



Nutritional Platform

**The role of Acemannan NaturMannan[®]
based food supplement as
Immunomodulator, pre-biotic agent and
as a dietary fiber**

Scientific review



Aloe-Vera

Aloe-Vera is a plant widely used in the biomedical, pharmaceutical, food, and cosmeceuticals industries. There are at least 420 different species of Aloe plant¹.

The plant leaves contain over 75 biologically active and naturally-occurring compounds, including polysaccharides, vitamins, minerals, enzymes, amino acids and natural sugars that functions in association with other compounds of the human body to deliver numerous health benefits²⁻⁵. The bioactive components in the Aloe-Vera have been reported to antiseptic, antiviral, antibacterial, antidiabetic, anti-inflammatory, antioxidant, immune-modulatory, gastro-protective, and wound healing properties.

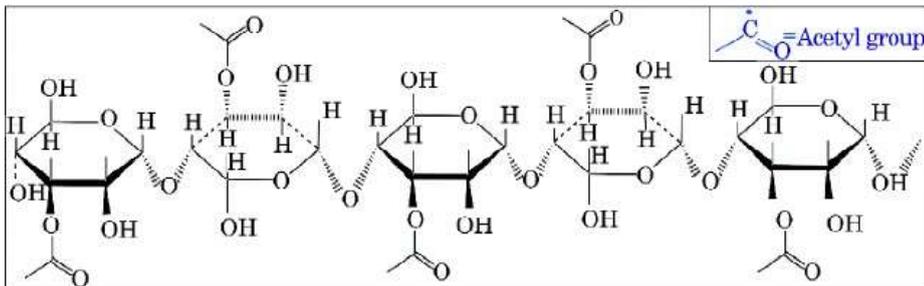
Biologically active components in Aloe-Vera may be labile, varied, or modified since the chemical composition of the Aloe-Vera varies and depends on the source, climate, region, and the processing method^{2,6}.

The active components of Aloe-Vera have been isolated and studied extensively. Polysaccharide derived from Aloe-Vera play an important role in immunomodulation, the predominant polysaccharide is Acemannan.

Acemannan is an organic Mannan polysaccharide derived from the Aloe-Vera plant. This polysaccharide is the primary active ingredient responsible for the majority of the biological activities from the use of the Aloe-Vera plant^{7,8}.

It constituted by acetyl- mannaose units united by β -(1,4) glycosidic bonds. Acemannan is a hydrophilic molecule with an average molecular weight of approximately 1-2 Million Daltons⁹.

Basic molecular structure of acetylated mannan or Acemannan is shown below ¹:



Acemannan has many nutritional qualities, and it is mostly responsible for the benefits Aloe-Vera offers ⁹. It has been extensively studied in the last 30 years and was shown to have many biological activities, including anti-cancer, anti-inflammatory, direct and indirect antibacterial and antiviral activity, cell proliferation, immunomodulatory, prebiotic and wound healing effects^{10,11}.

Biologically active components in aloe vera may be labile, varied, or modified since the chemical composition of the aloe vera gel varies even within the same species, the plant depends on source, climate, region, and the processing method ^{2,6}. For this reason, there is a big advantage of being able to use a relatively stable commercially available purified active ingredient rather than relying on freshly harvested material.

It is also important to note that the processing steps can alter the properties of polysaccharides by affecting their original structure, which may bring some changes in the proposed physiological and pharmaceutical properties of these constituents³. This is why the manufacturing process is a key factor for obtaining an extract that remain active, keeping all the beneficial properties of the plant.

Most of the beneficial effects of Acemannan are derived from its effect on the immune system. **The immune system** role is to defend the organism from diseases such as infectious diseases (such as viral, bacterial etc.), neoplastic, metabolic, and more. The immune system is subdivided into the innate and adaptive immune system. Both



subsystems use humoral immunity and cell-mediated immunity. In order to function, the immune system components communicate and work together. The immune system is composed of different types of cells, proteins, and organs. The fundamental cells are the white blood cells; those cells can communicate with each other by labyrinth language of cytokine and chemokine secretion and receptors¹². One of the main pillars of the immune system is specialized cells; Antigen-presenting cells (APC) such as dendritic cells and macrophages. APC's are capable of recognizing pathogenic agents that have penetrated the body, swallow it (phagocytosis), break it into small pieces (antigens) and present it to other immune cells such as B and T lymphocytes. The lymphocytes "learn" the antigen presented to them by the APC, and they can develop a specific and more efficient immune reaction. All of this process is regulated by receptors, hormones, cytokines, chemokines, and more¹².

Ingestion of Acemannan can be beneficial to the function of both the innate and adaptive immune system, because of its augmented and immunomodulation effect on it.

Immunomodulatory activity of Acemannan

The effect of Aloe-Vera extracts and specifically Acemannan were extensively investigated as immune system modulators^{3,8}. Those studies show that Acemannan has an augmenting effect on the innate and adaptive immune system^{5,8}.

It was shown that Mannan rich Acemannan activates Macrophages by binding to macrophage-mannose receptor (MMR). The binding of mannose to MMR induces macrophage activity, increases cytokines secretion, nitric oxide release, enhance phagocytosis, and intracellular killing¹³⁻¹⁷. The macrophages have an essential role in initiating the immune response. The macrophages are also responsible for mediating between the innate and the adaptive immune system.

Cell to Cell communication- Immune system recruitment and activation

Another *In-vitro* experiment showed that Acemannan have increased lymphocytic

alloantigen response in a dose response fashion. The same study also found that Acemannan helps the white blood cells to communicate; Acemannan permitted monocytes to enhance signals to T- Cells due to IL-1 release and induce cytotoxic T- Lymphocyte^{18,19}. Furthermore, another study was set to find the effect of Acemannan on dendritic cells. Dendritic cells are important parts of the immune system, they are mostly located in the skin and are responsible for initiation of the immune response and for presentation of pathological agent antigens to the adaptive immune system. It was shown that exposure of immature Dendritic cells to Acemannan induce their maturation and functionality²⁰.

It was also shown that Acemannan effect other cell factors; stimulate interactions between macrophages, T-lymphocytes and B-lymphocytes; enhance the generation of cytotoxic T-lymphocytes; induced B- and T-lymphocyte activation and upregulate phagocytic activity^{2,21}. In addition, investigators have reported on the functional maturation of immature dendritic cells when exposed to the compound, exposing immature dendritic cells to Acemannan increased MHC class II expression²⁰.

Figure 2- augmentation activity of Acemannan on the immune system²²

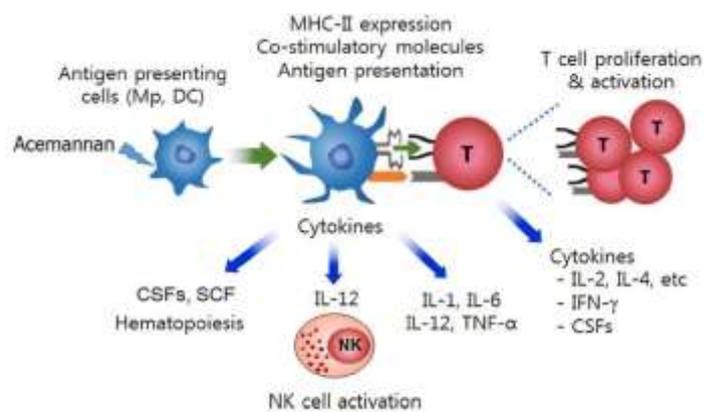


Fig. 2. Major mechanisms of the immunomodulating activities of acemannan.

Dietary fibers,

The American association of Cereal Chemists defined dietary fibers as “Dietary fiber is the edible parts of plants or analogous carbohydrates that are resistant to digestion and absorption in the human small intestine with complete or partial fermentation in the large intestine. Dietary fiber includes polysaccharides, oligosaccharides, lignin, and associated plant substances. Dietary fibers promote beneficial physiological effects including laxation, and/or blood cholesterol attenuation, and/or blood glucose attenuation.²³” In North America, the average person consumes less than 50% of the recommended daily intake, a factor considered as contributing to the obesity levels seen in many developed countries²⁴.

Dietary fibers have an important role in the function of the digestion system and metabolic process. They help to empty the digestive tract and loosen constipation. The dietary fibers have an essential role in the satiation feeling after a meal and have an effect on the glucose and cholesterol level in the blood. Furthermore, research shows that certain dietary fibers consumption reduces cardiovascular diseases and other chronic illnesses such as diabetes mellitus, obesity and colon cancer²⁴.

Natural polysaccharides, in the gastrointestinal tract, can be processed and degraded by enzymes or fermented by microbiota to a big quantity of oligosaccharides. Both poly and oligosaccharides can be fermented to SCFA. SCFA have an essential role in the promotion of intestinal epithelial cells barrier, supply energy to the enterocytes²⁴.

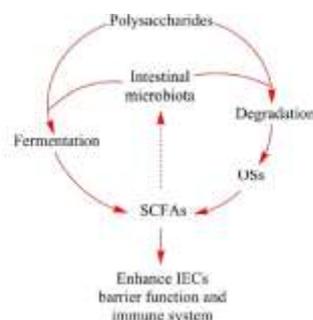


Figure 2. The role of natural polysaccharides in intestinal fermentation. Polysaccharides which cannot be processed by gastric and intestinal enzymes are degraded and fermented by specific intestinal microbiota. Degradation of polysaccharides produces a large number of oligosaccharides that are conducive to host health. Fermentation of polysaccharides and oligosaccharides produces SCFAs and other metabolites. SCFAs can be easily absorbed and promote the IECs barrier function and immune system. During the intestinal fermentation, polysaccharides, oligosaccharides or the metabolites like SCFAs may promote the growth of certain intestinal bacteria, thus changing the composition of intestinal microbiota and affecting the host health. Abbreviations: Oss, oligosaccharides; SCFAs, short-chain fatty acids; IECs, intestinal epithelial cells.

Dietary Fibers are known of its importance for human consumption, the FDA has recognized it and, as of 2008, the FDA approved food products making health claims for fiber^{24,25}.

NaturManan® are polysaccharide extracted from Aloe-Vera, the predominant polysaccharide is Acemannan (Mannan polysaccharide). It also contains pectin, and other natural dietary fibers. As described above Acemannan has an augmented effect on the immune system, Daily ingestion of Acemannan strengthen the immune system and help protect the body from different pathogenic agents such as viruses, bacteria, fungi, neoplasia and more.

Anti-Viral activity

Acemannan was proven as an antiviral agent in both *in vitro* and *in vivo* studies. It was shown to reduce herpes simplex infection in two cultured target cell lines, to have *in vitro* activity against HIV-1 and a dose dependent synergistic effect with AZT on HIV-infected cells (Kahlon JB et al., 1991; Sahu et al., 2013).

Sun et al., showed *in vitro* inhibition of influenza replication. Recorded by Transmission Electronic Microscopy, the long chain saccharide of Acemannan appears to interact with the influenza virus particles. Furthermore, in the same study, the researcher challenged mice that received oral administration of Acemannan with Influenza virus¹⁰. The results showed lower mortality rate, less clinical signs, less body weight reduction, less lung tissue damage and reduced viral load.

In other study on cats with Feline immunodeficiency virus oral administration of Acemannan improved their quality of life and life span²⁷.

Anti-Bacterial Activity

Aloe-Vera gel was bactericidal against *Pseudomonas aeruginosa* and Acemannan prevented it from adhering to human lung epithelial cells in a monolayer culture ⁸. Another *in vitro* study shows that Acemannan has anti-bacterial effect. In this study, Acemannan show antibacterial activity against four different bacteria stains. Two Gram-positive bacteria *S. aureus* and *Enterococcus faecalis* and two Gram-negative strains *E. coli*, and *P. aeruginosa*. Against those bacteria Acemannan showed inhibition greater than 98%. Furthermore, Acemannan had a strong *E.Coli* and *E.faecalis* biofilm inhibition effect and biomass eradication effect when used higher concentrations ¹¹.

Anti-Fungal activity

Candida Albicans is commonly used as biological model; it is an opportunistic pathogenic organism that can cause a superficial and local infections but also life threatening systemic infections²⁸. *In vitro* study proved that Macrophages that were exposed to Aloe-Vera Acemannan had a 98% killing and phagocytosis of candida albicans compared to the control group that had only 25% killing ¹³. *In Vivo* mice study revealed that feeding Aloe-Vera extract increase resilience to *C.Albicans* challenge ²⁹.

Anti-cancer

Acemannan and phenolic anthraquinones of the Aloe-Vera gel are considered to be prophylactic against certain types of cancer and many chronic degenerative diseases being the potential antioxidants or pro-oxidants with unique DNA breakage preventing potential. Acemannan also prevent malignancy by its potential immune-stimulant activity¹. In a study on mice that had previously been implanted with murine sarcoma cells, Acemannan stimulates the synthesis and release of interleukin-1 (IL-1) and tumor necrosis factor from macrophages in mice, which in turn initiated an immune attack that resulted in necrosis and regression of the cancerous cells ⁸.

Furthermore, Acemannan is licensed by the USDA for the treatment of sarcomas in dogs and cats^{30–32}

In Conclusion

NaturManan® is a natural and safe food supplement ingredient, with great beneficial potential in daily oral consumption. The immunomodulatory properties of Acemannan, and the great source of natural nutritional fiber supplementation have great potential in improving general health, strengthen the immune system, improve digestion and supply prebiotic components to the natural microflora in the digestive tract.

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