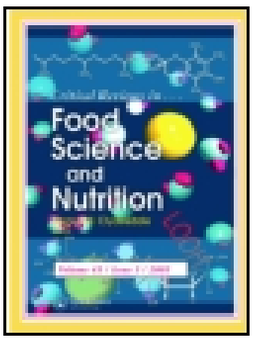

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A critical review on anti-diabetic and anti-obesity effects of dietary resistant starch

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ABSTRACT

"Diabesity" is the term to illustrate the interdependent relationship between obesity and diabetes. About 80% of the diabetic patients are diagnosed with obesity. Diabesity can be prevented by dietary interventions, especially by incorporating sufficient amount of resistant starch (RS). In the past few decades, RS has inspired the researchers due to its various health benefits. Differing from digestible starch, RS remains undigested in the small intestine, but in the large intestine, it is subjected to fermentation. This review intends to encapsulate the current information related to the dietary RS on diabetes and obesity. RS attenuate hyperglycemic, hyperinsulinemic and hyperlipidemic response in various subjects by restricting gluconeogenesis, bolstering glycogenesis, maintaining glucose and lipid homeostasis and ameliorating pancreatic dysfunction. Various food products were fortified with RS to enhance its dietary intake and were found to exhibit positive impact on human and animal models. This review identified and summarized the research gaps in the available literature.

KEYWORDS: Resistant starch (RS); satiety; obesity; glycemic index; insulin sensitivity

Introduction

The obesity prevalence has increased dramatically in recent years and has reached an epidemic level in both developed and developing countries (WHO, 2000). Obesity is a complex ailment associated with synergism of human genomes and environment (Tremblay et al., 2004). It also leads to metabolic syndrome that is acknowledged as a large scale public health issues including central adiposity, debilitated glucose tolerance, resistance to insulin, increased insulin in the circulating blood (hyperinsulinemia), abnormally elevated cholesterol or fats (lipids) in the blood (dyslipidemias) and high blood pressure (hypertension), this further elevates the risk of diabetes and cardiovascular diseases (Cornier et al., 2008). Globally, one in every eleven adults has diabetes (425 million) while on every two adults one goes undiagnosed (212 million). Devoid of intervention, the incidence of this disease will perhaps surpass 642 million by 2040 (IDF, 2018). Obesity, one of chronic diseases, is characterized by excessively dilated tissues (adipose). Approximately 80% of the diabetes mellitus type 2 (T2DM) patients suffer from obesity. Individuals who are identified with T2DM and have 20–30% excessive weight shows and enhanced mortality rate by almost three folds, as compared to the patients having weight of the body within the normal range (Maggio and Pi-Sunyer, 2003). The relative risk for an overweight patient developing T2DM is 10-folds in case of females while 11.2-folds for males (Field et al., 2001). A gradual defect in insulin secretion coalesced with a continuous rise in insulin resistance emerges very prematurely in obese patients which damagingly leads towards diabetes. This interdependent relationship between obesity and diabetes introduced a term ‘diabesity’ (Golay and Ybarra, 2005). Despite regulating the genetic background; diabesity can be obviated or tackled by managing the diet (quantity and quality) of the subjects. Obese individuals losing weight lead to several healthy results such as improved glucose metabolism, reduced levels of glucose in the plasma, elevated sensitivity towards insulin, remodeled lipid levels with deceased concentrations of the triglycerides and elevated HDL-cholesterol in the circulating blood (Pi-Sunyer et al., 2007). The clinical evidence also revealed that diabetes can be stopped or deferred by lifestyle interventions such as regulation of body weight, food habits and pervasive workouts diminishes the progressive impaired glucose tolerance (IGT) to T2DM (Tuomilehto et al., 2001; Knowler et al., 2002).

Recommended dietary intake for the management of metabolic syndrome

As per the FAO/WHO report, for carbohydrates the acceptable macronutrient distribution range (AMDR) is 55–75% of the net energy taken in whereas extra computed sweet substance (sugar) should not be more than10% of the net energy taken, and optimum intake of the net dietary fibers for men is around 38 g, but in women, it is required to be 25 g (WHO, 2002). Increased consumption of low glycemic index diet containing high fiber and resistant starch (RS) content is known to reduce obesity and diabetes risk (Gentile et al., 2015, Hedemann et al., 2017). Over intake of the grains in the food and cereal fiber have shown to reduce the risk of T2DM by at least 27% (Priebe et al., 2008). Grains are a prime origin for the dietary fiber (DF), but a typical diet pattern does not meet the recommended quantity of 25 to 35 g/day. Therefore, the consumption of additional grain-based fibrous food is recommended for the management of such chronic metabolic conditions.

Resistant starch

Predominant carbohydrate supplies in the human food are in the form of starch. Depending upon digestion (rate and extent), starch is of three types rapidly digestible starch (RDS), slowly digestible starch (SDS), and resistant starch (RS) (Englyst et al., 1992). RDS causes an immediate rise in the levels of glucose in the blood after consumption, while SDS gets digested in the small intestine at a much lesser rate as compared to RDS. RS is a starch type and/or starch hydrolyzed product that is undigested in the small intestine and undergoes fermenting in colon (Sajilata et al., 2006). The formation of RS was initially reported during the process of development of a technique to measure non-starch polysaccharides. It was observed that food processing lead to a limited portion of starch resistant to α-amylase digestion and this portion of starch was measured as "resistant starch" (Englyst et al., 1982).

Different types of resistant starch

The specific chemical properties of RS are responsible for their resistance to the digestion. On the basis of these properties, RS is categorized into four major types: RS1, R2, R3, RS4, RS5 (**Fig. 1**) (Zhang et al., 2015). RS1 is composed of a matrix of protein that obstructs its digestion and is predominantly present in full

(whole) grains or pasta made up of durum wheat. Its heat stable property makes it a popular ingredient for cooking operations and traditional eatables. It can be quantified as the glucose released from non-homogenized food sample or by enzymatic digestive mechanism of homogenized food material. RS2 are resistant to carbohydrases until ripens or cooked and present in food such as uncooked potatoes and unripe bananas. RS2 can be estimated by subtracting the discharged glucose by the enzymatic digestion of homogenized and boiled specimen or the unboiled, non-homogenized food sample. RS1 and RS2 contents are dissolved in the intestine gradually and imperfectly in the small intestine (Sajilata et al., 2006).

RS3 develops in starchy food during the cooling of gelatinized starch in the moist and hot food. It is a most resistant type of starch and is completely resistant to the actions of the pancreatic enzymes. It can be measured as a fraction of starch that opposes to be dispersed by boiling and enzymatic digestion. Recently, RS3 was produced from taro starch by applying heat, autoclaving, debranchment through enzymes, retrograding, and moistureless processes to taro starch twice. RS was loaded by 16 folds after this processing (Simsek and El, 2012). RS4 is an upgraded (chemically) form of starch that resists to be hydrolyzed by enzymes. In this case novel bonds other that α-(1-4) or α-(1-6) were formed.

Apart from these four typical forms, a newer form, RS5, has been acquainted recently. This was developed by complexing amylose with the lipids. It was reported that long hydrocarbon chains of fatty acids are responsible for the enzymatic resistance of RS5 (Hasjim et al., 2010, Okumus et al., 2018). Researchers are also focusing to increase the content of RS from the native starch in different food using various modifications. RS proportion in the chestnut native starch was increased by modifying it with amylosucrase from *Deinococcus geothermalis* (DGAS) (Lee et al., 2018). Different cooking processes are also reported to exhibit different impact on the RS content of the food material. Recently, it was reported that the long-grain rice which is refrigerated an then cooked in conventional cooker had maximum measure of RS (2.55 g RS/l00 g) than the short-grain rice which is refrigerated and cooked in a pressure cooker (LRS, 0.20 g RS/l00 g) (Chiu and Stewart, 2013).

Impact of resistant starch on diabetes and obesity

At present, RS has drawn the interest of researchers due to its health benefits and functional peculiarities. Various promising physiological benefits of RS included non-diabetic and diabetic people, it reduced the amplified levels of blood glucose and insulin, positive impact on bowel movements, restraining of colonic cancer, increase in the assimilation of minerals, prebiotic actions and enhanced fat oxidation (Kim et al., 2003; Mathers et al., 2012; Keenan et al., 2013; Gentile et al., 2015; Lin et al., 2015; Hedemann et al., 2017). In the current review, the effect of resistant starch, present in the diet, on diabetes and obesity in animals and human has been summarized.

Impact of dietary resistant starch on diabetes and obesity in animals

A high-amylose starch diet and amylopectin-rich starch diet was fed to rats having diet-induced obese condition. It was observed that the high-amylose starch diet leads to lower weight gain, adiposity and superior glycemic restrain than through a diet rich in amylopectin starch. A high RS content of high-amylose starch diet found to be responsible for this action (Aziz et al., 2009). Feeding RS4 diet to C57BL/6J mice mentioned to remarkably reduced the body and visceral fat weight, blood insulin and increased capacities for hepatic fatty acid oxidation than those fed with either RS2 diet or unmodified starch (Shimotoyodome et al., 2010). Dietary RS is reported to improve the outcomes of gestational diabetes. The consumption of RS2 by pregnant Goto-Kakizaki rats resulted in increased pancreatic insulin content and reduced fasting glucose. The offsprings also depicted better fasting glucose levels and orderly growth curves (Shen et al., 2011). Significantly higher insulin sensitivity was observed in these mice groups fed with the diet having 30% roasted wx/ae brown rice (rich in RS) for 16 weeks than that of control. This diet also reduced the fasting plasma triacylglycerol and fatty acids (non-esterified) levels. This roasted rice can be consumed without further processing. Thus the beneficial actions of the roasted wx/ae brown rice are also expected in human beings (Matsumoto et al., 2016). A substantial hypoglycemic activity was noted in type 2 diabetic rats which are treated with high-glucose-fat diet and low-dose streptozotocin (STZ) after the 150 and 200 g/kg of RS2 treatment given for 28 days (Sun et al., 2017). It was also reported that a diet containing enzymatically modified waxy maize starch with an increased degree of branching was unable to halt the onset of diabetes in

the Zucker diabetic fatty male rats whereas RS2 (high amylose corn starch) was successful under the same conditions (Hedemann et al., 2017).

It was also mentioned that impact of RS2 on adiposity reduction is dose-dependent. Rats susceptible to obesity attained lesser load with 4, 12 and 16% RS as distinguished with the 0% RS, but in obese-antagonistic animals, significant effect was observed exclusively at 16% RS. Food with ≥8% RS reported to reduce adiposity irrespective of phenotype. However, RS has not shown any effects on insulin sensitivity (Belobrajdic et al., 2012). RS prepared from indica rice is reported to have a significant impact on the body weight, blood glucose and lipid levels in the serum of the diabetic mice. It was also claimed that RS from indica rice could reduce intestinal emptying time and exhibit a positive impact on the intestinal health of the mice (Zhou et al., 2014). A combination of RS (high amylose maize starch) and chitosan was also reported to control body and adipose tissue weight along with the improvement in the blood lipid composition of the obesity-induced rats (Si et al., 2017). Administration of chito-oligosaccharides and resistant starch (Hi-maize™) (CO-RS) complex led to the minimum body and liver weight/index in excessively fat food fed rats compared to feeding RS or chito-oligosaccharides alone (Shang et al., 2017). In another study on obese C57BL/6 model mice, it was concluded that complemented DGAS-modified chestnut starch inevitably reduces the characteristics of obesity as compared to the native chestnut starch-fed mice (Lee et al., 2018).

Obesity enhances the risk of cardiovascular conditions like increased glucose in the blood, concentration of insulin and fasting plasma triglycerides along with the high low density lipid and low high density lipid cholesterol (Klop et al., 2013). Thus, the impact of RS from corn or rice at 16% (w/w) was also evaluated for cholesterol and lipid contents. It was observed that RS from corn significantly lowered the plasma cholesterol and lipid contents while the RS from rice was also reported to lower down the liver cholesterol contents in the diabetic rats (Kim et al., 2003).

Fermenting the RS in the colon also has a crucial role in fat loss of the subjects. In a study on obese mice been fed with RS2 (high amylase-resistant corn starch, Hi-Maize 260), no impact on body fat and glucose tolerance was observed. This observation was correlated with the impaired RS2 fermentation in the digestive

tract of obese mice (Zhou et al., 2009). The ovariectomized rats were reported to be highly prone towards weight gain. However, feeding these rats with resistant starch type 2 from high-amylose maize (HAM-RS2) resulted in reduced fat gain. Researchers had linked reduced fat gain with the fermentation of RS in large intestine of ovariectomized rats (Keenan et al., 2013).

Sorghum-resistant starch (SRS) was reported to prevent and treat obesity along with the improvement in the lipid metabolism of the high-fat diet-induced excessive weight and obese rats. The reason behind the SRS action is the secretion and synthesis of leptin and adiponectin, which leads to improvement in the intestinal flora (Shen et al., 2015). Table 1 presents the summary of the anti-diabetic and anti-obesity effects of RS in animals.

Impact of dietary resistant starch on diabetes and obesity based on human subjects

Extensive studies have also been conducted related to the influence of dietary resistant starch on diabetic and obese human subjects (Table 2). A study reported the impact of RS (Lintner) on the metabolic index and compared it with cellulose, as both these fibers have similar chemical and physical structure. It was concluded that ingestion of a 30 g RS (Lintner) exhibit similar responses towards the energy expenditure, glucose in the blood, insulin and free fatty acid levels except for colonic fermentation as that of cellulose (Ranganathan et al., 1994). A significant reduction in postprandial glycemia, insulinemia and capricious satiety feeling in healthy males was observed by replacing digestible starch (50 g pregelatinized starch) with RS (50 g raw potato starch) (Raben et al., 1994).

It was also reported that acute antecedent consumption of immense dosage of RS (60 g) (Novelose, 260) lower postprandial plasma glucose and insulin along with increased insulin sensitivity and C-peptide-to-insulin molar ratio in the healthy humans (Robertson et al., 2003). A reinstatement of 5.4% of net carbs in the diet with RS2 was found to be associated with enhanced oxidation of the post-prandial lipid. Hence, it reduces fatty assimilations in human subjects over a period of time (Higgins et al., 2004). However, a study revealed that bread containing RS3 has only slightly increased the postprandial blood glucose and insulin level in borderline diabetes affected people (fasting blood glucose $\geq$ 1.1 mg/mL) (Yamada et al., 2005). An

enhanced reduction in glycemic index of normal and overweight women was observed after consuming a meal with a combination of resistant starch and soluble fiber (33% and 59% lower AUC for glucose and insulin, respectively) (Behall et al., 2006). It was reported that different types of fiber have different satiety response. A study revealed that RS (Novelose 330 and Hi-Maize 260) and corn bran enhanced the short-term satiety in healthy subjects, whereas polydextrose behaved as light fiber and exhibited limited satiating capabilities (Willis et al., 2009). Consumption of RS2 was reported to improve insulin sensitivity in women with insulin resistance. This parameter was positively correlated with difference in waist measurement, fat accumulation in tibialis muscle and less significantly to the visceral-to-subcutaneous abdominal adipose tissue ratio (Johnston et al., 2010).

A meal containing RS3 also enhances satiety in 22 healthy subjects. It was reported that after consuming 25 g RS, incremental blood glucose and insulin levels were significantly lowered at 90 and 120 min than that in the control (Kendall et al., 2010). It is mentioned that consumption of bread with palmitic acid-conglomerated RS5 decreased postprandial plasma-glucose and insulin responses in healthy human subjects as compared to the ingestion of control wheat bread (Hasjim et al., 2010).

Distinctive types of RS were reported to extort contrasting glycemic responses. Consumption of cross-linked resistant wheat starch type 4 (RS4XL) was reported to remarkably reduce the glycemic response in the healthy subjects compared with the RS2. This response was attributed to the augmented extent of dietary fibers (91.9%) and more RS (83%) presented in RS4XL as compared to the fiber (60%) and RS content (46%) in RS2 (Haub et al., 2010). It was revealed that 48 g of RS over a day time duration might become useful for the control and manipulation of syndrome (metabolic) and hunger. As the consumption of 48 g RS2 resulted in significantly lower postprandial insulin response in healthy adult human males. Though an insignificant difference was observed in the postprandial plasma glucose concentrations and appetite between the RS and placebo (Bodinham et al., 2010). Dietary supplementation with hydroxypropyl distarch phosphate (HDP) modified RS4 (chemically modified) was reported to reduce postprandial glucose-dependent

insulinotropic polypeptide and increase postprandial resting and disbursement of the energies and its fat usage in the fit humans (Shimotoyodome et al., 2011).

Consumption of HAM-RS2 (40 g/d) was reported to improve peripheral insulin resistance but does not exhibit any impact on hepatic insulin resistance in subjects at an increased risk of T2DM (Robertson et al., 2012). A study concluded that inclusion of 25 g of soluble corn fibers in food has nil effects on hunger or ad libitum energy intake in healthy volunteers. However, RS3, alone or in combination with pullulan, symbolically decreased glycemic response unlike the control (Klosterbuer et al., 2012). Impact of RS on insulin sensitivity is also observed to be dependent on the gender of the subjects. It was observed that consumption of 15 and 30 g/d of high-amylose maize type 2 resistant starch (HAM-RS2) improved responsiveness to insulin in men. However, RS did not exhibit a significant impact on insulin sensitivity in women. The reason behind the gender-dependent response of RS on insulin sensitivity has to be determined (Maki et al., 2012). It was also mentioned that different RS content of rice samples does not exhibit physiological differences in glycemic indices of healthy adults. In spite of this, an enhanced apprehension fullness and a reduced eagerness to eat was reported in subjects as compared to control (Chiu and Stewart, 2013).

A study has also explored the effect of meals that have increased non-resistant starch or RS along and devoid of raised protein consumption of substrate, energy dissipation and satiety among underweight and excessively weighing/obese women. It was stated that combined consumption of RS4 and protein increases fat oxidation, peptide tyrosine-tyrosine (PYY), apprehension of satiety and fullness. These results might cause substantial suggestions for weight management if retained because of chronic ailments (Gentile et al., 2015). Ingestion of unripe banana flour (15 g/week) remarkably reduced hunger and increased satiety in healthy volunteers. Moreover, a decrease in the serum insulin (fasting) secretion was also observed in the subjects. These positive changes were associated with the high RS content in unripe banana flour (Hoffmann Sardá et al., 2016).

It was inferred that the fiber profile is a valuable factor for the effect of the dietary intervention. A pronounced reduction in total cholesterol and non-HDL-cholesterol was observed in RS consuming

overweight and obese subjects compared to the fiber consuming group (diet as recommended to patients with metabolic syndrome). However, a pronounced effect on glucoregulation was observed in the fiber group (Dodevska et al., 2016). It was concluded that colonic degradation of RS mixture consists of fibers of potatoes, wrinkled pea starch and high amylose maize starch to short-chain fatty acids (SCFAs) has trimmed down the production of carbohydrate-derived acetyl-CoA and contributes towards increased postprandial lipid oxidation by using fat-derived acetyl-CoA as a compensatory fuel source in healthy subjects (Wutzke and Schmidek, 2017). The native banana starch rich in RS was reported to induce a decrease in food intake, glucose area under the curve (AUC)-180 min, and insulin AUC-180 min in young subjects (Ble-Castillo et al., 2017).

Instead of using animal models and human subjects, the impact of RS on the glycemic index was also explored using *in vitro* method. It is considered as a simpler and inexpensive yet as effective as *in vivo* method. Glycemic index of taro RS derived from taro corm starch observed by in vitro methods and reported to exhibited low glycemic index (51.9±0.9) as compared to the parent starch (60.6±0.5). Thus, this RS can also be used in food formulations which are targeted for diabetes and weight management (Simsek and El, 2012). Researchers have also observed a significant negative correlation (R = -0.688) between RS5 of rice and glycemic index using in vitro method (Kumar et al., 2018).

Fortification of food products with RS

Fiber-enhanced functional foods can be used to increase fiber intake. There is a particular interest in RS as a high-fiber ingredient, as increasing the dietary RS intake is an established strategy for an improved glycemic control. Thus various researchers are focusing on fortification of food products with RS to enhance its dietary intake.

The bread is prepared from wheat with elevated amylose content (38%) and the baking conditions used were known to enhance the amylose retrogradation; thus, the resulting bread had higher RS content. This bread reduced the postprandial glucose response than conventionally baked white wheat bread. However, no significant differences were observed with respect to insulin responses in the healthy human subjects

(Hallstrom et al., 2011). The postprandial plasma-glucose and insulin responses of the healthy human male were evaluated after ingesting bread made from 60% (dry basis) novel RS. It was observed that this novel RS can be used for the interventions of insulin resistance and metabolic syndrome, including diabetes and obesity (Hasjim et al., 2010). It was reported that the consumption of HAM-RS2 bagel enhances the glycemic efficiency by lowering the amount of insulin required to manage postprandial glucose while improving fasting insulin sensitivity in human subjects (Dainty et al., 2016).

In another study, substitution of standard wheat starch with RS4XL led to attenuated postprandial glucose and insulin levels in humans. But it was unknown whether this response was due to the dietary fiber and/or resistant starch of the RS4XL bar (Al-Tamimi et al., 2010). High-amylose maize flour was used to make cookies having high RS content. Consumption of these cookies was found to be associated with a better glycemic control in young men (Luhovyy et al., 2014). A novel PPB-R-203-based staple food having starch components: retrograded starch (10%), amylose (20%), and amylopectin (70%) lead to improved insulin resistance through the reduction of postprandial hyperinsulinemia. This food led to improved postprandial hyperglycemia in T2DM patients without the menace of hypoglycemia (Lin et al., 2015). Bread containing High-maize™ 260 (RS) were consumed by African Americans subjects and it was revealed that African Americans are required to consume more than 12 g/day of RS to lower the risk of T2DM (Penn-Marshall et al., 2010). Male Wistar rats were fed with wheat bread, RS-wheat bread, maize bread and RS-maize bread, respectively. It was observed that maize bread had a lower glycemic index than wheat bread. The magnitude of the effect of RS on glycemic response depended on the type of bread (Brites et al., 2011).

These studies suggested that nutritional and health claims such as, “naturally increased resistant starch content” accompanied by “naturally low glycemic index” can be made for these RS-enriched food products.

Mechanism of action of resistant starch on diabetes and obesity

The process of colonic fermentation of RS was claimed to be the reason behind a higher insulin sensitivity, lower postprandial plasma glucose and insulin content in healthy subjects (Robertson et al., 2003). Three major phyla, *Firmicutes*, *Actinobacterium* and *Bacteroidetes*, were claimed to be involved in RS fermentation

(Birt et al., 2013). *Bifidobacterium* spp., with lactate and acetate as major products, *Bacteroides* spp., with acetate and propionate as major products, *Fusobacterium* and *Butyrivibrio*, with butyrate as the major product, were also identified as RS hydrolyzing strains in human fecal samples (Macfarlane et al., 1986). Furthermore, another study has also reported that *Bifidobacterium* spp. and *Clostridium butyricum* is the most efficient microbes involved in the fermentation process as compared to other bacterial strains under investigation (Wang et al., 1999). RS consumption also associated with the increased proportion of microbes such as *Lactobacillus* and *Bifidobacterium*, *Lachnospiraceae*, *Ruminococcaceae*, *Clostridium* and *Akkermansia* in mice (Zeng et al., 2017; Keenan et al., 2015; Tachon et al., 2013). The electron microscopic studies have confirmed that bacterial cells penetrate the starch granule resulting in the microbial degradation of these starch granules (Wyatt and Horn, 1988). Fermentation of RS yields gases (methane, hydrogen, carbon dioxide), principal SCFAs (acetate, propionate and butyrate) (Birt et al., 2013; Pryde et al., 2002, Louis et al., 2014, Koh et al., 2016) and much lesser amounts of SCFAs (isobutyrate and isovalerate), organic acids (lactate, succinate, and formate) and alcohols (methanol and ethanol) (Birt et al., 2013). It was also observed that feeding lotus seed RS increased the contents of formic, acetic, butyric, isobutyric, propionic, and lactic acids. Further, the intestinal microflora reported to convert acetic and lactic acid to butyrate using acetyl CoA pathway (Zeng et al., 2017). A significant amount beneficial SCFAs (acetate, propionate, butyrate) were detected after fermenting the four novel resistant starches using an in vitro fermentation system in the presence of human fecal slurries (Erickson et al., 2018). In another study, RS was fermented in the presence of human fecal slurries, and after 24 hours of fermentation, acetate, propionate and butyrate were observed to be the major SCFAs, whereas, iso-butyrate, iso-valerate, formate, valerate and lactate were detected in minor amounts (Reichardt et al., 2018). Different studies have also reported the production of significant amount of SCFAs (acetate, propionate, butyrate) due to the fermentation of RS (Cummings and Englyst, 1987; Englyst and Macfarlane, 1986; Zhou et al., 2009; Shen et al., 2011; Penn-Marshall et al., 2010; Matsumoto et al., 2016; Maki et al., 2012). Pathways for SCFAs production in large intestine due to the fermentation of RS is shown in Fig. 3. (Pryde et al., 2002).

In another study, the elevations in the systemic concentrations of ghrelin and SCFAs in response to the RS intake is found to be responsible for the treatment of insulin-resistant persons (Robertson et al., 2005). The colonic fermentation of RS led to the production of glucagon-like peptide-1, which in turn is associated with the improved glycemic control of pregnant Goto-Kakizaki rats (Shen et al., 2011). Another finding suggested that the mechanism for the improved insulin resistance by the RS diet involves a reduction of CD11c expression in adipose tissues that are strongly related to the development of insulin resistance (Harazaki et al., 2014).

RS consumption of about 8% of the total diet was reported to attenuate the metabolic disorders of glucose and lipid in diabetic rats. This action was correlated with up-regulation of glycogen synthesis genes (GS2 and GYG1), lipid oxidation gene (Acox1) and insulin-induced genes (Insig-1 and Insig-2) expression (Fig. 2). However, genes related to the triglycerides synthesis and metabolism (SREBP-1), fatty acid synthesis (Fads1) and gluconeogenesis (G6PC1) were significantly down-regulated (Zhou et al., 2015). Exploitation of chitosan oligosaccharides-RS as an anti-obesity intervention was explained by the reduced expression levels of peroxisome proliferator-activated receptor γ, sterol regulatory element-binding protein (SREBP) and lipogenesis-associated genes along with reduced mRNA levels of LXR (liver X receptor), SREBP-c, FAS (fatty acid synthase) and ACC (Acetyl-CoA carboxylase) (Shang et al., 2017). Hypoglycemic effect of RS2 in type 2 diabetic rats was associated with the down-regulation of the expression levels of key enzymes responsible for hepatic glucose metabolism and gluconeogenesis, such as phosphoenolpyruvate carboxykinase and glucose 6 phosphatase. The up-regulation of pancreatic duodenal homeobox-1, glucokinase and glucose transporter 2 expression levels were also observed to be associated with improved glycogen synthesis. The effect of RS2 can also be ascribed to the repairing of damaged pancreatic β-cells and an up-regulating insulin receptor substrate 1, insulin receptor substrate 2, pancreatic duodenal homeobox-1, glucose kinase, and glucose transporter 2 expression levels in the pancreas (Sun et al., 2017). The improvement in insulin resistance in response to COS-RS complexes was correlated with enhanced hepatic glucose conversion through up-regulation of glycogen synthase 2 (GS2) and glycogenin 1 (GYG1). The

reduced gluconeogenesis was associated with down-regulation of G6PC1 gene expression and the alteration in glucolipid metabolism was found to be related to the enhanced expression of Insig-2 (Wang et al., 2017). DGAS-modified chestnut starch was assumed to reduce the fat accumulation in white adipose tissue via GPR43-mediated suppression of insulin signaling (Lee et al., 2018).

It was also reported that RS in the diet may affect energy balance through its effect as a stimulator of gut peptide tyrosine tyrosine and glucagon-like peptide -1 expression. Thus the incorporation of RS in the human diet as a bioactive functional food component is a natural way to increase gut hormones that are effective in reducing energy intake and is a natural approach for the treatment of obesity (Keenan et al., 2006). The ability of RS to improve dyslipidemia and insulin resistance was associated with the restoration of the basal expression levels of transcription factors involved in lipogenesis (SREBP-1c, LXRs), cholesterol metabolism (SREBP-2, LXRs) and fatty acid oxidation (PPARα). Overall, this resulted in normalized cholesterol output and reduced fatty acid oxidation capacity (Polakof et al., 2013). It was also reported that RS intake led to changes in neuronal activity in hypothalamic appetite regulation centers that resulted into the indicative of satiation in mice (So et al., 2007). This satiation will reduce the food intake which in turn led to reduced incidence of obesity and related disorders.

Future perspective

RS, a fraction of starch, resistant to digestion in small intestine and passes to large intestine, where it undergoes colonic fermentation leading to the production of SCFAs. The chemical, physical, and enzymatic modification of native starch gives rise to different types of RS (RS1-RS5). RS has properties similar to fiber and drawn the attention in past few decades for its potential health benefits. An extensive research has been done to explore the influence of RS on obesity and diabetes in animals and human being. Among the various types of starch, RS2 is the most extensively explored RS. To improve or prevent the condition of obesity and T2DM, diet with high RS content has been recommended. Impact of these fortified food products on the obesity and T2DM has also been explored. RS in combination with other fibers or as an ingredient of food product exhibit positive impact on obesity and T2DM in both animal and human studies. Despite this

extensive research, there are a few gaps in the experimental or clinical studies. The comparison between various studies was observed to be unfeasible as the design of study including the time period of observation; subjects their species, metabolic conditions; type, dose and product containing RS were different. Mostly the studies have been carried out for short time period in healthy subjects and subjects with high risk of disease. Thus there is a great need for well-designed long-term studies in the obese and diabetic human subjects. Due to the dose issues, lifespan, anatomy, metabolic condition, or just species different extrapolation of animal studies to human may not be appropriate. Researchers have also made certain efforts to investigate the underlying mechanism of action by RS on obesity and diabetes. The colonic fermentation, production of SCFAs and modulations of expression level of certain genes were claimed to be a reason behind the actions of RS. Still, the exact biochemical and molecular mechanism has to be investigated.

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Conflict of interest

None

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Table 1. Summary of the anti-diabetic and anti-obesity effects of resistant starch in animals.

Diet formulation	**Type of starch**	**Subject/age/weight**	**Intervention period/Dose**	**Inferences**	**References**
Modified AIN-93G diet	RS2	Adult male Sprague-Dawley rats n = 150/250 g	4 week/ 23.4% of diet	Lower total energy intake, weight gain, fat pad mass, and glycemic response and higher insulin sensitivity index	(Aziz et al., 2009)
Modified AIN-93G diet	RS2	Male Sprague–Dawley rats n = 120/319 ±5 g	8 week/ 0, 4, 8, 12 and 16% RS	Reduced adiposity with ≥8% RS but no impact on insulin sensitivity	(Belobrajdic et al., 2012)
Test breads (Basic ingredients of the AIN-93G diet)	Substitution of casein with wheat, maize, RS-wheat, or RS-maize	Male Wistar Han rats n = 36/ ≈270 g	16 days/2 g of test diets,	Maize bread exhibit lower glycemic index than wheat bread and impact of RS on glycemic response depends of type of bread.	(Brites et al., 2011)
Modified AIN-93G diet	RS and enzymatically modified starch	Male Zucker Diabetic Fatty (ZDF) rats n = 48/5 wk	9 wk/ 52.95% starch	No signs of diabetes in RS fed rats whereas EMS did not delay the onset of diabetes in ZDF rats	(Hedemann et al., 2017)
Modified AIN-93 diet	RS2	Male OLETF rats n = 12/22 wk	5 weeks/55% RS	Improved insulin resistance, reduced mesenteric adipose tissue weight, enhanced number of small adipocytes and reduced CD11c protein expression.	(Harazaki et al., 2014)

Modified AIN-93G diet	RS from corn and rice	Male Sprague-Dawley streptozotocin-induced diabetic rats n = 32/4 wk	3 week/300g RS/kg of diet	Reduced plasma cholesterol and lipid contents, decreased intestinal transit time with both types of RS. RS from rice reduces liver cholesterol contents.	(Kim et al., 2003)
Modified AIN-93G diet	RS2 from high-amylose maize (HAM-RS2)	Virgin female Sprague Dawley rats Ovariectomized (OVX) rats n = 20, sham rats n = 20/10 wk	12 weeks/29.7 g RS/100 g diet	OVX increases adiposity. Due to the fermentation of HAM-RS2 in obese mice fat gain associated with OVX was attenuated.	(Keenan et al., 2013)
Test diet	RS2	Sprague-Dawley rats male n = 30/,8 wk, female n = 30/7-9 months	32-day study, 33% RS and 5 weeks, 29.7% RS	Energy dilution resulted in decreased abdominal fat, increased cecal weight and SCFAs, plasma PYY, GLP-1 and gene transcription for PYY and proglucagon.	(Keenan et al., 2006)
D12450B diet containing 30% rice	RS from Rice	T2DM Nagoya-Shibata-Yasuda mice n = 14/6 wk	16 weeks/ diet with wx/ae brown rice = 2.7% (w/w) RS; diet with Kinmaze<1.0 % (w/w) RS	Improved insulin sensitivity and reduced fasting plasma triacylglycerol and nonesterified fatty acids	(Matsumoto et al., 2016)
D12451 research diet	Native chestnut starch or DGAS-modified chestnut	Male C57BL/6 mice/8 wk	10 weeks/ 1500 mg per kg body weight for five days a week	Improved diet-induced obesity via GPR43-mediatedsuppression of insulin	(Lee et al., 2018)

	starch (DMCS)			signaling.	
Test diet	RS2	Wistar male rats n = 30/7 months	9 weeks/ 419g RS par kg diet	Normalized cholesterol output, reduced fatty acid oxidation capacity, improved hepatic glucose phosphorylation, muscle glucose transport and glucose tolerance.	(Polakof et al., 2013)
Modified standard diet	RS2	Sprague–Dawley male rats n = 40/8 wk/180–200 g	28 days/ RS2:10%, 15%, and 20%	Alteration in the expression levels of genes related to glucose metabolism and amelioration of pancreatic dysfunction lead to decreases in the blood glucose levels	(Sun et al., 2017)
RS and chitosan oligosaccharides (CO-RS) (1:5 v:v) administered orally	RS2	Male Sprague-Dawley rats n = 40/150 ± 10 g	6 weeks/CO: 0.3 g, RS: 1.2 g, and CO-RS: 1.5 g daily	CO-RS intervention lead to lightest body weight, lowest liver weight/index and highest level of total antioxidant capacity in serum.	(Shang et al., 2017)
Modified standard diet	Sorghum resistant starch	Male Sprague–Dawley rats n = 60/5 wk/140 ± 5 g	8 weeks, 30% RS	Synthesis and secretion of leptin (LP), adiponcetin (ADP)and improvement in intestinal flora helps to treat obesity	(Shen et al., 2015)

Modified standard diet	AMIOCA^{TM} starch and Hi-Maize^{TM} starch	Male mice C57BL/6 n = 40/3 wk	8 weeks/ free access to low RS and High RS diet	RS can significantly influence hypothalamus areas that impart major role in appetite regulation. HRS and LRS diet had similar impact on body weights.	(So et al., 2007)
Experimental diet	RS2	Female Goto–Kakizaki rats n = 20/5 wk/80–100 g	10 wk/ 30% (w/w) RS	Improved pancreatic insulin content, insulin sensitivity, GLP-1 levels and SCFAs in RS-fed dams. Offspring of RS-fed dams exhibit improved fasting glucose levels and normal growth curves.	(Shen et al., 2011)
Modified AIN-76 diet	Resistant starch (RS2), chitosan (CS) and chitosan-starch complexes (CL)	Healthy male Wistar rats n = 40/110 ± 10 g	6 week/ intervention of RS2, CS, CL: 2 g/day	CL exhibit more potent hypolipidemic effects and oxidative stress suppression due to elevated antioxidant enzyme activity, improved lipid oxidation, fatty acid and cholesterol homeostasis.	(Si et al., 2017)
Modified basic rat feed and oral administration of treatment dose	RS2, Chitosan oligosaccharide (COS), COS-RS (1:5, v:v)	Healthy male Sprague-Dawley rats n = 40/150 g ± 10 g	6 weeks/ COS: 0.3 g, RS: 1.2 g and COS-RS: 1.5 g per rat every day	COS-RS achieved significant improvement in blood glucose and insulin levels as compare to individual	(Wang et al., 2017)

				treatment.	
Modified AIN-93 diet	RS2 and RS3	42-44 Male C57BL/6J mice n = 42-44/5-7 wk	12-16 week/25-30% RS	The body fat reduction involves energy dilution as well as colonic fermentation of RS.	(Zhou et al., 2009)
Indica rice starch	Indica rice resistant starch (IR-RS)	Male; n = 48 and female n = 48 SCXK (su) 2009-001 mice	Once daily for 4 weeks/2, 4 and 8 g/kg IR-RS	Dual modification changed the structure and digestibility of IR starch. Low blood glucose levels in high treatment group.	(Zhou et al., 2014)
RS administered by oral gavage, using a feeding needle	RS2	Healthy male Sprague–Dawley rats n = 24/∼190±10 g	4 weeks/2 g once daily	Consumption of 8% RS improve insulin sensitivity and attenuates metabolic disorders of glucose and lipid.	Zhou et al., 2015)

Table 2. Summary of the anti-diabetic and anti-obesity effects of resistant starch in human subjects.

Source/Diet formulation	**Type of starch**	**Subject/age/weight or BMI**	**Intervention period/Dose**	**Inferences**	**References**
Nutrition bars	Cross-linked RS4	Normoglycemic adults, females n = 7, males n = 6/27±5 y/ 25±3 kg/m^2	Single study visit with seven-day washout/ 80 g	Attenuated postprandial glucose and insulin levels	(Al-Tamimi et al., 2010)
Rice	High RS rice and low RS rice	Healthy adults men n = 12, women n = 9/18-65 y	Single study visit with two days apart/ 4.4 g RS/50 g (High RS), 0.4 g RS/50 g available carbohydrate (low RS)	No significant impact on glycémic indices with different RS content of rice. Overall increased feeling of fullness and decreased desire to eat	(Chiu and Stewart 2013)
Test muffin	High-amylose corn starch	Normal-weight women n = 10/22.0 kg/m^2/43.5 y and Overweight women n = 10/ 43.3 y/30.4 kg/m^2	10 tolerance meals containing 0.71, 2.57, or 5.06 g RS/100 g muffin	Combination of RS and soluble fiber lead to 33% and 59% lower AUC for glucose and insulin, respectively	(Behall et al., 2006)
Flavoured mousse	Hi-Maize 260 (RS2)	Healthy males n = 20/ 19–31 y/23·2 kg/m^2	Two study visits one week apart/ 48 g RS	No impact on subjective appetite, postprandial plasma glucose level and reduced postprandial insulin response	(Bodinham et al., 2010)
Native banana starch	RS type 2	Healthy adult males and females, n = 28/18–25 y/18-29.9 kg/m^2.	Two study visits separated by at least one wk/ 40 g NBS (70.5%	Reduced food intake, glucose and insulin area under the curve. No effect on gut hormones.	(Ble-Castillo et al., 2017)

			RS2)		
Bagel	High-amylose maize resistant starch, type 2 (HAM-RS2)	Men and women with an increased risk of T2DM, n = 24/ 55.3-6 1.59 y/30.2 6 0.57 kg/m^2	8 wk/ 25 g HAM-RS2/day	Improved glycemic efficiency and fasting insulin sensitivity	(Dainty et al., 2016)
Diet similar to diets used in several big European projects on diabetes	Certain plant foods replaced with plant foods good sources of RS	Overweight and obese men and women with disordered glucoregulation and dyslipidaemia, n = 25/45–74 y/33.06 kg/m^2	12 months/ low-fat and high-fbre (>25 g/day)	RS-rich diet did not impact glycaemic control in contrast to the regular fibre-rich diet.	(Dodevska et al., 2016)
Banana	Unripe banana flour (UBF)	Healthy male and female n = 22/ 27.6 ± 5.1 y/22.8 ± 3.5 kg/m^2	6 wk/5 g RS/8 g UBF for 3 times a week	Reduced hunger, increased satiety parameters, improved glucose homeostasis.	(Hoffmann Sardá et al., 2016)
Ready-to-use sachets	RS2	Insulin resistant human subjects n = 20, 21--70 y	12 wk/40 g/ day	Improved insulin sensitivity but no direct relation between diabetes prevention and changes in body adiposity, blood lipids or inflammatory markers	(Johnston et al., 2010)
Wheat bread	RS content varies from 2.9-19% of total starch	Healthy subjects; females n = 7 and males n = 7/20-35 y/22.2±1.91 kg/m^2	Four test day/50 g RS per meal	Lower postprandial glucose response but no significant differences in insulin responses.	(Hallstrom et al., 2011)
RS bread made with novel RS	novel RS made by complexing high-amylose maize starch	Male human-subjects n = 20/ 19–38 y/21.0–42.8 kg/m^2	Single test day one-week washout	Reduced postprandial plasma-glucose and insulin	(Hasjim et al., 2010)

	VII (HA7) with palmitic acid (PA)		period/Bread containing 50 g of RS	responses after ingesting the RS bread made from 60% HA7+ISO+PA.	
Pancake test meal	RS4 and RS4+ whey protein	Women n = 24/ 45.8 ± 2.5 y/21.0-31.9 kg/m^2; % body fat = 23.9-41.2	four test days/ 40g RS and 20.5 g Whey protein	Consumption of RS4 and protein increases fat oxidation, peptide YY, feelings of satiety and fullness.	(Gentile et al., 2015)
Meal	RS2	Healthy adults; male n = 7 and female n = 5/ 28--45 y/ 20--28 kg/m^2	Single test day/ 0%, 2.7%, 5.4%, or 10.7% RS meal	5.4% RS in meal significantly increased post-prandial lipid oxidation	(Higgins et al., 2004)
RS diluted in water	RS2 and cross-linked resistant wheat starch (RS4XL)	Healthy females n = 7, males n = 4/ 24 ± 4 y/ 23.2 ± 3.8 kg/m^2	Two visits per wk, over a three-week period/30 g RS	RS4XL exhibit greater capacity to attenuate the glucose response as compare to RS2	(Haub et al., 2010)
Test breakfast	RS3 produce from heat moisture-treated high amylose maize starch	Healthy men and women; n = 20/18-60 y/ 18.5-27 kg/m^2	5 visits separated by washout period of 3 weeks/25 g soluble corn fiber (SCF) or RS alone or in combination with 5 g of pullulan (P)	No impact on satiety or energy intake compare to control.RS+pullulan treatment reduces glucose, insulin, and GLP-1.	(Klosterbuer et al., 2012)
Test meal	RS3 produced from heat moisture	Healthy subjects; Males n = 13, females n = 9/26±4	One test per week/ twice control meal	25 g RS resulted in lower postprandial glucose and insulin	(Kendall et al., 2010)

	treated high amylose corn starch	y/23.7±2.4 kg/m^2	and 5 test meals (5, 15, 25 g RS)	responses with greater satiety quotient for 45 min.	
Baked cookie bars	HAM-RS2	Healthy men n = 30/22.9 ± 0.6 y/22.6 ± 0.3 kg/m^2	Three consecutive weekly sessions/11. 1 g and 22.2 g of RS	Replacement of 67% wheat flour with 31.5 g of whole grain HAM flour lead to better glycemic control.	(Luhovyy et al., 2014)
RS enriched PPB-R-203-derived diet	RS3	Female with type 2 diabetes n = 44/48.9–55.3 yr/24.9–27.3, heathy female; n = 48/23.1-25.5 y/57.5-65.3 kg	3 day study with washout period of at least 2 days/10% RS	Reduced postprandial hyperglycemia in T2DM patients without increasing the risk of hypoglycemia or glucose excursion	(Lin et al., 2015)
Ready-to-use sachets	High amylose corn starch containing ~60% RS2	Healthy men n = 11 and women n = 22/18–69 y/≥35.0 kg/m^2	4 wk separated by 3 wk washouts/15, or 30 g/d of HAM-RS2	Consumption of 15–30 g/d of HAM-RS2 improves insulin sensitivity in men but no difference was observed in women at any treatment level.	(Maki et al., 2012)
Bread	RS2	African American men n = 8 and African American women n = 9 at risk for T2DM / 36.6±1.55 y/25 kg/m^2	6 wk/12.39 g RS per day	African Americans may need to consume more than 12 g/day of RS to lower the risk for T2DM	(Penn-Marshall et al., 2010)
Test meal diluted in 500 ml fruit syrup.	Raw potato starch	Healthy normal-weight male n = 10/ 20--31 y	Single test day/54.15% RS (w/v)	Reduced postprandial glycemia, insulinemia and subjective	(Raben et al., 1994)

				sensations of satiety.	
Ready-to-use sachets in habitual diet	RS2	Healthy subjects n = 10/ 24--61 y/18.4 to 32.3 kg/m^2	4 wk/30 g RS/d with 4 wk washout period and4 wk/20 g rapidly digestible starch/d	Increased insulin sensitivity in noninsulin-resistant subjects due to increased ghrelin and SCFAs.	(Robertson et al., 2005)
Maize starch (70% amylose)	RS (lintner)	Healthy male n = 6-7/23-26 y/20.2-21.6 kg/ m^2	30 g lintner in 200 mL water.	Characteristics of lintner with respect to blood glucose, insulin, FFAS, energy expenditure, and substrate oxidation are intermediate between those of pectin and cellulose, but closer to cellulose.	(Ranganathan et al., 1994)
Ready-to-use sachets to mix in with food/drink.	RS2	Men and women with insulin resistance n = 15 /25-70 y/33.8 1.9 kg/m^2	8 wk with 8 wk washout between treatments/40 g starch per day	Improved peripheral but not hepatic insulin resistance	(Robertson et al., 2012)
Modified basal diet	RS2	Healthy subjects; male n = 4, female n = 6/23-65 y/20.3-35.9 kg/m^2	Consumed 60 g high-resistant starch diet for 24 h before the study day.	Improved postprandial insulin sensitivity	(Robertson et al., 2003)
Pancake test meal	Hydroxypropyl-distarch phosphate from waxy maize	Healthy male subjects n = 10/35·2±1·9 y/23·6±1·3 kg/m^2	2 test days separated by at least 7 d	Reduced postprandial glucose-dependent insulinotropic	(Shimotoyodome et al., 2011)

	starch			polypeptide (GIP), increased postprandial resting energy expenditure and fat utilisation	
Low fiber and high-fiber muffins containing corn bran (CB), barley β-glucan + oat fiber (BG), RS, and polydextrose.	RS2	Healthy men and women n = 20/18-65 y/>30 kg/m^2	5 visits after consuming treatment muffin	RS and CB had significant impact on satiety, whereas polydextrose behaved like the LF treatment.	(Willis et al., 2009)
RS mixture (MIX) = potatoes fibre (FP)+wrinkled pea starch (WPS)+high amylose maize starch (HAMS) (HAMS)	FP and WPS, with an RS1 content of (12%) and an RS2 (70%), HAMS with an RS2 (70%)	Healthy female n = 10, male n = 6/18–58 y/ 48.0–102.0 kg	80 day/10g MIX or 10g HAMS in 100ml tea for 20 days and repeated after 10 days washout period	The colonic degradation of MIX and HAMS to short-chain fatty acids contributes to postprandial lipid oxidation	(Wutzke and Schmidek, 2017)
Bread	RS3 derived from tapioca	Adult men n = 9, women n = 11 /50.5±7.5 y/fasting blood glucose level 1.0-1.40 mg/mL	2 days, 2 week apart 6g/2slices	Increased postprandial blood glucose and insulin levels in borderline diabetic patients.	(Yamada et al., 2005)
Rice	RS5	*in vitro* methods		A significant negative correlation was observed between RS and glycemic index.	(Kumar et al., 2018)
Taro starch	RS3	*in vitro* methods		Taro RS exhibit low expected	(Simsek and El,

			glycemic index. Bile acid-binding capacity of taro RS indicated its possible cholesterol lowering effect.	2012)

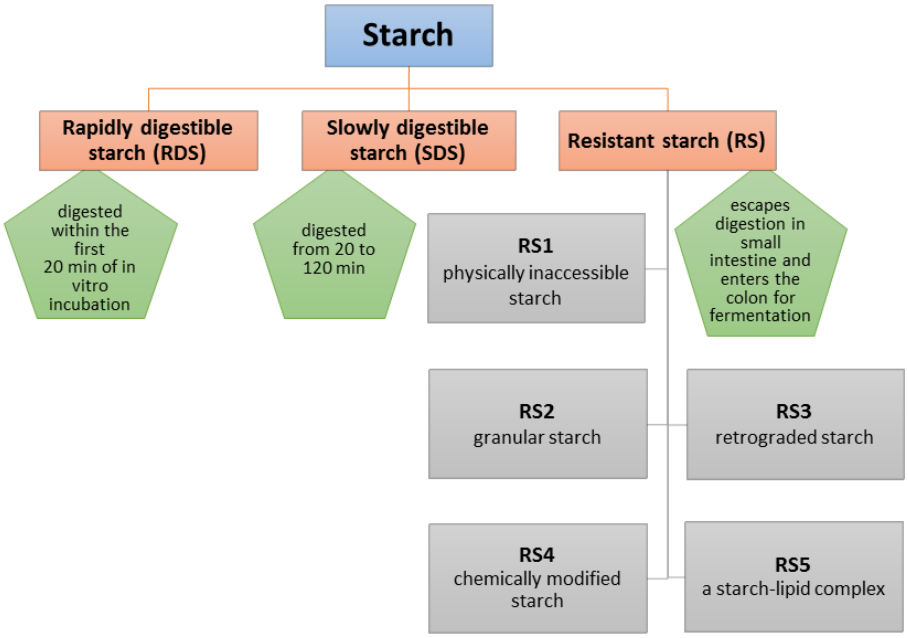

Figure 1. Classification of starch based on the extent of digestibility.

Figure 1.

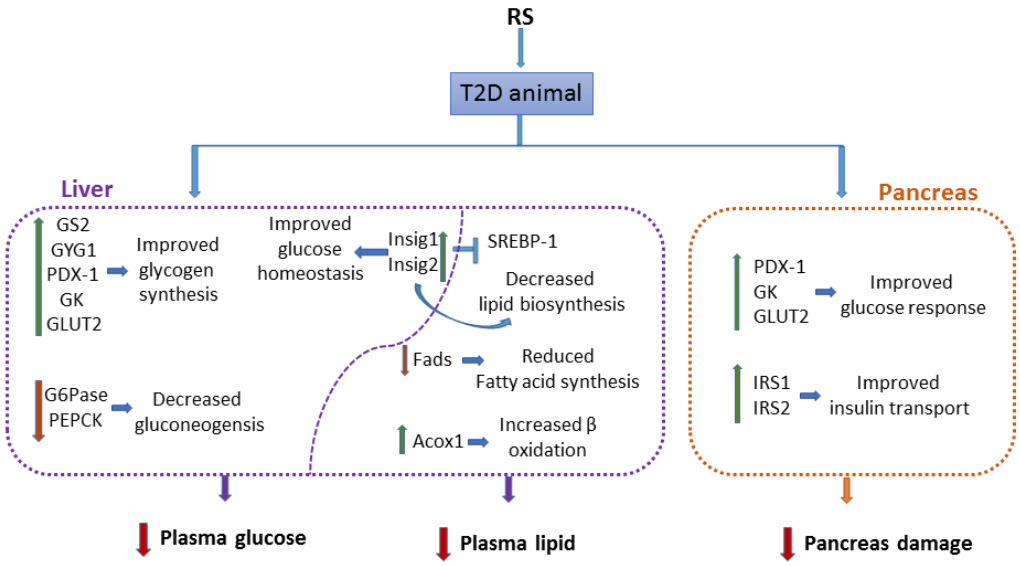

Figure 2. Metabolic pathways regulated by RS.

Figure 2.

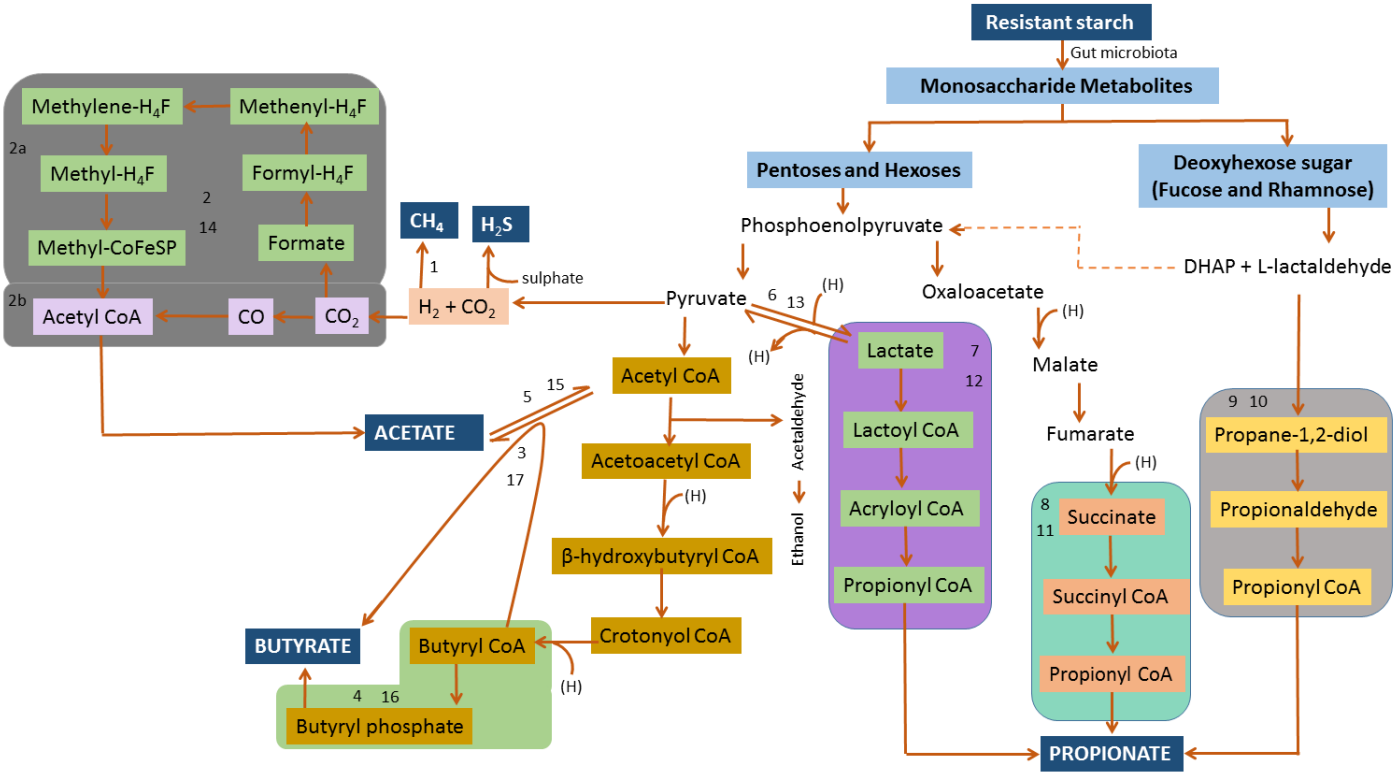

Figure 3. Pathways for resistant starch fermentation in large intestine. 1: methanogenesis, 2: Wood-Ljungdahl pathway; 2a: eastern branch; 2b: western branch, 3: butyryl CoA:acetate CoA transferase route, 4: phosphotransbutyrylase/butyrate kinase route, 5: phosphotransacetylase/acetate kinase, 6: lactate dehydrogenase, 7: acrylate pathway, 8: succinate pathway, 9: propanediol pathway, 10: *Salmonella* spp., *Rosrburia inulinivorans*, *Ruminococcus obeum*, 11: *Bacteroides* spp., *Phascolarctobacterium succinatutens*, *Dialister* spp., *Veillonella* spp., 12: *Megasphaera elsdenii*, *Coprococcus catus*, 13: *Eubacterium hallii; Anaerostipes* spp.; *Veillonella* spp.; 14: *Blautia hydrogenotrophica*, *Clostridium* spp., *Streptococcus* spp., 15: *Akkermansia muciniphila*, *Bacteroides* spp., *Bifidobacterium* spp., *Ruminococcus* spp., 16: *Coprococcus comes*, *Coprococcus eutactus,* 17: *Anaerostipes* spp., *Coprococcus catus*, *Eubacterium rectale*, *Eubacterium hallii*, *Faecalibacterium prausnitzii*, *Roseburia* spp., DHAP: dihydroxyacetonephospate

Figure 3.