A PHARMACY in a PLANT: *Aloe ferox*

SUMMARY:

Aloe ferox is among the tallest of the more than 400 aloe species and is native to southeastern and western regions of South Africa. Compared to the more widely known *Aloe vera*, *Aloe ferox* produces 20 times more bitter sap and has higher nutrient concentrations.

Two distinct parts of the aloe plant are used medicinally. Firstly the aloe exudate (**bitter** sap) and secondly the mucilaginous **gel** from the remainder of the leaf.

The aloe **bitter** is best known for its use as a laxative. However, in addition to the purgative effect the anthraquinone (**bitter**) substance is also an antioxidant, antiviral and effective for cancer prevention.

Numerous scientific studies on aloe **gel** are demonstrating its analgesic, anti-inflammatory, wound healing, immune modulating and anti-tumour activities as well as antiviral, anti-bacterial, antifungal and antiviral properties. The aloe **juice** has been shown to lower cholesterol and triglycerides while demonstrating anti-diabetic activity.

Aloe's medicinal properties can be attributed to the synergistic effect of the combined nutritional elements producing a more powerful effect than the individual components.

BOTANY:

Aloes are members of the Liliaceae family and are mainly succulents. The nearly 420 species of *Aloe* are confined mainly to Africa with *Aloe ferox* among the tallest. *Aloe ferox* occurs naturally in a broad belt along the southern and eastern coast of South Africa.

Aloe ferox is a robust, single stemmed, plant usually 2m (80") high, but up to 5m (200") tall in older specimens. They have broad, fleshy leaves that are dull green to greyish green with brown spines along the edges. The dry leaves are persistent on the lower portion of the stem. Bright red or orange flowers appear from May to August and are arranged in erect, candle-shaped clusters (Van Wyk 2003).

Pollination is by bees and nectar seeking birds and propagates with ease. New plants reach maturity (to flower and set seed) within four to six years. Under favourable conditions plants may become in excess of 50 years old.

Aloe ferox is not considered an endangered species. It is not listed on the United States Endangered Species Act list. Neither is it listed on the internationally maintained Red List of Threatened Species or on the CITES list of endangered species.

HISTORY:

All broad leaf *Aloe* species have basically the same leaf structure. A tough green outer layer encloses the translucent fleshy portion of the leaf. There are two distinct parts of the plant that are harvested.

Firstly the yellow exudate (better known as the **bitter** sap), which drains from the outer green skin of the leaves when cut, and the remainder of the leaf that contains the mucilaginous **gel**.

The traditional method of harvesting the leaves is still performed as practiced for more than 200 years.

The aloe is harvested by cutting 4 to 8 of the lower leaves from the plant. Roughly 200 leaves are stacked in a circle to allow the yellow **bitter** sap to drain from the leaves. The **bitter** sap is collected and boiled to remove excess water to produce the bitter crystals.

The harvested leaves are processed at the factory to manufacture the aloe **gel** and **juice**.

CHEMISTRY:

Aloe **bitters**: (Viljoen 1999, Van Wyk 1995)

- Anthrones and chromones are the two major classes of compounds, which are found in leaf exudates (22% – 29%)
    - Anthrones: aloin and barbaloin (collective name for aloin A and B)
    - Chromones: aloesin and aloeresin A.
- Anthraquinones, naphthalene, alkaloids and various other compounds may be present.

Aloe **gel**: (Mabusela 1990)

- Primary constituents are glucomannoglycan polysaccharides containing acetylated monosaccharides.
    - Acemannan (mannose) and glucomannan (glucose).
- Other constituents:
    - Amino acids.
    - Salicylic acid, lignin, saponins and sterols.
    - Fatty acids (gamma-linolenic acid [GLA]).
    - Enzymes, vitamins and minerals.

COMPARISON BETWEEN ALOE FEROX and ALOE VERA:

A comparison of the chemical composition of *Aloe ferox* and *Aloe vera* was performed based on values available in the literature (Femenia 1999, Mabusela 1990). It must be noted, however, that concentrations tend to vary seasonally and geographically (Grindlay 1986).

The different monosaccharide components of the polysaccharides present in the *Aloe ferox* and *Aloe vera* gel are compared (expressed as mol%).

Monosaccharide	***Aloe vera*** (gel)	***Aloe ferox*** (gel)
Rhamnose	1.69	3
Fucose	1.94	1
Arabinose	1.92	5
Xylose	2.34	13
Mannose	46.07	35
Galactose	4.97	5
Glucose	27.03	46

Similarly, scientific tests comparing the differences between *Aloe ferox* and *Aloe vera* plants **(whole leafs)**, growing side by side, were performed at the Kirstenbosch National Botanical Garden in Cape Town, South Africa.

The tests demonstrated the following:

1. The freshly cut leaf of *Aloe ferox* produced approximately **20** times more bitter sap, weight by weight, than the *Aloe vera*.

2. *Aloe vera* has a much softer and more translucent inner gel. It is also notably more mucinous.
3. After extraction, the juice of the *Aloe vera* leaves decolourizes and loses its viscosity much more rapidly than does the juice of *Aloe ferox*.
4. The solids content of the juice in *Aloe ferox* were constantly greater in volume than those obtained from *Aloe vera.*
5. The amino acid content of *Aloe ferox* is almost **double** that of *Aloe vera* (see table).

Amino acids	***Aloe vera*** (Whole Leaf)	***Aloe ferox*** (Whole Leaf)
Glutamic acid	4.70	2.8
Asparagine	3.29	14.47
Aspartic acid	1.75	1.41
Serine	1.27	1.69
Glycine	0.95	1.25
Alanine	0.91	1.04
Glutamine	0.83	3.82
Valine **	0.36	0.56
Threonine **	0.33	0.90
Proline	0.25	0.46
Lysine **	0.18	0.08
Arginine	0.12	0.05
Leucine **	0.09	0.12
Phenylalanine **	0.08	0.07
Isoleucine **	0.07	0.12
Tyrosine	0.06	0.05
Cystine	0.04	0.01
Histidine	0.03	0.02
Methionine **	0.02	0.07
Tryptophane **	0	0
Total Concentration (nMol/mg dry mass)	**15.33**	**28.99**

Aloe ferox and *Aloe vera* contain 7 of the 8 essential (** in table) amino acids and all the other 12 non-essential amino acids.

Similarly the mineral concentrations of *Aloe vera* (Femenia 1999) were compared to typical concentration measured in *Aloe ferox* (expressed as % of dry matter).

Minerals	***Aloe vera*** (Whole Leaf)	***Aloe ferox*** (Whole Leaf)
Calcium (Ca)	3.58	8.82
Magnesium (Mg)	1.22	1.68
Sodium (Na)	3.66	3.08
Potassium (K)	4.06	6.3
Phosphorus (P)	0.02	
Iron (Fe)	0.1	0.54
Copper (Cu)	0.06	0.04
Zinc (Zn)	0.02	0.8

It is evident that *Aloe ferox* contains a higher concentration of these minerals, which can potentially ascribed to its harvesting in its natural habitat and not in domesticated fields.

As can be seen the chemical composition of *Aloe vera* is comparable to that of *Aloe ferox*.

MEDICINAL PROPERTIES:

The healing properties of aloe have been known for millennia. The use of aloe was discovered on a Mesopotamian clay tablet (ca. 2100 BC). Aloes were listed in the Ebers papyrus (ca. 1500 BC) as an established cathartic.

Legend has it that aloe was an important part of the beauty regimen of the Egyptian queens, Nefertiti and Cleopatra. The Greek physician Dioscorides, while accompanying Nero's army, mentioned aloe in his writing (ca 100 AD). Alexander the Great (356–323 BC) was persuaded by Aristotle to capture the island of Socrota in the Indian Ocean to secure its aloe supplies to treat his wounded soldiers (Bruce 1975).

Numerous *Aloe* species have been used medicinally but only *Aloe ferox*, *Aloe perryi* and *Aloe vera* have demonstrated any commercial importance (Grindlay 1986). Scientific literature now documents various medical applications.

Aloe **gel** has demonstrated anti-inflammatory (Vázquez 1996, Bautista 2004), wound healing (Davis 1989, 1994, Heggers 1996), anti-tumour (Kim 1999, Pecere 2000), antiviral (McDaniels 1990a,b), anti-microbial (Wang 1998) and anti-diabetic (Reynolds 1999) activity. It has also shown immune stimulating (Zhang 1996, Strickland 2001) and cholesterol lowering activity (Tizard 1989).

The active constituent in the aloe exudate (**bitter**) is the anthrones. They are degraded in the colon by bacteria to aloe-emodin, which function as a stimulant laxative (Blumenthal, 1998).

Studies have also demonstated aloe-emodin to be antiviral (Sydiskis 1991), an antioxidant (Yen, 2000), effective for liver cancer prevention (Kuo 2002) and inhibits neuroectodermal tumor cell growth (Pecere 2000).

Anti-inflammatory

Inflammation is a non-specific immune response by the body to any type of injury. It is characterized by redness, heat, swelling and pain. According to Clayton (1993) the steps in inflammation are:

1. vasodilation that reduces blood pressure and increases blood flow (causing redness and heat)
2. followed by swelling due to an excessive amount of tissue fluid and
3. pain.

Vázquez (1996) demonstrated the anti-inflammatory effect of aloe gel. It inhibited prostaglandin E_2 production from arachidonic acid. While Yagi (1982) showed that the glycoprotein of aloe gel cleaved the bonds of the bradykinin molecule reducing pain and inflammation. In a later study (Bautista 2004) the antibradykinin effect was associated with the inhibition of prostaglandin synthesis.

Inflammation is also involved in conditions such as arthritis. Rheumatoid arthritis closely resembles adjuvant arthritis in rats and was studied by Davis (1992). According to this experiment aloe was injected and decreased inflammation (50%) and stimulated fibroblast growth repair.

Hanley (1982) showed when rat paws were injected with *A. ferox* it decreased inflammation (48%) and inhibited the immune response (72%). A subsequent study (Davis 1985) showed that when *A. ferox* was applied topically in a hydrophilic cream it reduced inflammation (39%) and subsequent arthritis (45%).

It has also been found that aloe has analgesic properties that can be ascribed to the presence of salicylates, which has an aspirin like effect (Shelton 1991).

Wound healing

A wound to the skin may pierce two layers, the dermis and epidermis. Healing follows the following steps (Reynolds 1999) by:

1. temporary repair is effected by fibrin clot to fill the gap which is invaded by cells that produce the inflammatory response and carry out the permanent repair.
2. The epidermis is repaired in 3 phases: (Davis 1994)
    a. fibroblasts migrate to the wound site causing granulation tissue to fill the gap,
    b. they proliferate and mature to produce collagen, elastin and proteoglycans.
    c. Proteoglycans form the basis in which collagen and other connective fibres are embedded.
3. It is essential to avoid microbial infection, as this will retard wound healing.

Wounds treated with aloe showed rapid granulation and increased oxygen supply as a result of the increased blood flow (Davis 1989). The skin punch wounds healed more rapidly. The aloe gel reduced wound diameter, seemed to reduce scarring and inhibited acute inflammation.

In another study, (Heggers 1996) stimulation of fibroblast activity and collagen proliferation was demonstrated. Aloe also expedites wound contraction and enhanced wound breaking strength.

Choi (2001) isolated a glycoprotein from *Aloe vera* that stimulated the formation of epidermal tissue. It also enhanced wound healing with significant cell proliferation and migration.

In the treatment of burn wound Heggers (1993) showed that the gel penetrated the tissue, relieve pain, reduce inflammation and increase blood supply by inhibiting the synthesis of thromboxane A_2, a potent vasoconstrictor.

A recent study (Barrantes 2003) demonstrated aloe **gel** enriched with aloins (**bitter**) to inhibit collagenase and metalloproteases activity, which can degrade collagen connective tissue when unchecked. This activity supports the use of aloe in the treatment of chronic ulcers, burns and wounds.

Immune modulation

Research on immune stimulation has indicated that acemannan, a polysaccharide within aloe, stimulated macrophage cytokine production and killer T cells (Zhang 1996).

Chronic exposure to UV radiation causes sunburn, premature aging of the skin and genetic mutations leading to skin cancer. UV radiation causes systemic suppression of immune responses. Strickland (2001) showed that the gel prevented systemic suppression of T cell mediated immune response and the production of IL-10. The aloe polysaccharides are immunostimulants by interfering with the activation of suppressor mechanisms.

Acemannan used for HIV-1+ patients showed a significant increase in the number of circulating monocytes and macrophages (McDaniels 1990a). In a pilot study treating HIV infected people acemannan increased the number of white blood cell and improved symptoms (McDaniels 1990b).

Gastrointestinal functions

The aloe **juice** has been used as a tonic in a series of trials (Bland 1985) on human patients. It indicated a tonic effect on the intestinal tract with:

1. a reduction in pH;
2. a reduction in bowel transit time;
3. intestinal bacterial flora benefited with a reduction in yeast;

4. bowel putrefaction was reduced and
5. protein digestion and absorption was improved.

Yamamoto (1973) showed that a component of *A. ferox* suppresses ulcer growth and L-histidine decarboxylase in rats. Recently the gastropreventative of aloe was demonstrated by inhibiting gastric acid secretion, which makes it suitable for peptic ulcer treatment (Yusuf 2004).

When **juice** is given orally to animals, mannans have been shown to lower cholesterol by inhibiting cholesterol absorption (Tizard 1986). In a small trial with monkeys it was found that aloe juice lowered total cholesterol by 61% with a proportionate rise in HDL (Dixit, 1983).

Aloe **juice** has been used with success to lower blood sugar and triglyceride levels. Diabetic patients that failed to respond to other medication responded to aloe treatment (Reynolds, 1999). It has been demonstrated that both the aloe exudate (**bitter**) and **gel** decreased blood glucose levels in mice. Similarly it has been found that both compounds have a protective effect against hepatotoxic liver injury (Can 2004).

The cathartic and laxative action of aloe **bitter** is well established. Its primary effect is caused by its influence on the motility of the colon. This results in an accelerated intestinal passage and a reduction in liquid absorption increasing water content in the faeces (Blumenthal 1998).

In addition to the purgative effect the anthraquinone (**bitter**) substances stimulate the flow of gastric juices thus improving digestion. Soeda (1964) found that fractions from *A. ferox* gave a prophylactic effect. While in a subsequent study, Soeda (1966) found the aloe juice to have inhibitory action against some bacteria and fungi, particularly *Pseudomonas aeroginosa* and *Proteus vulgaris*.

Anti-cancer activity

An early report by Soeda (1969) reported anti-tumour activity of *A. ferox*. Both plant fractions have been shown to inhibit tumour growth. Aloe-emodin has shown mutagenesis inhibition as well as the glycoproteins (lectins) and polysaccharides from the **gel**.

Kuo (2002) has demonstrated that aloe-emodin induced apoptosis (cell disintegration) and acted as an effective anticancer effect in human liver cancer. Similarly, Pecere (2000) found that aloe-emodin did not inhibit fibroblast proliferation while selectively inhibiting human neuroectodermal tumour cells.

A purified polysaccharide indicated anticarcinogenic effects by inhibiting the uptake of B[a]P and subsequently binding to cellular DNA. It also had no cytotoxic effect (Kim 1999). Strickland (2001) demonstrated the polysaccharides efficacy to prevent non-melanoma skin cancers by preventing T cell immune suppression.

Anti-microbial

Reynolds (1999) has reviewed the antimicrobial activity of aloe.

1. Antibacterial:
   - The aloe **gel** and **bitter** is bactericidal against:
     - a variety of common wound infecting bacteria: *Streptococcus pyogenes, Serratia marcescens, Klebsiella pneumonia, Staphylococcus aureus, E. coli, Mycobacterium tuberculosis, Pseudomonas auruginosa* and *Corynebacterium xerose.*
   - The **gel** is effective against:
     - *Streptococcus faecalis* responsible for urinary infection.
     - Ferro (2003) showed effective growth inhibition of *Shigella flexneri* and *Streptococcus pyogenes* responsible for gastroenteritis.
   - Aloe-emodin in **bitter** has been shown to inhibit:

    - growth of *Helicobacter pylori*, which is responsible for peptic ulcers (Wang 1998).
    - *Citrobacter*, *Enterobacter aerogenes, Serratia* and *Klebsiella* that cause gastroenteritis.
    - *Proteus vulgaris* an opportunistic pathogen of the urinary tract and
    - *Salmonella paratyphi* causing fever.
2. Antiviral:
    - Aloe **gel** has been proven to be virucidal to:
        - HIV-1+ patients showing increased numbers of white blood cells and improvement in symptoms (McDaniels 1990b).
        - Herpes simplex infection with significant faster healing time and higher number of healed lesions compared to the control (Syed 1997).
    - Aloe bitter was virucidal:
        - by disrupting the coating of the herpes and influenza virus (Sydiskis 1991).
3. Antifungal:
    - Aloe **gel** is shown to be fungicidal to:
        - *Candida albicans* responsible for yeast infections of the mucous membranes.
        - *Trichophyton* spp. by *A. ferox* **juice** (Soeda 1966) responsible for infections such as athlete's foot and candidiasis (thrush).

Skin

The skin is composed of polypeptide chains that form aggregates of collagen fibrils, which influences the swelling and water uptake by the skin. The diffusion of water through the skin is limited and controlled by the stratum corneum (skin surface) that is in equilibrium with the atmosphere and underlying tissue.

Since aloe is approximately 99% water it penetrates through the surface of the skin (stratum corneum) to the vascular dermal area thus hydrating the skin. Concurrently, the **gel** forms a cover to prevent the escape of moisture in the skin.

Aloe **gel** increases the penetration of the skin by water hydration, occlusiveness and by increasing compound solubility. Subsequently, Davis (1991) has demonstrated that aloe gel enhanced the penetration of hydrocortisone and adds to its biological activity.

Concomitantly, aloe **gel** increased oxygen supply as a result of increased blood flow (Davis 1989) and stimulates fibroblast activity and collagen proliferation (Thompson 1991) essential for skin tissue regeneration. Subsequently aloe gel it is used extensively in cosmetics.

Aloe gel reduces photo aging by restoring the activity of epidermal cells reduced by UV exposure. The **gel** increase soluble collagen levels and biosynthesis possibly through macrophage stimulation (Lindblad 1994)

In a large clinical trial Syed (1996) studied the effect of an Aloe cream on psoriasis vulgaris. They found that the aloe cream cured 83.3% of the patients compared to 6.6% of the placebo group with a concomitant clearing of the psoriatic plaques. There were no adverse drug reactions or side effects.

A study by Vardy (1999) has demonstrated the effectiveness of an aloe lotion for treating seborrheic dermatitis (excessive excretion of sebaceous glands, dandruff) when applied on the skin twice a day.

TOXICITY AND CONTRAINDICATIONS:

External use:

- Allergic reactions are rare and there is no reported toxicity.

Internal use:

- Aloe **juice:**
  - Aloe **juice** appears safe and there is no reported toxicity.
  - The mucilage in the aloe **juice** may interfere with the absorption of other oral medications taken concurrently
- Aloe **bitter:**
  - The anthraquinones in the aloe **bitters** can cause severe diarrhoea and intestinal cramping when overdosed. Chronic internal use of anthraquinones can lead to potassium loss, dehydration and intestinal dependence on laxatives.
  - The aloe **bitters** may reduce absorption of drugs due to decreased bowel transit time, may increase potassium loss in patients taking corticosteroids or thiazide diuretics, and may potentiate digitalis and other cardiac glycosides due to low potassium levels.
  - Aloe **bitters** is not recommended for people with intestinal obstruction, intestinal inflammation (eg. Crohn's disease, ulcerative colitis), appendicitis and abdominal pain of unknown origin.
  - It is clinically proven that the use of anthranoid laxatives, even in the long term, does not cause cancer (Nusko 2000).

REFERENCES:

BLUMENTHAL, M., BUSSE, W.R., GOLDBERG, A., HALL, T. et al. 1998. *German Commission E Monographs*. Austin:American Botanical Council and Integrative Medicine Communications.

BAUTISTA, R., SEGURA, D.& VAZQUEZ, B. 2004. In vitro antibradykinin activity of *Aloe barbadensis* gel. J. of Ethnopharmacology. In press.

BARRANTES, E. & GUINEA, M. 2003. Inhibition of collagenase and matalloproteinases by aloins and aloe gel. Life Sciences. vol.72. p 843-850.

BLAND, J. 1985. Effect of orally consumed Aloe vera juice on gastrointestinal function in normal humans. Preventive Medicine. vol.14. p 152-154.

BRUCE, W.G.G. 1975. Medicinal properties in the aloe. Excelsa. no.5. p 57-68.

CAN, A., AKEV, N., OZSOV, N., BOLKENT, S., ARDA, B.P., et al. 2004. Effect of Aloe vera leaf gel and pulp extract on the liver in type II diabetic rat models. Biol. Pharm. Bull. vol.27. no.5. p 694-698.

CHOI, S.W., SON, B.W., SON, Y.S., PARK, Y.I., LEE, S.K. & CHUNG, M.H. 2001. The wound healing effect of a glycoprotein fraction isolated from aloe vera. British J. of Dermatology. vol.145. no.4. p 535-545.

CLAYTON, L.T. (Ed.) 1993. Taber's Cyclopedic Medical Dictionary. Philadelphia:F.A. Davis Company.

DAVIS, R.D., SHAPIRO, E. & AGNEW, P.S. 1985. Topical effect of Aloe with ribonucleic acid and vitamin C on adjuvant arthritis. J. Am. Podiatric Med. Ass. vol.75. p 229-237.

DAVIS, R.D., LEITNER, M.G., RUSSO, J.M. & BYRNE, M.E. 1989. Wound healing. Oral and topical activity of Aloe vera. J. Am. Podiatric Med. Ass. vol.79. no.11. p 559-562.

DAVIS, R.D., PARKER, W.L., & MURDOCH, D.P. 1991. Aloe vera as a biological vehicle for hydrocortisone acetate. J. Am. Podiatric Med. Ass. vol.81. p 1-9.

DAVIS, R.D., STEWART, G.J. & BREGMAN, P.J. 1992. Aloe vera and the inflamed synovial pouch model. J. Am. Podiatric Med. Ass. vol.82. no.3. p 140-148.

DAVIS, R.H., DIDONATO, J.J., HARTMAN, G.M. & HAAS, R.C. 1994. Anti-inflammatory and wound healing activity of a growth substance in Aloe vera. J. Am. Podiatric Med. Ass. vol.84. no.2. p 77-81.

DIXIT, V.P. & JOSHI, S. 1983. Effect of *Aloe barbadensis* and clofibrate on serum lipids in triton induced hyperlipidaemia in *Presbytis* monkeys. Indian J. of Medical Research. vol.78. p 417-421.

FEMENIA, A., SANCHEZ, E.S., SIMAL, S, & ROSELLO, C. 1999. Compositional features of polysaccharides from Aloe vera (*Aloe barbadensis* Miler) plant tissue. Carbohydrate polymers. vol.39. p 109-117.

FERRO, V.A., BRADBURY, F., CAMERON, P., SHAKIR, E., RAHMAN, S.R. & STIMSON, W.H. 2003. In Vitro susceptibilities of *Shigella flexneri* and *Streptococcus pyogenes* to inner gel of *Aloe barbadensis* Miller. Antimicrobial Agents and Chemotherapy. vol.47. no.3. p 1137-1139.

GRINDLAY, D. & REYNOLDS, T. 1986. The *Aloe vera* phenomena: a review of the properties and modern uses of the leaf parenchyma gel. J. of Ethnopharmacology. vol.16. p 117-151.

HANLEY, D.C., SOLOMON, W.A.B., SAFFRAN, B, & DAVIS, R.H. 1982. The evaluation of natural substances in the treatment of adjuvant arthritis. J. Am. Podiatric Med. Soc. vol.72. p 275-284.

HEGGERS, J.P., PELLEY, R.P. & ROBSON, M.C. 1993. Beneficial effect of Aloe in wound healing. Phytotherapy Research. vol.7. p S48-S52.

HEGGERS, J.P., KUCUKCELEBI, A., LISTERGARTEN, D., STABENAU, J. et al. 1996. Beneficial effect of Aloe on wound healing in an excisional wound model. J. Altern. Complement Med. vol.2, no.2. p 271-277.

KIM, H.S., KACEW, S. & LEE, B.M. 1999. *In vitro* chemopreventive effects of plant polysaccharides (*Aloe barbadensis Miller*, *Lenticus edodes*, *Ganoderma lucidum* and *Coriolus versicolor*). Carcinogenesis. vol.20. no.8. p 1637-1640.

KUO, P-L, LIN, T-C. & LIN, C-C. 2002. The antiproliferative activity of aloe-emodin is through p53-dependent and p21-dependent apoptotic pathways in human hepatome cell lines. Life Sciences. vol.71. p 1879-1892.

LINDBLAD, W.J. & THUL, J. 1994. Sustained increase in collagen biosynthesis in acemannan impregnated PVA implants in the rat. Wound Repair and Regeneration. vol.2. p 84.

MABUSELA, W.T., STEPHEN, A.M. & BOTHA, M.C. 1990. Carbohydrate polymers from *Aloe ferox* leaves. Phytochemistry. vol.29. no.11. p 3555-3558.

MCDANIELS, H.,COMBS, H.R.M, CARPENTER, R., KEMP, M & MCNALLY, B. 1990a. An increase in circulating monocyte/macrophage (M/M) is induced by oral acemannan in HIV-1 patients. Am. J. Clinical Pathology. vol.94. p 516-517.

MCDANIELS, H., CARPENTER, R., KEMP, M. KAHLON, J. & MCNALLY, B. 1990b. Extended survival and prognostic criteria for acemannan (ACE-M) treated HIV patients. Antiviral Research Suppl. vol.1. p 117.
NUSKO, G., SCHNEIDER, B., SCHNEIDER, I., WITTEKIND, C. & HAHN, E.G. 2000. Anthranoid laxative use is not a risk factor for colorectal neoplasia: results of a prospective case control study. Gut. vol.46. no.5. p 651-655.
PECERE, T., GAZZALO, V., MUCIGNAT, C., PAROLIN, C., et al. 2000. Aloe-emodin is a type of anticancer agent with selective activity against neuroectodermal tumors. Cancer Research. vol.60. p 2800-2804.
REYNOLDS, T. & DWECK, A.C. 1999. Aloe vera leaf gel: a review update. J. of Ethnopharmacology. vol.68. p 3-37.
SHELTON, R.M. 1991. Aloe vera: its chemical and therapeutic properties. International J. of Dermatology. vol.30. p 679-683.
SOEDA M, FUKIWARA, M AND OTOMO, M. 1964. Studies on the effect of Cape aloe for irradiation leucopenia. Nippon Igaku Hoshasen Gakkai Zasshi. Dec. 24, p 1109-1112.
SOEDA, M., OTOMO, M., OME, M & KAWASHIMA K. 1966. Studies on anti-bacterial and anti-fungal activities of Cape aloe. Japan J. Bacteriology. vol.21, no.10, p 609-614.
SOEDA, M. 1969. Studies on the anti-tumor activity in Cape Aloe. J. of The Medical Society of Toho University. vol.16. p 365-369.
STRICKLAND, F.M. 2001. Immune regulation by polysaccharides: implications for skin cancer. J. of Photchemistry and Photobiology. vol.63. p 132-140.
SYDISKIS, R.J., OWEN, D.G., LOHR, J.L., ROSLER, K-H. A. & BLOMSTER, R.N. 1991. Inactivation of enveloped viruses by antraquinones extracted from plants. Antimicrobial Agents and Chemotherapy. vol.35. no.12. p 2463-2466.
SYED, T.A., AHMAD, S.A., HOLT, A.H., AHMAD, S.H. & AFZAL, M. 1996. Management of psoriasis with Aloe vera extract in a hydrop cream: aplacebo-controlled, double blind study. Trop. Med. Int. Health. vol.1. no.4. p 505-509.
SYED, T., AFZAL, M., ASHFOX, A., HOLT, A., ALI, A & AHMAD, S. 1997. Management of genital herpes in men with 0.5% Aloe vera extract in a hydrophilic cream: a placebo-controlled double blind study. J. of Dermatology Treatment. vol.8. p 99-102.
THOMPSON, J.E. 1991. Topical use of aloe vera derived allantoin gel in otolaryngology. Nose and Throat J. vol.70. p119.
TIZARD, I., CARPENTER, R.H., MCNALLY, B.H. & KEMP, M. 1989. The biological activity of mannans andrelated complex carbohydrates. Molecular Biotherapy. vol. 1. p 290-296.
VAN WYK, B-E., VAN RHEEDE VAN OUDTSHOORN, M.C.B. & SMITH, G.F. 1995. Geographical variation in the major compounds of *Aloe ferox* leaf exudates. Planta Med. vol.61, p 250-253.
VAN WYK, B-E. & SMITH, G. 2003. *Guide to the Aloes of South Africa, 2nd ed.* Pretoria:Briza.
VARDY, A.D., COHEN, A.D. & TCHETOV, T. 1999. A double-blind, placebo-controlled trial of Aloe vera (A. barbadensis) emulsion in the treatment of seborrheic dermatitis. J. Dermatology Treatment. vol.10. no.1. p 7-11.
VAZQUEZ, B., AVILA, G.,SEGURA, D. & ESCALANTE, B. 1996. Anti-inflammatory activity of extracts from *Aloe vera* gel. J. Ethnopharmacology. vol.55. p 69-75.
VILJOEN, A. 1999. *A chemotaxonomic study of phenolic leaf compounds in the genus Aloe*. PhD dissertation. Rand Afrikaans University.
WANG, H., CHUNG, J., HO, C., WU, L. & CHANG, S. 1998. Aloe-emodin effects arylamin N-acetyltransferase activity in the bacterium Helicobacter pylori. Planta Medica. vol.64. p 176-178.
YAGI, A., HARADA, N., YAMADA, H., IWADARE, S. & NISHIOKA, I. Antibradykin active material in Aloe saponaria. J. of Pharmaceutical Sciences. vol.71. no.10. p 1172-1174.
YEN, G-C., DUH, P-D & CHUANG, D-Y. 2000. Antioxidant activity ofanthraquinones and anthrone. Food Chemistry. vol.70. p 437-441.
YAMAMOTO, I. 1973. Aloe ulcin, a new principle of Cape aloe and gastrointestinal function, especially experimental ulcer in rats. J. of The Medical Society of Toho University. vol.17. p 243-347.
YUSUF, S., AGUNU, A. & DIANA, M. 2004. The effect of *Aloe vera* Berger (Liliacceae) on gastric acid secretion and acute gastric mucosal injury in rats. J. of Ethnopharmacology. In press.
ZHANG, L. & TIZARD, I.R. 1996. Activation of a mouse macrophage cell line by acemannan: the major carbohydrate fraction from aloe vera gel. Immunopharmacology. vol.35. no.2. p 119-128.