Research Highlight

Effect of Dietary Resistant Starch on Prevention and Treatment of Obesity-related Diseases and Its Possible Mechanisms*

ZHANG Lei1,2,†, LI Hua Ting1,†, SHEN Li3, FANG Qi Chen1, QIAN Ling Ling1,2, and JIA Wei Ping1,2,§

Overweight or obesity has become a serious public health problem in the world, scientists are concentrating their efforts on exploring novel ways to treat obesity. Nowadays, the availabilities of bariatric surgery and pharmacotherapy have enhanced obesity treatment, but it should has support from diet, physical exercise and lifestyle modification, especially the functional food. Resistant starch, an indigestible starch, has been studied for years for its beneficial effects on regulating blood glucose level and lipid metabolism. The aim of this review is to summarize the effect of resistant starch on weight loss and the possible mechanisms. According to numerous previous studies it could be concluded that resistant starch can reduce fat accumulation, enhance insulin sensitivity, regulate blood glucose level and lipid metabolism. Recent investigations have focused on the possible associations between resistant starch and incretins as well as gut microbiota. Resistant starch seems to be a promising dietary fiber for the prevention or treatment of obesity and its related diseases.

Obesity is a global public health problem, which has obviously increased the risk of many severe diseases, such as metabolic syndrome, type 2 diabetes mellitus (T2DM) and non-alcoholic fatty liver disease (NAFLD). Nowadays, the availabilities of bariatric surgery and pharmacotherapy have enhanced obesity treatment, but it should has support from diet, physical exercise and lifestyle modification, especially the functional food.

Resistant starch (RS), one of prebiotics which can alter the composition of organisms in the gut microbiome and can not be broken down by amylases in the upper digestive tract, but can be fermented by microbiota after passing into the large bowel and produce important metabolites which is good for health, including short-chain fatty acids (SCFAs)1-2. Health effects of RS diet have been appreciated for long time3. Classified by the source and processing procedure, RS currently consists of five categories: RS1, starch granule which is deep in some indigestible plant material, such as whole grains; RS2, native granular starch, such as raw potato, green banana, gingko or high-amylose maize etc.; RS3, retrograded amylose starch or crystallized starch such as cooked and cooled starchy foods; RS4, chemically modified starch, which is produced through esterification, cross-linking or transglycosylation; RS5, amylose-lipid complex, amylose and long branch chains of amylopectin from single-helical complexes with fatty acids and fatty alcohols when starch interacts with lipids4.

According to numerous previous studies it can be concluded that the RS can reduce fat accumulation, enhance insulin sensitivity, regulate blood glucose and lipid metabolism. Recent investigations have focused on the possible associations between RS and incretins as well as gut microbiota. In this review, we aim to summarize the effect of RS on weight loss and the possible mechanisms. Resistant starch seems to be a promising dietary fiber for the prevention or treatment of obesity and related diseases.

Resistant Starch and Energy Metabolism

Satiety Studies has revealed that RS might has effect to influence appetite and energy intake. Souza da Silva et al.5 found that in growing pigs, feeding

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1. Department of Endocrinology and Metabolism, Shanghai Jiao Tong University Affiliated Sixth People’s Hospital, Shanghai Diabetes Institute, Shanghai Key Laboratory of Diabetes Mellitus, Shanghai Clinical Center for Diabetes, Shanghai 200233, China; 2. Department of Medicine, Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China; 3. Department of Clinical Nutrition, Shanghai Jiao Tong University Affiliated Sixth People’s Hospital, Shanghai 200233, China.
RS (34% RS3 and 35% pregelatinized starch) for 14-d reduced the energy digestibility (digestible energy/gross energy) and metabolizability (metabolizable energy/gross energy), and decreased the energy intake at the same time. Furthermore, the observation indicated that pigs’ satiety seemed to be prolonged. In a human study, decreased energy intake was observed in acute consumption of RS (muffins containing 8.0 g RS for breakfast) in 20 healthy adults[6]. Recently, Harrold J et al[7] found that after consumption of two doses (20 and 30 g) of a ingredient comprised of a viscous fibre and whole-grain high-amylose corn flour (source of type 1 and type 2 RS) of breakfast, reductions of acute satiety responses and energy intake were observed in 3 h after breakfast and lunch in ninety adult subjects compared to a maltodextrin control intake. However, the reports of satiety responses to long-term RS intake in humans and rodents or other species are limited, thus further research is needed.

Body Weight and Abdominal Fat Many experiments in rodents showed that feeding RS could reduce body fat although it seemed to has no effect on total body weight and food intake (Table 1). The body fat percentage or visceral fat reduction after feeding RS has been observed in most studies using different rodent models, but the observations of the effect of RS on body fat distribution in other species, such as pigs, are limited[8,9]. In a recent study[9], obese rats were fed with fodder containing 55% RS for 5 weeks and a significant decrease of the mesenteric adipose tissue weight and an increase of the small adipocytes number were observed, while it seemed that this fodder contained too much RS and the effect might be overestimated. However, Most studies indicated that feeding RS could not reduce total body weight. There are several explanations. Firstly, some studies showed that cumc mass increased while fat mass decreased after feeding RS[10-11]. Secondly, the proportion of RS in fodder and the type of fodder (high fat or not) can affect the body weight. It was found that the body weight decreased only when the fodder contained 8% RS or more[12]. Thirdly, the feeding pattern of the animals also plays an important role in body weight. Aziz et al[13] found that feeding RS could decrease total energy intake, weight gain and fat pad mass when the subjects had ad libitum access to fodder rather than fodder restriction. Fourthly, the baseline status of animals, for example, obese or not, obese-prone or

**Table 1. Data from Rodent Studies of Effects of RS on Body Weight and Body Composition**

<table>
<thead>
<tr>
<th>Article</th>
<th>Animal Type</th>
<th>RS Intake</th>
<th>Duration (weeks)</th>
<th>Diets</th>
<th>Body Weight</th>
<th>Fat Mass</th>
<th>Cecum Mass</th>
<th>Food Intake</th>
<th>Adipocyte Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belobrajdic DP[12]</td>
<td>obese SD rats</td>
<td>0/4/8/12/16% RS</td>
<td>4</td>
<td>AIN-93 diet</td>
<td>↓(RS%≥8%)</td>
<td>\</td>
<td>↓</td>
<td>↓</td>
<td>\</td>
</tr>
<tr>
<td>Keenan MJ[11]</td>
<td>ovariectomized rats</td>
<td>29.7% RS</td>
<td>1</td>
<td>AIN-93G diet</td>
<td>-</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>\</td>
</tr>
<tr>
<td>Polakof S[14]</td>
<td>healthy Wistar rats</td>
<td>41.6% RS</td>
<td>9</td>
<td>HF diet</td>
<td>-</td>
<td>↓</td>
<td>\</td>
<td>\</td>
<td>\</td>
</tr>
<tr>
<td>Harazaki T[9]</td>
<td>Otsuka Long-Evans Tokushima Fatty rats</td>
<td>55% RS</td>
<td>5</td>
<td>AIN-93G diet</td>
<td>-</td>
<td>mesenteric adipose tissue↓</td>
<td>\</td>
<td>-</td>
<td>↓</td>
</tr>
<tr>
<td>Shen L[16]</td>
<td>SD rats</td>
<td>30% RS</td>
<td>9</td>
<td>equal energy density control diet</td>
<td>-</td>
<td>↓(fat%↓)</td>
<td>\</td>
<td>-</td>
<td>\</td>
</tr>
<tr>
<td>Shen L[10]</td>
<td>GK rats</td>
<td>30% RS</td>
<td>10</td>
<td>equal energy density control diet</td>
<td>(disembo-weled body weight)</td>
<td>bodyfat/disembo-weled body weight↑</td>
<td>\</td>
<td>-</td>
<td>\</td>
</tr>
<tr>
<td>Pawlak DB[17]</td>
<td>Partially pancreatectomised male SD rats</td>
<td>40% RS</td>
<td>18</td>
<td>weight maintenance diet</td>
<td>-</td>
<td>↓(fat%↓)</td>
<td>\</td>
<td>-</td>
<td>\</td>
</tr>
<tr>
<td>Higgins JA[15]</td>
<td>Obesity-prone weight reduced rats</td>
<td>5.9% RS</td>
<td>9</td>
<td>HC/HF* diet</td>
<td>\</td>
<td>mesenteric fat↓</td>
<td>\</td>
<td>-</td>
<td>↓</td>
</tr>
</tbody>
</table>

**Note.** HC/HF, high in carbohydrate and fat; -, No significant change; \, Not mentioned.
obese-resistant, also affect the results of energy intake and fat accumulation\textsuperscript{[12,14-15]}.

Furthermore, RS seems to be effective for weight loss maintenance during a long-term weight reduction program. Both RS and exercise independently attenuated weight regain by reducing the energy gap between the biological drive to eat and total energy requirements\textsuperscript{[15]}

The effect of body weight and energy intake changes induced by RS intake in human studies is analogous to that in animal studies (Table 2). In humans, the decrease of blood glucose and the increase of insulin sensitivity were observed after RS intake although no change was found in body weight or fat mass\textsuperscript{[18-20]}. However, in these human studies, no effects on visceral fat and cecum mass were reported, and the possibly increased cecum mass included in overall body weight and decreased abdominal fat may be ignored. Furthermore, the phenomenon that the increases of gene expressions of hormone sensitive lipase, perilipin, lipoprotein lipase and adipose triglyceride lipase after feeding fodder containing 30% RS2 for 4 weeks were observed in male Sprague Dawley rats compared with rats fed by fodder of equal energy density\textsuperscript{[11]} , suggesting that the activity of lipolysis increased after feeding RS. Human study may focus on long term intervention of RS diet in the future.

**Lipid Level** Close attention has been paid to whether RS intake can reduce the plasma lipid concentration or not. In rodent studies, it has been confirmed that feeding RS can reduce the plasma lipid concentration. Pawlak et al.\textsuperscript{[17]} found that male healthy rats fed with fodder containing 542 g 60% amylose/kg (the main component of RS) and 40% amylopectin starch/kg, the low-glycemic index (GI) food which can affect blood glucose level, for 18 weeks resulted in higher plasma adiponectin concentrations and lower plasma triglyceride concentrations than those fed with high-GI fodder containing 542 g 100% amylopectin starch/kg. It is reported that 5 week feeding of retrograded rice containing 13.9±0.98% RS3 significantly reduced plasma cholesterol level in Sprague-Dawley rats compared with the feeding of control rice containing 9.1±1.02% RS3\textsuperscript{[14]}. Recently Nichenametla et al.\textsuperscript{[23]} found that eating RS4-enriched flour food (30% v/v RS4) for 2-12 weeks could significantly reduce total cholesterol level and non-high density lipoprotein (HDL) cholesterol level in 89 patients with metabolic syndrome compared with eating regular flour food.

**Hepatic Steatosis** Only a few studies address the association between RS and hepatic steatosis. In rats, it was found that RS could ameliorate the high levels of cholesterol, triglyceride and glycogen in the liver caused by high fat fodder feeding, meanwhile the mRNA levels of genes involved in regulating hepatic lipid metabolism increased, such as lipogenesis, cholesterol metabolism and fatty acid oxidation\textsuperscript{[14]}. However, in pigs\textsuperscript{[25]}, it was found that feeding with fodder with higher amylose level (70% amylopectin and 30% amylose) could reduce the elevation of lipid content in liver tissues and the concentrations of serum cholesterol and insulin and lipogenic enzymes compared with feeding with fodder with lower amylose level (80% amylopectin and 20% amylose).

Simultaneously, feeding with fodder with high amylose level not only decreased the expression of lipogenic genes, but also up-regulated the expression of lipolytic genes. However, the effect of RS on fatty liver disease in human has never been reported and further research is needed.

**Resistant Starch and Glucose Metabolism** Numerous studies have confirmed that RS has good impact on glycaemic control. Many investigations in animals, such as rats and pigs, and humans indicated that RS could reduce fasting glucose concentration, increase insulin secretion and enhance insulin sensitivity.

Aziz et al.\textsuperscript{[13]} found that a 4-week ad libitum access to high-amylose starch (RS2) fodder (529.5 g/kg) led to lower glycemic response and higher insulin sensitivity in male obese SD rats than ad libitum access to high-amylopectin starch fodder (529.5 g/kg). In the study using type 2 diabetic rat model by Shen et al. the similar phenomenon was also observed\textsuperscript{[10]}. After a 10-week feeding with fodder containing 30% RS, obvious increases in pancreatic beta cell mass, insulin sensitivity and pancreatic insulin content were observed in the rats, even the fasting plasma glucose levels and normal growth curves were improved in the offspring of the diabetic rats. Furthermore, in pigs\textsuperscript{[8]}, to study the role of starch chemistry in kinetics of nutrient absorption, 4 fodders containing 70% purified starch (0-63.2% amylose content and 0.22 to 1.06%/min (slowly to rapidly) maximum rate of in vitro digestion) were provided for four healthy pigs for 7 d, respectively, in a 4×4 Latin square study, the result showed the fodder with high amylose and low in vitro digestibility decreased the kinetics of glucose absorption, insulin and GIP secretion.

The result of human experiment is consistent with those of healthy or diabetic animal models\textsuperscript{[26-28]}.
The glucose tolerance, blood glucose, insulin and colonic fermentation conditions (reduced stool pH and increased total SCFA production) greatly improved in healthy people and patients with T2DM after the eating of food containing RS\[^{28-30}\]. There are a series of studies including a two-step hyperinsulinemic-euglycemic clamp indicating that RS intake can enhance the peripheral hepatic insulin resistance rather than hepatic insulin resistance\[^{21}\]. In order to further explore the effects of RS on the pancreas, they used an insulin-modified frequently sampled intravenous glucose tolerance test (FSIVGTT) to assess insulin secretion, after a diet intervention with 40 g RS/d for 8 weeks, the insulin and C-peptide concentrations and first-phase insulin secretion during the FIVGTT significantly increased compared with those after taking the placebo in 12 overweight subjects\[^{19}\]. More recently, they observed the effects of RS in 17 patients with T2DM, but no significant change in insulin sensitivity was found by two-step hyperinsulinemic-euglycemic clamp after RS intake (40 g/d, 12 weeks), despite the positive improvement in oral glucose handling. This disparity between intravenous injection of glucose and oral glucose disposal might imply a gut-mediated factor to be responsible for the effects, a phenomenon often attributed to GLP-1\[^{22}\].

**Possible Mechanisms**

**Functions Differed with Traditional Dietary Fiber**

The mechanisms of how RS works are not clear now. The effect of dietary fiber in reducing energy intake and glycemic load is thought to be achieved by energy dilution and food expansion through traditional mechanisms. Energy dilution reduces the energy density of food intake, and food expansion prevents further food intake. However, Martin and his colleague\[^{10,31-32}\] found that the hypoglycemic effect of RS has other more important mechanisms in addition to the traditional mechanisms of dietary fiber. They observed that fodder intake of rats did not differ between RS group and control group and the fodders had equal energy density, so the confounding effects by energy dilution and food expansion could be eliminated. RS still significantly reduced blood glucose level and visceral fat content in rats in RS group compared with the rats in control group\[^{10,31-32}\]. Then some evidence indicated that the

<table>
<thead>
<tr>
<th>Article</th>
<th>Study Subjects</th>
<th>RS Intake</th>
<th>Duration (weeks)</th>
<th>Diets</th>
<th>Body Weight</th>
<th>Fat Mass</th>
<th>Fat%</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robertson MD[^{21}]</td>
<td>15 subjects with metabolic syndrome</td>
<td>40 g/d</td>
<td>8</td>
<td>as usual</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>gene expression for hormone sensitive lipase, perilipin, lipoprotein lipase and adipose triglyceride lipase ↑</td>
</tr>
<tr>
<td>Bodinham CL[^{19}]</td>
<td>12 subjects with metabolic syndrome</td>
<td>40 g/d</td>
<td>8</td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Maki KC[^{20}]</td>
<td>33 overweight or obese subjects</td>
<td>15 g/d or 30 g/d</td>
<td>4</td>
<td>\</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Bodinham CL[^{22}]</td>
<td>17 subjects with type 2 diabetes</td>
<td>40 g/d</td>
<td>12</td>
<td>diet and exercise controlled</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>No change: Subcutaneous and Internal adipose tissue, Pancreas fat, intrahepato-cellular lipid, soleus intramyo-cellular lipid, tibialis intramyo-cellular lipid</td>
</tr>
<tr>
<td>Johnston KL[^{18}]</td>
<td>10 subjects with insulin resistant</td>
<td>40 g/d</td>
<td>12</td>
<td>\</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>No change: fat storage in muscle, liver, or visceral depots</td>
</tr>
<tr>
<td>Nichenam- etla SN[^{23}]</td>
<td>86 healthy adults</td>
<td>30% v/v RS</td>
<td>12</td>
<td>ad libitum</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>fat-free mass ↑</td>
</tr>
</tbody>
</table>

**Note.** ↑, No significant change; \, Not mentioned.
mechanism of regulation of blood glucose level and lipid metabolism by RS was likely related to the RS fermentation in the large intestine and the production of SCFAs. Zhou et al.\textsuperscript{[33]} further clarified the importance of fermentation, under the condition of the equivalent energy dilution and food expansion of fodder, RS lost extra effect when the fermentation was inhibited. SCFAs are the fermentation products of RS, in which butyrate turned out to promote the release of the L-cells to secret incretins such as intestinal peptide YY (PYY, also called peptide tyrosine tyrosine), glucagon-like peptide-1 (GLP-1) hormones\textsuperscript{[32]}. Therefore, incretins are drawing increasing attention to be the possible interpretation of the effect of RS in reducing blood glucose level and fat content.

**Resistant Starch and Incretins** Current evidence suggests that the effect of RS on energy metabolism is closely related to incretins. Studies in rats suggested that incretins increased after feeding RS. Aziz et al.\textsuperscript{[11]} fed the obese male SD rats with 53% RS fodder for 4 weeks and found that proglucagon gene (the gene encoding GLP-1) expression significantly increased along with the increase in circulating GLP-1 and PYY, independent of the rats' feeding paradigm. Meanwhile, mRNA levels of key neuropeptide systems involved in the regulation of food intake were affected only when the energy intake is restricted, and the expression of uncoupling protein-1 in the brown adipose tissue increased in rats that had \textit{ad libitum} access to fodder. Martin and his colleague also confirmed the increase of circulating GLP-1 in other rodent models, such as healthy SD and Wistar rats\textsuperscript{[12,31]} and diabetic rats\textsuperscript{[10]}. In these studies, feeding RS could reduce the intestinal pH values, increase the cecal SCFAs concentration, promote proglucagon gene transcription and improve circulating GLP-1 concentrations accordingly. Furthermore, Zhou et al.\textsuperscript{[32]} found the plasma GLP-1 and PYY levels increased at various time points over a 24-h period in rats fed with RS fodder (53.7% RS2, 10 d), which is independent of the effect of dieters of different glycemic indexes, or the timing of blood sample collections. However, the study results in pigs were inconsistent with those in rats, it was found by Souza da Silva et al.\textsuperscript{[5]} that in RS-fed pigs (34% RS, 14 d) the GLP-1 levels were lower than that in control starch-fed pigs, and PYY levels did not differ between the two groups, though less feeding activity and higher SCFAs levels were observed in the RS-fed group. The conflict results in rodents and pigs indicated that the role of incretins in the effect of RS is controversial. Further investigations are needed.

Changes in incretins level after RS intake was also observed in human studies. Bodinham et al.\textsuperscript{[34]} found that the plasma GLP-1 concentrations significantly declined after acute consumption of 48 g dietary fiber RS2 in 30 healthy males. However, in a recent study\textsuperscript{[22]}, postprandial GLP-1 increased significantly after a 12-week 40 g RS /d intervention in 17 patients with T2DM. The controversial results in different subjects is not conclusive that more data in humans are needed.

**Resistant Starch and Gut Microbiota** More and more studies have focused on the fermentation of contents in large intestine by the microbial community and abundance of amylolytic bacteria affected by RS diet. It is found that the fermentation of RS in large intestine resulted in the increase of probiotics (microorganisms that are believed to have health benefits), especially the butyrate-producing microbial groups, and the decrease of pathogenic bacteria as well as the elevation of SCFAs concentrations. Shen et al.\textsuperscript{[10]} found the butyrate producing bacteria in cecal contents greatly increased after RS feeding (fodder with 30% RS) for 10 weeks in diabetic rats. In the further animal experiments, the specific bacterial species were detected. Kalmokoff et al.\textsuperscript{[35]} found that after rats fed by a diet containing 5% RS2 for 2 weeks the change in the gut community is dominated by four phylotypes homologous with Ruminococcus bromii, Bacteroides uniformis and with yet to be cultivated organisms aligning into the Family Porphyromonadaceae compared with rats ingesting the control diet. Furthermore, Haenen et al.\textsuperscript{[36]} found that the relative abundance of several butyrate-producing microbial groups, including the butyrate producers Faecalibacterium prausnitzii and Megasphaera elsdenii, is stimulated, and the abundance of potentially pathogenic genus Leptospira and the phylum Proteobacteria reduced after 34% RS feeding for two weeks compared with control starch feeding in adult male pigs, and three main plasma SCFAs acetate, propionate, and butyrate were significantly higher after RS feeding simultaneously; the similar result also found in adult female pigs\textsuperscript{[37]}. In human studies\textsuperscript{[38]}, the proportions of Ruminococcus bromii, Eubacterium rectale significantly increased after RS intake for 3 weeks in 10 healthy subjects. It is notable that in \textit{vitro} Ruminococcus bromii turned to be a keystone species for the fermentation of resistant starch in...
the human large intestine\(^{[39]}\).

**GLP-1 Secretion Stimulated by Fermentation Products SCFAs** How does the gut microbiota play a role in the metabolism of the host then? One possible mechanism is that the intestinal flora increases its fermentation products, SCFAs, especially butyrate\(^{[40]}\), which regulates the release of GLP-1 through its central and peripheral targets. Cani et al.\(^{[41]}\) confirmed that prebiotics can increase the normal breath hydrogen excretion (the mark of gut microbiota fermentation), as well as the increase plasma GLP-1 concentrations, so there may be some connections between the increase of GLP-1 and intestinal microflora by prebiotics. It is confirmed that the SCFAs as products of RS fermentation can present a significant increase in rodents, pigs and humans\(^{[5,10,35,42-46]}\). Tolhurst et al.\(^{[47]}\) found SCFAs stimulate the release of gut hormone GLP-1 *in vitro* with an according increase of the expression of receptors of SCFAs in L cells, and the secretion of GLP-1 stimulated by SCFAs reduced in SCFA receptor knock-out mice, which proved that SCFAs can promote the secretion of GLP-1. In a recent study\(^{[48]}\), it was found that it was the butyrate fermented in the cecum rather than the absorption from dietary sodium butyrate that promoted an increasing level of PYY and GLP-1 and reducing abdominal fat. Then, is the increase of GLP-1 related to the fermentation in the gut after RS-feeding? A study preliminarily revealed the relationship between RS intake and GLP-1 as well as fermentation. Proglucagon and PYY mRNA expression, along with plasma total GLP-1 and PYY, was higher in the cecum and colon, where RS fermentation occurs, in the rats in RS group compared with the rats in nonfermentable fiber control group\(^{[32]}\). Further explorations should be done to clarify the cause-effect relationship between GLP-1 and microbiota.

**Mutual Influences with Other Diets**

As a kind of functional nutrients, RS may interact with other foods. Chai et al.\(^{[49]}\) found that tea polyphenols could bridge high-amylose maize starch molecules together, leading to increasing amylose molecular sizes and low-ordered crystalline structure to produce a slowly digestible starch material that is beneficial to postprandial glycemic control and related health effects. In addition, Charrier et al.\(^{[50]}\) found that the consumption of high fat diet could attenuate the fermentation effect of RS2.

**Conclusions and Perspectives**

More recent data, consistent with earlier evidence, suggests that RS intake can reduce fat accumulation, enhance insulin sensitivity, regulate blood glucose, and lipid metabolism. Recent investigations revealed the possible associations between RS and incretins as well as gut microbiota, indicating that RS might be a promising food in dieteric treatment for obesity, T2DM and NAFLD. However, the effects of RS on the treatment of these diseases in humans are still unknown. Further human studies should be conducted to understand the effects of chronic consumption of RS on these diseases.

These authors equally contributed to this work and are co-first authors of this manuscript.

Correspondence should be addressed to JIA Wei Ping, professor, Tel: 86-21-64367289; Fax: 86-21-64368031; E-mail: wpjia@sjtu.edu.cn

Biographical note of the first author: ZHANG Lei, female, born in 1990, BD, majoring in endocrinology and metabolism.

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