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# NUTRITION AND IMMUNOMODULATION - FOCUS ON THE DIETARY FIBER RG-I

## RHAMNOGALACTURONAN-I TRAINS THE IMMUNE SYSTEM AND ACCELERATES IMMUNE RESPONSES

**KEYWORDS:** RG-I, nutrition, immune, microbiota, prebiotic, quality-of-life.

## ABSTRACT

Good nutrition is vital for maintaining health and supporting optimal immune function. Several essential micronutrients are known to contribute to normal functioning of the immune system and may carry health claims on products when they contain meaningful amounts. Certain dietary fibers, for example pectic polysaccharides from carrot that are rich in rhamnogalacturonan-I (cRG-I), have also been shown to play an important role as they can educate, regulate, and modulate immune cell responsiveness. The aim of this paper is to provide an overview of the scientific evidence supporting the immunomodulatory role of RG-I via nutrition.

### INTRODUCTION

A healthy immune system is a resilient system that manages daily challenges while maintaining responsiveness within a normal range and minimizing the notable impact of infections (1). Factors that can negatively impact the resilience of the immune system include ageing, an unhealthy diet and lifestyle, malnutrition, (chronic) illness, and medication (e.g., antibiotics). Good nutrition is one of the key factors that can positively influence the immune system. A nutritious diet provides a balanced supply of (micro)nutrients and is essential for maintaining health. While vitamins A, B6, B12, C, D, E, folate and zinc, copper, selenium, and iron support the normal function of the immune system (2–15), other food components and especially specific (non-digestible) dietary fibers can play an important role in the education and regulation of immune responses, both locally in the gut and beyond the gut in the rest of the body (16–18). Everything that is eaten is sampled by immune cells located in and around the small intestine, recognition of specific 'patterns' can result in priming or training and subsequent modulation of immune responsiveness (19). The sort of food that is eaten also influences the composition and function of the gut microbiota, e.g., dietary fibers increase the abundance of beneficial microorganisms which can lead to the production of active metabolites like short chain fatty acids (SCFA) (17).

### WHAT IS RG-I AND WHY IS IT SPECIAL?

RG-I is a domain within a pectic polysaccharide consisting of a backbone of galacturonic acid and rhamnose disaccharide repeating units. It constitutes 15-35% of the pectin molecule, depending on the plant source, and it is highly branched and naturally embedded in the pectinaceous network of plant cell walls (20–23). Extraction processes can differ depending on the plant source, to obtain RGI from carrots the process starts with steam peeling and pressing the carrots to remove the juice. Then an aqueous extraction in the presence of food-grade pectinolytic enzymes releases RG-I from the carrot pomace. After decanting and filtration, to remove non-soluble residues and small molecules, the cRGI enriched extract is pasteurized and spray-dried (24). The plant source as well as the extraction method determines the structure and functional properties of RG-I-enriched extracts (25–28). For example, cRG-I is not digested in the upper gastrointestinal tract (GIT) (29) and can be sensed by pattern recognition receptors (PRR) on innate immune cells located in and around the small intestine (30). Several studies have demonstrated that RG-I-enriched polysaccharide extracts modulate innate immune function in *in vitro* assays, in animal studies and in clinical trials following dietary supplementation (26, 31–34).

A prebiotic ingredient is a non-digestible polysaccharide that is not hydrolyzed by the host but fermented by the gut microbiota and is defined as "a substrate that is selectively utilized by host microorganisms conferring a health benefit" (35). The degradation of the complex structure of RG-I requires the cooperation between different gut commensal bacteria, including primary and secondary degraders such as *Bacteroides* or *Prevotella* species combined with secondary degraders such as *Bifidobacterium* species.

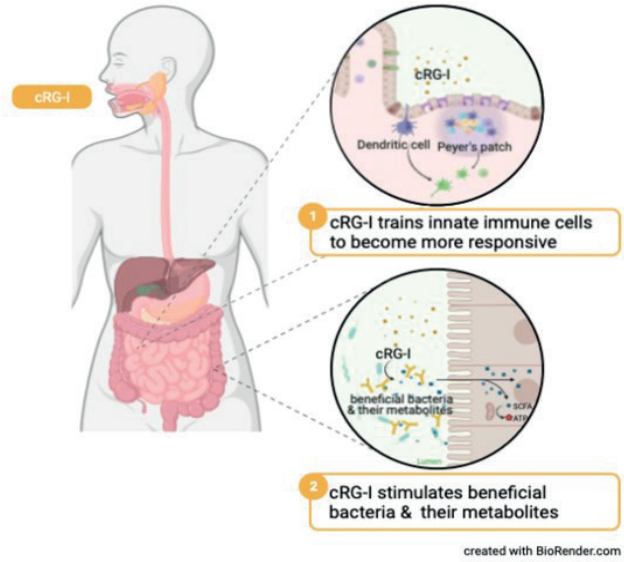


**Figure 1**. RG-I has a dual mode of action: (1) it is sensed by PRR on immune cells that sample the gut content as it passes through the small intestine; (2) RG-I is degraded by the microbiota which increases the abundance of beneficial bacteria, especially bifidobacteria, and increases the production of SCFA exerting pleiotropic effects that are beneficial for health.

The abundance of bifidobacteria, known for their local and systemic health-promoting effects, appears to be systematically increased in the presence of cRGI, revealing prebiotic properties already at a very low dose. The fermentation of cRG-I by the gut microbiota also leads to increased levels of SCFA, mainly acetate and propionate with some butyrate (16,29,32,36). Interestingly, unlike some less structurally complex dietary fibers, the fermentation of cRG-I by the gut microbiota does not lead to high levels of gas production, suggesting that unfavorable side-effects like bloating and abdominal pain might be less after consumption of cRG-I (29).

**Evidence supporting immunomodulation via nutrition**

***In vitro***: Extracts enriched with RG-I have been reported to enhance innate immune cell functions such as phagocytosis and natural killer cell activity *in vitro* (26,32,34,37). Cultures of isolated human peripheral blood mononuclear cells (PBMC), whole blood, cell lines or *ex vivo* immune cells (e.g., peritoneal macrophages) have been used as models to show that RG-I domains modulate immune functions such as the secretion of cytokines, chemokines, and reactive oxygen species (32,38,39). In PBMC cultures from healthy donors (i.e., no known micronutrient deficiencies) further supplementation with a selection of well-known immune supporting micronutrients (vitamin C, vitamin D and zinc) at doses reflecting 15-30% of the recommended daily allowance did not enhance immune function (Figure 2, left). In fact, maximum responses of these micronutrients did not exceed 3% of the cRG-I response. In contrast, the addition of cRG-I clearly induced a strong dose dependent increase in levels of selected pro- and anti-inflammatory cytokines (TNFa, IL-10, IL-6 and IL1b) (Figure 2, left). This supports the notion that, in a well-nourished (healthy) state, the intake of cRG-I works complementary to the intake of vitamins and zinc and enhances immune function.

Experiments in models that mimic the human GIT have shown that RG-I is rapidly fermented leading to the production of SCFA (Figure 2, right). The immunomodulatory role of SCFA has been described extensively. Briefly, SCFA are used as a major energy source by epithelial cells lining the gut, and they influence the expression of genes that are necessary for gut barrier and defense functions. SCFA modulate innate immune cells such as neutrophils, macrophages and DCs as well as T-cells and B-cells of the adaptive immune system (17,18). In a Caco-2/PBMC co-culture model of a gut barrier challenged by an inflammatory stressor, the metabolite pool resulting from the fermentation of RGI (containing SCFA and other metabolites) increased barrier integrity and decreased levels of pro-inflammatory mediators (29).

The *in vitro* evidence supports the postulate that RG-I has a dual mode of action, with a direct immunomodulatory effect on innate immune cells, and an indirect effect via modulation of the gut microbiota composition and production of metabolites including SCFA.

***In vivo* (animals)**: Research by Sun et al. showed that dietary intake of a polysaccharide extract derived from carrot pomace, which is likely RG-I based on the extraction method described by the authors, improved influenza vaccine efficacy in immunosuppressed mice via the activation of early innate immune responses (33). This carrot pomace polysaccharide (CPP) extract partially restored the immunosuppressive effect of cyclophosphamide with respect to the production of antibodies following an influenza vaccination. Increased activation of early innate immune responses mediated by dendritic cells and natural killer cells was observed in the mice that received the CPP extract in their diet.

Dietary intake of RG-I from bell pepper protected mice from the effects of a gastrointestinal infection caused by *Salmonella enterica* serovar Enteritidis (manuscript in preparation). RG-I provided colonization resistance, increased levels of IgA and decreased levels of systemic pro-inflammatory cytokines while increasing levels of the anti-inflammatory cytokine IL-10. In this study RG-I also modulated the gut microbiota composition with increased levels of bacteria that are recognized as beneficial for health, including bifidobacteria.

Importantly, these preclinical studies demonstrate that the ingestion of RG-I enhances natural immune function and modulates the gut microbiota *in vivo*.

***In vivo* (humans)**: In a proof-of-concept study in healthy volunteers, dietary supplementation with RG-I from bell pepper stimulated a dose-dependent increase in innate immune responsiveness after 4 weeks as assessed by phagocytic activity (32). In another randomized double-blind, placebo-controlled study in healthy volunteers, cRG-I was shown to accelerate and augment innate immune and anti-viral interferon responses to an immune challenge with a rhinovirus infection after 8 weeks supplementation (Figure 3, top) (31). Daily consumption of cRG-I also enhanced *ex vivo* immune responses of NK cells in blood (40). The immunomodulatory effects of cRG-I resulted in reduced severity (up to 33%) and duration (up to 3 days) of symptoms as well as a reduction in the negative effects of a common cold on quality of life, as depicted in figure 3 (bottom (31, 40).

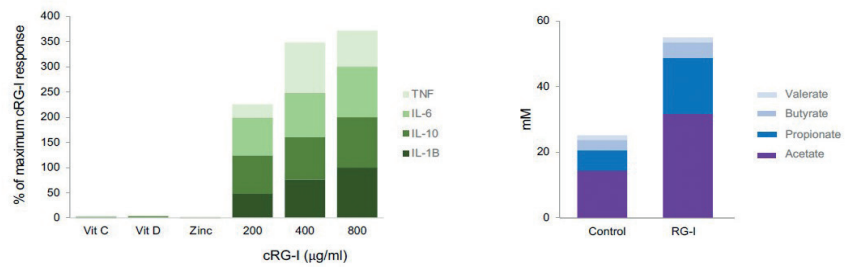


**Figure 2.** Left: Immunomodulatory effects of micronutrients and cRG-I (µg/ml) in PBMC from healthy donors. The following ranges were measured in this assay: TNFa from 18-72 pg/ml; IL-10 from 11-14 pg/ml, IL-6 from 1306-1742 pg/ml and IL-1b from 6-17pg/ml. Micronutrient responses were lower than 3% of the maximum cRG-I response for all cytokines assessed. Average from three healthy donors normalized to maximum cRG-I response per cytokine. Right: RG-I is fermented by the intestinal microbiota *in vitro* resulting in the production of beneficial metabolites like SCFA.

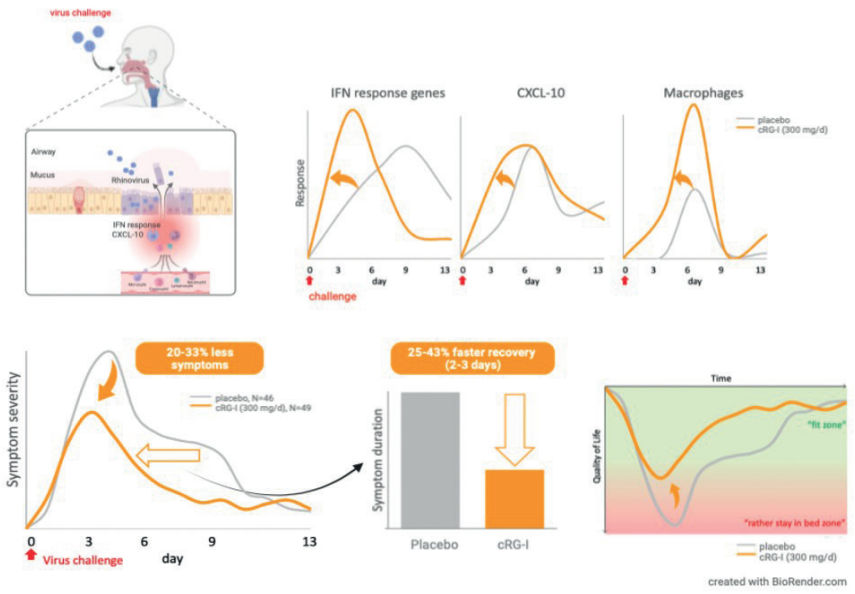


**Figure 3**. Dietary supplementation with 300mg/day cRG-I accelerates protective anti-viral immune responses in healthy volunteers challenged with a rhinovirus infection (top) leading to (20-33%) less severe symptoms, (28-43%) shorter duration and less impact on quality of life (bottom).

Changes in the fecal microbiota composition were also observed in studies following dietary intake of RG-I from bell pepper and carrot, as shown by an increase in health-promoting bifidobacteria with concurrent increases in propionate and butyrate producing metagenomic species (manuscript in preparation). As a consequence, the increased abundance of beneficial bacteria and the production of SCFAs following the dietary intake of RG-I can positively influence gut homeostasis and immune responsiveness.

## CONCLUSIONS

These studies support the notion that dietary RG-I is sensed by immune cells located in and around the small intestine which leads to priming or training of these cells. RG-I is also fermented by the gut microbiota resulting in the increased abundance of health-promoting bifidobacteria and the production of active metabolites like SCFA. The primed immune cells and some of the SCFA reach other parts of the body via the lymph and blood circulation where – in the event of an immune challenge like an infection – they can modulate responsiveness, for example by accelerating protective anti-viral responses which result in perceivable health benefits such as reduced severity of symptoms, faster recovery, and maintenance of quality of life (19,31,40).

Whole diets, individual (micro)nutrients and specific dietary fibers such as cRG-I have all been shown to influence distinct aspects of the immune system. Nutrition is clearly a key modifiable factor that affects immune function and can help to maintain homeostasis and to increase the resilience of the immune system, which is reflected as immune fitness and a healthy state of wellbeing.

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**Ruud Albers** founded NutriLeads in 2012 and is Chief Scientific Officer. Previously, Ruud successfully built and led the global expertise group on nutrition, immunity and gut health at Unilever. Ruud has initiated numerous (international) collaborations and is co-inventor of NutriLeads' first active ingredient. Ruud chaired the ILSI-Europe taskforce on nutrition and immunity that published seminal papers on immunomodulation in humans.