

Biological Activities of Acemannan

By

lex M. Cowser, PhD

December 8, 2010

Introduction

Aloe vera has been recognized as a medicinal plant for over 6,000 years and has been used for treatment of a wide range of medical indications from stomach disorders to cancer. Starting in the 1930's modern science has been applied to formally demonstrate the medicinal value of aloe vera, identify the active ingredient and elucidate the underlying mechanisms of action that account for its wide range of medically beneficial activities.

Acemannan, found predominately in the inner leaf gel of Aloe vera, was identified as the main active ingredient in the inner leaf gel (1). Scientific studies using purified Acemannan have characterized its chemical structure as high molecular weight polysaccharide and have provided insight into underlying cellular communication based mechanisms by which Acemannan provides medical benefit. Acemannan is composed of mannose, glucose and galactose in a 31:1:1 ratio. Mannose, glucose and galactose are each count among the eight essential monosaccharides critical to human health.

Role of Nutrition in Human Health

For optimal health the human body needs proper quantities and balance of a wide range of key nutritional elements. Broadly speaking these include antioxidants, carbohydrates, fats, minerals, phytoestrogens, proteins, and vitamins. In addition certain probiotic microorganisms are required in the digestive tract to facilitate the breakdown of certain food substances and prebiotics are required to support the health of probiotic microorganisms. Maintaining a proper balance of these nutritional elements, probiotics and prebiotics is critical to achieving and maintaining optimal health. Too little or too much of any one of these key nutrients can lead to potentially serious health consequences. While modern western diets provide many of these critical nutrients, due to excessive processing of food it is deficient in some areas and these must be supplemented through nutritional products.

Biochemistry and Structure of Saccharides

Saccharides (carbohydrates) are complex compounds made up of carbon, hydrogen and oxygen where there are at least three carbons. They can occur as linear molecules (such as glucose) or circular molecules (such as deoxyribose). Saccharides can occur as individual molecules termed monosaccharides or in complex polymers terms oligosaccharides or polysaccharides. Monosaccharides are found throughout the body including in the blood (blood glucose), or in individual cells where they serve as building blocks for larger saccharide structures, glycolipids and glycoproteins, or they can be metabolized to provide energy for the cell function and replication.

Monosaccharides can be characterized by the 3-D arrangement of their individual atoms. This approach to structural comparison is known as stereochemistry. From a stereochemistry perspective, monosaccharides are classified as either the D-isomer or the L-isomer depending upon the specific arrangement of atoms. An easy way to think about stereochemistry is that the D-form is the mirror image of the L-form. The stereochemistry of a monosaccharide plays an important role in the types of linkages that can be formed and biological function.

Monosaccharides can be covalently linked together through glycosidic bonds to form complex polymeric structures. There are four types of glycosidic bonds, O-glycosidic, S-glycosidic, N-glycosidic or C-glycosidic, depending upon whether oxygen, sulfur, nitrogen or carbon is used as the central linking molecule. O-glycosidic, S-glycosidic, N-glycosidic or C-glycosidic bonds can be mixed in a single oligosaccharide or polysaccharide to form complex structures. Glycosidic bonds can be further subdivided into α or β depending upon the stereochemistry of the individual monosaccharides being linked together. Because monosaccharides contain at least three and often many more carbons a numbering system has been devised to describe which carbons in each monosaccharide are joined via the glycosidic bond. One can easily appreciate that between the large number of individual monosaccharides, their stereochemistry, type of glycosidic bond, which carbons participate in the glycosidic bond, the orientation around those bonds and whether a polymer is linear, branched or cyclic that a nearly endless array of polysaccharides can be generated in nature.

Disaccharides are relatively simple oligosaccharides and are defined as two monosaccharides are linked together. For example when one glucose and fructose are linked together they form the disaccharide sucrose or table sugar. Following the descriptions above sucrose is formally known as β -D-fructofuranosyl-(2 \rightarrow 1)- α -D-glucopyranoside.

Oligosaccharides are larger polymeric structures where 3 to 10 monosaccharides are linked together. Fructooligosaccharides (FOS) are 3 to 10 fructose monosaccharides linked together by glycosidic bonds. FOS are found in many vegetables. In the human diet FOS are considered prebiotics that provide support for the intestinal probiotics. Oligosaccharides can also be chemically linked to a wide range of proteins and lipids in the body. In these cases the oligosaccharides provide critical cell recognition and cell communication function. For example oligosaccharides make up the ABO blood type specificity and provide critical cellular communication functions required for a healthy immune system.

Polysaccharides are larger polymeric structures where more than 10 monosaccharides are linked together. Polysaccharides with up to 2,500 monosaccharides linked together in highly branched arrays have been discovered. These can be all one monosaccharide such as starch which is composed exclusively of glucose and is an important component of the human diet. Acemannan is an example of a polysaccharide composed of mannose, galactose and glucose in a 31:1:1 ratio.

Scientists have identified over 200 different naturally occurring monosaccharides. Because of their critical role in cell biology and intracellular communication eight of these 200 are considered to be essential monosaccharides (see Table 1) and sometimes called glyconutrients.

1	Glucose
2	Mannose
3	Galactose
4	Fucose
5	N-AcetylGalactoseamine
6	N-AcetylGlucosamine
7	N-AcetylNeuraminic Acid
8	Xylose

Biochemistry of Acemannan

Acemannan is a complex polysaccharide found in the inner leaf gel of the Aloe plant where it is produced by a specialized cell called leucoplasts (2-4). As a polysaccharide Acemannan is composed of mannose, glucose and galactose monomers. The approximate monosaccharide composition of Acemannan is 31 β (1,4)-linked mannoses, 1 β (1,4)-linked glucose, and 1 α (1-6)-linked galactose. A few of the mannose monosaccharaides are modified by addition of an acetyl group (5).

Acemannan is produced as a long polymer with an average molecular weight of greater than 5 million Daltons (Da). Because Acemannan is predominately a liner molecule with little or no branching, it is much longer than it is wide and can therefore be thought of as a flexible piece of string.

Breakdown, Absorption, Distribution and Elimination of Acemannan

When considering the administration of any medicine or nutritional supplement it is critical to understand how it is broken down, absorbed into the body, distributed throughout the body, and eliminated from the body to ensure that it reaches the desired location in appropriate concentrations. It is important to understand how a medicine or nutritional supplement is eliminated from the body to establish the proper dose and schedule. For example if a medicine or nutritional supplement remains in the body for extended periods of time then frequent dosing could lead to accumulation with possible undesired side effects. Conversely if a medicine or nutritional supplement is rapidly eliminated then infrequent dosing may not achieve proper concentration at the desired location in the body and there would be no medical or nutritional benefit.

Because of its extremely large size Acemannan taken orally must be broken down into smaller pieces to facilitate absorption through the gut. Early studies suggested that β -linked polysaccharides could not be broken down into usable pieces by the cells lining the gut. However, today we know that probiotics (friendly microorganisms in the gut) can digest β -linked polysaccharides and specifically they can digest Acemannan (6, 7). Animal studies have shown that when Acemannan is administered orally it be detected in the blood within 90 minutes (8). Studies have shown that the epithelial cells lining the gut have mannose-specific receptors for the active uptake of mannose from the gut and transporting it to the blood stream (9-12). Once in the blood stream the majority of Acemannan is distributed primarily to the liver, followed by the spleen, brain, kidney, heart, pancreas and thymus.

When by passing the gut Acemannan must be mechanically broken down to facilitate cellular uptake. For example studies show that Acemannan must be broken down to an average molecular weight of 1 to 2 million Da to be an efficient topical agent (13, 14). To be used as an injectable Acemannan must be broken down to an average molecular weight of 100,000 Da (15-17).

Elimination studies using orally administered ¹⁴C-labeled Acemannan showed that 72 hours after administration 86.4% of the radioactivity can be found in expelled CO₂ (18). An additional 2.16% of administered radioactivity was found in the urine and feces. These data suggest that the majority of orally administered Acemannan is absorbed, distributed and metabolized. This also means that at 72 hours after administration 11.4% of the administered radioactivity remains in the body as part of the mannose pool. The fact that only 2.16% of the total dose was eliminated through the urine and feces shows that Acemannan is efficiently used by the body for energy production or inclusion into the mannose pool to maintain healthy structure and function of key components of the body.

Once in the blood the majority of Acemannan is distributed to the liver, followed by the spleen, brain, kidney, heart, pancreas and thymus. The liver is the major site of detoxification and synthesis of glycoproteins and oligosaccharides. The liver releases glycoproteins, glycolipids, and oligosaccharides into the blood stream where they are distributed to other cells, tissues and organs throughout the body. The facts that the majority of Acemannan is delivered to the liver and the majority of radioactivity from orally radiolabelled mannose is eliminated as CO₂, a major byproduct of energy production, are consistent with the known functions of the liver.

The spleen and thymus are important organs of the immune system. Given Acemannan's role in immune support it is not surprising that the spleen and thymus are sites of significant Acemannan uptake (19-21).

Cell-to-Cell Communication

The human body contains between 50 and 75 trillion individual cells. These cells can be divided into several hundred distinct types of cells each with unique functions. It is obvious that for optimal health these cells must function in harmony each making its own specific contribution to overall health in the right amounts at the right time. A well known example is the synthesis and release of insulin by the Islet cells of the pancreas in response to ingestion of food and the rise in blood glucose. Just as important is the termination of release of insulin when blood glucose levels return to normal levels. This is achieved through highly responsive and coordinated communication between various cell types. Disruption of this cell-to-cell communication can lead to disease which can often be eliminated by restoration of proper cell-to-cell communication.

The specificity of cell-to-cell communication is regulated by glycoproteins and glycolipids on the surface of cells. The specific array of glycoproteins and glycolipids on the surface of one cell is complementary to those on another cell such that when these cells come in contact they specifically recognize each other and initiate a biological response. Scientists have shown that the majority of the saccharide components

of these glycoproteins and glycolipids are composed of eight specific monosaccharides of which mannose is one.

Many cells, and particularly those of the immune system, release a wide variety of cytokines that facilitate cell-to-cell communication between cells at a distance. Acemannan has been shown to facilitate communication between cells at a distance by stimulating the release of cytokines (22-24).

Immune Stimulation by Acemannan

Macrophages are one of many specialized cells of the immune system and many tissues have their own tissue specific resident macrophages. One important role of macrophages is to travel throughout the tissue, organ or body and identify foreign substances or damaged cells and tissues. Foreign substances can range from bacteria and viruses, to damaged cells (burns and wounds), to diseased cells such as cancer. Once identified macrophages will engulf and digest these foreign substances and then initiate a proper biological response. In the case of bacterial or viral infection this response is to activate other cells of the immune system to migrate to the site and expand the immune response that can be local inflammation and or production of antibody. This activation is conducted through direct cell-to-cell contact or through the release of a wide variety of cytokines. In the case of a wound the response may be to active local fibroblast and epithelial cells to multiply and fill in the wound. In the case of cancer it may be to release anticancer factors such as TNF- α as well as initiate a cancer specific immune response which can include activation of Natural Killer Cells. All of these responses are regulated by glycoproteins or glycolipids that are present of the surface of the cells or oligosaccharides that are released from the macrophage and interact with remote cells causing them to migrate to the site or initiate a secondary biological response.

Acemannan has been shown to activate macrophages and induce many of the functions described above including recognition of foreign antigens (viruses, bacteria, and cancer), capture and removal of microorganisms and wound healing (21). This activity of Acemannan is attributed, in part, to the recognition of terminal mannose by macrophages as a foreign substance. Mannose is one of the eight essential monosaccharaides, but in humans mannose is rarely found on the end of polysaccharides or oligosaccharides. However, terminal mannose is common on the polysaccharides and oligosaccharides produced by many microorganisms. Thus to the human macrophage terminal mannose is recognized as foreign is positive stimulus to the immune system. The broad array of biological activities of Acemannan and the associated mechanisms of action are summarized in Table 2.

Anticancer

Acemannan has been shown to have anticancer activity and in December 2000 Carravet an Acemannan immunostimulant received USDA approval for treatment of fibrosarcoma in cats and dogs. Fibrosarcoma is a malignant tumor of connective tissue such as bone, muscle, and cartilage. While it is clear that there may be many different causes of cancer (i.e. chemical, radiation, sunlight, genetics) it is also clear that defects in the immune system such as chronic inflammation create an environment where cancer can progress and metastasize (25). Acemannan may be acting through an indirect mechanism by activating local macrophages and stimulating an immune response to the cancer as well as induction of anticancer cytokines such as Tumor Necrosis Factor α (26, 27).

Table 2: Mechanisms of action of Acemannan		
<i>Biological Activity</i>	Mechanism	
<i>Wound healing</i>	Stimulate fibroblast and connective tissue formation	
	Stimulate repair processes and epithelial cell growth	
<i>Anti-cancer</i>	Stimulate immune system	
	Stimulate the release of TNF and cytokines by macrophages	
	Retard cell division	
<i>Anti-inflammatory</i>	Block generation of histamine and bradykinin	
	Inhibit bradykinin activity	
	Inhibit eicosanoid formation	
	Inhibit PMM leukocyte infiltration	
	Inhibit histamine formation	
<i>Antibacterial</i>	Inhibit bacterial growth	
	Stimulate macrophages	
<i>Antiviral</i>	Increase production and function of cytotoxic T cells	
	Inhibit proper glycosylation of viral proteins	
	Direct inhibition of viral replication (HIV and HSV-1)	
<i>Immunomodulant</i>	Stimulate macrophages to produce nitric oxide and cytokines	
	Enhance phagocytosis by macrophages	
	Increase the number and activity of monocytes and macrophages	
	Activate complement via the alternative pathway	
<i>Diabetes</i>	Stimulate the synthesis and release of insulin	
<i>Psoriasis</i>	Inhibit oxygen consumption of cells	
	Reduce the size in the intracellular spaces	
	Induce mitochondrial damage	
	Retard cell division	

Regulatory Approvals of Acemannan

Given the deep understanding of the uptake, distribution, efficacy, mechanism of action, and elimination of Acemannan, it has received regulatory approval for several animal and human indications. Topical formulations of Acemannan have been approved for treatment of wounds in human and animals (28). An injectable vaccine adjuvant was sold for the prevention of Marek's disease in chickens and turkeys (29) and an injectable acemannan immunostimulant was approved as a prescription product for veterinarians to treat fibrosarcoma (a form of cancer) in dogs and cats (15-17, 26).

Summary

Monosaccharides, oligosaccharides and polysaccharides play a critical role in many aspects of cell biology and human nutrition and health. Of the more than 200 monosaccharides currently identified, 8 are regarded as essential because they occur almost exclusively in glycoproteins and glycolipids where their role is critical to the function of the molecule and or critical in cell-to-cell communication.

Acemannan is a mannose rich polysaccharide found in the inner leaf gel which has been used for medicinal purposes for over 6,000 years. Pointing to the essential role of mannose in human health scientific research has shown that the human body has evolved highly specific and efficient mechanisms to extract mannose, from the diet and has developed symbiotic relationships with probiotic microorganisms to process mannose rich polysaccharides such as Acemannan. Once in the blood stream mannose is efficiently directed to the liver where many critical mannose dependent polysaccharide metabolic and synthetic activities take place.

Scientific research has shown that mannose is fundamental to many important biological processes, which when disrupted, can result in significant disease. These insights have led to the recognition that the severity of many diseases may be reduced or the disease eliminated altogether simply by increasing mannose intake. Acemannan is a rich easily accessible source of mannose. This understanding of the role of mannose in disease and Acemannan as a rich source of mannose has led to approval by the US Food and Drug Administration (FDA) and the US Department of Agriculture (USDA) of several Acemannan based products. Given its broad activity it seems likely that other medical and nutritional uses for Acemannan will likely be discovered in the future.

Literature Cited

1. Johnson A, White A, & McAnalley B (1989) *Wounds: a compendium of clinical research and practice*. **1**, 186-192.
2. Ni Y, Turner D, Yates KM, & Tizard I (2004) *Int Immunopharmacol* **4**, 1745-1755.
3. Tai-Nin Chow J, Williamson DA, Yates KM, & Goux WJ (2005) *Carbohydr Res* **340**, 1131-1142.
4. Talmadge J, Chavez J, Jacobs L, Munger C, Chinnah T, Chow JT, Williamson D, & Yates K (2004) *Int Immunopharmacol* **4**, 1757-1773.
5. Manna S & McAnalley BH (1993) *Carbohydr Res* **241**, 317-319.
6. Sinnott RA, Kalns JE, Boyd S, Ramberg J, Duncan C, Kirchner JM, & Oubre C (2007) *4th Annual Natural Supplement Conference sponsored by the Scripps Center for Integrative Medicine, San Diego, California, January 19-21, 2007*.
7. Sinnott RA, Ramberg J, Kirchner JM, Oubre C, Duncan C, Boyd S, & Kalns JE (2007) *Int J Probiotics and Prebiotics* **2**, 97-104.
8. Fogelman RW (1990) *Waverly, PA: Pharmakon Research International*.
9. Alton G, Hasilik M, Niehues R, Panneerselvam K, Etchison JR, Fana F, & Freeze HH (1998) *Glycobiology* **8**, 285-295.
10. Cano M, Calonge ML, Peral MJ, & Ilundain AA (2001) *Pflugers Arch* **441**, 686-691.
11. De la Horra MC, Cano M, Peral MJ, Garcia-Delgado M, Duran JM, Calonge ML, & Ilundain AA (2001) *Biochim Biophys Acta* **1512**, 225-230.
12. Duran JM, Cano M, Peral MJ, & Ilundain AA (2004) *Glycobiology* **14**, 495-500.
13. McAnalley BH (1989) *United States Patent* 4,917,890.
14. Turner CE, Williamson DA, Stroud PA, & Talley DJ (2004) *Int Immunopharmacol* **4**, 1727-1737.
15. King G, Carpenter RH, & Yates KM (1991) *Paper presented at: 11th Annual Conference of Veterinary Cancer Society Symposium: 1991/10/27*.
16. King G, Carpenter RH, & Yates KM (1991) *Paper presented at: American College of Veterinary Surgeons (ACVS) Veterinary Symposium: Small Animal: 1991/10/13*.
17. King GK, Yates KM, Greenlee PG, Pierce KR, Ford CR, McAnalley BH, & Tizard IR (1995) *J Am Anim Hosp Assoc* **31**, 439-447.
18. Aboagye E & Peterson M (1996) *Madison, Wisconsin: Corning Hazelton, Inc.: 1996*.
19. Im SA, Lee YR, Lee YH, Lee MK, Park YI, Lee S, Kim K, & Lee CK (2010) *Arch Pharm Res* **33**, 451-456.
20. Im SA, Oh ST, Song S, Kim MR, Kim DS, Woo SS, Jo TH, Park YI, & Lee CK (2005) *Int Immunopharmacol* **5**, 271-279.
21. Zhang L & Tizard IR (1996) *Immunopharmacology* **35**, 119-128.
22. Marshall G (1993) *Paper presented at: American Aging Association's 23rd Annual Meeting; 1993/10/08*.
23. Marshall G, Gibbons A, & Parnell L (1993) *Paper presented at: 50th Annual Meeting of the American Academy of Allergy and Immunology; 1993/03/12*.
24. Smalley R & Oldham R (1987) *Principles of Cancer Biotherapy* **2**.
25. Weber D, Wheat JM, & Curri GM (2010) *Zhong Xi Yi Jie He Xue Bao* **8**, 1006-1013.
26. Harris C, Pierce K, King G, Yates KM, Hall J, & Tizard I (1991) *Mol Biother* **3**, 207-213.
27. Peng SY, Norman J, Curtin G, Corrier D, McDaniel HR, & Busbee D (1991) *Mol Biother* **3**, 79-87.
28. Roberts DB & Travis EL (1995) *Int J Radiat Oncol Biol Phys* **32**, 1047-1052.
29. Sharma JM, Karaca K, & Pertile T (1994) *Poult Sci* **73**, 1082-1086.