Starch

44

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Contents

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Abstract

Starch, a common constituent of higher plants, is the major form in which carbohydrates are stored. This chapter first introduces chemistry structure, synthesis, digestion, metabolism, and bioavailability of starch. Based on its digestion rate and extent, starch is classified into rapidly digestible starch, slowly digestible starch, and resistant starch. Resistant starch cannot be digested in the small intestine but can be fermented in the large intestine. This chapter introduces five kinds of resistant starch and commercially manufactured products and describes the fermentation process of resistant starch in detail, including the metabolism pathways, the bacteria involved, and end products. The fermentability of resistant starch depends on its physical and chemical structure. Particularly, short-chain fatty acids, mainly acetate, butyrate, and propionate, are produced during fermentation of resistant starch. These short-chain fatty acids have considerable bioactives. As a result, consumption of resistant starch has many benefits, including the prebiotic effect, decreasing protein fermentation, keeping colon healthy, the hypoglycemic effect, the anti-obesity effect, reducing inflammation and oxidative stress, improving mineral absorption, etc.

Keywords

Starch · Low digestion · Resistant starch · Fermentation · Gut bacteria · Colon health

44.1 Introduction

Starch, a common constituent of higher plants, is the major form in which carbohydrates are stored. It can be deposited in roots, tubers, fruits, seeds, etc. Humans and their ancestors always eat starchy foods derived from roots, tubers, fruits, or seeds (Miao et al. 2018). It is suggested that starch is of great importance for human evolution (Hardy et al. 2015). In addition, starch is widely used in our daily life. The history of starch is well documented by Schwartz and Whistler (2009). The use of starch products may date back to the pre-dynastic period when Egyptians cemented strips of papyrus together using starch adhesive made from wheat. Later, sheets were first coated with a high-fluidity starch to prevent ink penetration and then covered with powdered starch to improve their weight and thickness in China. Nowadays, Chinese people still use the starch paste made form rice gruel to stick the documents such as couplets on the wall, which is a tradition since a very long time ago. In the Middle Ages, several starches and starch-based products, such as wheat starch, potato starch, maize starch, dextrin, and starch syrups, appeared. The starch industry enormously expanded in the nineteenth century, largely due to demands of the textile, paper, and color printing industries and the emerging of dextrin. By the 1930s, numerous starch products were developed by carbohydrate chemists, which greatly expanded the application of starch.

Table 1 Roles starches play in various food systems (Mason 2009)

Functions	Foods
Adhesion	Battered and breaded foods
Binding	Formed meat, snack seasonings
Clouding	Beverages
Crisping	Fried and baked foods, snacks
Dusting	Chewing gum, bakery products
Emulsion stabilization	Beverages, creamers
Encapsulation	Flavors, beverage clouds
Expansion	Snacks, cereals
Fat replacement	Ice cream, salad dressings, spreads
Foam stabilization	Marshmallows
Gelling	Gum drops, jelly gum centers
Glazing	Bakery, snacks
Moisture retention	Cakes, meats
Thickening	Gravies, pie fillings, soups

Due to sustainability, biodegradability, biocompatibility, edibility, and low cost, starch is one of the most widely used raw materials in food, textile, and pharmaceutical industries. Unfortunately, native starches usually have some defects, which restrict their applications. Therefore, starch is usually modified physically, chemically, and/or enzymatically to enhance their positive attributes and/or to minimize their defects (Miao et al. 2018). For instance, pregelatinization achieves rapid dissolving of starch or starchy foods. Dextrinization increases water solubility of starch. Carboxymethyl starch has higher freeze-thaw stability, and cross-linking starches have greater resistance to stress. Therefore, modification extends application of starch. Generally, starch and starch derivatives are widely used in food products and play important roles, such as gelling agents, thickeners, emulsifying agents, and encapsulating agents (Table 1) (Mason 2009). Starch is also used in papermaking as wet-end additives for dry strength, surface sizes, and coating binders and as adhesives for warp sizing of textiles and glass fiber sizing (Chiu and Solarek 2009). Modified starches are the common ingredient in tablets. In recent years, some starch is used to make the plastic product due to its biodegradability. Therefore, the starch production is very large and increasing each year. The global annual production of pure native starch reached 73 MT in 2011 and was expected to reach 133.5 MT in 2018 (Blennow 2018).

44.2 Chemistry

44.2.1 Chemical Structure of Starch

Starch exists in the form of semicrystalline granules that consist of amylose and amylopectin with very small quantities of proteins, minerals, lipids, and ash. Amylose accounts for 20%–30% by weight in most native starches (Hu et al. 2018; Miao

et al. 2018); expect that waxy starches do not contain amylose. In recent years, genetic strategies have been used to enhance the amylose content in some starches. For instance, high-amylose maize starches have been developed, and there are commercial products, such as amylomaize V, VI, and VII, which correspond to the amylose content of approximately 50%, 60%, and 70%, respectively (Vineyard et al. 1958; Jiang et al. 2010). Amylopectin, the major component of most starches, is a complex branched polysaccharide. The degree of polymerization (DP) of amylopectin ranges 3×10^5–3×10^6 (Zobel 1988). The α-D-glucopyranosyl residues of chains are linked mainly by α-1,4-linkages, and these chains are linked together by α-1,6 bonds at the branch points to form branches (Buléo et al. 1998). Approximately 5%–6% of the glucosyl units in amylopectin are joined via (1-6) bonds, which introduce chain branches. The amylopectin chains are classified into A-, B-, and C-chains as defined by Peat et al. (1952). Each amylopectin molecule has one single C-chain (Pérez and Bertoft 2010). The C-chain contains the terminal reducing end oriented towards the center or hilum of the granule and carries other chains as branches. The B-chains are attached to the C-chain by α-1,6-linkages. The A-chains are the outer chains without any branches which are glycosidically linked at their potential reducing group through C6 of a glucose residue to B-chains. The B-chains carry A- or B-chains as branches. A- and B-chains form clusters and B-chains can carry multiple clusters. These chains are always different in DP, which leads to a broad distribution of the chain length. A-chains typically consist of 6–12 glucosyl units, while B-chains usually contain more glucosyl units. It is well-known that the chain length of amylopectin significantly affects the physicochemical properties. Therefore, chain length distribution is one of the key characteristics for amylopectin. Amylopectin structure usually varies between species and even differs in organelles within the same species (Jaiswal and Chibbar 2017). Potato starches carry more long chains than other starches (Semeijn and Buwalda 2018). The chain length distribution is usually analyzed by high-performance anion-exchange chromatography with pulsed amperometric detection and fluorophore-assisted capillary electrophoresis.

Some native starches, particularly potato starch, possess phosphorylation, and the phosphate groups are mostly monoesterified at the C-3 and C-6 positions of the anhydrous glucose residues of amylopectin in the amorphous parts of the starch granules (Hizukuri et al. 1970). The C-6 phosphate esters are in majority and account for approximately 70% of the total phosphorylation (Hizukuri et al. 1970; Tabata and Hizukuri 1971). These phosphate groups generate charge on the starch molecules, providing the starch with low temperature of gelatinization. Moreover, the starch paste is relatively clear with high viscosity.

Amylose was defined as a linear molecule whose α-D-glucopyranosyl units were linked by α-1,4-linkages, but today it is recognized that some amylose molecules are slightly branched by α-1,6-linkages like amylopectin. The DP of amylose ranges 1500–6000, which is much smaller than amylopectin (Zobel 1988). It is generally accepted that the crystalline part of starch granules is composed of double helices formed by side chains of amylopectin, while the branching point of amylopectin and amylose is located in the amorphous region. Both amylopectin and amylose can

interact with I_2 to form complex. The color and intensity of the starch-I_2 complex depend on the chain length of amylopectin or length of amylose (Baldwin et al. 1944). The amylose-I_2 complex is blue, and its maximum absorbance wavelength (λ_{max}) is approximately 620 nm. The color of the amylopectin-I_2 complex shifts to red-purple, and the λ_{max} shifts to lower wavelengths at 530–575 nm, since the chain length of amylopectin is much smaller than the length of amylose. The blue value (BV) which indicates the complex ability of starch and I_2 is defined as the absorbance at 680 nm of 1 mg starch in 100 mL solution containing 2 mg I_2 and 20 mg KI. Absolutely, amylose has higher BV at 1.01–1.63, whereas BV of amylopectin is low, ranking 0.08–0.38 (Bertoft 2018). Besides, amylopectin and amylose display other different properties, such as viscosity and crystallization behavior. Due to the difference of amylopectin and amylose, the amylose content is an important parameter of native starch.

44.2.2 Starch Synthesis

Amylopectin biosynthesis is executed by a coordinated series of enzymes, including ADP-glucose pyrophosphorylase (AGPase), soluble starch synthase (SS, including SSI, SSII, SSIII, and SSIV), and starch branching enzyme (BE, including BEI and BEII), whereas amylose is synthesized by AGPase and granule-bound starch synthase (GBSSI) (James et al. 2003; Jaiswal and Chibbar 2017). The general scheme of starch synthesis is summarized in Fig. 1 (Buléo et al. 1998). Glucose is first phosphorylated into α-glucose-6-P (P represents the phosphate group) via action of hexokinase, and then α-glucose-6-P is converted into α-glucose-1-P via action of phosphoglucomutase. Alternatively, α-glucose-1-P results from phosphorolytic degradation of starch, which is catalyzed by starch phosphorylase. The α-glucose-1-P should be activated into adenosine diphosphate-glucose (ADP-Glu), the glucosyl

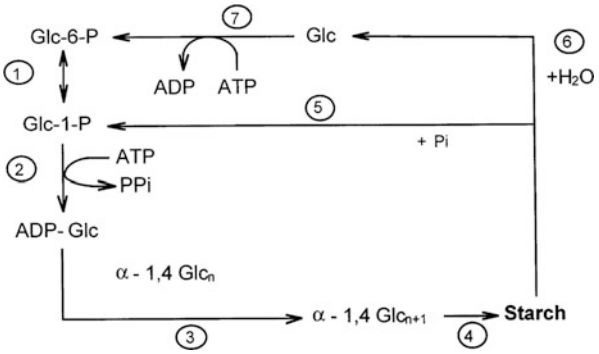

Fig. 1 General scheme for starch biosynthesis: (1) phosphoglucomutase; (2) ADP-glucose pyrophosphorylase; (3) granule-bound and soluble starch synthases; (4) branching enzymes; (5) starch phosphorylase; (6) amylases, branching enzymes, maltases; (7) hexokinase (Buléo et al. 1998). ADP represents adenosine diphosphate and ATP represents adenosine triphosphate

donor. This reaction is catalyzed by AGPase. Then, the glucosyl unit of ADP-glucose is transferred to the nonreducing end of a glucan chain by formation of α-1,4 glycosidic bond for elongation of linear glucan chain, which is catalyzed by SS or GBSS. Studies on roles of SS isoforms in chain length distribution of amylopectin indicate that SSI is primarily responsible for the synthesis of shortest chains (DP $\leq$ 10) (Keeling and Myers 2010). The longer chains of amylopectin are mostly synthesized by SSII and SSIII (Commuri and Keeling 2001). Accordingly, differences in contribution of starch synthases have been observed with respect to species and even different tissues in the same species, which cause variations in fine structure of amylopectin (Smith et al. 1997). The branches of the amylopectin and amylose molecules are produced by SBE, which cleaves internal α-1,4 glycosidic linkage and attaches the released chain through an α-1,6 glycosidic bond to a new site on the glucan molecule. BEI and BEII differ in terms of the lengths of chains transferred in vitro (James et al. 2003). Specifically, BEII transfers shorter chains than BEI. In another study, it was found that BEs might act sequentially during starch synthesis; BEII acted first and produced precursors which further acted as substrate for BEI (Seo et al. 2002). Mutations in many species suggest that starch synthesis also involves debranching enzymes (DBEs) (James et al. 2003). Two DBE families exist in plants, isoamylase type and pullulanase type. They hydrolyze α-1,6 bonds but differ in substrate specificity. Final packaging of starch granules requires trimming of extra branches, and DBEs play this role (Ahuja et al. 2013). Two mechanisms for DBE mode of action have been proposed. According to the preamylopectin-trimming model, the outer branches of preamylopectin molecules are trimmed by DBE to facilitate elongation of chains by SS. This results in amylopectin with an ordered branch structure and allows the molecules to package in starch granules. In addition, the glucan chains released by action of DBE on amylopectin can be used to form the amylose fraction by elongation action of GBSSI. According to the soluble glucan recycling model, DBE participates in degradation of short-chain glucans produced either by SS or SBE action to prevent accumulation of highly branched soluble polymers. This model is supported by the fact that phytoglycogen instead of amylopectin from soluble glucans is formed in endosperms deficient in DBE activity by lesions in DBE genes.

44.2.3 Modification of Starch

Food-grade enzymes, such as α-amylase, β-amylase, amyloglucosidase, and pullulanase, are used to produce maltodextrin, modified starches, or syrups (Jiang et al. 2014; Li et al. 2014; Qi et al. 2017). α-Amylase randomly breaks down the inner α-1,4 glycosidic bonds of starch (Miao et al. 2014d). β-Amylase acts from the nonreducing end of starch and hydrolyzes the second α-1,4 glycosidic bond, cleaving off two glucose units at a time and producing maltose (Miao et al. 2014c). But it cannot pass α-1,6 branch linkage. Therefore, only approximately 40%–60% of amylopectin is converted to maltose, and the remaining part is the β-limit dextrin (Tester and Qi 2011). Amyloglucosidase catalyzes the hydrolysis of both α-1,4 and

α-1,6 bonds, but the rate of hydrolyzing α-1,6 bond is much slower (Miao et al. 2014b). Pullulanase is often used to debranch starch due to its specificity on α-1,6 bond (Miao et al. 2009).

Every α-D-glucopyranosyl unit of starch molecules has three hydroxyl groups, which provides active sites for chemical modification (Lu et al. 2016). Generally, chemical modification of starch involves oxidation, etherification, esterification, or cross-linking of the available hydroxyl groups on the α-D-glucopyranosyl units of starch molecules; thus new groups are introduced to the starch polymer (Miao et al. 2011). Examples of esterified starches include hydroxypropyl starch, hydroxyethyl starch, or carboxymethyl starch, whose hydroxyl groups are partially substituted by hydroxypropyl, hydroxyethyl, or carboxymethyl group through the formation of an ether link (R-O-R), respectively (Masina et al. 2017). Starch octenyl succinate and starch acetate are generally obtained by the esterification of native starch with octenyl succinic anhydride (OSA) and acetic anhydride in the presence of an alkaline catalyst, respectively (Miao et al. 2014a). Cross-linking modification is intended to randomly produce intra- and intermolecular bonds between hydroxyl groups of starch. The commonly used agents to cross-link food-grade starches include sodium trimetaphosphate, sodium tripolyphosphate, monosodium phosphate, phosphoryl chloride, epichlorohydrin, vinyl chloride, and a mixture of adipic acid and acetic anhydride (Singh et al. 2007).

44.3 Metabolism and Bioavailability

44.3.1 Metabolism of Digestible Starch

Starch must be digested into glucose to be absorbed in the small intestine of human beings. Starch is firstly hydrolyzed by salivary α-amylase in oral cavity. Chewing comminutes the food and provides good interaction between salivary α-amylase and starch, which may protect the enzyme inside the bolus and continue to digest starch to some extent in the low-pH environment of the stomach. After the journey through the stomach, starch arrives at the small intestine and is hydrolyzed by pancreatic α-amylase. At this point, starch is hydrolyzed into glucose, maltose, maltotriose, α-limit dextrin, isomaltose, etc. Then these non-glucose molecules are further hydrolyzed into glucose by α-glycosidases at the brush border of the small intestine, including maltase-glucoamylase and sucrase-isomaltase. Maltose, maltotriose, and maltotetraose are hydrolyzed into glucose by maltase-glucoamylase via successive action from their nonreducing end. The α-1,6-linkages of hydrolyzed starch are hydrolyzed by sucrase-isomaltase. Finally, glucose can be actively transported across the enterocyte of the small intestine via the sodium glucose cotransporter 1 (SGLT-1) and enters the blood, thus increasing the blood glucose concentration.

The increasing of the blood glucose concentration leads to secretion of insulin, and the insulin facilitates tissue uptake of glucose to decrease the blood glucose concentration. Some glucose molecules are oxidized immediately to provide energy,

and some are used to synthesize glycogen in liver and muscle tissues. However, the capacity to synthesize glycogen for storing glucose of human body is limited. The maximum storage capacity for storing glucose by glycogen is approximately 700 g (Li 2018). This capacity in muscle is in majority. However, this capacity in the liver is limited, and only a maximum of approximately 150 g glucose can be stored in the liver of a normal 70 kg person. If the glucose intake exceeds both the oxidative and glycogen storage capacities, glucose will be converted into fat. The capacity to convert glucose into fat is much larger, which can explain why eating too much induces obesity. Liver glycogen can be degraded into glucose, and glucose is released to general circulation. Glycogenolysis which means degradation of glycogen into glucose functions according to the body's needs, which plays an important role in maintaining blood glucose levels constant during the intervals between meals (Blanco and Blanco 2017). However, muscle glycogen does not release glucose into the general circulation. Actually, muscle glycogen serves as an energy reserve for this tissue and is intensely utilized when muscle performs work, such as high-intensity exercise. In this case, breakdown of glycogen produces pyruvate and lactate in muscle.

The catabolism of glucose mainly takes place through glycolysis (also known as Embden-Meyerhof pathway), which is fully completed in the cell cytoplasm (Blanco and Blanco 2017). This pathway includes ten reactions (Fig. 2). Phosphorylation is the initial step for the metabolic utilization of glucose (Reaction (1)). The first metabolic transformation is the esterification with phosphate to form glucose-6-P. This reaction is catalyzed by hexokinase, an enzyme present in all cells, or glucokinase. The formation of glucose-6-P is important for converting glucose into a more reactive compound, which is suitable for further transformations. In addition, because glucose-6-P cannot pass through cell membranes, glucose is trapped into the cell via glucose phosphorylation. Moreover, rapid conversion of glucose to glucose-6-P maintains the intracellular glucose concentration at a low level, which facilitates the continual entry of glucose into the cell. In Reaction (2), the aldo sugar, glucose-6-P, is isomerized to the keto sugar, fructose-6-P. This reaction is catalyzed by phosphoglucoisomerase. Then, fructose-6-P is further phosphorylated at the other end by phosphofructokinase to generate fructose-1,6-bisphosphate (fructose-1,6-P_2) (Reaction (3)). This reaction requires the transfer of a phosphoryl group from ATP and is catalyzed by phosphofructokinase. In Reaction (4), fructose-1,6-P_2 is cleaved into two triosephosphate molecules: glyceraldehyde-3-P and dihydroxyacetone-P. Then, dihydroxyacetone-P is transformed into glyceraldehyde-3-P (Reaction (5)). These steps are usually considered as the first or early phase of glycolysis. In Reaction (6), glyceraldehyde-3-P is oxidized and phosphorylated into 1,3-bisphosphoglycerate. This reaction is catalyzed by glyceraldehyde- 3-phosphate dehydrogenase, an oxidoreductase that uses nicotinamide adenine dinucleotide (NAD^+) as coenzyme. Therefore, the acceptor of the reducing equivalents is NAD^+, and it becomes reduced nicotinamide adenine dinucleotide (NADH), while the second hydrogen is released simply as a proton in solution. Substrate-level phosphorylation occurs in Reaction (7). High-energy phosphate is transferred from 1,3-bisphosphoglycerate to ADP, which is catalyzed by phosphoglycerate kinase.

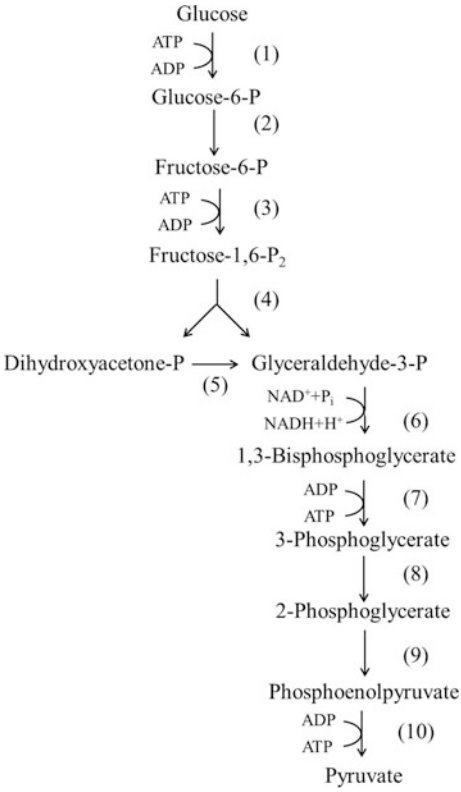

Fig. 2 Reactions of glycolysis

As a result, 3-phosphoglycerate and ATP are produced. Subsequently, 3-phosphoglycerate is converted into 2-phosphoglycerate via an intramolecular phosphoryl transfer (Reaction (8)), which is catalyzed by phosphoglycerate mutase. 2-Phosphoglycerate is dehydrated and intramolecularly redistributed, generating an energy-rich compound, phosphoenolpyruvate (Reaction (9)). The second substrate-level phosphorylation occurs in Reaction (10). The energy-rich phosphoenolpyruvate transfers a phosphate molecule to ADP, forming ATP and pyruvate. This reaction is catalyzed by pyruvate kinase.

The early steps of glycolysis actually consume two ATPs, but four ATPs are produced in the later reactions, resulting in a net production of two ATPs per glucose molecule. Therefore, glucose can quickly provide energy through glycolysis. In this catabolism pathway, two pyruvate molecules are obtained by cleaving a glucose molecule. The fate of pyruvate depends on the oxidative state of the tissue. For glycolysis to proceed, the NADH produced in Reaction (6) must be reoxidized back to NAD^+. Under aerobic conditions, the reducing equivalents from NADH are transferred to the mitochondrial electron transport chain and ultimately to molecular oxygen (Tornheim 2018). In this case, pyruvate produced from glycolysis is completely oxidized to CO_2 and H_2O, which is a complicated process. Pyruvate is first decarboxylated, which produces CO_2 and acetyl-coenzyme A (acetyl-CoA).

Acetyl-CoA moves into the citric acid cycle (also known as tricarboxylic acid (TCA) cycle or Krebs cycle), being completely oxidized to CO_2. The resultant reducing equivalents are transferred to the mitochondrial electron transport chain and ultimately to molecular oxygen, producing H_2O and more ATPs. However, when there is insufficient oxygen or insufficient activity of the electron transport chain, pyruvate must be used to oxidize NADH and regenerate NAD^+ in the lactate dehydrogenase reaction. In this case, pyruvate is reduced to lactate. This is the reason why strong muscular exercise produces lactate. Lactate formation is very important for muscle because it can rapidly use the ATP generated through glycolysis to contract. Increased levels of lactate can be detected in blood and urine after intense exercise, which directly indicates the level of glycolytic activity of muscle. Alternatively, if there is excess use of glucose beyond what would be necessary for energy production, acetyl-CoA can also be used for synthesis of fatty acids, the main constituent of fat (Tornheim 2018). Absolutely, aerobic catabolism of glucose is much more efficient but much slower in energy production than anaerobic catabolism. Particularly, glycolysis is the only pathway for energy production in mature red blood cells due to lack of mitochondria. In addition, the intermediates from glycolysis and citric acid cycle play important roles in supplying the carbon backbone for synthesis of many cell constituents. For instance, 2,3-bisphosphoglycerate which is generated from 1,3-bisphosphoglycerate is an important modulator of hemoglobin. Glycerol-3-P which is formed from dihydroxyacetone participates in the synthesis of triacylglycerols and phospholipids.

In most tissues, 80% or more of glucose catabolism initially enters glycolysis. The rest follows another pathway called the pentose phosphate pathway or the hexose monophosphate pathway. It can be divided into two phases (Fig. 3). The first phase is the oxidative phase. Here glucose-6-P undergoes two oxidations and decarboxylation and is transformed into ribulose-5-P. First, glucose-6-P is dehydrogenated and produces gluconolactone-6-P. This reaction is catalyzed by glucose-6-P dehydrogenase, which depends on nicotinamide adenine dinucleotide phosphate ($NADP^+$) as the hydrogen acceptor. Therefore, reduced nicotinamide adenine dinucleotide phosphate (NADPH) is produced. Then, gluconolactone-6-P is converted into gluconate-6-P. In Step 3, gluconate-6-P is oxidized and transferred into ribulose-5-P and CO_2, which is catalyzed by another $NADP^+$-dependent enzyme, gluconate-6-P dehydrogenase. Thus, NADPH is produced again. The second phase is the nonoxidative phase, which comprises a series of reversible reactions. Firstly, ribulose-5-phosphate produces two isomers: ribose-5-P and xylulose-5-P. They are then transferred into glyceraldehyde-P and sedoheptulose-7-P via action of transketolase, which in turn generate fructose-6-P and erythrose-4-P via action of transaldolase. Erythrose-4-P and xylulose-5-P are redistributed to form glyceraldehyde-3-P and fructose-6-P via action of transketolase. Obviously, glyceraldehyde-3-P and fructose-6-P are intermediates of glycolysis and can enter the glycolysis pathway. In summary, this pathway produces two important substances: pentose phosphate and NADPH (Tornheim 2018). Pentose phosphate is a precursor for synthesis of nucleotides and nucleic acids. On the other hand, NADPH is indispensable to anabolism as a reducing agent, which is used in various

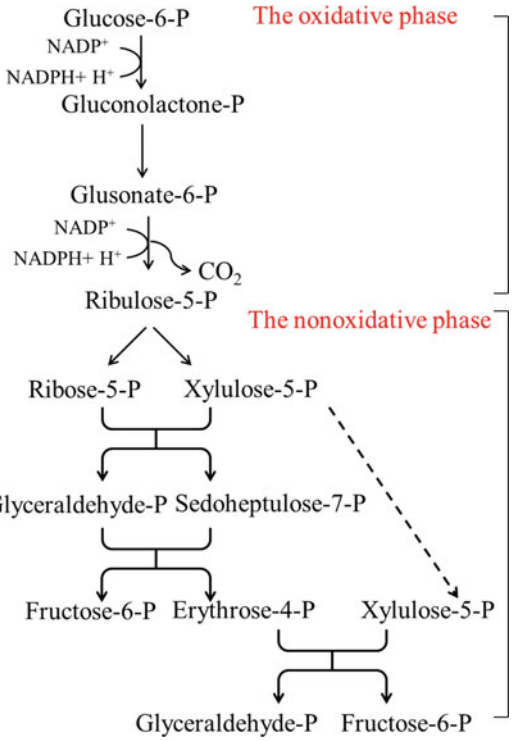

Fig. 3 The pentose phosphate pathway

processes, including fatty acid synthesis, regenerating reduced glutathione, cholesterol and bile acid synthesis, steroid hormone synthesis, and cytochrome P450-dependent biotransformation. Therefore, the pathway is very important for anabolism and is highly active in the tissues where these processes occur, such as liver.

44.3.2 Bioavailability of Starch According to Its Digestion Rate

Digestion of starch is affected by various factors that affect enzyme activity and the susceptibility of the starch substrate to the digestive enzyme (Miao et al. 2013, 2015b). For humans, enzyme activity is mainly affected by the starch structure and enzyme inhibitors either present in the food or generated during digestion of food. As stated above, the main hydrolysis of starch is performed by the α-amylases. Starch digestion by α-amylases requires a series of steps. The enzymes first have to diffuse to the starch matrix, then bind to starch, and finally cleave the α-1,4 glycosidic linkages. Physical entrapment of starch in the food matrix, starch granular structure, and crystallinity may affect the binding of enzymes to the starch substrate (Miao et al. 2015a). For starch granules, one of the limiting factors for the hydrolysis is the penetration of the enzyme into the granules by successive formation of pits and larger pores. On the other hand, the starch has to be properly oriented inside the

active side of the enzyme for the catalytic action of the enzyme to occur (Sun et al. 2019). Only the part of the starch that can fit into the active site cavity of the α-amylase can be hydrolyzed. Structures such as double helices are too big and rigid to fit into the active site cavity, which is another reason for why it is difficult for amylases to hydrolyze starch granules. Thus, the amorphous starch is less resistant to digestive enzymes than the crystalline starch. Similar phenomenon occurs to the starch-lipid complex with a left-handed helix, which is more resistant to enzymes. Molecular structure of starch also influences its digestion. As mentioned above, starch is comprised of amylopectin and amylose. Amylose is a linear polysaccharide whose glucose monomers are linked by α-1,4 glycosidic bonds, whereas the highly branched amylopectin contains α-1,6-linked glucose monomers that create branch points in addition to the linear α-1,4-linkages. The linear regions of the starch molecules are easily digested by human α-amylases. The digestion products of α-amylase, small sugar and oligosaccharide, are then digested further by the intestinal brush border enzymes. Therefore, humans hydrolyze α-1,6 glycosidic bonds more slowly than α-1,4 bonds. A linear portion of the starch chain has to fit in active site of α-amylase to be hydrolyzed. This linear portion must be long enough to favorably bind with the enzyme. Glucose units close to the branch points have less favorable binding with the active site of the enzyme, thus decreasing the hydrolysis efficiency. Thus, no matter what type of linkage that creates the branching of the starch chain, branch points create steric hindrance for α-amylase digestion. Chemical modification of starch usually introduces a bulky side group to the starch chains, which can be viewed as a modification that creates branches on the starch chains and brings steric hindrance to human digestive enzymes. Therefore, chemical modification including etherification, esterification, and cross-linking decreases the digestibility of starch. Particularly, cross-linking links two starch chains, in effect producing a branch on both starch chains.

Therefore, based on its rate and extent of digestion, starch has been classified into rapidly digestible starch (RDS), slowly digestible starch (SDS), and resistant starch (RS) (Englyst et al. 1992). RDS corresponds to the starch fraction digested within 20 min of incubation; SDS is the starch fraction digested within 20–120 min; and the remaining fraction is RS, which cannot be digested further in the small intestine (Miao et al. 2015a). Accordingly, RDS leads to a postprandial fluctuation in blood glucose with the blood glucose peak occurring 30–60 min after consumption (Hendrich 2018). For individuals with normal glucose metabolism, the blood glucose concentration is declined to the fasting state within ~2 h. Ingestion of SDS blunts and slows this pattern of blood glucose response. Ingestion of RS further blunts blood glucose response (Miao et al. 2015a).

44.3.3 Gut Bacterial Metabolism of RS

Generally, RS has been classified into four subtypes named RS1–RS4 (Englyst et al. 1992). RS1 refers to physically inaccessible starch that is enclosed in food matrixes. Starch granules are always surrounded by the protein matrix and cell wall materials.

For instance, it is confirmed that the protein matrix hinder digestion of rice starch (Ye et al. 2018). The whole cereal grains are digested much more slowly than flours, which suggests that the cell wall materials hinder digestion of rice starch. When cooked as whole kernels or coarsely ground seeds, the thick cell wall of legume seeds and the protein matrix in cereal grains prevent water penetration into the starch in the matrix (Birt et al. 2013). Therefore, starch granules do not have adequate moisture to fully swell and gelatinize. Without adequate swelling and gelatinization, starch is not readily susceptible to enzymatic hydrolysis. The cell wall material and the protein matrix also prevent enzymes from reaching and hydrolyzing starch through acting as a physical barrier. Examples of RS1-containing foods in the previous reports include pasta made from durum wheat by extrusion and breads made from whole or coarsely ground kernels of grains (Jenkins et al. 1988; Granfeldt et al. 1991). Durum wheat has a higher protein content and harder texture. Consequently, the postprandial glycemic response after ingesting semolina pasta is substantially lower than white bread. Residual starch that is not digested in the small intestine passes into the colon as RS1. However, these starches may become more accessible and less resistant after milling and chewing. RS2 is composed of native starch granules whose crystallinity makes them resistant to enzymatic hydrolysis. Examples of RS2 include uncooked potato starch, green banana starch, gingko starch, and high-amylose maize starch (Birt et al. 2013). However, after cooking, most of RS2 becomes highly digestible due to starch gelatinization and loss of the crystallites. An exception is high-amylose maize starch. This starch displays a high gelatinization temperature, above the boiling point of water. Therefore, under the common cooking conditions, this type of starch retains its crystalline structure and remains resistant to enzymatic hydrolysis. Retrograded starches formed after cooking belong to RS3. Examples include the starch found in cooked and cooled potatoes, bread crusts, cornflakes, and retrograded high-amylose maize starch. After cooked starchy foods are stored, particularly in a refrigerator, amylose molecules and long-chain branches of amylopectin are prone to forming double helices and lose their water-binding capacity. This process is called retrogradation. The double helices of starch molecules are resistant to amylases. Therefore, those factors which affect retrogradation of starch, such as the amylose content, chain length, and processing conditions, would influence the amount and quality of RS3.The amylose content is positively correlated with the RS3 yield. Several RS3 ingredients are in the market, which are usually derived from cooked and recrystallized maize or tapioca starch. Because amylose molecules have a greater tendency to retrograde than amylopectin molecules, high-amylose starch is often used to prepare RS3. To promote crystallization of starch and formation of RS3, the starch is usually debranched to increase the amount of linear chains (Maningat and Seib 2013). In addition, annealing and heat-moisture treatment can enhance the RS3 content, since more perfect structures are formed, resulting in an increase in enzyme resistance of the starch. RS4 includes chemically modified starches. The introduced groups, such as phosphate groups or octenyl succinic groups, partially inhibit the enzymatic hydrolysis of the starch molecule due to steric hindrance, resulting in RS.

Recently, a new type of RS, RS5, is proposed, which comes from the amylose-lipid complex (Ashwar et al. 2016). When starch interacts with lipids, the hydrocarbon chain of the lipid interacts with the hydrophobic moiety of the amylose chain and fills the central cavity of the amylose. The complex forms amorphous (Form I) or highly crystalline structures (Form II), which both show V-type crystallinity in the X-ray diffraction analysis. This complex occurs in small amounts to native starch, and its production can be enhanced by addition of exogenous fatty acids and heat processing, such as steam jet cooking, wet heat processing, and extrusion cooking (Panyoo and Emmambux 2017). The enzyme resistance of amylose-lipid complex is attributed to the helical conformation of the starch-lipid complex, which prevents amylose molecules from dispersing and interfering with enzymes for hydrolysis (Jane and Robyt 1984). Because the amylose-lipid complex is spontaneously formed during cooling after being heated above its dissociation temperature, RS5 is thermally stable (Panyoo and Emmambux 2017). In addition, the crystalline structure of the complex enhances its enzyme resistance. For instance, the crystalline amylose-lipid complex (Form II) is more resistant to amylolytic enzyme hydrolysis than the amorphous complex counterpart (Form I). The resistance of the complex also depends on the lipid structure. The complex made from longer length fatty acids has greater enzyme resistance, while fatty acids with a greater degree of unsaturation make the amylose-lipid complex with lower enzyme resistance (Hasjim et al. 2013).

Different from RDS and SDS, RS cannot be digested into glucose by the small intestine. Actually, RS passes through the upper digestive part and arrive at the colon where RS is fermented by gut bacteria. The fermentation products of RS by gut bacteria mainly include short-chain fatty acids (SCFAs, mainly acetate, butyrate, and propionate) and gases (methane, hydrogen, and carbon dioxide) (Birt et al. 2013). In addition, few branched-chain fatty acids (isobutyrate and isovalerate), organic acids (lactate, succinate, and formate), and alcohols (methanol and ethanol) are produced. Fermentation of RS is a cooperative process in the lower gut, including (1) degradation of starch polymers into glucose performed by amylolytic gut bacteria; (2) glycolysis with SCFAs or other organic acids as end products which is performed by butyrogenic bacteria; and (3) methane production by *methanogenic Archaea* spp. from formate, hydrogen, and carbon dioxide, the products of bacterial metabolism of RS (Flint et al. 2008).

A range of enzymes is involved in breakdown of RS in the gut, including α-amylases that cleave α-1,4-linkages, type I pullulanases that specifically hydrolyze α-1,6 bonds, and amylopullulanases that cleave both α-1,4 and α-1,6 bonds (Ramsay et al. 2006). By far, the greatest number of starch-degrading enzymes in the gut, including α-amylases, pullulanases, and amylopullulanases, belong to family 13 glycoside hydrolases (MacGregor et al. 2001). It was found that the majority of amylolytic isolates were identified as bifidobacteria (58%) and bacteroides (18%), and fusobacteria and butyrivibrios accounted for about 10% of starch-hydrolyzing bacteria isolated when using fresh feces to ferment soluble starch (Macfarlane and Englyst 1986). In another in vitro fermentation experiment, it was found that *Bifidobacterium* spp., *Bacteroides* spp., *Fusobacterium* spp., and strains

of *Eubacterium*, *Clostridium*, *Streptococcus*, and *Propionibacterium* could hydrolyze the gelatinized amylopectin and high-amylose maize starch, whereas only *Bifidobacterium* spp. and *Clostridium butyricum* could efficiently utilize ungelatinized high-amylose maize starch granules (Wang et al. 1999). Therefore, *Bifidobacterium* spp. and *Clostridium butyricum* would be particularly important to gut bacterial fermentation of insoluble starch. In addition, Ze et al. 2012 found that *Eubacterium rectale* and *Bacteroides thetaiotaomicron* showed limited ability to utilize RS2 and RS3 compared with *Bifidobacterium adolescentis* and *Ruminococcus bromii*. However, only *R. bromii* was proved to be able to stimulate RS2 and RS3 utilization by the other three bacterial species in co-culture, even in a medium that does not permit growth of *R. bromii* itself. These results suggested that *R. bromii* was a keystone species for degradation of RS in the human colon. A recent study in humans also confirmed that the primary degradation of RS2 was largely governed by features linked to *Firmicutes*, including *R. bromii* as a main taxon (Vital et al. 2018).

Bacterial binding to starch is important for fermentation of starch in some bacteria. The enzyme system in *B. thetaiotaomicron* responsible for soluble starch utilization has been well established (Reeves et al. 1996, 1997). The enzyme system is organized by an outer membrane protein complex, including starch-utilization-structure (Sus) gene clusters that bind to and hydrolyze starch. In the complex, these outer membrane Sus proteins regulate the binding and transporting products of starch from partial hydrolysis into the periplasm where they are hydrolyzed and processed further. Specifically, the membrane protein complex contains maltose-inducible outer membrane proteins, SusC, SusD, SusE, SusF, and SusG (Fig. 4) (Flint et al. 2008; Reeves et al. 1996, 1997). SusC and SusD are physically associated and majorly contribute to starch binding. It is likely that SusE and SusF also contribute to binding but not to the same extent as SusD. SusG seems to contribute little to starch binding but is essential for growth on starch. Starch-hydrolyzing activity in *B. thetaiotaomicron* is greatly cell-associated, with much of it being periplasmic. In *E. rectal*e, a complex which contains two glycoside hydrolase13 family enzymes and three ATP-binding cassette transporter solute-binding proteins at the cell surface is responsible for hydrolyzing starch and capturing the released maltooligosaccharides (Cockburn et al. 2015). A multi-domain cell wall-anchored amylase, one of the two enzymes, is tethered to the peptidoglycan layer and may bind the bacterium to starch via its five N-terminal carbohydrate-binding modules and one unknown domain. It preferentially targets starch or maltooligosaccharides longer than maltotriose. The main product is maltotetraose, and significant amounts of maltopentaose are also produced. The other enzyme is a membrane-associated maltogenic amylase, which breaks down maltooligosaccharides with higher DP than maltotriose. The three solute-binding proteins display a range of glycan binding specificities.

Recently, it is found that there is unique organization of extracellular amylases, which is called amylosomes, in the RS-utilizing human colonic *R. bromii* (Ze et al. 2015). Dockerin-cohesin interactions occur among the enzymes in the amylosomes. *R. bromii* is a specialized amylolytic bacterium belonging to the *Ruminococcaceae*, a

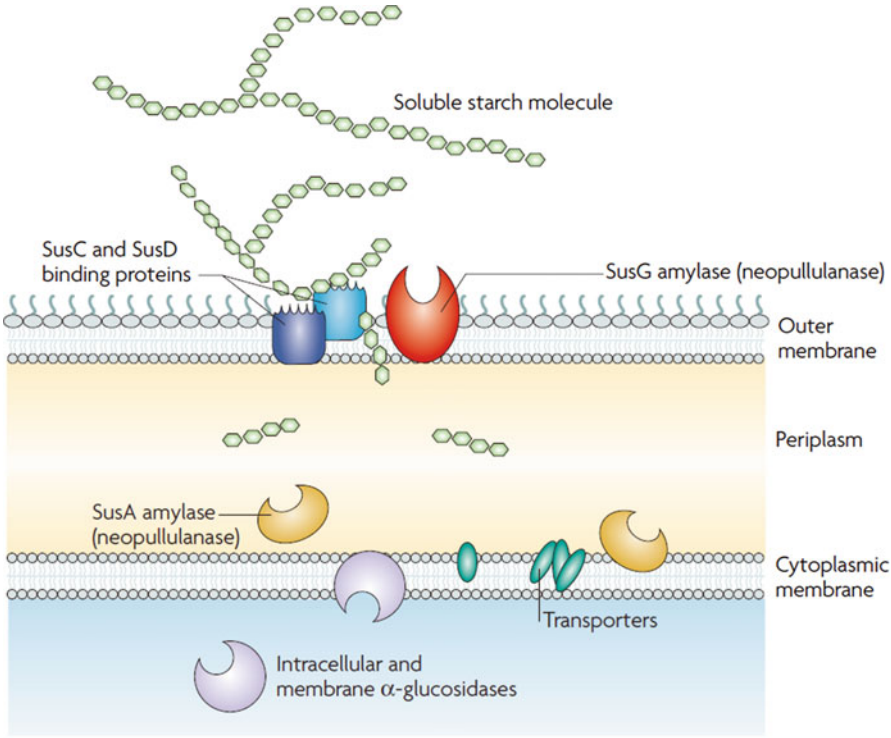

Fig. 4 The sequestration system for soluble starch in *B. thetaiotaomicron.* SusC and SusD are two proteins that have been shown to be essential in binding starch molecules to the cell surface. Limited hydrolysis by SusG is followed by more extensive hydrolysis in the periplasm and the uptake of oligosaccharides across the cytoplasmic membrane (Flint et al. 2008)

family of *Firmicutes* that is better known for the ability of certain rumen species to degrade cellulose. Compared with other amylolytic human intestinal bacteria such as *B. thetaiotaomicron*, *E. rectale*, and *B. adolescentis*, *R. bromii* shows high hydrolyzing activity against raw or boiled RS containing starch granules. It is observed that *R. bromii* cultures mainly have six extracellular GH13 amylases. They are four glycosidases, including Amy4, Amy1, Amy2, and Amy9, and two type I pullulanases, including Amy10 and Amy12. Amy4, Amy9, Amy10, and Amy12 carry dockerin, and Amy4 also carries a cohesin module. It is predicted that Amy4 and Amy9 bind a cohesin present in protein scaffolding. It is also inferred that further complexes are formed between the dockerin-carrying amylases Amy4, Amy9, Amy10, or Amy12 and two other cohesin-carrying proteins. In addition, Amy4 has the ability to autoaggregate, as its dockerin can recognize its own cohesin.

As stated above, glycolysis is the main pathway for glucose catabolism in human cells. Actually, glycolysis is a typical example of the unity of living organisms, since all living organisms have this route (Blanco and Blanco 2017). Many microorganisms metabolize glucose by this pathway through fermentation, but the end products

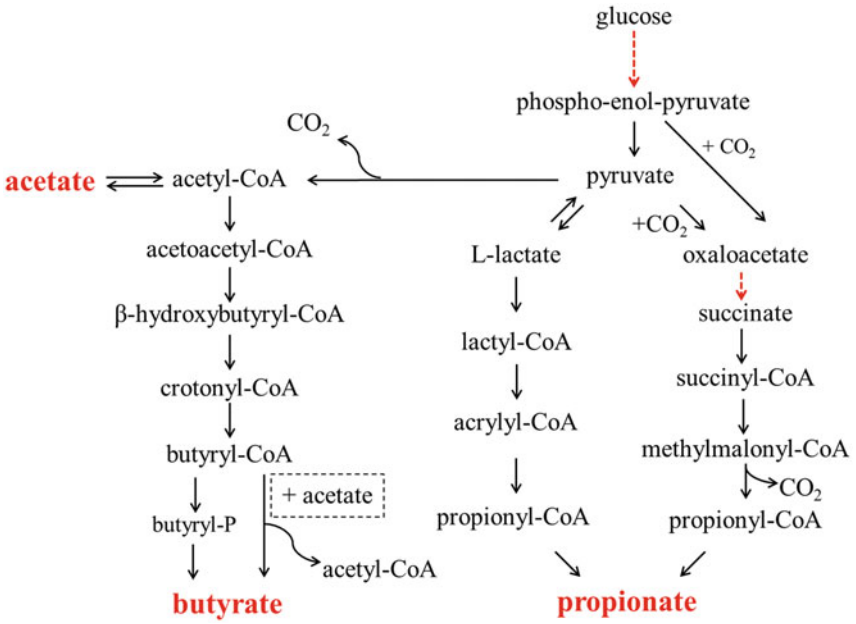

Fig. 5 Fermentation pathways leading to acetate, butyrate, and propionate formation from RS. Dotted arrow indicates several reactions

vary in different organisms. In the gut microorganisms, glycolysis is also the main pathway for glucose catabolism. After glycolysis, different pathways happen to pyruvate, resulting in different SCFAs. According to the previous reports (Pryde et al. 2002; Louis et al. 2007; Zhu et al. 2005), fermentation pathways leading to acetate, butyrate, and propionate are summarized in Fig. 5. Pyruvate is the major precursor of acetate and butyrate. Pyruvate is first decomposed into CO_2, one of the products for RS in gut, and acetyl-CoA. Acetyl-CoA is directly converted into acetate or participates in butyrate synthesis by butyrate kinase through a series of reactions. Acetate can act as a CoA acceptor and react with butyryl-CoA to synthesize butyrate, which is catalyzed by butyryl-CoA: acetate-CoA transferase. There are two routes to form propionate from glucose: the acrylate route from lactate is found in bacteria belonging to the clostridial cluster IX group, while *Bacteroides* species generally employ the succinate route to form propionate (Louis et al. 2007). Acetate accounts for approximately 60%–75% of the total SFCAs detected in feces and is formed by many of the bacteria, with around one-third coming from reductive acetogenesis (Miller and Wolin 1996). Butyrate-producing colonic bacteria generally belong to the clostridial clusters I, IV, XI, XIVa, XV, and XVI (Pryde et al. 2002). Two particularly abundant groups that together constitute 7%–24% of the total gut bacteria in healthy subjects are cluster IV bacteria related to *Faecalibacterium prausnitzii* and cluster XIVa bacteria related to *Eubacterium rectale* and *Roseburia* spp. The pathway employing butyrate kinase seems to widely

exist in different butyrate-producing *Clostridium* species and several clostridia (Zhu et al. 2005; Louis et al. 2007). The pathway employing butyryl-CoA:acetate-CoA transferase has been described in several bacteria, such as *Butyrivibrio fibrisolvens*, *Roseburia* sp., *F. prausnitzii*, and *Coprococcus* sp. (Diez-Gonzalez et al. 1997; Duncan et al. 2002).

Gas production is another fermentation outcome, and particularly the production of methane can be considered as the final end product consuming hydrogen and carbon dioxide (Li 2010). In ruminant animals, methanogens are ubiquitous. However, the distribution of methanogenic *Archaea* in human fecal bacterial populations is a good example of individual variability. Caucasians (48%) and Blacks (45%) had significantly more methane producers than Orientals (24%) and Indians (32%) by measuring breath hydrogen after lactulose intake (Pitt et al. 1980). On the other hand, it was reported that the abundance of methanogenic *Archaea* was negatively correlated to fecal butyrate concentration (Weaver et al. 1992; Belenguer et al. 2006). The production of methane mainly involves two parts as follows:

$$\text{Pyruvate} \rightarrow \text{CO}_2 + \text{H}_2 + \text{Formate}$$

$$\text{CO}_2 + 4\text{H}_2 \rightarrow \text{CH}_4 + 2\text{H}_2\text{O}$$

The microbial communities of the large intestine are characterized by high cell densities and interspecies cross-feeding of fermentation products. Without exception, metabolic cross-feeding between bacteria plays an important role in metabolism of RS. For instance, the potential for metabolic cross-feeding between *B. adolescentis* and lactate-utilizing, butyrate-producing *Firmicute* bacteria related to *Eubacterium hallii* and *Anaerostipes caccae* was investigated in vitro (Belenguer et al. 2006). *E. hallii* L2-7 and *A. caccae* L1-92 failed to grow on starch in pure culture but produced butyrate when in co-culture with *B. adolescentis* L2-32, which confirmed cross-feeding of metabolites to the lactate utilizers. In summary, the utilization of RS is a complex and cooperative process in the gut. Identifying bacteria or bacterial functions in fermentation of RS is important for predicting health outcomes of ingesting RS (Li 2010).

Obviously, fermentation of RS is affected by many factors. It is generally accepted that the production of SCFAs, particularly butyrate, is considered to be favorable. Therefore, fermentability of RS is often reflected by the total SCFA production and the butyrate production. Obviously, the amount of RS entering the large bowel influenced the total and individual SCFA productions. As RS must be depolymerized by bacterial hydrolytic enzymes prior to fermentation, the rate of depolymerization affected the degree at which RS become available for bacteria. As stated above, only several bacteria can utilize starch granules. Thus, it can be inferred that fermentation of RS containing starch granules may be much slower than that of non-granular RS. In addition, granule dimension and surface area of RS containing starch granules may affect hydrolysis of RS. For example, it was found that hulless barley cultivar CDC Fibar (waxy starch) and CDC McGwire (normal starch) started to ferment sooner (lag time of 0.7 and 0.9 h, respectively) than

SH99250 (high-amylose starch; 1.7 h) (Jha et al. 2011). It was confirmed that total and individual SCFA productions also depended on its composition and physical structure of RS. For instance, Martin et al. (1998) found that luminal total SCFA in the caeco-colon of pigs 7 h after feeding potato starch (RS2), high-amylose maize starch (RS2), and retrograded high-amylose maize starch (RS3) were 33, 78, and 105 mmol, respectively, with potato starch providing the highest production of butyrate. They also demonstrated that in vivo fermentation of diets containing raw potato starch, high-amylose maize starch, or retrograded high-amylose maize starch induced different patterns of SCFAs in the portal blood of pigs during a 14-h test period (Martin et al. 2000). In addition, it was observed that acetate and butyrate molar ratios in the SCFA profile differed in vitro fermentation of eight native purified starches (RS2), which suggested that fermentation of RS was influenced by chemical composition and physical form of RS fermented (Giuberti et al. 2013). Similar results were also reported by Torres et al. (2013), who found that the concentration and composition of SCFAs differed after in vitro fermentation of five tropical legume grains. In summary, both the total SCFA production and the profile of each individual SCFA depended on several factors, including chemical composition, physical form, and availability of RS to ferment as well as the microbial population during fermentation. Different RS sources and types also might affect the site of fermentation in the large intestine (Giuberti et al. 2015). Slowly fermentable RS types in diets may provide substrates generating SCFAs in the more distal parts of the colon. In addition, the mixture of RS with different fermenting rates may provide substrates generating SCFAs in the whole colon.

44.4 Bioactivities (Animal Experiments)

Usually, starch is not considered as the biological active substance. However, RS cannot be digested in the small intestine and serve as a carbon source for bacterial fermentation in the large intestine. Therefore, RS is often considered as dietary fiber and displays important bioactivities. In addition, SCFAs are the major end products of gut bacterial metabolism of RS. A number of animal and human studies found that RS increased fecal excretion of SCFAs, specifically butyrate (Li 2010, 2018). Particularly, esterified or acylated forms of RS such as acetylated, butyrated, or propionylated RS4 confer specificity in the delivery of SCFAs, because these starches already carry specific SCFAs (Li 2018). These SCFAs loaded on the starches are only released in the large intestine, leaving the residual starch available for fermentation. Therefore, RS have the bioactivities resulting from SCFAs.

SCFAs are rapidly absorbed in the cecum and colon with only 5%–10% being excreted in the feces (Topping and Clifton 2001). Butyrate is the preferred energy source of colonocytes where oxidation of butyrate accounts for at least 60% of the cell's energy requirements, while other absorbed SCFAs enter the portal vein. Propionate is metabolized in the liver and thus is only present at low concentration in the periphery. Therefore, acetate is the most abundant SCFA in peripheral

circulation (Cummings et al. 1987). Furthermore, acetate can pass through the blood-brain barrier and decrease appetite via a central homeostatic mechanism (Koh et al. 2016). Among the SCFAs, butyrate particularly attracts considerable scientific interest due to its high efficiency in most bioactivities. For normal colon, butyrate promoted the integrity of the mucosal barrier, modulated the immune and inflammatory response, moderated fluid and electrolyte flux, and regulated colonic motility and cell growth and differentiation (Topping and Clifton 2001; Hamer et al. 2008). Importantly, animal experiments demonstrated that butyrate lowered colorectal oncogenesis, including reducing cell proliferation and inducing apoptosis of colorectal tumor cell lines (Perrin et al. 2001; Clarke et al. 2008; Le Leu et al. 2009). The mechanisms of lowering colorectal oncogenesis were complicated. Firstly, butyrate was able to inhibit histone deacetylases (HDACs) and thus affects gene expression (Gupta et al. 2006). Histone acetylation emerged as a central switch that regulated interconversion between permissive (via acetylation) and repressive chromatin structures (via deacetylation) (Koh et al. 2016). Histone acetylation is thought to increase accessibility of the transcriptional machinery to promote gene transcription. Acetyl groups are introduced to histone tails by histone acetyltransferases (HATs) and are removed by HDACs. As a result, HDAC inhibitors can be used for cancer therapy. Compared with normal colonocytes that consume butyrate, butyrate was accumulated threefold in nuclear extracts of cancer cells that consume glucose, resulting in higher concentrations of butyrate in cancerous epithelial cells (Donohoe et al. 2012). Thus, butyrate might act as an efficient HDAC inhibitor in cancerous cells rather than in normal colonocytes. Secondly, in vitro studies demonstrated that cell cycle arrest and apoptosis were induced in both a p53-dependent and p53-independent manners by butyrate at physiologically relevant concentrations (0.6–5 mmol/L) (Janson et al. 1997). In colorectal cancer cell lines, butyrate downregulated the expression of p53 mRNA and protein and also directly increased the expression of p53 target genes to induce cell cycle arrest (Gope and Gope 1993; Nakano et al. 1997). Thirdly, butyrate also altered gene expression through regulating the expression of micro-RNA rather than inhibiting HDAC (Fung et al. 2012).

In addition to being an antitumor agent, SCFAs have the anti-inflammatory effect in the large bowel. Rectal administration of either SCFA mixtures or butyrate alone was shown to effectively ameliorate the clinical symptoms of the disease in patients with distal ulcerative colitis (Luhrs et al. 2002; Scheppach et al. 1992; Breuer et al. 1991). The molecular mechanisms might be that butyrate reduces the expression of interleukin-8 and inhibits inducible NO synthase expression (Huang et al. 1997; Stempelj et al. 2007). In addition, it was reported that butyrate suppresses pro-inflammatory effectors due to inhibition of HDAC (Chang et al. 2014). Butyrate was also reported to modulate oxidative stress of healthy humans by increasing the level of glutathione in colonic mucosa (Hamer et al. 2009).

Another well-recognized general effect resulting from increased concentrations of SCFAs is to decrease the pH of the proximal colon. The pH in the colon can markedly affect composition of the colonic microbiota. It was reported that the final butyrate concentrations were significantly higher at pH 5.5 than at pH 6.5, which correlated with a change in the composition of the microbiota (Walker et al. 2005).

That is, the lowering of pH in the colon may promote butyrate production and improve populations of butyrate-producing bacteria. Moreover, the lowering of pH curtailed the growth of *Bacteroides* spp., propionate-producing bacteria. The inhibition effect of acidic pH is already recognized as an important factor to restrict the populations of certain pH-sensitive pathogens in the gut (Louis et al. 2007). On the other hand, the mildly acidic pH improved Ca^{2+} reabsorption from the colon (Abrams et al. 2005).

Therefore, the RS has the following health benefits, including the prebiotic effect, decreasing protein fermentation, keeping colon healthy, deducing postprandial glycemic response, inhibiting fat accumulation, reducing inflammation and oxidative stress, and improving mineral absorption.

44.4.1 The Prebiotic Effect

RS is proved to have the prebiotic effect by different methods from pure culture studies to animal experiments. Prebiotics are defined as nondigestible food ingredient that are beneficial to the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon (Gibson and Roberfroid 1995). Therefore, prebiotics improve host health. In vitro tests suggested that the environment was found to be dominated by the probiotic strains of *Bifidobacterium* and *Lactobacillus* in co-cultures of intestinal and probiotic bacteria in the presence of tartaric acid-modified dextrin (RS) (Barczynska et al. 2012). A RS-rich diet significantly increased the *Lactobacilli*, *Bifidobacteria*, and *Streptococci* populations, decreased the enterobacteria population, and altered the microbial enzyme metabolism in the colon of rats (Silvi et al. 1999). In another study, feeding high-amylose maize starch, one kind of RS, increased fecal *Bifidobacterium* numbers in mice (Wang et al. 2002). Pigs consuming high-amylose starch had higher fecal concentrations and excretion of *B. longum* than those consuming a conventional starch (Brown et al. 1997), which confirmed the prebiotic action of RS. In addition, it was reported that fructooligosaccharides (FOS) and RS raised fecal *Bifidobacterium* numbers by approximately equal amounts when they were fed separately (Brown et al. 1998). This result also confirmed the prebiotic effect of RS, since FOS is a well-known prebiotic. Interestingly, when FOS and RS were fed together, the increase of *Bifidobacteria* numbers exceeded the increase induced by individual, which suggested that the combination of FOS and RS resulted in a synergistic prebiotic effect. Their synergistic prebiotic effect was also confirmed by experiments in the rats (Rodriguez-Cabezas et al. 2010).

44.4.2 Decreasing Protein Fermentation

High-protein diet could result in an increase in protein fermentation in the large intestine, leading to an increased production of branched-chain fatty acids (BCFAs) and potentially detrimental metabolites, such as ammonia, amines, *N*-nitroso

compounds, phenols, thiols, and indoles (Cummings et al. 1979). It was reported that the high-RS (39 g/d) diet daily significantly increased fecal nitrogen and reduced excretion of fecal phenols, fecal concentrations of ammonia, and pH of human subjects (Birkett et al. 1996). However, daily output of urinary ammonia, urea, phenols, and total nitrogen did not significantly alter. These results suggested that RS might hinder protein fermentation, thus significantly attenuating accumulation of potentially harmful by-products from protein fermentation in the human colon. In addition, it was reported that a high-protein (25% casein) diet for 4 weeks led to a twofold increase in damage to colonocyte DNA in male Sprague-Dawley rats compared with a low-protein (15% casein) diet, which was associated with thinning of the colonic mucous barrier and increased levels of fecal *p*-cresol (Toden et al. 2005). However, addition of RS to the diet increased cecal SCFA pools and attenuated DNA damage, which confirmed that RS might inhibit protein fermentation and result in less genotoxic agents. Similarly, it was observed that feeding digestion-resistant potato protein increased the protein fermentation products in male Sprague-Dawley rats, which was reduced by adding RS to the diet (Le Leu et al. 2007). In another study, mice were fed 15% or 30% protein using casein or red meat or 30% protein with 10% high-amylose maize starch (equivalent to 5% RS2) (Winter et al. 2011). It was found that high protein diets increased promutagenic adducts (O^6-methyl-2-deoxyguanosine, O^6MeG) in the colon, while addition of 5% RS2 to the high protein diets lowered adduct formation, apoptosis, and fecal products of protein fermentation and increased production of butyrate. It was also found that RS inhibited protein fermentation by inocula from the large intestine of pigs using in vitro cultivation (He et al. 2017). In this study, fermentation patterns were analyzed during a 24-h incubation of cecal and colonic digesta with different RS contents using casein protein as the sole nitrogen source. The results showed that as the corn resistant starch levels increased, the SCFA concentration and cumulative gas production were significantly increased, while ammonia-nitrogen and BCFAs were decreased. The total bacteria, *Bifidobacterium* and *Lactobacillus*, were significantly increased with the increasing of the RS content after incubation. Therefore, it was concluded that addition of RS weakened the protein fermentation by altering microbial population. In summary, RS has the ability to decrease protein fermentation, which may be due to producing SCFAs and altering microbial population.

44.4.3 Keeping Colon Healthy

It is generally accepted that RS is beneficial to keep colon healthy, partially because RS increases fecal excretion of SCFAs, particularly butyrate. In addition, the prebiotic effect of RS may play a role in colon health. Colon health involves maintaining normal function of the colon. Healthy colon has regular bowel movement once a day or more frequently with the feces being relatively soft but non-diarrhetic. Colon health can be reflected in the measurement of laxation. It was observed that the RS supplement increased the fecal bulk by 22 g/day compared with the low-fiber control, while the wheat bran supplement increased fecal bulk 96 g/day (Jenkins

et al. 1998). This result suggested that RS was able to increase the fecal weight, but its ability was much weaker than wheat bran. However, RS and wheat bran significantly increased fecal weight in another study and did not differ from each other when 14 subjects were given 25 g RS (PROMITOR^{TM}, Tate & Lyle Americas, Decatur, IL, USA) or wheat bran fiber per day for 14 days (Maki et al. 2009). The different result might be due to the difference of the RS type used.

The colon health also involves prevention of colon diseases. Several studies have investigated the effect of RS on colon cancer prevention by animal experiments. In most cases, RS has been fed in diets combining treatment by a chemical carcinogen to test its effect on preventing colon cancer. For instance, Sprague-Dawley rats were fed diets containing no RS or digestion-resistant potato protein (PP), 10% raw high-amylose corn starch (HAS, source of RS2), 15% PP, or 10% HAS and 15% PP for 4 weeks prior to treatment by azoxymethane (AOM), and colon cancers were assessed 30 weeks after AOM treatment (Le Leu et al. 2007). The RS inhibited colon tumor development and increased SCFAs including butyrate in the distal colon. In addition, the RS lowered production of potentially toxic protein fermentation products. These suggested that RS not only protected against intestinal tumorigenesis but also ameliorated the tumor-enhancing effects of feeding indigestible protein. They later confirmed that feeding the same RS2 protected against AOM-induced colon carcinogenesis and favorably influenced the colonic luminal environment (Le Leu et al. 2014). In the experiments, male Sprague-Dawley rats were provided with one of three diets, control (without RS), 10% HAS, and 20% HAS for 4 weeks, and then injected with AOM (15 mg/kg) during the 5th and 6th week. Data demonstrated that feeding RS significantly reduced the incidence and multiplicity of adenocarcinomas in the colon compared to the control diet. Both doses of HAS resulted in similar protection against colon tumorigenesis. Similarly, Yuan et al. (2017b) found that RS reduced the numbers of aberrant crypt foci (ACF) and aberrant crypts of mice with AOM-induced early colon cancer. In another study, the RS completely prevented the development of tumors in Sprague-Dawley rats, compared to rats fed control starch, when rates were fed RS for 20 weeks following treatment by 1, 2-dimethylhydrazine (Bauer-Marinovic et al. 2006). It was found that this effect was mediated by enhanced apoptosis of damaged cells accompanied by changes in parameters of dedifferentiation in colonic mucosa. Nakanishi et al. (2003) investigated the inhibitory effects of RS2 and *C. butyricum* strain MIYAIRI 588 (CBM588) on AOM-induced ACF formation in rats. Administering only CBM588 spores increased the concentration of butyrate in the cecum, but did not decrease in the number of ACF. Administering only RS2 or RS2 and CBM588 spores decreased the number of ACF. In these two groups, the concentrations of acetate and propionate in intestinal contents were significantly increased, but the concentration of butyrate did not change. However, the β-glucuronidase activity level of colonic contents was significantly decreased in the two groups of rats fed RS2. These results showed that RS and CBM588 changed metabolism of colonic microbiota and decreased the β-glucuronidase activity, which played a role in the inhibition of ACF formation in the rat colon. In summary, RS can help to prevent colon cancer, but the mechanism is complicated.

RS has been proved to be able to prevent or reduce inflammatory bowel diseases. For rats with colitis induced by trinitrobenzenesulphonate (TNBS), RS accelerated healing via prebiotic and butyrate effects (Jacobasch et al. 1999). Moreau et al. (2003) compared FOS and RS in healing colonic inflammation of dextran sulfate sodium (DSS)-induced colitis rat model and found that intake of RS significantly improved colon histopathology scores compared to control and FOS and also increased SCFA concentrations in cecal contents. Long-term intake of RS showed increased the butyrate content of pigs, reduced damage to colonocytes, improved mucosal integrity, and reduced colonic and systemic immune reactivity, which suggested that RS might help pigs to respond to intestinal inflammation better (Nofrarias et al. 2007).

In addition, long-term intake of RS diet increased crude protein and mucin contents and upregulated the expression of mucin genes MUC4, MUC5AC, and MUC12 in the colons of pigs, suggesting the potential of long-term intake of RS diets to improve colon health by increasing mucin secretion and reducing the harmful fermentation of protein (Zhou et al. 2017).

44.4.4 Reducing Postprandial Glycemic Response

Blood glucose concentration control after consuming a meal is primarily determined by the rate of appearance of glucose from the gastrointestinal tract and its clearance from the circulation (Robertson 2012). Many factors affect blood glucose concentration, but insulin is the most important one. Insulin controls the blood glucose concentration via a classical feedback loop. A rise of blood glucose concentration stimulates the secretion of insulin from β cells of the pancreas, and the resulting insulin stimulates muscle and adipose tissue to increase glucose uptake, thus declining blood glucose concentration. Insulin secretion indicates the ability of a rise in plasma glucose to stimulate insulin secretion, and insulin sensitivity indicates the ability of insulin to stimulate glucose uptake from the blood. Normally, insulin secretion maintains blood glucose concentration within a narrow range. However, insulin resistance, defects in insulin secretion, or both impair both fasting and postprandial glucose regulation of individuals, leading to a rise in the blood glucose concentration. As a result, diabetes may occur. Diabetes has serious complications, including heart disease, kidney disease, eye disease, cerebrovascular disease, and nerve damage. Reducing blood glucose levels can prevent and delay the onset of these complications or reduce the severity for patients with diabetes. It is also known that reducing postprandial glycemic response is beneficial to prevent type 2 diabetes for people with high blood glucose concentration or obesity. Consequently, reducing postprandial glycemic response is important for people with high blood glucose, particularly patients with diabetes and prediabetes.

The ability of RS to decrease blood glucose was confirmed in normal rice model. Male Wistar rats were divided into four groups and fed wheat bread, RS-wheat bread, maize bread, and RS-maize bread (Brites et al. 2011). It was found that the RS-wheat bread group significantly reduced feed intake, fecal pH, postprandial

blood glucose response, and total cholesterol. The RS-maize group significantly reduced body weight gain, fecal pH, and total cholesterol levels; but only a reduction in fasting level was observed in the glycemic response. These results confirmed the effect of RS on glycemic response and suggested that the magnitude of the effect of RS on glycemic response depended on other components of diets. Diabetes rice model was also used to confirm the hypoglycemic effect of RS. In a study, RS2 (Hi-maize starch containing 60% amylose) improved glucose tolerance and reduced body fat in the Goto-Kakizaki rat, a nonobese model of type 2 diabetes (Shen et al. 2011). Specifically, feeding RS greatly improved pancreatic β-cell mass, insulin sensitivity, pancreatic insulin content, total GLP-1 (glucagon-like peptide-1) levels, cecal SCFA concentrations, and butyrate-producing bacteria in cecal contents. In another study, the hypoglycemic effect of low, medium, and high doses of RS2 (Hi-maize 260;100, 150, and 200 g/kg) for 28 days was evaluated, and the potential mechanism of this effect was explored in type 2 diabetic rats treated with high-glucose/high-fat diet and low-dose streptozotocin (STZ) (Sun et al. 2018). Feeding RS induced better regulation of oral glucose tolerance test, insulin, glucose metabolism, lipid in plasma and liver, fructosamine, and pancreatic damage in diabetic rats. Interestingly, the medium-dose RS treatment had the best hypoglycemic activity. These results suggested that RS regulated the blood glucose levels of diabetic rats through altering the expression levels of the genes related to glucose metabolism and ameliorating pancreatic dysfunction.

In addition, studies have been done on the effect of different RS sources on blood glucose in humans. For instance, when patients with impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or newly diagnosed type 2 diabetes ($n = 90$) were randomly assigned to either a group ingesting rice containing 6.51 g RS daily or a control rice group for 4 weeks, the diet containing rice with RS reduced fasting insulin and insulin resistance, postprandial glucose and insulin levels at 30 min, and glucose and insulin areas under the response curve after the standard meal (Kwak et al. 2012). In another study, the test was conducted in 20 subjects (9 men and 11 women with a mean age of 50.5 years) using the crossover method, with a single ingestion of either bread containing RS3 (tapioca maltodextrins were debranched and then retrograded) or the placebo (Yamada et al. 2014). Postprandial increases in blood glucose and blood insulin were significantly decreased in subjects with the blood glucose level before ingestion $\geq$111 mg/dl who took the test food compared with the placebo group. Recently, Mah et al. (2018) designed one experiment in which 21 healthy adults consumed a baked breakfast bar containing tapioca-based RS4 (Actistar 75330; Cargill, Inc.) or a macronutrient-matched control bar and found that compared with the control food, consumption of the RS4 food decreased the incremental area under the curves from 0 to 120 min ($iAUC_{0–120\ min}$) for postprandial capillary glucose and $iAUC_{0–120\ min}$ of insulin by 22% and 37%, respectively. Similarly, it was found that adding a practical dose of RS4 (RSVERSAFIBE™ 2470) in muffin significantly reduced postprandial glucose and insulin responses in healthy adults, which was reflected by reduction in $iAUC_{0–120\ min}$ of glucose, maximum glucose concentration, and $iAUC_{0–120\ min}$ of insulin (Stewart and Zimmer 2018).

In summary, RS consumption has been proved to be able to improve glycemic control in both animal and human studies. Blood glucose level is affected by several factors, including absorption, clearance, and release from internal organs (Wong and Louie 2017). Due to escaping digestion of small intestine, RS absolutely lowers glycaemia when it replaces the available carbohydrate portion of a meal. This effect is reflected by the glycemic index (GI), which indicates glycemic response of different food items upon consumption. RS does not induce indicates glycemic response and belongs to low-GI food. Importantly, RS is able to decrease postprandial glycemic response when the available carbohydrate portion of the diet is not reduced, which suggests RS decreases postprandial glycemic response by other mechanisms. The mechanisms behind are complicated. Particularly, RS is able to improve insulin sensitivity and β-cell function (insulin secretion). Improvements in muscular and hepatic glucose handling may be another mechanism. For instance, it was found that the RS-treated mice expressed more G-protein coupled receptors (GPR) 41 and 43 than with normal rice-treated mice (Yuan et al. 2017a). The GPR 41 and GPR 43, which are SCFA receptors, have been found to lead to an increase in glucose uptake and glycogen storage at muscle tissues (Canfora et al. 2015). In addition, acetate was reported to reduce hyperglycemia in diabetic KK-A(y) mice through activating 5′-AMP-activated protein kinase (AMPK) in the liver, since AMPK played an important role in activating glucose and fatty acid uptake and oxidation (Sakakibara et al. 2006). Another possible mechanism where RS consumption may influence on blood glucose control is that RS upregulates gut hormones, including GLP-1 and peptide YY (PYY) (Zhou et al. 2008; Shen et al. 2011). These two hormones are naturally secreted in response to meal ingestion, but they are rapidly degraded after endogenous secretion or exogenous injection (Zhou et al. 2008). GLP-1, a potent incretin by the enteroendocrine L cells of the distal intestine, is shown to possess multiple effects on glucose metabolism, such as promoting pancreatic β-cell mass, stimulating glucose-dependent insulin secretion, and inhibiting glucagon secretion (Shen et al. 2011). PYY, a 36-amino-acid peptide hormone that is cosecreted from intestinal L cells with GLP-1, is initially found to inhibit appetite, thus lowering energy intake (Manning and Batterham 2014).

44.4.4.1 Inhibition of Fat Accumulation

RS, as one kind of the dietary fiber, was able to lower plasma cholesterol and triglyceride concentrations and reduce fat storage (Higgins 2004; Nugent 2005). Total cholesterol, low-density and very low-density lipoprotein cholesterol, and triglycerides were significantly lowered in serum of hamsters fed on the diet containing extruded cassava starch and RS by 17.87%, 62.92%, and 9.17%, respectively, as compared with the diet of cassava starch without added RS (Martinez-Flores et al. 2004). In another study, the effects of RS and cellulose on blood and liver lipids in hamster were compared, and it was observed that RS and cellulose decreased serum cholesterol level by 16.2% and 13.5%, respectively (Ranhotra et al. 1996a). Recently, the effects of RS on postprandial increases in blood triglyceride levels were investigated in rats using oral fat tolerance/loading tests (Matsuda et al. 2016). After administration of lipid meals, feeding RS evidently declined increases

in serum triglycerides levels of rats. In addition, rats fed corn oil containing 500 mg/mL RS has much greater fecal lipid volumes and wet weights following lipid meals than rats fed only corn oil, which confirmed that fat absorption was inhibited by RS. The RS type also affected its anti-obesity effect. For instance, mice fed the RS4 diet had lower body weight and visceral fat weight than those fed either the unmodified starch or RS2 diet, when male C57BL/6 J mice were fed on a high-fat diet containing unmodified starch, hydroxypropylated distarch phosphate (RS4) or RS2 (high-amylose starch) for 24 weeks (Shimotoyodome et al. 2010). In addition, mice fed the RS4 diet had a higher hepatic fatty acid oxidation capacity and related gene expression and lower blood insulin than the other two groups. When given with fat (trioleate) by gavage, dietary supplementation with RS4 stimulated a lower postprandial glucose-dependent insulinotropic polypeptide (GIP; incretin) response than RS2. The GIP could decrease fat utilization in high-fat diet-fed mice. These results suggested that RS4 attenuated high-fat diet-induced obesity more effectively than RS2, which may be due to lower postprandial GIP and increased fat catabolism in the liver.

As described above, the anti-obesity effect was usually accompanied by the hypoglycemic effect. Several reports have suggested that these effects are partially ascribed to increased SCFAs production in the bowel (Sakakibara et al. 2006; Yamashita et al. 2014; Gao et al. 2009; Arora et al. 2011; Lin et al. 2012). When acetate was orally injected to obesity-linked type 2 diabetic Otsuka Long-Evans Tokushima fatty rats at the dose of 5.2 mg/kg BW, acetate markedly reduced in lipid accumulation in the adipose tissue, protected against accumulation of fat in the liver, and improved glucose tolerance (Yamashita et al. 2014). In another study, supplementation of butyrate enhanced adaptive thermogenesis and fatty acid oxidation, and there is an increased mitochondria function and biogenesis in the skeletal muscle and brown fat when butyrate was administrated in dietary obese C57BL/6 J mice through diet supplementation at 5% w/w in the high-fat diet (Gao et al. 2009). Supplementation of butyrate prevented obesity in C57BL/6 J mice, while fasting blood glucose and insulin tolerance were observed in the mice fed on the high-fat diet. It had been shown that propionate inhibited hepatic cholesterol synthesis in humans and also played a role in regulating food intake in non-ruminants (Arora et al. 2011). In addition, a later study demonstrated that butyrate and propionate suppressed food intake, protected against high-fat diet-induced weight gain and glucose intolerance, and stimulated gut hormone secretion predominantly via free fatty acid receptors 3-independent mechanisms (Lin et al. 2012).

44.4.4.2 Reducing Inflammation and Oxidative Stress

Systemic inflammation and oxidative stress play an important role in the pathogenesis of cardiovascular diseases and complications of chronic kidney disease (Tayebi Khosroshahi et al. 2018). Therefore, it is important to reduce inflammation and oxidative stress. Yuan et al. (2017a) found that after diabetic mice were treated with normal rice, normal rice with RS, or normal rice with RS and Se for 4 weeks, supplementing with RS lowered levels of serum C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), nuclear factor-k-gene binding

(NF-κB), and leptin (LEP) and increased adiponutrin (ADPN) levels. In addition, Se and RS decreased CRP, IL-6, and NF-κB levels much more than RS. These results indicated that RS reduced inflammation and Se and RS might have synergistic effects on chronic inflammation. RS was also proved to reduce inflammation and oxidative stress in humans. For instance, it was found that 4-week dietary treatment with RS also reduced oxidative stress of patients with IFG, IGT, or newly diagnosed type 2 diabetes when this treatment reduced their blood glucose level (Kwak et al. 2012). In another study, 46 stable hemodialysis patients randomly consumed biscuits containing 20 g/day during the first 4 weeks and 25 g/day in the following 4 weeks of either RS2 or wheat flour (Tayebi Khosroshahi et al. 2018). RS2 significantly declined serum levels of TNF-a, IL-6, and malondialdehyde compared with the placebo. In addition, serum urea and creatinine concentrations were significantly decreased, and severity of constipation was improved in RS2-treated patients. These results suggested that administration of RS2 for 8 weeks significantly reduced levels of inflammatory and oxidative markers in hemodialysis patients. Similar results were obtained by Esgalhado et al. (2018). This study evaluated 31 hemodialysis patients assigned to either RS (16 g Hi-maize 260) or placebo (manioc flour) supplementation, which they received for 4 weeks on alternate days through cookies on dialysis days and powder in a sachet on non-dialysis days. It was found that the RS group had lower IL-6, thiobarbituric acid reactive substances plasma (TBARS), and indoxyl sulfate plasma levels, while no significant differences were observed in the placebo group. These reports confirmed that RS had the ability to reduce inflammation and oxidative stress.

44.4.4.3 Improving Mineral Absorption in Large Intestine

As mentioned above, SCFAs produced from fermentation of RS2 decreased the pH, which was beneficial to mineral absorption. Therefore, RS might improve mineral absorption, which was confirmed by several studies. For example, Lopez et al. (2000) investigated the effects of a natural source of phytic acid, wheat bran, in the presence or in the absence of RS on the assimilation of minerals (Ca, Mg, and P) and trace elements (Fe, Mn, Zn, and Cu) in rats adapted to semi-purified diets and found that absorption of Ca, Mg, and P in the cecal was 3.5-fold higher in the RS groups than in the control groups due to the hypertrophy of the cecal wall, low luminal pH, and improved concentrations of soluble minerals. Moreover, the apparent retention of all the above minerals was significantly enhanced by RS ingestion. The disappearance of phytic acid was twofold higher in rats fed the RS diet than those fed the control diet. Thus, it was concluded that the addition of RS into wheat bran diet allowed a greater mineral absorption by increasing the SCFA production and breaking down phytic acid in the large intestine. Likewise, Yonekura et al. (2003) found that RS2 restored Zn and Mg bioavailability suppressed by phytic acid in rats, which was due to that cecal fermentation of RS2 increased SCFA and succinate concentrations and reduced cecal pH. In another study, the effects of RS2 and RS3 on mineral absorption, including Ca, Mg, and Fe, were investigated (Zeng et al. 2017). Specifically, BALB/c male mice were fed five different diets: Diet 1 containing no RS; Diet 2, 3, and 4 containing 5, 10, or 15 g RS3/100 g diet; and

Diet 5 containing 15 g RS2/100 g diet. Data demonstrated that the apparent absorption of Ca was significantly greater in mice fed medium and high levels of RS3, as well as RS2, than in those fed the basal and the low-level RS3 diets. The mice fed high levels of RS3 displayed the greatest apparent absorption of Ca. Similar results were obtained when the effect of RS on Mg absorption was studied. In addition, mice fed on RS3 and RS2 exhibited greater apparent absorption of Fe, and the apparent absorption of Fe was enhanced as the RS3 dose increased. These results might be related to SCFAs by the intestinal microbial fermentation of RS. In addition, it was reported that bread with RS4 and garlic showed a prebiotic effect and increased Ca bioavailability and deposition in bones in male weaning Wistar rats, compared with wheat bread (Weisstaub et al. 2018). However, Schulz et al. (1993) found that apparent absorption of Ca and Mg in rats was improved by RS2 (uncooked high-amylose starch granules) but not by RS3 (cooked and cooled high-amylose starch). Compared with cooked normal starch, RS2 significantly lowered the ileal pH, while RS3 raised it. Cecal pH was lowered by the two kinds of RS. Ca concentrations in the liquid ileal contents were improved by RS2 but were significantly lowered by RS3 relative to control starch. Ma and Ca concentrations in liquid cecal contents were raised by RS2, but RS3 did not change them. These results suggested that RS3 might be not fermented in the ileum since the pH was not decreased. Thus, it was inferred that RS3 might be fermented at a very slow rate, resulting in no increase in Ca and Mg absorption. To summarize, consumption of RS may improve mineral absorption in large intestine. However, this effect may be removed once it is fermented too slowly.

44.5 Function in Human (Human Studies)

The function in human of starch mainly results from metabolism of glucose digested from starch. Glucose, an essential nutrient of living organisms, not only provides the potential energy but also acts as a precursor for metabolic intermediates in biosynthetic pathways (Miao et al. 2015a). Humans require a reliable source of glycemic carbohydrate to support the normal functions of our brain, red blood cells, muscles, kidney medulla, and reproductive tissues. Here, we summarized the function in humans of starch from mental and physical performance like Hendrich (2018).

44.5.1 Function in Mental Performance

Glucose is the main energy source for brain of humans, although brain has the ability to utilize other fuel molecules, such as ketone bodies (Nirmalan and Nirmalan 2017). The adult human brain accounts for only around 2% of body mass but around 20% of whole body resting energy expenditure (Wang et al. 2014; Mergenthaler et al. 2013). Thus, the brain is the main consumer of glucose, approximately consuming 5.6 mg glucose per 100 g human brain tissue per minute. In human newborns, the brain weighs approximately 11% of body weight but consumes >50% of energy (Wang

et al. 2014). Up to the age of 3, when the brain size rapidly increases, it is recommended that at least one-third of dietary energy should be supplied from carbohydrates (Bier et al. 1997). Neuronal computation and information processing, such as the generation of action potentials and postsynaptic potentials generated after synaptic events, consume the largest proportion of energy in the brain (Harris et al. 2012). In addition to providing primary energy of the brain, glucose metabolism plays an important role in physiological brain function through the foundation of neuronal and non-neuronal cellular maintenance and generating neurotransmitters (Mergenthaler et al. 2013). For instance, it seems that astrocytic glycogen is very important for learning, since glycogen selectively supplies carbon and supports de novo synthesis of transmitter glutamate by combined pyruvate dehydrogenation and carboxylation in astrocytes (Hertz and Gibbs 2009). Furthermore, breakdown of astrocytic glycogen and release of lactate from glycolysis are essential for forming long-term memory and for maintaining the long-term potentiation of synaptic strength elicited in vivo (Suzuki et al. 2011). Thus, the brain increases consumption of glucose upon activation (Sokoloff 1999).

In contrast to other tissues, the brain of humans at birth is very immature and undergoes substantial quantitative and qualitative changes during postnatal development, which need substance foundation and energy. Therefore, it seems that glucose metabolism is important for human brain evolution. In addition, abnormal glucose metabolism declines cognition. A meta-analysis of several hundred children with type 1 diabetes (T1D) showed that individuals with T1D had lower scores at overall IQ, executive function, and motor speed than control children without T1D (Tonoli et al. 2014). The same cognitive impairments were seen in adults with T1D, and memory of these adults was also impaired compared with control adults without T1D. In addition, it seemed that the longer the duration of T1D, the more cognition may be impaired. On the other hand, glucose-enhanced cognitive performance is consistently observed in populations who usually have poorer memories and glucose regulation, such as healthy elderly subjects and patients with Alzheimer's disease (Greenwood 2003). This result suggests that glucose can reverse or mask the memory deficits observed in those with poor gluco-regulatory status and/or underlying memory deficits (Greenwood 2003).

44.5.2 Function in Physical Performance

Physical activity requires energy for muscle contraction. As stated above, free glucose from muscle glycogen is not released into the circulation, which indicates that glucose is of great importance as a muscle fuel. Particularly, anaerobic metabolism of glucose can rapidly provide energy during very high-intensity physical activity such as a sprint. It is generally recognized that a decrease in carbohydrate availability can result in fatigue during prolonged exercise in humans (El-Sayed et al. 1997). During prolonged exercise, blood glucose and muscular glycogen are the two major sources of carbohydrate utilization by the active muscles. During exercise, the energy from blood sugar is limited for normal humans. Therefore, long-

term exercise performance may mainly depend on the muscle glycogen stores (Hendrich 2018). It has been shown that administration of glucose or other carbohydrates before or during exercise postpones fatigue, conserves muscle glycogen, and improves performance. Thus, replenishing enough muscle glycogen stores is the main concern for athletes who need extreme endurance.

Particularly, effects of starches on exercise of people with diabetes have been studied. A previous study compared metabolic responses and fuel use of participants with T1D during sub-maximal and high-intensity performance running following pre-exercise ingestion of 0.6 g/kg body mass waxy barley starch or dextrose (Gray et al. 2015). Interestingly, T1D individuals consuming waxy barley starch had a greater carbohydrate oxidation rate at rest and displayed an improved performance at the latter stages of a high-intensity run test, although waxy barley starch and dextrose led to similar hyperglycemic responses. In another study, people with type 2 diabetes (T2D) were fed on a vegetarian diet with 60% carbohydrate or a conventional diet with 50% carbohydrate for 12 weeks at 500 kcal restriction of daily energy requirement and had personalized daily exercise (Veleba et al. 2016). It was observed that the vegetarian diet improved fitness while the conventional diet did not. This suggests that a vegetarian diet higher in complex carbohydrates might benefit people with T2D, as improved physical fitness may help people persist with increased physical activity. Therefore, much work is required to determine what starch types optimize exercise performance for different people and the underlying mechanisms.

44.6 Safety

According to the long-term eating habits of humans, native starches are generally safe and well tolerated. They have little chance for adverse effects except those effects associated with long-term overconsumption (Hendrich 2018). The dose makes the poison, which is a central tenet of toxicology. Therefore, even glucose, the digestion product of safe starches, may be toxic to humans. As stated above, normal people can decline the postprandial blood glucose to the normal level. But some people suffer from hyperglycemia. Therefore, glucose toxicity occurs, and it usually refers to damaging effects of high blood glucose concentrations on body tissues and regulatory processes through several mechanisms (Brownlee 2005). First, the mechanisms involve the polyol pathway, particularly aldose reductase. Normally, aldose reductase reduces toxic aldehydes in the cell to inactive alcohols. However, when the glucose concentration in the cell becomes too high, aldose reductase also reduces glucose to sorbitol. During this process, NADPH is consumed as the cofactor of aldose reductase. But NADPH is also the essential cofactor for regenerating reduced glutathione. Due to the decreasing amount of reduced glutathione, the polyol pathway increases susceptibility to intracellular oxidative stress. Secondly, glucose can interact with free amines in body proteins and form advanced glycation end products (AGEs). AGEs can directly induce cross-linking of long-lived proteins such as collagen (Goh and Cooper 2008). Thus, vascular stiffness is promoted. In addition, AGEs can enhance oxidative stress and elaborate key

proinflammatory and prosclerotic cytokines via interaction with certain receptors (Wautier et al. 2017; Goh and Cooper 2008). Thirdly, the mechanisms involve the protein kinase C (PKC) pathway. In this pathway, hyperglycemia inside the cell increases the synthesis of diacylglycerol, which is a critical activating cofactor for the classic isoforms of protein kinase C, β, δ, and α. Once PKC is activated by intracellular hyperglycemia. It has a variety of effects on gene expression. The pathological effects that may result from activation of PKC include blood flow abnormalities, vascular permeability angiogenesis, capillary occlusion, vascular occlusion, proinflammatory gene expression, etc. Fourthly, some of fructose-6-P resulting from glucose gets diverted into a signaling pathway in which GFAT (glutamine:fructose-6-P amidotransferase) converts the fructose-6-P to glucosamine-6-P and finally to UDP (uridine diphosphate) *N*-acetylglucosamine. Subsequently, the *N*-acetylglucosamine is transferred onto serine and threonine residues of transcription factors, and overmodification by this glucosamine often results in pathologic changes in gene expression. A unified mechanism is that hyperglycemia increases superoxide production and oxidative stress. Therefore, rapidly digestible dietary starches may contribute to such pathologies for those who suffer from hyperglycemia.

Many chemically modified starches made for food use are safe because these modified starches are allowed to contain only small amounts of substituent groups (Singh et al. 2007). When starch octenyl succinates are produced for application in foods, the amount of OSA is limited to 3% based on the dry starch weight (the degree of substitution <0.0231) (Altuna et al. 2018). The maximum permitted amount of substitution groups for starch phosphates, starch acetates, and hydroxypropylated starches are 0.4%, 2.5%, and 10%, respectively (Chen et al. 2018). Similarly, cross-linked food starches are allowed to contain one substituent cross-linking group per 1000 or more anhydroglucose (Singh et al. 2007).

44.7 Products in Market

A vast range of native starches are already at the market, including maize starch, cassava starch, potato starch, wheat starch, rice starch, waxy starches, etc. Physicochemical properties of starches from different sources differ significantly. Worldwide, maize (82%), wheat (8%), potatoes (5%), and cassava (5%) are the main sources of starch (Corre et al. 2010). In the food industry, modified starches mainly include pregelatinized starch, maltodextrin, oxidized starch, hydroxypropyl starch, starch octenyl succinate, starch acetate, starch phosphates, and cross-linked starch.

In addition to natural food sources of RS stated above, increasing commercially manufactured forms of RS are available. Commercial sources of RS2, amylomaize VII (Cerestar Inc., Hammond, IN, USA), Hi-maize 260 (National Starch & Chemical Co, Bridgewater, N.J., USA), and Hylon VII (National Starch & Chemical Co, Bridgewater, NJ) are now available (Ranhotra et al. 1996b; Martínez et al. 2010; Hylla et al. 1998). CrystaLean (Opta Food Ingredients, Inc.), NOVELOSE 330® (National Starch & Chemical Co), Hi-maize 330 (National Starch & Chemical Co),

and Promitor Resistant Starch 60 (Tate & Lyle) are examples of commercially developed RS3 which are derived from high-amylose maize starch (Nugent 2005; Maningat and Seib 2013). To promote formation of RS3, the starch was first hydrolyzed by a debranching enzyme to increase the amount of linear chains, followed by crystallization of the linear chains to (Maningat and Seib 2013). One commercially available example of RS3 produced in this way is Actistar™ (Cargill Inc.), which is produced by debranching and crystallization of tapioca maltodextrin (US6043229) (Kettlitz et al. 2000). To further promote crystallization of starch, Tate & Lyle first treated starch with a glucanotransferase to elongate the external chains of amylopectin, followed by debranching and then crystallization of the linear chains to form RS3 (US7674897B2) (Norman et al. 2010). RS4 products are also commercially available. For example, Fibersym RW (MGP Ingredients, Atchison, Kansas, USA) is a phosphorylated cross-linked wheat starch (Woo and Seib 2002). Actistar 75330 is a phosphorylated RS4 derived from tapioca that is commercially available from Cargill, Inc. (Mah et al. 2018). VERSAFIBE™ 2470 is a newly developed RS4 by Ingredion Incorporated (Bridgewater, NJ) that is derived from high-amylose maize starch modified by acid hydrolysis and heat treatment (Stewart and Zimmer 2018). Dextrinization of starch can lead to the formation of potentially indigestible linkages. Thus, dextrinization is used by several companies to create indigestible dietary fiber ingredients that can be classified as RS4 (Maningat and Seib 2013). Nutriose® soluble fibers are food dextrins derived from wheat or maize starch (US5620871) (Caboche 1997), which are marketed by Roquette (Roquette Frères). Fibersol 2 is a resistant maltodextrin reported in the USA patent (US5358729) (Ohkuma et al. 1995) and is produced by dextrinization of starch followed by heating at 120 to 200 °C. This RS is produced and marketed by a joint venture between Archer Daniels Midland Company and Matsutani (Matsutani LLC). Tate & Lyle's Promitor™ Soluble Corn Fiber ingredients are characterized by a higher concentration of nonlinear saccharide oligomers, which result from treating starch by cooking, hydrolysis, enzyme depolymerization, fractionation, isomerization, etc. (US7608436) (Harrison et al. 2009).

44.8 Perspective

Glucose is an important fuel for humans, particularly brain, muscles, red cells, etc., and starches in human diets are the main providers of glucose. According to the previous results, dietary starch plays an important role in development of the human brain, and tightly regulating blood glucose may be better for cognition. Therefore, it is meaningful to discover, design, and further develop diets and starches that benefit brain development and cognition. Therefore, recommendations for human dietary patterns must include the dietary starch content and type (Hendrich 2018). In addition, there is an additional opportunity to design starches that benefit exercise performance. In summary, starch deserves more attention as a foundation of a healthy diet for cognitively sound and physically active humans (Hendrich 2018). That is, starch ingestion must be optimized and individualized to meet special needs of humans.

On the other hand, effects of RS on gut microbiota and effects of microbiota on RS metabolism are still the focus of scientists. It is possible that different forms of RS are accessible by different groups of colonic microorganisms. Thus, different types of RS may promote different groups of colonic bacteria. This could result in selective effects of RS intake upon the species composition of the colonic microbiota, as well as differential effects on gut metabolism. It highlights the need to consider both primary degraders of RS and specific more-downstream-acting bacterial groups in order to achieve desired intervention outcomes. The gained insights will assist the design of personalized treatment strategies based on an individual's microbiota (Vital et al. 2018). To better interpret the relationship between gut microbiota and RS, new techniques are required to analyze gut microbiota. In addition, new and advanced analytical methods for RS are required, because the analysis of RS still greatly depends on methods developed earlier for dietary fiber (Birt et al. 2013). On the other hand, the previous studies suggest that RS structure determines its rate and site of fermentation in the large intestine. The characteristics of dietary starch, including particle structure, crystallinity, branching, association with other polymers, retrogradation, and modification, are known to affect its digestibility in the small intestine (Miao et al. 2015a, 2018). It is inferred that these characteristics may also affect the rate at which RS is fermented in the colon. Rapid fermentation of RS may lead to complete fermentation in the proximal colon, whereas slower rates support fermentation in more distal regions, with the possibility of incomplete colonic fermentation overall. Fermentation kinetics, combined with information about the transit time, can give an indication about where ingredients are fermented and could therefore be used to select RS sources eliciting fermentation in specific places of the guts. Therefore, it seems possible to control the fermentation rate and site. Accordingly, different RS types in diets may provide enough substrates generating SCFAs in the more distal parts of the colon with more possible reduction in protein fermentation. Recently, imbalances in human gut microbiota are considered to be related to various noncommunicable diseases, such as colon cancer, type 2 diabetes, and obesity. Thus, RS have the potential to prevent these diseases, since RS can modulate gut microbiota. However, considerable research is required to identify the potential effectiveness of RS in preventing or even cure human diseases. Particularly, despite the tremendous diversity of RS in plants and commercial RS products, very few of them have been studied. In conclusion, future integrative research is needed to expand the potential uses of RS in health promotion of humans.

References

Abrams SA, Griffin IJ, Hawthorne KM, Liang L, Gunn SK, Darlington G, Ellis KJ (2005) A combination of prebiotic shorthand long-chain inulin-type fructans enhances calcium absorption and bone mineralization in young adolescents. Am J Clin Nutr 82:471–476. https://doi.org/10.1093/ajcn.82.2.471

Ahuja G, Jaiswal S, Chibbar RN (2013) Starch biosynthesis in relation to resistant starch. In:Shi Y-C, Maningat CC (eds) Resistant starch: sources, applications and health benefits. Wiley, pp 1–22. https://doi.org/10.1002/9781118528723.ch1

Altuna L, Herrera ML, Foresti ML (2018) Synthesis and characterization of octenyl succinic anhydride modified starches for food applications. A review of recent literature. Food Hydrocoll 80:97–110. https://doi.org/10.1016/j.foodhyd.2018.01.032

Arora T, Sharma R, Frost G (2011) Propionate. Anti-obesity and satiety enhancing factor? Appetite 56(2):511–515. https://doi.org/10.1016/j.appet.2011.01.016

Ashwar BA, Gani A, Shah A, Wani IA, Masoodi FA (2016) Preparation, health benefits and applications of resistant starch-a review. Starch-Stärke 68(3–4):287–301. https://doi.org/10.1002/star.201500064

Baldwin RR, Bear RS, Rundle RE (1944) The relation of starch-Iodine absorption spectra to the structure of starch and starch components. J Am Chem Soc 66:111–115. https://doi.org/10.1021/ja01229a032

Barczynska R, Slizewska K, Jochym K, Kapusniak J, Libudzisz Z (2012) The tartaric acid-modified enzyme-resistant dextrin from potato starch as potential prebiotic. J Funct Foods 4(4):954–962. https://doi.org/10.1016/j.jff.2012.07.003

Bauer-Marinovic M, Florian S, Muller-Schmehl K, Glatt H, Jacobasch G (2006) Dietary resistant starch type 3 prevents tumor induction by 1,2-dimethylhydrazine and alters proliferation, apoptosis and dedifferentiation in rat colon. Carcinogenesis 27(9):1849–1859. https://doi.org/10.1093/carcin/bgl025

Belenguer A, Duncan SH, Calder AG, Holtrop G, Louis P, Lobley GE, Flint HJ (2006) Two routes of metabolic cross-feeding between Bifidobacterium adolescentis and butyrate-producing anaerobes from the human gut. Appl Environ Microbiol 72(5):3593–3599. https://doi.org/10.1128/AEM.72.5.3593-3599.2006

Bertoft E (2018) Analyzing starch molecular structure. In: Sjöö M, Nilsson L (eds) Starch in food: structure, function and applications. Woodhead Publishing, pp 97–149. https://doi.org/10.1016/b978-0-08-100868-3.00002-0

Bier DM, Brosnan JT, latt JP, Hanson RW, Heird W, Hellerstein MK, Jequier E, Kalhan S, Koletzko B, Macdonald I, Owen O, Uauy R (1997) Report of the IDECG Working Group on lower and upper limits of carbohydrate and fat intake. Eur J Clin Nutr 53:S177–S178. https://doi.org/10.1038/sj.ejcn.1600759

Birkett A, Muir J, Phillips J, Jones G, Dea OK (1996) Resistant starch lowers fecal concentrations of ammonia and phenols in humans. Am J Clin Nutr 63:766–772. https://doi.org/10.1093/ajcn/63.5.766

Birt DF, Boylston T, Hendrich S, Jane JL, Hollis J, Li L, McClelland J, Moore S, Phillips GJ, Rowling M, Schalinske K, Scott MP, Whitley EM (2013) Resistant starch: promise for improving human health. Adv Nutr 4(6):587–601. https://doi.org/10.3945/an.113.004325

Blanco A, Blanco G (2017) Carbohydrate metabolism. In: Blanco A, Blanco G (eds) Medical biochemistry. Academic, pp 283–323. https://doi.org/10.1016/b978-0-12-803550-4.00014-8

Blennow A (2018) Starch bioengineering. In: Starch in food: structure, function and applications. Woodhead Publishing. https://doi.org/10.1016/b978-0-08-100868-3.00004-4

Breuer RI, Buto SK, Christ ML (1991) Rectal irrigation with short-chain fatty acids for distal ulcerative colitis. Dig Dis Sci 36:185–187. https://doi.org/10.1007/BF01300754

Brites CM, Trigo MJ, Carrapico B, Alvina M, Bessa RJ (2011) Maize and resistant starch enriched breads reduce postprandial glycemic responses in rats. Nutr Res 31(4):302–308. https://doi.org/10.1016/j.nutres.2011.02.001

Brown I, Warhurst M, Arcot J, Playne M, Illman RJ, Topping DL (1997) Fecal numbers of Bifidobacteria are higher in pigs fed *Bifidobacterium longum* with a high amylose cornstarch than with a low amylose cornstarch. J Nutr 127:1822–1827. https://doi.org/10.1093/jn/127.9.1822

Brown IL, Wang X, Topping DL, Playne MJ, Conway PL (1998) High amylose maize starch as a versatile prebiotic for use with probiotic bacteria. Food Austr 50:602–609

Brownlee M (2005) The pathobiology of diabetic complications: a unifying mechanism. Diabetes 54:1615–1625. https://doi.org/10.2337/diabetes.54.6.1615

Buléo A, Colonna P, Planchot V, Ball S (1998) Starch granules: structure and biosynthesis. Int J Biol Macromol 23(2):85–112. https://doi.org/10.1016/S0141-8130(98)00040-3

Caboche JJ (1997) Process for preparing optionally hydrogenated indigestible polysaccharides. USA Patent, US5620871

Canfora EE, Jocken JW, Blaak EE (2015) Short-chain fatty acids in control of body weight and insulin sensitivity. Nat Rev Endocrinol 11(10):577–591. https://doi.org/10.1038/nrendo.2015.128

Chang PV, Hao L, Offermanns S, Medzhitov R (2014) The microbial metabolite butyrate regulates intestinal macrophage function via histone deacetylase inhibition. Proc Natl Acad Sci U S A 111(6):2247–2252. https://doi.org/10.1073/pnas.1322269111

Chen Y-F, Kaur L, Singh J (2018) Chemical modification of starch. In: Sjöö M, Nilsson L (eds) Starch in food: structure, function and applications. Woodhead Publishing, pp 283–321. https://doi.org/10.1016/b978-0-08-100868-3.00007-x

Chiu C-W, Solarek D (2009) Modification of starches. In: BeMiller J, Whistler R (eds) Starch: chemistry and technology. Academic, New York, pp 629–655. https://doi.org/10.1016/B978-0-12-746275-2.00017-3

Clarke JM, Topping DL, Bird AR, Young GP, Cobiac L (2008) Effects of high-amylose maize starch and butyrylated high-amylose maize starch on azoxymethane-induced intestinal cancer in rats. Carcinogenesis 29(11):2190–2194. https://doi.org/10.1093/carcin/bgn192

Cockburn DW, Orlovsky NI, Foley MH, Kwiatkowski KJ, Bahr CM, Maynard M, Demeler B, Koropatkin NM (2015) Molecular details of a starch utilization pathway in the human gut symbiont *Eubacterium rectale*. Mol Microbiol 95(2):209–230. https://doi.org/10.1111/mmi.12859

Commuri PD, Keeling PL (2001) Chain-length specificities of maize starch synthase I enzyme: studies of glucan affinity and catalytic properties. Plant J 25:475–486. https://doi.org/10.1046/j.1365-313x.2001.00955.x

Corre DL, Bras J, Dufresne A (2010) Starch nanoparticles: a review. Biomacromolecules 11:1139–1153. https://doi.org/10.1021/bm901428y

Cummings JH, Hill MJ, Bone ES, Branch WJ, Jenkins DJA (1979) The effect of meat protein and dietary fiber on colonic function and metabolism II. Bacterial metabolites in feces and urine. Am J Clin Nutr 32:2094–2101. https://doi.org/10.1093/ajcn/32.10.2094

Cummings JH, Pomare EW, Branch WJ, Naylor CP, Macfarlane GT (1987) Short chain fatty acids in human large intestine, portal, hepatic and venous blood. Gut 28:1221–1227. https://doi.org/10.1136/gut.28.10.1221

Diez-Gonzalez F, Bond DR, Jennings E, Russell JB (1997) Alternative schemes of butyrate production in *Butyrivibrio fibrisolvens* and their relationship to acetate utilization, lactate production, and phylogeny. Arch Microbiol 171:324–330. https://doi.org/10.1007/s002030050717

Donohoe DR, Collins LB, Wali A, Bigler R, Sun W, Bultman SJ (2012) The Warburg effect dictates the mechanism of butyrate-mediated histone acetylation and cell proliferation. Mol Cell 48(4):612–626. https://doi.org/10.1016/j.molcel.2012.08.033

Duncan SH, Barcenilla A, Stewart CS, Pryde SE, Flint HJ (2002) Acetate utilization and butyryl coenzyme A (CoA):acetate-CoA transferase in butyrate-producing bacteria from the human large intestine. Appl Environ Microbiol 68(10):5186–5190. https://doi.org/10.1128/aem.68.10.5186-5190.2002

El-Sayed MS, DonMacLaren J, Rattu A (1997) Exogenous carbohydrate utilisation: effects on metabolism and exercise performance. Comp Biochem Physiol A Physiol 118:789–803. https://doi.org/10.1016/S0300-9629(97)00064-9

Englyst HN, Kingman SM, Cummings JH (1992) Classification and measurement of nutritionally important starch fractions. Eur J Clin Nutr 46:S33–S50

Esgalhado M, Kemp JA, Azevedo R, Paiva BR, Stockler-Pinto MB, Dolenga CJ, Borges NA, Nakao LS, Mafra D (2018) Could resistant starch supplementation improve inflammatory and oxidative stress biomarkers and uremic toxins levels in hemodialysis patients? A pilot randomized controlled trial. Food Funct 9(12):6508–6516. https://doi.org/10.1039/c8fo01876f

Flint HJ, Bayer EA, Rincon MT, Lamed R, White BA (2008) Polysaccharide utilization by gut bacteria: potential for new insights from genomic analysis. Nat Rev Microbiol 6(2):121–131. https://doi.org/10.1038/nrmicro1817

Fung KY, Cosgrove L, Lockett T, Head R, Topping DL (2012) A review of the potential mechanisms for the lowering of colorectal oncogenesis by butyrate. Br J Nutr 108(5):820–831. https://doi.org/10.1017/S0007114512001948

Gao ZG, Yin J, Zhang J, Ward RE, Martin RJ, Lefevre M, Cefalu WT, Ye JP (2009) Butyrate improves insulin sensitivity and increases energy expenditure in mice. Diabetes 58:1509–1517. https://doi.org/10.2337/db08-1637

Gibson GR, Roberfroid MB (1995) Dietary modulation of the human colonic microbiota introducing the concept of prebiotics. J Nutr 125:1401–1412. https://doi.org/10.1093/jn/125.6.1401

Giuberti G, Gallo A, Moschini M, Masoero F (2013) In vitro production of short-chain fatty acids from resistant starch by pig faecal inoculum. Animal 7(9):1446–1453. https://doi.org/10.1017/S1751731113001092

Giuberti G, Gallo A, Moschini M, Masoero F (2015) New insight into the role of resistant starch in pig nutrition. Anim Feed Sci Technol 201:1–13. https://doi.org/10.1016/j.anifeedsci.2015.01.004

Goh SY, Cooper ME (2008) Clinical review: the role of advanced glycation end products in progression and complications of diabetes. J Clin Endocrinol Metab 93(4):1143–1152. https://doi.org/10.1210/jc.2007-1817

Gope R, Gope ML (1993) Effect of sodium butyrate on the expression of retinoblastoma (RB1) and P53 gene and phosphorylation of retinoblastoma protein in human colon tumor cell line HT29. Cell Mol Biol (Noisy-le-Grand) 39:589–597

Granfeldt Y, Bjorck I, Hagander B (1991) On the importance of processing conditions, product thickness and egg addition for the glycemic and hormonal responses to pasta – a comparison with bread made from pasta ingredients. Eur J Clin Nutr 45:489–499

Gray BJ, Page R, Turner D, West DJ, Campbell MD, Kilduff LP, Stephens JW, Bain SC, Bracken RM (2015) Improved end-stage high intensity performance but similar glycaemic responses after waxy barley starch ingestion compared to dextrose in type 1 diabetes. J Sports Med Phys Fitness 56:1392–1400

Greenwood CE (2003) Dietary carbohydrate, glucose regulation, and cognitive performance in elderly persons. Nutr Rev 61:S68–S74. https://doi.org/10.1301/nr.2003.may.S68-S74

Gupta N, Martin PM, Prasad PD, Ganapathy V (2006) SLC5A8 (SMCT1)-mediated transport of butyrate forms the basis for the tumor suppressive function of the transporter. Life Sci 78(21):2419–2425. https://doi.org/10.1016/j.lfs.2005.10.028

Hamer HM, Jonkers D, Venema K, Vanhoutvin S, Troost FJ, Brummer RJ (2008) Review article: the role of butyrate on colonic function. Aliment Pharmacol Ther 27(2):104–119. https://doi.org/10.1111/j.1365-2036.2007.03562.x

Hamer HM, Jonkers DM, Bast A, Vanhoutvin SA, Fischer MA, Kodde A, Troost FJ, Venema K, Brummer RJ (2009) Butyrate modulates oxidative stress in the colonic mucosa of healthy humans. Clin Nutr 28(1):88–93. https://doi.org/10.1016/j.clnu.2008.11.002

Hardy K, Brand-Miller J, Brown KD, Thomas MG, Copeland L (2015) The importance of dietary carbohydrate in human evolution. Q Rev Biol 90:251–268. https://doi.org/10.1086/682587

Harris JJ, Jolivet R, Attwell D (2012) Synaptic energy use and supply. Neuron 75(5):762–777. https://doi.org/10.1016/j.neuron.2012.08.019

Harrison MD, Purdue JC, Patton PA, Hoffman AJ, Gaddy JM, Liu CL, Schanefelt RV (2009) Process for producing saccharide oligomers. USA Patent, US7608436

Hasjim J, Ai Y, Jane J-L (2013) Novel applications of amylose-lipid complex as resistant starch type 5. In: Shi Y-C, Maningat CC (eds) Resistant starch: sources, applications and health benefits. Wiley, pp 79–94. https://doi.org/10.1002/9781118528723.ch4

He X, Sun W, Ge T, Mu C, Zhu W (2017) An increase in corn resistant starch decreases protein fermentation and modulates gut microbiota during in vitro cultivation of pig large intestinal inocula. Anim Nutr 3(3):219–224. https://doi.org/10.1016/j.aninu.2017.06.004

Hendrich S (2018) Starch: physical and mental performance, and potential health problems. In: Sjöö M, Nilsson L (eds) Starch in food: structure, function and applications. Woodhead Publishing, pp 855–871. https://doi.org/10.1016/b978-0-08-100868-3.00023-8

Hertz L, Gibbs ME (2009) What learning in day-old chickens can teach a neurochemist: focus on astrocyte metabolism. J Neurochem 109(Suppl 1):10–16. https://doi.org/10.1111/j.1471-4159.2009.05939.x

Higgins JA (2004) Resistant starch: metabolic effects and potential health benefits. J AOAC Int 287:761–768. https://doi.org/10.1007/s003840050212

Hizukuri S, Tabata S, Nikuni Z (1970) Studies on starch phosphate. Part 1. Estimation of glucose-6-phosphate residues in starch and the presence of other bound phosphate(s). Starch-Stärke 22:338–343. https://doi.org/10.1002/star.19700221004

Hu X, Wang Y, Liu C, Jin Z, Tian Y (2018) 1-Butanol-hydrochloric acid hydrolysis of high-amylose maize starch. Starch-Stärke 70(5–6):1700359. https://doi.org/10.1002/star.201700359

Huang N, Katz JP, Martin DR, Wu GD (1997) Inhibition of IL-8 gene expression in Caco-2 cells by compounds which induce histone hyperacetylation. Cytokine 9:27–36. https://doi.org/10.1006/cyto.1996.0132

Hylla S, Gostner A, Dusel G, Anger H, Bartram H-P, Christl SU, Kasper H, Scheppach W (1998) Effects of resistant starch on the colon in healthy volunteers: possible implications for cancer prevention. Am J Clin Nutr 67:136–142. https://doi.org/10.1093/ajcn/67.1.136

Jacobasch G, Schmiedl D, Kruschewski M, Schmehl K (1999) Dietary resistant starch and chronic inflammatory bowel diseases. Int J Color Dis 14:201–211. https://doi.org/10.1007/s003840050212

Jaiswal S, Chibbar RN (2017) Amylopectin small chain glucans form structure fingerprint that determines botanical origin of starch. Carbohydr Polym 158:112–123. https://doi.org/10.1016/j.carbpol.2016.11.059

James MG, Denyer K, Myers AM (2003) Starch synthesis in the cereal endosperm. Curr Opin Plant Biol 6(3):215–222. https://doi.org/10.1016/s1369-5266(03)00042-6

Jane J-L, Robyt JF (1984) Structure studies of amylose-V complexes and retro-graded amylose by action of alpha amylases, and a new method for preparing amylodextrins. Carbohydr Res 132:105–118. https://doi.org/10.1016/0008-6215(84)85068-5

Janson W, Brandner G, Siegel J (1997) Butyrate modulates DNA-damage-induced p53 response by induction of p53- independent differentiation and apoptosis. Oncogene 15:1395–1406. https://doi.org/10.1038/sj.onc.1201304

Jenkins DJA, Wesson V, Wolever TMS, Jenkins AL, Kalmusky J, Guidici S, Csima A, Josse RG, Wong GS (1988) Wholemeal versus wholegrain breads – proportion of whole or cracked grain and the glycemic response. BMJ 297:958–960

Jenkins DJA, Vuksan V, Kendall CWC, Würsch P, Jeffcoat R, Waring S, Mehling CC, Vidgen E, Augustin LSA, Wong E (1998) Physiological effects of resistant starches on fecal bulk, short chain fatty acids, blood lipids and glycemic index. J Am Coll Nutr 17(6):609–616. https://doi.org/10.1080/07315724.1998.10718810

Jha R, Bindelle J, Rossnagel B, Van Kessel A, Leterme P (2011) In vitro evaluation of the fermentation characteristics of the carbohydrate fractions of hulless barley and other cereals in the gastrointestinal tract of pigs. Anim Feed Sci Technol 163(2–4):185–193. https://doi.org/10.1016/j.anifeedsci.2010.10.006

Jiang H, Jane JL, Acevedo D, Green A, Shinn G, Schrenker D, Srichuwong S, Campbell M, Wu Y (2010) Variations in starch physicochemical properties from a generation-means analysis study using amylomaize V and VII parents. J Agric Food Chem 58(9):5633–5639. https://doi.org/10.1021/jf904531d

Jiang H, Miao M, Ye F, Jiang B, Zhang T (2014) Enzymatic modification of corn starch with 4-α-glucanotransferase results in increasing slow digestible and resistant starch. Int J Biol Macromol 65:208–214. https://doi.org/10.1016/j.ijbiomac.2014.01.044

Keeling PL, Myers AM (2010) Biochemistry and genetics of starch synthesis. Annu Rev Food Sci Technol 1:271–303. https://doi.org/10.1146/annurev.food.102308.124214

Kettlitz BW, Coppin JVJM, Roper HWW, Bornet F (2000) Highly fermentable resistant starch. USA Patent, US6043229

Koh A, De Vadder F, Kovatcheva-Datchary P, Backhed F (2016) From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites. Cell 165(6):1332–1345. https://doi.org/10.1016/j.cell.2016.05.041

Kwak JH, Paik JK, Kim HI, Kim OY, Shin DY, Kim HJ, Lee JH, Lee JH (2012) Dietary treatment with rice containing resistant starch improves markers of endothelial function with reduction of post-prandial blood glucose and oxidative stress in patients with prediabetes or newly diagnosed type 2 diabetes. Atherosclerosis 224(2):457–464. https://doi.org/10.1016/j.atherosclerosis.2012.08.003

Le Leu RK, Brown IL, Hu Y, Morita T, Esterman A, Young GP (2007) Effect of dietary resistant starch and protein on colonic fermentation and intestinal tumourigenesis in rats. Carcinogenesis 28(2):240–245. https://doi.org/10.1093/carcin/bgl245

Le Leu RK, Hu Y, Brown IL, Young GP (2009) Effect of high amylose maize starches on colonic fermentation and apoptotic response to DNA-damage in the colon of rats. Nutr Metab (Lond) 6:11. https://doi.org/10.1186/1743-7075-6-11

Le Leu RK, Brown IL, Hu Y, Esterman A, Young GP (2014) Suppression of azoxymethane-induced colon cancer development in rats by dietary resistant starch. Cancer Biol Ther 6(10):1621–1626. https://doi.org/10.4161/cbt.6.10.4764

Li L (2010) Assessing prebiotic effects of resistant starch on modulating gut microbiota with an in vivo animal model and an in vitro semi-continuous fermentation mode. Iowa State University, Ames

Li X (2018) Resistant starch and its applications. In: Jin Z (ed) Functional starch and applications in food. Springer Nature Singapore Pte Ltd., Singapore, pp 63–90. https://doi.org/10.1007/978-981-13-1077-5_3

Li X, Miao M, Jiang H, Xue J, Jiang B, Zhang T, Gao Y, Jia Y (2014) Partial branching enzyme treatment increases the low glycaemic property and α-1,6 branching ratio of maize starch. Food Chem 164:502–509. https://doi.org/10.1016/j.foodchem.2014.05.074

Lin HV, Frassetto A, Kowalik EJ Jr, Nawrocki AR, Lu MM, Kosinski JR, Hubert JA, Szeto D, Yao X, Forrest G, Marsh DJ (2012) Butyrate and propionate protect against diet-induced obesity and regulate gut hormones via free fatty acid receptor 3-independent mechanisms. PLoS One 7(4): e35240. https://doi.org/10.1371/journal.pone.0035240

Lopez HW, Coudray C, Bellanger J, Levrat-Verny M-A, Demigne C, Rayssiguier Y, Remesy C (2000) Resistant starch improves mineral assimilation in rats adapted to a wheat bran diet. Nutr Res 20:141–155. https://doi.org/10.1016/S0271-5317(99)00146-3

Louis P, Scott KP, Duncan SH, Flint HJ (2007) Understanding the effects of diet on bacterial metabolism in the large intestine. J Appl Microbiol 102(5):1197–1208. https://doi.org/10.1111/j.1365-2672.2007.03322.x

Lu K, Miao M, Ye F, Cui SW, Li X, Jiang B (2016) Impact of dual-enzyme treatment on the octenylsuccinic anhydride esterification of soluble starch nanoparticle. Carbohydr Polym 147:392–400. https://doi.org/10.1016/j.carbpol.2016.04.012

Luhrs H, Gerke T, Muller JG, Schauber J, Boxberger F, Scheppach W, Menzel T (2002) Butyrate inhibits NF-kappaB activation in lamina propria macrophages of patients with ulcerative colitis. Scand J Gastroenterol 37:458–466. https://doi.org/10.1080/003655202317316105

Macfarlane GT, Englyst HN (1986) Starch utilization by the human large intestinal microflora. J Appl Bacteriol 60:195–201. https://doi.org/10.1111/j.1365-2672.1986.tb01073.x

MacGregor EA, Janeck S, Svensson B (2001) Relationship of sequence and structure to specificity in the α-amylase family of enzymes. Biochim Biophys Acta 1546:1–20. https://doi.org/10.1016/S0167-4838(00)00302-2

Mah E, Garcia-Campayo V, Liska D (2018) Substitution of corn starch with resistant starch type 4 in a breakfast bar decreases postprandial glucose and insulin responses: a randomized, controlled, crossover study. Curr Dev Nutr 2:1–6. https://doi.org/10.1093/cdn/nzy066

Maki KC, Sanders LM, Reeves MS, Kaden VN, Rains TM, Cartwright Y (2009) Beneficial effects of resistant starch on laxation in healthy adults. Int J Food Sci Nutr 60(Suppl 4):296–305. https://doi.org/10.1080/09637480903130538

Maningat CC, Seib PA (2013) RS4 -Type resistant starch: chemistry, functionality and health benefits. In: Shi Y-C, Maningat CC (eds) Resistant starch: sources, applications and health benefits. Wiley, pp 43–77. https://doi.org/10.1002/9781118528723.ch3

Manning S, Batterham RL (2014) The role of gut hormone peptide YY in energy and glucose homeostasis: twelve years on. Annu Rev Physiol 76:585–608. https://doi.org/10.1146/annurev-physiol-021113-170404

Martin LJM, Dumon HJW, Champ MMJ (1998) Production of short-chain fatty acids from resistant starch in a pig model. J Sci Food Agric 77:71–80. https://doi.org/10.1002/(SICI)1097-0010(199805)77:1%3C71::AID-JSFA3%3E3.0.CO;2-H

Martin LJM, Dumon HJW, Lecannu G, Champ MMJ (2000) Potato and high- amylose maize starches are not equivalent producers of butyrate for the colonic mucosa. Br J Nutr 84:689–696. https://doi.org/10.1017/s0007114500002038

Martínez I, Kim J, Duffy PR, Schlegel VL, Walter J (2010) Resistant starches types 2 and 4 have differential effects on the composition of the fecal microbiota in human subjects. PLoS One 5: e15046. https://doi.org/10.1371/journal.pone.0015046.g001

Martinez-Flores HE, Chang YK, Martinez-Bustos F, Sgarbieri V (2004) Effect of high fiber products on blood lipids and lipoproteins in hamsters. Nutr Res 24:85–93. https://doi.org/10.1016/S0271-5317(03)00206-9

Masina N, Choonara YE, Kumar P, du Toit LC, Govender M, Indermun S, Pillay V (2017) A review of the chemical modification techniques of starch. Carbohydr Polym 157:1226–1236. https://doi.org/10.1016/j.carbpol.2016.09.094

Mason WR (2009) Starch use in foods. In: BeMiller J, Whistler R (eds) Starch: chemistry and technology. Academic, New York, pp 746–795. https://doi.org/10.1016/B978-0-12-746275-2.00020-3

Matsuda H, Kumazaki K, Otokozawa R, Tanaka M, Udagawa E, Shirai T (2016) Resistant starch suppresses postprandial hypertriglyceridemia in rats. Food Res Int 89(Pt 1):838–842. https://doi.org/10.1016/j.foodres.2016.10.022

Mergenthaler P, Lindauer U, Dienel GA, Meisel A (2013) Sugar for the brain: the role of glucose in physiological and pathological brain function. Trends Neurosci 36(10):587–597. https://doi.org/10.1016/j.tins.2013.07.001

Miao M, Jiang B, Zhang T (2009) Effect of pullulanase debranching and recrystallization on structure and digestibility of waxy maize starch. Carbohydr Polym 76:214–221. https://doi.org/10.1016/j.carbpol.2008.10.007

Miao M, Jiang B, Zhang T, Jin Z, Mu W (2011) Impact of mild acid hydrolysis on structure and digestion properties of waxy maize starch. Food Chem 126:506–513. https://doi.org/10.1016/j.foodchem.2010.11.031

Miao M, Jiang H, Jiang B, Li Y, Cui SW, Jin Z (2013) Elucidation of structural difference in theaflavins for modulation of starch digestion. J Funct Foods 5:2024–2029. https://doi.org/10.1016/j.jff.2013.09.021

Miao M, Li R, Jiang B, Cui SW, Zhang T, Jin Z (2014a) Structure and physicochemical properties of octenyl succinic esters of sugary maize soluble starch and waxy maize starch. Food Chem 151:154–160. https://doi.org/10.1016/j.foodchem.2013.11.043

Miao M, Xiong S, Jiang B, Jiang H, Cui SW, Zhang T (2014b) Dual-enzymatic modification of maize starch for increasing slow digestion property. Food Hydrocoll 38:180–185. https://doi.org/10.1016/j.foodhyd.2013.12.006

Miao M, Xiong S, Jiang B, Jiang H, Cui SW, Zhang T (2014c) Improved the slow digestion property of maize starch using partially β-amylolysis. Food Chem 152:128–132. https://doi.org/10.1016/j.foodchem.2013.11.148

Miao M, Xiong S, Ye F, Jiang B, Cui SW, Zhang T (2014d) Development of maize starch with a slow digestion property using maltogenic α-amylase. Carbohydr Polym 103:164–169. https://doi.org/10.1016/j.carbpol.2013.12.041

Miao M, Jiang B, Cui SW, Zhang T, Jin Z (2015a) Slowly digestible starch – a review. Crit Rev Food Sci 55:1642–1657. https://doi.org/10.1080/10408398.2012.704434

Miao M, Jiang B, Jiang H, Zhang T, Li X (2015b) Interaction mechanism between green tea extract and human α-amylase for reducing starch digestion. Food Chem 186:20–25. https://doi.org/10.1016/j.foodchem.2015.02.049

Miao M, Jiang B, Jin Z, BeMiller JN (2018) Microbial starch-converting enzymes: recent insights and perspectives. Compr Rev Food Sci Food Saf 17:1238–1260. https://doi.org/10.1111/1541-4337.12381

Miller TL, Wolin MJ (1996) Pathways of acetate, propionate, and butyrate formation by the human fecal microbial flora. Appl Environ Microbiol 62:1589–1592

Moreau NM, Martin LJ, Toquet CS, Laboisse CL, Nguyen PG, Siliart BS, Dumon HJ, Champ MMJ (2003) Restoration of the integrity of rat caeco-colonic mucosa by resistant starch, but not by

fructo-oligosaccharides, in dextran sulfate sodium-induced experimental colitis. Br J Nutr 90(01):75. https://doi.org/10.1079/bjn2003867

Nakanishi S, Kataoka K, Kuwahara T, Ohnishi Y (2003) Effects of high amylose maize starch and *Clostridium butyricum* on metabolism in colonic microbiota and formation of azoxymethane-induced Aberrant Crypt Foci in the rat colon. Microbiol Immunol 47:951–958. https://doi.org/10.1111/j.1348-0421.2003.tb03469.x

Nakano K, Mizuno T, Sowa Y, Orita T, Yoshino T, Okuyama Y, Fujita T, Ohtani-Fujita N, Matsukawa Y, Tokino T, Yamagishi H, Oka T, Nomura H, Sakai T (1997) Butyrate activates the WAF1/Cip1 gene promoter through Sp1 Sites in a p53-negative human colon cancer cell line. J Biol Chem 272:22199–22206

Nirmalan N, Nirmalan M (2017) Hormonal control of metabolism: regulation of plasma glucose. Anaesth Intensive Care Med 18(10):502–507. https://doi.org/10.1016/j.mpaic.2017.06.019

Nofrarias M, Martinez-Puig D, Pujols J, Majo N, Perez JF (2007) Long-term intake of resistant starch improves colonic mucosal integrity and reduces gut apoptosis and blood immune cells. Nutrition 23(11–12):861–870. https://doi.org/10.1016/j.nut.2007.08.016

Norman B, Pedersen S, Stanley KD, Richmond P (2010) Production of crystalline short chain amylose. USA Patent, US7674897B2

Nugent AP (2005) Health properties of resistant starch. Br Nutr Found Nutr Bull 30:27–54. https://doi.org/10.1111/j.1467-3010.2005.00481.x

Ohkuma K, Matsuda I, Nogami Y (1995) Indigestible dextrin. USA Patent, US5358729

Panyoo AE, Emmambux MN (2017) Amylose-lipid complex production and potential health benefits: a mini-review. Starch-Stärke 69(7–8):1600203. https://doi.org/10.1002/star.201600203

Peat S, Whelan WJ, Thomas GJ (1952) Evidence of multiple branching in waxy maize starch. J Chem Soc 4:546–4548

Pérez S, Bertoft E (2010) The molecular structures of starch components and their contribution to the architecture of starch granules: a comprehensive review. Starch-Stärke 62(8):389–420. https://doi.org/10.1002/star.201000013

Perrin P, Pierre F, Patry Y, Champ M, Berreur M, Pradal G, Bornet F, Meflah K, Menanteau J (2001) Only fibres promoting a stable butyrate producing colonic ecosystem decrease the rate of aberrant crypt foci in rats. Gut 49:53–61. https://doi.org/10.1136/gut.48.1.53

Pitt P, Debruijn KM, Beeching MF, Goldberg E, Blendis LM (1980) Studies on breath methane the effect of ethinic origins and lactulose. Gut 21:951–954

Pryde SE, Duncan SH, Hold GL, Stewart CS, Flint HJ (2002) The microbiology of butyrate formation in the human colon. FEMS Microbiol Lett 21:133–139. https://doi.org/10.1111/j.1574-6968.2002.tb11467.x

Qi Y, Miao M, Hu X, Jiang B, Jin Z, Zhang T (2017) Impact of glucansucrase treatment on structure and properties of maize starch. Starch-Stärke 69:1600222. https://doi.org/10.1002/star.201600222

Ramsay AG, Scott KP, Martin JC, Rincon MT, Flint HJ (2006) Cell-associated alpha-amylases of butyrate-producing Firmicute bacteria from the human colon. Microbiology 152(Pt 11):3281–3290. https://doi.org/10.1099/mic.0.29233-0

Ranhotra GS, Geloth JA, Glaser BK (1996a) Effect of resistant starch on blood and liver lipids in hamsters. Cereal Chem 73:176–178

Ranhotra GS, Gelroth JA, Glaser BK (1996b) Energy value of resistant starch. J Food Sci 61:453–455. https://doi.org/10.1111/j.1365-2621.1996.tb14215.x

Reeves AR, D'Elia JN, Frias J, Salyers AA (1996) A *Bacteroides thetaiotaomicron* outer membrane protein that is essential for utilization of maltooligosaccharides and starch. J Bacteiol 178:823–830. https://doi.org/10.1128/jb.178.3.823-830.1996

Reeves AR, Wang GR, Salyers AA (1997) Characterization of four outer membrane proteins that play a role in utilization of starch by Bacteroides thetaiotaomicron. J Bacteiol 179:643–649. https://doi.org/10.1128/jb.179.3.643-649.1997

Robertson MD (2012) Dietary-resistant starch and glucose metabolism. Curr Opin Clin Nutr Metab Care 15(4):362–367. https://doi.org/10.1097/MCO.0b013e3283536931

Rodriguez-Cabezas ME, Camuesco D, Arribas B, Garrido-Mesa N, Comalada M, Bailon E, Cueto-Sola M, Utrilla P, Guerra-Hernandez E, Perez-Roca C, Galvez J, Zarzuelo A (2010) The combination of fructooligosaccharides and resistant starch shows prebiotic additive effects in rats. Clin Nutr 29(6):832–839. https://doi.org/10.1016/j.clnu.2010.05.005

Sakakibara S, Yamauchi T, Oshima Y, Tsukamoto Y, Kadowaki T (2006) Acetic acid activates hepatic AMPK and reduces hyperglycemia in diabetic KK-A(y) mice. Biochem Biophys Res Commun 344(2):597–604. https://doi.org/10.1016/j.bbrc.2006.03.176

Scheppach W, Sommer H, Kirchner T, Paganelli G-M, Bartram P, Christl S, Richter F, Dusel G, Kasper H (1992) Effect of butyrate enemas on the colonic mucosa in distal ulcerative colitis. Gastroenterology 103:51–56. https://doi.org/10.1016/0016-5085(92)91094-K

Schulz AGM, Van Amelsvoort JM, Beynen AC (1993) Dietary native resistant starch but not retrograded resistant starch raises magnesium and calcium absorption in rats. J Nutr 123:1724–1731. https://doi.org/10.1093/jn/123.10.1724

Schwartz D, Whistler RL (2009) History and future of starch. In: BeMiller J, Whistler R (eds) Starch: chemistry and technology. Academic, New York, pp 1–10. https://doi.org/10.1016/B978-0-12-746275-2.00001-X

Semeijn C, Buwalda PL (2018) Potato starch. In: Sjöö M, Nilsson L (eds) Starch in food: structure, function and applications. Woodhead Publishing, pp 353–372. https://doi.org/10.1016/b978-0-08-100868-3.00009-3

Seo BS, Kim S, Scott MP, Singletary GW, Wong KS, James MG, Myers AM (2002) Functional interactions between heterologously expressed starch-branching enzymes of maize and the glycogen synthases of Brewer's yeast. Plant Physiol 128(4):1189–1199. https://doi.org/10.1104/pp.010756

Shen L, Keenan MJ, Raggio A, Williams C, Martin RJ (2011) Dietary-resistant starch improves maternal glycemic control in Goto-Kakizaki rat. Mol Nutr Food Res 55(10):1499–1508. https://doi.org/10.1002/mnfr.201000605

Shimotoyodome A, Suzuki J, Fukuoka D, Tokimitsu I, Hase T (2010) RS4-type resistant starch prevents high-fat diet-induced obesity via increased hepatic fatty acid oxidation and decreased postprandial GIP in C57BL/6J mice. Am J Physiol Endocrinol Metab 298: E652–E662. https://doi.org/10.1152/ajpendo.00468.2009

Silvi S, Rumney CJ, Cresci A, Rowland IR (1999) Resistant starch modifies gut microflora and microbial metabolism in human flora-associated rats inoculated with faeces from Italian and UK donors. J Appl Microbiol 86:521–530. https://doi.org/10.1046/j.1365-2672.1999.00696.x

Singh J, Kaur L, McCarthy OJ (2007) Factors influencing the physico-chemical, morphological, thermal and rheological properties of some chemically modified starches for food applications – a review. Food Hydrocoll 21(1):1–22. https://doi.org/10.1016/j.foodhyd.2006.02.006

Smith AM, Denyer K, Martin C (1997) The synthesis of the starch granule. Annu Rev Plant Physiol Plant Mol Biol 48:67–87. https://doi.org/10.1146/annurev.arplant.48.1.67

Sokoloff L (1999) Energetics of functional activation in neural tissues. Neurochem Res 24:321–329

Stempelj M, Kedinger M, Augenlicht L, Klampfer L (2007) Essential role of the JAK/STAT1 signaling pathway in the expression of inducible nitric-oxide synthase in intestinal epithelial cells and its regulation by butyrate. J Biol Chem 282(13):9797–9804. https://doi.org/10.1074/jbc.M609426200

Stewart ML, Zimmer JP (2018) Postprandial glucose and insulin response to a high-fiber muffin top containing resistant starch type 4 in healthy adults: a double-blind, randomized, controlled trial. Nutrition 53:59–63. https://doi.org/10.1016/j.nut.2018.01.002

Sun H, Ma X, Zhang S, Zhao D, Liu X (2018) Resistant starch produces antidiabetic effects by enhancing glucose metabolism and ameliorating pancreatic dysfunction in type 2 diabetic rats. Int J Biol Macromol 110:276–284. https://doi.org/10.1016/j.ijbiomac.2017.11.162

Sun L, Warren FJ, Gidley MJ, Guo Y, Miao M (2019) Mechanism of binding interactions between young apple polyphenols and porcine pancreatic α-amylase. Food Chem 283:468–474. https://doi.org/10.1016/j.foodchem.2019.01.087

Suzuki A, Stern SA, Bozdagi O, Huntley GW, Walker RH, Magistretti PJ, Alberini CM (2011) Astrocyte-neuron lactate transport is required for long-term memory formation. Cell 144(5):810–823. https://doi.org/10.1016/j.cell.2011.02.018

Tabata S, Hizukuri S (1971) Studies on starch phosphate. Part 2. Isolation of glucose 3-phosphate and maltose phosphate by acid hydrolysis of potato starch. Starch-Stärke 23:267–272. https://doi.org/10.1002/star.19710230803

Tayebi Khosroshahi H, Vaziri ND, Abedi B, Asl BH, Ghojazadeh M, Jing W, Vatankhah AM (2018) Effect of high amylose resistant starch (HAM-RS2) supplementation on biomarkers of inflammation and oxidative stress in hemodialysis patients: a randomized clinical trial. Hemodial Int 22(4):492–500. https://doi.org/10.1111/hdi.12653

Tester RF, Qi X (2011) β-Limit dextrin – properties and applications. Food Hydrocoll 25(8):1899–1903. https://doi.org/10.1016/j.foodhyd.2011.03.011

Toden S, Bird AR, Topping DL, Conlon MA (2005) Resistant starch attenuates colonic DNA damage induced by higher dietary protein in rats. Nutr Cancer 51(1):45–51. https://doi.org/10.1207/s15327914nc5101_7

Tonoli C, Heyman E, Roelands B, Pattyn N, Buyse L, Piacentini MF, Berthoin S, Meeusen R (2014) Type 1 diabetes-associated cognitive decline: a meta-analysis and update of the current literature. J Diabetes 6(6):499–513. https://doi.org/10.1111/1753-0407.12193

Topping DL, Clifton PM (2001) Short-chain fatty acids and human colonic function: roles of resistant starch and nonstarch polysaccharides. Physiol Rev 81:1031–1063

Torres J, Muñoz LS, Peters M, Montoya CA (2013) Characterization of the nutritive value of tropical legume grains as alternative ingredients for small-scale pork producers using in vitro enzymatic hydrolysis and fermentation. Anim Physiol An N 97(6):1066–1074

Tornheim K (2018) Glucose metabolism and hormonal regulation. In: Huhtaniemi L, Martini L (eds) Encyclopedia of endocrine diseases, 2nd edn. Academic, pp 87–94. https://doi.org/10.1016/b978-0-12-801238-3.03816-2

Veleba J, Matoulek M, Hill M, Pelikanova T, Kahleova H (2016) "A vegetarian vs. conventional hypocaloric diet: the effect on physical fitness in response to aerobic exercise in patients with type 2 diabetes." A parallel randomized study. Nutrients 8(11):671. https://doi.org/10.3390/nu8110671

Vineyard ML, Bear RP, MacMasters MM, Deatherage WL (1958) Development of amylomaize corn hybrids with high amylose starch I. Genetic considerations. Agron J 50:595–598

Vital M, Howe A, Bergeron N, Krauss RM, Jansson JK, Tiedje JM (2018) Metagenomic insights into the degradation of resistant starch by human gut microbiota. Appl Environ Microbiol 84: e01562–e01518. https://doi.org/10.1128/AEM.01562-18

Walker AW, Duncan SH, McWilliam Leitch EC, Child MW, Flint HJ (2005) pH and peptide supply can radically alter bacterial populations and short-chain fatty acid ratios within microbial communities from the human colon. Appl Environ Microbiol 71(7):3692–3700. https://doi.org/10.1128/AEM.71.7.3692-3700.2005

Wang X, Conway PL, Brown IL, Evans AJ (1999) In vitro utilization of amylopectin and high-amylose maize (amylomaize) starch granules by human colonic bacteria. Appl Environ Microbiol 65:4848–4854

Wang X, Brown L, Khaled D, Mahoney MC, Evans AJ, Conway PL (2002) Manipulation of colonic bacteria and volatile fatty acid production by dietary high amylose maize (amylomaize) starch granules. J Appl Microbiol 93:390–397. https://doi.org/10.1046/j.1365-2672.2002.01704.x

Wang SP, Yang H, Wu JW, Gauthier N, Fukao T, Mitchell GA (2014) Metabolism as a tool for understanding human brain evolution: lipid energy metabolism as an example. J Hum Evol 77:41–49. https://doi.org/10.1016/j.jhevol.2014.06.013

Wautier MP, Guillausseau PJ, Wautier JL (2017) Activation of the receptor for advanced glycation end products and consequences on health. Diabetes Metab Syndr 11(4):305–309. https://doi.org/10.1016/j.dsx.2016.09.009

Weaver GA, Krause JA, Miller TL, Wolin MJ (1992) Cornstarch fermentation by the colonic microbial community yields more butyrate than does cabbage fiber fermentation; cornstarch

fermentation rates correlate negatively with methanogenesis. Am J Clin Nutr 55(1):70–77. https://doi.org/10.1093/ajcn/55.1.70

Weisstaub AR, Salinas MV, Correa MJ, Barchuk M, Berg G, Zuleta A (2018) Effects of the intake of white wheat bread added with garlic and resistant starch: action on calcium bioavailability and metabolic parameters of growing Wistar rats. Food Funct 9(11):5707–5714. https://doi.org/10.1039/c8fo01407h

Winter J, Nyskohus L, Young GP, Hu Y, Conlon MA, Bird AR, Topping DL, Le Leu RK (2011) Inhibition by resistant starch of red meat-induced promutagenic adducts in mouse colon. Cancer Prev Res (Phila) 4(11):1920–1928. https://doi.org/10.1158/1940-6207.CAPR-11-0176

Wong THT, Louie JCY (2017) The relationship between resistant starch and glycemic control: a review on current evidence and possible mechanisms. Starch-Stärke 69(7–8):1600205. https://doi.org/10.1002/star.201600205

Woo KS, Seib PA (2002) Cross-linked resistant starch: preparation and properties. Cereal Chem 79:819–825. https://doi.org/10.1094/CCHEM.2002.79.6.819

Yamada Y, Hosoya S, Nishimura S, Tanaka T, Kajimoto Y, Nishimura A, Kajimoto O (2014) Effect of bread containing resistant starch on postprandial blood glucose levels in humans. Biosci Biotechnol Biochem 69(3):559–566. https://doi.org/10.1271/bbb.69.559

Yamashita H, Fujisawa K, Ito E, Idei S, Kawaguchi N, Kimoto M, Hiemori M, Tsuji H (2014) Improvement of obesity and glucose tolerance by acetate in type 2 diabetic Otsuka Long-Evans Tokushima Fatty (OLETF) rats. Biosci Biotechnol Biochem 71(5):1236–1243. https://doi.org/10.1271/bbb.60668

Ye J, Hu X, Luo S, McClements DJ, Liang L, Liu C (2018) Effect of endogenous proteins and lipids on starch digestibility in rice flour. Food Res Int 106:404–409. https://doi.org/10.1016/j.foodres.2018.01.008

Yonekura L, Tamura H, Suzuki H (2003) Chitosan and resistant starch restore zinc bioavailability, suppressed by dietary phytate, through different mechanisms in marginally zinc-deficient rats. Nutr Res 23(7):933–944. https://doi.org/10.1016/s0271-5317(03)00086-1

Yuan H, Wang W, Chen D, Zhu X, Meng L (2017a) Effects of a treatment with Se-rich rice flour high in resistant starch on enteric dysbiosis and chronic inflammation in diabetic ICR mice. J Sci Food Agric 97(7):2068–2074. https://doi.org/10.1002/jsfa.8011

Yuan H, Zhu X, Chen D, Wang W, Meng S, Wang J (2017b) Effects of dual modified resistant indica rice starch on azoxymethane-induced incipient colon cancer in mice. Exp Ther Med 13(5):2036–2042. https://doi.org/10.3892/etm.2017.4172

Ze X, Duncan SH, Louis P, Flint HJ (2012) *Ruminococcus bromii* is a keystone species for the degradation of resistant starch in the human colon. ISME J 6:1535–1543. https://doi.org/10.1038/ismej.2012.4

Ze X, David YB, Laverde-Gomez JA, Dassa B, Sheridan PO, Duncan SH, Louis P, Henrissat B, Juge N, Koropatkin NM, Bayer EA, Flint HJ (2015) Unique organization of extracellular amylases into amylosomes in the resistant starch-utilizing human colonic Firmicutes Bacterium *Ruminococcus bromii*. MBio 6:e01058–e01015. https://doi.org/10.1128/mBio.01058-15

Zeng H, Huang C, Lin S, Zheng M, Chen C, Zheng B, Zhang Y (2017) Lotus seed resistant starch regulates gut microbiota and increases short-chain fatty acids production and mineral absorption in mice. J Agric Food Chem 65(42):9217–9225. https://doi.org/10.1021/acs.jafc.7b02860

Zhou J, Martin RJ, Tulley RT, Raggio AM, McCutcheon KL, Shen L, Danna SC, Tripathy S, Hegsted M, Keenan MJ (2008) Dietary resistant starch upregulates total GLP-1 and PYY in a sustained day-long manner through fermentation in rodents. Am J Physiol Endocrinol Metab 295:E1160–E1166. https://doi.org/10.1152/ajpendo.90637.2008

Zhou L, Fang L, Sun Y, Su Y, Zhu W (2017) Effects of a diet high in resistant starch on fermentation end-products of protein and mucin secretion in the colons of pigs. Starch-Stärke 69(7–8):1600032. https://doi.org/10.1002/star.201600032

Zhu Y, Liu X, Yang ST (2005) Construction and characterization of pta gene-deleted mutant of *Clostridium tyrobutyricum* for enhanced butyric acid fermentation. Biotechnol Bioeng 90(2):154–166. https://doi.org/10.1002/bit.20354

Zobel HF (1988) Molecules to granules: a comprehensive starch review. Starch-Stärke 44:44–50. https://doi.org/10.1002/star.19880400203