

Rethinking the impact of RG-I mainly from fruits and vegetables on dietary health

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ABSTRACT

Rhamnogalacturonan I (RG-I) pectin is composed of backbone of repeating disaccharide units $\rightarrow 2\text{-}\alpha\text{-L-Rhap-(1}\rightarrow 4\text{)-}\alpha\text{-D-GalpA-(1}\rightarrow$ and neutral sugar side-chains mainly consisting of arabinose and galactose having variable types of linkages. However, since traditional pectin extraction methods damages the RG-I structure, the characteristics and health effects of RG-I remains unclear. Recently, many studies have focused on RG-I, which is often more active than the homogalacturonan (HG) portion of pectic polysaccharides. In food products, RG-I is common to fruits and vegetables and possesses many health benefits. This timely and comprehensive review describes the many different facets of RG-I, including its dietary sources, history, metabolism and potential functionalities, all of which have been compiled to establish a platform for taking full advantage of the functional value of RG-I pectin.

KEYWORDS

Pectin; dietary sources; diseases; bioactivity; metabolism of RG-I; gut microbiota fermentation

Introduction

Pectin, the important cell wall component, is an essentially heteropolysaccharide having an average molecule weight of 10-5000 kDa, which is mostly found in primary cell walls (Silva et al. 2018), and it is a collection of galacturonic acid (GalA)-rich polysaccharides (Obro et al. 2004; Strasser and Amado 2001). The “pectin” word came from the Greek word “pektikos” and was coined by a French chemist in 1825 (Ferrari et al. 2013). For nearly two centuries, pectin has been widely studied by many fields.

Pectic polysaccharides occurring in plants are extremely large biopolymers having a high level of structure complexity (Chen et al. 2013). Various types of pectin structure have been isolated and investigated including homogalacturonan (HG), rhamnogalacturonan I (RG-I), rhamnogalacturonan II (RG-II), xylogalacturonan (XGA), apiogalacturonan (ApGA), galactogalacturonan (GGA), galacturonogalacturonan (GaGA) and arabinogalacturonan (ArGA) (Ridley, O'Neill and Mohnen 2001; Vincken et al. 2003; Yapo 2009). Both “smooth” and “hairy” regions constitute pectin molecule. HG, a linear polymer of D-galacturonic acid linked $\alpha\text{-1,4}$ (Lama-Muñoz et al. 2012), corresponds to the smooth region, while the hairy region includes varying structural blocks where RG-I designates the most ramified structure (Zhang et al. 2012). RG-I is comprised of backbone, repeating disaccharide units composed of $\alpha\text{-D-GalpA}$ and rhamnosyl (Rha), branched with diverse side chains, including

linear or branched arabinogalactans (AG), consisting of $\alpha\text{-L-arabinofuranosyl (Araf)}$ and $\text{galactopyranosyl (Galp)}$, with a varying degree of polymerization (Ai et al. 2018). RG-I plays a key role in the structure integrity of pectin complex, to which HG and RG-II are notably attached (Park et al. 2017; Cornuault, Pose and Knox 2018).

RG-I is present in the fruits, roots, stems and leaves of plants, linking with cellulose and hemicellulose, as well as cell wall proteins (Tan et al. 2013) and plays an important role in the large load-bearing network of plant cell wall (Broxterman and Schols 2018). The composition and structure of plant cell wall is quite complex. Cellulose, the main polysaccharide in all plant cell wall is in the form of thin microfibril, cross-linking with other matrix polysaccharides, such as hemicelluloses and pectic substances. RG-I is believed to interact with cellulose to make up the load-bearing network in cell wall (Phyo et al. 2017), filling the cellulose interfibrillar space with its rhamnogalacturonan backbone linking to cellulose while its Ara and Gal side-chains remain highly mobile (Phyo et al. 2017). The structural heterogeneity of plant cell walls renders it difficult to target the selective extraction of RG-I pectin. Some research has provided evidence that RG-I regions participate more in cross-linking other cell wall components than HG (Ralet et al. 2016). Moreover, the presence of lignin protects the secondary cell walls from chemical pretreatment and enzymatic degradation, posing major difficulties in RG-I extraction (Cheng, Sorek, et al. 2013). This represents an important

reason for the lack of research on the dietary function of RG-I.

In dietary network, RG-I pectin is widely present in fruits and vegetables. Most of the RG-I pectin used in the food industry is extracted from orange peel or apple pomace (Babbar et al. 2016). Nowadays, many new sources of RG-I have been reported, such as pumpkin, okra, potato and tomato (Zhao et al. 2017; Liu et al. 2018; Khodaei et al. 2016; Kapoor and Dharmesh 2017). However, the monosaccharide composition, molecular size, and structural features of RG-I pectins appear to be highly variable from source to source (Torkova et al. 2018). Even though the backbone of RG-I is simply composed of Rha and GalA, the diverse degree of methylation and acetylation considerably changes the structural features of the rhamnogalacturonan backbone. In addition, variable glycosyl linkages and chain lengths as well as their varying distribution make RG-I pectins a family of highly heterogeneous polysaccharides. Health benefit properties presumably correspond to the unique structures in RG-I pectin, and different dietary RG-I pectins certainly differ in functional properties. Therefore, it is important to compile information about the myriad RG-I characteristics to study their structure-activity relationships.

Recent studies on RG-I pectins demonstrate that these structures contribute to polysaccharide activities significantly more than other pectic fractions (Zhang et al. 2012; Zhang, Zheng, et al. 2016). There are an increasing number of studies aim at RG-I bioactivities, and some purified RG-Is have shown various beneficial health effects (Zou et al. 2014a; Kapoor and Dharmesh 2017; Gao et al. 2013; Manjgowda, Rajagopal and Dharmesh 2017), but it is difficult to clarify the mechanisms of action and to determine the specific segments required for activity. It is also necessary to consider the metabolism of RG-I in digestive system. Since the native RG-I macromolecule is typically of too high a molecular weight to be directly absorbed and the saliva, gastric fluids and small intestine have no ability to broke down RG-I (Chen, Xie, et al. 2018), the human gut microbiota present in the large intestine are viewed as critical for RG-I utilization. It has been reported that polysaccharide utilization loci (PULs) activated by different RG-I domains can recruit specific enzymes for metabolism of RG-I pectin molecules (Luis et al. 2018). A myriad of glycoside hydrolases (GHs) and polysaccharides lyases (PLs), produced by colonic species, are believed important for the degradation of RG-I side-chains and backbone. Thus, a comprehensive understanding of RG-I metabolism in the human digestive system is essential.

Most reviews, to date, have been compiled to provide information on the whole pectic polysaccharide, and describe the nature and chemistry of pectin, potential sources of pectin, various pretreatment methods and the activities of pectin. There are no reviews that focus on the distribution of RG-I pectin in dietary system as well as its metabolism and bioactivity. A detailed analysis of the literature on RG-I is required for the in-depth study and efficient utilization of pectins. In the current review, we summarize the history of RG-I, the distribution of RG-I in the primary

cell wall, the dietary sources of RG-I, the bioactivities and the metabolism of RG-I as well as its application in food system.

The origin of RG-I

History of RG-I

The study of RG-I began over 50 years ago. In 1968, Aspinnall and coworkers found some acidic oligosaccharides including 2-O-(α -D-galactopyranosyluronic acid)-L-rhamnose following the acid hydrolysis of pectin (Aspinnall et al. 1968). A tetrasaccharide involving the alternating residues of GalA and Rha was found in soy-beans polysaccharides (Aspinnall et al. 1967). Until 1973, the “hairy region” of the pectic polymer was believed to have a linear galactan and a branched arabinan, in the form of side chains attached to the rhamnogalacturonan consisting of α -1,4 galacturonan interspersed with 2-linked Rha residues (Talmadge et al. 1973). In 1980, the term “RG-I” was first used to describe the rhamnose-rich portion of pectic polymer (Mcneil, Darvill and Albersheim 1980, 1982). However, the secret of RG backbone was not revealed until 1988. Komalavilas P and coworkers used anhydrous hydrogen fluoride (HF) to degrade plant cell walls and obtained high amount of \rightarrow 2)- α -L-Rhap-(1 \rightarrow 4)- α -D-GalpA-(1 \rightarrow disaccharides, suggesting a fairly strict repeating sequence for the disaccharides comprising the rhamnogalacturonan backbone. Moreover, nuclear magnetic resonance (NMR) spectroscopy showed approximately 30% acetylation at the O-3 of the GalA residues in RG-I backbone (Komalavilas and Mort 1989).

In subsequent decades, many researchers have studied RG-I. Although the structural complexity of RG-I is still not fully understood, the structural properties of RG-I are constantly updated with the rapid development of analytical technologies, including NMR spectroscopy (solution and solid-state NMR), mass spectrometry (MS) and atomic force microscopy (AFM). Different structural determination technologies have provided novel insights into RG-I structure. RG-I has a fairly conserved rhamnogalacturonan backbone and is defined as a pectic polymer containing backbone of $[\rightarrow$ 2)- α -L-Rhap-(1 \rightarrow 4)- α -D-GalpA-(1 \rightarrow]n (n \geq 1) and various branched or linear side-chains mainly covering neutral glycosyl residues. It is still quite challenging to analyze the fine structure of RG-I and a variety of emerging analytical techniques should be comprehensively utilized to obtain more complete insights into RG-I structure.

RG-I in the primary cell wall of plants

RG-I is derived from the plant cell wall, and it has a complex connection with other wall polysaccharides. It is important to consider the co-digestion of RG-I with other cell wall polysaccharides in food from plant sources. Therefore, understanding the plant cell wall structure is helpful in exploring the utilization and the distribution of RG-I in the foods.

The cell wall structure has been of great interest to plant scientists and scientists in the food processing industry. The first cell wall model, proposed in 1973, depicted a covalently cross-linked model, where a key feature was its covalent linkages of matrix biopolymers, such as cellulose, hemicellulose (xyloglucan), RG-I pectin and glycoproteins. The covalently cross-linked hemicellulose-cellulose network provided the cell wall tensile strength and the considerable amount of RG-I pectin was linked to structural proteins within the cellulose microfibrils (Talmadge et al. 1973). Researchers next established some pectic matrix models, where the pectic polysaccharides were speculated to comprise a loading matrix and RG-I appeared to be in the hydrated state (Cosgrove 2014). Recently, an alternative model has suggested that there are a significant number of cellulose-RG-I pectin interactions present in cell wall while the xyloglucan seems to be entrapped between cellulose microfibrils at a small number of sites (Phyo et al. 2017). There is strong evidence to verify the covalent interactions between cellulose and RG-I pectin in the carrot. After sequential alkali extraction destroying hydrogen bonds and possible ester linkages, glucanase still releases about 27% of the 6M alkali residue, which mainly represents RG-I pectin (Broxterman and Schols 2018). Also, a significant number of RG-I-cellulose cross-links have been observed using solid-state NMR spectroscopy (Wang et al. 2015). Moreover, some studies suggest RG-I pectin-hemicellulose interactions in the cell wall, such as RG-I pectin-xylan complexes (Broxterman and Schols 2018). The structure of xyloglucan can be altered because of transgenic modification of pectin, representing xyloglucan linked to pectin, where the RG-I regions are the predominant linker (Huang, Jiang, et al. 2017). Some research has provided evidence that RG-I regions participate more than HG regions in cross-linking other cell wall components (Ralet et al. 2016).

Most recent cell wall models highlight the importance of RG-I. Based on current models, the distribution of RG-I in cell walls is depicted as shown in Fig. 1. RG-I exists within a bundle of cellulose microfibrils in mainly two forms. Some RG-I is linked to cellulose through its RG backbone in the form of static semi-rigid chains, which will play a role in cell wall weight bearing (Broxterman and Schols 2018). Other RG-I remains between the microfibril bundles of cellulose, showing high mobility, and its mobile side-chains are able to interact with some hemicelluloses, such as xylan and xyloglucan, which is crucial in cell wall structure remodeling and tissue softening (Ulvskov et al. 2005). Moreover, the changes of RG-I structure are closely correlated with different periods of tissue development in plants, which has great importance in the ripening and texture of fruit and vegetables.

RG-I in different pectin sources

Pectin, a key component in plant cell wall, exists in many vegetables and fruits within our food products. However, RG-I appears to be highly variable from source to source. Even in a single botanical source, organ-specific differences in RG-I exist and its structure and chemical composition

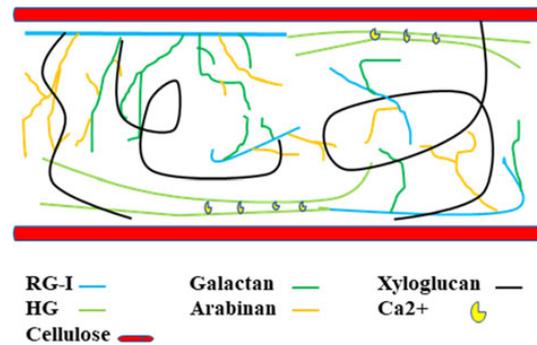


Figure 1. Model of RG-I, HG, Xyloglucan distribution in cell wall.

will be influenced by the growing area (Chen, Zhu, et al. 2017). Nowadays, the application of RG-I is receiving increasing attention. Moreover, since the pectin demand in global market has been increasing, with over an average total production capacity of 45-50 million tons annually (Valdés et al. 2015), there has been an increased interest in RG-I pectin extraction from the agro-industrial by-products of many botanical sources (Kostalova and Hromadkova 2019; Kazemi et al. 2019). Researchers from different laboratories have investigated RG-I components in different pectin resources having different structural characteristics (Table 1). Analyzing the RG-I distribution in our dietary food products is necessary for the in-depth study and industrial application of pectin products. The composition of some common dietary sources of RG-I pectin are provided in Fig. 2.

Citrus

Citrus pectin is a complex heteropolysaccharide predominantly consisting of HG, with a few RG-I domains and a minor RG-II component (Yapo et al. 2007). Under acid-extraction condition, the mass distribution of HG/RG-I/RG-II are reported to be approximately 88/11/1 (Yapo et al. 2007). However, recovered citrus pectin from canning processing water is dominated by RG-I domains (Chen, Cheng, et al. 2017). Citrus fruit are one of most important fruits grown and consumed worldwide (Aggarwal and Sandhu 2004), and China is the largest citrus planting and harvesting country in the world with annual production of 38 million tons (National Bureau of Statistics of China 2017). With the development of citrus canning industry, the byproducts of industrial processing containing peels and segment membranes are huge source of citrus RG-I (Chen, Cheng, et al. 2017).

The HG regions are postulated to be of almost same length whatever the citrus origin, while the RG-I contains polysaccharide populations of varying contents and integrity, which suggests that the structural variability of citrus pectin appears not to be related to HG regions but instead to the RG-I domains (Cornuault, Pose and Knox 2018; Kaya et al. 2014). There has been excellent extraction of RG-I reported from mandarin citrus peel. Using the low-temperature alkali extraction, the citrus RG-I exhibits high ratio of arabinose,

Table 1. Monosaccharides composition (mol%) and macromolecular features of RG-I pectin from different dietary sources.

	Extraction methods	Sugars (%)										Rha/GalA ratio	(Gal + Ara) /Rha	RG-I (%)	Mw (kDa)	Ref.
		Gala	Rha	Fuc	Ara	Xyl	Man	Gal	Glc	GlcA						
Citrus	Sodium hydroxide extraction	20.3	11.7	n.d.	40.6	n.d.	18.5	8.9	n.d.	n.d.	5.05	0.58	82.5	743	Zhang et al. 2018a	
	Acid extraction	84.5	2.8	n.d.	1.4	0.4	9.2	2.0	n.d.	3.79	0.03	16.2	81	Colodel et al. 2018		
	Acid extraction	88.1	1.6	0.08	4.07	0.25	n.d.	5.04	0.45	0.36	5.69	12.31	442	Fishman et al. 2019		
	Ultrasound-assisted acid extraction	65.3	2.8	n.d.	2.5	2.0	n.d.	25.1	0.4	n.d.	9.86	0.04	33.2	–	Hosseini et al. 2019	
Apple	IMEP	70.74	6.69	n.d.	9.20	0.32	10.79	0.25	n.d.	2.99	0.09	33.37	349	You et al. 2019		
	CDTA extraction	85	3	–	5	1	5	tr	tr	3.33	0.04	16	–	Prabasari et al. 2011		
	NaCO ₃ extraction	25	6	–	31	2	33	2	tr	10.67	0.24	76	–			
	Ultrasound extraction	54.20	4.32	–	1.82	–	8.76	28.67	–	4.81	0.04	19.22	706	Zhang et al. 2013		
Sugar beet	Malic acid extraction	43.29	7.8	1.22	16.77	–	17.07	8.63	–	4.34	0.18	49.44	372	Cho et al. 2019		
	Enzymatic extraction	74.7	1.38	0.25	3.92	1.54	5.27	4.05	–	6.66	0.02	11.95	419	Wikiera et al. 2016		
	Oxalate extraction	59	1.6	n.d.	5.9	1.0	n.d.	5.5	1.8	n.d.	7.13	14.6	166	Liu et al. 2019		
	Acid extraction	66.2	3.6	–	5.0	1.2	–	7.1	0.3	–	3.36	19.3	651	Pi et al. 2019		
Potato	Enzymatic extraction	44.80	16.79	–	0.79	5.22	8.68	12.57	–	0.23	0.37	43.05	319	Pacheco et al. 2019		
	Acid extraction	36.9	1.9	n.d.	3.6	0.1	54.31	3.1	0.1	28.45	0.06	61.71	258	Yang et al. 2018		
	Enzymatic extraction	15.2	1.2	n.d.	1.6	0.1	81.2	0.5	n.d.	67.75	0.08	85.2	62.2	Khodaei and Karboune 2016		
	UWAE	41.78	3.8	n.d.	2.047	0.26	49.38	2.6	0.072	12.65	0.11	59.03	154	Yang, Mu and Ma 2019		
Pumpkin	Alkali extraction	39.7	11.7	n.d.	4.1	n.d.	44.4	n.d.	n.d.	4.15	0.29	71.9	22.6	Zhao et al. 2017		
	Heated water extraction	62.0	5.2	1.2	6.4	0.0	3.3	18.6	3.3	n.d.	0.08	35.4	26.96	Torkova et al. 2018		
	Microwave heating	73.8	4.2	0.4	4.6	0.9	7.2	6.6	1.5	2.81	0.06	20.2	139	Košťálová, Aguedo and Hromádková 2016		
	Heating extraction	66.3	4.6	0.6	4.1	4.3	9.0	11.2	2.1	2.85	0.07	22.3	289	Kpodo et al. 2017		
Okra	Aqueous extraction	64.7	11.1	n.d.	2.3	n.d.	18.4	n.d.	0.9	1.88	0.17	42.7	1202	Li, Dong, et al. 2019		
	Ultrasound extraction and purification	25.9	7.4	0.6	1.9	0.5	50.5	8.2	2.9	7.08	0.29	67.02	110-550			
Grapefruit	Microwave assisted extraction	40.79	21.69	n.d.	6.94	n.d.	25.38	n.d.	n.d.	1.49	0.53	75.7	1391-5859	Yuan, Lin, et al. 2019		
	ACAE	53.76	7.43	0.71	16.74	3.2	10.94	3.25	1.35	3.73	0.14	42.54	312	Wang, Wu, et al. 2017		
Jackfruit	CHE	68.96	8.35	0.56	3.54	1.25	11.3	1.3	1.49	1.78	0.12	31.54	317			
	Subcritical water extraction	52.27	9.14	0.17	8.11	n.d.	1.18	24.35	4.77	3.55	0.17	50.74	113	Li, Fan, et al. 2019		
	Acid extraction	56.99	9.68	0.34	5.18	n.d.	1.05	23.31	3.45	2.94	0.17	47.85	174			
	UME	31.82	5.68	n.d.	9.10	n.d.	n.d.	11.36	42.05	n.d.	3.6	31.82	51.5	Xu et al. 2018		
Strawberry	CHE	37.35	4.82	n.d.	6.02	n.d.	12.05	39.76	n.d.	3.75	0.13	27.71	52.3	Zhang, Zhao et al. 2018		
	Ultrasound assisted chelating extraction	35.45	4.66	n.d.	10.25	8.04	26.72	12.20	n.d.	7.93	0.13	46.29	–			
Chicory pulp	Acid extraction	71.9	3.4	–	3.0	0.7	9.4	0.5	–	3.65	0.06	19.2	260	Pi et al. 2019		

n.d., not detected.

"–" Negative result indicating no domain.

Tr, trace (<0.5 mol%).

RG-I (%) was calculated according to Correa-Ferreira et al. 2018.

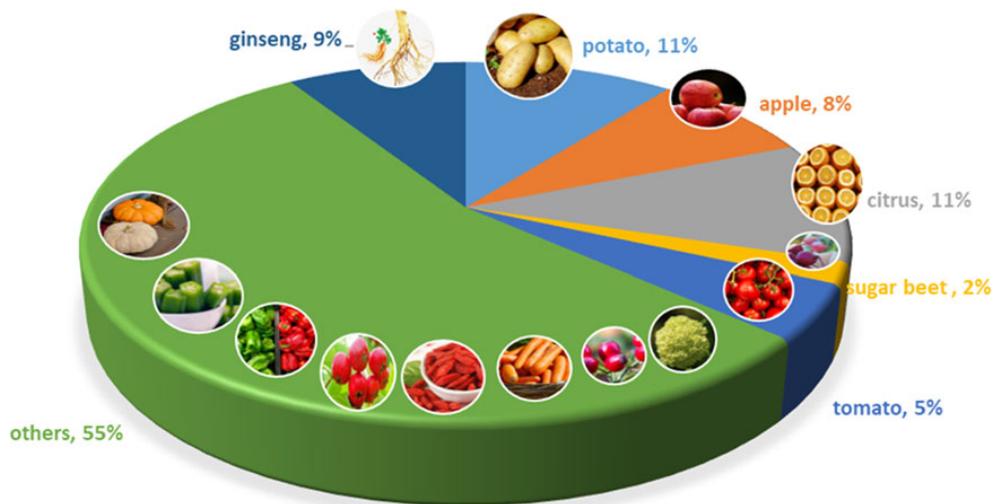


Figure 2. Composition of research papers about some common sources of RG-I pectin in dietary system.

with only 9% attached galacturonic acid (Zhang et al. 2018a). Similarly, the citrus RG-I recovered from the alkaline citrus canning water also contains high amount of arabinose side chains resulting in a high viscosity, which might be potentially used in gelling and thickening agents (Chen, Cheng, et al. 2017). Also, RG-I regions mainly branched by galactans have been found in Ponkan peel (Colodel et al. 2018). The low amount of arabinose might be due to different species or extraction method.

Apple pomace

In apple processing industry, the majority of apple fruit is used for production of concentrated juice with approximately 25% of apple mass discarded as waste from apple processing industry (Gullon et al. 2007; Cho et al. 2019). Apple pomace reportedly contains high amounts of vitamins, minerals, organic acids and polysaccharides with 8.3% pectin (Voragen et al. 2009; Jiang and Du 2017), among which highly branched RG has been found, and the RG-I is especially rich in arabinan side-chain, making the neglected apple pomace a useful raw material for RG-I (Schols et al. 1995). As for different apple cultivars, like 'Royal Gala' and 'Scifresh', their chemical composition differs from one another. For example, 'Scifresh' contains a much higher amount of galactose in its RG-I than 'Royal Gala'. In contrast, the extent of branching in apple RG-I shows little differences in the ripe tissue between the two cultivars (Ng et al. 2015). There have been studies suggesting the potential of apple pectin as anti-obesity drugs, the mechanism of which might be that carboxyl groups of pectin cross-link with the histidine in the active site of pancreatic lipase resulting in the inhibition of lipase action (Kumar and Chauhan 2010). However, it is presently unclear whether the carboxyl groups in HG or RG-I is involved in the formation of pectin-lipase complex.

Potato pulp

Potato pulp reportedly contains 17% pectic polysaccharide on dry weight basis (Birch et al. 2012), and it has a distinct pectin composition with a high proportion of RG-I (75%) (Eriksson et al. 2016) having long galactan side chains (63% of RG-I) (Khodaei and Karboune 2013, 2016). The average annual harvest of potato in the world is 368 million tons, mainly used for production of potato starch (Guo et al. 2019). In China, every ton of starch produced will generate approximately 4.5–5.0 tons of fresh potato pulp (Yang, Mu and Ma 2018) and, thus, the residue of potato starch extraction represents a huge resource for RG-I extraction and its recovery would surely alleviate environmental pollution. There has been excellent enzymatic extraction of RG-I from potato by-products. The selected reaction parameters resulted in different yield and side-chains content. Under the optimal conditions, the yield of RG-I can rise to more than 63% (Khodaei et al. 2016).

Tomato

Tomato is a common fruit rich in nutrients and can be eaten raw, cooked, or processed into ketchup, puree, juice or produced as cans of whole fruit, thus, tomato RG-I is omnipresent in our daily diet. Since more than a third of tomato production is used in manufacturing processes, a large amount of waste, including 56% pulp and skin is obtained as dried biomass that is discarded or used as animal feed (Martínez-Romero et al. 2009). This represents a huge resource for pectin extraction (Alancay et al. 2017). As a agro-industrial by-product, tomato waste contains considerable pectin at the ratio of over 36%, and the utilization of sonication make it possible to finish the extraction within 15 min (Grassino et al. 2016) without prominent changes in pectin structure. The chemical structure of tomato fiber pectin shows the presence of RG-I domain, observed in pectin from tomato puree, and the extent of branching can be

reduced by the high pressure homogenization (Santiago et al. 2017). Pectic oligosaccharides have been purified from tomato and are reported to contain RG-I with AG (Arabinogalactan) attached to the backbone (Kapoor and Dharmesh 2017). Compared to other vegetables like carrot and broccoli, tomato pectin possesses higher linearity and lower degree of branching in its RG-I regions, forming of long linear chains of high molar mass (Houben et al. 2011). The role of RG-I pectin in the wall properties during cell growth has also been evaluated using immunodetection experiments. At early stages of fruit development, high amount of galactan-rich or arabinan-rich RG-I was synthesized next to HG, distributing mainly in the middle lamella. Then both middle lamella and primary wall contain RG-I backbone. In contrast, partially degraded galactan side-chains were observed only in the primary wall, while arabinan side chains were restricted to the adhering region. Both of arabinan and galactan in RG-I region exhibited extensive and flexible linkages to other wall polysaccharides, suggesting the vital role of tomato RG-I in cell wall remodeling (Guillon et al. 2017). And the amount of rhamnose increases during the ripening stage, indicating a greater occurrence of RG-I in the tomato cell wall tissue (Xin et al. 2010).

Sugar beet pulp

Sugar beet pulp (SBP) is an important agro-industrial side-product arising from the sugar extraction process. Currently, 160 kg of fresh pulp is produced when processing approximately one ton of sugar beets (Cardenas-Fernandez et al. 2018). Sugar beet pulp consist of approximately 22–24% cellulose, 30% hemicellulose, 3% ash and 6% lignin on dry matter base, also contains 15–25% pectin (Elst et al. 2018), which makes sugar beet pulp an attractive candidate for the extraction of RG-I pectin.

In contrast to pectins obtained from other sources, such as citrus, apples, or chicory root pulp, sugar beet pectin (SBP) is comprised of low-methylated and highly-acetylated HG with intermittent blocks of RG-I, containing high concentrations of neutral sugars, such as linear galactans and highly branched arabinans formed of L-arabinose (Cardenas-Fernandez et al. 2018; Pi et al. 2019). It has been reported that the proportion of arabinose is about 70% in SBP RG-I (Abdel-Massih et al. 2007), which is predominantly present as terminal (1→5)-linked, (1→3, 5)-linked and (1→2, 3, 5)-linked residues (Cardenas-Fernandez et al. 2018). Moreover, sugar beet RG-I contains high amounts of ferulic acid, which is attached to the O-2 position of (1→5)-linked arabinose residues or the O-6 position of (1→4)-linked galactose residues (Karnik et al. 2016). Ferulic acid groups promote the cross-linking of neutral sugars in RG-I through di-ferulic bridges and influence the molecular weight in cell wall as well as contribute to the poor gelation properties of sugar beet pectin (Oosterveld et al. 2001).

Pumpkin biomass

Pumpkin pectin is an interesting source of RG-I with distinctive characteristics such as high degree of branching and esterification (Cui and Chang 2014). Pectin-rich fibers have been isolated from pumpkin including its pulp, peel and seeds (Wang, Liu, et al. 2017). In particular, the pumpkin biomass obtained from seed oil production, can be used to develop products such as thickeners and stabilizers because of its high amount of pectin (Košťálová, Hromadkova and Ebringerova 2013). Pumpkin RG-I, with the branching extent of approximately 29%, has been extracted using a low-temperature alkali treatment. The side-chains of this RG-I are dominated with long β 1→4-D-galactan chains carrying terminal non reducing α -Araf residues (Zhao et al. 2017). Compared to the commercial apple pectin or citrus pectin, pumpkin pectin has the highest macromolecule mass and degree of side chain branching, suggesting the presence of more RG-I regions (Torkova et al. 2018). Recently, scientific studies focused on the functionalities of pumpkin pectin have implicated the structure and composition of this RG-I to its antioxidant properties (Torkova et al. 2018).

Others

RG-Is from other dietary sources have attracted increased attention in recent years due to possible health benefits. Okra is a widely planted vegetable in tropical and subtropical regions. The backbone of okra RG-I was different from a previously reported composition, which was identified as \rightarrow 4)-D-GalpAMe-(1→2)-L-Rhap-(1→. The side-chains of okra RG-I predominantly consist of \rightarrow 4)- β -D-Galp-(1→ and arabinose usually located in the end of side-chain as a minor component (Liu et al. 2018). The pectic polysaccharides extracted from green sweet pepper also contains RG-I with AG-I side chains anchored to rhamnogalacturonan, exhibiting potential therapeutic value (Adami et al. 2018). The pectic polysaccharides extracted from rose hip contains 5.5% galactose and 4.7% arabinose, mainly representing RG-I regions (Ognyanov et al. 2016). Recently, studies about the eggplant have revealed that eggplant calyx contain 44% RG-I (Kazemi, Khodaiyan and Hosseini 2019). The pulp of gabiropa fruits contain 65.3% RG-I domain with high amount of arabinose (Barbieri et al. 2019). Peels and membranes of pomegranate also contain a minor amount of RG-I with partially 2-O- and/or 3-O-acetylation (Shakhmatov, Makarova and Belyy 2019). In addition to vegetables and fruit, many traditional medicines in China also contains various active polysaccharides, suggesting the presence of RG-I in Chinese herbs. *Panax ginseng* C. A. Meyer, as a traditional Chinese herb, has a long history for over 2000 years and wide application among potential therapeutics (Sun et al. 2019). The total ginseng polysaccharides include starch and pectin, and ginseng pectin accounts for around 20% of water-soluble polysaccharides (Zhang, Zhang, et al. 2018). A series of pectic fractions from ginseng have been isolated through different chromatographic steps, two of which belong to RG-I composed of major neutral sugars (Gao et al. 2013). Bioactivity analysis have indicated

that ginseng RG-I domain exhibits better health effects than other pectic domains (Zhang et al. 2012). *Cynanchum auriculatum* Royle ex Wight, commonly called as Baishouwu in China, has a wide distribution in Asian regions (Miao et al. 2012), this heteropolysaccharide might be an interesting candidate for RG-I extraction (Yuan et al. 2017). RG-I regions with AG-I and AG-II side-chains have been elucidated to be predominant structure of high molecular weight polysaccharide from elderflower pectin (Ho et al. 2016). *Gentiana crassicaulis*, another well-known Chinese medicinal herb, similarly contains RG-I regions and AG-I/AG-II side-chains in pectic polysaccharide, which can be used as natural immunomodulator and a functional food supplement (Zou et al. 2017).

Fine structure of different RG-Is

Based on the above discussion, it is clear that RG-I is widely distributed in dietary products, and represents a vital bioactive compound within foods. From all have mentioned above, the RG-Is from diverse plethora of diet sources shows considerable variability in the fine structure. Generally speaking, citrus fruit is rich in RG-I stretches with high amount of neutral sugar side chains (Kaya et al. 2014; Zhang et al. 2018a; Colodel et al. 2018) and potato RG-I is characterized by long galactan sidechain. Sugar beet RG-I exhibits high molecule weight due to cross-linking with high amount of ferulic acid, while tomato RG-I tends to show higher linearity, might containing low branching degree and short side chains. And okra RG-I possesses rhamnogalacturonan backbone with high degree of methyl esterification. When it comes to the fine structure of sugar chain in RG-I, Zhou lab (Gao et al. 2013; Shi et al. 2017) has carried out series of work in the structural analysis of ginseng RG-I, containing the distribution of side chains, the ratio of long and short galactan sidechain and the type of arabinose residue. However, it still remains great difficulty to grasp the integral information of native RG-I structure in cell wall because of the destruction caused by extraction treatment.

Bioactivities of RG-I

Recent studies have suggested that various RG-Is possess important activities related to human health (Table 2). Food selection and eating habits are significant factors affecting the health of human beings. Simple foods are inextricably linked to human health problems and diseases. Changes in human dietary habits and lifestyle have resulted in increased incidences of chronic metabolic diseases, immune diseases, heart disease, cancers and other health challenges. While ubiquitously present in the human diet, increased intake of certain RG-I structures might relieve many human health problems, as depicted in Fig. 3. RG-I from different pectin sources clearly exhibit different specific compositions and structures that must, necessarily, be related to their biological functions.

Modulating chronic metabolic disease

Anti-hyperglycemic activity

Hyperglycemic symptoms have always posed a major problem in human health. Usually, the human body can ensure appropriate and balanced blood glucose levels by hormonal regulation and neuromodulation. However, when the combined effect of genetic factors, such as family history of diabetes and environmental factors (poor diet, obesity, etc.) are present disorderedly, hyperglycemic level can appear (Mohan and Elyas 2019). Insulin plays the key role in glucose metabolism and causing hyperglycemia (Ohtsubo et al. 2011).

Pectic fiber can limit the release of glucose in gastrointestinal tract alleviating diabetes (Benítez et al. 2017). In addition to its effects on GI system, the therapeutic mechanism of pectic fiber's anti-diabetic action in signaling pathways has been reported in a study of pectic polysaccharide from the fruits of *Ficus pumila* Linn (FPLP) (Wu et al. 2017). Oral administration of FPLP for 5 weeks significantly reduced serum glucose levels along with increasing glycogen metabolism in the liver of C57BL/KsJ db/db mice. Both IRS-1/PI3K/Akt/GSK3 β /GS and AMPK/GSK3 β /GS signal pathways were activated. Moreover, the regulation of some important enzymes (glucokinase, glucose-6-phosphatase, phosphoenolpyruvate carboxykinase) occurred in hepatic glycogenolysis and glycogenesis.

In the past ten years, the application of RG-I pectin has been a hot research topic for lowering the blood glucose levels. One potential mechanism for RG-I activity might be through stimulating insulin release and promoting glycogen synthesis. An acid pectin fraction of ginseng polysaccharide, WGPA, is an HG and RG-I enriched pectin, which effectively lowers blood glucose in streptozotocin (STZ)-induced diabetic mouse model. The oral administration of 10 mg/kg WGPA increased insulin level and hepatic glycogen production (Sun et al. 2014). Similarly, okra RG-I, water-extracted and purified from okra pod, having a different backbone, composed of repeating Rha and GalAMe units, significantly exhibited hypoglycemic effects *in vivo*. The body weight of mice in the different groups show no differences but the blood glucose level and glucose tolerance clearly decreased in high-dose RG-I group (Liu et al. 2018). Both the source and extraction method can influence the activity of an RG-I pectin. It has been reported that heat processing improves the *in vivo* hypoglycemic activity of pectin in animal experiment (Jiao et al. 2014) and that this may be due to the conversion of esterified GalA into unesterified form of GalA.

Anti-hyperlipidemic activity

Hyperlipidemia is viewed as the leading cause of metabolic diseases. Apart from its anti-hyperglycemic effects, RG-I pectin also show significant anti-hyperlipidemic activity in mice with hyperlipidemia induced by a high-fat diet. After 30 days of pectic oligosaccharide treatment, the fat deposition in liver was reduced notably compared to the HF group, and the proportion of monounsaturated fatty acid and saturated fatty acid changed, which suggested that

Table 2. Selected RG-I with respective bioactivities and possible mechanisms.

RG-I pectin source	Key domain	Extraction method	Bioactivities	Possible mechanism	Ref.
<i>Prunus avium</i>	RG-I	90 °C water extraction	Immunomodulatory activity	Inducing the NO release and expression of several immune-related molecular	Cao et al. 2018
<i>Gentiana crassicaulis</i>	RG-I with AG-I/AG-II	100 °C water extraction	Immunomodulatory activity	Complement fixation activity	Zou et al. 2017
<i>Sambucus nigra</i>	RG-I	50 °C EtOH extraction; 100 °C water extraction	Immunomodulatory activity	Complement fixation activity; macrophage stimulating activity	Ho et al. 2016
<i>Terminalia macroptera</i>	RG-I	50 °C distilled water extraction and pectinase degradation	Immunomodulatory activity	Complement fixation activity	Zou et al. 2015
<i>Lessertia frutescens</i>	Galactose-rich RG-I	50 °C and 100 °C water extraction	Immunomodulatory activity	Effect in the complement system	Zhang et al. 2014
<i>Tilia tomentosa</i>	Glucuronidated RGI	100 °C water extraction	Immunomodulatory activity	Stimulating neutrophil and macrophage	Georgiev et al. 2017
<i>Panax ginseng C.A. Meyer</i>	RG-I	100 °C water extraction	Immunomodulatory activity	Stimulating NO secretion and lymphocyte proliferation	Zhang et al. 2012
Potato	RG-I	Modified with pH, heat and enzymes	Antitumor activity	Inducing the detachment of cancer cells and inhibiting the gene expression of ICAM1	Maxwell et al. 2015
Tomato	RG-I rich in galactose	Acetic acid extraction	Antitumor activity	Inhibiting galectin-3; inducing degradation or fragmentation of DNA	Kapoor and Dharmesh 2017
Papaya	AGII	Chloroform and methanol extraction	Antitumor activity	Damaging the interaction of cell lines and EMPs; delaying culture wound healing time	Prado et al. 2017
Ginseng	RG-I	Chemical and enzymes modification	Antitumor activity	Inhibiting galectin-3	Cui et al. 2019
Pumpkin	RG-I with AGI	Low-temperature alkali treatment	Antitumor activity	Inhibiting galectin-3	Zhao et al. 2017
Sugar beet	RGI and HG	Alkali extraction	Antitumor activity	Inducing apoptosis of cancer cells	Maxwell et al. 2016
<i>Lonicera japonica</i>	RG-I	100 °C water extraction	Antitumor activity	Inhibiting the growth of cancer cells	Lin et al. 2016
Okra	RG-I	Hot water extraction	Chronic metabolism disease	Antihyperglycemic effect; decreasing blood glucose level and glucose tolerance; keeping body weight	Liu et al. 2018
<i>Panax ginseng C.A. Meyer</i>	WGPA fraction	Hot water extraction and DEAE cellulose column fractionation	Chronically metabolic disease	Hypoglycemic effect and anti-oxidative activity	Sun et al. 2014
<i>P. ginseng</i>	RG-I	Heat processing	Chronically metabolic disease	Anti-diabetic activity; stimulating insulin release and promoting glycogen synthesis	Jiao et al. 2014
Haw	Pectic oligosaccharide	Acidified water extraction and purification	Chronically metabolic disease	Antihyperlipidemic activity; decreasing fat deposition in liver	Li et al. 2014
<i>Fortunella margarita (Lour.) Swingle</i>	Pectin containing RG-I	80 °C water extraction and fractionation	Chronically metabolic disease	Antihyperlipidemic activity; inhibiting pancreatic lipase activity and binding bile acid	Zeng et al. 2016
<i>Pseudostellaria heterophylla</i>	RG-I and HG	Hot water extraction	Chronically metabolic disease	Hypoglycemic action; Improving cellular exudation of insulin	Chen, Pang, et al. 2018
<i>Acmella oleracea (L.) R.K. Jansen</i>	RG-I	Water extraction	Gastroprotective activity	Protecting the gastric mucosa; reducing inflammatory parameters and oxidative stress	Maria-Ferreira et al. 2018
Prune	RG-I	Water extraction and fractionation	Gastroprotective activity	Keeping the gastric mucosa; inhibiting the lesion area	Cantu-Jungles et al. 2014
Black cummin	RG-I	boiling water extraction with ammonium oxalate	Gastroprotective activity	Ameliorating gastric ulcer; mediating ulcer healing process	Manjegowda et al. 2017
<i>A. vasica</i> leaves	AG	Low-temperature water extraction	Antitussive activity	Inducing cough reflex and specific airway resistance	Chattopadhyay et al. 2011
			Anti-fatigue activity	–	

(continued)

Table 2. Continued.

RG-I pectin source	Key domain	Extraction method	Bioactivities	Possible mechanism	Ref.
<i>Malpighia emarginata</i>	arabinan-rich RG-I	Boiling water extraction	Anti-Alzheimer activity	Suppressing $A\beta_{42}$ secretion in cell lines models	Klosterhoff et al. 2018
<i>Lycium barbarum</i> L.	RG-I	Water extraction, isolation, fractionation			

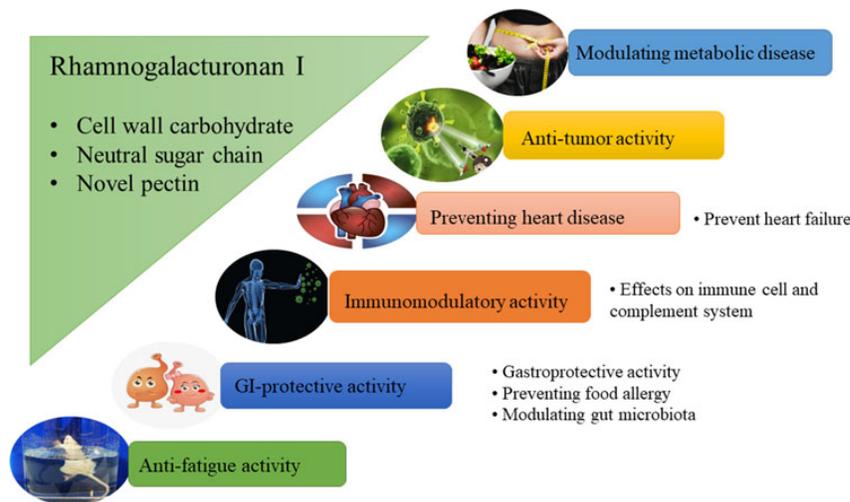


Figure 3. RG-I's effects on human body health.

pectin was able to normalize the fatty acid metabolism (Li et al. 2014). High-fat diet directly induces obesity and it is widely accepted that gut microbiota has a crucial role in this development (Rosenbaum, Knight and Leibel 2015). Pectin containing RG-I regions can modulate the composition of obesity-related intestinal microbiota and increased the production of butyrate, which is a dominant protective agent against obesity. When combined with the prebiotic, *Bifidobacterium longum* BB-46, citric pectin play the predominant role (Bianchi et al. 2018).

Some studies suggest that the mechanism of hypolipidemic action might impact the metabolism of purine, fatty acids, tryptophan, and energy (Niu et al. 2012). After two weeks of supplementing pectin in rats with type 2 diabetes, several potential biomarkers were determined in urine. The results showed increasing of some metabolism products, such as inosine and serotonin, suggesting that pectin may modulate the blood lipid level by regulating the metabolism of DNA, organic acids and steroid hormones. The pear pectin has been reported to lower plasma cholesterol level through the bile acid-binding mechanism (Fernandez, Trejo, and McNamara 1990). Polysaccharides is indigestible in the upper gastrointestinal (GI) tract and passes through to the colon usually as intact molecules (Ding et al. 2019). However, studies suggest that pumpkin polysaccharides, containing high amount of RG-I branching, could significantly decrease the levels of the total cholesterol in plasma (Zhao et al. 2014), suggesting the potential of RG-I to contribute to the reduced circulation of glucose and fatty acids

in vivo. FMPS3 pectin with high RG-I branching might possess anti-hyperlipidemic activity due to strongly inhibiting pancreatic lipase, and the monosaccharide composition, glycosidic linkage, chain conformation, and molecular weight can influence the hypolipidemic activity of pectin fractions (Zeng et al. 2016). Also, the pectic oligosaccharides, containing RG-I regions, have been proved to be able to lower the accumulation of body fat in mice (Li et al. 2010). Moreover, RG-I also show a beneficial effect on nutrient absorption at the epithelial surface. As the abundant compound in the plant-base foods, pectin in the cell wall can bind to intestinal mucin through mucoadhesive interactions or by polymer network cross-linking (Meldrum et al. 2017), facilitating the absorption of smaller molecules like phytochemicals since it takes an extended time for digestive enzymes to break down this complex component.

Gastroprotective activity

The gastrointestinal tract plays a vital role in the digestion of food, and many recent studies have shown that RG-I can protect the digestive system and ameliorate gastric diseases. Dietary fibers cover a broad array of RG-I forms and have been proposed improve the status of the colonic mucus barrier, maintain intestinal integrity, resist bacterial invasion, and prevent inflammation. Dietary fiber deprivation results in damage to the mucus barrier by microbiota and increases pathogen susceptibility (Desai et al. 2016). Soluble dietary fiber from yellow passion fruit peel (PFP) reportedly

possesses gastroprotective activity (Abboud et al. 2019). PFP by oral pretreatment, or by treatment through an intraperitoneal route, significantly reduces gastric ulcer lesions in ethanol-induced gastric-ulcer model of rats by more than 72%. Thus, RG-I can maintain gastrointestinal function through a mechanism of action possibly involving the regulation of mucus, oxidative stress, and inflammatory level. For example, RG-I from black cumin (BCPP) can ameliorate gastric ulcers. BCPP mediates ulcer healing by modulating key molecules involved in gastric ulcers. In a rat ulcer-model, BCPP-fed groups showed up to 85% of gastric ulcer healing (Manjegowda, Rajagopal and Dharmesh 2017). A pectic polysaccharide containing HG and RG-I, from *Ligusticum chuanxiong* effectively promoted intestinal oxidant defense by up-regulating the levels of PGC-1 α (a regulator of ROS scavenging) as well as some antioxidant enzymes (Huang, Cao, et al. 2017). RG-I from the dried fruit of prunes exhibit gastroprotective properties. In an ethanol-induced gastric lesion model in rats, the oral administration of prune RG-I could prevent the necrotic action of ethanol in gastric mucosa, inhibiting the lesion area by 84% (Cantu-Jungles et al. 2014). Pectin from *Sedum dendroideum* leaves and *Opuntia microdasys* var. *rufida* cladodes also exhibits the potential for treating gastritis (Maria-Ferreira et al. 2018). There are some interesting studies on the anti-ulcerogenic activity of the RG-I (RGal) from *Acmella oleracea* (L.) R.K. Jansen. RGal can prevent gastric mucus damage in an ethanol-induced acute lesion model. In a chronic ulcer model, RGal is able to accelerate the healing process by promoting mucus content, enhancing cellular proliferation and suppressing the oxidative stress and inflammatory factors. Moreover, there was no toxicity observed during the period of treatment (Jouini et al. 2018), suggesting the pharmacological potential of RG-I for peptic ulcer.

Immunomodulatory activity

Immunomodulatory activity is a most significant potential application of RG-I pectic polysaccharides, an important bioactive component of plants. A great number of RG-I domains have been reported with potent immunological properties, particularly towards macrophages, lymphocytes and the complement system. For example, two typical pectin fractions, GCP-I-I and GCP-II-I, were extracted from *Gentiana crassi-caulis* roots. Both of these show potent immunomodulatory activity but the GCP-I-I pectin fraction showed three-fold higher potency. Structure analysis revealed that GCP-I-I has a higher molecular weight and contains more RG-I and shorter HG domains, suggesting that the HG regions may reduce the complement fixation activity while RG-I enhance complement activation (Zou et al. 2017). The pectic polysaccharides from *Terminalia macroptera*, also exhibit high complement fixation activity, and structure-activity relationship analysis suggests that RG-I mainly contributes to these activities (Zou et al. 2015). Research on pectin from *Lessertia frutescens* leaves also suggest that RG-I can cause a substantial increase in complement fixing activity. Moreover, galactose-rich RG-I

was thought to be more important based on comparison of different RG-I sub-fractions (Zhang et al. 2014). Pectic polysaccharide fractions rich of RG-I, referred to PLBP-I-I and PLBP-II-I, isolated and purified from the pedicel of the Chinese traditional herb *Lycium barbarum* L, exhibit prominent complement fixating activity and pro-antioxidant defense activity, respectively. PLBP-I-I is rich in branching chains, AG-I and AG-II, which may be responsible for immunomodulation activities (Yao et al. 2018). Similarly, pectic polysaccharide from *Codonopsis pilosula* Nannf. var. *modesta* L.T. Shen roots possess excellent immunological activity, which was mainly found in the rhamnose rich regions of pectin (Zou et al. 2014a). RG-I containing high amount of arabinose and galactose from *Nerium indicum* flowers mediates the immune system by stimulating the NO production of macrophages (Dong et al. 2010). PAPS-1 and PAPS-2, two RG-I pectic polysaccharides from *Prunus avium* with high levels of arabinose were also able to significantly induce the release of NO in RAW264.7 cell lines and various immune factors, such as IL6, IL10 and TNF- α (Cao et al. 2018). Two unusual RG-I pectins, PSII and PSIII, were obtained from silver linden flowers, and they appeared to be highly acetylated and glucuronidated. These immune-active compounds can exert significant immunomodulatory bioactivity by stimulating neutrophils and macrophages and suppressing tumor cell lines (Georgiev et al. 2017). In addition, an *in vivo* study unraveled that anti-inflammatory activity of pectin can results in excellent inhibition on xylene-induced ear edema and carrageenan-induced paw edema (Jouini et al. 2018), which might be attributed to the effective regulation of intestinal immunology (Sheng et al. 2017).

It is interesting that the AG-I and AG-II side-chains in RG-I display prominent immunomodulatory activity. These siechains play really important a role for RG-I's function. RG-I regions, sub-fraction-I and sub-fraction-II, were obtained from elderflowers through 50% EtOH, 50 °C water, 100 °C water extraction followed by enzymatic hydrolysis of endo- α -D-(1-4)-polygalacturonase. Then the complement fixating and macrophage stimulating tests were employed to better understand the structure-immunomodulatory activity relationship of these fractions. Interestingly, the sub-fraction-I, containing more RG-I regions with large amounts of AG-I and AG-II, showed higher bioactivity than the starting pectin or other fragments (Ho et al. 2016). The RG-I pectin from leaves, stem bark and root bark was examined and root bark RG-I, having both AG-I and AG-II, exhibited the highest complement fixing bioactivity (Zou et al. 2014b). Rose petal waste can also provide RG-I pectins, having potent intestinal immune system modulating activity, and type II side-chains of arabino-3,6-galactan was the most active fraction (Slavov, Kiyohara and Yamada 2013). Likewise, RG-I from the inner bark of Norway spruce also showed potent complement fixation and microphage stimulation bioactivity, and there were large amounts of highly-branched arabinans but the actual bioactive domain was not determined (Le Normand et al. 2014).

Interestingly, RG-I may selectively act on certain targets and introducing different blocks could result in different immune effects. Studies focusing on different domains in RG-I suggested special effects. For example, there is an RG-I fraction with long type II arabinogalactan (AG-II) side chains that exert potent immunological activity by stimulating the proliferation of lymphocytes, the phagocytosis of macrophage and nitrite production. The removal of Ara residues increases the activity of macrophage phagocytosis while reducing the effects on lymphocytes and nitrite production (Zhang et al. 2012), consistent with the structure-immunological activity relationship of bee pollen RG-I (Li, Yang et al. 2018). It is likely that both galactose and arabinose have their own individual targets. RG-I from *Diospyros kaki* also exhibits potential immunoinhibitory activity, but selectively suppresses LPS-induced B lymphocyte proliferation and is unable to inhibit ConA-induced T lymphocyte proliferation (Duan et al. 2010). Similarly, some pectins exhibit immunomodulation activity while only acting on the complete system and do not activate macrophages (Tvete Inngjerdingen et al. 2013). Moreover, RG-I extracted from alfalfa (*Medicago sativa* L.) stem shows immunomodulatory activity owing to its suppression on mRNA expression of certain pro-inflammatory cytokines (Chen et al. 2015). Most interestingly, some studies, focused on gut microbiota degradation of pectin, implicate RG-I exerting immunomodulatory ability by promoting anti-inflammatory commensal microbiota (Chung et al. 2017). Thus, it is truly essential to identify the detailed action mechanism of RG-I on immunomodulation activity.

There are some *in vivo* study about the immunomodulatory activity of RG-Is. For instance, the RG-I substituted by glucuronic acid in okra polysaccharide, named RPS-2, not only exhibit modulation effects on RAW264.7 macrophages *in vitro*, but also improve the spleen index and thymus index in mice of immunosuppression. And after treated with RPS-2, the cytokine level could be modulated in murine serum (Chen et al. 2016). Recently, ginseng RG-I pectin has been proved to exert modulatory activity on tumor immune tolerance in mice. It mainly targeted on T cell in immune system and the studies revealed that only T-cell apoptosis was inhibited without any effects on T-cell activation (Xue et al. 2019). These studies really plays a role in the selective effects research of RG-I's activities.

Anti-tumor activity

Cancer is a devastating disease with high mortality rate. Many studies have demonstrated that RG-I pectin as well as its synthesized branches can effectively suppress the growth of cancer cells through tumor growth inhibition, anti-metastasis activity, regulating gene expression, and immunology system (Han et al. 2018; Xue et al. 2019; Cai et al 2017). For example, RG-I reportedly reduces the proliferation of cancer cells by inhibiting the gene expression of Intercellular Adhesion Molecule 1 (ICAM1), which directly results in cell detachment. While RG-I containing HG segments exhibit enhanced bioactivity, the detailed structural requirements

for RG-I activity has not been determined (Maxwell et al. 2015). RG-I-AG from tomato pectin (SrTPO1) is an efficient inhibitor for gastric cancer. Tomato RG-I at 30 $\mu\text{g}/\text{mL}$ concentration can achieve 70% inhibition of the gastric cancer cell AGS with normal-NIH3T3 cells being unaffected. SrTPO1 also induces apoptosis of cancer cells and this degradation or fragmentation of DNA might be one possible mechanism (Kapoor and Dharmesh 2017). Similarly, swallow root pectic polysaccharide (SRPP) inhibits B16F10-mouse melanoma cells, and the data indicate that a Gal-3 blockade, attributable to the RG-I regions in SRPP, was responsible for this anti-metastatic activity. And the presence of arabinose and galactose, as well as their precise sequence and distribution are important for pectin bioactivity (Venkateshaiah et al. 2017). Pectin undergoes depolymerization during fruit ripening, which changes its bioactivity. Studies have shown that pectin from intermediate phases of papaya ripening maintains its AGII in RG-I regions, and, thus, retains significant anticancer activity resulting from its damaging to the interaction of cell lines and EMPs (extracellular matrix proteins), and through promoting cancer cell detachment, apoptosis, necrosis, and delaying culture wound healing time (Prado et al. 2017).

Galectin-3 (Gal-3), a nucleo-cytoplasmic β -galactoside specific lectin, plays significant regulatory roles in tumor progression, promoting cancer cell invasion, transformation and migration by binding carbohydrate moieties on the cell surface (Dange et al. 2014). Targeting on this unique carbohydrate binding protein has emerged as a new strategy for some diseases and galectin-carbohydrate interactions are commonly associated with cancer treatment (Laaf et al. 2019). RG-I pectins from myriad of sources, including pumpkin RG-I, citrus RG-I, and ginseng RG-I, exhibit excellent Gal-3 binding activity (Zhao et al. 2017; Zhang, Lan, et al. 2016; Zhang et al. 2017; Gao et al. 2013). Three RG-I fractions obtained from Panax ginseng flower buds possessed excellent activities as a Gal-3 binders with dissociation constant (K_D) values of 4.9 μM , 0.71 μM and 0.24 μM , while the HG pectin shows weak or no binding with Gal-3 (Cui et al. 2019). The RG-I-4 in ginseng pectin is reportedly the strongest Gal-3 binder (Gao et al. 2013). The MIC of RG-I-4 measured by Gal-3-mediated hemagglutination assay was 0.25 $\mu\text{g}/\text{ml}$ as determined in SPR experiments and the K_D was 22.2 nM for RG-I-4, whose binding affinity of Gal-3 was higher than any other pectic fractions (Gao et al. 2013). Studies targeting the modified citrus pectin also suggested the importance of RG-I against Gal-3 (Zhang, Lan et al. 2016). This study demonstrate that RG-I-rich pectins with 1,4-linked β -galactan side-chains possess more activity than the other RG-I-rich and HG-rich pectins.

Nowadays, several approaches have been developed to enrich RG-I regions in pectin and enhance the anti-tumor activities of these pectin fractions. Modified citrus pectin (MCP), a Gal-3 binder, was employed as a new radiosensitizing agent for ionizing radiation (IR) (Conti et al. 2018), suggesting yet another application for RG-I pectin. The effects on prostate cancer (Pica) were evaluated by combining IR with MCP and the findings demonstrated MCP

inhibited the expression of anti-apoptotic Gal-3, causing Pica cells more sensitive to IR. One chemically modified RG-I, SRO1 obtained from swallow root, possessed potential anti-Gal-3 activity, inhibiting Gal-3-mediated cancer progression. SRO1 could effectively restrain the Gal-3 mediated agglutination with an MIC value of 1.08 µg/mL. Moreover, SRO1 was able to down regulate the gene expression of Gal-3 as well as other proteins in the cancer promoting pathway (Mallikarjuna and Dharmesh 2018). Modified pectic polysaccharide from turmeric (MTrPP) exhibited binding to Gal-3, even though MTrPP contained high amounts of HG Galactans in side-chain of RG-I acted as the key factor inhibiting the inflammatory marker, Gal-3, inducing higher anti-ulcer potential (Harsha, Prakash and Dharmesh 2016). Modified apple pectin, containing high amounts of galactose indicating the presence of RG-I, significantly reduced the tumor development in a mouse model of colon cancer. The potential mechanism was suggested to be the binding between RG-I and Gal-3 (Yu et al. 2010). Moreover, there were some excellent *in vivo* studies suggesting MCP's activity against Gal-3 (Li, Yang et al. 2018). With the MCP-supplemented drinking water, mice treated by cisplatin injection exhibited attenuated renal fibrosis and increased renal function, due to the protective of Gal-3 inhibition.

However, there are some literatures holding conflicting findings about Gal-3 inhibitor. Okra RG-I plays a pivotal role in antiproliferative and pro-apoptotic effects on B6F10 melanoma cells (Vayssade et al. 2010). It significantly reduces cells aggregation *in vitro* and increases apoptotic cells. However, all these results occurred at a higher expression of Gal-3. This suggests that RG-I might activate other key molecular signal pathways by binding with Gal-3 through its short galactan side-chains. Though high combination affinity can be observed, it has been reported that Gal-3 is not involved in the cell migration inhibition by RG-I-rich pectins (Fan et al. 2018). Also, some modified polysaccharides used in clinical trials make effects only at high doses, such as GCS-100, implying action without targeting of Gal-3 (Laaf et al. 2019). In this case, specificity is the most important factor in research about the activity of galectin-3 and normal body function, because at least 15 galectins have been reported to be able to bind beta-galactose (Heusschen, Griffioen and Thijssen 2013). So most *in vitro* study can not exclude the possibility that other galectins participate the interaction with MCP. Thus, more systematic investigation of *in vivo* studies are certainly needed to better understand the potential mechanism of antitumor activity by RG-I pectin and whether Gal-3 could be the reasonable target need more strong evidence.

Preventing/controlling heart disease

Heart diseases is one of the leading causes of death in the world and pectin has been recommended as a dietary change associated with decreased risk of cardiac disease. The effect of pectin on low density lipoprotein (LDL) metabolism has been investigated in the male guinea pigs. By dietary supplement of 1% pear pectin, a 33% decrease was observed

in LDL levels (Fernandez, Trejo, and McNamara 1990), which might be due to the altered hepatic cholesterol homeostasis (Fernandez et al. 1994). Moreover, MCP, the modified pectin, could improve cardiac function in heart failure rabbits (Li, Li, et al. 2019). MCP can down-regulate Gal-3 effect as an inhibitor (Ibarrola et al. 2018), due to the galactose sidechains in RG-I regions. Observational studies have determined the effects of Gal-3 on extracellular matrix synthesis of cardiac fibroblasts suggesting a possible mechanism (Stoltze Gaborit et al. 2016; Luo et al. 2017). Researchers have recently investigated Gal-3 modulation of oxidative stress to promote cardiac inflammation and fibrosis. Similarly, Gal-3 positively correlates with peroxide and negatively correlates with antioxidant levels in patients with aortic stenosis. MCP is recommended as an excellent Gal-3 inhibitor and contains high amount of galactan side-chain of RG-I that can specifically bind to the CRD region of Gal-3, thus inhibiting cardiovascular remodeling in animal model of diet-induced obesity (Martinez-Martinez et al. 2015).

Other activities

Many new human health benefits for RG-I have been investigated in recent years. For example, in a weight load swim test, designed to determine the anti-fatigue activity in mice, supplementation with an arabinan-rich pectin from acerola, could lengthen swimming time and promote the respiratory capacity of muscle and the antioxidant status (Klosterhoff et al. 2018). Okra RG-I also showed anti-fatigue activity. The results of weight-loaded mouse swimming test showed that okra RG-I-treated mice keep swimming for a longer time, and RG-I regulation of serum urea nitrogen, blood lactic acid and glycogen synthesis were also observed in this study (Gao et al. 2018). More interestingly, RG-I were found to play a role in for preventing food allergies (Golovchenko et al. 2012). The polysaccharides extracted from onion, mainly containing RG-I regions, can significantly decrease absorption of ovalbumin (OVA) in digestive tract, which is the dominant allergen in egg white, and as a result, the serum OVA level in mice administrated with onion RG-I was threefold lower compared with the control group. Moreover, it has been revealed that *Arctium lappa* L pectin, containing 59.2% RG-I, could exhibit anti-constipation activity by modulating gastrointestinal transit and defecation function (Li, Zhu et al. 2019). RG-I also can potentially impact bronchial disease. Arabinogalactan (AG) of RG-I from *Adhatoda vasica* has the potential for being an antitussive drug. Test results suggest that oral administration of AG reduced the cough times in guinea pigs, possibly through bronchiectasis warranting further studies (Chattopadhyay et al. 2011).

The study of structure-activity relationship should be the focus of research on RG-I's health effects. When an RG-I is obtained from a single source, different regions can exert different effects. Since RG-Is come from a myriad of dietary sources, it is likely that similar structures result in similar activities. For example, RG-Is enriched with AG-I and AG-

Table 3. Gut microbiota and degradation of the RG-I substrates.

Phylum	Species	PUL	CAZymes	Primary substrate	Ref.
Bacteroidetes	<i>B. thetaiotaomicron</i>	Ara-PUL	BT0360 and BT0367 (α -1,5-arabinanases)	Arabinan	Luis et al. 2018
		Gal-PUL	Endo-galactanase BT4667 (β -1,4-galactosidase)	Galactan Galacto-oligosaccharide	
		RGI-PUL	Endo-PLs BT4146, BT4153 and BT4149 (GH28 rhamnogalacturonidases)	RG backbone [β -GalAp- α -1,2-l-Rhap] _n (n \geq 2) RG-I	
Bacteroidetes	<i>B. thetaiotaomicron</i>	BT4145-83	–		Martens et al. 2011
		BT4667-72	–	Galactan	
		BT0348-69	–	Arabinan	
		BT0262-90	–	Arabinogalactan	
Bacteroidetes	<i>R. intestinalis</i> XB6B4 and <i>E. rectale</i> A1-86	Ros-5	GH2, GH3, GH8, GH42, GH43, GH53, GH115, GH51, GH127	Xlyan Arabinogalactan	Sheridan et al. 2016
		Ros-8	GH51, GH127	Arabinan	
		Ros-9	GH2, GH5, GH53, GH130, CE1F	Arabinogalactan Glucomannan	
		Eub-2	GH2, GH53	Arabinogalactan	
Bacteroidetes	<i>B. thetaiotaomicron</i> <i>B. vulgatus</i> <i>B. ovatus</i>	–	–	Rhamnogalacturonooligosaccharides	Van Laere et al. 2000
Firmicutes	<i>M. pectinilyticus</i>	Pectin clusters	PL9, PL11, GH43, GH97, GH105	Arabinan; Rhamnogalacturonooligosaccharides	
Firmicutes	<i>E. eligens</i>	–	GH28, GH105, PL1, PL9, CE1, CE12	RG; arabinan; Galactan	Caroline et al. 2019
Firmicutes	<i>Faecalibacterium prausnitzii</i>	–	–	Pectic oligosaccharides	Chung et al. 2017
Firmicutes	<i>Bifidobacterium longum</i> B667	–	α -L-Arabinofuranosidase	Pectin; galacturonic acid	Lopez-Siles et al. 2012
Actinobacteria	<i>Bifidobacterium longum</i> B667	–	α -L-Arabinofuranosidase	Arabinan	Margolles and los Reyes-Gavilan et al. 2003

orderly cooperation of the microbiota within and outside the mucosal layer. Generally, macromolecular glycans are degraded into oligosaccharides by anaerobic bacteria and then the various oligosaccharides are transported into the periplasm through Sus_{C_H}-Sus_{D_H} transporters, which are encoded by each pectin PUL and are specific for the target glycans. For instance, only the BT0363–BT0364 complex encoded by Ara-PUL displays the affinity for arabinooligosaccharide products (Luis et al. 2018).

With respect to the degradation of RG-I, various carbohydrate enzymes are encoded by different PULs from each strain and the coordinated metabolism of several species are prominent features of glycan utilization. The elaboration of enzymes enables the removal of different domains inside the RG-I region. Some target the arabinan and galactan, while others are responsible for exposing the rhamnogalacturonan backbone. Some organisms can also release the acetyl groups, contributing to the backbone degradation.

The degradation of RG-I backbone is initiated by endo-PLs encoded by RGI-PUL in *Bacteroides*, which resides in the colonic mucosal layer. The rhamnogalacturonan lyase BT4170 was viewed as an important RG-I-degrading enzyme. This enzyme has a conserved structure and specificity determinants locating outside the active sites distinguish it from the HG lyase for targeting RG-I. In addition, extracellular β -1,4-galactanases are able to partially prune the RG-I side-chains (Sheridan et al. 2016). Oligosaccharides entering the periplasm are then cleaved by exo-GHs

with different specificities, ensuring the occurrence of (Rha-GalA)_n polymer in concert with side-chain removal. Then the rhamnosidase or the rhamnogalacturonidases from the GH105, GH106 and GH28 family target the resultant oligosaccharides of DP \geq 2 or enable the cleavage of terminal L-Rhap residues. In addition to the depolymerization of backbone, RGI-PUL also encodes some enzymes like BT4175 to remove single sugar side-chains appended to rhamnose units (Luis et al. 2018). Recently, a novel glycan-degrading bacteria, *Monoglobus pectinilyticus*, has been found with a highly specialized glycomiome for RG-I degradation, which a unique distribution of CAZyme genes within its genome. The *M. pectinilyticus* depolymerizes RG-I with increasing oligosaccharides accumulation, but no L-Rhap monomers are observed, suggesting the lack of rhamnosidase-related genes (Caroline et al. 2019), also illustrating the significance of gut microbiota symbiosis. No growth of *M. pectinilyticus* has been observed on the galactan and arabinan side-chains but it shows highly specific targeting of rhamnogalacturonan backbone. Moreover, it has been observed that some species of HGM *Firmicutes*, the presence of which is related to obesity, can not utilize the RG-I due to the lack of genes encoding RG-I lyases (Wegmann et al. 2014; Desai et al. 2016), suggesting the potential of RG-I to resist the pathogen invasion.

For the degradation of side-chains, transcriptomic analysis has identified the PULs activated by galactan and arabinan (Martens et al. 2011). The GH2 β -galactosidase and a

surface GH53 endo- β 1,4-galactanase was encoded by the *B. thetaiotaomicron* Gal-PUL, which can coordinate to hydrolyze galactan into galactose (Luis et al. 2018). But there still be other large number of *B. thetaiotaomicron* β -galactosidases that remain unknown. The Gal-PUL in other *Bacteroides* species encode a new carbohydrate-degrading enzyme, GH147 β -galactosidase, which also plays a critical role in galactan metabolism (Luis et al. 2018). Similarly, a *R. faecis* strain, which has a gene encoding an endo- β 1,4-galactanase, is capable of growing on galactan and several species were able to utilize the type 2 arabinogalactan (β -1,3-galactan backbone) and type 1 arabinogalactan (β -1,4-galactan backbone) (Sheridan et al. 2016). A metabolic pathway for galactan in *Bifidobacterium* species had been described that contains GH53 and GH42 galactosidase to degrade galactan into galactose (Gibson et al. 2017; Motherway, Fitzgerald and Van Sinderen 2011). It is noteworthy that the galactan of RG-I promotes the co-existence of different organisms without competition since some *Bifidobacterium* species can only grow on the galacto-oligosaccharides produced by *B. thetaiotaomicron* within the same niche (Luis et al. 2018). With respect to the depolymerization of arabinan, approximately 60% of *Bacteroides* species exhibit growth on the arabinose polymer. The arabinan degradation is initiated by two surface enzymes, BT0360 and BT0367. Both are α -1,5-arabinanases, which display exo- or endo-processing activity to cleave arabinan side-chains, and then L-arabinofuranosidases from GH51 and GH146 depolymerize these oligosaccharides in the periplasm (Luis et al. 2018). *B. thetaiotaomicron* reveals three GH43 enzymes that can target decorated and linear arabinan (Cartmell et al. 2017). The PUL of Ros-8 in *R. intestinalis* XB6B4 and *E. rectale* A1-86 utilize arabinan as its substrate (Sheridan et al. 2016). Moreover, *Bi. Breve*, *Bi. Adolescentis* and *Bi. longum* can also ferment arabinan oligosaccharides to some extent (Van Laere et al. 2000; Margolles and de los Reyes-Gavilan 2003). The galactose and the arabinose, produced in the periplasm, play a very important role for the colonization of some health-beneficial organisms.

With the increasing studies on the probiotic function of RG-I, more and more human gut microbiota that can degrade RG-I have been discovered. The discovery of various RG-I-PUL helps to clarify mechanism of pectin degradation. Recently, many studies have shown that RG-I can fill the nutrient-niche of a variety of beneficial bacteria, thereby maintaining the stability of the flora and resisting the invasion of pathogens (Maltby et al. 2013; Conway and Cohen 2015). Thanks to the HGM, human beings can benefit from an RG-I-rich diet.

Food-based properties

Traditional commercial pectin mainly consists of HG segment and the high temperature and acid extraction conditions can lead to the destruction or loss of RG-I structure. Thus, the application of RG-I in the food products was previously ignored. In recent years, more attention has been paid to RG-I as it has been reported that RG-I is an integral

part of pectin and participates in the good performance of pectins within food products. Research suggests that tomato fiber pectin containing RG-I might be utilized in the low fat beef burger as fat replacer (Namir, Siliha and Ramadan 2015). Moreover, pectin extracted chemically from the husk tomato waste shows a good fit to the Cross gel model with thermostable property, suggesting the potential application in food formulation (Morales-Contreras et al. 2018).

In food industry, pectins are used as stabilizers, thickeners and gelling agents, while pure RG-I shows poor gelling property. Nevertheless, it has been reported that the branching degree can influence rheology properties by participating in the entanglements. Some research has studied the impact of RG-I side-chains on gelling properties. Debranched pectin exhibits an obvious decrease in gelling temperature and strength, suggesting that RG-I side-chains might play a significant role on polymer rheology (Souza et al. 2015). The water-soluble mucilage, extracted from the leaves of *Hoheria populnea*, has been shown to contain several structurally discrete RG-I type polymers having similar viscoelastic behaviors with intermolecular entanglement property of linear region. Mucilage exhibits rheological behavior with little pH dependence, which is advantageous in industrial applications as a food ingredient (Sims et al. 2018). Moreover, new applications for RG-I pectins are constantly developing and its potential as a fat replacer is one of the newest ones. RG-I pectin recovered from citrus canning wastewater has been used as a fat alternative in ice cream. When 0.72% RG-I is added, fat content can decrease by 45%. This accompanied by high scores in surface color, flavor and textural hardness compared with commercial ice cream, suggesting the potential value of RG-I pectin in low calorie foods (Zhang et al. 2018b).

Concluding remarks

RG-I pectins are the constituents of primary cell walls in a variety of fruit and vegetables within food products. In addition to the significance in foods, a growing body of evidence indicates that because of their special structure RG-I pectins possess a wide array of interesting beneficial health properties such as hyperglycemic and gastroprotective activities. However, there are still a few challenges for developing RG-I as functional dietary ingredient.

1. A novel targeted-RG-I extraction method needs to be conducted to obtain pure RG-I for a complete study of its structure-activity relationships. To date, most of studies were performed on RG-I enriched pectin, where other segments including HG or RG-II can influence these activity studies. RG-I pectins has been extracted from various sources by different methods making it hard to compare structures and activities.
2. An understanding of the fine chain structure of RG-I is necessary for further verifying the mechanism and molecular origins of its bioactivities. So far, the most common approaches, HPLC and NMR, only can

provide the general information and the fine chain structure of most RG-I pectins have not yet been unraveled.

3. Since the gastrointestinal tract is critical for RG-I absorption and metabolism, the impact of complex food systems and its co-digestion with other food components needs to be further investigated. It is also necessary to study what form of RG-I is absorbed by the digestive system.
4. The apparatus by which different HGM phylum (more than one phyla, Bacteroidetes) metabolize RG-I is only poorly understood. Thus, the function of specific PULs needs to be characterized.
5. A combination of molecular, chemical and biochemical approaches will be necessary to fully understand the activity of RG-I. The in vitro methods are lack of synergistic or antagonistic effects, which cannot simulate the internal environment of human body. Thus, in vivo models are required to verify RG-I bioactivity and to determine potential mechanisms of action.

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