Immunomodulatory dietary polysaccharides: a systematic review of the literature

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Abstract

Background: A large body of literature suggests that certain polysaccharides affect immune system function. Much of this literature, however, consists of in vitro studies or studies in which polysaccharides were injected. Their immunologic effects following oral administration is less clear. The purpose of this systematic review was to consolidate and evaluate the available data regarding the specific immunologic effects of dietary polysaccharides.

Methods: Studies were identified by conducting PubMed and Google Scholar electronic searches and through reviews of polysaccharide article bibliographies. Only articles published in English were included in this review. Two researchers reviewed data on study design, control, sample size, results, and nature of outcome measures. Subsequent searches were conducted to gather information about polysaccharide safety, structure and composition, and disposition.

Results: We found 62 publications reporting statistically significant effects of orally ingested glucans, pectins, heteroglycans, glucomannans, fucoidans, galactomannans, arabinogalactans and mixed polysaccharide products in rodents. Fifteen controlled human studies reported that oral glucans, arabinogalactans, heteroglycans, and fucoidans exerted significant effects. Although some studies investigated anti-inflammatory effects, most studies investigated the ability of oral polysaccharides to stimulate the immune system. These studies, as well as safety and toxicity studies, suggest that these polysaccharide products appear to be largely well-tolerated.

Conclusions: Taken as a whole, the oral polysaccharide literature is highly heterogenous and is not sufficient to support broad product structure/function generalizations. Numerous dietary polysaccharides, particularly glucans, appear to elicit diverse immunomodulatory effects in numerous animal tissues, including the blood, GI tract and spleen. Glucan extracts from the Trametes versicolor mushroom improved survival and immune function in human RCTs of cancer patients; glucans, arabinogalactans and fucoidans elicited immunomodulatory effects in controlled studies of healthy adults and patients with canker sores and seasonal allergies. This review provides a foundation that can serve to guide future research on immune modulation by well-characterized polysaccharide compounds.
Methods

Literature review

Studies were identified by conducting electronic searches of PubMed and Google Scholar from their inception to the end of October 2009. The reference lists of the selected articles were checked for additional studies that were not originally found in the search.

Study selection and data extraction

The following search terms were combined with the term polysaccharide: dietary AND immune, or oral AND immune, or dietary AND inflammation, or oral AND inflammation. When specific polysaccharides or polysaccharide-rich plants and fungi were identified, further searches were conducted using their names with the same search terms. Studies were selected based on the following inclusion criteria:

1. Rodent or human studies
2. The presence of test group and control group (using either placebo, crossover, sham, or normal care)
3. Studies reporting statistically significant immunomodulatory effects
4. English language
5. Studies published up to October 2009.

Two researchers (JER, EDN) reviewed the list of unique articles for studies that fit the inclusion criteria. Uncertainties over study inclusion were discussed between the researchers and resolved through consensus. Searches were then conducted to obtain specific polysaccharide product information: safety (using the search terms: toxicity, NOAEL, LD50), composition and structure, and disposition.

Quality assessment

Each study was assessed as to whether or not it reported a significant outcome measure for the polysaccharide intervention group.

Results

A total of 62 rodent publications (Tables 1, 2 and 3) and 15 human publications (Table 4) were deemed appropriate for inclusion in this review. Available structural and compositional information for these immunomodulatory polysaccharides are provided in Table 5 and safety information is provided in Table 6. The majority of animal studies explored models in which animals were injected or implanted with cancer cells or tumors, were healthy, or were exposed to carcinogens. Other studies investigated immunodeficient, exercise-stressed, aged animals, or animals exposed to inflammatory agents, viruses, bacterial pathogens, pathogenic protozoa, radiation or mutagens. Human studies assessed immunomodulatory effects in healthy subjects, or patients with cancers, seasonal allergic rhinitis or aphthous stomatitis. Because of the limited number of human studies, we included some promising open-label controlled trials. Human study durations ranged from four days to seven years; daily doses ranging from 100-5,400 mg were reported to be well-tolerated.

A number of studies in healthy human adults demonstrated immune stimulating effects of oral polysaccharides. Arabinogalactans from *Larix occidentalis* (Western larch) were shown in RCTs to increase lymphocyte proliferation and the number of CD8+ lymphocytes [18] and to increase the IgG subtype response to pneumococcal vaccination [19]. A furanose extract from *Panax quiquefolium* (North American ginseng) was shown in an RCT of healthy older adults to decrease the incidence of acute respiratory illness and symptom duration [20]. Finally, an RCT of healthy adults consuming *Undaria pinnatifida* (wakame) fucoidans found both immune stimulating and suppressing effects, including increased stromal-derived factor-1, IFN-g, CD34+ cells and CXCR4-expressing CD34+ cells and decreased blood leukocytes and lymphocytes [21].

Studies in healthy animals showed a number of immune stimulating effects of various glucan products from *Agaricus subrufescens* (*A. blazei*) (aqueous extracts [22], aqueous extracts with standardized β-glucans [23], α-1,6 and α-1,4 glucans [24], and whole plant powders [25]); *Lentinula edodes* (shitake) (lentinan [26] and β-glucans [27]); *Sachcharomyces cerevisiae* (β-1,3-glucans [27,28]); *Laminaria digitata* (laminarin [29]); *Sclerotium rorii* (glucan phosphate [29]); *Sclerotinia sclerotiorum* (SSG [30]); and *Phellinus linteus* (powder [31] and aqueous, alcohol-precipitated extract [32]). A furanose extract from *P. quiquefolium* and pectins from *Buplerum falcatum* and *Malus* (apple) spp. have also been shown to enhance immune function in healthy young animals [33-35]. *Cyanopsis tetragonolobus* galactomannan (guar gum) or highly methoxylated pectin feeding exerted numerous stimulating effects on antibody production in older animals [36].

Evidence for the effectiveness of oral polysaccharides against infection and immune challenges has been mainly demonstrated in animals. Immune stimulating effects have been shown in resting and exercise-stressed animals with thioglycollate, clodronate, or HSV-1 injections fed *Avena* (oat) spp. soluble glucans [37-41]; animals injected with or fed *E. vermiformis* and fed *Avena* spp. particulate glucans [42,43]; animals with *E. coli* injections fed *L. digitata* glucans (laminarin) [44]; animals with HSV injections fed *U. pinnatifida* fucoidans [45]; animals with *Staphylococcus aureus* or *Candida*
| Source | Extract | Animal | Dose/day | Duration of study | Treatment | Effects | Reference |
|--------|---------|--------|----------|------------------|-----------|---------|-----------|
| *Agaricus* (A. blazei) subrufescens | α-1,6 and α-1,4 glucans | 8-week ♀ C3H/He mice (5/group) | 100 mg/kg IG every 3 days | 1 month | Healthy animals | ↑ #s splenic T lymphocytes (Thy1.2, CD4+ and CD8+) | [24] |
| | | 7-9-week ♀ Balb/cByJ mice (40/group) | 1 ml 0.45N, 0.6N, or 3N aqueous extract | 2 months | | All doses ↑ serum IgG levels, CD3+ T cell populations and PML phagocytic activity | [22] |
| | | | 7-9-week male Balb/cByJ mice (40/group) | 1 ml 0.45N, 0.6N, or 3N aqueous extract | 10 weeks IP injection of OVA at 4 weeks | 0.6N and 3N ↑ levels of OVA-specific serum IgG 28 days post-immunization; all doses ↑ delayed-type hypersensitivity and TNF-α secreted from splenocytes at 10 weeks; 0.6N ↑ splenocyte proliferation at 10 weeks | |
| | | 5-6-week ♀ BALB/cHsdOla mice (8/group × 2) | One 200 μl extract day 1, orogastric intubation | 1 week | Injected IP fecal solution day 2 | ↓ CFU in blood of mice with severe peritonitis & improved overall survival rate in all peritonitis groups | [46] |
| | | | | | | ↓ tumor size & weight after 21 days treatment | [65] |
| Aqueous, acid treated | 6-week ♀ C57BL/6 mice (10/group) | 20, 100 or 500 μg/ml, drinking water | 9 days | Injected IP human ovarian cancer cells day 1 | 500 μg/ml ↓ tumor weight | [66] |
| | | | 20, 100 or 500 μg/ml, drinking water | 3 weeks | Injected IV murine lung cancer (3LL) cells | 100 & 500 μg/ml ↓ #s metastatic tumors | |
| Aqueous, with 200 ng/day β-glucan | 6-week ♀ BALB/c mice (10/group) | 200 ng days 5-21 | 3 weeks | Injected Meth A tumor cells day 1 | ↓ tumor size & weight | [23] |
| | | | 2 weeks | Injected Meth A tumor cells | ↑ cytotoxic T lymphocyte activity & spleen cell IFN-α protein | |
| | | | | | | ↑ splenic NK cell activity | |
| *Avena* spp. | β-glucans (particulate) | 6-7-week ♀ C57BL/6 mice (7/group) | 3 mg every 48 h, days 1-3 | 1 month | Oral E. vermiciformis oocysts day 10 | ↓ E. vermiciformis fecal oocyte #s; increased intestinal anti-merozoite IgA; ↓ # of IL-4-secreting MLN cells | [42] |
| | | | 3 mg on alternating days, days 1-10 | 22 days | Injected IP Eimeria vermiformis day 10 | ↓ E. vermiciformis fecal oocyte #s; ↑ anti-merozoite intestinal IgA | [43] |
| | β-glucans (soluble) | 4-week ♀ CD-1 mice (24/group) | 0.6 mg/ml 68% β-glucan, drinking water | 1 month | Resting or exercise-stressed (days 8-10) animals administered HSV-1 IN day 10 | ↓ morbidity in resting and exercise-stressed animals; ↓ mortality in exercise-stressed animals; pre-infection, ↑ Mø anti-viral resistance in resting and exercise-stressed animals | [38] |
| | | | ~3.5 mg days 1-10, drinking water | | Resting or exercise-stressed (days 5-10) animals administered HSV-1 IN day 10 | Pre-infection, ↑ Mø antiviral resistance in resting animals | [41] |

[45] Ramberg et al. Nutrition Journal 2010, 9:54
http://www.nutritionj.com/content/9/1/54
### Table 1 Immunomodulatory Glucan Extracts: Oral Animal Studies (Continued)

| Extract Source | Formulation | Tumor Model | Dose | Treatment | Effect注 | Reference |
|----------------|-------------|-------------|------|-----------|---------|-----------|
| Hordeum vulgare | β-1,3,1,4 or β-1,3,1,6-D-glucans | Athymic nu/nu mice (4-12/group) | 40 or 400 μg IG for 4 weeks | 31 weeks | Mice with human xenografts (SRM128 melanoma, A431 epidermoid carcinoma, BT474 breast carcinoma, Daudi lymphoma, or LAN-1 neuroblastoma) ± mAb (R24, 528, Herceptin, Rituximab, or 3F8, respectively) therapy twice weekly | 400 μg + mAb ↓ tumor growth & ↑ survival; higher MW ↓ tumor growth rate for both doses |
| *Grifola frondosa* D fraction | BALB/c mice (10/group) | 1.5 mg every other day, beginning day 2 | 13 days | Implanted SC: 1) Sarcoma-180, 2) MM-46 carcinoma, or 3) IMC carcinoma cells | ↓ tumor weight & tumor growth rate: 1) 58%, 2) 64%, and 3) 7% | 71.0 |
| *Ganoderma tsugae* Aqueous | BALB/cByJ/Narl mice (14/group) | 0.2-0.4% of diet (young fungi); 0.33 or 0.66% of diet (mature fungi) | 5 weeks | Injected IP OVA days 7, 14, 21; aerosolized OVA twice during week 4 | In splenocytes, both doses of both extracts ↑ IL-2 and IL-2/IL-4 ratios, 0.2% young extract and 0.66% mature extract ↓ IL-4; in Mø, 0.66% mature extract ↑ IL-1β, both doses of both extracts ↑ IL-6 | 53.0 |
| *Ganoderma tsugae* Aqueous | 4-week CD-1 mice (20/group) | Resting or exercise-stressed (days 8-10) animals administered IN clodronate-filled liposomes to deplete Me days 8 & 14 & infected IN with HSV-1 day 10 | 1 month | ↓ morbidity in exercise-stressed & resting animals; ↓ mortality in exercise-stressed animals | 39.0 |
| *Ganoderma lucidum* Aqueous | 7-week CD-1 mice (26/group) | 5% of diet | 5 months | Injected IM DMH once a week, weeks 1-10 | ↓ aberrant crypt foci per colon, tumor size, cell proliferation, nuclear staining of β-catenin | 69.0 |
| *Ganoderma tsugae* Aqueous | 8-week CD-1 mice (26/group) | 50, 100, or 200 mg/kg, oral | 10 days | Injected SD Sarcoma 180 cells | ↓ of tumor weight was dose dependent: 27.7, 55.8, 66.7%, respectively | 67.0 |
| *Ganoderma lucidum* (mycelia) Aqueous | 4-week CD-1 mice (19-30/group) | 0.8 mg/ml 50% β-glucan, days 1-10, drinking water | 10 days | Resting or exercise-stressed (days 8-10) animals administered HSV-1 IN day 10 | ↑ neutrophil mobilization in resting & moderately exercised animals; ↑ neutrophil respiratory burst activity in resting and fatiguing exercised animals | 37.0 |
| *Ganoderma lucidum* (mycelia) Aqueous | 7-week CD-1 mice (14/group) | 0.2-0.4% of diet (young fungi); 0.33 or 0.66% of diet (mature fungi) | 5 weeks | Injected IP OVA days 7, 14, 21; aerosolized OVA twice during week 4 | In splenocytes, both doses of both extracts ↑ IL-2 and IL-2/IL-4 ratios, 0.2% young extract and 0.66% mature extract ↓ IL-4; in Mø, 0.66% mature extract ↑ IL-1β, both doses of both extracts ↑ IL-6 | 53.0 |
| *Ganoderma tsugae* Aqueous | 8-week CD-1 mice (26/group) | 50, 100, or 200 mg/kg, oral | 10 days | Injected SD Sarcoma 180 cells | ↓ of tumor weight was dose dependent: 27.7, 55.8, 66.7%, respectively | 67.0 |
| *Hordeum vulgare* | Athymic nu/nu mice (4-12/group) | 40 or 400 μg IG for 4 weeks | 31 weeks | Mice with human xenografts (SRM128 melanoma, A431 epidermoid carcinoma, BT474 breast carcinoma, Daudi lymphoma, or LAN-1 neuroblastoma) ± mAb (R24, 528, Herceptin, Rituximab, or 3F8, respectively) therapy twice weekly | 400 μg + mAb ↓ tumor growth & ↑ survival; higher MW ↓ tumor growth rate for both doses | 75.0 |
| *Ganoderma lucidum* Aqueous | Athymic BALB/c mice | 4, 40, or 400 μg for 3-4 weeks | 1 month | Mice with neuroblastoma (NM-B7, LAN-1, or SK-N-ER) xenografts, ± 3F8 mAb therapy twice weekly | 40 and 400 μg doses + mAb ↓ tumor growth; 400 μg dose ↑ survival. Serum NK cells required for effects on tumor size | 76.0 |
| *Ganoderma tsugae* Aqueous | Athymic BALB/c mice | 4, 40, or 400 μg for 3-4 weeks | 1 month | Mice with neuroblastoma (NM-B7, LAN-1, or SK-N-ER) xenografts, ± 3F8 mAb therapy twice weekly | 40 and 400 μg doses + mAb ↓ tumor growth; 400 μg dose ↑ survival. Serum NK cells required for effects on tumor size | 76.0 |
| *Hordeum vulgare* | Athymic BALB/c mice | 4, 40, or 400 μg for 3-4 weeks | 1 month | Mice with neuroblastoma (NM-B7, LAN-1, or SK-N-ER) xenografts, ± 3F8 mAb therapy twice weekly | 40 and 400 μg doses + mAb ↓ tumor growth; 400 μg dose ↑ survival. Serum NK cells required for effects on tumor size | 76.0 |
Table 1 Immunomodulatory Glucan Extracts: Oral Animal Studies (Continued)

| β-glucans | Laminaria digitata | Lentinula edodes | Saccharomyces cerevisiae |
|-----------|--------------------|----------------|------------------------|
| β-glucans | Fox Chase ICR immune-deficient (SCID) mice (9/group) | 400 μg days 1-29 | 0.1 ml water with 10% SME/10 g body weight days 1-19, 33-50 |
| Female    | Mice with human (Daudi, EBV-BLCL, Hs445, or RPMI6666) lymphoma xenografts, ± Rituximab mAb therapy twice weekly | 50 days | 50 days |
|           | +mAb ↓ tumor growth and ↑ survival |  | +mAb ↓ tumor growth and ↑ survival |
| Laminarin | ICR/HSD mice (3/group) | 1 mg | 1 mg |
| Female    | Healthy animals | 1 day | 1 day |
|           | ↑ Ma expression of Dectin-1 in GALT cells; ↑ TLR2 expression in Peyer’s patch dendritic cells | | |
|          | Wistar rats (7/group) | 5% of diet days 1-4, 10% of diet days 5-25 | 26 days |
| Male      | Injected IP E. coli LPS day 25 | | |
|          | ↓ liver ALT, AST, and LDH enzyme levels; ↑ ED2-positive cells, ↓ peroxidase-positive cells in liver, ↓ serum monocytes, TNF-α, PGE2, NO3 | | |
|          | Laminarin | 6-week nude mice | 5%-6-week athymic mice (10/group) |
| Female    | 0.1 ml water with 10% SME/10 g body weight | 50 days | 5 weeks |
|           | Injected SC prostate cancer (PC-3) cells day 1 | Injected SC colon cancer (LoVo and SW48, SW480 and SW620, or SW403 and SW1116) cells day 7 | |
|           | ↓ tumor size | | |
|          | Ψ 3- and 8-week BALB/c mice (15/group) | 50, 100 or 250 μg | 3 mg, days 1-7 |
| Male      | Healthy animals | 1-2 weeks | 3 weeks |
|           | 250 μg dose ↑ spleen cell IL-2 secretion | | |
|          | Ψ 3- and 8-week BALB/c mice (15/group) | 50, 100 or 250 μg | 5 weeks |
| Female    | Injected murine mammary carcinoma (Ptas64) cells into mammary fat pads 2 weeks before treatment | | |
|           | ↓ tumor weight | | |
|          | 5-6-week pre-leukemic AKR mice (10/group) | 3 mg, days 1-7 | |
| Male      | Injected SC K36 murine lymphoma cells day 7 | | |
|           | ↓ tumor weight; ↑ tumor inhibition rate (94%) | | |
|          | 5-6-week athymic mice (10/group) | | |
| Male      | Injected SC colon cancer (LoVo and SW48, SW480 and SW620, or SW403 and SW1116) cells day 7 | | |
|           | ↓ tumor weight; ↑ tumor inhibition rate (>90%) | | |
|          | Ψ AKR mice | 3 mg | 3 mg |
| Female    | Pre-leukemic mice | 1 day | 1 day |
|           | ↑ serum IFN-α and TNF-α, peak at 4 h and then back to normal at 24 h; ↑ IL-2 and IL-1α, peak at 2 h and back to normal at 24 h; ↑ CD4+ T, CD3+ T, B lymphocytes | | |
|          | Phellinus linteus | Aqueous, alcohol-precipitated | |
| Male      | C57BL/6 mice (10-50/group) | 200 mg/kg in drinking water | |
|           | Healthy animals | 1 month | 1 month |
|           | ↑ production and secretion of IFN-γ by con A stimulated T cells | | |
|          | Saccharomyces cerevisiae | Scleroglucan | |
| Male      | ICR/HSD mice (3/group) | 1 mg one day before challenge (day 1) | |
|           | IV Staphylococcus aureus or Candida albicans day 2 | 6 days | |
|           | ↑ long-term survival | | |
|          | Ψ 1,3,1,6 glucans (particulate) | 3 and 8-week BALB/c mice (15/group) | |
| Female    | Injected murine mammary carcinoma (Ptas64) cells into mammary fat pads 2 weeks before treatment | 50, 100 or 250 μg | 1-2 weeks |
|           | ↓ tumor weight | | |
albicans injections fed S. cerevisiae glucans (scleroglucan) [29]; and animals with fecal solution injections fed an aqueous extract of A. subrufescens (A. blazei Murrill) [46].

Additional controlled human and animal studies have shown anti-inflammatory and anti-allergy effects of some polysaccharide products. In an RCT of adults with seasonal allergic rhinitis, S. cerevisiae β-1,3;1-6 glucans decreased IL-4, IL-5 and percent eosinophils, and increased IL-12 in nasal fluid [47], while a placebo-controlled study of patients with recurrent aphthous stomatitis (canker sores) consuming β-1,3,1-6 glucans found increased lymphocyte proliferation and decreased Ulcer Severity Scores [48].

Animal models of inflammatory bowel disease have shown anti-inflammatory effects of Cladosiphon okamuranus Tokida fucoidans [49], Cyamopsis tetragonolobus galactomannans [50], Malus spp. pectins [51], and mixed polysaccharide supplements [52]. Animals challenged with ovalbumin have demonstrated anti-inflammatory/allergy effects of A. subrufescens aqueous extracts [22], an aqueous extract of Ganoderma tsugae [53], and Pyrus pyrifolia pectins [54]. Anti-inflammatory effects have also been seen in animals with cotton pellet implantations fed a Pholiota nameko heteroglycan (PNPS-1) [55].

Trametes versicolor glucans have demonstrated anti-cancer effects in humans. In two RCTs and five controlled trials, PSK from T. versicolor mycelia increased survival of advanced stage gastric, colon and colorectal cancer patients [56-62] with one study showing increased immune parameters (including blood NK cell activity, leukocyte cytotoxicity, proportion of helper cells

Table 1 Immunomodulatory Glucan Extracts: Oral Animal Studies (Continued)

| Glucan Extract | Species | Dose | Route | Age | N | Outcome | Reference |
|----------------|---------|------|-------|-----|----|---------|-----------|
| β-1,3-glucan   |         |      |       |     |    |         |           |
| WT or CCD11b- |         | 0.4 mg for 3 weeks | Injected SC RMA-S-MUC1 lymphoma cells ± 14.G2a or anti-MUC1 mAb IV injection every 3rd day | Healthy animals | All 3 doses ↑ phagocytic activity of blood monocytes & neutrophils & ↑ spleen cell IL-2 secretion | [73] |
| C57BL/6 mice  |         |      |       |     |    |         |           |
| 25 mg          |         | 1 week | Healthy animals | All 3 doses ↑ phagocytic activity of blood monocytes & neutrophils & ↑ spleen cell IL-2 secretion | [73] |

Sclerotinia sclerotiorum SSG 6-8-week specific pathogen-free σ CDF1 mice (3/group) 40 or 80 mg/kg days 1-10 2 weeks Healthy animals 10 mg dose ↑ acid phosphatase activity of peritoneal Mø (day 14) [30]

6-8-week specific pathogen-free σ CDF1 mice (3/group) 40, 80 or 160 mg/kg days 2-6 35 days Implanted SC Metha A fibrosarcoma cells day 1 80 mg dose ↓ tumor weight [94]

6-8-week specific pathogen-free σ mice of BDF1 and C57BL/6 mice (7/group) 40, 80 or 160 mg/kg days 2-11 2-3 weeks Injected IV Lewis lung carcinoma (3LL) cells 2 mg ↓ # of 3LL surface lung nodules at 2 weeks [83]

Sclerotium rolfsii Glucan phosphate σ ICR/HSD mice (3/group) 1 mg 1 day Healthy animals ↓ systemic IL-6; ↑ Mø expression of Dectin-1 in GALT cells; ↑ TLR2 expression in dendritic cells from Peyer’s patches [29]

Trametes (Coriolus) versicolor PSP 6-8-week σ BALB/c mice (10/group) 35 μg days 5-29 in drinking water 29 days Implanted SC Sarcoma-180 cells day 1 ↓ tumor growth & vascular density [94]
| Extract          | Source                                | Animal                                | Oral dose/day | Duration | Treatment                   | Significant effects                                                                 | Reference |
|------------------|---------------------------------------|---------------------------------------|---------------|----------|-----------------------------|--------------------------------------------------------------------------------------|-----------|
| Fucoidans        | Cladosiphon okamuranus Tokida          | 8-week ♀ BALB/c mice, 10/group         | 0.05% w/w of diet | 56 days | DSS-induced UC              | ↓ disease activity index and myeloperoxidase activity; ↓ # of B220-positive colonic B cells; ↓ colonic MLN IFN-γ and IL-6 and ↑ IL-10 and TGF-β; ↓ colonic IgG; ↓ colonic epithelial cell IL-6, TNF-α, and TLR4 mRNA expression | [49]      |
| Undaria pinnatifida | 5-week ♀ BALB/c mice (10-12/group)    | 5 mg, days 1-14 or 7-14               | 2 weeks       | Injected HSV into cornea day 7 | ↓ facial herpetic lesions; ↑ survival, particularly in pre-treated animals               | [45]      |
| Furanose (COLD-FX®) | Panax quinquefolium                   | Weanling ♀ SD rats (10/group)          | 450 or 900 mg/kg in food | 1 week | Healthy animals              | Both doses ↑ spleen Il-2 and IFN-γ production following ConA or LPS stimulation; ↓ proportion of total MLN and Peyers patch CD3+ cells & activated T cells; high dose ↑ spleen cell IL-1β production following 48 h ConA stimulation. | [33]      |
| Galactomannan (partially hydrolyzed guar gum) | Cyamopsis tetragonolobus              | 10-week ♀ BALB/c mice, 11-15/group    | 5% of diet    | 3 weeks | DSS-induced UC at beginning of week 3 | ↓ disease activity index scores, ↓ colonic mucosal myeloperoxidase activity & lipid peroxidation; ↓ colonic TNF-α protein levels & mRNA expression up regulated by DSS exposure | [50]      |
| Galactomannans (guar gum) | Lentinula edodes                     | 8-month- ♀ SD rats, 5/group            | 5% of diet    | 3 weeks | Older animals                | ↓ serum IgG, ↑ MLN lymphocyte IgG, IgM and IgG production | [36]      |
| Glucomannan (KS-2) | A. subrufescens                      | DD1 mice (10-20/ group)               | 140 mg/kg days 2-13 | 50 days | Injected IP Ehrlich asites tumor cells day 1 | ↑ survival | [84]      |
| Heteroglycan (ATOM) | A. subrufescens                      | Mice (10/group); 1) 5-week ♀ Swiss/ NIH; 6-week ♀ DS mice; 2) 8-week ♀ BALB/c nude; 3) 5-week ♀ C3H/HeN | 100 or 300 mg/kg days 2-11 | 8 weeks | Implanted SC 1: Sarcoma-180, 2: Shionogi carcinoma 42, 3: Meth A fibrosarcoma, or 4: Ehrlich asites carcinoma cells | Both doses ↓ Sarcoma-180 tumor size at 4 weeks & ↑ survival; 300 mg/kg ↑ peritoneal macrophage and C3-positive cells; 300 mg/kg ↓ Shionogi and Meth A tumor sizes at 4 weeks. Both doses ↑ survival of Ehrlich asites mice | [93]      |
### Table 2 Immunomodulatory Non-Glucan Extracts: Oral Animal Studies (Continued)

| Heteroglycan (LBP3p) | Lycium barbarum |♂ | Kunming mice (10/group) | 5, 10 or 20 mg/kg | 10 days | Injected SC Sarcoma-180 cells | S & 10 mg/kg ↑ thymus index; all doses ↓ weight, ↓ lipid peroxidation in serum, liver and spleen & ↑ spleen lymphocyte proliferation, cytotoxic T cell activity, IL-2 mRNA |
|----------------------|----------------|---|------------------------|-------------------|--------|-----------------------------|---------------------------------|
| Heteroglycan (PNPS-1) | Pholiota nameko |♂ | SD rats (5/group) | 100, 200 or 400 mg/kg days 1-8 | 8 days | Implanted SC cotton pellets in scapular region day 1 | ↓ granuloma growth positively correlated with dose: 11%, 18% and 44%, respectively |
| Heteroglycan (PG101) | Lentinus lepideus |♀ | 8-10-week BALB/c mice (3/group) | 10 mg | 24 days | 6 Gy gamma irradiation | ↑ colony forming cells, granulocyte CFUs/Mø, erythroid burst-forming units, and myeloid progenitor cells in bone marrow; induced proliferation of granulocyte progenitor cells in bone marrow; ↓ serum levels of GM-CSF, IL-6, IL-1β |
| Mixed polysaccharides (Ambrotose® or Advanced Ambrotose® powders) | Aloe barbadensis, Larix spp, and other plant polysaccharides |♂ | SD rats (10/group) | 37.7 or 377 mg/kg days 1-8 | 8 days | Injected IP OVA day 7, provoked with OVA aerosol day 21 | ↓ bronchial fluid ↓ IFN-γ & ↑ IL-5; splenic cells: ↑ IFN-γ, ↓ IL-5; normalized pulmonary histopathological changes; ↓ serum IgE |
| Pectin | Pyrus pyrifolia |♂ | 6-8-week BALB/c mice (11/group) | 100 μg days 1-7 | 22 days | Injected SC AOM once a week | ↓ colon tumor incidence |
| Pectins (bupleurum 2IIc) | Bupleurum falcatum |♀ | specific-pathogen-free C3H/HeJ mice | 250 mg/kg | 1 week | Healthy animals | ↑ spleen cell proliferation |
| Pectins (highly methoxylated) | Malus spp. |♀ | 8-month- specific-pathogen-free C3H/HeJ mice | 5% of diet vs. cellulose control | 3 weeks | Older animals | ↑ MLN lymphocyte IgA & IgG |
| Pectins Citrus spp. | Malus spp. |♀ | 5-week F344 rats (30/group) | 15% of diet | 34 weeks | Injected SC AOM once a week, weeks 4-14 | ↓ colon tumor incidence |
| | Malus spp. |♀ | 5-week BALB/c mice (6/group) | 5% of diet | 2 weeks | Healthy animals | ↑ fecal IgA and MLN CD4+/CD8+ T lymphocyte ratio & IL-2 & IFN-γ secretion by ConA-stimulated MLN lymphocytes |
| | |♀ | 5-week BALB/c mice (6/group) | 5% of diet days 5-19 vs. cellulose control | 19 days | DSS-induced UC days 1-5 | Significantly increased MLN lymphocytes IgA, and significantly decreased IgE; significantly decreased ConA-stimulated IL-4 and IL-10 |
| | 4-week ♂ Donryu rats (20-21/group) |♀ | 20% of diet | 32 weeks | Injected SC AOM once a week, weeks 2-12 | ↓ colon tumor incidence |
| | 4-week ♂ Donryu rats (19-20/group) |♀ | 10 or 20% of diet | 32 weeks | Injected SC AOM once a week, weeks 2-12 | Both doses ↓ colon tumor incidence; 20% ↓ tumor occupied area & ↓ portal blood and distal colon PGE2 |
### Table 2 Immunomodulatory Non-Glucan Extracts: Oral Animal Studies (Continued)

| Source | Pectins (modified) | Citrus spp. 2-4-month BALB/c mice (9-10/group) | 0.8 or 1.6 mg/ml drinking water, days 8-20 | 20 days | Both doses ↓ tumor size | [87] |
|--------|---------------------|-----------------------------------------------|------------------------------------------|---------|------------------------|------|
|        |                     | NCR nu/nu mice (10/group) | 1% (w/v) drinking water | 16 weeks | Orthotopically injected human breast carcinoma cells (MDA-MB-435) into mammary fat pad on day 7 | ↓ tumor growth rate & volume at 7 weeks, lung metastases at 15 weeks, # of blood vessels/tumor at 33 days post-injection | [89] |
| SD rats | (7-8/group) | 0.01%, 0.1% or 1.0% wt/vol of drinking water, days 4-30 | 1 month | Injected SC MAT-LyLu rat prostate cancer cells | ↓ lung metastases; 1.0% ↓ lymph node disease incidence | [88] |

### Table 3 Immunomodulatory Polysaccharide-Rich Plant Powders: Oral Animal Studies

| Source | Animal | Oral dose/day | Duration | Treatment | Significant effects | Reference |
|--------|--------|---------------|----------|-----------|---------------------|-----------|
| Agaricus (A. blazei) subrufescens (fruit bodies) | 6-week ♂ C57BL/6, C3H/HeJ and BALB/c mice (3/group) | 16, 32 or 64 mg | 2 weeks | Healthy animals | 32 and 64 mg ↑ liver mononuclear cell cytotoxicity | [25] |
| Grifola frondosa | 6-week ♀ ICR mice (10-15/group) | 5% of diet | 36 weeks | Oral N-butyl-N'-butylnitrosamine daily for first 8 weeks | ↓ #s of animals with bladder tumors; ↑ tumor weight; ↑ peritoneal Mø chemotactic activity, splenic lymphocyte blastogenic response & cytotoxic activity | [70] |
| Laminaria angustata | Weanling SD rats (58/group) | 5% of diet | 26 weeks | IG DMBA, beginning of week 5 | ↑ time to tumor development and ↓ # of adenocarcinomas in adenocarcinoma-bearing animals | [77] |
| Lentinula (Lentinus) edodes | 6-week ♀ ICR mice (10-17/group) | 5% of diet | 36 weeks | Oral BBN daily for first 8 weeks | ↓ # of animals with bladder tumors; ↓ tumor weight; ↑ Mø chemotactic activity, splenic lymphocyte blastogenic response, cytotoxic activity | [70] |
| | 7-8-week ♀ Swiss mice (10/group) | 1%, 5% or 10% of diet of 4 different lineages days 1-15 | 16 days | Injected IP N-ethyl-N-nitrosourea day 15 | All 3 doses of one lineage and the 5% dose of two other lineages ↓ # of micronucleated bone marrow polychromatic erythrocytes | [79] |
| Lentinula edodes (fruit bodies) | 5-week ♀ ICR mice (14/group x 2) | 10%, 20% or 30% of diet | 25 days | Injected IP Sarcoma-180 ascites | All 3 doses ↓ Sarcoma-180 tumor weight | [78] |
| | Mice: 1) CDF1; 2) C3H; 3) BALB/c; 4,5) C57BL/6N (9/group x 3) | 20% of diet | 25 days | Injected SC 1) IMC carcinoma, 2) MM-46 carcinoma, 3) Meth-A fibrosarcoma, 4) B-16 melanoma, or 5) Lewis lung carcinoma cells | ↓ growth of MM-46, B-16, Lewis lung, and IMC tumors; ↑ lifespan in Lewis lung and MM-46 animals | |
| | ICR mice (14/group x 2) | 20% of diet | 20% of diet days 1-7, days 7-31 or days 14-31 | 31 days | Injected IP Sarcoma-180 ascites | ↓ tumor weight & growth when fed days 7-31 or 14-31 | |
| | Mice: 1) CDF1; 2) C3 H (5/group x 4) | 20% of diet | 7-12 days | Injected SC 1) IMC carcinoma or 2) MM-46 carcinoma cells | ↑ spreading rate of activated Mø ↑ phagocytic activity | |
| Phellinus linteus | 4-week ♀ ICR mice (10/group) | 2 mg | 1 month | Healthy animals | ↓ serum & splenocyte IgE production; ↓ proliferation of splenic CD4+ T cells & splenocyte IFN-γ production | [31] |
| Pleurotus ostreatus | 6-week ♀ ICR mice (10-20/group) | 5% of diet | 36 weeks | Oral BBN daily for first 8 weeks | ↓ #s of animals with bladder tumors; ↓ tumor weight; ↑ plasma Mø chemotactic activity, splenic lymphocyte blastogenic response, cytotoxic activity | [70] |
Table 4 Immunomodulatory Polysaccharide Products: Oral Human Studies

| Extract                          | Source                          | Study design                        | Population                              | N (experimental/control) | Dose/day | Duration | Significant effects                                                                 | Reference |
|----------------------------------|---------------------------------|-------------------------------------|-----------------------------------------|--------------------------|----------|----------|-------------------------------------------------------------------------------------|-----------|
| Arabino-galactans                | Larix occidentalis              | Randomized, double-blind, placebo-controlled | Healthy adults                         | 8/15                     | 4 g      | 6 weeks  | ↑ % CD8+ lymphocytes & blood lymphocyte proliferation                               | [18]      |
| Arabino-galactans (ResistAid™)   |                                 |                                     | Healthy adults given pneumococcal vaccinations day 30 | 21/24                    | 4.5 g    | 72 days  | ↑ plasma IgG subtypes                                                                 | [19]      |
| Fucoidans                        | Undaria pinnatifida sporophylls | Randomized, single-blind, placebo-controlled | Healthy adults                          | 25 (75% fucoidan, 6 (10% fucoidan)/6) | 3 g      | 12 days  | 75% fucoidan; ↓ #s blood leukocytes, lymphocytes; ↑ plasma stromal derived factor-1, IFN-γ, CD34+ cells; ↑ % CXCR4-expressing CD34+ cells | [21]      |
| Furanose extract (Cold-FX™)      | Panax quinquefolium             | Randomized, double-blind, placebo-controlled | Healthy older adults given influenza immunization at the end of week 4 | 22/21                    | 400 mg   | 4 months | During weeks 9-16, ↓ incidence of acute respiratory illness, symptom duration         | [20]      |
| Glucans                          | Agaricus subrufescens           | Randomized, double-blind, placebo-controlled | Cervical, ovarian or endometrial cancer patients receiving 3 chemotherapy cycles | 39/61                    | 5.4 g (estimated) | 6 weeks  | ↑ NK cell activity, ↓ chemotherapy side effects                                       | [64]      |
| Glucans (β-1,3;1,6)              | Not identified                  | Placebo-controlled                  | Recurrent aphthous stomatitis patients   | 31/42                    | 20 mg    | 20 days  | ↑ PBL lymphocyte proliferation, ↓ Ulcer Severity Scores                               | [48]      |
| Glucans (β-1,3;1-6)              | S. cerevisiae                   | Randomized, double-blind, placebo-controlled | Adults with seasonal allergic rhinitis | 12/12                    | 20 mg    | 12 weeks | 30 minutes after nasal allergen provocation test; nasal lavage fluid; ↓ IL-4, IL-5, % eosinophils, ↑ IL-12 | [47]      |
| Glucans (PSK)                    | Trametes versicolor             | Randomized, controlled              | Patients with curatively resected colorectal cancer receiving chemotherapy | 221/227                  | 200 mg   | 3-5 years | ↑ disease-free survival and overall survival                                           | [56]      |
| Controlled                       |                                 |                                     | Post-surgical colon cancer patients receiving chemotherapy | 123/121                  | 3 g for 4 weeks, alternating with 10 4-week courses of chemotherapy | 7 years  | ↑ survival from cancer deaths; no difference in disease-free or overall survival     | [57]      |
|                                  |                                 |                                     | Post-surgical colorectal cancer patients receiving chemotherapy | 137/68                   | 3 g daily | 2 years  | ↑ survival in stage III patients; ↓ recurrence in stage II & III patients             | [58]      |
|                                  |                                 |                                     | Post-surgical gastric cancer patients receiving chemotherapy | 124/129                  | 3 g for 4 weeks, alternating with 10 4-week courses of chemotherapy | 5-7 years | ↑ 5-year disease-free survival rate, overall 5-year survival                           | [59]      |
Table 4 Immunomodulatory Polysaccharide Products: Oral Human Studies (Continued)

| Glucans (PSP) | Trametes versicolor | Randomized, double-blind, placebo-controlled | Conventional-treatment stage III-IV non-small cell lung cancer patients | Pre-surgical gastric or colorectal cancer patients | Post-surgical stage III/IV colorectal cancer patients | Randomized, double-blind, placebo-controlled | Controlled |
|---------------|---------------------|---------------------------------------------|---------------------------------------------------------------------|-----------------------------------------------|-----------------------------------------------|---------------------------------------------|-----------|
|               |                     |                                             |                                                                     | 16 daily; 17 every other day/13               | 3 g daily or on alternate days before surgery | 56/55                                       | 32/21 |
|               |                     |                                             |                                                                     | <14 days or 14-36 days                        | 8-10 years                                    | 3 g for 2 months, 2 g for 22 months, 1 g thereafter | 3 g |
|               |                     |                                             |                                                                     | ≥14 day treatment: ↑ peripheral blood NK cell activity, PBL cytotoxicity, proportion of PBL helper cells; ↓ proportion of PBL inducer cells; <14 day treatment: ↑ PBL response to PSK and Con A, proportion of regional node lymphocyte suppressor cells | remission & survival rates | 1 year | survival time |
|               |                     |                                             |                                                                     |                                               |                                               |                                               |                       |
|               |                     |                                             |                                                                     |                                               |                                               |                                               |                       |

and lymphocyte suppressor cells) [62]. An RCT of advanced stage lung cancer patients consuming PSP from *T. versicolor* fruit bodies found increased IgG and IgM antibodies and total leukocyte and neutrophil counts, along with a decrease in the number of patients withdrawing from the study due to disease progression [63]. An RCT of ovarian or endometrial cancer patients consuming *A. subrufescens* glucans showed increased NK cell activity and fewer chemotherapy side effects [64].

In numerous animal models of cancer, a wide range of polysaccharides have shown anti-tumorogenic effects. Glucan products sourced from *A. subrufescens* demonstrating anti-cancer activities in animal models include an aqueous extract [65], an aqueous, acid-treated extract [66], and an aqueous extract with standardized levels of β-glucans [23]. Anti-cancer effects have been reported following intake of aqueous extracts of *G. lucidum* [67-69]; the powder and D fraction of *G. frondosa* [70-72]; *Hordeum vulgare* β-glucans [73-76]; *Laminaria angustata* powder [77]; *Lentinus edodes* products (powders [70,78,79], SME [80], β-glucans [27], and lentilinan [81,82]); *Pleurotus ostreatus* powder [70], *Saccharomyces cerevisiae* particulate β-1,3;1,6 and β-1,3glucans[27,73]; and a glucan from *Sclerotinia sclerotiorum* (SSG) [30,83]. A glucomannan from *L. edodes* (KS-2) improved survival of animals with cancer cell injections [84]; apple and citrus pectins have exerted anti-cancer effects, including decreased tumor incidence [85-90]. Finally, heteroglycans from *Lycium barbarum* (LBP3p), *Lentinus lepidus* (PG101) and *A. subrufescens* (ATOM) demonstrated a number of immune stimulating effects in animal cancer models [91-93]. Interestingly, only one animal study has been performed using glucans from *T. versicolor* (PSP): animals with cancer cell implantations showed decreased tumor growth and vascular density [94].

Most polysaccharide products appear to be safe, based on NOAEL, acute and/or chronic toxicity testing in rodents (Table 6). As would be expected, powders, extracts and products that have not been fully characterized pose the most concerns. Other than for aloe vera gel, which was shown in a small human trial to increase the plasma bioavailability of vitamins C and E [95], the impact of polysaccharide intake on the absorption of nutrients and medications is not known. While one rat toxicity study raised concerns when guar gum comprised 15% of the daily diet [96], the product was safe in human studies when 18-39.6 g/day was consumed for up to a year (Table 4). Product contamination may pose the most concerns. Other than for aloe vera gel, which was shown in a small human trial to increase the plasma bioavailability of vitamins C and E [95], the impact of polysaccharide intake on the absorption of nutrients and medications is not known. While one rat toxicity study raised concerns when guar gum comprised 15% of the daily diet [96], the product was safe in human studies when 18-39.6 g/day was consumed for up to a year (Table 4). Product contamination may explain three case reports of hepatotoxicity and/or death following intake of an *A. subrufescens* aqueous extract [97]. Seven animal studies reporting positive immunologic effects of *A. subrufescens* extracts in healthy animals or animals with cancers found no evidence of toxicity (Tables 1 and 2). In humans, six weeks of *A. subrufescens* glucans intake was safe for cancer patients, and four months of 3 g/day intake by 24 healthy adults and 24 adults with liver disease reported no evidence of toxicity (Table 4). Another case report associated liver toxicity with *G. lucidum* intake, but the elderly subject also took an unidentified product a month previous to her admission for testing [98]. Three animal studies reported immunologic benefits and no adverse effects
| Source                        | Category | Features                                                                 | MW                  | Monosaccharide composition                                                                 | Reference                           |
|------------------------------|----------|--------------------------------------------------------------------------|---------------------|--------------------------------------------------------------------------------------------|-------------------------------------|
| *Agaricus subrufescens* (A. blazei) | Extract  | β-1,6-D-glucan                                                         | 10,000              | NA                                                                                         | [66]                                |
| *Agaricus subrufescens* (fruit body) | Extract  | α-1,6- and α-1,4 glucans with β-1,6-glucopyranosyl backbone (629.2 mcg/mg polysaccharides, 43.5 mcg/mg protein) | 170,000             | glucose                                                                                     | [24]                                |
|                             |          | α-1,4 glucans & β-1,6 glucans with β-1,3 side branches; α-1.6 glucans, β-1,6, 1-3 glucans, β-1,4 glucans, β-1,3 glucans, α-1.3 glucans; riboglucons, galactogluconamans, β-1,2, β-1.3 glucoomannans | NA                  | glucose, mannoside, galactose, ribose                                                      | [25,117,118]                       |
| *Agaricus subrufescens* (mycelia) | Extract  | β-1,6-D-glucan, protein complex, 5% protein                            | 100,000-1,000,000   | mannose, glucose, galactose, ribose                                                        | [93]                                |
| *Aloe barbadensis* (leaf gel) | Whole tissue | Dry weight: 10% polysaccharides; acemannan, aloemannan, aleride, pectic acid, galactans, arabinans, glucomanans | average 2,000,000   | mannose, glucose, arabinose, xylene, rhamnose                                               | [119,120]                           |
|                             |          | neutral partially acetylated glucomanan, mainly β-1,4-mannans           | >200,000            | mannose                                                                                     | [121]                               |
|                             |          | NA                                                                       | 4,000,000-7,000,000 | 37% glucose, 23.9% galactose, 19.5% mannoside, 10.3% arabinose                             | [122]                               |
|                             |          | β-1,4 acetylated mannan                                                  | 80,000              | mannoside                                                                                   | [123]                               |
| *Aloe barbadensis*, (leaf gel), *Larix* sp. (bark), *Anogeissus latifolia* (bark), *Astragalus gummifer* (stem), *Oryza sativa* (seed), glucosamine | Extracts (Ambrotose® powder) | β-1,4 acetylated mannan, arabinogalactans, polysaccharide gums, rice stach, 5.4% protein | 57.3% ≥ 950,000, 26.4% < 950,000 and ≥80,000, 16.3% ≤ 10,000 | mannoside, galactose, arabinose, glucose, galacturonic acid, rhamnose, xylene, fructose, fucose, glucosamine, galacturonic acid (unpublished data, Mannatech Incorporated) | |
|                             |          | β-1,4 acetylated mannan, arabinogalactans, polysaccharide gums, rice stach, 5.4% protein | 13% = 1,686,667; 46% = 960,000; 30% <950,000 and ≥70,000, 11% ≤ 10,000 | mannoside, galactose, arabinose, glucose, galacturonic acid, rhamnose, xylene, fructose, fucose, glucosamine, galacturonic acid (unpublished data, Mannatech Incorporated) | |
| *Avena* spp. (seed endosperm) | Extract  | β-1,3;1,4 particulate (1-3 μ) glucans                                   | 1,100,000           | glucose                                                                                     | [43]                                |
| *Avena* spp. (seed)          | Extract  | β-1,4,1,3 particulate glucans (linear chains of β-D-glucopyranosyl units; 70% β-1,4 linked) | 2,000,000           | NA                                                                                         | [41,124]                           |
| *Bupleurum falcatum* (root)  | Extract  | 6 linked galactosyl chains with terminal glucuronic acid substituted to β-galactosyl chains | NA                  | galactose, glucuronic acid, rhamnose                                                        | [35]                                |
| *Citrus* spp. (fruit)        | Extract  | α-1,4-linked partially esterified D-anhydroglacturonic acid units interrupted periodically with 1,2-rhamnose | 70,000-100,000      | galactose, galacturonic acid, arabinose, glucose, xylene, rhamnose                          | [125]                               |
| *Cladosiphon okamuranus* (frond) | Extract  | α-1,3-fucopyranose sulfate                                              | 56,000              | fucose, glucuronic acid (6:1:1:0)                                                          | [126]                               |
| *Cordyceps sinensis* (mycelia) | Extract  | β-1,3-D-glucan with 1,6-branched chains                                  | NA                  | NA                                                                                         | [127]                               |
| *Cyamopsis tetragonolobus* (seed) | Extract (gum) | Main chain of β-1,4-mannopyranosyl units with α-galactopyranosyl units | 220,000             | mannoside, galactose                                                                        | [36,128]                           |
| Product                          | Extract Type                  | Components                                      | Molecular Weight | Structure Comments                                                                 |
|---------------------------------|-------------------------------|-------------------------------------------------|------------------|------------------------------------------------------------------------------------|
| Flammulina velutipes Extract    | NA                            | 20,000 mannose, galactose                       | [50]             |                                                                                  |
| Flammulina velutipes (fruit body) Extract | β-1,3 glucan | NA glucose, mannose, galactose                 | [117]            |                                                                                  |
| *Ganoderma lucidum* Whole tissue | Linear β-1,3-glucans with varying degrees of D-glucopyranosyl branching, β-glucan/protein complexes, heteropolysaccharides | 400,000-1,000,000 glucose, galactose, mannose, xylose, uronic acid | [130]            |                                                                                  |
| *Ganoderma lucidum* (fruit body) Extract | β-linked heteroglycan peptide | 513,000 fructose, galactose, glucose, mannose, xylose (3.167:0.556:6.89:0.549:3.61) | [15]             |                                                                                  |
| *Ganoderma tsugae* Extract      | NA                            | 7,000-9,000 NA                                  | [67]             |                                                                                  |
| *Ginkgo biloba* (seed) Extract  | 89.7% polysaccharides         | NA glucose, fructose, galactose, mannose         | [131]            |                                                                                  |
| *Grifola frondosa* Whole tissue | β-1,3, 1, 6-glucans, α-glucans, mannosylglycans, xyloglucans, mannogalactofucans | NA glucose, fucose, xylose, mannose, galactose   | [117]            |                                                                                  |
| *Grifola frondosa* (fruit body) Extract (D fraction) | β-1,6-glucan with β-1,3 branches, 30% protein | NA glucose | [132]            |                                                                                  |
| *Grifola frondosa* (fruit body) Extract (X fraction) | β-1,6-D-glucan with α-1,4 branches, 35% protein | 550,000-558,000 glucose | [75]             |                                                                                  |
| *Hordeum spp.* (seed) Extract   | β-1,3,1,4-and β-1,3,1,6-D-glucans | 45,000-404,000 glucose | [124]            |                                                                                  |
| *Laminaria spp.* (frond) Extract (laminarin) | β-1,3,1-6 glucan | 7,700 glucose | [29]             |                                                                                  |
| Laminaria spp. (frond) Extract  | β-1,3 glucan with some β-1,6 branches and a small amount of protein | 4,500-5,500 glucose | [44]             |                                                                                  |
| *Larix occidentalis* (bark) Extract | β-1,3,1,6-D-galactans with arabinofuranosyl and arabinopyranosyl side chains | 19,000-40,000 galactosearabinose (6:1), uronic acid | [128,134]        |                                                                                  |
| *Lentilina edodes* Extract (SME) | β-1,3-glucans (4-5%), α-1,4-glucan (8-10%), protein (11-14%) | NA glucose | [80]             |                                                                                  |
| *Lentilina edodes* Whole tissue  | Linear β-1,3-glucans, β-1,4,1,6-glucans, heterogalactan | NA glucose, galactose, mannose, fucose, xylose | [135]            |                                                                                  |
| *Lentilina edodes* (fruit body) Extract (lentinin) | β-1,3-glucan with 2 β-1,6 glucopyranoside branchings for every 5 β-1,3-glucopyranoside linear linkages | 500,000 glucose | [136]            |                                                                                  |
| *Lentilina edodes* (fruit body) Extract (KS-2) | Peptide units and mannan connected by α-glycosidic bonds | 60,000-90,000 mannose, glucose | [137]            |                                                                                  |
| Lentinula edodes (mycelia or fruit body) | Extract | Triple helical β-1,3-D glucan with β-1,6 glucoside branches | 1,000,000 glucose | [3] |
| Lentinula edodes (mycelia) | Extract (LEM) | 44% sugars, 24.6% protein | ~1,000,000 xylose, arabinose, glucose, galactose, mannose, fructose | [3] |
| Lentinula edodes (mycelia) | Extract (PG101) | 72.4% polysaccharides, 26.2% protein, 1.4% hexosamine | NA | [138] |
| Lycium barbarum | Whole tissue | α-1,4,1,6-D-glucans, lentinan, β-1,3,1,6 heteroglucans, heterogalactans, heteromannans, xyloglucans | NA | [139] |
| Lycium barbarum (fruit body) | Extract (LBP3p) | 88.36% sugars, 7.63% protein | 157,000 glucose, galactose, mannose, xylose (molar ratio of 1:2.12:1.25:1.01:2.5:1.76) | [91] |
| Panax quinquefolium (root) | Extract | Poly-furanosyl-pyranosyl saccharides | NA | [33] |
| Panax quinquefolium (root) | Extract (Cold-FX®) | 90% poly-furanosyl-pyranosyl-saccharides | NA | [20] |
| Phellinus linteus (fruit body) | Extract | α- and β-linked 1,3 acidic proteoglycan with 1,6 branches | 150,000 glucose, mannose, arabinose, xylose | [141] |
| Phellinus linteus (mycelia) | Extract | 83.2% polysaccharide (4.4% β-glucan), 6.4% protein, 0.1% fat | NA | [142] |
| Pholiota nameko (fruit body) | Extract (PNPS-1) | NA | 114,000 mannose, glucose, galactose, arabinose, xylose (molar ratio of 1:8.4:13.6:29.6:6.2) | [55] |
| Pleurotus ostreatus (mycelia) | Extract | β-1,3,1,6-D-glucans | 316,260 glucose | [143] |
| Saccharomyces cerevisiae | Extract (WGP) | Particulate β-1,3,1,6-D-glucan | NA | [144] |
| Saccharomyces cerevisiae | Extract | β-glucans with β-1,6 branches with a β-1,3 regions | NA | [124] |
| Saccharomyces cerevisiae | Extract (SBG) | soluble β-1,3-D-glucan with β-1,3 side chains attached with β-1,6 linkages | 20,000 glucose | [145] |
| Sclerotinia sclerotiorum (mycelia) | Extract (SSG) | β-1,3-D-glucan, <1% protein (>98% polysaccharide) | NA | [83] |
| Sclerotium rolfsii | Extract (scleroglucan) | β-1,3,1,6 glucan | 1,000,000 glucose | [29] |
| Trametes versicolor (fruit body) | Extract (PSP) | α-1,4, β-1,3 glucans, 10% peptides | 100,000 glucose, arabinose, mannose, rhamnose | [146] |
| Trametes versicolor (mycelia) | Extract (PSK) | β-1,4,1,3,1,6-D-glucans, protein | 94,000 glucose (74.6%), mannose (15.9%), xylose (4.9%), galactose (2.7%), fucose (2.4%) | [137,147] |
| Undaria pinnatifida (sporophyll) | Extract | Galactofucan sulfate | 9,000 fucose:galactose 1:0.1 | [148] |
| Undaria pinnatifida (sporophyll) | Extract | Galactofucan sulfate | 63,000 fucose:galactose:gluc-uronic acid (1:0.1:0.04) | [149] |
| Undaria pinnatifida (sporophyll) | Extract | β-1,3-galactofucan sulphate | 38,000 fucose, galactose | [150] |
| Unidentified source | Extract (modified citrus pectin) | NA | 10,000 galactose, rhamnose, uronic acid | [125] |
| Unidentified source | Extract (highly methoxylated pectin) | NA | 200,000 NA | [36] |
| Category          | Source                                      | Test group         | Test                          | Design                   | Results                                      | Equivalent human dose* | Reference |
|-------------------|---------------------------------------------|--------------------|-------------------------------|--------------------------|----------------------------------------------|-------------------------|-----------|
| Arabinogalactans  | Argemone mexicana (arabinogalactan protein) | Pregnant rats      | Developmental toxicity       | 250, 500, or 1,000 mg/kg, gestational days 5-19 | No developmental toxicity: NOAEL = 1 g/kg | 68 g        | [151]    |
|                   |                                             | ☞ and ☞ rats       | Fertility                    | 250, 500, or 1,000 mg/kg, 1 month | No effects on reproduction: NOAEL = 1 g/kg |                         |           |
| Fucoids           | Undaria pinnatifida                         | Rats               | Subchronic toxicity          | 1.35 g/kg, 1 month       | No evidence of toxicity                      | 91.8 g                  | [152]    |
| Galactomannans    | Cyamopsis tetragonolobus                    | Adolescent and adult ☞ rats | Subchronic and chronic toxicity | 8% of diet, 6-67 weeks | No evidence of toxicity                      | 8% of diet              | [153]    |
|                   |                                             | Rats               | Acute toxicity               | One 7.06 g/kg dose; observed 2 weeks | All doses ↓ ☞ BW; 7.5-15% ↓ ☞ BW; 15% ↓ bone marrow cellularity; ↓ kidney and liver weights | 1-15% of diet           | [96]     |
|                   |                                             | Rats               | Subchronic and chronic toxicity | 1, 2, 4, 7.5 or 15% of diet, 3 months | No evidence of toxicity                      |                         |           |
|                   |                                             | 19 adults with hypercholesterolemia | Subchronic and chronic toxicity | 18 g/day, 1 year         | Short-term gastric bloating/loose stools, in 8 subjects, resolved in 7-10 days, 2 withdrew because of diarrhea. No toxicity for 13 subjects completing study | 18 g                   | [154]    |
|                   |                                             | 16 Type II diabetics | Subchronic toxicity         | 26.4-39.6 g/day, 6 months | No effects on hematologic, hepatic, or renal function | 39.9 g                  | [155]    |
|                   |                                             | 18 Type II diabetics | Subchronic toxicity         | 30 g/day, 4 months       |                                                   | 30 g                    |           |
|                   | Cyamopsis tetragonolobus (partially hydrolyzed guar gum) | Mice & rats       | Acute toxicity               | One 6 g/kg dose; observed 2 weeks | LD₅₀ > 6 g/kg                                   | >408 g                  | [156]    |
|                   |                                             | Rats               | Subchronic toxicity         | 0.2, 1.0 or 5% of diet, 13 weeks | No evidence of toxicity                       | 5% of diet              |           |
|                   |                                             | Rats               | Subchronic toxicity         | 0.5 or 2.5 g/kg, 1 month  | NOAEL > 2.5 g/kg                                | >170 g                  | [157]    |
|                   | S. typhimurium                              | Mutagenicity       | Ames test                    | Not mutagenic               |                                               | NA                      | [97]     |
| Glucans           | Agaricus subrufescens (aqueous extract)     | Rats               | Subchronic toxicity         | 0.63, 1.25, 2.5 or 5% of diet, 3 months | NOAEL = 5% of diet                           | 5% of diet              | [158]    |
|                   |                                             | 3 women with advanced cancers | Specific identity of products, doses, and durations of intake unknown | Severe hepatotoxicity; two patients died |                                               | NA                      | [97]     |
|                   | Agaricus subrufescens (freeze dried powder) | 24 normal adults and 24 adults with liver problems | Subchronic toxicity         | 3 g, 4 months               | No evidence of toxicity                       | 3 g                    | [159]    |
|                   | Ganoderma lucidum (supplement)              | Elderly woman      | Case report                  | 1 year G. lucidum (and another unidentified product, initiated one month previous) | Elevated liver enzymes and liver tissue damage | NA                     | [98]     |
|                   | Grifola frondosa (powder)                   | Rats               | Acute toxicity               | One 2 g/kg dose            | No evidence of toxicity                       | 136 g                  | [160]    |
following intake of *G. lucidum* aqueous extracts; in one study intake was 5% of the diet for 5 months (Table 1). While adverse effects were also reported in a study in which 10 adults consumed 4 g/day *L. edodes* powder for 10 weeks \[99\], immunologic animal studies reported no ill effects of either *L. edodes* powder (5 studies, up to 5% of the diet up to nine months) or extract (7 studies, up to 40 days intake) (Tables 1 and 3). Finally, while intake of 319 mg/kg of an aqueous extract of *P. ostreatus* by mice for 1 month caused hemorrhages in multiple tissues \[100\], there was no reported toxicity when mice consumed the mushroom powder as 5% of their diet for nine months (Table 3). While ≥1 gram/day of *T. versicolor* glucan products were safely consumed by cancer patients for up to 10 years, the long-term effects of ingestion of the other polysaccharide products discussed in this review is also not known.

**Discussion**

The majority of studies that qualified for inclusion in this review employed models investigating immune stimulation; fewer explored anti-inflammatory effects. Animal studies reported immune system effects in the gut, spleen, bone marrow, liver, blood, thymus, lungs, and saliva; controlled human studies reported evidence of immune stimulation in the blood, anti-inflammatory

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**Table 6 Safety of Immunomodulatory Polysaccharide Products Following Oral Intake (Continued)**

| Polysaccharide Product | Organisms | Route of Administration | Dose | Toxicity | LD₅₀ or NOAEL | Ref. |
|------------------------|-----------|-------------------------|------|----------|---------------|------|
| Lentinula edodes (powder) | 10 adults | Safety | 4 g/day for 10 weeks, repeated 3-6 months later | 50% of subjects experienced blood eosinophilia, ↑ eosinophil granule proteins in serum and stool, ↑ GI symptoms | 4 g [99] |
| Lentinula edodes (SME) | Nude mice | Safety | 10% of diet days 1-18, 33-50 | No adverse events | 10% of diet [80] |
| | 61 men with prostate cancer | 0.1 g/kg, 6 months | No adverse events | 6.8 g |
| Lentinus lepideus (PG101) | Female mice | Subchronic toxicity | 0.5 g/kg, 24 days | No evidence of toxicity | 34 g [92] |
| Phellinus linteus (crude extract) | Rats | Acute toxicity | One 5 g/kg dose; observed 2 weeks | LD₅₀ > 5 g/kg | 349 g [161] |
| Pleurotus ostreatus (aqueous extract) | Mice | Acute toxicity | One 3 g/kg dose; observed 1 day | LD₅₀ > 3 g/kg | >204 g [100] |
| | | Subacute toxicity | 319 mg/kg, 1 month | Hemorrhages in intestine, liver, lung, kidney, inflammation and microabscesses in liver | 21.7 g |
| Saccharomyces cerevisiae (particulate glucan [WGP]) | Rats | Acute toxicity | One 2 g/kg, observed 2 weeks | LD₅₀ > 2 g/kg | >136 g [144] |
| | | Subchronic toxicity | 2, 33.3 or 100 mg/kg, 3 months | NOAEL = 100 mg/kg | 680 g |
| Heteroglycans Trametes versicolor (PSP) | Rats | Subchronic toxicity | 1.5, 3.0 or 6.0 mg/kg, 2 months | No evidence of toxicity | 408 mg [162] |
| | Rats & monkeys | Subchronic and chronic toxicity | 100-200X equivalent human dose, 6 months | No evidence of toxicity | NA |
| Trametes versicolor (PSK) | Humans with colon cancer | Safety | 3 g/day, up to 7 years | No significant adverse events | 3 g [57] |
| | Humans with colorectal cancer | 3 g/day, 2 years | 3 g [58] |
| Mannans Aloe vera gel | Dogs | Acute toxicity | Fed one 32 g/kg; observed 2 weeks | LD₅₀ > 32 g/kg | >2,176 g Bill Pine, personal communication |
| | Rats | | One 21.5 g/kg, observed 2 weeks | LD₅₀ > 10 g/kg | >680 g |

*150 lb adult
effects in nasal lavage fluid and improved survival in cancer patients. The literature is highly heterogenous and is not sufficient to support broad structure/function generalizations. For the limited number of studies that investigated well-characterized, isolated products (primarily glucan products), effects can be unequivocally attributed to polysaccharides. Such associations are certainly more tenuous when considering product powders or products obtained by extraction methods designed to isolate polysaccharides, but without complete compositional analyses.

Dietary polysaccharides are known to impact gut microbial ecology [101,102], and advances in microbial ecology, immunology and metabolomics indicate that gut microbiota can impact host nutrition, immune modulation, resistance to pathogens, intestinal epithelial development and activity, and energy metabolism [103-107]. Other than fucoidans, the polysaccharides discussed in this review appear to be at least partially degraded by bacterial enzymes in the human digestive tract (Table 7). Arabinogalactans, galactomannans, a glucan (laminarin), glumomannans, and mixed polysaccharide products (Ambrotose® products) have been shown to be metabolized by human colonic bacteria. Orally ingested fucoidans, glucans and mannans (or their fragments) have been detected in numerous tissues and organs throughout the body [73,108,109], (Carrington Laboratories, personal communication). We know of no study that has determined the specific identity of orally-ingested polysaccharide end products in animal or human tissues.

One can only speculate upon the mechanisms by which the polysaccharides discussed in this review influence immunologic function, particularly when one considers the exceedingly complex environment of the GI tract. It is possible that fragments of polysaccharides partially hydrolyzed by gut bacteria may either bind to gut epithelia and exert localized and/or systemic immune system effects, or be absorbed into the bloodstream, with the potential to exert systemic effects. Current studies investigating the link between the bioconversion of dietary polysaccharides, their bioavailability and their downstream effects on the host

| Table 7 Fate of Immunomodulatory Polysaccharide Products Following Oral Intake |
|----------------------------------------|------------------|-----------------|-----------------|-----------------|
| Category                              | Product          | Metabolized by human gut bacteria? | Study type | Fate (method: tissues detected) | References |
| Arabinogalactans                      | Larix spp.       | yes             | in vitro | NA                            | [163-169]  |
| Fucoidans                             | Undaria pinnatifida | no               | in vitro | Ab: human plasma               | [108,170] |
| Galactomannans                        | Cyamopsis tetragonolobus (partially hydrolyzed guar gum) | yes         | in vivo | NA                            | [171]      |
| Glucans                               | Hordeum vulgare  | NA              | in vivo | Fluorescein-labeled: mouse Mø in the spleen, bone marrow, lymph nodes | [73]       |
|                                       | Laminaria digitata (laminarin) | yes           | in vitro | NA                            | [29,170,172] |
|                                       | Sclerotium rolfs (scleroglucan) glucan phosphate, Laminaria spp. (laminarin) | NA         | in vivo | Alexa Fluor 488-labeled: mouse intestinal epithelial cells, plasma, GALT | [29]       |
|                                       | Saccharomyces cervisiae (particulate) | NA         | in vivo | Fluorescein-labeled: mouse macrophage in the spleen, bone marrow, lymph nodes | [73]       |
|                                       | Trametes versicolor (PSK) | NA         | in vivo | 14C-labeled: rat and rabbit serum; mouse GI tract, bone marrow, salivary glands, liver, brain, spleen, pancreas | [173]       |
| Mannans                               | Aloe barbadensis (aloemannan) | yes      | in vitro | FITC-labeled: mouse, GI tract | [121,174] |
|                                       | Aloe barbadensis (gel powder) | NA        | in vitro | NA                            | [163]       |
|                                       | Aloe barbadensis (acemannan) | NA        | in vivo | 14C-labeled: dog systemic, particularly liver, bone marrow, gut, kidney, thymus, spleen | (Carrington Laboratories, personal communication) |
| Mixed polysaccharide products         | Ambrotose complex®, Advanced Ambrotose® powder | yes | in vitro | NA                            | [163,175] |
| Pectins                               | NA              | yes             | in vitro | NA                            | [165-167,176] |
|                                       | Bupleurum falcatum (bupleuran 2Ic) | NA         | in vivo | Ab bound: mouse Peyer’s patch, liver | [109]       |
metabolism and physiology are utilizing metabolomic and metagenomic approaches that can detect and track diverse microbial metabolites from immunomodulatory polysaccharides [103]. These and other innovative approaches in the field of colonic fermentation are providing novel insights into gut microbial-human mutualism [110,111], its impact on regulating human health and disease, and the importance of dietary modulation [112-115].

Additional RCTs of well-characterized products are needed to more completely understand the immunomodulatory effects and specific applications of oral polysaccharides. Such studies will need to better investigate the optimal timing and duration for polysaccharide ingestion. That is, should they be consumed continuously, before, at the time of, or after exposure to a pathogen or environmental insult? Only a few studies have actually investigated the impact of timing of polysaccharide intake to achieve optimal benefits. Daily feeding with some polysaccharides appears to result in tolerance (and diminished benefits); this has been demonstrated for some mushroom β-glucans [3,26]. For those polysaccharides whose immunologic effects are dependent on their prebiotic activities, regular feeding would be presumed necessary.

Conclusions

The dietary polysaccharides included in this review have been shown to elicit diverse immunomodulatory effects in animal tissues, including the blood, GI tract, and spleen. In controlled human trials, polysaccharide intake stimulated the immune system in the blood of healthy adults, dampened the allergic response to a respiratory inflammatory agent, and improved survival in cancer patients. Additional RCTs of well-characterized products are needed to more completely understand the immunomodulatory effects and specific applications of oral polysaccharides.

List of abbreviations

♀: female; ♂: male; Ab: antibody; AIDS: autoimmune deficiency syndrome; AOM: azoxymethane; BBN: N-butyl-N'-butanolnitrosamine; BLCL: Burkitt’s Lymphoma Cell Line; BW: body weight; CBC: complete blood count; CD: cluster of differentiation; CFU: colony forming unit; ConA: concanavalin A; CXCR: CXC chemokine receptor; DMBA: 7,12-dimethylbenz(a)anthracene; DMH: N-N’-dimethylhydrazine; DMN: dimethylhydrazine; DSS: dextran sulfate sodium; EBV: Epstein-Barr virus; GALT: gut-associated lymphoid tissue; GI: gastrointestinal; H2O2: hydrogen peroxide; HSV: herpes simplex virus; IEL: intraepithelial lymphocytes; IFN-γ: interferon gamma; IG: intragastric; IgA: immunoglobulin A; IgE: immunoglobulin E; IgG: immunoglobulin G; IgM: immunoglobulin M; IL: interleukin; IMC: invasive micropapillary carcinoma; IN: intranasally; IP: intraperitoneal; IV: intravenous; LPS: lipopolysaccharide; Mø: macrophage; mAb: monoclonal antibody; 3-MCA: methylcholanthrene; MLN: mesenteric lymph nodes; MM-46 carcinoma: mouse mammary carcinoma; MW: molecular weight; NK: natural killer; NOAEL: no observable adverse effect level; OVA: ovalbumin; PBL: peripheral blood leukocytes; PBMC: peripheral blood mononuclear cells; PHA: phytohaemagglutinin; PMA: phorbol 12-myristate 13-acetate; PML: polymorphonuclear lymphocyte; RCT: randomized, controlled trial; RNA: ribonucleic acid; SC: subcutaneous; SD rats: Sprague Dawley; TLR: toll like receptor; TNF-α: tumor necrosis factor alpha; UC: ulcerative colitis; WT: wild type.

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Authors’ contributions

JER and EDN conducted literature searches and wrote the manuscript. RAS provided technical guidance. All authors read and approved the final manuscript.

Competing interests

The authors are employees of the Research & Development Department at Mannatech, incorporated, which sells two of the polysaccharide products (Ambrotose® powder and Advanced Ambrotose® powder) discussed in this review.

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