



Review on Characteristics of Resistant Starch in Traditional Chinese Medicine Based on the Theory of 'Unification of Medicines and Excipients'



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Abstract

Starch, one of the most important natural carbohydrates in human diet, is widely distributed in plants and is particularly abundant in multitudes of traditional medicines, for instance, Dioscoreae Rhizoma, Notoginseng Radix et, Curcumae Rhizoma, Alismatis Rhizoma, Trichosanthis Radix and Moutan Cortex. During the isolation of active components in Traditional Chinese Medicine, starch was discarded which cause great waste. Systematical researches and summaries are absent about how starch in Traditional Chinese Medicine could be used. Herein, characteristics of resistant starch as excipients and adjuvants elaborated systematically based on 'the unification of medicines and excipients' in Traditional Chinese Medicine preparations. As functions of resistant starch provided in this paper, there are great application potentials of starch in Traditional Chinese Medicine and some waste was hoped to be avoid in future.

Keywords: Traditional chinese medicine; Resistant starch; Unification of medicines and excipients

Abbreviations: DSC: Differential Scanning Calorimetry; FDS: Fast Digested Starch; ΔH : Enthalpy; MCC: Microcrystalline Cellulose; MT: Matrine; NO: Nitric Acid; PGE2: Prostaglandin 2; RS: Resistant Starch; SCFA: Small Chain Fatty Acid; SDS: Slow Digested Starch; SEM: Electron Scanning Microscope; TCM: Traditional Chinese Medicine; Tc: End Phase Transition Temperature; To: Onset Temperature; Tp: The Peak Temperature

Introduction

As the philosophical wisdom contained in Traditional Chinese Medicine (TCM) preparation, 'Unification of medicines and excipients' has existed for a long time. It means that some drugs in TCM preparations not only have pharmacology effects, but also have special physical and chemical properties that could act as excipients [1]. There are numbers of examples of 'Unification of medicines and excipients' used in preparation of TCM. In clove rotten rice pills (*Dingxiang lanfan wan*), japonica rice is used as paste powder after crushing in paste pills making. In Suzhishuixie preparation, japonica rice accounts for 63.8 % mass, part of the japonica acted as excipient in granulation making after grinding, as another part of japonica was paste in the preparation after it was deal with boiling water. In this preparation, japonica also helps pills to adhere to the intestinal wall in stopping diarrhea [2].

In recent years, resistant starch (RS) has drawn more and more attention due to its physicochemical characteristics and novel applications in food and pharmaceutical industries. The great mass of RS comes from foods such as corn, wheat, beans and so on. Meanwhile, starch is abundant in multitudes of different species of TCM [3]. For example, starch makes 60% of the total biomass in *Rhizoma Dioscorea Thunb* and 40% in lotus seeds. In accordance with first volume of edition 2015 of 'Chinese Pharmacopoeia', 107 kinds of medicines rich in starch applied in Chinese medicine prescriptions, especially in tablets and granules [4]. As starch was widely spread in Chinese medicine and preparation, researches have focus on the RS modified from starch in TCMs and attempted to exploit its utilization in TCM preparations under the instruction of 'unification of medicines and excipients' [5]. The systematic

summaries are still absent in these aspects. In this paper, excipient and auxiliary pharmacological effects of RS have presented with 'unification of medicines and excipients. Through this paper, we hope some possible ways about utilization of resistant starch will be exploit in the future to save the great mass of starch in TCM.

Definition of Resistant Starch

Starch is the main polysaccharide reserved in higher plants and the significant energy source for humans and animals. For bioavailability, starch is comprised of fast digested starch (FDS),

slow digested starch (SDS) and resistant starch (RS) [6-7]. At present, according to the difference of starch source and enzymatic hydrolysis, RS was divided into 5 types: RS1, RS2, RS3, RS4 and RS5 [8]. Types, food resources, absorption characteristics in small intestine and literature resources about RS have summarized in Table 1. It should be note that almost all uncooked starch and as a result, all high amylose starches are "resistant", also, not all RS types are relevant to TCM, e.g.: chemically modified starch. Table 1 types, food sources, absorption characteristics in small intestine and literature resources about resistant starch.

Table 1: Types of resistant starch, food sources, absorption characteristics in small intestine.

Types of RS	Description	Food Sources	Absorption Characteristics in Small Intestine	Literature Resources
RS1	Physically inaccessible to digestion by entrapment in a non-digestible matrix	Whole or partly milled grains and seeds, legumes, pasta	Slow rate, partial degree, totally digested if properly milled	[9-11]
RS2	Ungelatinized resistant granules with type B crystallinity, slowly hydrolyzed by amylase	Raw potatoes, green bananas, some legumes, high amylose corn starches	Very slow rate, little degree, totally digested when freshly cooked	[12-14]
RS3	Formed when foods containing starch have been subjected to one or more heating and cooling cycles	Cooked and cooled potatoes, bread, corn flakes, food products with prolonged and/or repeated moist heat treatment	Slow rate, partial degree, reversible digestion, digestibility improved by reheating	[15-18]
RS4	Selected chemically modified resistant starches and industrially processed food ingredients	Some fibers, drinks, foods in which modified starches have been used (certain breads and cakes)	Resisted hydrolysis after chemical modified, less susceptible to digestibility in vitro	[19-22]
RS5	Resistant maltodextrins	Crops or foods contain starch and lipid	Slow rate	[23-25]

General Properties of Resistant Starch

The general properties of RS include solubility, swelling power, water holding capacity, viscosity, pasting property, freeze-thaw stability and transparency, and so on. Among them, powder density, flow property and viscosity are closely related to filling, disintegration, and adhesion functions of RS as excipient of some TCM preparations [9,10]. It is one reason that makes RS the suitable excipient in some TCMs preparations. Moreover, physical properties such as swelling power, water holding capacity and pasting property make contribute to the emulsion capacity and gelatinization properties of RS. By DSC, the onset temperature (T_o) the peak temperature (T_p) the end phase transition temperature (T_c) and enthalpy (ΔH) of RS were higher than that of starch [11]. With the results of X-ray diffraction, RS samples exhibited B+V-type complex crystalline structure, which is crucial in anti-digestion property during digestion process [12-13]. In addition, the SEM results suggested that compact pack and smooth surface of the short chain amylose crystallite might hinder the enzyme's access to the matrix [14]. These properties may be the reasons of indigestible and gastric acid resistance functions of RS.

Functions of Resistant Starch with 'the Unification of Medicines and Excipients'

TCMs that rich in starch

In TCM prescribes, if medicines that are rich in starches are included, they would exert some beneficial functions; for instance, filling granule, assisting in disintegration, reducing the production cost in forming of formulations, with 'Unification of medicines and excipients' [15]. TCM that rich in starch were summarized in Table 2 with families, medicinal parts and frequencies of their use in TCM tablets preparations on the first volume of edition 2015 of Chinese Pharmacopoeia. Table 2 Medicines sufficient with RS, families and frequencies used in TCM preparations [4].

The filling action of resistant starch

Unlike general tablets and granules, which are generally prepared by mixing medicines with additives (for example, dextrin, cellulose, starches, etc.), the great mass of granules and tablets of Chinese Medicine are prepared without addition of additives. The reason is that medicines rich in starches are frequently present in most of prescriptions of Chinese medicine.

As TCMs preparations are prepared, these medicines were made into powder and act as filling agent in the preparation of granules and tablets of Chinese medicine. For example, *Radix angelicae dahuricae*, *Radix puerariae*, *Radix trichosanthis* and other starch-

rich drugs have used as filling agent in TCMs tablet by powdering, thus, there was no need to formulate the preparation with starch from outside [16,17].

Table 2: Medicines sufficient with RS, families and frequencies used in TCM preparations.

TCM Name	Botanical Name	Latin Name	Family	Medicinal Parts	Frequencies used in TCM preparations
Sanqi	<i>Panax notoginseng (Burk.) F.H.Chen</i>	<i>Notoginseng Radix et Rhizoma</i>	Araliaceae	rhizome	15
Chuanxiong	<i>Ligusticum chuanxiong Hort</i>	<i>Chuanxiong Rhizoma</i>	Umbelliferae	rhizome	14
Renshen	<i>Panax ginseng C.A. Mey</i>	<i>Ginseng Radix et Rhizoma</i>	Araliaceae	rhizome	12
Baifuling	<i>Smilax glabra Roxb.</i>	<i>Smilacis glabrae Rhizoma</i>	Liliaceae	rhizome	12
Shanyao	<i>Dioscorea opposita Thunb.</i>	<i>Dioscoreae Rhizoma</i>	Dioscoreaceae	rhizome	12
Huanglian	<i>Coptischinensis Franch</i>	<i>Coptidis Rhizoma</i>	Ranunculaceae	rhizome	10
Baizhu	<i>Atractylodes macrocephala Koidz</i>	<i>Atractylodis macrocephalae Rhizoma</i>	Composite	rhizome	6
Xiangfu	<i>Cyperus rotundus L</i>	<i>Cyperis Rhizoma</i>	Cyperaceae	rhizome	5
Baizhi	<i>Angelica dahurica</i>	<i>Angelicae dahuricae Radix</i>	Umbelliferae	root	17
Muxiang	<i>Aucklandia lappa Decne</i>	<i>Aucklandiae Radix</i>	Composite	root	12
Jiegeng	<i>Platycodon grandiflorum</i>	<i>Platycodonis Radix</i>	Campanulaceae	root	11
Baishao	<i>Paeonia lactiflora Pall</i>	<i>Paeoniae Radix alba</i>	Ranunculaceae	root	10
Huangqin	<i>Scutellaria baicalensis Georgi</i>	<i>Scutellariae Radix</i>	Lamiaceae	root	7
Huangqi	<i>Astragalus membranaceus (Fisch.) Bge</i>	<i>Astragali Radix</i>	Leguminosae	root	7
Tianhuafen	<i>Trichosanthes kirilowii Maxim</i>	<i>Trichosanthis Radix</i>	Curcubitaceae	root	4
Gegen	<i>Puerarialobata (wild.) Ohwi</i>	<i>Puerariae lobatae Radix</i>	Leguminosae	root	4
Yanhusuo	<i>Corydalis yanhusuo WT</i>	<i>Corydalis Rhizoma</i>	Papaveraceae	bulbus	7
Chuanbeimu	<i>Fritillaria cirrhosa D. Don</i>	<i>Fritillariae cirrhosae bulbus</i>	Liliaceae	bulbus	5
Heshouwu	<i>Polygonum multiflorum Thunb.</i>	<i>Polygoni multiflori Radix</i>	Polygonaceae	tuberous root	6
Wenyujin	<i>Curcuma wenyujin Y.H. Chen et C. Ling</i>	<i>Curcuma Radix</i>	Zingiberaceae	tuberous root	5
Banxia	<i>Pinelliaternate (Thunb) Breit</i>	<i>Pinelliae Rhizoma</i>	Araceae	stem tuber	4
Zexie	<i>Alisma orientale (Sam.) Juaep</i>	<i>Alismatis Rhizoma</i>	Alismataceae	stem tuber	8
Dahuang	<i>Rheum palmatum L</i>	<i>Rhei Radix et Rhizoma</i>	Polygonaceae	Root and rhizome	14
Jinyinhua	<i>Lonicera japonica Thunb</i>	<i>Lonicerae Japonicae Flos</i>	Caprifoliaceae	flower	6
Tianma	<i>Gastrodia elata Bl</i>	<i>Gastrodiae Rhizoma</i>	Orchidaceae	tuber	6
Mudanpi	<i>Paeonia suffruticosa Andr.</i>	<i>Moutan Cortex</i>	Ranunculaceae	velamen	3

Disintegration action of resistant starch

As we know, some large molecular substances, such as polysaccharides and proteins, are widely spread in TCMs extractions, which increases their viscosity. With tablet machine, TCM powders pressed to a tablet. During the process, compounds or the powders are easy to compress. However, effective constituent of TCM are hard to escape from tablet in dissolving experiment, especially for rapidly disintegrating tablets [18]. The viscosity of RS was lower than original starch. Experiments take RS replace original starch in medicine preparation thus active substances more easily escaped from drugs to exert their pharmacological effects [19]. As demonstrated by Wentao et al. [20], RS of polygonum multiflorum used as a material in targeted colon pellets. Compared with the original auxiliary materials, microcrystalline cellulose (MCC), RS promoted the release of model drug-Matine (MT) in vitro experiment. Based on this study, RS promoted the formation of pellets, resisted changes in pH in the gut, slowly released the drug under microbial fermentation, and act as a promising potential carrier material for colonic target preparation.

Adhesion action of resistant starch

In China, many prescriptions of TCM made to pills. Prescription is composed of medicines from few to dozens.

Usually, prescriptions are different from each other. Suitable adhesive is significant to the formulation of pill [21]. In general, according to the inherent viscosity of powders and the purpose of usage, water and honey or juice could choose as adhesive in pills formation. If sugar, starch, and protein are the main components in a prescription, viscosity of TCM powder will too strength to make a proper fill [22]. For instance, in *fulingtusi* pills, powder of medicines is higher viscosity. Pills could not made by adding original starch. *Poriacocos* RS modified from original starch in the prescription. During pills making, RS of *Poriacocos* mixed with other medicine powders in this prescription [23]. Through water adding and temperature adjusting, viscosity can precisely regulate to form propriety pills. During this process, *Poriacocos* has its own pharmacological effect and act as adhesive with its suitable sticky in the prescription.

Auxiliary Pharmacology Functions of Resistant Starch

RS cannot readily digested with ordinary starch, which could leads to its great biological importance, including some possible aids in prevention of gastrointestinal disease, reduction of insulin response and levels of serum cholesterol, promotion of beneficial bacterial growth, and promotion of mineral absorption [24,25]. Sources of RS from TCM, physiological effects and functions listed in Table 3.

Table 3: Physiological effects of resistant starch from TCM.

TCM source of RS	Physiological effects	Function mechanisms	Literatures
<i>Puerariaelobatae Radix</i>	Improving syndromes of diabetes	Lowed glycemic index, reduced the blood sugar, improved lipid metabolism, enhanced anti-oxidative stress	[48-51]
<i>Dioscoreae Rhizoma</i>	Prevented and promoted cardiovascular disease and lipid metabolism syndromes	Improved blood lipid profile, facilitated the metabolism of cholesterol and triglycerides	[52-55]
<i>Fritillariaussurensis Maxim</i>	Alleviated chronic nephritis, alleviated the inflammatory reaction of colitis, facilitated the colonic health	Improved inflammation and oxidative stress response,	[56-59]
		reduced kidney injury and kidney dysfunction, increased fecal moisture content	
<i>Polygonum Multiflorum</i>	Prevented obesity, weight control	Increased satiety, reduced energy supplied, promoted lipolysis	[43-47]
<i>Lotus seeds</i>	Acted as probiotic similarity functions	Stimulated the growth and activity of beneficial gut flora, fermented RS into SCFA	[60-63]

Aids in treatment of obesity

According to the present researches, RS cannot degrade into glucose and supply energy directly to the body. It can only degrade by fermentation of intestinal flora into metabolites of small molecular weight, such as SCFA, meaning that little energy could provide by RS [26]. It has said that the energy supplied by RS was less than one-tenth of that the digestible starch provided to body [27,28]. Furthermore, leptin and adiponectin are endogenic substances that are helpful to weight control. RS accelerated

synthesis and secretion of them, which could be another way of RS to help treat obesity [29,30].

Aids in treatment of type 2 diabetes

RS has a low glycemic index, so that it could control postprandial blood glucose, thus may help to treat type 2 diabetes [31,32]. The RS-chitosan oligosaccharide complex prepared by crosslinking method. After that, the compound had some extraordinary functional activities. It promoted the growth of probiotics and inhibited spoilage bacteria, so that intestinal micro

ecological environment was improved, and lipid metabolism was regulated. The descending of lipids was deeper than RS or chitosan oligosaccharide used individually [33]. Yan [34] prepared the inclusion compound that used RS and ganoderma lucidum as raw materials and studied its effects on type 2 diabetes. The results showed that RS and ganoderma lucidum had synergistic effect on reducing blood glucose, improving lipid metabolism disorder and enhancing anti-oxidative stress ability. This experiment may provide a new idea for seeking a valid dietary intervention to alleviate the symptoms of diabetes.

Aids in ameliorating cardiovascular symptoms

RS plays a role in regulating lipids in blood, ameliorating symptoms of cardiovascular disease, lipid metabolism syndromes, and facilitating the metabolism of cholesterol and triglycerides [35,36]. The possible mechanisms were that:

- i. RS could reduce the amount of fat absorbed into the body.
- ii. RS could also promote the excretion of bile acid in the fecal, which caused the cholesterol to be converted to bile acid and reduced the cholesterol content in the body.
- iii. propionic acid, a metabolite generated by resistant starch fermentation, regulated lipid metabolism and inhibited cholesterol synthesis in the liver [37,38].

Alleviation of chronic nephritis symptoms

RS may alleviate Chronic nephritis by improving inflammation and reducing oxidative stress response, shrinking kidney injury and kidney dysfunction, and increasing fecal moisture content [39]. Pharmacology researches about RS modified from *Fritillaria ussuriensis* Maxim done to observe the anti-inflammation and antioxidant activities. Results showed that RS of *Fritillaria ussuriensis* Maxim inhibited platelet aggregation, alleviated inflammation, and regulated secretion of inflammatory factor [40]. The anti-inflammation effect might relate to inhibit formation of PGE2 and MDA in inflammatory fluid. It also found that the modified starch inhibited host cells attack by free radicals, reduced cell damage, and alleviated inflammatory reaction. In addition, decreasing NO generation might also be another mechanism of its anti-inflammation effect [41,42].

Prebiotic function to improve the health of human body

RS may also benefit the human body through a role of prebiotic. Prebiotics are indigestible food ingredients that selectively stimulate the growth and activity of one or a limited number of bacteria present in the gut, thereby having a beneficial effect on the body [43,44]. According to this definition, RS were indigested in small intestine but fermented by microbial flora to SCFAs, including acetic acid, propionic acid, butyric acid, which play

roles in human body health through decreasing pH and nutrition supply [45]. Shan [46] prepared RS derived from Lotus seeds and investigated its probiotic effects. It verified that RS promoted the proliferation of the beneficial bacterium and enhanced the content of SCFAs, especially butyric acid, which could improve body health. Table 3 Physiological effects of resistant starch from Traditional Chinese Medicine [47-53].

Conclusions

'Unification of medicines and excipients' is the pharmaceutical idea, the pharmaceutical experience and the philosophical wisdom contained in TCMs preparation. Due to the diversity of TCM sources, the complexity of material properties and the special preparation technology, the 'unification of medicine and excipient' is very common in TCM preparations. With this idea, the consumption of excipients has largely saved in processes of TCM production. In addition, excipients applied under this conception exert synergistic effect with main drugs thus decreasing the required dosage in prescription but keeping same or better function of clinical therapy. Moreover, side effects also limited by using nature material as excipients and lowering dosage of main drugs.

RS, as a special kind of starch, formed by some physical and chemical modification methods. Under the guidance of 'combination of medicine and excipient', RS not only has abilities that resemble normal starch such as filling, diluting, disintegrating in TCM preparation, but also has pharmacological activities of its own. As starch is widely spread in multitudes of different species of TCM, it was discarded during the isolation of active components. In this paper, physicochemical properties, pharmacy and pharmacological advantages of RS presented with the concept of 'Unification of medicines and excipients. With broader and more in-depth research, RS will have promising potential application in TCM preparation [54-63].

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