Immunomodulatory and Protective Action of *Aloe arborescens* and *Aloe barbadensis (Aloe vera)*

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Throughout a lifetime, each of us will experience a number of illnesses caused by infectious organisms or exposure to chemical agents that cause allergic responses. These reactions are initiated and usually carried through to healing by the immune system. The immune system is the major entity that protects the body against potentially harmful foreign substances and the multiplicity of potentially infectious agents.

Immunity may be either natural or acquired. Natural immunity is species specific, which is why humans do not contract various animal diseases. Acquired immunity is that protection a person acquires through active or passive means.

Active immunity is acquired through immunization or actually having a disease. It is long-lived immunity developed by the body's own immune system. Active immunity does not provide immediate protection upon first exposure to an invading agent or vaccine. It takes a few days to weeks before the immune response is sufficiently developed to contribute to the destruction of the pathogen. With subsequent exposure to the same agent, however, the immune system is usually able to react within minutes to hours.

Passive immunity is temporary immunity transmitted or borrowed from another source. An infant receives passive immunity from its mother in utero and from antibodies it receives from its mother's breast milk. Passive immunity can also be transferred through injection of antiserum that contains the antibodies for a number of diseases. Both antiserum and gamma qlobulin are obtained from blood plasma.

Aloe arborescens and *Aloe vera* and Anticancer Activity

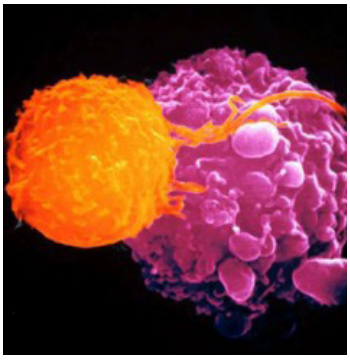
Aloe is a genus of plants with a notable history of various medical uses. Basic research studies over the past couple of decades have revealed the growing extent of pharmaceutical potential, particularly against neoplastic diseases. The two mostly used *aloe* species are *Aloe arborescens* and *Aloe barbadensis (Aloe vera).*

These *aloe* species contain several very large polysaccharides (many sugars) consisting of glucose (blood sugar) and mannose (various plants) which, when administered to animals and humans, cause the release of substances from certain white blood cells that form and activate natural killer cells (NKC) that attack cancer cells and cause their demise (death).

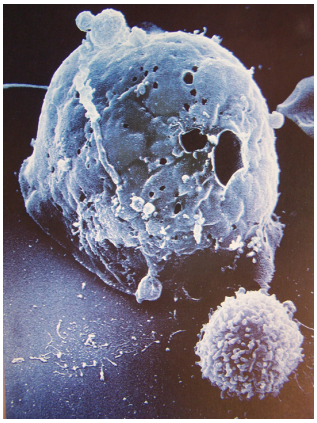
(1) Natural killer cells are part of the natural immune system and they kill tumor cells and cells infected by viruses.

(2) Natural killer cells do not require programming by prior contact with antigens.

(3) Natural killer cells attach to a cancer cell and inject chemicals that can kill the cancer cell in less than five minutes.



A natural killer cell (small sphere) binding to cancer tumor cell



In less than 5 minutes the natural killer cell has punctured and destroyed a larger tumor cell.

The tumor cell's structural matrix is all that remains after its encounter with the natural killer cell which moves on to another cancer cell.

One of the great advantages of such a system for destroying cancer cells is that it can destroy every last cancer cell, something none of the other modes of treatment can accomplish.

Unlike chemotherapy (destruction of cancer cells by chemicals) and radiotherapy (destruction by irradiation), stimulation of natural killer cells does not destroy normal cells in the body as the only targets are cancer cells.

[Leung MY, Liu C, Zhu LF, Hui YZ, Fung KF: Chemical and biological characterization of a polysaccharide biological response modifier from *Aloe vera*. Glycobiology 14 (6): 501, 2004]

The large polysacharides are found in the central portion of the *aloe* leaf called the fillet.

A fillet freshly removed from its green rind.

A second group of *aloe* constituents contain the laxative anthraquinones found in the yellow sap that comes from small tubules in the thick green rind. The yellow sap consists of several potent laxative agents including: Atoin A (barbaloin); Aloin B (isobarbaloin);*Aloe-emodin*; and Emodin.

Yellow sap or latex streaming out of the pericyclic tubes immediately after sectioning of a leaf

These constituents are chemically known as anthraquinones and have potent anti-cancer activities in addition to their laxative actions.

Aloe-emodin

Aloe-emodin, besides being a laxative agent, is a potent anti-leukemia constituent. [Kupchan SM, Karim A: *Aloe emodin*: Anti-leukemic principle isolated from Rhamnus Frangula L. Lloydia 39(4):223-224, 1976].

This compound was found to show significant anti-leukemic activity against P-388, L-1210, HCT-15, SK-HeP-G-1 mouse splenocytic and lymphocytic leukemia in mice.

Aloe emodin (0.25 mg/ml 1.25 mg/ml 2.5 mgjmL and 5.0 mg/ml showed dose-dependent cytoxicity against cancer cell lines, while the *aloe* extract stimulated the growth and proliferation of normal mouse splenocytes.

[Pya Myoung-Yun, Youn Jee-Hyeun: Effects of *aloe vera* on the cytotoxicity of anticancer drugs in vitro. Yakhak Hoeji 43(1): 104-110, 1999]

DEHP- (diethylhexylphtlalate)

Tests were performed on three human leukemic cell lines - K562 , HL60 and U937 -exposing the cancer cells to various concentrations of DEHP.

% Inhibition			
DEHP Concentration	Cell Lines		
1 ug/mL.	50%	51%	52%
10 ug/mL.	74%	83%	81%
100 ug/mL.	95%	97%	95%

[Lee KH, Kim JH, Lim OS, Kim CH: Antileukaemic and antimutagenic effects of di(2-ethylhexyl) phthalate isolated from *Aloe vera* Linne. J Pharmacy & Pharmacology 52 (5):593-598,2000]

[Lee KM, Hong HS, Lee CH, Kim CH: Induction of apoptosis in human leukemic cell lines K562, HL60 and U937 by diethylhexylphthalate isolated from *Aloe vera* Linne. J. Pharmacy % Pharmacology 52(8):1037-1041, 2000]

The Italian Experience

For several decades in Italy and other parts of Europe, health practioners have been using a mixture of the juice from *Aloe arborescens*, a cousin of *Aloe vera* and honey to treat a very large number of patients with all varieties of malignant diseases with extraordinary success.

This Brazilian immune health formula was published by Brazilian scholar Father Romano Zago and was used in clinical studies in collaboration with Paolo Lissoni, Oncologist at the Division of Radiation Oncology, St. Gerardo hospital, Monza, Milan, Italy.

More recently, a study on Wistar rats was performed using the *Aloe vera/ honey* preparation. Tumor growth, tumor size, and apoptosis (cell death) were evaluated.

Cell proliferation rate (Ki67-L1) and BaxlBcl2 expression were determined at 7, 14 and 20 days after Walker 256 carcinoma cells were implanted in the Wistar rats. Control rats were given 0.9% sodium chloride (table salt) by gavage (stomach tube) while the experimental animals were given the *Aloe vera*/ honey mixture.

The tumor growth in the *Aloe vera*/ honey animals compared with the control animals was reduced as was the relative weight of Ki67-L1 tumors compared with the control group. *Aloe vera*/honey modulated tumor growth by reducing cell proliferation and increasing susceptibility to apoptosis (cell death).

Honey has also been shown to have anticancer properties, including inhibition of tumor cell transformation and proliferation and induction of apoptosis. Based on ethnopharmalogical studies, the combination of honey and *Aloe arborescens* or *Aloe vera* is a common practice in alternative medicine, especially used in Brazil and South America.

[Tomasin R, Gomes-Marcondes MC: Oral administration of *Aloe vera* and honey reduced Walker tumor growth by decreasing cell profileration. Phytotherapy Research 25(4):619-123,2011]

Giuppe Naci, M.D. of Trieste, Italy, in his book - "Mille Piante Per Guarire Dal Cancro Senza Chemio" - (Thousand Plants to Recover from Cancer Without Chemotherapy), 1700 Official Scientific Publications with 1750 Various Bibliographic Refernces published in 2007, recommends using the liquid formula of whole leaf of *Aloe arborescens* plant juice plus raw organic honey with the proportions consisting of two volumes of honey to each volume of plant liquid. Honey protects the active ingredients of the plant extract and acts as a powerful antiseptic agent by inactivating potentially injurious micro-organisms.

Tumorlytic Activity of *Aloe arborescens* var. natalensis

I. Potent antitumor (anti-cancer) activities have been shown to be attributed to *aloe* molecules consisting of glucose and mannose sugars, in substances called polysaccharides (many sugars). One of the earliest research reports providing this information comes from Dr. Akira Yagi and his collaborators in Japan. These early studies were accomplished nearly thirty years ago.

[Yagi A, Nishimura H, Shida T, Nishioka 1: Structure determination of polysaccharides in *Aloe arborescens* var. natalensis. Planta Medica 51 :213-217, 1986]

II. *Aloe* juices contain about 300 different substances with molecular weights less than 100 and up to 10,000,000 Daltons. One of the smaller molecules in *Aloctin-A* a glycoprotein that possesses a variety of chemical and pharmacological activities including inhibition of gastric acid (HCI-hydrochloric acid) secretion and potent anti-tumor effects.

[Saito H: Purification of active substances of *Aloe arborescens Miller* and their biological and pharmacological activity. Phytotherapy Research 7: S14-S19,1993]

III. *Aloe* has been used as a folk medicine for centuries all over the world. Among the many components of *aloe*, low molecular weight components have been used as laxative agents both in humans and animals. High molecular weight components havebeen successfully used in skin injuries andthermal burns and, in addition, as a potent inflammatory agent. This article describes the antitumor activity of *Aloctin-A* in mice with malignant fibrosarcoma tumors. Complete anti-tumor inhibition of the sarcoma was demonstrated in 65% of the mice.

[Imanishi, K: *Aloctin-A*, an active substance of *Aloe arborescens* Miller as an immunomodulator. Phytotherapy Research 7:S20-S-22, 1993]

IV. Four-week old rats were fed a control diet or experimental diets containing 1% or 5% *Aloe* for five weeks. One week later, the animals were injected with a chemical that causes cancerous changes in colon and rectal cells. In the animals fed the *aloe* diets, no abnormal colorectal cells were observed as were seen in the control specimens. In addition, liver enzyme functions were protected against the abnormal changes seen in the control animals .

[Shimpo K, Chicara T, Beppu H, Ida C, Kaneko T, Nagatsu T, Kuzuya H: Inhibition of azoxymethane-induced aberrant crypt foci formation in rat colorectum by whole leaf *Aloe arborescens Miller* var. natalensis Berger.
Phytotherapy Research 15(8):705-711,2001]

V. Modification effects of freeze-dried *aloe* (*Aloe Arborescens*) whole leaf powder was given to female Syrian hamsters

given 0, 1 or 5% *aloe* in the diet for five weeks. At week five of the experiment, all surviving animals were sacrificed and the development of pancreatic cancer or precancer changes were assessed histopathologically. The incidences of precancerous cells and pancreatic cancer cells were significantly decreased in the group fed the 5% *aloe*, and reduced in the group fed the 1% *aloe*. In a satellite experiment, pretreatment with *aloe* significantly reduced precancerous cancerous changes in pancreatic duct cells.

[Furukawaa F, Nishikawda A, Chiharab T, Kimpob K, Beppub H, Kuzuyab H, Leec IS, Hirosea M: Chemopreventive effects of *Aloe arborescens* on N-nitrosobis(2-oxopropyl) amine-induced pancreatic carcinogenesis in hamsters. Cancer Letters 178;117-125, 2002]

VI. A study was planned to include 240 patients with metastatic solid tumors who were randomized to receive chemotherapy with or without *Aloe*. According to tumor histotype and clinical status, lung patients were treated with cisplatin and ectoposide or weekly vinoselbine, colorectal patients received oxaliplatic plus 5-fluorouracil (5-FU), gastric cancer patients received weekly germcitobine. *Aloe arborescens* was given orally at a dose 10 ml thrice daily of a mixture consisting of 300 g of *Aloe* fresh leaves in 500 g of honey plus 40 ml. of 40% alcohol, every day without interruption, either during or after chemotherapy, until the progression of disease, starting six days prior to the onset of chemotherapy. *Aloe* mixture was supplied by Deca (Isernia, Italy). The percentage of both objective tumor regression and disease control was significantly higher in patients concomitantly treated alone, as well as the percent of 3-year survival patients.

The study suggests that *aloe* may be successfully associated with chemotherapy to increase its efficacy in terms of both tumor regression rate and survival time.

[Lissoni P, Rovelli F, Brivio F, Zago R, Colciago M, Messinga G, Mora A, Porro G: A randomized study of chemotherapy versus biochemotherapy with chemotherapy plus *Aloe arborescens* in patients with metastatic cancer. In vivo 23: 171-176, 2009].

VII. A chemical investigation of arborescent *aloe* (*Aloe arborescens Miller*) in order to determine the characteristics of the accumulation of carotenoids, chlorophylls, carbohydrates and phenolic compounds in different parts of the leaf, as well as depending on the age of leaves, were realized.

- photosynthetic pigment
- carotenoids
- chloropylls
- free carbohydrates -glucose, sucrose, fructose; only glucose in inner gel
- pectin substances and glucanes
- phenolic compounds - aloenin, aloins, *aloe-emodin*
- No anthraquinones in inner part of leaves (gels)

[Olennikov DN; Zilfikarov LN; Ibragimov T A: Investigation of chemical composition of arborescent *aloe* (*Aloe arborescens*). Chemistry of Plant Raw Material3:77-82, 2010]

VIII. *Aloe* constituents possess free radical scavengers, antiproliferatives, and immunostimulating properties preventing and treating cancer.

Aloctin-A induced antitumor effects in murine fibrosarcoma and lymphatic leukemia in mice. Showed anti-tumor activity against implanted sarcoma 180 in mice, exhibited resistance against liver cell cancer cell proliferation.

Harlev E, Neva E, Lansky EP, Ofir R, Bishayee A. [Anticancer potential of *Aloe*s: Antioxidant, antiproliferation and immumodulatory attributes: Planta Medica 78:843-852,2012.]

Tumorlytic Diversity of *Aloe arborescens* and *Aloe barbadensis*

(312) Sarcoma-180

Yagi A, Makino K, Nishioka L, Kuchino Y: *Aloe* mannan, polysaccharide, from *Aloe arborescens* var. natalensis. Planta Medica 311 (1=17-20, 19 77.

Sarcoma-180, implanted in mice-15,000 MW, tumor growth inhibited by 38.1% at 5 mgjkg x 10 days and 48.1% at 200 mgjkg x 10 days.

(808) Lip, anus, breast, larynx, nose, prepuce, stomach, uterus, skin

Duke JA: Handbook of Medicinal Herbs. CRC Press, Inc., Boca Raton, Florida,1985: *Aloe barbadensis Mill*., pp 31-32.

(446) Mammary carcinoma; Erlich carcinoma; Melanoma

Chiunq-hua C, Yeng-chuan C, Dien-dong Li: The effect of rhein and emodin on transplantable tumors in animals. Yau Hsurah Hsueh Pao 13(5):363-366, 1966.cute

{581) Acute lymphcytic leukemia

Suzuki I: Alexin B. Jpn Kokai Tokkyo Koho 79113,41405 Sep 79

{582) Methyl cholanthrene-induced fibrosarcoma

Imanishi K, Ishiguro T, Saito H, Suzuki I: Pharmacological studies on a plant lectin, *Aloctin A*.. I. Growth inhibition of mouse methyl cholanthrene-induced fibrosarcoma (Meth A) in ascites form by *Aloctin A*. Experientia 37:1186-1187, 1981.

(2000) (OEHP) Antileukemia

Lee KH, Kim JH, Lim OS, Kim Cl-1: Antileukemic and antimutagenic effects of di(2ethylhexyl)phthalate isolated from *Aloe vera* Linne. J Pharmacy and Pharmacology 52(5):593-598, 2000.

(2000) (OEHP) Antileukemia

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(2006-28) Human bladder cancer

Lin JG, Chen GW, Li TM, Chouh ST, Tan TW, Chung JG: *Aloe-emodin* reduces apoptosis in T24 human bladder cancer cells through the p53 dependent apoptotic pathway. Journal of Urology 175(1):343-347, 2006.

(2006-60) Breast, ovarian cancer

Esmat AY, EI-Gerzawy SM, Rafaal A: DNA ploidy and S phase fraction of breast and ovarian tumor cells treated with a natural anthracycline analog (aloin). Cancer Biology Therapy 4(1): 108-112,2005.

(2007-15) Human lung nonsmall carcinoma

Lai MY, Hour MJ, Wing-Cheung Leung H, Yang WH, Lee HZ: Chaperones are the target in *aloe-emodin*-induced human lung nonsmall carcinoma H460 cell apoptosis, European Journal of Pharmacology 73(1-3):P1-10, 2007.

(2007-19) Cervical Carcinoma

Niciforovic A, Adzic M, Soaasic SO, Radojcic MB: Antitumor effects of a natural anthraxcycline analog *(Aloin)* involve altered activity of antioxidant enzymes in HeLa53 cells. Cancer Biology & Therapy (8):1200-1205,2007.

(2007-46) *Anthraquinones (emodin)* inhibiting cellular proliferation, induction of apoptosis, prevention of metastasis

Huang Q, LuG Shen HM, Chung MC, Ong CN: Anticancer properties of anthraquinones from rhubarb. Medical Research reviews 27(5):609-630, 2007.

{2007-47) *Aloe-emodin* for cancer

Dorsey JF, Kao GO: *Aloe*-emodin for cancer?

{2007-33) Gastric carcinoma

Chen SH, Lin KY, Chang CC, Fang Cl, Lin CP: *Aloe-emodin*-induced apoptos is in human gastric carcinoma cells. Food % Chemical Toxicology 45(11):2296-2303,2007

{2007-46) Anti-tumor of apoptosis

Huang Q, LuG, Shen HM, Chung MC Ong CN: Anti-cancer properties of anthraquinones from rhubarb. Medicinal Research Reviews 27(5):609-630, 2007

{2007-47) *Aloe-emodin* for cancer

Dorsey JF, Kao GO: *Aloe*-emodin for cancer? More than just a comforting salve. Cancer Biology & Therapy 6(1):89-90, 2007.

{2007-48) *Aloe-emodin* and gastric cancer

Guo J, Xiao B, Zhang S, Liu 0, Sun G: Growth inhibitory effects of gastric cancer cells with an increase in S phase and alkaline phosphatase activity repression by aloeemodin. Cancer Biology Therapy 6(1):85-88,2007.

{1-19) *Aloe-emodin* induces cell cycle arrest and apoptosis in human colon cancer cells

Suboj P, Babykutty S, Srinivas P, Gopala S: *Aloe-emodin* induces G2/M cell cycle arrest and apoptosis via activation of caspase-6 in human colon cancer cells. Pharmacology 89(1-2) :91-98.2012.

{I -30) *Aloe-emodin* inhibits colon cancer

Suboj P, Babycutty S, VaJiyaparambii Gopi DR, Nair RS, Seinivas P, Gopala S: *Aloe-emodin* inhibits colon cancer cell migration/ angiogenesis by downregulating MMP2/9, RhoB and VEGF via reduced DNA binding activity of NF-kappB, European Journal of Pharmaceutical Sciences 45(5):581-91,2012 Apr 11.

(11-8) *Aloe-emodin* exerts an anti-cancer effect in hepatic hepatocellular carcinoma cells

Jean W, Jean YK, Nam MJ: Apoptosis by *aloe-emodin* is mediated through downregulation of calpain-2 and ubiquitin-protein ligase E3A in human hepatoma Huh-7 cells. Cell Biology International 36(2): 163-16 7,2012.

{11-9) A rhein-*aloe-emodin* hybrid molecule showed a better in vitro anti-tumor effect than rhein and *aloe-emodin* alone.

Yuan YF, Hu XV, HeY, Deng JG: Synthesis and anti-tumor activity evaluation of rhein-*aloe-emodin* hybrid molecule. Natural Product Communication 7(2):207-210, 2012.

{11-24) *Aloe-emodin* can promote macrophage differentiation as a selective agent for treatment of leukemia.

Tabolacci C, Oliverio S, Lentini A, Rossi S, Galbiati A, Montesano C, Mattioli 0, Provenzano B, Facchiano F, Beninati S. Aloeemodin as antiproliferative and differentiating agent on human U937 monoblastic leukemia cells. Life Sciences 89 (2122): 812-820,2011.

{11-42) Dietary aloin, aloesin, or *aloe*-gel exerts anti-inflammatory activity activity in a rat colitis model.

Park MY, Kwon HJ, Sung MK: Dietary *aloin, aloesin, or aloe-gel* exerts anti-inflammatory activity in a rat colitis model. Life Sciences 88(11-12):486-492, 2011.

{11l-24) Rhein showed an important role in apoptotic induction of human breast cancer cells.

Chang CY, Chan HL, Lin HY, Way TO, Kao MC, Song MZ, Lin YJ, Lin CW: Rhein induces caspase-9 mediated apoptosis in human breast cancer cells. Evidence-based Complementary and Alternative Medicine (Art. No. 962504),2012.

{11l-85) *Emodin* induces apoptosis against neuroectodermal tumor cells.

Ahiwar K, Jain SK: *Aloe-emodin* novel anticancer herbal drug. International Journal of Phytomedicine 3(1):27-31,2011.

{IV-62) *Aloe-emodin* has been shown to have anticancer activity in various human cell lines including monoblastic leukemia.

Tabolacci C, Oliverio S, Lentini A, Rossi S, Galbiati A, Montesano C, Mattiolo P, Provenzano B, Facchiano F, Beninati S: *Aloe-emodin* as antiprotective and differentiating agent on human U937 monoblastic leukemia cells. Life Sciences 89(2122): 812-820,2011.

IX. An evaluation of antimetastic properties of succus Aloes was carried out using three types of experimental tumors of rice and rats. It was found that succus Aloes treatment contributes to reductions of tumor mass, metastic foci and metastis frequency at different stages of tumor progress without affecting major tumor growth. Succus Aloes potentiates the antitumor effect of 5-fluorouracil and cyclophosphamide as components of combination chemotherapy.

Gribel NV, Pashinskii VG. PMID: 3798837
[PubMed - indexed for MEDLINE.

To learn more about Aloe *Arborescens* scientific research and the Brazilian Aloe *Arborescens* Formula for Supreme Immune Health Support go to www.aloearborescens.org