain fatty acids (SCFA) concentration and higher Langerhans islets as compared to rice variety C4 (23). It was concluded that RS and dietary fibre were associated with blood glucose lowering effect by analog rice diet mediated by SCFA as a RS fermentation product in the colon (23).

In another study done by Wahjiningsih et al., treatment with Sagu Analog Rice (SARD) and Sagu Kidney Bean Analog Rice (10% kidney bean) (SARKBD) in streptozotocin-induced diabetic rats for 4 weeks improved insulin resistance and increased the number of pancreatic β-cell islets in male white Wistar rats (23). The tissue staining indicated that the number of Langerhans islets in the SARKBD was higher as compared to the Menthik Wangi Rice Diet (MWRD) group and the control group. HOMA-IR at the end of the SARD and SARKBD treatment groups was slightly higher than the control group STD. This provides evidence on the potential of SARD and SARKBD treatment in reducing insulin resistance and improving the number of pancreatic β-cell islets (32).

Coleus tuberosus flour and crackers rich in RS type 3 intake have been shown to improve lipid profile and glucose in diabetic mice induced with alloxan. The results of this study suggested that the raw material of Coleus tuberosus flour and crackers which are high in RS type 3 can possibly be taken as a functional food, which may improve lipid and glucose profiles in diabetes (24). The postprandial blood glucose level of super-hard brown rice bread blended with black rice bran (SRBBB) was also evaluated in C57BL/6 mice. The blood glucose levels in mice fed with SRBBB after 12 weeks were significantly reduced as compared to the control-treated group. The results indicate promising effects of SRBBB in preventing postprandial blood glucose spikes (9).

To evaluate the role of the gut microbiota in mediating the metabolic benefits, both germ-free C3H (GF) and conventionalised (CVZ) B6 mice were treated for 8 weeks with either a control Western diet (WD) or a WD enriched with10% RS. The results showed that in CVZ mice, the RS4-supplemented WD group showed significantly decreased plasma insulin. They concluded that improved insulin levels by RS occur independently of the microbiota and might involve bile acid cycle alterations and adipose tissue immune modulation (26).

Consuming an enzymatically modified waxy maize (EMS) diet did not affect the progression of diabetes in Zucker diabetic fatty (ZDF) rats and there were no signs of diabetes in rats fed with RS. They also observed that compared to rats fed with the RS diet, rats receiving a gelatinised corn starch (S) diet for 9 weeks generally had intermediate signs, increased HbA1c and HOMA-IR, with slight hypercholesterolemia and intermediate excretion of urinary metabolites associated with T2D (27).

Rats fed with AIN-93G diet containing 550 g/kg of HAM (HRS) for 6 weeks indicated lower fasting blood glucose concentrations by 20% and 1.5-fold higher serum insulin concentrations compared to AIN-93G control diet containing 550 g/kg of corn starch (DC), although HbA1c levels were increased by 21%. HOMA-β% was calculated to further evaluate the β-cell function. HRS rats showed the highest HOMA-β values compared to DC and AIN-93G diet containing 275g/kg of corn starch and 275 g/kg of HAM (MRS) rats, with no significant difference compared to lean Zucker rats.

There were no significant changes in blood glucose or insulin concentrations, HbA1c%, HOMA-β and serum insulin levels for rats treated with DC or MRS (28).

Sitagliptin (SG) (4g/1000g diet) was tested with three dosages of dietary RS (HAM-RS2) at 0, 15 and 28g/100g diet in diabetic-induced male C57BL/6 (WT) mice using streptozotocin and a high-fat diet (HFD). For the second experimental design, male GLP-1R KO mice were used and hyperglycaemia was induced with streptozotocin and HFD and treated with sitagliptin and HAM-RS2 (28% weight of diet) (SG+RS). They concluded that consumption of sitagliptin through dietary supplementation helped to improve glucose metabolism and reduced adiposity in obese and diabetic mice (25).

A novel gene network analysis was performed in diabetic-induced rats liver tissues fed with high amylose maize (Hi-maize™) treatment using an oligonucleotide microarray. The microarray results indicated the upregulation of 173 genes and the downregulation of 197 genes with RS treatment. The gene expression was related to glucose metabolism (phosphotransferase, hexokinase, pyruvate kinase) and lipid metabolism (fatty acid transporter, beta hydroxyl butyric dehydrogenase, carnitine palmitoyl transfer 1). Most of the glucose metabolism-related genes were shown to be up-regulated and expressed in response to RS treatment (ratio > 1). The results showed that the decrease in blood glucose levels was mediated by the activation of glucose metabolism process triggered by RS. They showed that the RS may cause direct signals to rat liver cells and regulate gene expression. The gene expression alterations in response to RS treatment suggest that the array of complications in diabetic mammals might be associated with the candidate genes and their surrounding network partners (33).

Feeding high-amylose maize to diabetic Male Sprague-Dawley rats induced with streptozotocin reduced blood glucose concentrations at 2nd week but did not differ at 5th week from those of the diabetic group rats. Furthermore, they showed that adding RS in the streptozotocin-induced diabetic rats' diet regulated the megalin and Dab2 expression. RS also prevented urinary excretion of 25D3 and DBP. However, they concluded that the protection of the kidney by RS was not the result of blood glucose reduction. This is because no significant difference was observed in the blood glucose levels of the diabetic vs diabetic rats after 5 weeks' treatment (31).

A high-fat diet containing 25% of wx/ae brown rice or Koshihikari brown rice in T2D NSY/Hos was fed to mice for 10 weeks. The results showed the pathological score of glycosuria and fasting blood glucose of the wx/ae group were significantly lower compared to Koshihikari group indicating the potential of wx/ae brown rice in glucose regulation (29). In another study, an in vivo acute oral tolerance test (ORTT) was performed on Zucker diabetic fatty rats. The results showed that compared to rats fed the wild-type (WT) rice, the rats directly fed with high RS transgenic rice (HA2) showed lower plasma glucose levels. They also found that HA2 which was fed to normal Sprague Dawley rats and T1D streptozotocin-induced rats showed no difference in blood glucose-lowering effects within 3h compared with the WT rice. This novel rice with its high amylose content (AC), RS and total dietary fibre (TDF) may potentially provide benefits in food products, medical values as well as industrial applications (34).

The potential of dietary RS in terms of therapeutic importance for diabetes treatment and improvement in pregnancy outcomes due to diabetes was investigated. In this study, a diet containing 30% type 2 RS (Hi-Maize® corn-starch containing 60% amylose) was fed to Goto kakizaki (GK) rats. The equal energy density control (EC) diet with 100% amylopectin corn starch was given to Wistar rats, representing the control group. The results indicated that insulin sensitivity in pregnant GK rats was improved in response to dietary-RS as indicated by HOMA-IR. Furthermore, lower fasting glucose and fasting serum insulin concentrations were observed in the RS-fed pregnant GK rats as compared to EC-fed pregnant GK rats (30).

This review revealed the role of different types of RS in glycaemic control in healthy and diabetic animal models. Similar to humans, rodents also develop diabetes due to varying degrees of β-cell failure and insulin resistance leading to hyperglycaemia (40). Rodent models of diabetes may not demonstrate similar diabetic characteristics as humans and it appears that no single animal model may precisely represent diabetic conditions in humans, but several models are being developed which mimic specific conditions and characteristics as seen in humans (41). Therefore, this justifies the use of various rodent models to investigate the effects of RS in diabetic management.

King et al. suggests that in order to observe the diversity seen in human diabetic patients, more than one animal model should be tested. Like human, the rodent models also consist of T1D and T2D (40). In T1D rodents, the insulin production deficiency can be produced by different mechanisms including the

destruction of the β-cells with chemicals and also by breeding rodent models that have the ability to develop autoimmune diabetes spontaneously. The induction mechanisms in T1D rodents include chemical induction (streptozotocin and alloxan), spontaneously autoimmune (NOD mice, BBR rats), genetically induced (AKITA mice) and virally induced (Coxsackie B virus, Kilham rat virus). In T2D rodents, hyperglycaemia is caused by insulin insensitivity and pancreatic insulin secretion failure. Rodent models of T2D include genetically induced models of β-cell dysfunction (hIAPP mice and AKITA mice), obese models (monogenic: Zucker diabetic Fatty rats and polygenic: KK mice, OLETF rat, NZO mice), non-obese models (Goto kakizaki rat) and induced obesity (High-fat diet feeding mice or rats, Desert gerbil and Nile grass rat) (40).

Research done by the authors of this review compilation has provided useful new evidence on the potential health benefits of RS, indicating that different characteristics of RS may influence blood glucose. The summary of the effects of RS in rodents based on this current review is shown in Figure 2. The mechanisms of glucose-lowering effects by RS as shown in those studies may involve different mechanisms which are mainly in the gastrointestinal digestive tract system. There are several factors that influence the amount of RS in food such as the ratio of amylose to amylopectin, amylopectin structure and starch granule characteristics (10). In principle, high GI foods intake led to blood glucose and insulin spikes. Insulin improves glucose uptake into the hepatic tissue as well as the skeletal muscle, which is then stored as glycogen. In diabetes subjects, postprandial hyperglycaemia and insulin resistance contribute to the progression and development of cardiovascular disease (42). Since RS resists digestion in the small intestine and is fermented by microbiota in the colon instead, consuming it with a low GI helps to prevent glucose spikes and lower postprandial glucose (6,7). This may explain the glucose reduction and improvement in insulin sensitivity in different types of animal models after treatment with RS.

Interestingly, the effects of RS on pancreatic islets have been performed by identifying the pancreatic β-cell function (28) pancreatic islet content, (23,30,32) densities and shape (30). Despite fewer islets found in the GK groups with disrupted configuration and irregular capsule islet shapes, Shen et al., found that GK rats fed with RS significantly increased β-cell density which raised an interesting question about the cause of such changes in RS-fed GK rats. In contrast to GK, Wistar rat islets were round in shape with clearly defined boundaries and homogeneously stained β-cells with high β-cell relative densities (30). In GK rats, histopathological changes in the pancreas include fibrosis, irregular shape and progressive reduction of islet β-cells which progress depending on the colonies and age. The progressive depletion and reduction of islet β-cells were more pronounced with age, which is associated with diabetes (43).

Islets consist of different types of cells secreting different hormones such as the β-cells for insulin production, α-cells for glucagon production, δ-cells for somatostatin release and others. In humans, the percentage of islets is about 30% α-cells, 60% β-cells, with the rest consisting of 10% γ- or PP cells (pancreatic polypeptide), δ-cells (somatostatin) and ε-cells (ghrelin) (44). The anatomical locations and the percentage of these cells in islets vary between species. The majority of cells in the pancreas of rodents are β-cells (65–85%), α-cells (10–25%), δ-cells (5–10%) and others (45). About 300-600 islets can be obtained from a single rat pancreas which possesses similar insulin-secreting functions to human islets, making it an ideal source to represent studies on pancreatic β-cell function (46). Therefore, the improvement of β-cell islet content in the Wistar rats, β-cell density in GK rats and β-cell functions by RS in Zucker diabetes rats done in the previous studies may contribute to the glucose homeostasis in diabetes.

Glucose homeostasis is achieved by maintaining glucose utilisation and production in the peripheral tissues via insulin actions. After carbohydrate consumption, glucose is mainly taken up by the liver (~33%), muscle and adipose tissues (~33%) whereas the remaining is utilised by the brain, kidney and red blood cells (47). Defective insulin secretion by pancreatic β-cells and insulin insensitivity in the specific tissues lead to hyperglycaemia (48). Therefore, to understand the mechanisms of glucose lowering by RS, several pathways including glycolysis, gluconeogenesis and glycogenesis (49) can be further explored in vivo using different types of animal models as suggested previously. It would be interesting to evaluate the effects of RS on hepatic glucose production and glucose uptake both in the muscle, liver and adipose tissues.

This review showed the beneficial effects of different types of RS on diabetes, however, there are several limitations to the studies conducted. The type of animal models selected, age groups, gender and duration of treatment may give different outcomes on

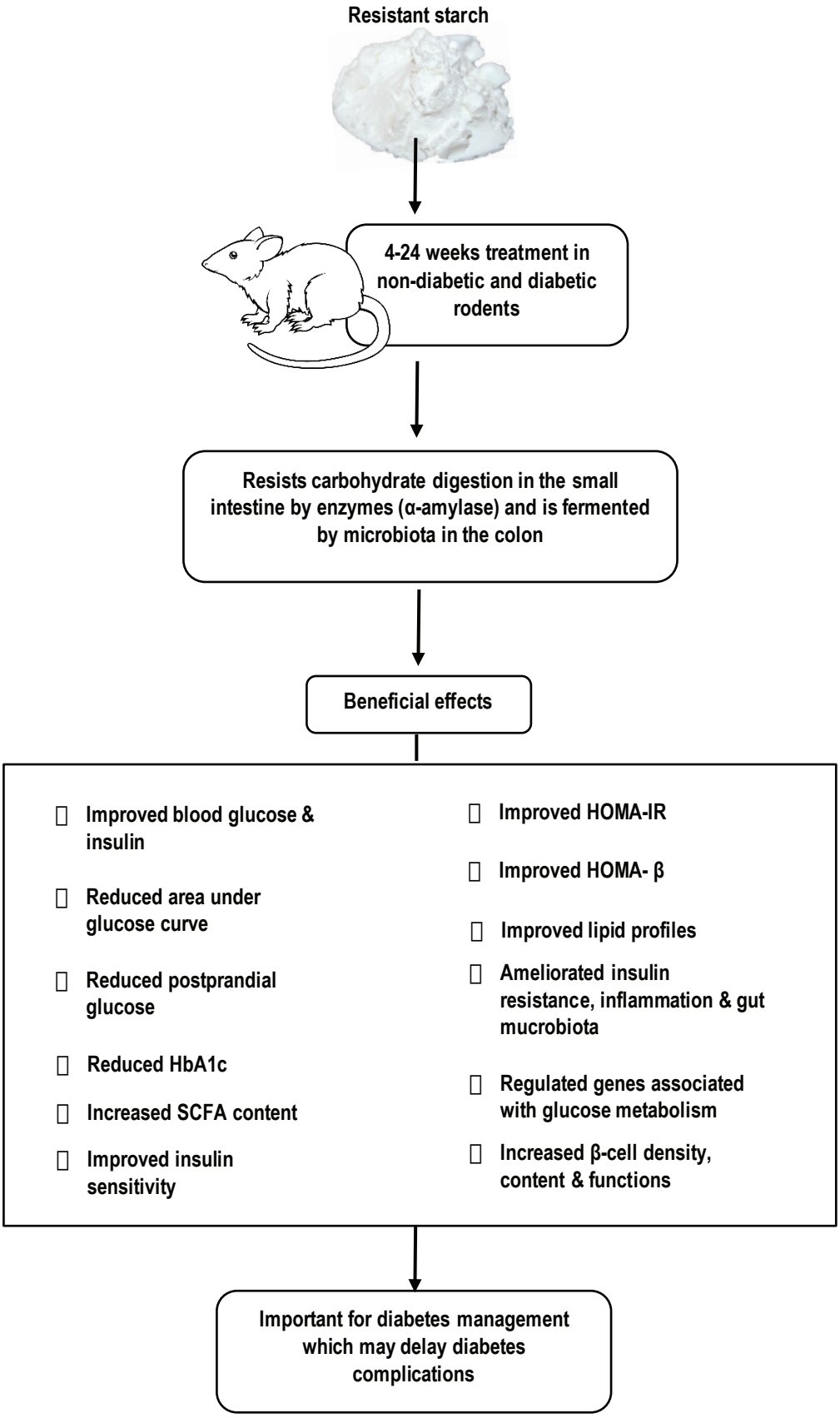

Figure 2. Summary of potential health benefits of different types of RS in non-diabetic and diabetic rodents at different treatment duration affecting glucose and insulin regulation, gut and pancreatic islets.

blood glucose, insulin and hormone levels in response to RS depending on the diabetes stage of the rodents. Compared to spontaneously diabetic rodents with a homogenous genetic background, the use of chemically diabetes-induced rodents which have a direct action on β-cells may result in different degrees of pancreatic islets destruction and cause toxicity to vital organs. Treatments that work in animals may not necessarily show similar effects in humans, however, pre-clinical data obtained from this review may justify translation to human clinical trials.

CONCLUSION

This review showed that the glucose-lowering effects of several types of RS are evident in healthy and different types of diabetes animal models which provide valuable pre-clinical information about the beneficial effects. Further tests on RS can be carried out using different types of animal models, genders, age groups and treatment duration to evaluate the stimulation of insulin from the pancreas and insulin sensitivity in specific tissues. Clinical trials are also warranted to further validate the pre-clinical studies found previously on the antidiabetic properties of RS.

CONFLICT OF INTEREST

All authors have read and agreed to the published version of the manuscript. The authors declare no conflict of interest.

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