Research report

Larch arabinogalactan

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ABSTRACT

This paper discusses some of the applications and characteristics of naturally occurring arabinogalactans, with a special emphasis on those arabinogalactans derived from Western Larch. The unusual immunological properties of larch arabinogalactan (wood gum, wood sugar, larch gum, "Stractan", "Ara-6") suggest it may be used in numerous, exciting future applications. Evidence of this can be seen in the medicinal chemical, pharmaceutical, and bio-technical fields where current research and development has resulted in the creation of arabinogalactan-based products with unique characteristics. Larch arabinogalactan possesses minimal toxicity and is approved for food use. *(55 references, 1 illustration)*

PHYSICAL CHARACTERISTICS

Arabinogalactans are class of long, densely branched high-molecular polysaccharides MW: 10,000-120,000 (1). In nature, arabinogalactans are found in several microbial systems, especially acid-fast *Mycobacteria* (2) 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 include leek seeds (4), carrots (5), radish (6), black gram beans (7), pear (8), maize (9), wheat (10,11), red wine (12,13), Italian ryegrass (14), tomatoes (15), ragweed (16), sorghum and bamboo grass (17), coconut meat and milk (18). Several of the major naturopathic immune "enhancer" herbs contain signifcant amounts of arabinogalactans, such as *Echinacea purpurea, Baptisia tinctoria, Thuja occidentalis* (19), *Angelica acutiloba* (20) and *Curcuma longa* (21).

The major commercial source of arabinogalactan is the Larch tree. Two sources are Western Larch *(Larix occidentalis)* and Mongolian Larch *(Larix dahurica)* (22). Most commercial arabinogalactan is produced from Western Larch, a renewable resource, through a counter-current extraction process. The resultant liquor is refined into a light cream-colored powder having an indefinite shelf life. High-grade larch arabinogalactan is composed of greater than 98% arabinogalactan. Arabinogalactan gum is 100% water soluble and produces low viscosity solutions. As produced, larch arabinogalactan is a dry, free-flowing powder, with a very slight pine-like odor and sweetish taste. As compared with other natural polysaccharides, the unique properties of larch arabinogalactan are: ease of solution, complete solubility; good body properties without viscosity buildup; excellent dispersant and surfactant properties; and stability over a wide range of concentrations, pH and temperature.

CHEMICAL NATURE

Larch arabinogalactan is composed of galactose and arabinose units in a 6:1 ratio, with a trace of uronic acid. The molecular weights of the major fractions of arabinogalactan in larch are 16,000 and 100,000. Gel chromatography indicates arabinogalactan is a single species of 19 kDa, while light scattering gave a molecular weight of 40 kDa. Glycosyl linkage analysis of arabinogalactan is consistent with a highly branched structure comprising a backbone of 1,3-linked galactopyranose connected by 1,3-glycosidic linkages, comprised of 3,4,6-,3,6-, and 3,4- as well as 3-linked residues (23). *[See figure 1]*

EFFECT ON IMMUNOLOGIC SYSTEMS

Natural Killer cell (NK) and Macrophage activation

The receptor specificity of arabinogalactan is not well characterized. Cultures of human peripheral blood mononuclear cells as well as cultures of preseparated peripheral non-adherent cells and monocytes showed enhancement of natural killer cytotoxicity against K562 tumor cells when pretreated with larch arabinogalactan for 48-72 h. *Moreover, preseparated peripheral non-adherent cells and monocytes of individual donors could exhibit various responses to arabinogalactan when cultures derived from bleedings after intervals of several months were assayed.* Arabinogalactan-mediated enhancement of NK cytotoxicity was not initiated directly but was found to be governed by the cytokine network. Generally, larch arabinogalactan pretreatment induced an increased release of interferon gamma (IFN gamma), tumor necrosis factor alpha, interleukin-1 beta (IL-1 beta) and IL-6 but only IFN gamma was involved in enhancement of NK cytotoxicity (1).

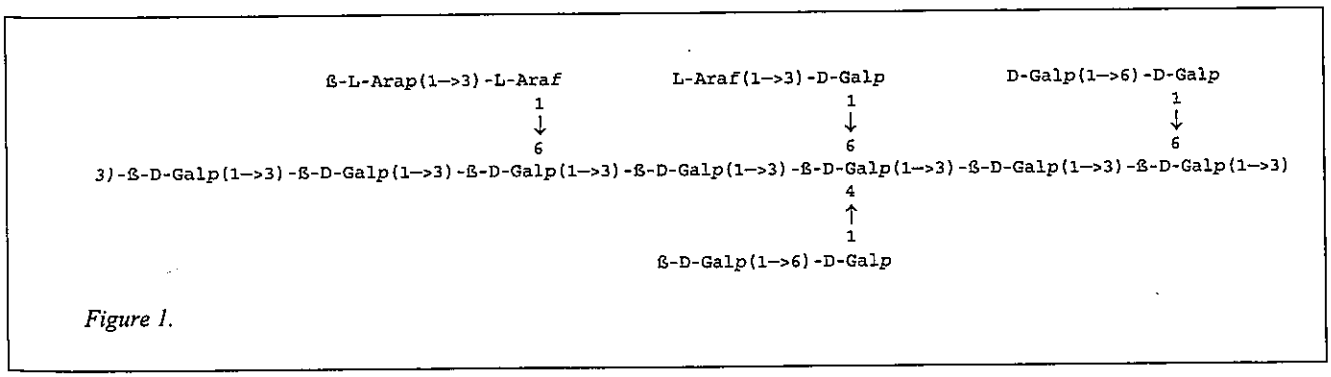

Figure 1.

A similar response has been noted for arabinogalactans isolated from *Echinacea purpurea* (47) This polysaccharide induced macrophages to produce tumor necrosis factor (TNF-alpha), interleukin-1 (IL-1), and interferon-beta.

Acidic arabinogalactan, a highly purified polysaccharide from plant cell cultures of *Echinacea purpurea*, with a molecular weight of 75,000, was effective in activating macrophages to cytotoxicity against tumor cells and microorganisms *(Leishmania enrietti)*. This arabinogalactan did not activate B cells and did not induce T cells to produce interleukin-2, interferon-beta 2, or interferon-gamma, but it did induce a slight increase in T-cell proliferation. When injected ip, arabinogalactan stimulated macrophages.

Other known immunomodulatory plants with effects known to be derived from their polysaccharide fraction include *Baptisia tinctoria, Angelica acutiloba*, and *Thuja occidentalis.* Researchers have concluded that the antigenic regions of immunoreactive arabinogalactans from all the sources, *(Echinacea, Baptisia, Thuja* and *Larix)* show structural differences (19). Initial information obtained from comparative studies indicates that larch arabinogalactan presumably interacts with a receptor that showed specificity for a NK-cytotoxicity-enhancing oligo-saccharide from *Viscum album,* since the action of both components was not synergistic but rather competitive (1).

Reticuloendothelial activation

Low to middle MW (5,000—50,000) arabinogalactan polysaccharrides were found to have strong immunostimulating properties with simultaneous anti-inflamatory properties, and were especially suitable as radiation protecting agents in doses as low as 20-50mg orally (47). The anti-inflamatory effects were also shown to be effective in the treatment of numerous allergies (46).

Ukonan C, a phagocytosis-activating arabinogalactan isolated from the rhizome of *Curcuma longa L.*, was found to have reticuloendothelial system-potentiating action. Oxidation caused a decrease in or disappearance of the immunological activities (21). Sanchinan-A, a reticuloendothelial system-activating arabinogalactan has also been isolated from sanchi-ginseng (roots of *Panax notoginseng*) (22).

Saposhnikovan A, an acidic arabinogalactan polysaccharide isolated from the roots and rhizomes of *Saposhnikovia divaricata*, showed remarkable reticuloendothelial system-potentiating activity in a carbon clearance test (24).

Effects on complement

An anti-complementary polysaccharide, AR-arabinogalactan, was isolated from the roots of *Angelica acutiloba Kitagawa* (Japanese name = Yamato-Tohki), After incubation of serum with AR-arabinogalactan in the absence of Ca2+ ions, a cleavage of C3 in the serum was detected by immunoelectrophoresis as well as from the consumption of complement when rabbit erythrocytes were used in the assay system. A marked consumption of C4 was also observed to have occurred when serum was incubated with AR-arabinogalactan in the presence of Ca2+ ions. Collectively considered these results indicate that the mode of complement activation by AR-arabinogalactan is via both the alternative and the classical pathway (25,26).

AR-arabinogalactan is comprised of comprised one neutral and two acidic arabinogalactan units and one neutral arabinan unit). Neutral arabinogalactan showed the most potent anti-complementary activity, while both acidic arabinogalactans had simliar moderate activities, but arabinan had weak activity. Acidic arabinogalactan anti-complemenary activity is expressed mainly through the classical pathway, whereas neutral arabinogalactan had markedly increased activity through the alterative pathway (27).

Ukonan C, the reticuloendothelal actvating arabinogalactan from the rhizome of *Curcuma longa* L., was also found to have anti-complementary activities (21).

Antiviral effects

Arabinogalactans enhance the effectiveness of viral nucleotide analogs. Daily injections of a conjugate consisting of adenine arabinoside 5'-monophosphate (araAMP, vidarabine monophosphate) and arabinogalactan (7.9 residues araAMP per molecule arabinogalactan), at a dose of 3 mg of araAMP/kg, into woodchuck carriers of woodchuck hepatitis virus (WHV) decreased serum levels of WHV DNA. A dose of 3 mg/kg of unconjugated araAMP was ineffective, while a higher dose of araAMP (15 mg/kg, 14 days) produced a slight drop in WHV DNA. After cessation of dosing with the conjugate, serum viral DNA levels remained depressed for 42 days. In contrast, after cessation of dosing with araAMP alone, WHV DNA rapidly returned to original levels (28).

EFFECTS IN METASTATIC DISEASE

Blocking of organ-specific experimental metastasis

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 glycocongates on the metastatic cells and a hepatic-specific lectin (e.g., the D-galactose-specific hepatic binding protein) found in liver parenchyma. Several studies have compellingly shown that arabinogalactan inhibits this reaction, thus acting as a "reverse lectin."

In one study, the effects of arabinogalactan was investigated in a syngeneic tumor-host system using a new 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. Treatment with arabinogalactan reduced the amount of liver metastases and prolonged the survival times of the animals in both studies. Host treatment was more effective than tumor cell pretreatment. This was shown to be an effect of arabinogalactan blockade of potential liver receptorsby covering of galactose-specific binding sites (29). Ths was also verified in a repeat study (30).

In a third study, the rapid clearance and uptake by the liver of tritiated alpha 1-acid (asialo)glycoprotein from the circulation of Balb/c mice was markedly delayed after preinjection of D-galactose or arabinogalactan. The preinjection (1 h) and regular application (for 3 days after tumor cell inoculation in Balb/c mice) of the receptor blocking agents D-galactose and arabinogalactan prevented the settling of sarcoma L-1 tumor in the liver completely. Other galactans, dextrans, and phosphate-buffered saline showed no effect. Therefore, when lectins were blocked with competitive-specific glycoconjugates, colonization was prevented (31).

Arabinogalactan completely prevented the settling of metastatic cells of sarcoma L-1 tumor in the liver of Balb/c mice and greatly reduced the colonization process of highly metastatic Esb lymphoma cells of the liver of DBA/2 mice. Therefore, when hepatic lectins were blocked with competitive glycoconjugates, tumor cell colonization of the liver could be prevented in two different model systems (32).

USES IN LABORATORY PRACTICE

Contamination of platelets

Contamination with plasma proteins could not be detected with use of unlabeled platelets that had been incubated with radiolabeled plasma proteins followed by washing with larch arabinogalactan ("Stractan"). The arabinogalactan washed platelets were assessed for function by using aggregometry. The response of arabinogalactan washed platelets to collagen and thrombin was identical to that of unwashed platelets. The morphology of the arabinogalactan-washed platelets indicated that degranulation had not occurred. With use of antibodies directed against the alpha granule membrane protein GMP-140 or fibrinogen, no evidence of secretion or plasma protein contamination was observed. The results indicate that this procedure is a convenient method for the separation of platelets from platelet-rich plasma, free of plasma proteins, which are suitable for bioassays, functional studies, and morphologic investigations (33).

As a carrier molecule for drug or diagnostic agents

Arabinogalactan has properties that make it suitable as a carrier for delivering diagnostic or therapeutic agents to hepatocytes via the asialoglycoprotein receptor (23). Arabinogalactan produced no adverse reactions in single intravenous dose (mouse, 5000 mg/kg) and repeat dose toxicity studies (rats, 500 mg/kg/day, 90 days) (23). The 9 kDa and 37 kDa fractions from larch arabinogalactan are apparently the best candidates for use in hepatocyte directed drug delivery (34). Larch arabinogalactan improves liver contrast enhancement, and has a significant effect on hepatic lesion detection as assessed by CNR (35).

EFFECTS ON VASCULAR PERMIABILITY

Several studies have shown larch arabingalactan to enhance vascular permiability (36). Intravenous injection of arabinogalactan together with pontamine sky-blue dye into mice increased vascular permeability and led to marked blueing of the ears. Arabinogalactan caused a rapidly progressing ear blueing (maximal coloration 20-30 min after injection). This response was suppressed by pretreating the animals with the histamine H1-antihistamines levocabastine and loratadine (37).

OCCURENCE IN MICROBIAL SYSTEMS

As a component of Mycobacteria

As previously mentioned, arabinogalactan is a structural component of the cell wall of most acid-fast bacteria, including *M. Tuberculosis* (3), *M. Leprae* (38) and *M. smegmatis* (39). The antitubercular drug ethambutol's mechanism of action is thought to be through the inhibition of arabinogalactan synthesis (40). During tuberculosis, exposure of monocytes to circulating factors, including arabinogalactan, may induce the suppressor activity observed in some anergic patients. In addition, TB plasma and arabinogalactan directly inhibited the phytohemagglutinin-stimulated responses of T lymphocytes. In a quantitative assay of monocyte attachment to plastic, both TB plasma and AG significantly increased monocyte adherence from basal levels, suggesting that arabinogalactans circulating alone or bound in immune complexes may account for the observed effects of TB plasma.

Similar in vivo exposure may contribute to the cell-mediated suppression of lymphocyte responses in tuberculosis (41), although it is highly unlikely that that larch arabinogalactan could produce the same effects, as particular arabinogalactan receptors are highly individualized (1,19), and much of the anergy-inducing activity of TB arabinogalactan is probably produced by its matrixing with peptidoglycan (41). Until appropriate studies are performed, I would not recommend using arabinogalactans in an active tuberculosis patient. Nonetheless, it is intriguing to note the often observed lack of malignant disease in tubercular populations (52).

Fecal breakdown

Larch arabinogalactan is also an excellent source of dietary fiber (48), and has been shown to increase the production of short-chain fatty acids (SCFA), principally butyrate. Butyrate has a particularly important role in the colon. It is the preferred substrate for energy generation by colonic epithelial cells (49) and it has also been shown that butyrate protects these cells against agents that lead to cellular differentiation (50).

In one study *in vitro* faecal incubation system was used to study the metabolism of complex carbohydrates by intestinal bacteria. Homogenates of human faeces 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 h of incubation. Arabinogalactan increased the yield of SCFA and acetate in all samples at all times and butyrate concentrations exceeded propionate in all samples. Faecal homogenates incubated with cellulose showed no greater SCFA production than controls. Pectin and arabinogalactan also decreased ammonia generation, but the reductions were not significant unless subjects were pre-fed these materials; cellulose had no effect on ammonia generation (42,43). Larch arabinogalactans are easily digested by human colonic *Bacteroides* growing in continuous culture, yielding butyrate (44).

E.coli adherance

Arabinogalactans are useful for therapeutic treatment of infections caused by pathogenic microorganisms, particularly intestinal bacteria, such as Gram-negative types. Treatment with arabinogalactan is particularly applicable to bacterias of the *Enterobacteriaceae* type such as *Escherichia coli* bacteria, particularly those strains manifesting K88+ fimbrae. Arabinogalactans were shown to have dramatic effects on bacterial adherence (45).

Blood group activity

Some arabinogalactans appear to have blood group H activity, although this may be species specific (51).

SAFETY AND TOXICITY

Preliminary acute toxicity tests performed on albino rats have indicated that larch arabinogalactan is significantly less toxic than methyl cellulose (48). Other studies have shown that laboratory diets comprising of up to 50% larch arabinogalactan had no apparent ill-effects on animal subjects after 6 months (47).

Larch arabinogalactan is FDA approved for use in food applications as per 121.1174 and 121.1219 (Code of Federal Regulations, Title 21, 1974)and may be safely used as anemulsifier, stabilizer, binder, or bodying agent in essential oils, nonnutritive sweeteners, flavor bases,non-standard dressings, and pudding mixes. The use of Larch arabinogalactan has also been formally approved by the Canadian Governor-in-Council.

DISCUSSION

It is possible that the multiplicity of biologic actions in those medicinal plants known to contain polysaccharides result from a series of "ranges" in which certain size polysaccharides produce either immune augmentation or inhibition?

In general, it may be said that "low" molecular weight polysaccharides (5,000-15,000) tend to produce more of an anti-inflamatory, anti-complementary, anti-allergy effect (25,46); whereas "high" molecular weight polysaccharides (75,000-125,000) produce more reticuloendothelial stimulation (21,24) and monocyte-enhanced natural killer cytotoxicity (1). The "mid" weight polysaccharides (15,000-50,000) seem to act in an altogether different way, enhancing carbon and other types of toxin clearance by macrophages (24). The molecular weights of the major fractions of larch arabinogalactan are 16,000 (low/mid) and 100,000 (high) which perhaps explain its peculiarly diverse actions.

Use in conjunction with other agents

In general, oxidative agents inhibit the activity of most polysaccharides (21) whilst reduction can notably enhance them (53), typically by "reducing" side chains into more antigenic forms. Thus, concurrent administration of arabinogalactans with anti-oxidants such as ascorbate may enhance their efficacy. The use of halide donors, such as potassium iodide, in conjunction with arabinogalactan and ascorbate can produce quite prodigious increases in cellular myeloperoxidase activity, as measured by a candicidal index (54). Myeloperoxidase levels are typically depressed in chronic candidasis and increased in breast cancer (55).

The reticuloendothelial-activating effects of arabinogalactan would certainly dovetail well in such a therapeutic scenario. Larch arabinogalactan has been studied for use in experimental models of metastatic disease spread to the liver, including its use in conjunction with modified citrus pectin. Both polysaccharides work in essentially the same way, that is, by inhibiting the attachment of metastatic cells to liver parenchyma by competive binding to a liver lectin, the hepatic galactose receptor.

Use in pediatric otitis media

Prophylactic use of larch arabinogalactan can decrease the frequency and severity of pediatic otitis media (54), especially in circumstances where the predominant organisms are gram negative rods (46). This may be the result of phagocytosis enhancement, improvement in opsonization, competitive binding of bacteral fimbrae, or all three.

Use in HIV

Although shown to produce only slight increases in CD4 cells, treatment of HIV disease with larch arabinogalactan can result in significant improvement in succeptibility of HIV related opportunistic infections (54). This may result from activation or enhancement of macrophage/monocyte/NK cell activity, typically the role of CD4 cells.

Use as a delivery adjunct

Because of its effects on vascularity and rate of hepatic uptake, concurrent administration of larch arabinogalactan with other therapeutic agents can be considered rational. This may apply to anti-hepatitis agents in addition to hepatoprotective drugs. The immunoaugmentive effects, anti-radiation effects and drug facilitative effects of larch arabinogalactan indicate promise as a concurrent therapy in patients undergoing conventional cancer treatment.

Use as a fiber supplement

Because of its ability to increase colonic butyrate and decrease colonic amonia concentrations, arabinogalactan may be a preferable form of fiber therapy, as the major commercial source, methyl cellulose does not do this to any significant degree (in addition to having a lower LD50!)

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