The Role of Lectins in the Formation of Disease and Their Potential Use in Treatment

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Abstract

The properties of lectins have been known for some time and extensively studied. Their ability to cause disease and to function as markers which delineate specific pathological processes has been reported, but until recently, the role of lectins in the treatment of disease has only been suggested by a variety of sources. It wasn't until the introduction of lectin chemistry into clinical practice by naturopathic physicians that their potential has been explored.

Introduction

The concept that foods could cause diseases as well as prevent them is not new in medicine. It wasn't until the 1960s that this concept was introduced into clinical medical practice by Dr. James D'Adamo in ***One Man's Food is Someone Else's Poison*** (1). Based primarily on clinical observation he delineated specific dietary regimens for his patients based on their blood types. Later, Dr. Peter D'Adamo expanded upon this work by determining the scientific basis of his father's clinical research. In his investigations into the role specific foods played in the development of disease, he determined that his father's observations were based largely on the effects of dietary lectins. From his own research (2, 3) Dr. Peter D'Adamo has further elucidated the role of lectins in the treatment and prevention of disease.

Until recently, most work on the medical significance of lectins has focused on their role as causes of disease or as immune system modulators (4,5,6). In the 1950s, 1960s and early 1970s, specific investigations of their role in causing certain diseases were undertaken by a variety of authors (7,8, 9,10). Most investigations of lectins have been primarily focused on their diagnostic role as markers of specific disease states, but some later studies (11) have begun to look at their potential as therapeutic agents.

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It has long been recognized that lectins have the ability to severely disrupt the intestinal protective barrier, resulting in malabsorption and nutritional deficiencies as well as causing a type I non-specific immune reaction (12). Despite considerable evidence that lectins readily and selectively attach themselves to a variety of tissues causing an immunologic response, few modern day researchers have made the connection between this phenomenon and subsequent formation of disease. Rather, much of present day lectin research has focused on their use in identifying specific loci of cellular damage and elucidating specific biochemical pathways inherent in the pathophysiology of the disease process (11,13).

The work begun by Dr. James D'Adamo and further developed by Peter D'Adamo, ND has proven to be a clinically effective and scientifically demonstrable naturopathic therapy. As with most scientific endeavors, what began as a clinical observation was further defined, first by the formation of a hypothesis, followed by a review of the literature and a subsequent testing of the hypothesis. What makes this uniquely naturopathic is the emphasis on clinical application and outcomes rather than being purely an exercise in scientific research.

This is a review of the role lectins play in the disease process as well as their future role in the treatment of specific disease conditions. Many clinicians have begun to utilize food lectins as therapeutic options in the treatment of specific diseases. Clearly,

a standardization of therapeutic protocols is needed, and it is hoped that clinical outcomes research will be forthcoming. The proof of the effectiveness of lectins in the prevention and treatment of disease will not be determined from placebo-controlled, double-blind studies, but rather from clinical outcomes research. This is because, as with other holistic therapies, it is often difficult to determine what specifically caused the clinical improvement experienced by the patient as there are a multiplicity of factors to be considered. Clinical outcomes research allows the patient to be their own control, is more cost effective and puts research in a setting where it is beneficial to the patient.

What are Lectins

The word lectin is from the Latin *legere* which means "to bind" or to "pick and choose." Lectins are abundant in nature, and were first isolated in 1888 by Stillmark at Estonia University (2). Lectins are found in most plants but are particularly high in legumes and grains (14). Seafood such as shellfish, eel, halibut and flounder also have high lectin contents. The amount of lectin concentration generally accounts for 1% to 3% of the protein content of the specific food, and in the case of plants, the amount is dependent upon the degree of plant maturation (2).

Lectins are non-immunologic protein-polysaccharide molecules having a strong binding affinity for the complex carbohydrates which are abundant on cell surfaces (15). Lectins bind in a manner similar to antibodies, forming an irreversible covalent bond. The binding of lectins can often be inhibited by specific monosaccharides (2,12, 16). An example of a high molecular weight polysaccharide which conveys a protective effect is arabinogalactan, found in a variety of foods and herbal medicines. This class of molecules has been shown to occupy the binding sites of various microorganisms, preventing them from attaching to cellular surfaces and making it easier for the immune system to eliminate them (12). Another example is *Fucus vesiculosis* (Bladderwrack), which forms a protective barrier, especially for group O (substance H) cells (17).

Actions of Lectins in the Formation of Disease

Lectins are largely resistant to the process of digestion and heating. Some possess a high degree of resistance to cooking, passing relatively intact into the intestinal tract, while others are relatively resistant to enzyme and hydrochloric acid activity, even with optimal digestion. Of the lectin ingested, it is estimated that anywhere from 1% to 5% passes unscathed into the intestinal lymphatics, an amount sufficient to cause an immune reaction (2,12). This occurs despite the abundance of intestinal mucopolysaccharide which forms the protective layer for the gut mucosa.

Higher lectin loads are seen with raw food diets, especially if the foods have been picked before they fully ripen. Foods ingested before they are fully mature contain a decreased amount of naturally occurring digestive enzymes, while possessing an increased number of inhibitory enzymes. As well, decreased amounts of hydrochloric acid secretion by the stomach or a deficiency in secretory IgA in the intestinal tract also contribute to an increased lectin absorption. In grains and legumes, which normally contain large amounts of lectin, lower concentrations are found in their sprouted counterparts, due to their utilization during the sprouting process.

The ability of the body to digest various lectins is felt to be due to the concentration of disulphide cross linkages in the lectin itself, i.e., the greater the number the more resistant to denaturation (12). Additionally, many foods contain lectins which are enzyme inhibitors, thus adding to their ability to bind to cellular surfaces (18). An example of this is lectin induced plasmacytosis by *Phytolacca decandra* (PWM) and other herbal compounds such as *Echinacea angustifolia*, which seemingly make their way through the intestinal border intact (12). Once they have reached the intestinal lymphatics they bind to lymphocytic cell surfaces causing T and B cell activation, promoting humoral and cellular immunity.

The amount of lectin exposed to the brush border is dependent upon the health of the digestive tract, and the many factors which come to play during the digestive process. Because of the affinity of lectins to irreversibly bind to many sites at once, which results in agglutination, they can cause considerable gastrointestinal discomfort in high concentrations (19). The discomfort may occur in the stomach soon after ingestion, or much later and further along in the intestinal tract. The degree of symptomatology is probably a function of the extent of individual susceptibility (formation of immune response) and general health of the gastrointestinal tract.

The binding of lectins to human gastric mucosa tends to be patchy and variable, which may be a reflection of the amount of surface glycoproteins available. The quantity may also be a function of cell surface antigens such as ABO, Rh(D), M,N, Lewis A/B, and others (20,21). Stressors, secretor status (one who secretes A,B,H and other antigens), digestive ability, ingestion of dietary toxins and intestinal microflora may also play a role.

It has been shown that certain lectins such as wheat germ agglutinin (WGA), have a strong affinity for gut mucosa (21) as well as for the mucous secretions of salivary glands (12). WGA-gut mucosa interaction leads to a patchy and irregular binding which exposes the previously protected gut epithelial cells to lectin-cell interaction. In some experimental models, this lectin-epithelial interaction is seen as a precursor to the development of malignancy (12,22). Additionally, a disruption of the gut protective layer by lectin is thought to be the impetus for the proliferation and adherence of abnormal bacteria such as Helicobacter pylori with the type I immune reaction resulting in inflammation. Both are implicated in the generation of peptic ulcer disease. This disruption of the gut protective layer makes it easier for abnormal bacteria to establish linkage with epithelial cells, also by lectin-cellular interaction (12,20).

Even under optimal digestive conditions a small amount of ingested lectin binds to the M cells of Peyers patches, causing stimulation of lymphocytes. Specific serum IgM and IgG antibodies have been found against foods which have only been ingested so the antibodies were not acquired through immunization or desensitization (23,24). Certainly exposure to environmental as well as food sources is responsible for immune system development and is thought to be one of the

mechanisms of early development of immunity in young children. Clinically it is not unusual to see children with frequent colds, influenza, respiratory infections and respiratory distress. These children often present with chronic mucous secretions perhaps brought on by ingestion of dietary lectin. Clinical observation and allergy testing have confirmed that dietary lectins associated with dairy products, wheat and corn are among foods causing the greatest amount of mucous production and predisposition to gastrointestinal diseases (25). An orderly introduction of foods into a child's diet acts to enhance, rather than over stimulate, a child's immune system development thus eliminating an excess of mucous production (26). Beginning with simple foods which are easily digested and contain not only lectin to stimulate immune production but protective substances, such as arabinogalactans, to help modulate it, aids the immune system in developing incrementally rather than over-taxing its resources. A gradual increase in the complexity of foods as the gastrointestinal system develops helps to keep the child from developing allergies to multiple foods (10).

In response to assault by lectins, the gastrointestinal mucosa increases secretion of a sialic acid-rich mucous protective layer. The enzyme neuraminidase removes the sialic acid residues from the protective mucosal barrier, thus rendering it ineffective against gut microorganisms, poorly digested macromolecules and lectin exposure (12). The enzyme is secreted by a number of pathogenic bacteria which may have developed the enzyme as a survival mechanism. Because of the exposure to different dietary stressors over thousands of years in blood group A individuals, the ability to secrete a mucous protective barrier is enhanced, whereas in blood group O individuals it is not as great. This is felt to be due to higher amounts of hydrochloric acid secreted by blood group O persons which effectively sterilizes the food before it enters the small bowel. This, as well as some of the inherent properties of the specific blood group cells (22) is thought to be one of the reasons that there is a greater incidence of gastric ulcer disease related to Helicobacter pylori in blood group O individuals than in blood group A.

Sialic acid residues which are secreted as part of the mucous protective barrier increase the affinity of complement to bind, thus making it easier for the immune system to eliminate harmful microorganisms or lectins. In persons whose mucous secretions do not contain as many sialic acid residues (non-secretors), the ability to modulate the resulting inflammatory reaction is not as great, resulting in prolonged inflammation. Thus a greater amount of damage to the underlying tissues ensues. Sialic acid residues have a profound anti-microbial and anti-lectin effect, which is probably the reason there seems to be a greater number of non-secretors who are suffering from chronic autoimmune and infectious diseases.

Mucous secretions in the gastrointestinal tract, as well as other organ systems, are a way of protecting the system from contact with foreign antigens from an external source, such as a virus or bacteria, or from an internal source such as an ingested lectin. During times of increased stress (cold, flu and allergy season, dietary indiscretions, etc.), the body increases its mucous production in order to eliminate the offending agents. Therefore, an increase in mucous production signifies some sort of insult on the body's defenses, and needs to be addressed with immune support rather than suppressed by administration of over-the-counter medications such as antihistamines and decongestants. Suppression decreases the production of the mucous protective barrier and secretory IgA needed to eliminate the microorganism or lectin which is the cause of its production.

In addition to increasing the production of intestinal mucus, lectins can also elicit a trophic effect upon gut epithelial cells. In a study to determine the effects of lectin on growth of intestinal cells, it was found that red kidney bean phytohemagglutinin (PHA) produced a "potent trophic effect" on the small, but not large intestines of rats (23). The maximal area of lectin stimulated growth was in the jejunum, with lower amounts seen in the ileum. The authors felt that this may have been due to lectin load, the greater amount of exposure being in the jejunum. Other studies suggested that blood group H (type O) was found in greater amount in sloughing intestinal cells as opposed to group A and B glycolipids, suggesting a greater turn-over of group O cells (27). Interestingly, despite the blunting and flattening of intestinal villi, the affected rats did not suffer from nutrient deficiencies as evidenced by an increase in growth (21). Additionally, PA-I lectin, isolated from the human pathogen *Pseudomonas aeruginosa*, has been shown to stimulate small intestine metabolism and growth (28). The growth was found to be similar to that induced by kidney bean lectin. This observation may explain the preponderance for blood group O persons to develop irritable bowel and Celiac disease (12,21,27).

As the protective barrier becomes less effective in scavenging excess lectin, the exposure of lectin to cell membranes becomes greater. When exposed to the cell membrane, mitogenic lectins exhibit a phenomenon of "positive cooperativity" (12). In this scenario the first few lectins binding to the cell membrane rearrange it in such a way that further lectin binding is enhanced (12,29). As the lectin content of the cell surface increases, the ability of the cell to conform to different surroundings becomes impaired due to its inelasticity and stickiness. In other words the cell becomes more rigid and less adaptable. Further changes take place at the cellular level resulting in a decreased ability to absorb nutrients, increased gut permeability, a reduction in cellular enzyme systems and changes in the DNA structure and content (12,14,19,30). Lectins can also mimic hormone function by attaching to and activating specific sites on the cell surface (31). These factors are felt to contribute to apoptosis and possibly malignant transformation as the cell attempts to conform to the new environment (32).

Once bound to cellular surfaces, it is felt that lectins do not induce much of a humoral response but rather a cell-mediated response involving the alternative complement pathway. In the gastrointestinal tract, IgA is secreted in large amounts in order to maintain a bacterial balance as well as to absorb allergens. When the foreign material attempts to pass through the brush border, IgA effectively binds to it forming an immune complex. These complexes are mostly destroyed at the site of attachment of the gut wall but also in the liver if passage into the enterohepatic circulation occurs. In cases where lectin

becomes bound to cellular surfaces, the alternative pathway of the complement system is then activated, destroying the cell-lectin-IgA complex. This may be the cause of acute appendicitis (33).

Along with complement activation, seratonin, histamine and bradykinins become activated resulting in an increase in capillary permeability and the migration of blood cells into the extravascular spaces. If this reaction is prolonged or not well modulated, as in a non-secretor, white blood cells, macromolecules and circulating immune complexes cross the brush border entering the circulation (34). Immune complex formation has the effect of further potentiating the inflammatory reaction at other sites in the body, which eventually may become the precursor to the formation of autoimmune diseases.

Depending upon the tissue affected and the amount of lectin bound, tissue turn-over rates will be variable, thus allowing for an expeditious or gradual resolution of the inflammation. This is seen for example in the affected synovial tissue in persons with rheumatoid arthritis (RA) who experience considerable pain, inflammation and swelling. As turn-over of synovial tissue is at a slower rate compared to gastrointestinal mucosa, it takes longer for the inflammation to resolve (35). Comparatively, gastrointestinal inflammation should resolve more quickly but can become chronic due to a high rate of lectin exposure. Therefore, in cases of chronic gastrointestinal distress, as well as other immune complex generated conditions, identification of the offending allergen becomes all-the-more important as elimination prevents additional pathological changes from taking place. The slower turn-over rates in some tissues accounts for the longer healing times associated with some diseases, such as RA (35).

Evidence supports the findings that malignant transformation of otherwise normal cells is associated with alterations at the cell surface which can be detected by lignin/lectin binding. These findings have led to a plethora of studies outlining the use of lectins not only to determine the extent and specificity of pathology, but also demonstrating that a progression of stages occurs during malignant transformation (11,30, 36,37,38,39,40,41,42).

With inflammation of the kidney, Tamm-Horsefall glycoprotein is secreted by the collecting tubules as a response to the offending agent. Studies have shown that one of its functions is to eliminate wheat germ agglutinin (WGA) by precipitation before it can irreversibly attach to kidney cells. Additionally, Tamm-Horsefall glycoprotein has been shown to provide a protection against the toxic effects of *Ricinis communis* (ricin), *Viscum album* (mistletoe) and *Abrus precatorius* (abrin-a) (43). Thus, casts which are primarily composed of Tamm-Horsefall mucoprotein, seen on microscopic examination of the urine, signify cellular insult by an offending agent be it toxin, lectin, or microorganism, and represent the body's attempt to clear it.

Lectins are known to cause a number of biological effects including lymphocyte proliferation (blastogenesis) and the induction of cytokine production (44, 45, 46) as well as having the ability to inhibit specific antibody stimulated T cell activity (46). Concavallin A (Con A), a methyl-alpha-mannose lectin, binds to the surface of mononuclear cells, most notably CD4 and CD36 cells and is involved with the inhibition of production of interferon-alpha/beta (IFN-a/b). Con A also inhibits CD45 lymphocyte surface antigen which is a potent regulator for lymphocyte activation. This becomes important in viral infections where T and B lymphocytes and IFN-a/b are needed to fight the infection. While RNA viral activity also induces IFN-a/b, Con A lectin activity seems to affect IFN-a/b at an earlier stage thus allowing for the effects of the virus. Additionally, Con A inhibits the formation of phagoglycosomes causing interference with the intracellular digestion of phagocytosized materials (44).

Lectins and the Development of Autoimmunity

Specific lectin binding to cells occurs based primarily on ABO blood group determinants as well as other surface antigens because of their affinity for sialic acid rich glyco-conjugates (47). Because of this, lectins can be used to delineate the microscopic structures of the tissue in order to study the pathophysiology of the disease process. In one study specific blood group reactive lectins were delineated in human kidney samples as to the region of affinity (48). Blood group A reactive lectins, all specific for alpha-D-N-acetyl-galactosamine (GalNAc) were *Helix aspersa* (HAA), *Helix pomatia* (HPA), and *Griffonia simplicifolia* I-A4 (GSA-I-A4). These agglutinins bound to the endothelium in specimens with blood groups A and AB, while in other samples, they reacted predominantly with tubular basement membranes, and with certain tubules. Lectin from *Dolichos biflorus* (DBA) and *Vicia villosa* agglutinins (VVA), reacting with blood group A1 substance, showed an irregular binding pattern to tubules in all blood groups. Blood group B-reactive lectins, specific for alpha-D-galactose (alpha-Gal) or GalNAc were shown to be *Griffonia simplicifolia* I-A4 and *Sophora japonica* agglutinin (SJA). They selectively bound to the endothelia in specimens from blood group B or AB while in other specimens bound only to certain tubules. Among the blood group O-reactive lectins, specific for alpha-L-fucose (Fuc), *Ulex europaeus* I agglutinin (UEA-I) conjugates bound strongly to endothelia in specimens with blood group O. The reactivity of UEA-I conjugates was found to be less in specimens of other blood groups.

An experimental model of glomerulonephritis shows a mechanism of disease development by ingested lectin. Lectin-induced circulating immune complexes initially demonstrate a diffuse but not granular accumulation on the endothelial cell surfaces of the kidney glomerulus. Usually within 3 hours following the insult immune deposits are found to have localized to the subendothelial region where they remain for a longer period of time (approximately a week). After this period the antigen-antibody complexes move from the subendothelial region to the subepithelial region, probably because of the filtration pressure, again forming immune deposits (29, 49). Possibly the reason that the immune complexes remain in the subendothelial region for so long is because of the surface charges which help maintain the integrity of the glomerular basement membrane. Additionally, damage from complement and cytokine activation may also contribute, but would not explain damage when complement is absent from the process. Following the initial period of insult, mesangial cell proliferation takes place, probably because of the

prolonged glomerular inflammation. The exact mechanism of this is unknown.

One of the mechanisms of autoimmunity has been postulated to be the work of viruses, the viral capsid antigens believed to cause the inflammatory reactions which eventually lead to the development of the autoimmune process. But viruses only fulfill one of two criteria for the formation of autoimmunity: 1. antigens from an outside source, and 2. the presence of class II histocompatibility antigens. Class II histocompatibility antigens are involved with CD4+ cells and cell surface antigen recognition (12,34). While viral activation of interferon is thought to play a role in the development of autoimmunity, lectins fulfill both requirements by binding directly to HLA-DR antigens. Thus, the body recognizes its own tissues, not as self but as a foreign substance which it attempts to remove. The amount of inflammation is variable in part due to genetic predisposition. Other studies (28,50,51) have shown a relationship between microorganisms and their ability to cross react with otherwise healthy tissue. An example of this is Candida antigen which cross reacts with healthy thyroid tissue and has been implicated as a cause of thyroiditis. *Yersinia enterocolitica*, a bacterial organism, also has been shown to cross react with healthy thyroid as well as ovarian tissue (3).

A number of diseases including systemic lupus erythematosus, rheumatoid arthritis (RA), Behcet's disease and IgA Nephropathy are mediated by the O-linked disaccharide Gal beta 3GalNAc on their cell surfaces to which a T-cell surface lectin binds. This is especially seen in rheumatoid arthritis where the terminal GlcNAc residues on oligosaccharides can bind to the C-type lectin and serum mannose binding protein, thus activating the classical complement pathway (52). This is one of the reasons for the severe and chronic inflammation experienced by patients with RA as well as with the other diseases. In general, complement fixation by the lectin-cell interaction induces a more severe and potentially greater damaging inflammatory process than if complement isn't utilized.

In a study conducted by Krugluger (53), the expression of different leukocyte surface antigens and the binding of various lectins in inflamed gingival tissue was examined. It was found that the gingival tissue of patients with active periodontal disease contained between 5% and 50% CD45+ mononuclear cells, consisting mainly of B lymphocytes. Peanut agglutinin (PNA; specificity for galactose) showed an affinity for infiltrating cells while soy bean agglutinin (SBA; specificity for N-acetyl-galactosamine) bound to epithelial cells. Specific cellular molecules involved in cell adhesion during chronic inflammation of the gingiva were also examined. Blood type specificity was not determined.

Lectins as a Therapeutic Tool

Certain researchers and clinicians now theorize that the same properties of lectins which have the ability to cause a disease process should also be useful as a therapeutic agent if used in proper dosage and under particular conditions. This is because of the apparent specificity of lectins for a variety of mucopolysaccharides and their ability to alter the surface proteins of a variety of organisms thus affecting cellular function. Certainly this has been the case with herbal medications which in part exert their effect by lectin activity. Therefore, identifying lectins and their appropriate utilization can be of benefit. Peter D'Adamo, ND reports that he has successfully applied this principal over the past 10 years (17). He has been effectively treating a variety of diseases by eliminating the lectin burden as well as utilizing their properties in the treatment of cancer and other diseases. Recently a number of other researchers have begun to explore the potential of lectins as therapeutic agents as well (11,54,55,56). Research utilizing lectins as carriers of monoclonal antibodies or specific chemotherapeutic agents has been conducted. Some data as to the effectiveness of specific plant lectins upon cancer cells is available, confirming the anticancer properties of a variety of herbal medicines (55, 56,57,58). Clinical trials have not yet been done, but some physicians have begun to employ lectins therapeutically based on these data. Until further studies are conducted we will not be able to fully evaluate the therapeutic effect of lectins, nor establish optimal dosages.

In general, higher concentrations of specific lectins cause normal cells to undergo agglutination and modification of cellular function. The therapeutic effects of lectins seem to take place at lower concentrations rather than the higher ones experienced with an every-day dietary intake. Concentrations of lectin needed to afford a therapeutic effect seems to be on the order of microgram doses (59,60,61).

Lectins can also have a beneficial effect upon cells. Here too, modification of the cell surface or attachment to a foreign antigen induces the beneficial activity. Macrophages, white blood cells derived from monocytes and active in a variety of immune system functions, have been shown to be involved in both inflammatory reactions as well as tumoricidal activity. Activated macrophage surface markers determine which functions they will perform, including tumor lysis. Specifically, galactose/N-acetylgalactose-amine (Gal/GalNAc) lectin on the macrophage surface seems to be involved with the uptake and recognition of tumor cells (62,63). Once this function has occurred, cell lysis can then take place unimpeded. Cells with the TN antigen, most notably cancer cells (64) have a very strong affinity for macrophage binding sites. Those cells with fully sialylated carbohydrate chains showed a weaker binding pattern (57). This is probably related to the secretor status, and confirms the observation of D'Adamo that the immune responses of secretors, especially blood group A secretors, have more difficulty dealing with tumor activity.

Lectins have demonstrated antiviral activity as seen when WGA attaches to the cell surface keeping the herpes simplex virus (HSV) from attaching. Additionally, Con A also prevents HSV attachment to cell surfaces but does so by attaching to the viral capsid itself. While the antiviral activity of lectins has been demonstrated, certain viruses can in turn be transformed by lectins, resulting in disease. Adenoviruses, bovine leukemia virus and HIV can be transformed from the asymptomatic state to a symptomatic and active condition (12). Whether the lectin does this by causing a transformation in the virus itself or altering the cell surface is largely unknown. Here too, the concentration of lectin may affect its ability to activate or inactivate viral activity.

Lectin derived from the snail, *Achatina fulica* (AF), has been shown to specifically bind to the 9-O-acetyl sialic acid residue associated with acute lymphocytic (ALL) and acute myelogenous (AML) leukemias while having no effects upon normal cell structures (57). Neuraminidase-treated ALL and AML cells did not react to AF lectin, suggesting that the lectin is specific for 9-O-acetyl sialic acid residues (30).

Use of bacterial lectin inhibitors such as mannose to prevent the adhesion of *Eschericia coli* to bladder epithelial cells has been employed in clinical practice for some time. Other bioglycans, such as that from *Crenomytalus grayanus* (mussels), have been found to considerably decrease the adhesion of the bacteria *Eschericia coli, Staphylococcus aureus* and *Pseudomonas aeruginosa* (65). Other plant lectins such as those from *Datura stramonium, Robinia pseudoacacia* and *Dolichos biflorus* agglutinated Streptococcal Group C bacterial cells (66) which prevents them from adhering to human cell surfaces. Because of similar properties exhibited between bacterial cell walls and that of many tumor cells, bacterial inhibition studies utilizing specific glycoconjugates have shown promise as agents to prevent tumor metastases (50). Specifically, PA-I lectin has shown some cytotoxicity against Lewis lung cancer cells (67).

Modified citrus pectin (MCP), but not citrus pectin (CP), has been shown to combine with a variety of galactose-specific proteins on cancer cell surfaces (68). MCP inhibits metastases in rat prostate cancer by adhering to the cancer cell surface thus making it unavailable for aggregation and adhesion needed for metastases. The studies show that MCP does not inhibit the cancer growth but makes it difficult to spread. MCP has been shown to affect not only the metastases of human prostate adenocarcinoma, but human breast cancer, malignant melanoma, and laryngeal epidermoid carcinoma as well (69).

Lectins with specificity for the terminal alpha-1-3 and alpha-1-6-mannose terminals on HIV will cause a neutralization of the viral capsid *in vitro. Galanthus nivalis* (snow drop) has been shown to afford cellular protection by blocking the HIV's ability to bind to cell surfaces. Additionally, it may protect cellular surfaces by blocking HIV binding sites before the virus can attach. This is especially felt to be the case with CD4 cells as they contain a large number of alpha-1-3 and alpha-1-6-mannose terminals (59, 60). Other lectins such as those from lentil, wheat germ agglutinin and *Phaseolis vulgaris* have also shown an effect upon the ability of HIV to bind to cell surfaces (70).

Sato and his associates (71) found that *Triticum vulgaris* (WGA) and *Ricinus communis* (RCAI) significantly bound to the viral capsids of both hepatitis B and C *in vitro*. Their conclusions were that the viral capsids of both hepatitis B and C possessed similar glycoprotein sequences. WGA has also been shown to prevent herpes simplex virus from adhering to cell surfaces by obstructing its attachment site (72).

The intestinal binding ability of the parasite *Giardia lamblia*, as well as its ability to reproduce, were found to be decreased by both WGA and tomato lectin (*Lycoperscion esculenium*), lowering the infectivity and severity of the infection. The degree of inhibition was dose related with maximal effects being seen after 72 hours of exposure. Additionally, a modified WGA, succinylated-WGA was found to be less harmful to normal intestinal cells but as effective against *G. lamblia*. Of importance is that development of resistance to WGA by *G. lamblia* was not noted. Prevention of infection and growth inhibition probably resulted from an inability of *G. lamblia* to adhere to cell surfaces thus arresting cell division (61). In a study conducted on commonly used plant medicines in Zimbabwe for the treatment of Schistosomiasis, the extracted properties of *Abrus precatorius* (Leguminosae), *Pterocarpus angolensis* (Leguminosae) and *Ozoroa insignis* (Anacardiaceae) were found to be lethal to *Schistosoma haematobium* (73). The exact properties of the extracts were not identified but these plants possess high lectin concentrations. Studies on the parasite *Trypanosoma cruzi* showed the organism's ability to infect humans is related to its interactions with cell surface glycoproteins (74). Eggs from the parasites *Haemonchus contortus, Ostertagia circumcincta* and *Trichostrongylus colubriformis*, were found to be agglutinated by a variety of lectins (75).

It has been shown that cancer of the prostate (CAP) is found to a lesser degree in Asian men than in western cultures. Studies have credited this to dietary measures such as the large soy protein ingestion in the Asian population. This has been further confirmed by other studies, which show an increase in CAP in Asian men who adopt a western diet, e.g., high in saturated fats, sugar, dairy and animal products (76,77, 78,79). A study conducted by Evans, Griffiths and Morton (80) showed that a reduction in activity of the enzyme 5 alpha-reductase could be induced by the glycoside genistein found in soy. The enzyme 5 alpha-reductase is responsible for the conversion of testosterone to its more potent form dihydrotestosterone (DHT) which has been implicated in the formation of benign prostatic hypertrophy and CAP. Soy lectin reduced the activity of 5 alpha-reductase by greater than 80% and was found in higher concentration in the prostate gland itself compared to blood levels. The lectin effects were greater at the lower pH (pH 5.5) found in the prostate. Additionally, it was suggested that soy lectin's effect also translated to a reduction in tumor transformation with breast cancer (42,80).

Soybean agglutinin (SBA) has been used for the selective elimination of breast cancer cells from human bone marrow. With this technique, normal hematopoietic cells were not affected, thus making SBA highly selective for breast cancer cells (81,82).

Peanut (*Arachis hypogaea*) agglutinin (PHA) has been shown to agglutinate breast cancer cells, probably at the site of the Thomson-Friedenreich antigen (T, Tn) (81). This is presumed to be the mechanism by which peanut agglutinin selectively attacks breast cancer cells while leaving normal cells relatively untouched.

Autoimmune thyroiditis has been shown to be suppressed by administration of phytohemagglutinin (PHA). PHA reduces the humoral response as well as decreasing infiltration of the thyroid gland (83).

In a study of the traditional Chinese medicine, *Pinellia ternata*, an extract of lectin (PTL) from the rhizome was found to facilitate the release of acetylcholine in mouse motor terminals as well as enhance the permeability of calcium, sodium and potassium channel ions. The

usually irreversible effect of lectin was found to be reversed by mannan, the specific binding sugar for PTL (84).

In an analysis to determine their affinity for certain lectins (85), sarcoma and normal tissue plasma membrane lectin-reactive glycoproteins were studied. The analysis showed that two peanut agglutinin-reactive N-acetylgalactosamine-containing glycoproteins and one lentil agglutinin-reactive mannose/N-acetylglucosamine(-fucose)/sialic acid-containing glycoprotein were detected in osteosarcoma and malignant fibrous histiocytoma (MFH). Additionally, neither of these glycoproteins were detected in normal tissue plasma membranes. The high specificity of these lectins for sarcoma tissue was confirmed by monoclonal antibody studies. Lentil-reactive glycoproteins which were isolated from MFH plasma membranes, exhibited significant binding to membranes isolated from osteosarcoma and liposarcoma as well as MFH. Additionally, moderate binding to synovial sarcoma, aggressive fibromatosis and fibrosarcoma was found. There was minimal to no binding to other soft tissue sarcoma plasma membranes. This suggests that lectin specificity for these types of cancers can be used as a therapeutic tool without an effect upon normal tissues. Specifically, lectin from the Chinese herb Bupleurum (*Bupleuri Radix*) has been shown to promote the cytotoxic activity of macrophages, natural killer (NK) and lymphokine activated killer (LAK) cells against tumor cells, as well as increase the number of tumor infiltrating lymphocytes against sarcoma cells (86).

Purified jack fruit (*Artocarpus integrifolia*) lectin (JFL) was isolated and conjugated to horse-radish peroxidase (HRP) and used to study the cell surface carbohydrate profile of the cytological smears of the uterine cervix. While normal endocervical cells showed weak binding in the membrane and cytoplasm, carcinomatous cells showed strong binding towards JFL. Carcinoma *in situ* cells showed a binding pattern similar to that of carcinoma. Cells with mild, moderate and severe dysplasia showed differences in the intensity of binding of JFL, increasing with the severity of the dysplasia. The authors conclude that "the nature and intensity of binding of jack fruit lectin with cancer tissues suggest that this lectin may be of use as a diagnostic aid in exfoliative cytology" (87). It is theoretically possible that the lectin content of *Sanguinaria canadensis* contributes to the effectiveness of its use as an escharotic agent in the treatment of cervical dysplasia (88). In all probability it is the lectin content of *Sanguinaria canadensis* which contributes to the treatment's effectiveness. JFL may offer another approach, possibly by oral administration.

Amaranthus caudatus agglutinin (amaranthin or ACA), which binds to the Thomsen-Friedenreich antigen (T-antigen) is a histochemical marker with specificity for proliferating cells in human colonic tissues. T and Tn antigens are almost always found on human cancer cells and are the precursors of human blood groups MN. They have the ability to link complex carbohydrates to their protein backbone thus making them detectable by immunochemical studies (64). ACA bound selectively to the cells at the base of the colonic crypt, which is the zone of proliferation, while preferentially labeling cytoplasmic and apical membrane glycoconjugates. As would be expected, a marked increase in histochemical labeling by ACA was seen in adenomatous polyps and adenocarcinoma of the colon, due to the higher concentrations of the T and Tn antigen. Transitional mucosa and connective tissue adjacent to cancers were also labeled by ACA. Neuraminidase studies on colon cancer specimens indicated that removal of sialic acid residues enhanced binding by peanut agglutinin (which also recognizes the T-antigen) but not ACA (89). While the results suggest that ACA may be useful for identifying foci of abnormal proliferation in familial colorectal cancer syndromes, they also raise the question as to ACA's potential as a therapeutic tool.

Specific binding of lectin to Chlamydial cell wall structures is demonstrated by the binding of *Galanthus nivalis* lectin (GNA). Binding of sialic acid residues to peanut agglutinin (PNA), and jackfruit lectin (JFL), were also found in two Chlamydial glycopeptides (90). The study suggests that lectins may be of use as therapeutic agents to keep Chlamydial organisms from entering human cells, thus rendering them more susceptible to immune system elimination.

The herbal *Viscum album* (Mistletoe) lectin (ML-1), has been shown to have antitumoral activity because of its ability to modulate and activate natural killer cells (91). ML-1 also induces apoptosis in myelomonocytic leukemia (92). Another herbal medicine *Agaricus bisporus* lectin (ABL), has also been shown to reverse the proliferation of colorectal and breast cancer cells in humans (93).

An increase in the number of articles relating to the effects of lectins on their abilities to detect specific pathologies and to determine histochemical and cytochemical changes between normal and abnormal tissues underscores their increasing importance in medicine. While few, if any, clinical studies are available to measure the therapeutic effectiveness of lectins, a strong argument is slowly emerging that they possess tremendous therapeutic potential. Within the present allopathic model, the utilization of foods and their properties as medicine stands little chance of being fully developed. It therefore becomes important that the naturopathic profession continues to explore the use of lectins as therapeutic tools and conducts the necessary clinical trials to validate their effectiveness.

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TABLE 1

LECTINS WHICH HAVE DEMONSTRATED THERAPEUTIC AND POTENTIAL THERAPEUTIC BENEFITS

Lectin Source	Disease	Reference
Helix pomatia (snail)	Breast cancer	#17
Arachis hypogaea (peanut lectin)	Breast cancer	#42
Achatina fulica snail	ALL, AML	#65
Galanthus nivalis (Snowdrop)	HIV	#59,60
Triticum vulgaris (WGA)	Giardia	#61
Lycoperscion esculenium	Giardia	#61
Phaseolis vulgaris (kidney bean)	HIV	#70
Lens culinaris (lentil)	HIV	#70
Triticum vulgaris (WGA)	Hep B/C virus	#71
Triticum vulgaris (WGA)	HSV	#72
Glycine max (genistein/soy)	BPH,CAP,Breast CA	#80,81
Pinellia ternata	Nerve function	#84
Lens culinaris (lentil)	Sarcoma/MFH	#85
Bupleuri Radix	Sarcoma	#86
Artocarpus integrifolia (JFL)	Cervical dysplasia	#87
Amaranthus caudatus	Colon cancer	#89
Galanthus nivalis lectin	Chlamydia	#90
Arachis hypogaea, peanut lectin	Chlamydia	#90
Artocarpus integrifolia (JFL)	Chlamydia	#91
Helix pomatia (snail)	Colon cancer	#94
Rana catesbeiana/ japonica	Leukemia/tumors	#95

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