

THE ROLE OF ALOE VERA BARBADENSIS MILLER IN A KETOGENIC DETOX PROGRAM

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Abstract

It has been known for centuries that ketogenic diet mimic the body’s response to starvation by using fat as the primary energy source and the liver uses the fatty acids to make ketone bodies which can cross the blood brain barrier and substitute for glucose as an energy source.

In fact, ketosis is a metabolic state associated with ketogenic diet and it is considered a physiological condition characterized by an acute state of elevated serum ketone body concentration, from 0.5 to 3.0 mm that is not to be confused with ketoacidosis, a pathological condition with elevated serum ketone levels (3.8-25mm).

The acetoacetic acid is the only true ketoacid chemically among the three major ketone bodies: beta-hydroxybutyric acid is a hydroxy acid, while acetone is an actual ketone. This biochemical cascade is stimulated by the combination of low insulin levels and high glucagon levels (i.e., a low insulin/glucagon ratio). Actually, several studies have been increasingly consolidated on the benefits that the ketogenic dietary regime brings in pathological states, such as diabetes mellitus and many other syndromes and neuro-pathological conditions (1-8). However, this dietary regime subjects the whole organism to considerable metabolic stress and it is used to propose protocols to support detoxification. *Aloe vera* Barbadensis Miller can represent an excellent protection of nutritional integration through its beneficial effect, in the first instance on the gut microbiota.

Keywords: *ketogenic diet, Aloe vera, gut microbiota, acemannan.*

Introduction

Aloe vera is one of the traditional medicines of the World Pharmacopoeia, including the Italian one. In fact, its use has been referred, until the last decades, to the portion of anthraquinone drug, used as a potent laxative. Recently *Aloe Vera* has emerged as a celebrated and successful detoxing plant for every kind of diseases. In fact, in this article, deals with the aloe gel from the leaf, a portion purified from anthraquinones and used as a food supplement with countless beneficial uses and very few contraindications.

Aloe Barbadensis Miller (Aloe Vera)

About 350 species of *Aloe* are known and of these, 125 are distributed in South Africa; among all, the most used one in phytotherapy is *Aloe Vera*. The etymological meaning of *Aloe* comes from the Greek word "salt": in fact, they are plants which have sea areas as ideal habitat. It is likely that the name of the plant comes from the Arabic word, which means "bitter", alluding to the juice of the plant that is, in fact, very bitter.

There are very numerous references of ethnobotany to *Aloe Vera* and we can retrace the most significant stages in the history of this plant.

The Assyrians used *Sibaru* juice, "a plant whose leaves resembled sheaths of knives", or *Aloe* juice, to reduce abdominal swelling and as an antidote to the ingestion from damaged foods.

Egyptians considered "Aloe Vera" the plant of immortality in fact it was placed at the entrance of the pyramids to show the deceased Pharaohs the way to the land of the dead. In the "Papyrus of Ebers" you will find a very detailed botanical description of *Aloe Vera* and a long list of its healing properties. *Aloe* juice was a fundamental ingredient of the secret mixture used for the mummification of Egyptian kings and it seems that Cleopatra, famous for her baths in goat's milk, ordered to add *aloe* to massage creams or to chop it finely so as to obtain eye drops to make the color of her eyes brighter. Some propitiatory potions of Egyptian mythology required the juice of *Aloe* and still today in Egypt this plant is placed in front of the door of the house to ensure happiness and protection.

According to legend, Alexander the Great, wounded in battle by an arrow, was cured with a miraculous ointment based on *Aloe* collected in the island of Socotra. For this reason, he was advised to conquer the island, rich in these plants, to have the *Aloe* juice available to heal the wounds of his soldiers and even make them invincible.

In a passage from the Gospel of John, it is said that a mixture of Myrrh and *Aloe* was made to prepare the body of Christ for burial.

Dioscorides and Pliny the Elder described the therapeutic uses of *Aloe* juice in cases of abdominal pain, constipation, headaches, insomnia, skin and oral irritation.

In Ayurvedic medicine, *Aloe Vera* is called a friend of women and still today, *Aloe* gel is a very effective tonic for female disorders, as well as an excellent liver detoxifier.

In the Million, Marco Polo describes the spread of this plant in the Chinese Empire and then get to the Far East. Christopher Columbus notes in his diary that you must always have on board "the medicine in a pot" (*Aloe Vera*). In Japan, the plant is associated with an ideogram that, translated literally, means "you don't need the doctor".

In 1852, two English researchers managed to isolate for the first time in *Aloe* an active ingredient with laxative action that they called *aloin*.

In 1934, the first scientific research on *Aloe* was published in the United States, demonstrating the extraordinary efficacy of this plant in the treatment of a serious form of radiodermatitis in a woman with cancer.

In the following years, clinical studies demonstrated the therapeutic properties of *Aloe* in peptic ulcers, in dermatological pathologies, in stomatological diseases, in some bacterial and viral infections and in the treatment of herpes, in even serious burns, in gastrointestinal disorders, in diabetes.

Recent scientific studies, have deepened above all the antioxidant and immunomodulating power of *Aloe*.

The pharmacological activity of *Aloe Vera* is very complex precisely because the chemical constituents of the plant are many and the therapeutic effects of *Aloe* are the result of the synergistic interaction of active ingredients with

receptive molecules of the human body. Aloe Vera is a perennial herbaceous plant, up to one meter high, the leaves (from twelve to thirty units) are arranged in a tuft like the rose's petals, they are long lanceolate, with acute apex, have a very thick cuticle and spines only along the sides, are fleshy, light green in color and can fade to grey-green. When the leaves are cutting, we notice an almost immediate wound healing of the cut; in fact, the plant releases a protective exudate which prevents the lymph from escaping (9-13).

In Summer, the flowers of Aloe emerge at the center of the leaves, from rigid and woody stems. They have the shape of a bunch in the shades of red, yellow and orange with bright colors. It is a plant of African origin (hence the popular name Desert Lily) that prefers warm and dry climates; it adapts to any type of soil, but should never be excessively humid. There are plantations of Aloe in every continent, in Europe the largest producer is Spain.

From Aloe plant we may obtain two types of extracts (condensed juice and gel), both with verified pharmacological activity. The juice contains anthraquinone glucosides (among which aloin, also called barbaloin, and aloe-hemodine), and it is to these compounds that we can attribute the drastic purgative effect that characterizes the aloe juice.

The mucilaginous internal gel is slimy to the touch and has a high content of polysaccharides, in particular deriving from mannose and various other important components (lipids, essential amino acids, vitamins, hormones and minerals) in appreciable concentration.

On the market, we may buy the aloe juice a kind of drink obtained from the aloe gel made liquid by various treatments to make it easier to take.

What is used for the production of the gel is the central gelatinous part of the leaf (central parenchymatous part), from which a product without, or at least with very low quantities, anthraquinones principles is obtained.

Chemical constituents

It is necessary to specify that the main constituent is water to the extent of more than 90%. Below, in brief, a hint at the chemical composition

and functions of the categories to which the approximately 75 bioactive compounds:

Sugars: both simple forms such as mannose 6-phosphate and complex polysaccharides such as acemannan. Recently a glycoprotein with anti-allergic properties, alprogen, and a new anti-inflammatory compound, C-glucosyl chromone, has been isolated from Aloe vera gel (12).

Enzymes: Most of the enzyme fraction is represented by peroxidase, catalase and amylase. The most interesting for inflammatory processes is bradykinase.

Vitamins: trace amounts of both fat-soluble vitamins (A and E) and water-soluble vitamins such as C and, quite rare in the plant world, B12, as well as folic acid and choline are found here.

Fatty acids (vegetable steroids): lupeol, cholesterol, campesterol, β -sisosterol, all of which have anti-inflammatory properties.

Amino acids: 7 essential activity is mainly based on gibberelline and auxins, which have functions in the healing processes of injured skin with anti-inflammatory valence.

Minerals: the main micronutrients such as calcium, chromium, copper, selenium, magnesium, manganese, potassium, sodium and zinc, which play a key role in cell metabolism, are present in traces.

Saponins: they are present in the gel to the extent of about 3% of the total and perform an important antibacterial and antiseptic function in general.

Lignin: this organic polymer has the characteristic of increasing the skin absorption of the gel.

Salicylic acid: also present in reduced quantities, it strengthens the anti-inflammatory and antibacterial properties.

Human gut microbiota

According to medical scientists the microbiota, is the community of individual microorganisms, bacteria, fungi, archeobacteria and protozoa, and viruses that live and colonize a specific environment in a given time.

In fact, the term gut microbiota refers to the fundamental domains of microorganism present in the intestinal tract.

However, the whole body, except the brain and the circulatory system, according to recent estimates, hosts a total of about 10^{14} bacteria. The most

abundant phyla are Firmicutes and Bacteroides. (14-15)

Recent studies suggest that the influence of microbiota in regulation of metabolic activity is now recognized with more and more supporting evidence. In the same way, an impact of the gut microbiota on psychological states has been discovered due to the influence on the hypothalamic-pituitary-adrenal axis and on the serotonergic system. Another feature of the human microbiota is its role in the development of the immune system during the first part of childhood and, consequently, in the state of inflammation of the body (16-17).

The microbiota is altered more or less significantly and rapidly by external factors, such as diet, type of birth or type of microorganisms present in the daily environment (18).

From a state of equilibrium called eubiosis we can then move on to the opposite condition of dysbiosis. It is to the latter that we owe the increased incidence of metabolic, cardiovascular, inflammatory, neurological, psychic and oncological diseases called "diseases of progress". (19-22)

Today, the importance of microbiota in maintaining human health is clear. Commensal microorganisms, in fact, not only support the functions of the human organism such as metabolism and the immune system, but they also act against the proliferation of pathogens (23-24).

To explain how the microbiota supports the human organism, it is appropriate to introduce the concept of microbiome.

Microbiome

The term microbiome is intended to focus on the totality of the genome expressed by the microbiota. With reference to the totality of the human microbiome, the genomic portion referred to the microbiota represents up to 99% of the total and is of fundamental importance for the coding of bioactive compounds that play a key role in the metabolism of the host.

The microbiome, in particular, expresses a genetic heritage that can be defined as complementary to the human one and this characteristic is of crucial importance in digestion

and immune modulation, in addition to the synthesis of significantly bioactive substances such as certain vitamins and neurotransmitters: this state of equilibrium between microbial populations and the host is called Eubiosis.

If, on the contrary, conditions alter this balance, such as a sudden change in lifestyle, prolonged antibiotic treatment, exposure to pollutants, etc., this cooperation with the host can turn into a difficult coexistence, with the pathogenic portion of the microbiota coding of compounds that can even be harmful: this state is referred to as Dysbiosis.

For these reasons, changes in the microbiota and, consequently, in the microbiome have an impact on the body's homeostasis.

If today we can study (although only with regard to the bacterial part) the composition of the microbiota, we owe it to metagenomics, which bases its investigations on the microbiome. (25-30)

Properties of Aloe gel

Aloe Vera is a succulent plant. Succulents are xerophytes, which are adapted to living in areas of low water availability and are characterized by possessing a large water storage tissue. The main feature of the Aloe Vera plant is its high water content, ranging from 99–99.5%. The remaining 0.5–1.0% solid material is reported to contain over 75 different potentially active compounds, including water- and fat-soluble vitamins, minerals, enzymes, simple/complex polysaccharides, phenolic compounds, and organic acids. If we study the composition of the structural components of the Aloe Vera plant leaf portions, we can highlight that the rind was found to be 20–30% and the pulp 70–80% of the whole leaf weight. On a dry weight basis, the percentages of the rind and pulp represented as lipids (2.7% and 4.2%) and as proteins (6.3% and 7.3%) only accounted for a minor fraction. However, the no-starch polysaccharides and lignin represent the bulk of each leaf fraction and were found to be 62.3% and 57.6% of the dry weight of the rind and pulp, respectively. Aloe Vera gel polysaccharides consist of linear chains of glucose and mannose molecules, of which mannose is more concentrated than glucose, thereby the molecules are referred to as polymannans. The series consists of linear chains

with a size ranging from a few to several thousand monomers. The main polysaccharide constituent of the gel, acemannan, is made up of various polymers composed of repeated units of glucose and mannose in a 1:3 ratio: the molecular weight varies between 30 and 40 kDa (31).

This polysaccharide of which the gel is particularly rich, is used as an anti-inflammatory and immunostimulant. Among the most important properties, the gel is used for external use to treat burns, erythema, wounds and scars.

Currently, it has been reported that Aloe Vera possesses, both in vitro and in vivo, antimicrobial properties. The bacteriostatic effect on *Listeria monocytogenes*, a bacterium responsible for foodborne diseases was observed (32). Aloe gel and its extracts also exert antimicrobial activity against multidrug-resistant bacteria (MDR) from clinical isolates (33). In the study of Kwon et al. (34), the antimicrobial activity of Aloe Vera peel extract in distilled water against *Staphylococcus aureus*, *Bacillus* spp., *Enterococcus* spp., *Escherichia coli*, *Salmonella typhimurium*, *Pseudomonas aeruginosa* and *Vibrio* spp. was ascertained. The number of bacterial colonies was significantly reduced and the observed effect was especially strong against *E. coli* and *Vibrio* spp. ($p < 0.01$).

The research also highlighted the in vivo antimicrobial activity of the gel against *Salmonella typhimurium* in mice. Gupta et al. (35) reported growth inhibition activity by aloe gel on isolated colonies of MDR *Mycobacterium tuberculosis*. On the other hand, it was observed that Aloe Vera juice, incorporated into the growth media of *Lactobacilli* at a concentration of 5%, was effective in promoting the growth of *L. acidophilus*, *L. plantarum* and *L. casei*. Whereas, concentration higher than 25% showed an inhibitory effect. Authors concluded that aloe gel might be used in a lower concentration in combination with probiotic *Lactobacillus* strains as a therapy for gastrointestinal disorders. The produced greater amounts of short chain fatty acids (SCFA), while the branched-chain fatty acids (BCFA) did not increase with these polysaccharides. Acemannan increased significantly acetate concentrations. Therefore, also Aloe Vera polysaccharides have prebiotic potentials (36),

Aloe gel possesses also anti-inflammatory properties. The main polysaccharide called aloemannan or acemannan is a D-isomer glycosaminoglycan extracted from the leaves of *Aloe barbadensis*, it consists of units of β -D-mannan with a molecular weight of about 15,000 daltons. This macromolecule has been classified among the hemicellulose by its structure and its metabolic properties, showing possible properties such as immunostimulant, antiviral, antineoplastic and beneficial on some gastrointestinal disorders.

The substrates selectively promoted the growth of *Bifidobacterium*, *Lactobacillus*, and *Bacteroides* species (37). In particular, we suggest that acemannan is also actively used as a substrate by the intestinal population of yeasts that contribute to maintaining the balance (eubiosis) of the human intestinal microbiota (38-39).

According to different authors, there is the necessity to find better strategies to maximize the benefit of VLCKD (Very Low Carb Ketogenic Diet). It may be useful implementing VLCKD with specific pre and probiotics, which has been found to be drastically reduced during VLCKD. With regard to intestinal function, very interesting studies have also emerged on the link between the composition of the intestinal microbiota and a diet rich in quality dietary fats, as in the case of ketogenic nutrition: in this specific case the intake of a high fat content, of which a good quantity of polyunsaturated fats together with vegetable proteins, would prove to be positive for intestinal function. As a matter of fact, many patients undergoing the ketogenic regime complain about changes in the opposite direction: Aloe Vera gel supplementation could overcome this inconvenience, promoting the transition towards a healthier microbiota composition. Additionally, promising evidence comes from randomized control trials suggesting that quality dietary fats highly affects the gut microbiota composition. Diets with a high fat content and good quality of polyunsaturated fats and plant-derived protein are able to maintain normal gut function (40). It has also been suggested that a supplementation with prebiotics, such as inulin, lactulose, fructooligosaccharides (FOS) and galactooligosaccharides (GOS) that increases

Bifidobacteria, may prevent undesired changes in the gut microbiota (41-43).

The nutraceutical properties of Aloe Vera have been attributed to acemannan. Recently, information has been published about the presence of fructans in Aloe Vera: this study investigated in vitro the prebiotic properties of these polysaccharides and demonstrated that fructans from Aloe Vera induced bacterial growth better than inulin (commercial FOS). Acemannan stimulated bacterial growth less than fructans, and as much as commercial FOS (44). The authors of this work used the qPCR technique to study the microbiota from human faeces fermented in a bioreactor simulating the colon environment: the results highlighted the ability of fruit trees to encourage an increase in the population of the Bifidobacterium species, resulting in increased production of short-chain fatty acids (SCFA) (45). On the contrary, there was no significant increase in the concentration of branched-chain fatty acids (BCFA); it was also shown that acemannan has favoured an increase in acetate concentration. It can therefore be concluded that the polysaccharide portion of Aloe Vera gel also has a prebiotic value (46-47), it was also observed that Aloe Vera juice incorporated into the growth media of Lactobacilli at a concentration of 5% was effective in promoting the growth of *L. acidophilus*, *L. plantarum* and *L. casei*.

Authors concluded that aloe gel in a lower concentration might be used in combination with probiotic Lactobacillus strains as a therapy for gastrointestinal disorders (48).

In our opinion, it is not risky to say that even acemannan, such as galactoglucomannan (GGM) and arabinoglucuronoxylan (AGX), hemicellulose predominant in wood, based on the structure similarity with common dietary fibers, GGM and AGX may be postulated to have prebiotic properties microbiota (49). Many studies have shown that the structural characteristics of plant polysaccharides, such as molecular weight, chemical composition, branching structure and conformation, affect their biological activity. First, acetyl is an important reactive group in acemannan. Studies have shown that different processing conditions will affect the acetylation of polysaccharides (50).

The biological action of this molecule is probably expressed also as a donor source of acetyl groups, whose centrality in metabolism is confirmed. In eukaryotic cells, acetylation occurs as a co-translational or post-translational modification of proteins, as in histones, p53 protein or tubulins. The central focus on the biological activity of acemannan (50) comes most probably from the presence of the acetyl group. In fact, its removal has the effect of reducing its inductive action on cell proliferation: acetyl groups, as demonstrated in a study, demonstrate regulatory capacity on the immune system and hydroxyl groups have a scavenging value of free radicals (51).

In particular, N-alpha-terminal acetylation is a common post-translational modification in eukaryotes cells. (52-53) 40-50% of yeast proteins and 80-90% of human proteins may undergo such changes. The enzymes performing this are N-alpha-acetyltransferase (NAT), a subfamily of GNAT acetyltransferases, which includes histone acetyltransferase. GNAT transfers the acetyl group from an acetyl-coenzyme A molecule to an amino group.

These processes have been studied and relations are found both with the cell cycle in general and with several cancerous forms. (54,55).

With regard to the safe use of Aloe Vera gel as part of a ketogenic diet, there may be doubts about the amount of monosaccharides that would be administered. In the literature, we have not been able to identify studies of quantitative dosage of these nutrients, however, evince studies already mentioned (56-57) that the amount of glucose in particular, can be considered so negligible as not to be actively significant in influencing a possible positive effect on insulin synthesis.

Finally, an important work in 2012 on rats, through the isolation of two phytosterols, namely lophenol and cycloartanol, found the ability to induce in the liver the reduction of fatty acid synthesis and a tendency to increase the oxidation of fatty acids, a phenomenon that promotes the reduction of intra-abdominal fat and the improvement of hyperlipidemia (58).

In conclusion, the integration with an Aloe Vera gel preparation in patients undergoing a ketogenic nutritional therapy proves to be advantageous not

only with regard to the mere regulation of intestinal activity, but may represent a plus in terms of reduction of systemic inflammation carried out through o in positive bacterial populations (*Bifidobacterium* spp.) and possible epigenetic valence due to the biological activity of acetyl groups of acemannan, a peculiar characteristic of this gel.

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