

## Review Paper

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# THE *ALOE VERA* PHENOMENON: A REVIEW OF THE PROPERTIES AND MODERN USES OF THE LEAF PARENCHYMA GEL

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## Summary

The mucilaginous gel from the parenchymatous cells in the leaf pulp of *Aloe vera* has been used since early times for a host of curative purposes. This gel should be distinguished clearly from the bitter yellow exudate originating from the bundle sheath cells, which is used for its purgative effects. *Aloe vera* gel has come to play a prominent role as a contemporary folk remedy, and numerous optimistic, and in some cases extravagant, claims have been made for its medicinal properties.

Modern clinical use of the gel began in the 1930s, with reports of successful treatment of X-ray and radium burns, which led to further experimental studies using laboratory animals in the following decades. The reports of these experiments and the numerous favourable case histories did not give conclusive evidence, since although positive results were usually described, much of the work suffered from poor experimental design and insufficiently large test samples. In addition some conflicting or inconsistent results were obtained. With the recent resurgence of interest in *Aloe vera* gel, however, new experimental work has indicated the possibility of distinct physiological effects.

Chemical analysis has shown the gel to contain various carbohydrate polymers, notably either glucomannans or pectic acid, along with a range of other organic and inorganic components. Although many physiological properties of the gel have been described, there is no certain correlation between these and the identified gel components.

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## Introduction

There can be few plants whose reputed medicinal properties have aroused

so much controversy as those of *Aloe vera*. *Aloe vera* (L.) Burm. f. has a history of use in folk medicine for skin and other disorders which dates back thousands of years (Morton, 1961; Crosswhite and Crosswhite, 1984). Today the processing of *A. vera* gel, derived from the leaf pulp of the plant, for medicinal and cosmetic use, has become a big industry in the United States, one of the largest based on botanicals. Yet the scientific literature on *A. vera* is very confused, with a number of contradictory reports and inconclusive experiments. There are also several properly conducted studies, but these do not always receive the recognition they deserve. While some writers disclaim any of the supposed physiological effect of *A. vera* gel, others fully endorse them. There is, however, considerable belief in the beneficial action of the gel among the general public, particularly in the USA, and *A. vera* is one of the few botanical medications with widespread domestic use in Western society.

Associated with the promotional activities of the manufacturers of *A. vera* gel products there has grown up a plethora of legends about its history and properties, for example that it was the secret of Cleopatra's beauty, or even that it is some kind of miraculous gift from the gods, capable of curing virtually any illness (see Gjerstad and Riner, 1968; Spoerke and Ekins, 1980). The exaggerated claims made in the past by some companies for amazing, but unsubstantiated cures in a whole variety of conditions have only helped to confuse the issue and have given the whole subject a less than respectable air.

This paper presents a comprehensive and objective view of the literature and experimental work which has been carried out on *A. vera* gel, and examines reasons why the use of the gel has become such a popular but controversial part of modern urban ethnopharmacology.

### **The use of aloes in folk medicine**

It is important from the outset to differentiate clearly between the two medicinal components of the *Aloe* leaf. Some writers have confused the gel with the exudate, or have not clearly distinguished between the two (e.g. Cheney, 1970). Experimental work on *A. vera* is difficult to evaluate if it is not clear which part of the leaf has been used. *A. vera* "juice" is a term best avoided, as it could mean either the exudate from the bundle-sheath cells, or the gel after extraction from the leaf. Using the word "Aloe" on its own when *Aloe vera* gel is meant is also misleading, since "Aloe" has official standing in pharmacopoeias and formularies as the drug derived from the dried leaf exudate (see Madis Laboratories, 1983).

Numerous *Aloe* species have been used medicinally, but few on a widespread basis. Bruce (1975) gives a useful review, while Reynolds (1950, 1966) details the recorded uses for each species he describes. Many folk uses of aloes in Southern Africa are reported by Watt and Breyer-Brandwijk (1962). Only a few species have had any commercial importance, the main

species used being *Aloe ferox* Miller (Cape Aloes) *Aloe perryi* Baker (Socotrine Aloes) and *Aloe vera* (Barbados or Curaçao Aloes). These species are harvested for their bitter leaf exudate or "latex", important in trade as the source of drug aloes or "aloin", used for its purgative effects (Hodge, 1953; Mapp and McCarthy, 1970; Morton, 1977; Trease and Evans, 1978; Anon, British Pharmacopoeia, 1980; Ovanoviski, 1983). Drug aloes is less commonly employed now because it tends to cause griping, and has an effect persisting over several days. *Aloe* exudates contain a number of pharmaceutically active phenolic compounds, including anthraquinones and their glycosides; these have been reviewed by Bruce (1975), Suga and Hirata (1983) and Reynolds (1985).

While *A. vera* has long been grown to supply drug aloes, it has over the last fifty or so years become more widely known for its gel. The folk uses of *Aloe* gel, in particular that of *A. vera*, have been well described in the excellent article by Morton (1961), while Crosswhite and Crosswhite (1984) discuss the mythology and symbolism associated with the use of *A. vera* throughout history. The plant was widely used by the Egyptians, Assyrians, and Mediterranean civilisations, and in Biblical times. The dried leaf exudate was the main medicinal product, though it seems that the gel was also used. Dioscorides used *Aloe* as a purge, and to treat wounds, mouth infections, to soothe itching and to cure sores (Gunther, 1934). He also described the use of the leaves "for ye conglutinating of wounds, being laid on when it is beaten small".

*Aloe vera* still has an important role in the traditional medicine of many contemporary cultures. In India, *A. vera* medications are used for a variety of conditions, particularly for their cathartic, stomachic, emmenagogic and anthelmintic properties (Chopra and Ghosh, 1938; Chopra et al., 1956; Dastur, 1962). Whole leaves, the exudate, and the fresh gel are all used. In China *A. vera* has been an important medicine for centuries, and it is still a common household remedy (Cole and Chen, 1943; Tchou, 1943). In Mexico, the leaves are gathered from plants growing semi-wild to treat burns, bruises, skin irritations, and even leprosy (Diez-Martinez, 1981). *A. vera* is also widely used as a folk remedy across the rest of Middle America and the West Indies, as reviewed by Morton (1981). In all these countries *A. vera* is an introduced species, but has been rapidly adopted as an essential part of local materia medica.

In present day Western society, most notably in the USA, *A. vera* has fairly frequent use in homeopathy and herbalism (Panos and Heimlich, 1980). It is commonly grown in America and the tropics as a pot plant on kitchen windowsills, so the leaves are on hand to treat burns, to soothe the pain and promote healing. The plant has additional use to treat sunburn and various dermatological conditions and taken internally, as a general tonic. Madis Laboratories (1984) list over a hundred medical disorders that have at some time been treated, such as arthritis, gout, acne, cuts, dermatitis, headache, high blood pressure, indigestion, hair loss, rheu-

matism, peptic ulcers, mouth diseases, pruritis, psoriasis and, of course, burns. The medicinal use of *A. vera* is particularly widespread in Florida (Galban, 1952). Some of the more unusual applications include bee stings (Nieberding, 1974) and jelly-fish stings (Bovik, 1966). *A. vera* has also had considerable use as a folk remedy for farm animals, as described by Anderson (1983) and Diez-Martínez (1981).

There can be no doubt that there is widespread belief in *A. vera* among the general public, particularly in the USA. According to Anderson (1983): "Judging from the purported skyrocketing sales of *aloe vera* cosmetics, many people truly believe that they have found the fountain of youth in the aloe vera plant". It does seem to be thought by some that *A. vera* is some kind of "miracle plant" or "wonder drug". The symbolic association of *A. vera* with embalming, enduring life and immortality and the boundary between life and death as described by Crosswhite and Crosswhite (1984) has found its way into modern advertising and beliefs about the plant. As Norris (1973) wrote: "If a plant is able to heal its own wounds, to survive without nourishment, even seemingly to return from the dead, might not its power somehow be applicable to man's own maladies?"

A multitude of articles and books have been written on *A. vera* to meet scientific and public interest, e.g. Foster (1961, 1965, 1973), Batchelder (1964), Norris (1973), Bruce (1975), Gates (1975), Skovsen (1977), Coats (1979), Taylor-Donald (1980, 1981), Heinerman (1982), Lutomski (1984) who surveys the East European literature and Grindlay (1985a,b). There are also others less accurate or more fanciful (e.g. Morales, N.D.).

*Aloe arborescens* Miller is a species which has been used in a similar manner to *A. vera*. It has traditionally been used to treat burns in China (Reynolds, 1950) and the USSR (Nikolaeva, 1979), while Watt and Breyer-Brandwijk (1962) describe its medicinal use by the Zulus. Lowenthal (1949) successfully used leaves of *Aloe arborescens* to treat X-ray burns in South Africa when *A. vera* was not available. According to Hirata and Suga (1977), *A. arborescens* is used in Japan as a folk remedy for gastrointestinal complaints, burns, insect bites and athlete's foot, and Kameyama and Shinho (1980) patented an emulsion from *A. arborescens* for the treatment of wounds. Yagi, Shibata et al. (1982) mention the use in Japan of yet another species, *Aloe saponaria* (Ait.) Haw. in a similar manner.

### Botany of *Aloe vera*

Aloes are members of the Liliaceae and are mostly succulents with a whorl of elongated, pointed leaves. Reynolds (1950, 1966) described 314 species in his classic monographs; there are now over 360 accepted species (Harding, 1979). Some species are tree-like with long stems, while others are small, with their leaves at ground level. They occur over most of Africa, Southern Arabia and Madagascar, but not in rain forest regions or dry deserts. A few species have been carried in cultivation around the Mediterr-

anean, and from there have reached as far as Japan in the east and America in the west.

The nomenclature of *A. vera* has been very confused, and the plant has been known under a variety of names (Reynolds, 1966), most notably *Aloe barbadensis* Miller, *Aloe vera* Tourn. ex. Linn., and *Aloe vulgaris* Lamarck. While *Aloe barbadensis* Miller was until recently the official name, the plant was still popularly known as *Aloe vera*, and Newton (1979) argued that the scientific name should also be *Aloe vera*. N.L. Burman had used this name for what was previously described by Linnaeus as a variety *vera* of *Aloe perfoliata*. Burman had priority over Miller's later use of the name *A. barbadensis*, but perhaps only by a period of 10 days. Following this argument, the correct name is thus *Aloe vera* (L.) Burm. f.

The geographical origin of *A. vera* is not known for sure, since it has been introduced and naturalised throughout most of the tropics and warmer regions of the world, including the West Indies and Bahamas, southern USA, Mexico, Central America, Arabia, and India and other parts of Asia. According to Harding (1979) its probable origin was in North Africa, or the Canary, Madeira and Cape Verde islands. However, Brandham (1985) thinks this is unlikely, and suggests, "In view of its use by ancient Egyptian and Mediterranean cultures, a more likely area of origin would be the upper Nile area in Sudan, or possibly the Arabian peninsula, in both of which areas many species of *Aloe* are native."

*Aloe vera* is a perennial with fleshy leaves arising in a rosette from a short stem. In young plants the leaves appear at ground level, but the stem can grow up to 25 cm long in older plants. There may be 15 to 30 leaves per plant, the young leaves more or less erect and the older, lower ones more spreading. The leaves are up to 0.5 m long and 8–10 cm across at the base, tapering to a point, with saw-like teeth along their margins. In transverse section the leaves are slightly concave on their adaxial surface, while the lower, abaxial surface is markedly convex. In young plants and in the suckers which arise from the plant base, the leaves are a bright green colour, with irregular whitish spots on both sides. As the rosettes mature, successive leaves have fewer spots, and fully mature leaves are a spotless glaucous grey-green colour. The inflorescence is a dense raceme borne on a peduncle some 30–50 cm long arising from the centre of the leaf rosette. The flowers are pendent, with a tubular yellow perianth around 2 cm long.

There seems to be considerable variation among plants described as *A. vera*. Some follow the description given here, while others have dark green leaves arranged more in a fan-shape than in a rosette. Correct identification is very important. Abraham and Prasad (1979) reported a triploid form from southern India, and other ploidy variations may possibly exist. Wood (1983) discusses the various varieties which have been described within the *A. vera* species.

The epidermis of the leaves has a thick cuticle, and beneath is a zone of chlorenchyma. The central bulk of the leaf contains the colourless mucic-

luginous pulp, made up of large thin-walled mesophyll cells containing the *A. vera* gel itself. Along the junction between the pulp and the chlorenchyma are arranged the numerous vascular bundles, with accompanying inner bundle sheath cells. The bundle sheath cells at the phloem poles are thin-walled and axially elongated, and contain the bitter yellow sap which exudes from the leaves when they are cut.

### Clinical use of *Aloe vera* gel in the 1930s

Research into the medicinal effects of *A. vera* gel began in the 1930s. Before then a considerable amount of work had been done on the purgative properties of *Aloe* exudates, but the gel was virtually ignored. Scientific interest was aroused in 1935 by the paper of Collins and Collins, "Roentgen dermatitis treated with whole leaf of *Aloe vera*". According to Cutak (1937). Collins and Collins tried *A. vera* for radiation burns because it was used for severe sunburn in Florida, while Goldberg (1944) describes how they had seen Seminole Indians using the leaves to treat burns.

When X-rays (or "roentgen rays") began to be used therapeutically for cancer, eczema and other related skin conditions, and as a depilatory treatment, it was found that accidental overexposure could cause radiation burns or "roentgen dermatitis". The medical workers giving the radiation therapy were particularly at risk, and the principal treatment was usually surgery (Wright, 1936). The problem was clearly considered very serious. Rowe (1940) wrote: "So far as is known, there is no proven curative treatment for third-degree roentgen reactions", while Loveman (1937) wrote: "Anyone who has seen the horrible suffering endured by patients with some of the late sequelae of roentgen and radium irradiation and who realises the utter futility of previous methods of treatment will concur that any therapeutic procedure which offers relief from the pain and suffering, let alone cure, is worthy of reporting".

Early treatments with *A. vera* involved the use of fresh leaves which were applied to the burn. Collins and Collins (1935) split the leaf to remove the rind from one side, and macerated the gel, before binding it in place with wax paper and a bandage. Similar methods of application are described by Mackee (1938) and Fine and Brown (1938).

Cutak (1937) reported: "Several months ago the Missouri Botanical Garden had a request for fresh leaves of *Aloe vera* . . . This curious request was granted when it was stated that the leaves were to be used in treating a severe radiation burn. Since that time the Garden has continued to supply the leaves". Soon, however, the demand for *A. vera* became so great that doctors had problems obtaining the leaves. According to Fine and Brown (1938): "We have found that supplies of the leaf at times are difficult to procure, and in the case of indigent patients, to be so expensive as to limit or forbid its use". Fine and Brown had so many problems obtaining

leaves from properly identified *A. vera* plants that they began propagating their own from a plant supplied by the Cincinnati conservatory.

The paper of Collins and Collins (1935) was in fact a report of a single case, a woman with a patch of severe roentgen dermatitis on her forehead. Various treatments had been tried by other doctors, but the condition had worsened. The pain and discomfort were so severe that the woman had to wear gloves at night to stop her scratching at the wound. The doctors were going to apply a skin graft, but as a temporary measure gave her fresh whole *A. vera* leaves to apply, which they hoped would reduce the itching. In fact, "Twenty-four hours later she reported that the sensation of itching and burning had entirely subsided", and by 5 weeks "there was complete regeneration of the skin of the forehead and scalp, new hair growth, complete restoration of sensation, and absence of scar". When she was last seen, 5 months after treatment was started, they reported she was completely cured.

While only one case was presented, this paper was intended as a preliminary report of promising findings. As the authors wrote in their introduction, "It is because complete cures have been reported in so few of these severely burned cases that we think it worth while to record an evident cure in the following typical but not selected case". This paper has been criticised as it gives only a single case history, but as trained workers in the field of radiation burns, Collins and Collins would be aware of the normal course of these lesions, and so would recognise unusual healing. Gjerstad (1969) suggested that the cure might have been psychological, because the patient wanted to avoid a skin graft operation.

Following this work, Wright (1936) used *A. vera* gel on X-ray sequelae which were of longer duration. Eight cases of radiation telangiectasis (abnormal enlargement of blood vessels) were treated, but the only effect observed was an improvement in skin texture. Good results were obtained, however, with two cases of long-standing X-ray ulceration, including almost complete healing of accidental acute radiation dermatitis on a doctor's hand 3 weeks after the start of *A. vera* treatment.

Loveman (1937) reported treatment of two more cases of radiation ulcers, one showed complete healing after rapid epithelisation and relief of pain, and the other a much slower response over a period of 5–6 weeks. He was of the opinion that fresh leaves were the most effective. A year later Fine and Brown (1938) noted that they had used *A. vera* "in several cases following intensive radiation in order to assist healing, and we have found epithelization to be hastened . . . application of the leaf is extremely soothing, and allays the discomfort considerably".

Crewe (1937) reported that he had used the pulp of fresh *A. vera* leaves to treat eczema with some success, and he also obtained promising results treating ulcers on amputation stumps. There had been a cessation of pain, and healing was progressing well before he ran out of leaves. Subsequently he tried using commercial powdered Socotrine aloes in a lanolin base to

treat ulcers, pruritis, breast cancer lesions, poison ivy rashes, and burns, and reported variable but generally encouraging results. Powdered Socotrine aloes is the dried leaf exudate of *Aloe perryi*, though Crewe thought it was made from *Aloe* gel. Crewe reported some adverse reactions, as might be expected, including catharsis and skin allergies. However, he concluded that both the fresh leaves and his aloes ointment and powder would relieve pain, had some sort of antiseptic action, and would stimulate granulation and growth of new tissue.

In a further paper (Crewe, 1939) he reported using either Socotrine or Barbados aloes, which are derived from the leaf exudates of *A. perryi* and *A. vera*, respectively, in mineral oil and vaseline to treat scalds, burns and severe sunburn. He found that the ointment had "distinct analgesic qualities", while in burns there was rapid healing without infection or scarring. However, contrary to his 1937 paper, he said he had seen no side effects due to absorption, and had treated two pregnant women without harm, despite the drug's potential harmful effects during pregnancy (Schenkel and Vorherr, 1974).

The use of *A. vera* gel to treat five cases of radiation ulcers, including one of ulceration of mucous membranes of the mouth, was reported by Mandeville (1939). In the latter case the ulceration was due to treatment of the mouth with radium and X-rays. The gel was reported to have healed the ulcers, and the patient had survived for 2 years without further problems. The treatment had involved the patient holding the gel in his mouth for an average of 7 hours a day for 8 weeks. While this must have been very inconvenient, the condition was a serious one, and any method which reduced pain was considered useful. One of the effects which Mandeville reported was a definite and rapid relief of the pain of the lesions.

Mackee (1938) included a review of early work on *A. vera* in his book on the use of radiation in dermatology. He clearly stated that it was the gel that was being used, nor the rind or exudate, and stressed the need of fresh leaves for effective treatment. He reported: "The treatment seems to be inefficacious for roentgen or radium sequelae — atrophy, telangiectasia, sclerosis and keratosis. It appears most effective in the case of indolent roentgen and radium ulcers. Often the pain disappears within a day or two and healing takes place in a few weeks or months — more often the latter. The writer can vouch for the good results in a fairly large percentage of indolent ulcers. Good results have been obtained also in ulcers that occur early in third-degree reactions."

Spoerke and Ekins (1980) rightly point out that the literature in the 1930s consisted primarily of reports of case histories. This point was earlier borne out by Rowe (1940) who wrote: "All of the work has been done on individual cases, and no reports have been made on experimental work in which controls were used". It is true that these early papers are not clinical studies, and lack large samples and the use of controls to allow comparison with other treatments. However, this was a new subject, and one would



expect preliminary case studies to be reported first, with follow-up trials to follow. It must be pointed out that the writers of the papers were doctors familiar with the normal poor course of radiation burns, so they should have been able to recognise any beneficial effects.

### Clinical and experimental studies from 1940

In an attempt to substantiate previous reports of treatment of individual cases, Rowe (1940) investigated the effects of fresh *A. vera* "jell" on third-degree radiation burns in white rats under laboratory conditions. Anaesthetised rats were irradiated on two areas of the back so that by 3 weeks severe third-degree X-ray reactions had been induced; treatment was then started. In each animal, fresh *A. vera* gel was applied to one lesion over a period of 14 days, and the other areas were treated with a saline solution as a control. There were also check control animals given no treatment at all. In the 28 surviving experimental animals, 50% of the lesions treated with the gel showed an increased rate of healing, and 36% showed virtually complete healing at the end of the experiment, twice the number showing improvement with saline. Rowe included a very simple statistical analysis: "The probability that there is benefit with the jell is 9/10. This is not considered certainty". However, it must be pointed out that results were variable; one group of rats showed reversed results, better with the saline and worse with the gel. Rowe realised the experiment was not conclusive, and continued his studies with more rats over a longer time scale.

In Rowe et al. (1941), different parts of the *A. vera* leaf were tested in a larger-scale experiment using a total of 44 rats. Healing of the radiation burns was apparently estimated by visual examination of the lesions. They found that 64% of the rats treated with the gel showed an increased rate of healing, 9.5 times the number in the control group. They also observed that if beneficial results did not occur within 2 weeks of starting application of the gel, then further treatment was not likely to be of benefit. Partially decomposed leaf pulp gave improvements in 87.5% of the rats tested (though only 8 rats were used); as the writers pointed out, this was contrary to Mackee (1938), who was of the opinion that the gel had to be fresh.

Most interestingly, Rowe et al. (1941) found that fresh rind from one of their shipments gave 100% complete healing in 8 rats within 6 days, although the rind from two other shipments gave negative results. They concluded: "It is believed, from our observations, that the healing agent of the leaf is concentrated in the rind". They thought that this agent passed into the gel from the rind on standing. The negative results obtained with the other two shipments were thought to be due to different times of collection or the condition of the leaves. The variability which they observed between leaf shipment is important — such variation is commonly reported to occur in *A. vera* (Leung, 1977, 1978; Anon., 1977; Madis Laboratories, 1984), and this could explain variable or poor results obtained in some studies.

Having tried some other commonly used treatments, including an ointment of powdered Curaçao aloes as used by Crewe (1937, 1939) they reported that “results obtained with aloe ointment, scarlet red ointment and urea ointment show that none of these are effective in promoting healing of acute third-degree X-ray reactions in the skin of white rats”.

A far less convincing but widely quoted study was that of Barnes (1947), who investigated the action of *A. vera* extracts in petroleum on abrasions to the finger tips of human volunteers. Wound healing was measured with a potentiometer, and expressed as “per cent wound potential lost per hour”. While Barnes reported considerably quicker healing with *A. vera* than with the controls or with the two other ointments tried, since the extract was only applied to a total of 12 abrasions, and no measure of variation was allowed for, the results can hardly be considered statistically significant. The method could perhaps be of value if carried out on a much larger scale.

Meanwhile, *A. vera* gel seems to have been widely accepted in the USA in the 1940s for the treatment of radiation ulcers. Demand for the leaves was still high. Goldberg (1944) reported: “In New York the leaf is a relatively rare and expensive product, often kept wrapped in tin foil and usually refrigerated”. Horn (1941) in an article impressively titled “Botanical Science Helps to Develop a New Relief for Human Suffering” wrote: “More recently, in response to equally urgent requests, the New York Botanical Garden has served the demand for leaves used by hospitals in the metropolitan area until the stock of this species at the Garden became reduced to only a few specimens . . . Doctors kept begging for more leaves while the Garden’s supply was temporarily depleted”.

As atomic energy developed, the United States Government had begun to take an interest in *A. vera*, because it had possible applications in military and civilian radiation medicine. Lushbaugh and Hale (1953), working for the U.S. Atomic Energy Commission at the Los Alamos Research Laboratory, produced one of the most convincing studies of the effects of *A. vera* gel. Twenty albino rabbits were exposed to beta radiation, and different treatments applied to quadrants of the affected areas on each animal. The treatments used were fresh *A. vera* leaf, a commercial *A. vera* ointment, application of a dry gauze bandage, and an uncovered, untreated control. Treatment was started immediately after irradiation, and the healing of the lesions followed over a period of 58 days by visual assessment. Histological examinations were carried out on a further 10 rabbits.

Both fresh *A. vera* and the *A. vera* ointment gave clear improvements in healing compared to the controls, with accelerated ulceration followed by more rapid epithelisation, so that “complete healing was obtained by the ointment at the end of two months and was not obtained by the end of four months in either of the two untreated areas”. The healing of the treated areas had occurred without the scabbing and telangiectasis seen in

the controls. Microscopic examination showed accelerated cytological changes in the treated lesions, with strong leucocytic activity and early sloughing of necrotic epithelium. Re-epithelisation had begun by 10 days in the treated lesions, but only by 21 days in the controls.

Lushbaugh and Hale (1953) were of the opinion that "These experimentally observed beneficial alterations in the course of the radiodermatitis treated with *A. vera* would seem to substantiate firmly previous clinical experiences with the plant in the treatment of human radiodermatitis". They concluded that "*A. vera* contains substances that are stimulatory both to the delayed development and delayed healing of ulcerative radiodermatitis and that because of the growing modern importance of this injury further investigation of the action of *A. vera* should be pursued".

Workers in Russia were also beginning to show interest. Aleshkina and Rostotskii (1957) reported on the use of an *Aloe* extract to heal lesions caused by radiotherapy treatment for cancer. They used an emulsion from "biostimulated" leaves of an unnamed *Aloe* species (probably *A. arborescens*), containing castor oil, eucalyptus oil and an emulsifier, according to the method of a certain Academician V.P. Philatov, though no reference was given. An experiment was described using 12 rabbits exposed to radiation. Six rabbits treated with the emulsion healed in 12 days, while the controls took 20 days. In a second experiment the *Aloe* emulsion was compared to the emulsion without the *Aloe* extract as a control. The six rabbits treated with the *Aloe* emulsion healed in 8 days, with smooth pink skin and some hair regrowth, while the six controls with the emulsion base took 12 days.

Ashley et al. (1957), working under contract to the US Army, carried out extensive clinical and laboratory studies on *A. vera* which suggested that the plant did not have any useful curative properties. Their series of animal experiments were well-documented, with detailed photographs and biopsy samples. The first two experiments studied the healing of uniform third-degree thermal burns from a soldering iron applied under anaesthetic, using 16 white rats and 27 rabbits. Half the rats were treated with a commercial *A. vera* ointment, and the other half were controls, treated by an open method rather than using wet dressings. There was found to be no significant difference in the healing rate of the ulceration, both groups of rats healing in 27–32 days. The rabbits were divided into three groups of nine, one group a control as before. The second group was treated with the fresh gel of split *A. vera* leaves bound to the burn lesions, while the members of the third group were treated with one from a selection of three commercial *A. vera* ointments. There was no difference between the fresh leaf treatment and the controls, both taking an average of 25 days to heal, while the lesions treated with the commercial ointments took 28 days. In a further experiment, 12 rabbits were given burns, and 4–6 days afterwards, split skin autografts were grafted on. Three rabbits were treated

with the commercial ointments, 4 with the fresh leaf and 5 were controls. After 7 days, the untreated controls showed only 25% necrosis of each graft, but with the leaf-treated grafts there was around 50% necrosis and with the grafts treated with the ointment 75–100% necrosis.

Similar experiments were carried out to investigate the healing of radiation burns. Eighteen rats and 22 rabbits were exposed to gamma radiation to produce uniform ulcers. With the rats, the control group of nine animals took an average of 67 days to heal, while the group treated with *A. vera* ointment took 86 days. Of the 32 ulcers produced in the rabbits, nine were treated with the three ointments, 12 with fresh leaf and 11 were controls. The controls and the ulcers treated with the ointments both took an average of 95 days to heal, but those treated with the fresh leaf took only 85 days. A very heavy gamma irradiation was also tried on 26 rabbits. While 19 of these animals died, the ulcers treated with ointment or fresh leaf seemed more inflamed. With beta-irradiation given to 14 rabbits, the ulcers treated with ointment or fresh leaf took an average of 70 days to heal, while the controls took 67 days.

Ashley et al. (1957) also carried out clinical studies on six human patients with bilateral second- and third-degree thermal burns of the lower extremities. There was found to be no difference between lesions treated with *A. vera* ointment and the controls treated by exposure and/or bland ointment. Nine patients under treatment for carcinoma of the skin were given two similar irradiation burns. Half of the ulcers were treated with three commercial *A. vera* ointments, and half with bland ointment. There was no difference in healing time between the two types of treatment. Some of the patients given the *A. vera* ointment complained of pain or itching, so treatment was stopped in these cases.

Their conclusion was: “from these studies there would seem to be no indication to use Aloe Vera in presently available forms for mass treatment of thermal or irradiation burns”. Certainly their results seem conclusive in the case of the commercial ointments. Unfortunately they do not say which ointments they actually used. The fresh leaf was not tried in all the experiments. In one case, with mild gamma radiation on rabbits, the fresh leaf did accelerate healing by 10 days compared to the control, and in most of the others the fresh leaf treatments were at least no worse than the controls.

Rovatti and Brennan (1959) used albino rabbits to study histological changes in thermal burns over the complete time scale of the healing process. Biopsy samples were taken during the initial stages over the first 48 h, and over a longer period of 5 weeks after application of the burns. Six animals were used for the initial controls to study changes in untreated burns, while 4 batches of 3 animals were used to investigate the effects of various medications. In the latter animals one side was left untreated as a further control. The treatments used were “Aloe Creme Ointment”, “Alo-Creme Ointment” with 5% cystine, 1% trinitrophenol butylaminobenzoate oint-

ment, and petrolatum with a gauze dressing. Application began immediately after burning, and continued twice a day over the 5-week period of the study.

The two *A. vera* ointments gave similar results, the lesions being more pliable and less inflamed than the untreated controls, with a sloughing of the surface layers. Healing occurred in 2 weeks, without the scarring observed in the control burns, which took 4 weeks to heal. The animals treated with the trinitrophenol ointment died through haemorrhage, while those treated with the petrolatum and gauze showed swelling, haemorrhaging and the development of abscesses, and healing only occurred after 4 weeks with scarring. The biopsy samples from the *A. vera* treated groups showed reduced necrosis of the dermis and decreased thrombosis of capillaries compared to the treated burns.

A possible criticism of this paper could be the small size of sample used, but at least there was a control and treated area on each animal, as well as the preliminary group of control animals. Despite this, Gjerstad and Riner (1968) were critical of the experimental design — “No control groups with which to compare these chemical agents and no single or double blind cross over tests were apparently used here to preclude any bias”. Spoerke and Ekins (1980) comment: “This study would have been more definitive had the four areas used the aquaphor only, the *Aloe vera* in aquaphor, the whole leaf product, and no active treatment”. Yet Rovatti and Brennan (1959) did report preliminary experiments which showed that “*Aloe vera* gel alone was not suited for continuous dressing of the thermally injured skin and an ointment consisting of lanolin base alone was not effective in the treatment of these experimental burns”.

Goff and Levenstein (1964) investigated the effect of various medications on the healing of skin wounds in mice. They used a tensiometric method to measure wound healing by the force needed to separate the edges of a standardised skin incision. This was an improvement over earlier studies which had relied on visual assessment of the wounds to gauge healing. Samples of 6–10 mice were used for each determination to allow some measure of variation, and measurements of wound strength taken at intervals between 6 and 21 days after the wounds were made. The treatments included an ointment containing vitamins A and D, an *A. vera* ointment, a corticosteroid, *Artemesia* extract and an allantoin-coal tar ointment. There were also untreated controls.

Results were expressed as graphs of tensile strength against time, with an increase in wound strength as healing progressed. They showed that there was “some transitory degree of stimulation of healing by *Aloe vera*”, while the corticosteroid in fact delayed healing. The *A. vera* preparation gave significantly large tensile strengths at 9 and 15 days, but not at 21 days, when both the control and *A. vera* curves were levelling off as the wounds healed over. The description of this as a “transitory degree of stimulation of healing” was perhaps an unfortunate choice of words, since

once the wounds had healed, one would not expect a difference between the *A. vera* treatment and the control. What was significant was that *A. vera* had hastened the healing process. The authors did not say which part of the *A. vera* leaf was used for their extract, though presumably it was the gel.

### Recent medical, dental and veterinary studies

The use of *A. vera* gel taken internally to treat peptic ulcers was reported by Blitz et al. (1963). Twelve patients diagnosed as suffering from peptic ulcers, confirmed by X-ray evidence of duodenal lesions, were given an emulsion of *A. vera* in petrolatum. Complete cures were claimed, even after a period of a year, and they wrote that "Usually, such unmistakable lesions are accompanied by exacerbations of distress once and more often twice a year under any form of medical treatment, but no such episodes were experienced in this series of cases". They also reported that X-ray examination showed complete healing. The effect of the *A. vera* gel was attributed by the writers to coacervation of pepsin, inhibition of hydrochloric acid secretion and a general detoxifying effect. This work has not been followed up by a full clinical trial to the present knowledge of these authors, but Blitz et al. (1963) pointed out that if *A. vera* was not pharmacologically active "as the indictment of western medicine has intimated" then the observed 100% complete recovery would not be expected, nor would the cessation of pain at mealtimes which accompanied the *A. vera* treatment.

*Aloe vera* gel has also been used to treat a variety of dental conditions. Bovik (1966), himself a qualified dentist, reported his own personal experiences after he had a complete upper gingivectomy performed. As an experiment he treated one side with *A. vera* "juice" and found it caused rapid healing and a cessation of pain; in fact he found the *Aloe vera* treatment preferable to the conventional periodontal pack applied to the other side.

Payne (1970) reported experiments where *A. vera* gel was used in five patients to reduce pain and accelerate healing after periodontal flap surgery. He treated some quadrants with *A. vera* so the patients did not know which part had the gel applied, and found that although there was some variability, the patients reported less pain and swelling from the *A. vera* quadrants. Also in 4 out of the 5 cases the *A. vera* quadrant was chosen by an "unbiased observer" as being least inflamed after one week's treatment.

A relatively modern description of the clinical use of *A. vera* is given by El Zawahry et al. (1973) who used *A. vera* gel on chronic leg ulcers. Three case histories were described, with apparently successful results. They were careful to drain the exudate before extracting the gel from the leaves. The fresh gel was then applied to the ulcers on gauze bandages 3-5 times a day. While there were no controls used, the writers pointed out that there would be inherent variations in healing rate between patients, and suggested it would be useful to carry out trials on patients with bi-

lateral ulcers. In the cases described the ulcers were of long standing, of from 5 to 15 years duration, so the observed improvements would seem to be due to the *A. vera* treatment. El Zawahry and his colleagues believed that the effects of the *A. vera* gel were due to increased vascularisation, which was thought to be the cause of a temporary increase in pain observed when treatment was first started. Encouraging results were also reported in treating hair loss due to seborrhea, as well as good control of acne vulgaris in three women patients. However, it must be stressed that these were case reports, and in no way represented conclusive clinical trials.

Ship (1977) writing in reply to a question sent into the Journal of the American Medical Association, was sceptical about the effects of *A. vera* gel. He suggested that the results obtained in the treatment of burns were due to the "oil content" preventing the wounds drying out and so reducing pain, in a similar way to the application of butter and other home remedies containing oils. Although *A. vera* was being used in some hospitals to keep burns soft and pliable, Ship reported that "patients were more satisfied with a good cream lotion than with aloe vera".

The use of *A. vera* gel has also been described in veterinary medicines. Northway (1975) used a commercial extract to treat a number of external conditions in a total of 76 animals in his practice. He reported "good" (equal to the best of the other drugs on the market) or "excellent" (better than other available drugs) results in ringworm, allergies, abscesses, fungal infections and various types of inflammation. Pain and itching seemed to be relieved very rapidly after application. Northway wrote: "Although no firm conclusion can be drawn from treatment of 76 patients and a study involving no controls, my observation is that response of fungal infections and local allergic reactions to aloe vera therapy is excellent and that good response is achieved in treatment of mixed bacterial infections caused by susceptible organisms".

Anderson (1983) reviewed the use of *A. vera* "juice" in veterinary treatment, acknowledging the number of exaggerated, word of mouth claims made for miraculous cures. He felt there was a need for convincing experiments "to satisfy the most discerning observer" but remarked that "If aloe vera juice has even a fraction of the claimed benefits, veterinary professionals need to know about it".

In the last 5 years new work has been done by a team of workers in the USA studying the effects of *A. vera* in topical applications. Cera et al. (1980) reported in detail two cases where a commercial *A. vera* cream ("Dermaide Aloe") was successfully used to treat severe accidental thermal burns in dogs. Two of the writers were professors of plastic surgery with particular interest in burns. In a previous paper (Robson et al., 1979) the *A. vera* product used had been shown to have antibacterial and antiprostaglandin effects, and preserved the vascular supply to the dermis in experimentally burned animals. According to Cera et al. (1980), in dogs the progress is generally poor if more than around 15% of the body surface is

badly burned, while euthanasia is recommended if more than 50% is burned.

While the *A. vera* treatment was being carried out on the dogs, biopsy samples were taken to test for *Pseudomonas* infection and to determine prostaglandins and thromboxanes by an immuno-histological technique. In the first dog re-epithelisation and superficial healing was complete by 7 days, and hair was beginning to grow by 17 days. In the second dog re-epithelisation had occurred after 17 h and the wound had healed without scarring 10 days after burning, apparently because treatment had been carried out sooner after the burn had occurred. The biopsies before and after treatment showed that the *A. vera* product had an apparent anti-prostaglandin effect, which prevented dermal ischaemia. Infection by *Pseudomonas aeruginosa* was also inhibited.

Raine et al. (1980) reported experiments on the treatment of frostbite in the ears of experimental rabbits using antiprostaglandins and antithromboxanes. Four treatments were used, including an *A. vera* cream, methylprednisolone, methimazole, and acetylsalicylic acid, as well as a control. Four animals were used for each treatment. All the treatments showed statistically better tissue survival than the control. It was thought that tissue loss was reduced by counteracting the effects of thromboxanes and prostaglandins, which are vasoconstrictors, tissue loss in frostbite being at least partly due to vascular deprivation.

Following up their study in dogs, Cera et al. (1982) reported a course of treatment on a Rhesus monkey which had been brought to them with full-thickness burns over 70% of its body after accidental scalding. The treatment included sedation and an intravenous drip, and topical application of *A. vera* cream. By 7 days re-epithelisation was extensive, and recovery was complete within 30 days. A number of detailed photographs were included showing the improvement over the period of treatment.

### **The *Aloe vera* industry**

Commercial exploitation of *A. vera* gel has continued for at least 50 years. A number of companies in the USA act as primary growers and processors of the plant and manufacture bulk supplies of the gel for domestic and export markets. Many more companies are secondary producers of *A. vera* products, and cosmetic firms and chain stores often buy the gel for incorporation into their own brand name products.

*Aloe vera* gel has become an important selling point in cosmetic products. Some companies which process *A. vera* gel confine their activities to making cosmetics and products for topical use only (Anon, 1977). *A. vera* gel is widely believed to have a valuable moisturising emollient effect (Feil, 1980; Meadows, 1980; Anon, 1981). The cosmetic formulations available include a large range of moisturising creams, cleansers, shampoos and soaps. In Japan, *Aloe* extracts have been incorporated into shaving creams and lotions to promote the healing of cuts (Lion Corp., 1981). One of the major cos-



metic applications is in suntan lotions and in sunburn treatments (Flagg, 1959; Bovik, 1966). For tanning products the *Aloe* exudate or "aloin" is used because of its properties as a sunscreen (Bader et al., 1981; Proserpio, 1976).

An important factor in the use of *A. vera* gel in cosmetics is the requirement for stringent safety testing; *A. vera* is generally agreed to be harmless and non-toxic (Spoerke and Ekins, 1970; Madis Laboratories, 1984), though a few cases of allergic reactions have been reported (Morrow et al., 1980). Under the Federal Food, Drug and Cosmetic act, the standard of hygiene in the production of *A. vera* products is strictly controlled, and each line must state all its contents.

The manufacture of *A. vera* products for cosmetic and medicinal use can be very lucrative, but it is also highly competitive and commercially orientated. Hard-sell techniques are often used, with promotional meetings and testimonies to the gel's effects. As a result, some outrageous, exaggerated claims have been made — see for details Gjerstad and Riner (1968) and Spoerke and Ekins (1980). Pyramid-selling has been used by some companies to promote *A. vera* products (Levene, 1983), and there has been controversy over this.

The use of *A. vera* in cosmetics is becoming more well known in Europe (e.g. Baruzzi and Rovesti, 1971; Hoffenberg, 1979). It is now common for European cosmetic companies and chain stores to buy *A. vera* gel in bulk from the USA for incorporation into their own brands of cosmetic products, and various firms in the USA produce extracts and dried products in various formulations for export to meet this market.

Medical products on the market include burn treatments, ointments and medicated creams and lotions. Bottled *A. vera* gel or "juice" is widely available in the USA for internal consumption as a tonic, and it has been claimed to cure many illnesses such as gout, constipation and arthritis. *A. vera* has become an important part of the health foods craze in the USA, and many people add powdered extracts to their food or take one of the many flavoured *A. vera* drinks that are on widespread sale. *A. vera* products are also widely promoted for use by joggers and keep fit fanatics (Taylor-Donald, 1981). In Europe, however, the sale of *A. vera* gel has so far been confined almost exclusively to cosmetic products.

Commercial cultivation of *A. vera* for its gel began in Florida in the 1920s, as described by Morton (1961). When demand increased in the 1930s and 1940s, there was a corresponding expansion of production. Goldberg (1944) wrote: "Recently while in Miami I was able to observe several thousands of these plants being grown for commercial purposes. I was fortunate in being able to visit an *Aloe vera* farm, which is located about 25 miles (40 kilometers) southwest of Miami. This farm is one of several in the vicinity".

Today the main areas of cultivation of *A. vera* in Florida are around Homestead, on the eastern edge of the Everglades National Park south-

west of Miami, and in the Belle Glade area further to the north. Cultivation of the plant has also become important in Mexico and Arizona, and in the Rio Grande valley on the southern border of Texas. *A. vera* is grown by farmers contracted to processors, or on farms owned by the processing companies themselves. For example, in their promotional literature the Terry Corp (N.D.) claim to grow around 2000 acres of *A. vera* — “We now have the largest reserve of *Aloe* leaves of any supplier in the world”.

*Aloe vera* grows best in a dry chalky soil or in a sandy loam; good drainage is essential to prevent “root rot”. While the plant needs warm semi-tropical conditions, it dislikes overexposure to the sun, which causes stunted plants with a low gel content. Shade is thus important, and *A. vera* is commonly interplanted with other crops such as fruit trees. Interplanting also reduces damage by cold or frost in the winter, which can be highly destructive; in 1983, the *A. vera* plantations in Texas were decimated by an unexpected severe frost. Since *A. vera* is a perennial, occupying the soil for 8 years or more, a heavy input of fertiliser is essential to obtain high yields of gel. During the dry season, careful irrigation is also required. Water is needed to swell the leaves with gel, but overwatering will cause rotting of the plant bases. The plants are normally propagated from offshoots growing around the main stem base, but they can also be grown from seed. The plants are transplanted in the spring when conditions favour optimum growth, and take around 3 years to reach maturity with leaves of a harvestable size. They can continue to produce leaves for 7 or 8 more years. Methods of cultivation of *A. vera* have been improved over the years, helped by the Federal Department of Agriculture and the American Aloe Growers Association.

Harvesting of *A. vera* is done by hand, the leaves being cut off at the base with a sharp knife so that the cut surface seals over to prevent the exudate leaking out, as it is strongly staining. The harvesters have to wear gloves and protective clothing because of the leaves’ sharp spines. Once harvested, the leaves may be individually wrapped up, before being crated and transported to the processing plant, which is generally nearby.

At the factory, the leaves are first of all cleaned, being placed in a tank to soak and then sprayed with water and a mild chlorine solution. Alternatively, washing may be by hand, when the leaves are scrubbed clean with brushes. Next the outer layers of the leaf including the pericyclic cells are removed by filleting with a knife to remove the central “fillet” of gel. This is a skilled operation, and care is taken not to tear the green rind which can cause contamination with the leaf exudate. Once the gel is extracted, the processors remove the cell walls, lignified fibres, and various contaminants. This can either be done by squeezing and filtering or by a decantation process.

Finally the gel may be decolorised and undergo a “stabilisation” process before it is bottled. The whole procedure is carried out under FDA-controlled standards of hygiene similar to those in the food industry, with

sterilisation of containers and equipment, and protective clothing for the workers.

The original use of *A. vera* involved fresh whole leaves; much has been made of the supposed instability of the gel's activity once it has been extracted from the leaves (e.g. Morton, 1961; Leung, 1977, 1978). Various companies have developed and often patented their own methods to preserve the gel (see Moroni, 1982; Madis Laboratories, 1984).

A common method is to use high temperature to "stabilise" the gel, supposedly by denaturing the enzymes which cause browning and loss of activity (Ashleye, 1983; Waller, N.D.). High Temperature Short Time (HTST) treatment involves heating to 75–80°C for less than 3 min; it is in effect a method of pasteurisation to prevent deactivation of the gel, with minimal denaturing. An advantage of this method is that the gel can be processed quickly. High temperature treatments of longer duration, over a number of hours, are more likely to change the chemical nature of the gel. Other methods used include ultraviolet stabilisation in the presence of catalysts, or chemical oxidation with hydrogen peroxide combined with heating. Preservatives and additives which are used include vitamins, Irish moss extract, and sorbic acid.

Various *A. vera* gel extracts are available, intended to supply the active gel in a stable form with reduced volume and weight, and so facilitate shipping to secondary manufacturers. Different companies make various claims as to the effectiveness of their own particular products. Powdered forms are common, to be reconstituted for use in cosmetics. The various commercial lipid extracts have a widespread use in sun creams and lotions, although according to Leung (1977, 1978) they do not contain any of the active ingredients from the gel.

### Chemical constituents

The components of *Aloe* leaf exudates have been studied in some detail, in particular the purgative principles (reviewed by Fairbairn, 1952, 1964; McCarthy, 1971). The gel has received less intensive chemical investigation, and the results of those studies that have been made are often conflicting. As Leung (1977, 1978) comments, "few of the studies have been well controlled or confirmed". Many reviews do not clearly distinguish between the components found in the gel and those in the exudate (e.g. Henry, 1979), though some make a clearer distinction (e.g. Spoerke and Ekins, 1980). Certainly the bulk of the gel is a mucilage of a polysaccharide nature, with smaller amounts of various other compounds.

An early, detailed chemical investigation of *A. vera* which distinguished between the different parts of the leaf was that of Rowe and Parks (1941), who analysed the leaf pulp separately from the rind. The pulp was found to contain 98.5% water, and its alcohol-insoluble portion was a mucilage with a high content of uronic acid, fructose and hydrolysable sugars. Enzymes

such as an oxidase, a catalase and an amylase were reported to be present, but tannins, pectins, and vitamins A and D were absent, and there was only a small nitrogen content. The leaf pulp did not respond to tests for "aloin".

Roboz and Haagen-Smith (1948) examined the chemical components of the gel scraped from the leaves after the exudate had been drained off. The crude gel had an ash content of 12.9%, removable by dialysis. A white water-soluble mucilage was purified which on hydrolysis was found to contain equal amounts of glucose and mannose as the main constituents, with a small amount of uronic acid (2.37%). Ketoses were thought to be absent. They also reported that some aloin was present in the crude gel, despite bleeding off the exudate from the leaves.

Somewhat later, Farkas (1963) reported glucose and mannose (48.8% each), and uronic acids (2.4%) in gel hydrolysates, very similar to the results of Roboz and Haagen-Smit (1948). Another study showed mannose and glucose to be present in a 9–10:1 ratio (Segal et al., 1968). Traces of arabinose, galactose and xylose were also found, but uronic acids were not detected. Waller et al. (1978) carried out a detailed analysis of *A. vera* leaves, including a sugar determination of the hydrolysed lyophilised gel which showed mannose and glucose in a 5:4 ratio, and trace amounts of xylose, rhamnose, galactose, and either arabinose or fucose.

Recent work has involved the separation of the gel carbohydrate polymers into their polysaccharide components. Considerable variations occur between the different studies. Gowda et al. (1979) separated the gel polysaccharides from an *A. vera* plant from South India into four partially acetylated glucomannans, the whole having an average glucose/mannose ratio of 1:6, although the individual ratios varied from 1.5:1 to 1:19. The molecules were linear with 1–4 linkages between the sugar units. Traces of galacturonic acid, galactose, xylose and arabinose were also found.

A study by Mandal and Das (1980a) on a plant from West Bengal named as *Aloe barbadensis* showed quite a different constitution. The principal component of the gel was a pectic substance containing mainly galacturonic acid, and was accompanied by lesser amounts of a galactan, an arabinan and a non-acetylated glucomannan. Mandal and Das suggested that the apparent chemical differences were due to the existence of as yet undelimited varieties within the species and to seasonal variation. Plants harvested in April were found to contain 85% galacturonic acid, while those analysed in October of the same year contained only 70% of galacturonic acid. The D-galactan had galactosyl residues joined with 1–4 linkages in the main chain, with branches connected by 1–6 linkages, and a molecular weight of  $3.74 \times 10^4$ . In further work (Mandal and Das, 1980b) the glucomannan was found to have a glucose/mannose ratio of 1:22, with a 1–4 linked main chain and 1–6 linked branching points. Its molecular weight was  $1.4 \times 10^4$ . Mandal et al. (1983) hydrolysed purified pectic acid from their *A. barbadensis* plants, and obtained an acidic oligosaccharide with a 1:5

galacturonic acid/galactose ratio. The main chain consisted of 1–4 linked galacturonic acid residues.

Polysaccharides from the gel of other *Aloe* species have been found to contain similar components. Thus polysaccharides containing galacturonic acid (Ovodova et al., 1975; Hranisavljevic-Jakovljevic et al., 1981) or mannose (Yagi et al., 1977) have been described in the gel from *A. arborescens*. The mannan was partly acetylated and seemed to be free of glucose. *A. plicatilis* (L.) Miller was found to contain a single type of unbranched acetylated glucomannan (Paulsen et al. 1978), and a similar substance with a glucose-mannose ratio of 1 : 3 was described from *A. vahombe* Decorse & Poisson (Radjabi et al., 1983); again the sugar chain contained 1–4 linkages (Radjabi-Nassab et al., 1984). *A. saponaria* gel contains two polysaccharides, one an acetylated linear mannan and the other an acetylated branched glucomannan with a glucose-mannose ratio of 1:19 (Yagi et al., 1984). The variations in molecular structure in the few species examined is perhaps reflected in the variations of texture of the gel parenchyma cells when squashed between the fingers.

A number of substances other than polysaccharides have been found in the gel. Thus Gjerstad (1971) found small quantities of free sugars in *A. vera* "juice", of which he identified glucose and an aldopentose. He also found 2.5% (dry weight) of protein in which he recognised 18 common amino acids. The fresh gel was found to contain 99.52% water, and Gjerstad concluded with the dismissive comment; "Considering the fact that an allegedly usual dose of 1 tablespoonful (15 ml) would contain maximally 75 mg of solid material, composed of numerous individual chemical entities (e.g. less than 1 mg each), it appears difficult to visualize that *Aloe vera* juice might logically constitute a panacea."

Waller et al. (1978) analysed an aqueous acetone extract of macerated whole leaves. Apart from the polysaccharide components, 17 common amino acids were also detected in the free state, arginine being the most abundant, as well as traces of lupeol, cholesterol, campesterol and  $\beta$ -sitosterol. Another, somewhat confused, analysis of the gel by Khan (1983) revealed the presence of 20 amino acids, of which aspartic acid, glutamic acid, serine and histidine were apparently present in the largest amounts.

Bouchev and Gjerstad (1969) used neutron activation analysis of a "lyophilised extract of *Aloe vera* juice" and found it to contain an inorganic ion content of 4.7% calcium, 1.5% sodium, 6.6% potassium, 0.01% manganese and 12.2% chlorine. Robson et al. (1982) carried out an analysis of a proprietary 99.5% pure *A. vera* gel extract with a computerised multi-analyser. Trace metal analysis was carried out with an atomic absorption spectrophotometer. Glucose, uric acid, salicylic acid, lactate, cholesterol and triglycerides were among the organic constituents, while sodium, potassium, calcium and magnesium ions were also noted in significant amounts. They thought that the only components which might affect burns were

salicylic acid, magnesium ions and fatty acids.

A factor neglected in many analyses is the effect of seasonal and cultivar variation. Thus Leung (1977, 1978) wrote: "None of the studies took into consideration seasonal, climatic and soil variations which may strongly affect composition of the gel." These factors could explain the different results obtained by different experimental workers. According to Rowe et al. (1941), "The healing agent may not be present in the leaves at all times but is found there only during certain seasons of the year." Fluctuations have been well documented in the components of the exudate of various species of *Aloe* (McCarthy and Rheede von Oudtshoorn, 1966; McCarthy, 1968; Suga et al., 1974; Koshioka et al., 1982; Beaumont et al., 1984). Mandal and Das (1980a) found considerable variations in the gel carbohydrates of *A. vera* due to time of harvesting and to race differences. More recently, Pierce (1983) showed large differences in the nutritional content of *A. vera* gel due to cultural conditions. "Conventionally grown" plants had gel with 0.3% carbohydrates while the gel of plants grown hydroponically had 0.8%. Hydroponic culture also gave increases of 200% in the amino acid content, 200% in total calories, 180% in free acids, 25% in calcium and 200% in iron. Hydroponically grown plants also had a much higher Vitamin C content in their gel (22.5–23.1 mg/100 g fresh gel as opposed to 0.5–4.2 mg/100 g in the plants grown conventionally).

Analyses of other *Aloe* species with medicinal uses are commonly quoted in reviews on *A. vera*, but they cannot be directly related to the composition of *A. vera* gel. Whole leaf extracts of *A. arborescens* contain *n*-alkanes, fatty acids, fatty esters, sitosterol, glucose and magnesium lactate, in addition to the phenolic compounds in the exudate (Hirata and Suga, 1977; Suga and Hirata, 1983). Other studies with this species have demonstrated the presence of glycoproteins with lectin activity (Fujita et al., 1978; Suzuki et al., 1979), while Stepanova et al. (1977) found that dried extracts of *A. arborescens* leaves caused increased phagocytic activity in guinea-pig leucocytes in vivo. A separation of the mucilaginous pulp of *A. saponaria* yielded calcium isocitrate which acted as a potent cardiac stimulant (Yagi et al., 1982a) and a glycoprotein with antibradykinin activity (Yagi et al., 1982b).

The anthraquinone derivatives of *Aloe* exudates have been shown to have various physiological properties in addition to their purgative effects. Most work has been carried out in the USSR and in Japan. Soeda et al. (1964) found that fractions from Cape Aloe gave a prophylactic effect against radiation leucopenia, while Soeda (1969) found antitumour activity in Cape Aloe. Soeda et al. (1966) found that an ointment containing 5% Aloe was an effective treatment for trichophytiasis, and "Aloe Juice" was found to have inhibitory action against some bacteria and fungi, in particular *Pseudomonas aeruginosa* and *Proteus vulgaris*. Noskov (1966) used injections of an "Aloe extract" to treat the early stages of periodontitis; this followed on from earlier Russian work on the physiological effects of *Aloe* compounds, including their influence on the phosphorus-calcium metabolism of the blood.

## Physiological activity

Various mechanisms have been proposed for the alleged healing properties of *A. vera* gel; it is possible that the gel may have more than one physiological effect. Since no single, definitive active ingredient has been found, it is commonly suggested that there is a synergistic effect between the various components and the polysaccharide base (Leung, 1977, 1978; Henry, 1979).

According to Mackee (1938), vitamin D was the healing agent, but Rowe (1941) reported the absence of both vitamins A and D. Barnes (1946) implied that chlorophyll might be responsible. An interesting theory was suggested by Morton (1961); "It is possible that the seeming efficacy of aloe pulp may be attributable not to any 'miracle ingredient' but merely to the fact that it is 96% water and provides a means of making water available to injured tissue without sealing it off from the air. This thought is supported by recent indications that cold water may be the best emergency treatment for burns." This theory would explain the instant soothing effect *A. vera* gel has on burns, but would not account for the long-term effects on healing. A common belief is that the action of *A. vera* is due simply to its moisturising and emollient effects (Spoerke and Ekins, 1980; Meadows, 1980), hence its use in cosmetics (Anon., 1981)..

Clinical work on *A. vera* gel has indicated that it might have antibacterial properties (Crewe, 1939; Northway, 1975). Gottshall et al. (1949) surveyed 28 *Aloe* species including *A. vera* for activity against *Mycobacterium tuberculosis*, but only *A. chinensis* (sic) and *A. succotrina* were inhibitory. Fly and Kiem (1963) tested macerates of *A. vera* leaves, including the gel on its own in 1:5 and 1:10 dilutions against *Staphylococcus aureus* and *E. coli*, but observed no antibiotic properties.

Lorenzetti et al. (1964) tested leaves of *A. vera* against a variety of bacteria. They cut the leaves and allowed the "juice" to drain out. This "juice" inhibited *Staphylococcus aureus* when fresh, but the activity was unstable unless the extract was refrigerated, or heated and then freeze-dried. The freeze-dried extract inhibited some species of *Staphylococcus*, *Corynebacterium*, *Streptococcus* and *Salmonella* tested, but not others. The other parts of the leaf including the mesophyll did not have these properties. From the description it would seem to be the leaf exudate which was active, rather than the gel, but when Lorenzetti et al. tested exudate components such as aloe-emodin, emodin and chrysophanic acid, they were not found to inhibit *S. aureus*.

Bruce (1967) found antibacterial activity in the pericyclic juice from a number of *Aloe* species, particularly against gram-positive bacteria and against the human tubercle bacillus. Curaçao aloes (the dried exudate of *A. vera*) showed the highest activity, detectable at dilutions down to 1:1600. Fractionation indicated that the greatest antitubercular activity was in the anthraquinone compounds, contrary to the results of Lorenzetti et al. (1964).

Solar et al. (1979) reported immunostimulant properties in an extract from *Aloe vahombe*. The extract markedly increased the resistance of mice to infection by *Klebsiella pneumoniae*, apparently through effects on the host physiology rather than by an antibiotic effect.

Hegggers et al. (1979) tested two commercial *A. vera* gel products at various concentrations for antibacterial activity against 10 test organisms, determining the minimum lethal concentration in each case. They found that one product showed a "marked bactericidal effect" at a 60% concentration, while the other was active at 80–90%. The work of Hegggers et al. (1979) was followed up by Robson et al. (1982) who used the more effective of the two products on 12 test species to determine minimum inhibitory and lethal concentrations. For nine of the species (mainly gram-negative), concentrations down to 60% or 70% were found to be bactericidal; for two other, gram-positive species, the extract was bactericidal at 80–90%. *B. subtilis* was resistant even at 100% concentrations. Comparison with silver sulfadiazine showed the *A. vera* product to be almost as effective. It would be useful to know if the product contained only *A. vera* gel as the active ingredient (the product was "99.5% pure *Aloe vera* extract"). Robson et al. thought that variable or poor results obtained with *A. vera* in earlier experiments had been because the extracts were too diluted, and were of the opinion that "a concentration of the extract at 70% or greater, when combined with a cream base, becomes an effective topical antimicrobial against the organisms most frequently isolated as etiologic agents of burn wound sepsis". Interestingly, Cheney (1970) had pointed out that while *Pseudomonas aeruginosa* caused 70% of burn septicaemias, no convincing report of effectiveness of *A. vera* against this organism were then available. Robson et al. (1982), however, found that *P. aeruginosa* was inhibited at gel concentrations of 60–70%.

It has often been suggested that *A. vera* gel has some kind of anti-inflammatory effect, as discussed by Rubel (1983). A number of Japanese workers have found anti-inflammatory compounds in *Aloe* species other than *A. vera*. Yagi et al. (1982b) discovered antibradykinin activity in *A. saponaria*, while Fujita et al. (1976, 1979) showed bradykinase and carboxypeptidase activity in *A. arborescens*. If such material was present in *A. vera* gel, though this has not been demonstrated, then it would cause breakdown of bradykinin and activation of angiotensin to reduce pain and inflammation. Saito et al. (1982) discovered that the lectin Aloctin A which they had found in *A. arborescens* was active against oedema and adjuvant arthritis in rats. They had already found that Aloctin A had anticancer effects (Imanishi et al., 1981) and promoted mitosis in lymphocytes (Suzuki et al., 1979). The latter could aid in tissue regeneration after wounding. However, since these reports were on different *Aloe* species, and not necessarily gel components, it cannot be presumed that *A. vera* gel contains such compounds or has the same physiological effects. This has however been implied in some reviews and promotional literature.



Hirata and Suga (1977) found magnesium lactate in *A. arborescens*, and Rubel (1983) proposed that since it is an inhibitor of histidine decarboxylase, it might prevent histamine production. Many workers have attributed pain-relieving properties to *A. vera* gel (e.g. Collins and Collins, 1935; Fine and Brown, 1938; Crewe, 1939). Robson et al. (1982) found salicylate, lactate and magnesium in an *A. vera* extract, and suggested that the anaesthetic property could either be due to an aspirin-like effect or the high magnesium ion content, or possibly both acting synergistically. They further postulated that anthraquinone-type compounds such as emodin and barbaloin could be broken down by the Kolbe reaction to salicylates.

Gupta et al. (1981) investigated the analgesic effect of evaporated "juice" from leaves of plants named as *Aloe barbadensis*. They used a rat tail hot wire method, with six albino rats for each treatment, and found that the *Aloe* extract increased the latent period to 15 s, 60 min after injection, compared to a latent period of 12 s before the treatment. The analgesic quality was not as strong as that of the pain-relieving drug Novalgin.

Recent research would seem to indicate that *A. vera* gel has antiprostaglandin effects. Prostaglandins and thromboxanes are compounds involved in the long-term inflammatory response in damaged tissue. They have a number of different physiological effects including vasoconstriction, promotion of fever and pain, and they also have an influence on the immune system (Raine et al., 1980; Heggers and Robson, 1983). There is some evidence that *A. vera* gel inhibits the synthesis of prostaglandins from arachidonic acid. Penneys (1982) described the inhibition of arachidonic acid oxidation in vitro by a number of vehicle components used as carrier bases for active drugs. They included a commercial lyophilised aloe gel preparation and fresh gel in their tests. The % inhibition was found to increase according to the concentration of the commercial product. Thus in clinical application to burns and similar lesions *A. vera* could cause reduced vasoconstriction and preserve the dermal vasculature. Other recent studies support this theory (Cera et al., 1980; Raine et al., 1980).

Robson et al. (1982) tested *A. vera* gel on thermal burns in a standard guinea pig experiment. The depth of dermal ischaemia was measured by perfusion with Indian ink. Thirty-five guinea pigs were used for each of the four treatments. The control animals were burned and untreated, while the other three groups were burned and treated every 8 h with methylprednisolone (a corticosteroid), methimazole, or a commercial 70% *A. vera* cream. An immunohistochemical analysis was used to analyse levels of prostaglandins and thromboxanes. They found that *A. vera* had similar effects to the methylprednisolone and methimazole, giving improved perfusion of capillaries and a reduction in thromboxane B<sub>2</sub> and prostaglandin F<sub>2</sub> compared to the control animals, which showed complete dermal ischaemia by 24 h.

Heggers and Robson (1983) suggested that *A. vera* gel products contain anthraquinone and related compounds, such as barbaloin and aloe-emodin,

in sufficient quantities to act as false substrate inhibitors blocking prostanoïd synthesis, since they have a similar chemical structure to prostaglandin substrates. During commercial extraction of *A. vera* gel it is virtually impossible to prevent contamination by the leaf exudate as the leaves are cut. In addition, in intact leaves anthraquinones and their derivatives may diffuse into the gel from the bundle sheath cells; this would support the conclusion of Rowe et al. (1941) that the healing agent passed from the rind into the gel on standing. While some manufacturers claim that anthraquinones are contaminants of the gel (Madis Laboratories, 1984), and pure "aloin" does cause irritation of the skin, trace amounts of these phenolic compounds may enhance the beneficial effects of the gel, perhaps having synergistic action with the polysaccharide matrix. Certainly anthraquinone derivatives have been used on the skin with some success (Crewe 1937, 1939). Anton and Haag-Berrurier (1980) discuss the medical use of anthraquinones from various plant sources, particularly in the treatment of conditions such as psoriasis.

Capasso et al. (1983) found that aloin and 1,8-dioxanthraquinone stimulated production of prostaglandins in isolated rat colon; this effect was thought to contribute to the laxative effect of these compounds. Indomethacin would prevent the increased prostaglandin production. While this seems to go against the theory of Heggers and Robson (1983), perhaps large concentrations of anthraquinone-type compounds increase prostaglandin levels, but trace amounts, as in *A. vera* gel, inhibit prostaglandin synthesis. Alternatively skin tissue and colon tissue could have different physiological responses.

Brasher et al. (1969) studied the effect of *A. vera* gel and two anti-inflammatory drugs, indomethacin and prednisolone, on HeLa cells of the Gey strain and rabbit kidney fibroblasts grown under tissue culture. They found that not only was *A. vera* less toxic, but at low concentrations it also produced higher cell counts than in the control cultures. Early workers (e.g. Lushbaugh and Hale, 1953) had concluded that *A. vera* contained some kind of growth-stimulatory substance.

Winters et al. (1981) found that fresh *A. vera* leaves contained lectin-like compounds which enhanced the growth of normal human cells in tissue culture, but not tumour cells. They also damaged the cell monolayers to stimulate wounding, and found that *A. vera* promoted cell attachment and growth. However, a commercial *A. vera* product gave disappointing results, and even seemed cytotoxic.

### Concluding comments

*Aloe vera* is of particular interest because it has found considerable popular acceptance as a home medication in Western society, as well as being used in the traditional ethnic medicine of less developed countries. While various botanicals have at one time or another been popular, *A. vera*

is one of the few that have maintained their popularity for a long period of time, despite its detractors in the scientific press. As Cera et al. (1980) remarked: "It has maintained its status as a folk lore remedy, while its curative tonic counterparts have fallen into disrepute."

Reviewing the history of the use of *A. vera* gel, some interesting questions arise. Why, for instance, after the enthusiasm shown by doctors in the 1930s and early 1940s, and after the encouraging results obtained by Lushbaugh and Hale in 1953 (working after all for the US government), was so little further clinical work carried out? Lushbaugh and Hale themselves remarked that interest had already by then declined, and since that time only sporadic experimental reports have been published.

The unfounded claims made for *A. vera* gel in promotional literature in the past, as quoted by Gjerstad and Riner (1968) and Spoerke and Ekins (1980), have aroused considerable scepticism among scientists. Criticism of the use of *A. vera* gel is partly due to such exaggerations. It is also due to the general lack of thorough clinical trials to follow up the early scientific reports, through poorly designed experiments with insufficiently large samples and from confusion of the properties attributed to the gel and the exudate.

Some writers are not at all convinced about *A. vera*; Gjerstad (1969) concluded that *A. vera* gel was "almost effective as baptismal water, but infinitely more expensive". Spoerke and Ekins (1980) wrote: "Today we have various drugs and medicines for topical use which decrease pain, facilitate healing and reduce inflammation . . . The currently available products are useful and are not shrouded in mystery or high costs as are the Aloe vera products."

Perhaps the main reason for the controversy over *A. vera* gel and the lack of clinical trials is the fact that it is so easy to produce. While most drugs, even when botanically derived, need advanced knowledge and chemical technology for their production, basically anyone can grow *A. vera* and extract its gel, so one would expect variations in efficacy. Gjerstad and Riner (1968) remarked: "The question logically arises why some larger research or pharmaceutical company has not followed up on this apparently valuable medicinal agent." It might be that drug firms do not think that there is enough evidence for *A. vera* to make it worth their while investigating it. But also, since no one has apparently succeeded in isolating a single definitive active compound from *A. vera* gel, and there is the possibility of a synergistic action between the components of the whole gel, it has been difficult for drug firms to isolate and market a patentable drug.

In a similar manner, the present lack of major clinical trials could either be because few in the medical profession think it is worth trying, or else be due to the fact that such trials are expensive and are generally financed by large drug companies. Probably the wide availability and range of products already on the market would mean it would not be worthwhile to make very large investments. *A. vera* processors tend to be smaller com-

panies and generally less concerned with medical proof for their products, since they sell well with the general public anyway.

Doubts as to the consistent reliability of treatments using *A. vera* products have been voiced even by manufacturers and reflect the lack of intensive scientific experimentation. Thus Madis Laboratories (1984) state "A batch of harvested *Aloe vera* leaves varies from lot to lot and are inherently biochemically unstable and deteriorate during a short period of time." Along the same lines Terry Corporation (Anon, 1977): "There is considerable variation in the composition of *Aloe vera* depending upon season, location etc. This perhaps explains why certain investigators have reported finding compounds that others failed to find. Also it is most probable that some reported components were, in fact, degradation products." Another possible cause for the variability in the results obtained in experimental work on *A. vera* could be genetic variation within the species. The apparent morphological types within the species could well vary in chemical composition as well — compare for example the work on carbohydrate structure of Gowda et al. (1979) and Mandal and Das (1980a,b). It is essential that any further work uses correctly identified plants of known origin.

Yet another factor that must be taken into account is that variations in response in human case studies could be due as much to natural variations in the physiology of the patients themselves as to the constituents of the gel. Certainly some people fail to respond, or show adverse effects (Ashley et al., 1957; Morrow et al., 1980).

While most of the research work on *A. vera* has been carried out by unbiased observers, the objectivity of some reports must be in doubt, since the plant is of great commercial importance. Many articles about *A. vera* are written by the manufacturers themselves, and often do not mention the less favourable results obtained in some studies.

The literature reviewed here shows that there is evidence from scientific investigations reported in reputable journals that *A. vera* gel is of value at least for burns and certain other dermatological conditions, and that it does have definite physiological effects. Certainly *A. vera* cannot be dismissed out of hand, since there is sufficient indication that some people benefit from its use. The "scientific" evidence for its rejection is almost countered by the "scientific" evidence for its beneficial properties.

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