Larch Arabinogalactan: Clinical Relevance of a Novel Immune-Enhancing Polysaccharide

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Abstract

Larch arabinogalactan is composed of greater than 98-percent arabinogalactan, a highly branched polysaccharide consisting of a galactan backbone with side-chains of galactose and arabinose sugars. Larch arabinogalactan is an excellent source of dietary fiber, and has been approved as such by the FDA. It has been shown to increase the production of short-chain fatty acids, principally butyrate and propionate, and has been shown to decrease the generation and absorption of ammonia. Evidence also indicates human consumption of larch arabinogalactan has a significant effect on enhancing beneficial gut microflora, specifically increasing anaerobes such as Bifidobacteria and Lactobacillus. Larch arabinogalactan has several interesting properties which appear to make it an ideal adjunctive supplement to consider in cancer protocols. Experimental studies have indicated larch arabinogalactan can stimulate natural killer (NK) cell cytotoxicity, enhance other functional aspects of the immune system, and inhibit the metastasis of tumor cells to the liver. The immune-enhancing properties also suggest an array of clinical uses, both in preventive medicine, due to its ability to build a more responsive immune system, and in clinical medicine, as a therapeutic agent in conditions associated with lowered immune function, decreased NK activity, or chronic viral infection.
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Introduction

Arabinogalactans are a class of polysaccharides found in a wide range of plants; however, they are most abundant in plants of the genus Larix.[1] Because of their potent biological activity, immune-enhancing properties, and peculiar solution properties, this unique dietary fiber is receiving increased attention as a clinically useful nutraceutical agent.

The primary source of arabinogalactan is the larch tree (*Larix sp.*), and although larch arabinogalactan can be extracted from either of two sources – western larch (*Larix occidentalis*) or Mongolian larch (*Larix dahurica*) – most commercially available arabinogalactan is produced from the western larch.

High-grade larch arabinogalactan (the grade typically utilized for clinical applications) is composed of greater than 98-percent arabinogalactan. As produced, larch arabinogalactan is a dry, free-flowing powder, with a very slight pine-like odor and sweetish taste. It is 100-percent water-soluble and produces low-viscosity solutions. Because of its excellent solubility and mild

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taste, the powder mixes readily in water and juices for ease of administration. It was the naturopathic physician Peter D'Adamo who first introduced larch arabinogalactan into clinical practice.

Biochemistry and Chemical Nature of Larch Arabinogalactan

Arabinogalactans are a class of long, densely branched polysaccharides with molecular weights ranging from 10,000-120,000.[2] In nature, arabinogalactans are found in several microbial systems, especially acid-fast Mycobacteria, where it is complexed between peptidoglycans and mycolic acids as a component of the cell wall, and influences monocyte-macrophage immunoreactivity of tubercular antigen.[3] Many edible and inedible plants are rich sources of arabinogalactans, mostly in glycoprotein form, bound to a protein spine of either threonine, proline, or serine ("arabinogalactan protein"). These plants include leek seeds, carrots, radish, black gram beans, pear, maize, wheat, red wine, Italian ryegrass, tomatoes, ragweed, sorghum, bamboo grass, and coconut meat and milk. Many herbs with well established immune-enhancing properties, such as *Echinacea purpurea*, *Baptisia tinctoria*, *Thuja occidentalis*,[4] *Angelica acutiloba*,[5] and *Curcuma longa* [6] contain significant amounts of arabinogalactans.

All arabinogalactans isolated from *Larix sp.* are water-soluble, nitrogen-free polysaccharides of the 3,6-beta-D-galactan type. Experimental analysis has determined larch arabinogalactan to be a highly branched molecule with a 3,6-galactan backbone. Side-chains consist of combinations of single galactose sugars, as well as longer side-chains comprised of both 3, 4, 6-; 2, 3, 6-; 3, 6-; 3, 4-; and 3-linked beta-galactose and beta-arabinose residues. The galactose and arabinose units (consisting of beta-galactopyranose, beta-arabinofuranose, and beta-arabinopyranose) are in a molar ratio of approximately 6:1, and comprise greater than 99 percent of the total glycosyl content. A trace amount of glucuronic acid is generally also found.[1, 7]

Pharmacokinetics of Larch Arabinogalactan

The pharmacokinetics of larch arabinogalactan following an oral dose have not been well elaborated in humans. The absolute concentration of larch arabinogalactan absorbed following an oral dose is unclear; however, non-absorbed larch arabinogalactan is fermented vigorously by gastrointestinal microflora.[8]

In animal models, following injection, larch arabinogalactan is cleared from the blood with a half-life of 3.8 minutes. Ninety minutes post-injection, concentrations are highest in the liver (52.5%) and in urine (30%), with hepatic clearance following first order kinetics and having a half-life of 3.42 days.[7]

Purified arabinogalactans derived from the western larch are known to bind *in vitro* with liver asialoglycoprotein receptors. *In vivo* experimental evidence also demonstrates this strong binding property to liver asialoglycoprotein receptors. Larch arabinogalactan, reaching the liver through the portal circulation, is rapidly and specifically internalized within hepatocytes by receptor-mediated endocytosis. Because of the high percentage of larch arabinogalactan arriving at the liver, and its active uptake by hepatocytes, Groman et al have suggested arabinogalactan might be an ideal vehicle to deliver drugs to the liver.[7]

Larch Arabinogalactan as a Dietary Fiber

Arabinogalactan is an excellent source of dietary fiber, is approved as a dietary fiber by the United States FDA, has been shown to increase the production of short-chain fatty acids (SCFAs), principally butyrate and

propinate, and has been shown to decrease the generation and absorption of ammonia.[8, 9] Evidence also indicates human consumption of larch arabinogalactan has a significant effect on enhancing gut microflora, specifically increasing anaerobes such as Bifidobacteria and Lactobacillus, while decreasing Clostridia.[10]

Carbohydrate fermentation into SCFAs by intestinal microflora is now regarded to be of critical importance to large bowel function, and might be a contributing factor in hepatic and peripheral tissue metabolism.[9] Butyrate plays an important role in colon health. It is the preferred substrate for energy generation by colonic epithelial cells,[11] it is believed to protect the mucosa against a variety of intestinal diseases, and it has been shown to protect these cells against cancer-promoting agents.[12] The ability of arabinogalactan to increase concentrations of butyrate suggests some significant health benefits subsequent to oral administration of this polysaccharide.

Arabinogalactan is fermented vigorously by gastrointestinal microflora, resulting in the production of SCFAs. The high production of SCFAs suggests almost complete fermentation by gut microflora of any non-absorbed arabinogalactan as it transits through the large intestine.[8] In a study by Vince et al, an *in vitro* fecal incubation system was used to study the metabolism of complex carbohydrates by intestinal bacteria. Homogenates of human feces were incubated anaerobically with added lactulose, pectin, arabinogalactan, and cellulose, both before and after subjects had been pre-fed each carbohydrate. Fermentation of added substrate was assessed by the production of short-chain fatty acids and suppression of net ammonia generation over 48 hours of incubation. The authors reported arabinogalactan increased the yield of SCFAs and acetate in all samples at all times, with butyrate concentrations exceeding propionate

in all samples. Fecal homogenates incubated with cellulose showed no greater SCFA production than controls.[8]

Englyst et al investigated the breakdown of larch arabinogalactan and three other polysaccharides by human fecal bacteria by observing the production of SCFAs in different polysaccharide substrates. They found the backbone and side-chain sugars of arabinogalactan were co-utilized as fermentation substrates; however, these sugars were broken down more slowly than either starch or pectin. Their experiments suggest arabinogalactan to be of particular benefit in increasing concentrations of propionate. Although starch was the most effective polysaccharide in generating high butyrate concentrations, arabinogalactan had significantly more butyrate-generating activity than either pectin or xylan.[9]
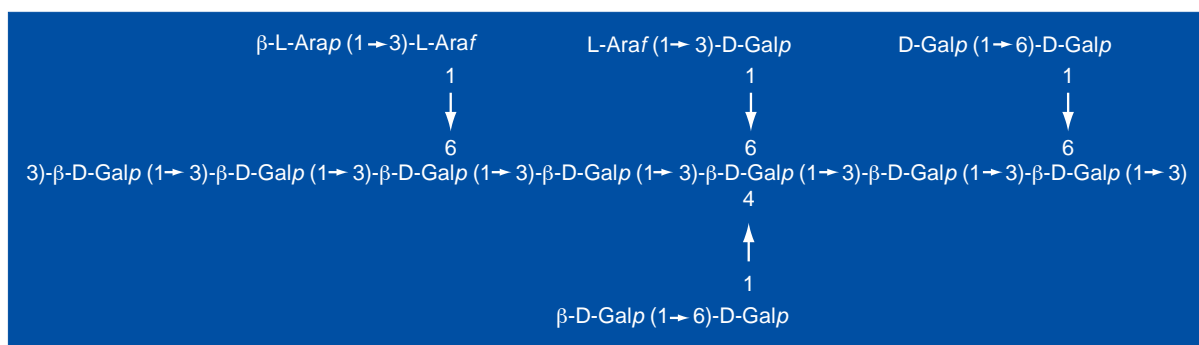
Pre-feeding subjects with arabinogalactan decreases ammonia generation;[8, 9] however, this action is not common to all dietary fibers as cellulose has been shown to have no effect on ammonia generation.[8] Vince et al have suggested arabinogalactan might have clinical value in the treatment of porto-systemic encephalopathy because of this ability to lower the generation and subsequent absorption of ammonia.[8]

Larch arabinogalactan can promote an increase in Bifidobacteria, particularly *Bifidobacterium longum,* which appears to have the most specificity to ferment arabinogalactan.[13] Unpublished evidence following a controlled study of larch arabinogalactan supplementation in human volunteers has similarly demonstrated an ability to promote an increase of Bifidobacteria, as well as other anaerobes such as Lactobacillus.[10]

Larch Arabinogalactan and Cancer

Larch arabinogalactan has several interesting properties which appear to make it

Larch Arabinogalactan

β-L-Ara*p* (1→3)-L-Ara*f*   L-Ara*f* (1→3)-D-Gal*p*   D-Gal*p* (1→6)-D-Gal*p*

1   1   1

↓   ↓   ↓

6   6   6

3)-β-D-Gal*p* (1→3)-β-D-Gal*p* (1→3)-β-D-Gal*p* (1→3)-β-D-Gal*p* (1→3)-β-D-Gal*p* (1→3)-β-D-Gal*p* (1→3)-β-D-Gal*p* (1→3)

4

↑

1

β-D-Gal*p* (1→6)-D-Gal*p*

an ideal adjunctive supplement to consider in cancer protocols. Experimental studies indicate larch arabinogalactan stimulates natural killer cell cytotoxicity, enhances other functional aspects of the immune system, and inhibits the metastasis of tumor cells to the liver. All of these activities have significant utility as strategies to support conventional cancer treatment

Natural Killer (NK) Cytotoxicity: Many of the new adjuvant approaches to cancer treatment include the use of biological response modifiers which have the potential to modulate immune function. At present, the most promising approach to immune modulation appears to be the utilization of biotherapeutic agents capable of positively impacting natural killer cell cytotoxicity. As defined by Hauer and Anderer, human NK cytotoxicity is, "the ability to mediate spontaneous cytotoxicity against a variety of tumor cells and virus-infected cells without prior sensitization by antigen and restriction by products of the major histocompatibility gene complex."[2]

In general, NK cell activity is an excellent functional marker of health. Reports in the medical literature indicate decreased NK cell activity is linked to a variety of chronic diseases including cancer,[14] chronic fatigue syndrome (CFS),[15] autoimmune diseases, such as multiple sclerosis,[16] and viral hepatitis.[17] In CFS, for example, restoration of NK cell activity is associated with clinical recovery;[18] while in multiple sclerosis, a relationship between reductions in NK cell activity and the development of active lesions has been reported.[16] In prostate cancer, changes in NK activity were found to be associated with both the likelihood of metastasis and tumor response to therapy. In fact, it was found to be as reliable as the specific tumor markers reflective of prostate cancer.[19]

Some oligo- or polysaccharide molecules of plant origin are known to be inducers of NK cell activity and can enhance human NK cytotoxicity against cancer cells. The rhamnogalacturonan from mistletoe (*Viscum album*) is an example of a plant saccharide with known NK cytotoxicity-enhancing properties.[20, 21]

Hauer and Anderer investigated the ability of larch arabinogalactan (derived from *Larix occidentalis*) to stimulate NK cell cytotoxicity against K562 tumor cells in cell cultures. Under experimental conditions, cultures of human peripheral blood mononuclear cells, as well as cultures of pre-separated, peripheral non-adherent cells and monocytes, showed enhancement of natural killer cytotoxicity against K562 tumor cells when pretreated with larch arabinogalactan for 48-72 hours. The larch arabinogalactan-mediated enhancement of NK cytotoxicity did not appear to be initiated directly, but was found to be governed by the cytokine network. Generally, larch arabinogalactan pretreatment induces an increased release of interferon gamma (IFN gamma), tumor necrosis factor alpha, interleukin-1 beta (IL-1 beta) and

interleukin-6 (IL-6); however, experimental evidence suggests the increase in IFN gamma was most responsible for the observed enhancement of NK cytotoxicity.[2]

The initial observations of Hauer and Anderer indicated larch arabinogalactan interacted with the same receptor that showed specificity for an NK-cytotoxicity-enhancing oligo-saccharide from *Viscum album*. They reported no synergism in the NK-cytotoxicity-stimulating activity of a combination of the *V. album* oligosaccharide and larch arabinogalactan. Both compounds demonstrated similar ability to promote NK cytotoxicity; however, neither component added a significant effect to the NK cytotoxicity induced by the other compound. As compared with the oligosaccharide from *V. album*, arabinogalactan consistently demonstrated a far greater ability to induce IFN gamma.[2]

Of note, this cell culture study was conducted on healthy individuals and, although not all individuals were responsive to stimulation of NK cytotoxicity by larch arabinogalactan (37-percent non-responders), 63 percent of individuals tested were responsive, and 33 percent of those tested were considered high responders, experiencing at least a doubling of NK cytotoxicity after pretreatment with larch arabinogalactan.[2]

Since the spontaneous cytotoxicity of donors prior to treatment was highly variable, it is not surprising to find the response to larch arabinogalactan pretreatment was also variable. It is possible a more predictable response might have been obtained if the population studied had consisted of individuals with a variety of chronic diseases, since, in general, these individuals would have been expected to have lower initial NK cytotoxicity.

Reticuloendothelial and Complement Activation: Low to middle molecular weight (5,000-50,000) arabinogalactan polysaccharides isolated from larch[1] and non-larch sources [4, 6] have been shown to have strong immunostimulating properties, including the ability to activate phagocytosis and potentiate reticuloendothelial system action.[1,4,6] Several arabinogalactans (isolated from non-larch sources) have also been shown to have anti-complement activity.[5,22,23]

Although larch arabinogalactan was not utilized in these studies, it is possible it would have similar activity. In fact, recent unpublished findings demonstrated larch arabinogalactan ingested by human volunteers had a significant dose-dependent *in vivo* effect on enhancing the function of the mononuclear portion of the immune system.[24]

Anti-metastatic Activity: Metastatic disease most commonly spreads to the liver, in preference to other organ sites. This has been theorized to be the result of a reaction between the galactose-based glycoconjugate on the metastatic cells and a hepatic-specific lectin-like receptor (e.g., the D-galactose-specific hepatic binding protein) found in liver parenchyma. Several compelling studies show arabinogalactan inhibits this reaction. Modified citrus pectin (MCP) has also been mentioned as a possible anti-metastatic agent in cancer;[25] however, larch arabinogalactan, while having the same anti-metastatic mechanism of action as MCP, also offers immune-modulating activity not offered by this other natural substance.

In one animal study, the effects of arabinogalactan were investigated in a syngeneic tumor-host system using a tumor which primarily colonizes the liver upon intravenous injection. The study included systemic treatment with D-galactose and arabinogalactan as well as cell pretreatment with arabinogalactan and two other glycoconjugates. Although all test animals eventually succumbed to liver metastasis, host treatment with arabinogalactan significantly reduced the amount of liver metastasis and prolonged the survival times of the animals. This was shown to be an effect of arabinogalactan's blockade

of potential liver receptors by covering galactose-specific binding sites.[26] Similar results were previously demonstrated in an experimental study by Uhlenbruck et al.[27]

In a third study, pretreatment and regular application (for three days after tumor cell inoculation) of arabinogalactan as a receptor blocking agent completely prevented the settling of sarcoma L-1 tumor cells in the liver of experimental animals. Other galactans, dextrans, and phosphate-buffered saline showed no effect. These results indicate when lectin-like liver receptors are blocked with the competitive polysaccharide from arabinogalactan, tumor metastasis may be prevented.[28] Beuth et al repeated these results in a subsequent animal model and also demonstrated that arabinogalactan greatly reduced the colonization process of highly metastatic Esb lymphoma cells.[29]

Larch Arabinogalactan and Pediatric Otitis Media

Otitis media is a common pediatric medical problem. It seems prudent that in children with a history of chronic otitis media, building a powerful immune system along with reestablishing gut microflora balance (potentially disrupted following antibiotic use) would be reasonable therapeutic goals. D'Adamo reports clinical experience of a decrease in frequency and severity of pediatric otitis media with larch arabinogalactan.[30] While formal outcome data has yet to be published, it seems reasonable that, due to the combination of known immune-enhancing properties and effects on gut microflora, this intervention might indeed produce good clinical outcomes. Due to the solubility of larch arabinogalactan in fluids such as water or juice, the long-term administration of this substance to pediatric patients might be accomplished with a great deal less difficulty than other available immune-modulating herbal or nutritional substances.

Side Effects and Toxicity

Larch arabinogalactan is FDA-approved for use in food applications. Toxicity tests on rats indicate larch arabinogalactan is significantly less toxic than methylcellulose. In acute toxicity studies, mice and rats showed no signs or symptoms of toxicity at a dose of 5000 mg/kg, while in prolonged toxicity studies, doses of 500 mg/kg for 90 days resulted in no evidence of toxicity.[7]

Clinical feedback suggests an occasional reaction of bloating and flatulence in less than three percent of individuals. This side-effect might be secondary to the effect larch arabinogalactan has on beneficially altering gut microflora.

Conclusions

Although outcome studies on the clinical applications of this novel polysaccharide have not been conducted to date, its physiological properties suggest a broad range of potential therapeutic applications. As a dietary fiber supplement, larch arabinogalactan has several beneficial properties, including the ability to promote the growth of friendly bacteria, increase the production of SCFAs, and decrease ammonia generation. Since most diets are deficient in dietary fiber, the ability to simultaneously enhance immune activity, while boosting fiber intake, suggests a dual advantage of this unique polysaccharide as a dietary fiber.

As a biological response modifier, larch arabinogalactan also appears to offer substantial promise. The currently documented effects on NK cytotoxicity, along with its effects on the function of the mononuclear portion of the immune system, suggest an array of clinical uses both in preventive medicine, due to its ability to build a more responsive immune system, and in clinical medicine, as a therapeutic agent in conditions associated with lowered immune function or decreased NK

activity. The prophylactic applications might include use as an immune-building agent for individuals with a propensity to ear infections and other upper respiratory infections. As a therapeutic agent, larch arabinogalactan appears to hold the most promise as an agent in conditions characterized by reduced NK activity and chronic viral infections, such as CFS and viral hepatitis.

Perhaps the greatest potential of this polysaccharide is as a biological response modifier to support conventional cancer treatments. The combination of its immune-enhancing properties along with its anti-metastatic activity fulfills two therapeutically desirable goals. While modified citrus pectin has received attention in both conventional and alternative medical journals for its anti-metastatic activity, larch arabinogalactan works in essentially the same manner, that is, by inhibiting the attachment of metastatic cells to liver parenchyma via competitive binding to liver hepatic galactose receptors; larch arabinogalactan, however, offers the additional advantage of enhancing immune function.

Larch arabinogalactan's NK-modulating activity appears to be similar in nature to the mechanism of action of *Viscum album*. Based on available evidence of a lack of synergism, no advantage appears to exist in combining these two substances. The use of larch arabinogalactan offers anti-metastatic activity, as well as its positive effects on gut microflora and SCFAs, the latter two benefits not found with *V. album*.

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