

In Shape for '97 - Supporting the claim
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Substantiating Naturals

The claims substantiation for natural materials is no different to that required for any other material - all materials with a claimed benefit require substantiation!

The session will look at three claims.

Moisturising

Jojoba oil

The first will be the claim that a particular product is moisturising, and relies on a natural oil to achieve this benefit. Does something as simple as moisturising require a lot of work? What means can be used to support this claim? How much oil is needed to achieve the desired effect?

The marketing department have insisted that we look at Jojoba oil in one of our emulsions and want to claim that the product is moisturising. They also want to use some folk lore about the oil to make the pack copy more appealing. The first task is to look at the data supplied by the manufacturer or any other source and assess how much needs to be used, we find an article by F.J. Flider where he says:

“Efficacious effect in skin care is generally observed at usage above 1%. At 3% some moisturising activity is observed, but 5-10% seems to be optimal.” In these circumstances we should aim to use at least 5% and preferably around 7% to be sure that the claim will stand up to scrutiny. Much of the data seems to relate to the use of the oil undiluted.

We should also look at the chemistry of the oil and assess from our knowledge of existing materials whether those components are likely to have moisturising potential. Jojoba oil is composed of long-chain liquid wax esters. These esters are composed primarily of C20 to C22 long chain unbranched monoenic fatty acids and fatty alcohols.

It has been described as a liquid wax, and from the chemistry we would expect the material to be slightly occlusive and have moisturising properties.

There is considerable data relating to the folk lore as can be seen from the data in Appendix I, and this could be adapted for our needs.

As with all formulations, we have to be certain that the use of Jojoba oil is safe for use on the skin. The data available suggests that far from being a skin risk, there is likely to be a real benefit associated with the use of the oil.

In the Lawrence Review of Natural Products July 1988 (updated Sept 1995), we read not only of the beneficial effects that are attributed to the oil, but also of the good toxicological data that is available.

Having formulated the final product, it would be sensible to perform a simple corneometer test to measure the increase of moisture within the skin when the product is used. It would also be prudent to also carry out a volunteer panel test of the product to ensure that the moisturising properties of the product are perceivable in human terms

Cooling, soothing

Aloe vera

The second claim will relate to the cooling properties afforded by an aqueous plant extract. Do we need to look at the concentration of the plant material in the extract, how it was harvested, how it was stored, which part of the plant was used? Is it important that we consider the chemicals present in the plant, in order to explain why the plant is soothing. How do we ensure that the phytochemicals are present in our product. How much extract should we use? Where do we obtain our data?

The marketing department have picked up on a trend towards the use of Aloe vera in many commercial products and they have set a very tight budget on the formulation, believing the cost of the aloe vera to be an almost insignificant amount of the total cost of the formula. They want to use Aloe vera as a cooling and soothing ingredient, which will go right across their range.

On the face of it, this seems to be a very simple project, but further examination of the properties of Aloe vera and its processing will prove you wrong to hold that belief. Some suppliers extract the aloe vera gel exclusively from the central gel and totally exclude the outer leaf, especially the green parts. Some achieve this by careful filleting, others by squashing the gel out of the surrounding leaf by using heavy rollers. Other suppliers now process the whole leaf and sell this as the gel.

Are the chemicals in the outer leaf the same as those in the gel? Most certainly they are not! Are the chemicals present in the outer leaf beneficial to the skin? Most certainly they are not!

The chemicals within the gel rapidly degrade in air, and processing the gel into a concentrated form 10:1, 40:1, 100:1 (powder) and 200:1 (powder) increases the degradation of the gel as the concentration of the form is increased. Examination of the analytical data will be extremely difficult, since none of the suppliers actually know what their products contain, this is because of the complex nature of the chemicals present, particularly the composition of the polysaccharides.

The choice of substantive data must therefore come from clinical studies that have been carried out using the gel. In all cases this refers to use of the 100% pure gel, and so any product that contains less than 50% aloe vera gel is unlikely to stand up to scrutiny.

Appendix II shows the chemical composition of *Aloe barbadensis* Miller, where it will be noticed that the composition is complex.

Appendix III shows a summary of just some of the clinical studies.

Appendix IV shows the safety studies carried out on the aloe gel.

There is absolutely no problem in substantiating the claims, but the thought of aloe vera as a cheap ingredient is really not justified, if it is to be used at realistic concentrations.

Anti-inflammatory

The third claim will relate to the use of an exotic plant for its anti-inflammatory properties. In addition to all of the questions above, we also need to look at the implications of the wording on our pack copy (do we have a physiological effect on the skin?). This is a plant about which we have little European data, but we do have a fair amount of ethnobotanical data and folklore. How do we assess the efficacy and safety of the plant? The use of inter-relational chemical data will also be considered.

In this case the marketing department have read with interest of the great potential of plants obtained from the South American Rainforest. They are determined to find something exotic and rather like the name Cat's Claw, which they saw mentioned in one of the Sunday supplements. They also want some exciting copy and have suggested anti-inflammatory as a good word for their pack copy.

In a data sheet from Maruzen Pharmaceuticals (through K&K Greeff) we read that the thorns and partial stems are used to produce an extract that is analgaesic. This lack of information does not lead to a great deal of enthusiasm.

We take to the reference books, the material has not been extensively reported from the South American continent, much of the information refers to Chinese and African experience;

Keys, D.: Chinese Herbs - Their Botany, Chemistry and Pharmacodynamics. 1976 (1990 in paperback) Charles E. Tuttle. ISBN No. 0-8048-1667-0 says the stems and spines are officinal. The drug contains the alkaloid rhynchophylline, which lowers blood pressure and paralyses sympathetic nerve ending. Employed as a sedative, antispasmodic in infantile nervous disorders. Dose 5-10g. (In Japan, *Naucea rhynchophylla* Miq. [Syn. *Uncaria rhynchophylla* Miq., *Ourouparia rhynchophylla* Miq.] is used.)

Abbiw in Useful plants of Ghana - West African use of wild and cultivated plants. Intermediate Technology Publications and the Royal Botanic Gardens Kew. 1990. ISBN No. 1-85339-043-7 or 1-85339-080-1 (Hardback) - recommends the plant for wounds, cuts and sores. *Nauclea latifolia* - African Peach (Sukisia), application of powdered, ground roots or root-bark used.

Tang and Palmer in Chinese Herbal Prescriptions - A practical and authoritative self-help guide. 1986. Rider & Company, an imprint of Century Hutchinson Ltd. ISBN No. 0-7126-9470-6 say that it is also known as *Uncaria macrophylla* or *Uncaria sessilifructus*. The thorn is the part used to stop convulsions, spasms and tics, this herb is given with *Gastrodia elata*. For the treatment of reddened eyes caused by headache, it is prescribed together with chrysanthemum (*Chrysanthemum morifolium*), mulberry leaves (*Morus alba*) and menthol. It does not need boiling. Dosage: 6-12 g.

Reid: Chinese Herbal Medicine. Shambhala (Boston) 1993. ISBN NO. 0-87773-397-X and ISBN No. 0-87773-398-8 (paperback) - refers to the plant as *Uncaria rhynchophylla* or Morning Star or Gou Teng in Chinese. It is a member of the Rubiaceae family, and found in Central China. The stems and spines are used. Sedative to liver; antipyretic; antispasmodic in children's nervous disorders. Indications: Ailments of liver-yang ascending: pressure and pain in head, dizziness, blurry vision; body heat due to excess heat; convulsions and spasms in children; fainting and convulsions during the 6th, 7th and 8th month of pregnancy. Dosage: 5-10 g. The drug dilates the capillaries and other blood vessels and is now used to lower blood pressure as well.

This information is clearly unsatisfactory, and the only option that remains is to seek further data, which needs to come from other sources.

The first option was to search the Internet, where a number of fairly dubious reports were found. The next option was to look at Medline, where some very technical information was discovered. It was this information that confirmed that the plant does have some anti-inflammatory activity, though the major use of the plant has greater implications as a systemic drug.

Deciding which part of the plant to use and in what form to make the extract is an absolute minefield, and to make life even more difficult, there is very little in the literature to recommend the dosage level. However, if pushed for a decision, then 3-5% of the bark decoction (possibly hydroethanolic) should be used.

The use of the words "anti-inflammatory" is not allowed, since this would be taken to be a physiological effect on the skin, so we must look at less emotive words, such as skin calming or soothing. It would most certainly be recommended that the product be tested externally using both a human patch test of the final product (under the supervision of a dermatologist) and also be evaluated using a piece of equipment such as an erythema-meter.

In terms of safety, it would probably be most sensible to collect more data before making a decision on the use of this medicinal plant in your product.

APPENDIX I

REFERENCES

JOJOBA

Simmondsia chinensis (link) Schneider

Simmondsia californica Nuttall.

1. In the Lawrence Review of Natural Products July 1988 (updated Sept 1995), we read that Jojoba is a desert shrub indigenous to Arizona, California and Northern Mexico. It grows in a number of deserts, including Israel's Negev desert. The mature plant produces 5-10 pounds of seeds. While birds and rodents eat the seeds, it is toxic to humans and most animals.

Family: Buxaceae

Indians and Mexicans have for a long time used jojoba oil as a hair conditioner and restorer, and in medicine, cooking and rituals. It is used as a lubricant, since it does not break down under high temperature or pressure. It is also used in the Toiletry and Cosmetic industry.

Chemistry

Jojoba seeds produce 50% by weight a colourless, odourless oil comprising (97%) straight chain monoesters of C20 and C22 alcohols and acids with two double bonds. The acids have been identified as a mixture of cis-11-eicosenoic (C-20) and cis-13-docosenoic (C-22, erucic) acids. The alcohols have been identified as mixtures of cis-11-eicosenol, cis-13-docosenol and cis-15-tetracosenol (C-24). These alcohols are potentially valuable in the production of detergents, wetting agents, dibasic acids etc. Also included are small quantities of sterols (less than 0.5% of a total mixture of campesterol, stigmasterol and sitosterol). Jojoba oil is essentially triglyceride.

Pharmacology

Jojoba oil is a liquid wax. Studies carried out at the Ben Gurion University Medical Centre (Israel) indicate that the wax may be of value in the management of acne and psoriasis. Other topical irritations such as sunburn and chapped skin appear to respond to topical jojoba therapy. There is a substantial body of anecdotal evidence that suggests that the wax is beneficial in alleviating minor skin irritations.

There has also been considerable interest and success in marketing jojoba preparations to stimulate hair growth and rejuvenation - there are no publications to support this. Jojoba oil penetrates skin and skin oils easily - unclogging hair follicles and preventing sebum build up which could easily lead to hair loss.

In a rabbit study, ingestion of jojoba oil as a 2% supplement to an atherogenic diet produced a 40% reduction of blood cholesterol, although the mechanism by which this occurred was not determined.

Recent study has shown antioxidant activity of jojoba. This activity is related to the content of α -tocopherol found in the leaves.

Toxicology

The LD50 of crude jojoba wax is greater than 160 g/kg in mice. In ocular tests, it was only slightly irritating compared to olive oil, and was less irritating than mineral oil. Hypoallergenic sensitivity to the wax has been reported, and cases of dermatitis have been reported in persons using jojoba oil as shampoo or hair conditioner.

Topical administration of the refined wax to guinea pigs for 20 weeks resulted in no systemic effects; a reversible swelling accompanied by reduced skin flexibility and an increased sensitivity to shaving was observed. There were, however, no histological changes in skin tissues.

Subcutaneous injection of 1mL/kg for 6 weeks in test animals resulted in no systemic effect, although some systemic accumulation was observed.

2. In a data sheet from Jan Dekker (undated with no reference) we read that as early as 1769, the famous Spanish missionary Junipero Serra reported that he had seen California Indians harvesting Jojoba beans from the wild bushes in the desert, using the jojoba oil as a healing agent and for cooking. Jojoba oil is not an oil but a liquid wax. It is extremely stable to extreme temperatures. It is not toxic, it is biodegradable, it does not go rancid (a 25 year old sample was found to be chemically the same as oil from freshl picked seeds). It has an extremely precise and clean molecular structure and has almost no impurities and it is polyunsaturated.

It is readily absorbed into the skin, imparting a luxurious and velvety resistant feel. It offers new avenues for acne research. It nourishes the skin the way Nature intended and retains moisture better better. The most interesting market for jojoba may be the pharmaceutical industry. Preliminary reports by BGU medical researchers suggest that the oil may have value in the treatment of skin diseases such as eczema, psoriasis and acute acne.

3. G.J.Arndt reported in an article called "Jojoba". Cosmetics and Toiletries Vol 102, June 1987 p.68-69. He said that Jojoba produces a coffee bean-like seed which contains 50% jojoba oil.

Unlike all other vegetable oils which consist of triglycerides, jojoba oil is composed of long-chain liquid wax esters. These esters are composed primarily of C20 to C22 long chain unbranched monoenic fatty acids and fatty alcohols. Jojoba oil exhibits remarkable oxidative and thermal stability which is bolstered by the presence of tocopherols, and other naturally occurring antioxidants. The paper goes on to describe various processing techniques. Extensive safety and toxicity testing has shown jojoba oil to be perfectly safe for use as a cosmetic oil. Additionally it has been shown to be noncomedogenic and nonantigenic. Jojoba is readily absorbed by the skin and is miscible with sebum. As a result it leaves no greasy afterfeel.

Jojoba Oil appears to be effective in controlling transpirational water loss, having the water vapour porosity necessary to permit the skin to function normally while still providing emolliency. Jojoba effectively controls skin sloughing without the greasiness associated with occlusivess such as petrolatum. As an added benefit, jojoba oil has been shown to significantly soften the skin as measured by viscoelastic dynamometry.

Recent studies carried out by the Ben_Gurion University indicate that the jojoba oil may be effective in alleviating the symptoms of psoriais and in controlling acne outbreaks. Additional research has shown that jojoba oil may also have an anti-inflammatory effect under certain conditions. Jojoba is an excellent scalp conditioning agent. Due to its ability to penetrate skin and its miscibility with sebum, it is very effective in unclogging hair follicles and keeping them free of sebum build up which may cause hair loss.

4. In a Dragoco report we read that it was first written about by the Spanish missionary Junipero Serra in 1769. It has a characteristic odour which can easily be masked. It is exceptionally stable, resistant to heat. It is of low viscosity.

It has a positive effect on skin and hair, having excellent spreading qualities, and good skin penetration without leaving a greasy film. Jojoba oil supports the natural protective function of the skin, and skin care products with jojoba oil give the skin a non-greasy feel and a pleasant, velvety softness. Hair care products with jojoba make hair look more shiny and improve its suppleness.

5. In a paper by J.H.Brown "Jojoba Liquid Wax - a substitute for spermacetti." Manufacturing Chemist and Aerosol News June 1979 . He says that the seeds contain 44-58% oil, and is free from rancidity etc (see comments above!) It has been used medicinally for the treatment of burns and sores etc. In the opinion of the

author it is unsurpassed as an emollient. It will prolong the residence of sun screens on the skin owing to its miscibility with the sebum naturally on the skin.

Toxicity studies have shown jojoba to reveal no significant concerns. Acute toxicity in mice, eye irritation from refined oil in rabbits, repeated patch test in guinea pigs and patch tests on human skin. The conclusions were, that apart from patients with inherent allergy to cosmetic oils, crude and refined jojoba oil can be considered safe for human skin.

6. In the Extract from Nature Book (B47) we read that this rich nourishing oil comes from the seeds of a small tree belonging to the box family. It is a common ingredient in beauty preparations for its nutrient qualities. It regulates skin function, is an excellent cleanser, conditions and restores the quality of the hair and is active against dandruff.

7. The CTFA Ingredient Handbook (B63) describes jojoba Oil as a skin conditioning agent - occlusive; hair conditioning agent.

8. The Merck Index 11th edition reports that the oil is an alternative to spermacetti wax. It is highly stable and resistant to rancidity and bacterial degradation.

9. Bloomfield (B57) has written a short book on Jojoba and Yucca. It would be impossible to reiterate all of this reference.

1789 Francisco Clavijero, a traveller and Mexican historian wrote that the plant was celebrated for its medicinal value, especially curing the suppression of the urine from mucous concretions, for facilitating childbirth, and for wounds. The oil which is derived from it is an excellent remedy for cancer and is also edible.

1794-95 Father I Pfefferkorn wrote that it was good for stomach disorders. The Apache Indians used the plant for the healing of wounds. The Seri Indians used the plant for sores on the head. To relieve eye soreness, the fruit was ground and wrapped in a cloth, which was then squeezed and the liquid put in the eyes.

Recent research has suggested that the oil is anti-inflammatory in its action. The American Indian tribes used jojoba consistently for the treatment of wounds and swellings. Controlled experiments have confirmed that jojoba does not seem to bring about allergic reactions.

The book then discusses how jojoba can be used in cases of acne, arthritis, cancer, chapped skin, childbirth, common colds, constipation, dandruff, dry skin, inflamed eyes, healthy hair, skin inflammations, over-active sebaceous glands, sores, stomach ache, sunburn, warts and water retention problems.

10. D.J.Ricks: Functional Natural oils. Cosmetics and Toiletries, vol 106,p.77, Feb 1991. For centuries the oil of this desert shrub has been held in high regard for its unique cosmetic properties and qualities. Originally the natives of the American Sonora desert used jojoba oil for various applications such as hair dressings, skin salves, medicinal preparations and food.

The natives attributed magical powers to the oil; legends that it could cure cuts, scratches and sores or promote hair growth were widely accepted.

Researchers investigating the legends discovered that it is not an oil but a unique mixture of long chain linear monoesters. It is a pure oil and does not contain tars, resins, alkaloids, phosphatides, chlorophyll and other impurities. The oil is also mild; not a primary irritant to the eyes or skin, not comedogenic, and not a promoter of allergenic contact sensitisation.

It is an excellent emollient, completely miscible with sebum. Unlike heavy occlusives, it significantly reduces transepidermal water loss without totally blocking the transportation of gases and water vapour. It has superior lubricity and spreading properties and leaves a rich velvety feel on the skin.

Percutaneous absorption studies show that it penetrates quickly into the skin. Absorption is apparently via a transappendeal mechanism through the pores and follicles. From the hairs and follicles it apparently diffuses into the corneal layer of the skin via a pilosebaceous mechanism. There, it appears to act with intercellular lipids to further reduce water loss.

Visoelastic dynamometric tests have registered a 37% increase after application of jojoba oil. Moisturising efficacy experiments have demonstrated that jojoba oil can effectively reduce superficial facial lines by 26%, 28% and 11% after one, four, and eight hours respectively. Gas-bearing electrodynamic studies using jojoba oil and cosmetic preparations incorporating jojoba oil have shown increased skin softness continuing more than 8 hours after application.

11. SPC December 1990, p.43, we read that it is not an oil but a liquid wax which comes from the seeds of jojoba, a dioecious, perennial bushy shrub native to the arid and semi-arid regions of southern and Baja California, Arizona and Mexico.

The liquid expressed from the the shrub is not a triglyceride oil but is chemically a liquid wax ester, comprising a mixture of long chain mono-unsaturated fatty acids such as octadecenoic acid and long chain mono-unsaturated alcohols such as eicosenol, ducosenol and tetracosenol.

It is a light non-tacky oil which spreads easily on the skin and gives a silky smooth residual feel.

It has been stated that tests carried out with jojoba oil in cosmetics have shown, that with the exception of patients with skin disorders who are inherently allergic to cosmetic base oils, crude and refined jojoba oil can be considered safe for human skin. It has natural antioxidative properties and does not require any chemical preservatives. It is an excellent emollient and will prolong the residence of sunscreen on the skin.

12. Flider, F.J.: Jojoba: Finally, a real industry has emerged. HAPPI May 1987. Jojoba oil is one of North America's oldest skin care products, having been used hundreds of years ago by the indians of the Sonoran desert for its skin conditioning and healing effects.

In 1936 it was reported that jojoba oil was similar in composition to sperm whale oil, a commodity which was of extreme importance to the lubrication and cosmetics industries. As early as 1942, the unique properties of jojoba were noted in the cosmetic literature.

It is composed of mainly C40-C44 liquid wax esters. The esters are composed of straight-chain monoene fatty alcohols and acids unsaturated at the w-9 position. Jojoba oil is essentially free of triglycerides and contains only minor quantities of free fatty acids and alcohols.

The chemical structure of jojoba oil imparts qualities and properties to skin care products that are difficult to match with other cosmetic oils. Jojoba increases the lubricity of emulsion systems, resulting in improved skin spreading and aesthetic qualities and, unlike mineral oil, petrolatum, lanolin and triglycerides, leaves no greasy or oily afterfeel. Furthermore, jojoba oil is rapidly absorbed by the skin. Absorption is thought to occur via a trans-appendeal mechanism; that is through the pores and hair follicles. The result of rapid absorption is that the pores and hair follicle remain open and can function freely.

A unique function of jojoba oil is its ability to control transpirational water loss. It appears to have a water vapour porosity sufficient to permit the homeostatic mechanism of the sweat glands to function optimally. Jojoba oil is very effective in the control of exfoliation, flaking and dryness. Because of its miscibility with sebum, it adds a non-greasy lipid layer to the skin which retards scaling and sloughing to a degree approaching petrolatum in effectiveness.

An interesting attribute of jojoba is its apparent ability to retard sebum excretion in people with oily skin, although the mechanism has not yet been ascertained. It is suspected that sub dermal jojoba may somehow mimic sebum, thus "tricking" the skin into stopping production of sebum.

Viscoelastic measurements revealed that jojoba oil has a significant skin softening effect. In one test with 20 women, skin "compliance" increased 37% after 30 minutes and remained there for an hour. Further studies indicate that continued use of jojoba results in an additive effect. In the same study, jojoba oil was effective in reducing superficial facial lines. The reductions were 26, 18 and 11% after one, four and eight hours respectively, and the effect appears to be additive.

A prevailing myth with jojoba oil is that it can regenerate hair. As with most myths, there seems to be some basis for the belief. Certain types of baldness are caused by excess sebum production by the scalp. The sebum blocks the hair follicles, literally suffocating them. This eventually leads to the loss of the hair shaft and ultimately the death of the follicle. Jojoba has been shown to be readily absorbed through the hair follicles. Because of its miscibility with sebum, jojoba dissolves and displaces hardened sebum which may be blocking the follicle. This cleansing effect allows the follicle to resume its normal function, assuming that it has not yet been destroyed.

Efficacious effect in skin care is generally observed at usage above 1%. At 3% some moisturising activity is observed, but 5-10% seems to be optimal.

Jojoba has also been shown to improve the aesthetic qualities of ointment for treating psoriasis.

13. David Mitchell and Malcom James: Plant derived ingredients. Manufacturing Chemist, November 1987, p.73.

Jojoba oil, a remarkable oil if many marketing stories are to be believed, is a liquid wax, i.e. an oil which contains large molecules made up of long carbon chains, which would normally be waxes if it was not for a structural hindrance to solidification.

Contains eicosenoic acid and eicosenol alcohol (C20) with docosenoic acid and docosenol alcohol (C22). Molecular weight at about 600g/molecule.

A liquid wax has several benefits to the formulator. It offers a richer feel than normal oils because the oil is absorbed by the upper layers of the skin, which is softened without the greasiness that could possibly be associated with a lighter oil. It is also possible that similar conditioning effects could be achieved in formulations for the hair and scalp.

13. Roberta Wilson: 'Jojoba Oil seen ready to prosper with "green"'. Drug and Cosmetic Industry May 1992, p.32-35.

As cosmetic ingredient go, Jojoba is a relative newcomer. Harvested from wild plants in the 1970s it was advocated as a substitute for whale oil. It has been clinically tested and is a safe cosmetic ingredient.

The paper describes the growing conditions and ills to which the plant is prone. It is botanically *Simmondsia chinensis*, which is not a pretty plant and produces bean-like seeds, with an average oil content of 50%. It is not a normal oil in the sense that it is not composed of the normal triglyceride esters.

Jojoba's water-binding qualities are key to emolliency and moisturisation, spreadability and luxurious afterfeel. The oil controls TransEpidermal Water Loss (TEWL) and water vapour porosity that permits skin to function normally while providing emolliency. Excess sloughing of dead skin cells seems to be minimised with jojoba use, and it displays lubricity without oiliness common to other lipids (especially lanolin and petrolatum).

Percutaneous absorption studies show jojoba penetrates the skin through pores and hair follicles, diffusing through a pilosebaceous mechanism where it acts with intercellular lipids to further reduce moisture loss.

Advocates of the oil report that it demonstrates the ability to reduce superficial facial lines by up to 26% and that its skin softening effects continue over eight hours.. Suppleness also persists for many hours, perhaps because the occlusive layer increases hydration to the surface of the stratum corneum (or both).

Jojoba oil seems to have greater compatibility with the skin than do triglycerides or mineral oils. After pressing, it is relatively pure and so does not require heavy refining. It is devoid of tars, glycerides, resins, alkaloids, glucosides, chlorophyll and other impurities, making it non-irritating, non-sensitising, non-comedogenic and unlikely to produce allergic reactions.

It is used especially for skin of people suffering dehydration and extreme dryness of the skin, in the elderly and those with skin disorders marked by scaliness and sebum imbalance. Anti-inflammatory qualities of Jojoba make it helpful in treating skin disorders triggered by inflammation.

In preliminary trials done in Israel, jojoba showed promise in controlling both psoriasis and acne; and because of its penetration, jojoba is being investigated for use in trans-dermal patches for drugs, as well as a base for topical ointments.

14. In a data sheet from the Desert King Jojoba Corporation (through Honeywill and Stein) we read that the oil is obtained from the seeds of **Simmondsia chinensis**. It does not contain triglycerides or have a fishy odour.

It is non-greasy, has superior transpirational water control, enhanced cellular regeneration, excellent keratoplastic effect, high miscibility with sebum, effective control of exfoliation, flaking and drying, mildness, hypoallergenicity, thermal and oxidative stability, biodegradability.

It is non-toxic, non-irritating to the eyes, non-comedogenic and shows no allergenic contact sensitisation.

Percutaneous absorbability of the oil is superior. Due to its wax ester composition, jojoba oil exhibits a greater hydrophilic potency and penetrates skin more easily and quickly than other oils and fats. Absorption of jojoba oils by the skin is via transappendeal system (pores and hair and hair follicles). Diffusion of oils into the corneal layer of the skin is via a pilosebaceous system, allowing the oils to soften the skin from within. Routine application of jojoba softens the skin, increases the skin's elasticity and compliance and enhances the skin's cellular regeneration processes.

Jojoba oils prevent transpirational water loss from the skin. Unlike occlusive materials such as lanolin and petrolatum, jojoba reduces evaporation without inhibiting the passage of gases and water vapour. Jojoba oil has been shown to reduce superficial facial lines by 26%, 18% and 11% at one, four and 8 hours respectively following application. Jojoba oil smooths rough, dry skin and inhibits excess flaking of epidermal cells leaving skin robust and velvety to the touch.

15. In a data sheet from Blagden Chemicals we read of Jojoba meal. This is a powder prepared by the controlled grinding of the jojoba nut. It is a mild abrasive that is compatible with anionic, nonionic and cationic surfactants.

The particle size is carefully controlled to ensure consistent performance and low odour.

16. Wilson, Roberta: DCI November 1992, p.43. Jojoba and Jojoba derivatives.

Wilson says that it binds moisture, softens the skin, is thermally stable, extremely safe on the skin, and resists oxidative breakdown. The oil comes from slow growing desert botanical **Simmondsia chinensis**, the female jojoba bushes producing seeds that yield about 50% oil. This light golden oil is exceptionally pure and stable,

retaining freshness and demonstrating long shelf life. It is a straight chain wax ester consisting primarily of C20 and C22 mono-saturated fatty acids and alcohols.

Jobba's emolliency imparts a smooth, luxurious afterfeel and provides superb spreadability, without leaving shine on the surface - an important attribute in facial creams and moisturisers.

In a study by the Institute for Applied Pharmaceutical Research (Merion, Pa.), jojoba oil demonstrated an average increase in skin softness of 37% on 20 human subjects. Ingredient that increase skin softness by 20% are considered effective emollients. Skin softness permits the skin to stretch and move without developing cracks and tears on the surface that are perceived as scaliness. The skin softening effect of jojoba oil lasts for more than 8 hours.

The article goes on to consider modified jojoba derivatives, such as esters, hydrogenated jojoba wax, ethoxylates.

17. Roberta Wilson: "Desert plants - derivatives for personal products. DCI January 1993.

Jojoba is the ultimate example of a successful conversion of a desert wild plant into a domesticated agricultural commodity. The fact of the oil's remarkable affinity for skin and hair, its ability to replace petroleum-based ingredients and whale oil in formulae (since when? - ACD), and its ability to replace oil-based lubricants all played a role in its eventual cultivation for commercial use.

Jojoba is known as an excellent agent for softening and protecting skin from environmental damage while providing smooth afterfeel.

18. Kenneth McClatchy, Carl L. Pierson and William J. Ferrell.: In vitro antimicrobial effects of jojoba oil. Reference and date unknown.

Abstract

The effect of jojoba oil on the growth of skin pathogens is largely unknown. Five species of bacteria and four species of fungi were tested for their ability to grow in jojoba oil preparation. Each organism was tested in at least one of four different culture methods: agar well diffusion, agar surface plating, microscope slide culture and MS-2 system growth analysis. No method used showed evidence of bacterial or fungal growth in jojoba oil; however, the oil did not appear to be directly toxic to the organisms tested. Death of the cells appeared to be due to their inability to use the oil as a primary source of energy and/or nutrient.

19. Letter from Elias Packman dated 26th Nov 1985 to Frank F. Flider of JMC Technologies. The following tests were conducted, the conclusions are included.

Moisturising efficacy as measured by superficial facial line reduction

A half face study used on 20 subjects 35-55 years of age.
Also a half face cross-over study

The above sample significantly reduced superficial facial lines over an 8 hour period.

Skin softness as measured by viscoelastic dynamometry

A significant difference was measured. Substantial increases in skin surface softness were observed in all subjects from 0.5-2.0 hours after the oil was applied. The magnitude and duration of the effect compares favourably with leading emollient preparations.

Cellular regeneration as measured by the dansyl chloride staining

The effect of the oil on turnover was marginal, and not different from that induced by Oil of Ulay. Both products caused a slight increase in the regeneration rate of the stratum corneum. 10% of the oil in propylene glycol and propylene glycol alone caused no discernible change in turnover.

Irritation-sensitisation studies

No acute irritation or sensitisation seen

20. F. Wankte, W. Hemmer, M. Gotz and R. Jarisch: Contact dermatitis from jojoba oil and myristyl lactate/maleated soybean oil. Short communications. Contact Dermatitis: 1996, **34**, 71.

Case of woman using Clinique Advance Cream is reported.

Discussion

The patient had allergic contact dermatitis from Clinique Advanced Cream, proven in three consecutive patch tests over a period of 2 years. According to a personal communication from Clinique Austria in 1993, the preparation of the cream had changed about 2 years ago, since when 2 further cases of suspected contact dermatitis seem to have occurred in Austria.

Jojoba oil is widely used in cosmetics, such as moisturisers, sunscreens, shampoos and conditioners. Contact dermatitis from jojoba oil 20.0% has been described in 5 patients. Glyceryl stearate is extensively used as an emollient, opacifier and emulsifier in cosmetics. Contact dermatitis from glyceryl stearate is probably extremely rare: only 3 reported cases exist. In our patient, a positive reaction was obtained to the mixture of glyceryl stearate and polyoxyethylene 23-laurylether (Laureth 23).

Myristic acid and its derivatives are used as emulsifiers. Contact dermatitis from the fatty acid ester myristate octyl dodecyl 10.0% was first described by Sanz de Galdeano et al. Myristyl lactate did not react singly, though the mixture of myristyl lactate and maleated soybean oil, as used in the product, repeatedly gave positive reactions. As there was a doubtful reaction to maleated soybean oil in the final patch tests, and also with reference to the recent literature, we suggest that the maleated soybean oil was the cause of the allergic reaction.

APPENDIX II

PHARMACEUTICAL CHEMISTRY

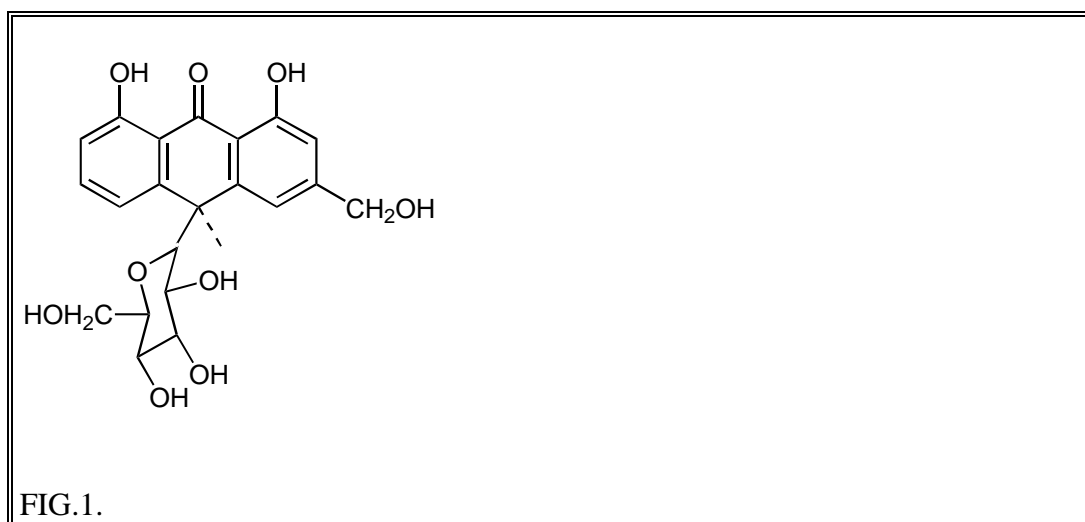
Aloe barbadensis Miller

CHEMICAL CONSTITUENTS

HYDROXY ANTHRACENE DERIVATIVES OF ANTHRONE TYPE CHRYSALOINES

1. BARBALOIN or ALOIN A

10-(1',5'-anhydroglucosyl)-aloe-emodin-9-anthrone



2. ISOBARBALOIN or ALOIN B

10-(1',5'-anhydroglucosyl)-aloe-emodin-9-anthrone

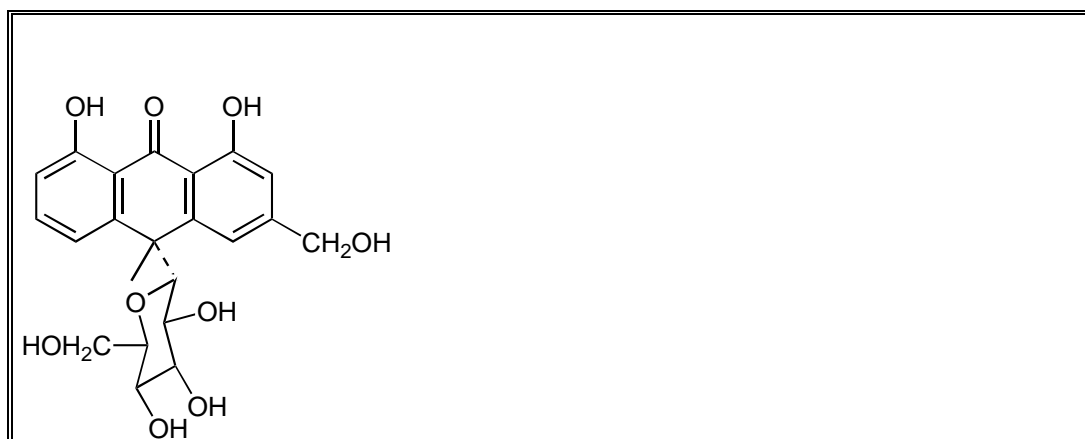


FIG.2.

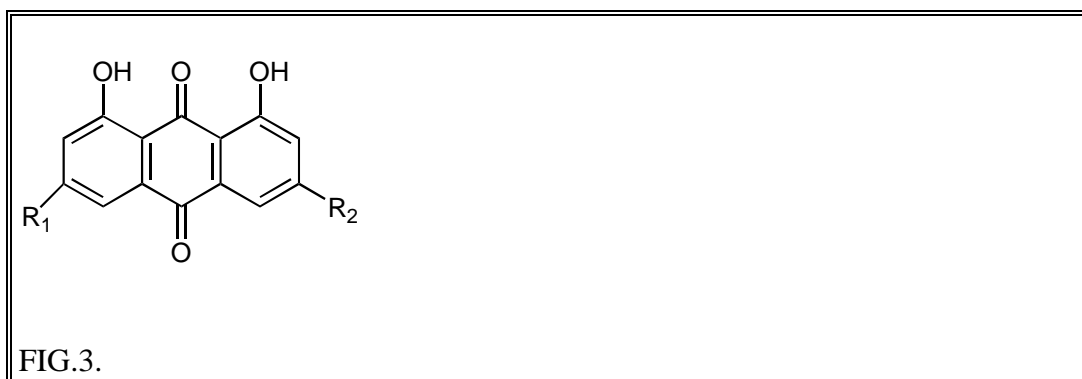
These two chemicals are present as a mixture of:
10-C- β -L-glucosyldiastereo isomer of aloe-emodin anthrone and
10-C- β -D-glucosyldiastereo isomer of aloe-emodin anthrone

They are present at 25-40% or 500mg/100g in the prepared aloe vera gel.

3 ANTHRAQUINONE DERIVATIVES

R ₁	R ₂	Chemical Name
H	CH ₃	CHRYSOPHANOL
H	CH ₂ OH	ALOE-EMODOL
H	COOH	RHEINE
H	CH ₃	EMODOL

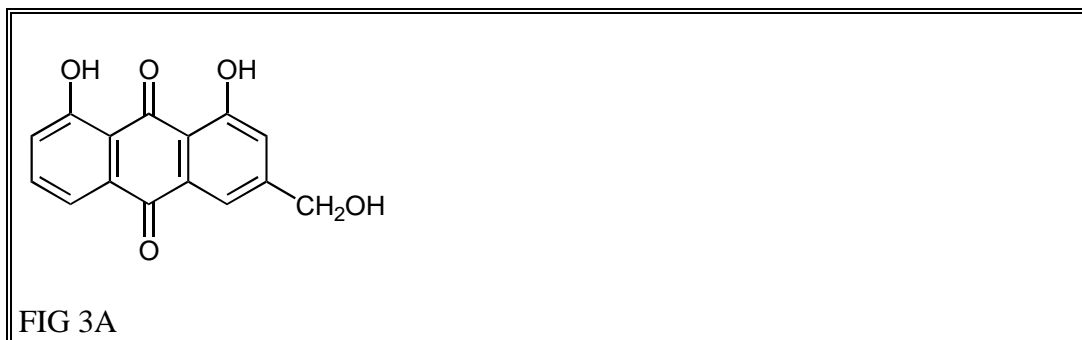
Table 1



3a. ALOE-EMODIN or ALOE-EMODOL

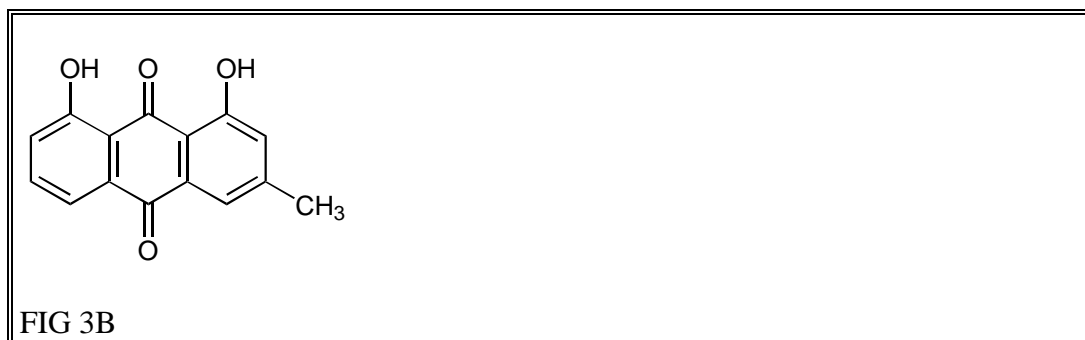
3-Hydroxymethyl anthraquinone
1,8-dihydroxy-3-hydroxymethyl-9,10-anthracenedione

Typically present at 2.05-2.2% in the aloe vera gel.



3b. CHRYSOPHANOL OR CHRYSAROBIN

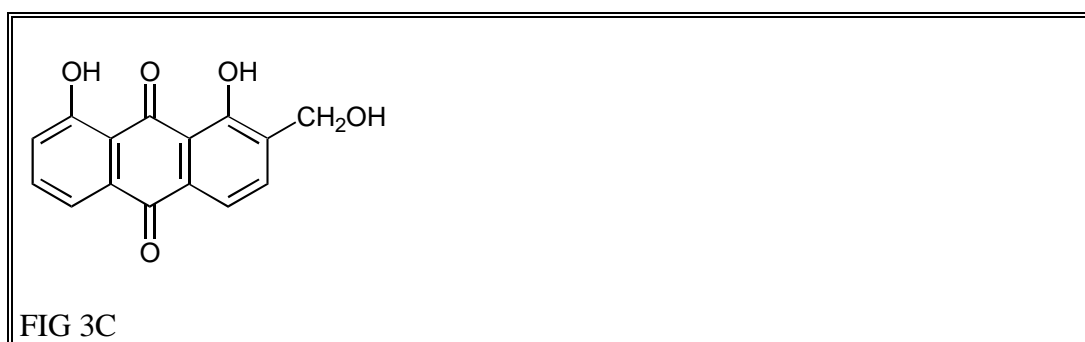
(Sometimes referred to Chrysophanic acid, which is a misnomer.)



3C. ALOETIC ACID

Also mentioned is aloetic acid, which has a similar structure, but is not widely mentioned in the literature.

2-Hydroxymethylanthroquinone



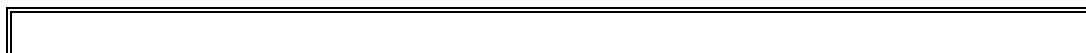
CHROMONE DERIVATIVES

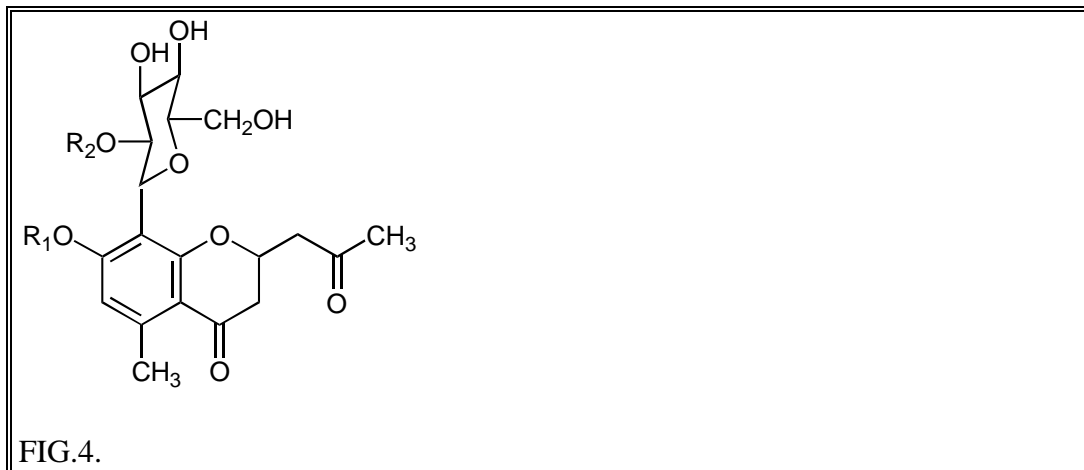
ALOE RESINS

4. ALOERESIN A, ALOERESIN B and ALOERESIN C

R ₁	R ₂	Chemical Name
H	p-coumaroyl	ALOERESIN A
H	H	ALOERESIN B
Glucosyl	p-coumaroyl	ALOERESIN C

Table 2





Aloeresin A is 2-*p*-coumaroyl aloeresin
 Aloeresin B is 8-C-glucosylchromone aloeresin B
 Aloeresin C is 7-O-β-D-glucoside of aloeresin A

5. ALOESONE

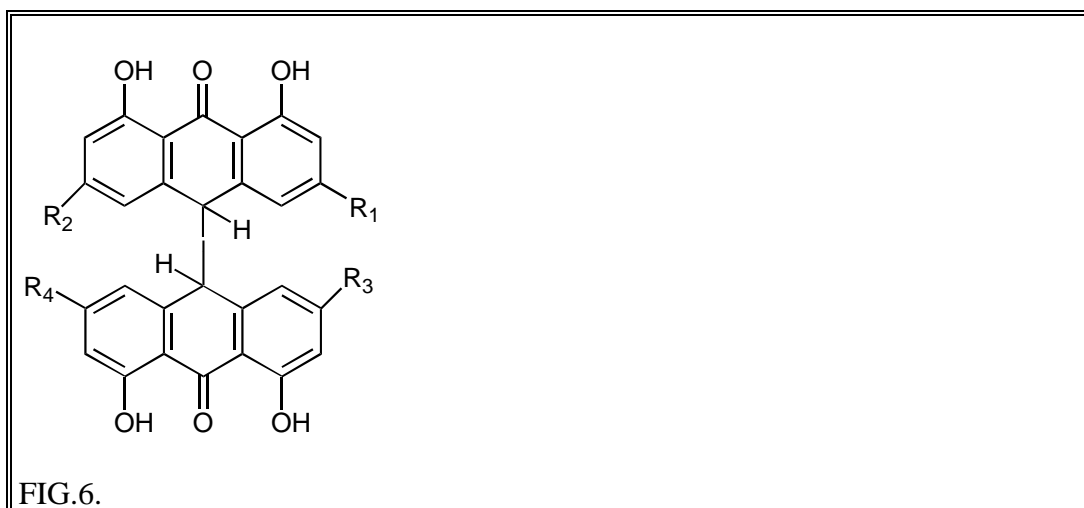
The aglycone of aloeresins A, B and C.
 This is only present in trace amounts.

HOMODIANTHRONES

6. SENNIDIN A and B

R ₁	R ₂	R ₃	R ₄	Chemical Name
COOH	H	COOH	H	SENNIDIN A, B
CH ₂ OH	H	COOH	H	SENNIDIN C, D

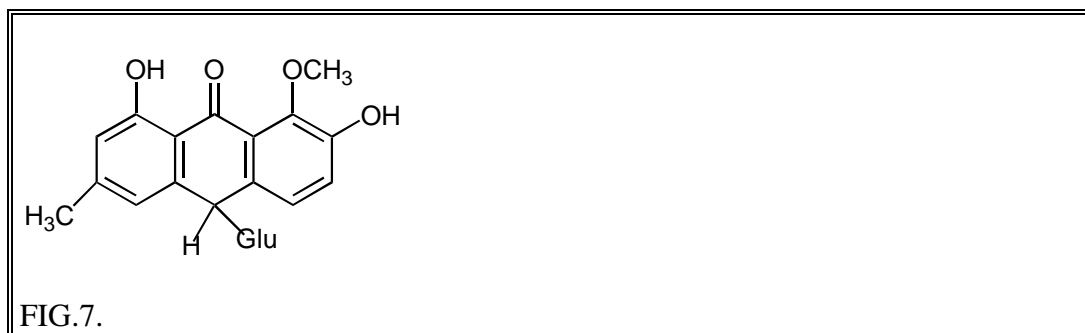
Table 3



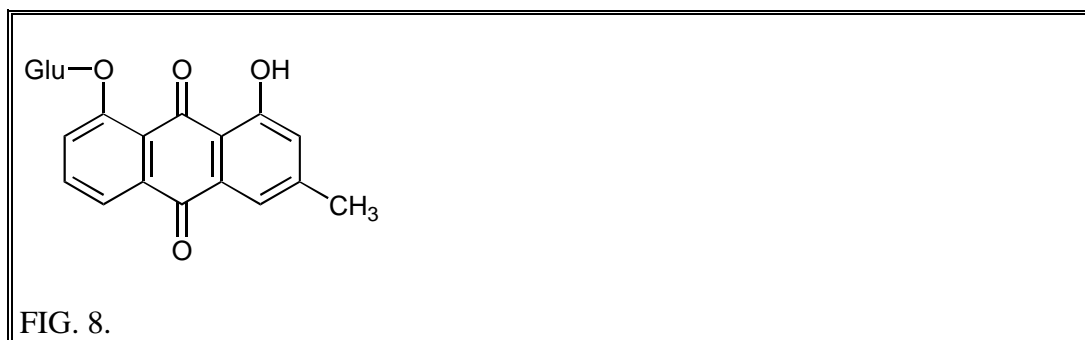
GLUCOSIDES

Various glucosides are present

7. HOMONATALOIN



8. CHRYSOPHANOL GLYCOSIDE



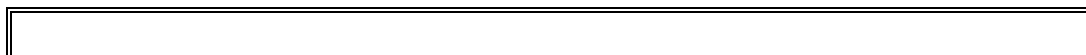
OTHER STRUCTURES PRESENT

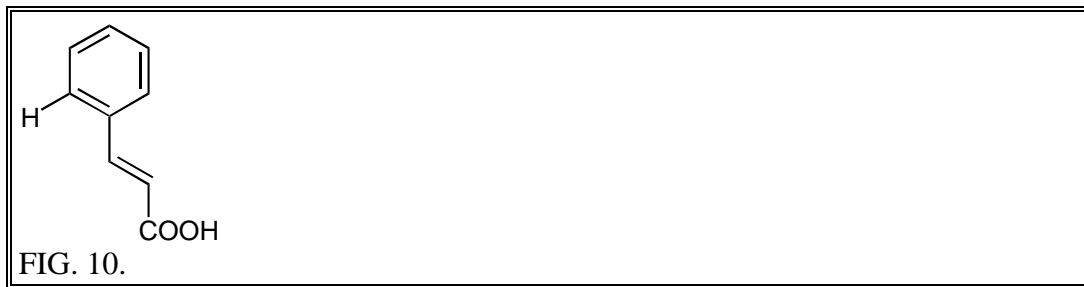
9. COUMARIC ACID

p-coumaric acid



10. CINNAMIC ACID

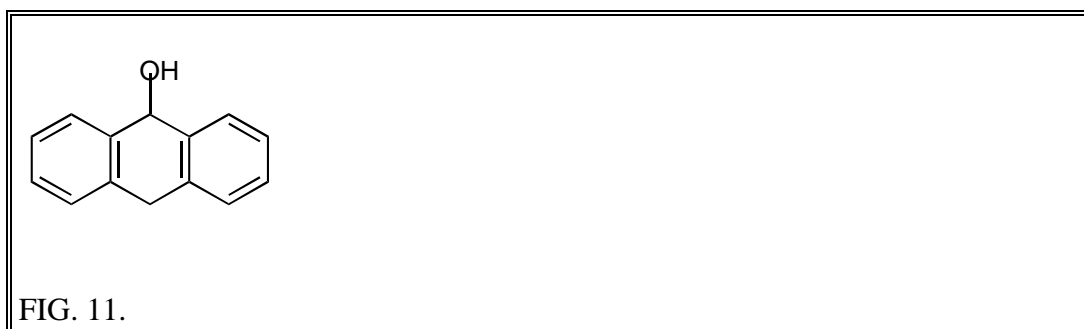




11. RESISTANNOLS

These are the alcohol derivatives of cinnamic acid.

12. ANTHRANOL



13. SALICYLIC ACID



PLANT STEROIDS

14. β -SITOSTEROL

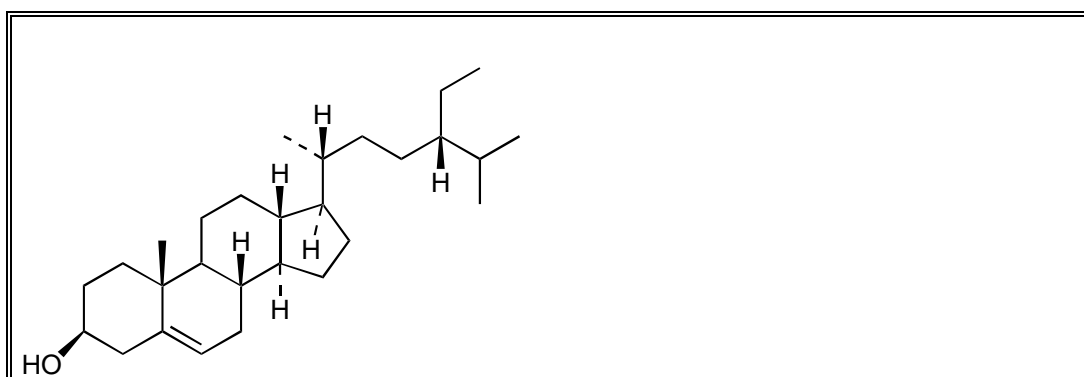


FIG. 13.

In addition, it has been reported that small amounts of cholesterol may also be present.

ESSENTIAL AMINO ACIDS

Lysine	Leucine
Threonine	Isoleucine
Valine	Phenylalanine
Methionine	Glutamine
Tryptophane	Cystine
Asparigine	

SECONDARY AMINO ACIDS

Histidine	Proline
Arginine	Glycine
Hydroxyproline	Alanine
Aspartic acid	Serine
Tyrosine	Glutamic acid

MONOSACCHARIDES, POLYSACCHARIDES, MUCOPOLYSACCHARIDES

Cellulose	Glucose
Mannose	L-Rhamnose
Uronic acid	Aldopentose
Arabinose	Galactose
Xylose	

ENZYMES

Oxidase	Lipase
Amylase	Aliinase
Cellulase	Catalase
Alkaline Phosphatase	Bradykininase

VITAMINS

Vitamin A (probably in the form of β -carotene or Provitamin A)

Vitamin B1 : 3-(4-Amino-2-methylpyrimidin-5-ylmethyl)-5-(2-hydroxyethyl)-4-methylthiazolium chloride

Vitamin B2: 7,8-Dimethyl-10-(1'-D-ribityl)isoalloxazine or 3,10-Dihydro-7,8-dimethyl-10-(D-ribo-2,3,4,5-tetra hydroxy pentyl)benzopteridine-2,4-dione

Vitamin B6: 3-Hydroxy-4,5-bis(hydroxymethyl)-2-picoline hydrochloride

Choline : (2-Hydroxyethyltrimethylammonium chloride)

Folic acid: (N-[4-(2-amino-4-hydroxypteridin-6-ylmethyl amino) benzoyl]-L(+)-glutamic acid)

Niacinamide or Nicotinamide
Pyridine-3-carboxamide

Vitamin C
Vitamin E

MINERALS

Calcium
Sodium
Chlorine
Iron
Zinc
Chromium

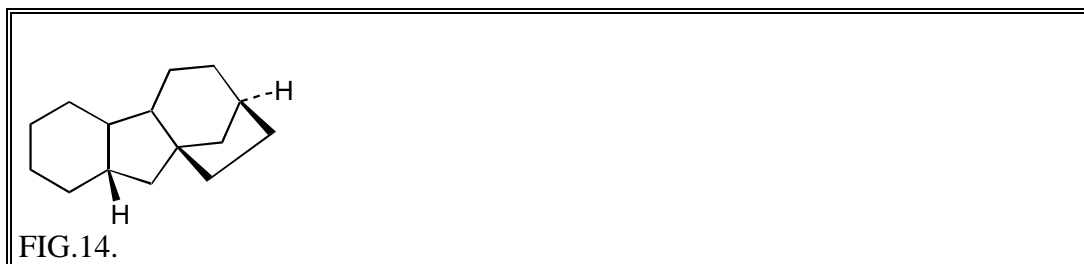
Potassium (present as the sorbate salt?)
Magnesium
Sulphur
Copper
Manganese

MISCELLANEOUS

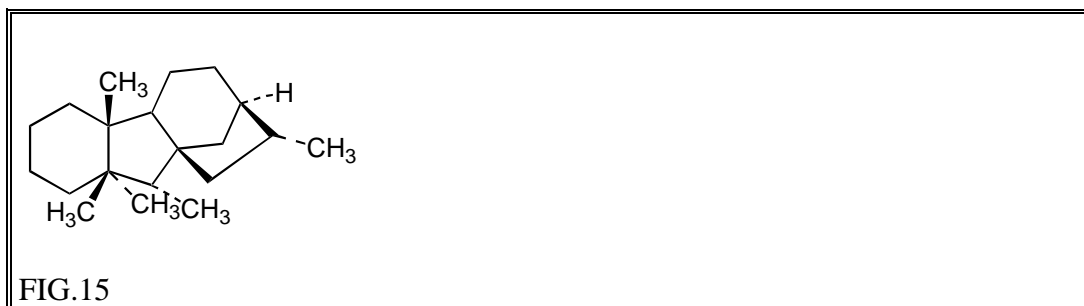
Uric acid
Triglycerides
Gibberellin
Salicylic acid
Cholesterol

Steroids
 β -Sitosterol
Lignins
Lectin-like substances

Gibbane



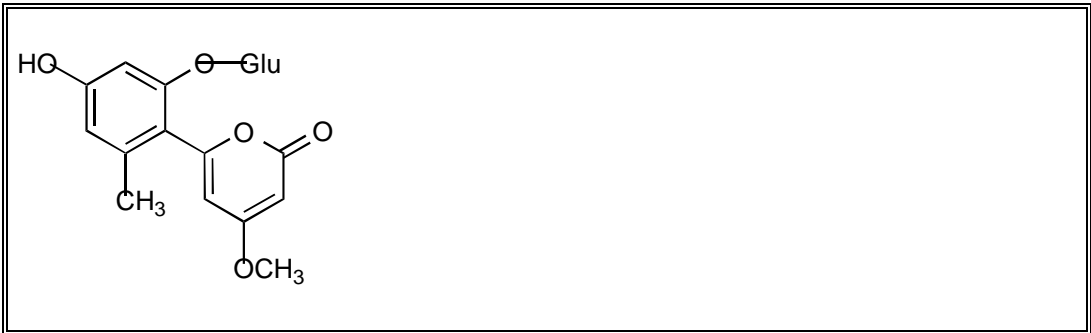
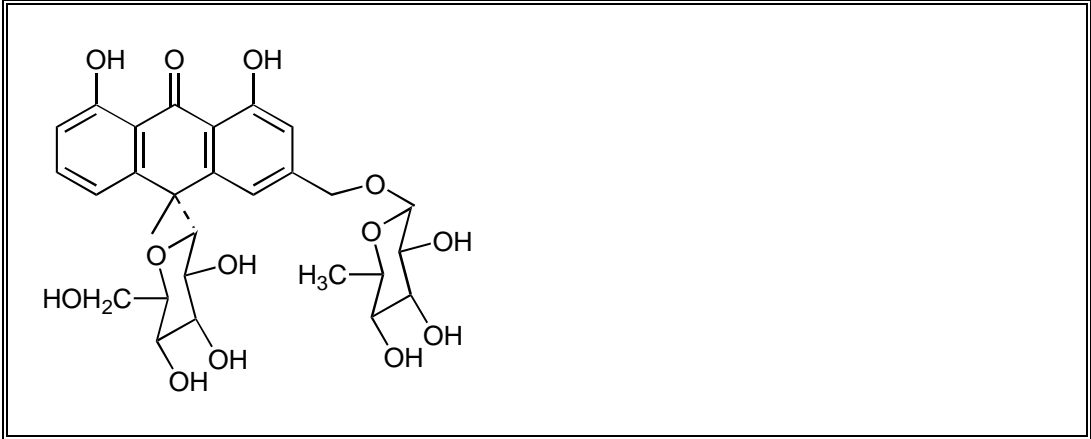
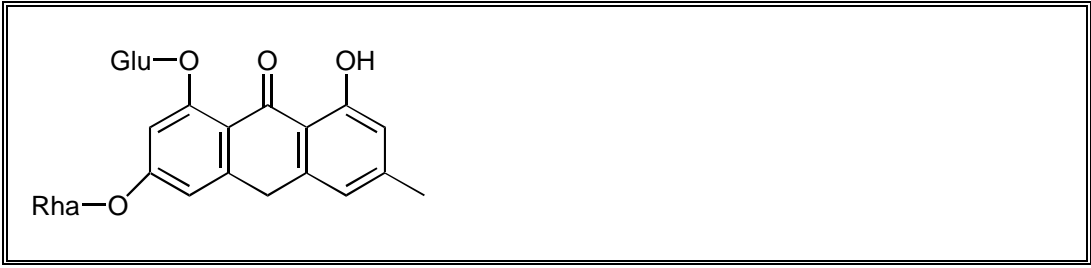
Gibberellane



Auxin

Lectin-like substances (e.g. Aloctin A), glycoproteins with the ability to bind to sugars, e.g. galactose.
Mannose-6-phosphate, Glucose-6-phosphate (probably from part of the polysaccharide chain in aloe).

Tannins



APPENDIX III

CLINICAL STUDIES

A summary of the clinical and animal studies carried out on *Aloe barbadensis* Miller and related species.

ASTHMA AND RELATED CONDITIONS

Afzal et al.¹ reports that the present study was prompted by a report on the efficacy of *A. barbadensis* extracts in treating adult bronchial asthma and pharyngitis. Extracts of above-ground parts contained endogenous arachidonic acid, a potential precursor for prostanoid synthesis. The presence of endogenous cyclooxygenase was established by radiometric assay. Relatively high proportions of PGE₂ (a bronchodilator) and TXB₂ (a bronchoconstrictor) and low proportions of other prostaglandins were identified in the plant extract when incubated with [14C]-arachidonic acid. There were also high percentages of phosphatidylcholine and cholesterol. It has been suggested that the enhancement of phagocytosis in adult bronchial asthma is due to the nondialysable material from the pulp fraction of the plant. However, this activity was only exhibited if the plant extracts were kept in the dark at 4-30°C for a period of 3-10 days. These storage conditions were just right for the hydrolysis of phospholipids, thus releasing arachidonic acid to synthesize prostanoids involving endogenously present cyclooxygenase as indicated by the results.

Yagi et al.² showed that a mixture of cysteine and proline (1:1) extracted from *Aloe arborescens var. natalensis* significantly enhanced the depressed phagocytosis of neutrophils in adult bronchial asthma.

WOUND HEALING

Swaim³ et al. describe the healing of open pad wounds in dogs, the Aloe-treated wounds had a smaller unhealed area than did untreated control wounds and wounds treated with antibiotics.

Davis⁴ reports that Aloe vera improves wound healing and inhibits inflammation. Since mannose-6-phosphate is the major sugar in the Aloe gel, the authors examined the possibility of its being an active growth substance. Mice receiving 300 mg/kg of mannose-6-phosphate had improved wound healing over saline controls. This dose also had anti-inflammatory activity. The function of mannose-6-phosphate in *A. vera* is discussed.

Fulton⁵. Full-face dermabrasion provided an ideal opportunity to document the effects of dressings on wound healing management. Following the procedure, the abraded face was divided in half. One side was treated with the standard polyethylene oxide gel wound dressings. The other side was treated with a polyethylene oxide gel dressing saturated with stabilized aloe vera.

The polyethylene oxide dressing provided an excellent matrix for the release of aloe vera gel during the initial 5 days of wound healing. By 24-48 hours there was dramatic vasoconstriction and accompanying reduction in edema on the aloe-treated side. By the third to fourth day there was less exudate and crusting at the aloe site, and by the fifth to sixth day the reepithelialization at the aloe site was complete. Overall, wound healing was approximately 72 hours faster at the aloe site. This acceleration in wound healing is important to reduce bacterial contamination, subsequent keloid formation, and/or pigmentary changes. The exact mechanism of acceleration of wound healing by aloe vera is unknown.

Davis et al.⁶. The influence of Aloe vera, orally and topically, on wound healing was studied. Wounds were induced on both sides of the vertebral column of ICR mice using a biopsy punch. For the oral study,

experimental animals received *A. vera* in their drinking water for 2 months, whereas the control animals received only water. In the topical study, experimental animals were given 25% *A. vera* in Eucerin cream topically. The control animals received cream only. A 62.5% reduction in wound diameter was noted in mice receiving 100 mg/kg/day oral *A. vera* and a 50.8% reduction was recorded in animals receiving topical 25% *A. vera*. These data suggest that *A. vera* is effective by both oral and topical routes of administration.

Watcher et al.⁷ Eight topical agents in current use were studied for their effects on wound contraction and rate of reepithelialization of full-thickness excisions using a porcine animal model. The following agents were applied daily for a period of 27 days: scarlet red ointment, benzoyl peroxide lotion, bacitracin ointment, silver sulfadiazine cream, aloe vera gel, tretinoin cream, capsaicin cream, and mupirocin ointment. The rate of reepithelialization was significantly enhanced by treatment with capsaicin, bacitracin, silver sulfadiazine, and scarlet red, and was markedly retarded by treatment with tretinoin. Wound contraction was significantly retarded by mupirocin, bacitracin, and silver sulfadiazine. Knowledge of the effects of topical agents on various aspects of healing allows the clinician to choose the most appropriate material to use in a given clinical situation to optimize the healing process and produce the best final result.

Davis et al.⁸ Aloe vera at doses of 100 and 300 mg/kg daily for 4 days blocked the wound healing suppression of hydrocortisone acetate up to 100% using the wound tensile strength assay. This response was because of the growth factors present in *A. vera* masking the wound healing inhibitors such as sterols and certain amino acids. The sterols showed good anti-inflammatory activity (-36%) in reducing the croton oil-induced ear swelling. This activity displayed a dose-response relationship.

Davis⁹ further examines wound healing in a further paper.

Fan et al.¹⁰ looked at hepatic lesions. The injection (10-15 ml/kg/d, ip x 4), total glycoside (125-225 mg/kg/d, ip x (3-4); 600 mg/kg/d, ig x 3) and crystal III (120 mg/kg/d, ip x 4) of *Aloe vera* var. *chinensis* were found to be effective in lowering the elevated sGPT induced by CCl₄, thioacetamide and D-aminogalactose in mice or rats. It was also observed that these agents could protect hepatic cells from the CCl₄-induced injury. When dogs were given in with Aloe injection of 0.1 ml/kg/d x 180, no toxicity was noted. The total effective sGPT-lowering rate of Aloe injection on 38 patients of chronic hepatitis with positive HBsAg was 86.8%.

Zawahry et al.¹¹ describe the use of aloe in treating leg ulcers.

Kligman¹² writes in his conclusions: It is our opinion that the *Aloe vera* materials tested did not interfere with the normal rate of superficial dermal wound re-epithelialisation nor did they enhance the process any faster than the covered non-treated control wounds at the end of three weeks. It can be stated that the wounds treated with *Aloe vera* healed better than uncovered wounds and were more cosmetically gratifying.

RADIOTHERAPY

Sato et al.¹³ report on the protective qualities of *Aloe arborescens* against radiation. Protective effects of *Aloe arborescens* (AA) on mouse skin injury induced by soft X-irradiation were examined. The mechanisms on radiation protection by measuring scavenge activity of activated oxygen, protective effects of nucleic acid, induction of antioxidative protein and so on were further investigated. Consequently a significant protective effect of skin injury was observed in AA S6-3-b. As the mechanisms of radiation protection in AA, the following matters were found. AA S6-3-b showed scavenge activity of hydroxyl radicals generated by Haber-Weiss reaction. AA S6-3-b suppressed the

changes of activity in superoxide dismutase and glutathione peroxidase at 7d after soft X-irradiation. Metallothionein was induced in the skin and liver against normal mice at 24 h after administration of AA S6-3-b.

Iena¹⁴ gives formulae of mixtures with aloe which may be used in domestic conditions for increasing the defensive forces of the body during radiation lesions.

Sato et al.¹⁵. Protective effects of *Aloe arborescens* (AA) on mouse skin injury induced by soft X-irradiation were examined. The mechanisms on radiation protection by measuring scavenge activity of activated oxygen, protective effects of nucleic acid, induction of antioxidative protein and so on were further investigated. Consequently a significant protective effect of skin injury was observed in AA S6-3-b. As the mechanisms of radiation protection in AA, the following matters were found. AA S6-3-b showed scavenge activity of hydroxyl radicals generated by Haber-Weiss reaction. AA S6-3-b suppressed the changes of activity in superoxide dismutase and glutathione peroxidase at 7d after soft X-irradiation. Metallothionein was induced in the skin and liver against normal mice at 24 h after administration of AA S6-3-b.

Lushbaugh and Hale¹⁶ looked at the experimental acute radiodermatitis following Beta Irradiation versus histopathological study of the mode of action of therapy with *Aloe vera*.

Their experiments showed objectively that *Aloe vera* has a remarkably curative effect upon radiodermatitis in the rabbit. It was found to increase greatly the development of the lesion by apparently doing away with the so-called latent period. Either as a result of earlier development of necrosis and ulceration, or from a specific effect upon the adjacent epithelium, re-epithelialisation occurred much earlier than usual and was more hypoplastic in character. The inhibition of the fibroplasia was also overcome earlier than usual so that new connective tissue was produced throughout the dermis as re-epithelialisation was occurring.

As a result of the enhancement of the healing processes, the damage to the original connective tissue seemed to be restricted and usually did not proceed so extensively as the untreated lesions. While in occasional treated specimens what appeared to be new capillaries were seen, granulation tissue did not actually develop, and defects were obliterated by fibroplasia and contraction of the connective tissue. No histological explanation could be found for the absence of telangiectatic vessels in the healed treated lesions other than that the treated ulceration, being shallower, might not have led to the exposure and subsequent elevation to the surface of the larger vessels of the deep dermis. Degenerative vascular changes secondary to the radiation appeared to be the same with or without treatment. These experimentally observed beneficial alterations in the course of the radiodermatitis treated with *Aloe vera* would seem to substantiate firmly previous clinical experiences with this plant in the treatment of human radiodermatitis.

No information was gained from these experiments concerning the mechanism by which *Aloe vera* produced these changes.

CHEMOTHERAPY

Nersesian et al.¹⁷. General and local nonspecific immunity was studied in 143 new cases of pulmonary tuberculosis (71 and 72 persons, respectively). The results showed that combination of chemotherapy using desensitizing agents and tissue preparations according to V. P. Filatov (a suspension of placenta tissue and aloe) had an immunomodulating effect. The efficacy of the combined chemotherapy amounted to 87 per cent with an account of the general immunity status.

IMMUNOLOGY

L.A. 't Hart et al.¹⁸ showed that biological activity of the polysaccharides was shown by the opsonization of zymosan in human pooled serum, their adjuvant activity on specific antibody production and the induction of delayed type hypersensitivity in mice.

REVIEW ARTICLES

Klein et al.¹⁹ reviews the literature on Aloe vera (*A. barbadensis*) and its products. *A. vera* is known to contain several pharmacologically active ingredients, including a carboxypeptidase that inactivates bradykinin in vitro, salicylates, and a substance(s) that inhibits thromboxane formation in vivo. Results of some studies offer evidence for antibacterial and antifungal properties of substance(s) in *A. vera*. Studies and case reports provide support for the use of *A. vera* in the treatment of radiation ulcers and stasis ulcers in man and burn and frostbite injuries in animals. The evidence for a potential beneficial effect associated with the use of *A. vera* is sufficient to warrant the design and implementation of well-controlled clinical trials.

Grindlay and Reynolds²⁰ - A review and discussion. The literature reviewed here provides evidence that *A. vera* [*A. barbadensis*] gel is of value for treating burns and certain other dermatological conditions and that it has definite physiological effects (although there is no certain correlation between these and the identified gel components).

GASTRIC ULCERS

Parmar et al.²¹ say that despite previous reports, no activity was found with *A. vera* [*barbadensis*] exudate or gel.

Davis et al.²² recommends Aloe vera as a natural approach for treating wounds, edema, and pain in diabetes.

BIOLOGICAL ACTIVITY

Yagi et al.²³ reported that three neutral polysaccharides (A, B and C) and a glycoprotein were isolated by gel filtration from a nondialyzable fraction of leaf extract. In vitro assays showed that polysaccharide C (which had a structural profile similar to that of the anti-tumour compound aloemmannan) and the glycoprotein had phagocytic activity.

Erazo et al.²⁴ reported on the humectant properties of a related aloe species. The gel and mucilage of *A. perryi* closely resembled those of *A. barbadensis*. The mucilages of both species were incorporated into oil/water emulsions (10%). Both increased the hydration of human skin to a similar extent when applied for 30 days.

Ralamboranto et al.²⁵. An immuno-modulator fraction (Alva) extracted from an endemic plant, in the south of Madagascar, the *Aloe vahombe*, significantly protects mice against bacterial, parasitic and fungal infections. Wishing to verify whether the fraction Alva was active in tumour reduction, we studied its effect on the development of experimental fibrosarcoma and melanoma in mice by intravenous and intracutaneous injections and injections directly into the tumour of the immunostimulant fraction. We have observed cures, only in the case of the McC3-1 tumour but it is encouraging to note that under different experimental conditions the rate of growth of tumours in animals which were treated is slower than in those not treated. The Alva fraction is a substance which is hydrosoluble, thermostabile, having a

molecular weight exceeding 30,000 and is a polysaccharide. The predominant sugars are glucose and mannose in 3:1 ratio. Preliminary studies of its action seem to indicate that the Alva fraction acts upon non-specific response and could possibly stimulate the phagocyte activity of the peritoneal macrophagus.

Michel, Pignon et al.²⁶ looked at a prospective study of the immunomodulator properties of i.m. administered "ALVA" extract in patients with solid tumors under a course of chemical immunosuppressive therapy.

Peng et al.²⁷ An extract from the parenchyma of *Aloe barbadensis* Miller shown to contain long chain polydispersed beta (1,4)-linked mannan polymers with random O-acetyl groups (acemannan, Carrisyn) was found to initiate the phagocyte production of monokines that supported antibody dependent cellular cytotoxicity and stimulated blastogenesis in thymocytes. Acemannan, in both enriched and highly purified forms, was administered intraperitoneally to female CFW mice into which murine sarcoma cells had been subcutaneously implanted. The rapidly growing, highly malignant and invasive sarcoma grew in 100% of implanted control animals, resulting in mortality in 20 to 46 days, dependent on the number of cells implanted.

Approximately 40% of animals treated with acemannan at the time of tumor cell implantation (1.5 x 10⁶ cells) survived. Tumors in acemannan-treated animals exhibited vascular congestion, edema, polymorphonuclear leukocyte infiltration, and central necrosing foci with hemorrhage and peripheral fibrosis. The data indicate that in vivo treatment of peritoneal macrophages stimulates the macrophage production of monokines, including interleukin-1 and tumor necrosis factor. The data further indicate that sarcomas in animals treated i.p. with acemannan at the time of tumor cell implantation were infiltrated by immune system cells, became necrotic, and regressed. The combined data suggest that acemannan-stimulated synthesis of monokines resulted in the initiation of immune attack, necrosis, and regression of implanted sarcomas in mice.

Sydiskis et al.²⁸ determined the extent of antiviral activity present in a number of plant extracts, hot glycerin extracts were prepared from *Rheum officinale*, *Aloe barbadensis*, *Rhamnus frangula*, *Rhamnus purshianus*, and *Cassia angustifolia* and their virucidal effects were tested against herpes simplex virus type 1. All the plant extracts inactivated the virus. The active components in these plants were separated by thin-layer chromatography and identified as anthraquinones. A purified sample of aloe emodin was prepared from aloin, and its effects on the infectivity of herpes simplex virus type 1 and type 2, varicella-zoster virus, pseudorabies virus, influenza virus, adenovirus, and rhinovirus were tested by mixing virus with dilutions of aloe emodin for 15 min at 37 degrees C, immediately diluting the sample, and assaying the amount of infectious virus remaining in the sample. The results showed that aloe emodin inactivated all of the viruses tested except adenovirus and rhinovirus. Electron microscopic examination of anthraquinone-treated herpes simplex virus demonstrated that the envelopes were partially disrupted. These results show that anthraquinones extracted from a variety of plants are directly virucidal to enveloped viruses.

Fujita et al.²⁹ looked at the effect of leaf extracts of *Aloe arborescens* Mill subsp. *natalensis* Berger on growth of *Trichophyton mentagrophytes*.

Brossat et al.³⁰ A partially purified extract of leaves of *Aloe vahombe*, a plant endemic in the south of Madagascar, administered intravenously to mice, protects them against infection of bacteria (*Listeria monocytogenes*, *Yersinia pestis*), parasites (*Plasmodium berghei*) and fungus (*Candida albicans*). The protective fraction must be administered two days before inoculation of the pathogenic agent. These results significantly confirm those we obtained in earlier study on mice infection by *Klebsiella pneumoniae*. Currently we are testing the protective action of the purified extract on the experimental development of sarcomas, and we are in the process of analysing the mode of action of this non specific immunostimulant.

Winters et al.³¹ Fractions of leaf extracts from *Aloe barbadensis* (AVB) and *A. saponaria* were prepared by differential centrifugation and tested by in vitro assays for the presence of lectin-like activities. Fractions were also tested for effects on the attachment and growth of human normal fetal lung (HFL) and human cervical carcinoma (ME180) cells grown on confluent plates and monitored by hemagglutination (HA) and immunodiffusion (ID) tests. Comparable fractions from all *Aloe* sources after separation had approx the same ratio of recoverable supernatant fluids to high speed pellet materials. In ID tests all *Aloe* sources reacted with human and baboon sera, and none of the fractions reacted with canine sera from normal and two tumor-bearing adult dogs.

Human RBC were more sensitive indicators of HA than canine RBC for tests of *Aloe* fractions, while both human and canine RBC were equally sensitive in HA tests of the control lectin, Concanavalin A. Neither HFL or ME180 cells in single cell suspensions were aggregated when mixed with dilutions of AVB fractions. Attachment of HFL cells was markedly enhanced by 1:10 dilutions of concentrated, particle-free supernatant. Counts Of cells at the edges of wounds in monolayer HFL and ME180 cell cultures treated with AVB were higher than cell densities at wound edges in other cultures treated with high speed supernatant and pellet fractions or those in untreated cultures. Treatment of monolayer cultures of both cells with fractions of a 'stabilized' commercial *A. vera* gel caused marked cellular granularity and inhibition of attachment of cells within 2 days. These cytotoxic responses prevented the completion of cell attachment and growth experiments using *A. vera* gel fractions. (17 Refs)

BURNS

Yagi et al.³² reported on the effect of *aloe* lectin on deoxyribonucleic acid synthesis in baby hamster kidney cells. It is suggested that this lectin may be responsible for the therapeutic effect of *aloe* gel on burns.

Strickland³³ investigated the ability of *Aloe barbadensis* gel extract to prevent suppression of contact hypersensitivity (CHS) and delayed-type hypersensitivity (DTH) responses in mice by ultraviolet (UV) irradiation. Topical application of 0.167-1.67% *Aloe* gel after each irradiation significantly reduced this suppression. *Aloe* treatment partially preserved the number and morphology of Langerhans and Thy-1+ dendritic epidermal cells in skin, compared to those in the skin of mice given only UVR or UVR plus the vehicle. Experiments using a single (2 kJ/m²) dose of UVR followed by *Aloe* treatment showed that the effect of *Aloe* was not due to screening of the UVR. Treatment of the UV-irradiated skin with *Aloe* immediately after irradiation prevented suppression of both DTH to *Candida* and CHS to FITC. *Aloe* treatment did not prevent the formation of cyclobutyl pyrimidine dimers in the DNA of UV-irradiated skin or accelerate the repair of these lesions. These studies demonstrate that topical application of *Aloe barbadensis* gel extract to the skin of UV-irradiated mice ameliorates UV-induced immune suppression by a mechanism that does not involve DNA damage or repair.

Crowell et al.³⁴ *Aloe vera* does not affect cutaneous erythema and blood flow following ultraviolet B exposure.

Rodriguez-Bigas³⁵. An experimental study was designed using Hartley guinea pigs, who received full-thickness burns covering 3 percent of their body surface area by direct contact with a hot plate. A total of 40 animals were equally divided among four modalities of closed burn wound management as follows: group I: silver sulfadiazine (Silvadine); group II: *aloe vera* gel extract (Carrington Dermal Wound Gel); group III: salicylic acid cream (aspirin); and group IV: plain gauze occlusive dressing only. The dressings were changed daily, and the size and appearance of each burn wound were recorded until complete healing. On the sixth postburn day, quantitative burn wound cultures were made. The average time to complete healing in the control group was 50 days, and the only significant difference was found in the *aloe vera*-treated animals, which healed on an average of 30 days (p less than 0.02).

Wound bacterial counts were effectively decreased by silver sulfadiazine ($p = 0.015$) and by aloe vera extract ($p = 0.015$). From our data it appears that aloe gel extracts permit a faster healing of burn wounds.

McCauley³⁶ says that if frostbite is to be treated successfully, direct and indirect effects of injury must be understood. Rapid rewarming helps to preserve tissue by limiting the amount of direct cellular injury. Selective management of blisters helps protect the subdermal plexus, and application of Aloe vera cream (eg, Dermaide Aloe Cream) combats the local vasoconstrictive effects of thromboxane. Oral administration of ibuprofen decreases systemic levels of thromboxane.

Cera et al³⁷. A therapeutic protocol that included topical and systemic administration of a thromboxane inhibitor was used to successfully treat a burned Rhesus monkey. Accidental exposure of the animal to steam and water (180°C) for 5 minutes had caused full-thickness dermal injury to its entire body surface area (BSA). Animals with full-thickness burns involving more than 50% BSA are generally regarded as having remote chances of recovery. Based on the favourable outcome obtained, the therapeutic protocol that was used for this monkey is advocated for general use.

Rovatti et al.³⁸ looked at a comparative study of the immediate and delayed histopathological changes of the skin in untreated and treated thermal burns. Their conclusions based on gross and microscopic observations showed that in deep dermal burns an eschar forms and separates microscopically in 24 to 48 hours and grossly the eschar separated in 10 to 14 days if the skin is not treated with ointment after burning.

The study of the burned skin in the untreated group, showing this clear cut separation and demarcation, suggest that early treatment should be directed toward the prevention of the changes which produce the eschar within the first 24 hours.

The first group I (treated with Aloe-Creme ointment): The skin burned and treated with Aloe-Creme ointment remained pliable and soft during the first week with slight and continuous superficial debridement of the upper dermis and without gross or microscopic separation of an eschar. These lesions healed in two weeks without gross evidence of scarring.

The second group II (treated with Aloe-Creme Ointment containing cysteine): Identical burns treated with Aloe-Creme Ointment containing 5% cysteine showed during the second week more superficial debridement than observed in animals of group I. There was no gross or microscopic separation of an eschar and no gross scarring occurred. There was little or no difference between this group and group I.

The third group, (treated with trinitrophenol ointment): the appearance of the skin was comparable during the first 24 hours to that observed in Groups I and II. Then these lesions became grossly and microscopically haemorrhagic and the separation of an eschar was evident microscopically at 24 hours. None of the animals survived the tenth day and haemorrhages were found in the skin at the end of the first week.

The fourth group IV (treated with petrolatum and gauze): during the first three days there was a gradual development of congestion, oedema and focal haemorrhages of the skin area in these burns. Microscopically an eschar did develop and separate during the first 48 hours. By the end of the first week there were numerous haemorrhages and several small abscesses. At the end of the second week the entire dermis was debriding in large masses and the lesions healed by scarring during the third and fourth week.

Cera et al.³⁹. It is generally accepted that in the canine species with a 50% or more partial or full thickness burn over the body surface area (BSA), recovery is remote and euthanasia is recommended.

They presented two case histories where a therapeutic modality employing an Aloe vera cream (Dermaide Aloe) and tablets, reversed the dermal ischemia of burns due to prostaglandins and abrogated a *Pseudomona aeruginosa* infection in animals with over a 35% burn.

Both bacteriological and immunohistochemical data presented confirms the bactericidal and antiprostaglandin effect of Aleo cream/ Dermaide Aloe) and substantiates its efficacy in the management and treatment of thermal injuries in the canine species.

ANTI-INFLAMMATORY

Davis⁴⁰ showed that administration of air under the skin produced a pouch wall that closely resembled a synovium in that the inner lining was made up of macrophages and fibroblasts. Administration of 1% carrageenan directly into the 7-day-old air pouch produced an inflammation characterized by an increased number of mast cells in pouch fluid as well as an increase in wall vascularity. A punch biopsy weight of the pouch wall did not reveal an increase in 1% carrageenan-treated animals. However, a 10% Aloe vera treatment of carrageenan-inflamed synovial pouches reduced the vascularity 50% and the number of mast cells in synovial fluid 48%. The pouch wall punch biopsy weight was increased by A. vera, which was verified by histologic examination of the inner synovial lining. Aloe vera stimulated the synovial-like membrane, as evidenced by an increased number of fibroblasts, suggesting that A. vera stimulated fibroblasts for growth and repair of the synovial model. The synovial air pouch can be used to study simultaneously the acute anti-inflammatory and fibroblast stimulating activities of A. vera.

Davis et al.⁴¹. An Aloe vera extract was prepared with 50% ethanol. The resultant supernatant and precipitate were tested for anti-inflammatory activity using the croton oil-induced ear-swelling assay. The supernatant fraction decreased inflammation, when applied topically, by 29.2%, and the precipitate decreased inflammation by 12.1%. The authors have shown that the anti-inflammatory activity (inhibitory system) resides in the supernatant of a 50% ethanol extract.

Davis et al.⁴² found in the present work, the precipitate fraction decreased the wound diameter by an average of 47.1% (stimulatory system). Little or no wound healing activity was found in the supernatant. Aloe vera appears to act as a modulatory system toward wounds and inflammation and is a potentially valuable tool for managing lower extremity conditions.

't Hart et al.⁴³. In traditional South-East Asian medicine the therapeutic value of the parenchymous leaf-gel of Aloe vera for inflammatory-based diseases is well-reputed. The aim of this study is to investigate at which level gel-constituents exert their activity. We show here that low -Mr constituents of an aqueous gel-extract inhibit the release of reactive oxygen species (ROS) by PMA-stimulated human PMN. The compounds inhibit the ROS-dependent extracellular effects of PMN such as lysis of red blood cells. The capacity of the PMN to phagocytose and kill micro-organisms at the intracellular level is not affected. The inhibitory activity of the low-Mr compounds is most pronounced in the PMA-induced ROS production, but is significantly antagonized by the Ca-ionophore A23187. It is shown that the inhibitory effect of the low-Mr compounds is the indirect result of the diminished availability of intracellular free Ca-ions.

There exists some conflicting data...

Schmidt et al.⁴⁴ evaluated the time interval required for wound healing using a standard wound management protocol with and without aloe vera gel. Twenty-one women were studied who had wound complications requiring healing by second intention after cesarean delivery or laparotomy for gynecologic surgery. Wounds treated with standard management healed in a mean (+/- SD) time interval of 53 +/- 24 days, whereas those treated with aloe vera gel required 83 +/- 28 days (P = .003). The use of

aloe vera dermal wound gel was associated with a significant delay in wound healing compared with treatment with an otherwise identical regimen that did not include aloe vera.

Hunter et al.⁴⁵ Three women and one man aged forty-one to sixty-five years experienced a severe burning sensation following the application of aloe vera or vitamin E preparations to a skin area that had been subjected to a chemical peel or dermabrasion. Subsequently, a severe dermatitis occurred that required hospitalization of one patient and intravenous administration of steroids. The dermatitis abated very slowly in all patients: full recovery took three months or more. One patient resumed the use of vitamin E creams two years after the episode of dermatitis and experienced no adverse effect. Patients undergoing dermabrasion or chemical peel procedures should be cautioned specifically against the use of aloe vera or vitamin E topically in the first weeks after surgery.

Davis et al.⁴⁶ Aloe vera preparations were evaluated for topical anti-inflammatory activity using the croton oil-induced edema assay. The results show that small amounts of A. vera given topically will inhibit inflammation induced by a moderate amount of irritant. In general, the decolorized Aloe was more effective than the colorized Aloe (with anthraquinone). A 47.1% inhibition of inflammation was obtained by 5% decolorized irradiated Aloe. These results may be used as a baseline to assess the biologic activity of A. vera in the treatment of inflammation by podiatric physicians.

Davis et al.⁴⁷ The authors have evaluated the spectrum of anti-inflammatory activity of A. vera in a number of models of inflammation in the hind paw of the experimental rat induced by kaolin, carrageenan, albumin, dextran, gelatin, and mustard. Croton oil was used in a topical model of inflammation to determine the oral activity and time-dependent dosing of A. vera. The authors found that A. vera was active in all models of inflammation.

Of the various irritants tested, A. vera was especially active against gelatin-induced and kaolin-induced edema and, in contrast, had minimal activity when tested against dextran-induced edema. Oral activity of A. vera was demonstrated to be dependent on the presence of anthraquinones. The various irritant-induced edema models provided a broad spectrum of anti-inflammatory activity for A. vera.

Davis et al.⁴⁸ Aloe vera inhibits inflammation and adjuvant-induced arthritis. The authors' laboratory has shown that A. vera improves wound healing, which suggests that it does not act like an adrenal steroid. Diabetic animals were used in this study because of their poor wound healing and anti-inflammatory capabilities. The anti-inflammatory activity of A. vera and gibberellin was measured in streptozotocin-induced diabetic mice by measuring the inhibition of polymorphonuclear leukocyte infiltration into a site of gelatin-induced inflammation over a dose range of 2 to 100 mg/kg. Both Aloe and gibberellin similarly inhibited inflammation in a dose-response manner. These data tend to suggest that gibberellin or a gibberellin-like substance is an active anti-inflammatory component in A. vera.

Davis et al.⁴⁹ Aloe vera improves wound healing and inhibits inflammation. Since mannose-6-phosphate is the major sugar in the Aloe gel, the authors examined the possibility of its being an active growth substance. Mice receiving 300 mg/kg of mannose-6-phosphate had improved wound healing over saline controls. This dose also had anti-inflammatory activity. The function of mannose-6-phosphate in A. vera is discussed.

Davis et al.⁵⁰ Aloe vera, as a biological vehicle for hydrocortisone 21-acetate, was tested topically and systemically against acute inflammation. Systemically, the combination of A. vera and hydrocortisone produced a maximum 88.1% inhibition of edema. Polymorphonuclear leukocyte infiltration was reduced 91.1%. The topical inhibition of edema peaked at 97%. The possibility that A. vera has significant potential as a biologically active vehicle for steroids is discussed.

Davis et al.⁵¹ examines topical anti-inflammatory activity of Aloe vera as measured by ear swelling.

Davis^{52,53} examines another aspect of the anti-inflammatory activity in relation to arthritis.

Saito et al.⁵⁴ found a glycoprotein, Aloctin A, which was isolated from Aloe arborescens Mill, markedly inhibits adjuvant arthritis in rats and carrageenin-induced edema in rats.

Timchenko et al.⁵⁵ described a complex method of treating chronic inflammatory diseases of the internal female genitalia of nonspecific etiology.

Swingle et al.⁵⁶ look at the anti-inflammatory effects of aloe vera on various induced inflammations using croton oil and cantharidin.

BLOOD

Ajabnoor⁵⁷. The acute and chronic effects of the exudate of Aloe barbadensis leaves and its bitter principle were studied on plasma glucose levels of alloxan-diabetic mice. Aloes was administered orally, 500 mg/kg, and the bitter principle was administered intraperitoneally, 5 mg/kg. The hypoglycemic effect of a single oral dose of aloes on serum glucose level was insignificant whereas that of the bitter principle was very highly significant and extended over a period of 24 h with maximum hypoglycemia observed at +8 h. In chronic studies, aloes was administered twice daily and the bitter principle was administered once a day for 4 days. The maximum reduction in plasma glucose level was observed at the 5th day in both cases. The hypoglycemic effect of aloes and its bitter principle may be mediated through stimulating synthesis and/or release of insulin from the beta-cells of Langerhans.

CORNEAL or OCULAR

Lawrence⁵⁸ recommends aloe vera for treatment for flash burns of the conjunctiva.

Bakurskaia⁵⁹ examined the effects of tissue therapy and vitamin therapy on unconditioned vascular reflexes and intraocular pressure in glaucomatous patients.

Dumbrova et al.⁶⁰ examined the effect of aloe on the resistance of the optic nerve system of the eye.

Mortada et al.⁶¹ describe the use of aloe extracts in the treatment of experimental corneal ulcers.

APPENDIX IV

TOXICITY

A summary of the toxicity studies carried out on *Aloe barbadensis* Miller and related species.

Literature survey.

Jeffrey Bland¹ evaluates the effects of oral Aloe vera juice supplementation on gastric pH, stool specific gravity, protein digestion/absorption, and stool microbiology. Results indicate that supplemental oral Aloe Vera juice is well tolerated by most gastrointestinal parameters. A discussion of the potential role of Aloe vera juice on inflammatory bowel disorders based upon this work is presented. No adverse reports noted, improved bowel motility, reduced flatulence and improved colonic bacterial function are recorded.

The Dawson Research Corporation² showed Aloe vera Lipo Quinone extract administered orally to 20 nine to ten week old Charles River outbred albino rats at a dosage of 16 g/kg caused very slight depression three hours after dosing in all rats and soft cream-coloured faeces 7-8 hours after dosing. No other effects were seen during the 14 day post dosing observation period. The LD50 of this compound is greater than 16 g/kg.

The Dawson Research Corporation³ also showed Aloe vera aqueous gel administered in a single oral dose at 16 g/kg to 10 male and 10 female 7-8 week old Charles River outbred albino rats caused slight depression for about ONE hour in all rats. No other effects were seen. The LD50 of this compound is greater than 16 g/kg.

Food and Drug Research Laboratories Inc.⁴ looked at AVA Aloe vera gel-A. 10 repeated Insult patch test, 52 subjects completed test; 9 subjects discontinued for personal reasons and **not** because of adverse reactions to the test product; 2 subjects violated the protocol and discontinued. Only **slight transient reactions** were observed during testing. Under 10 RIPT experimental procedures, aloe vera gel **did not induce irritation nor sensitisation** in human subjects.

Council of Europe⁵ under toxicological data, have tested the eye irritation in animals, skin irritation in animals and mutagenicity. No adverse effects were recorded and so the material is classified as Group 3 (recommended for use).

Morimoto et al.⁶ carried out the mutagenicity screening of crude drugs with Bacillus subtilis rec. assay and Salmonella/microsome reversion assay and found no adverse results.

Further tests carried out by InVitro International⁷ show excellent '*in vitro*' results.

100% / 100µl

In Eytex UMA class minimal, predicted in vivo minimal - EDE 5.40

In Eytex UMA class minimal, predicted in vivo minimal - EDE 7.50

100% / 200µl

In Eytex HSA EDE 3.00 Class Non-irritant/Minimal

100% / 300µl

In Eytex HSA EDE 2.90 Class Non-irritant/Minimal

The results indicate extremely safe to use in vitro.

Danof IE and McAnalley⁸ found that an EC50 value of any test material in the '*in vitro*' system is inversely related to its toxicity potential; however, an EC50 value could not be calculated for the test material labelled as 0205-0 in this assay since this material was essentially non-toxic (EC50 >> 100%). In fact, this test material appears to have caused a stimulation of cellular activity, such that this material enhances cellular activity and viability instead of causing toxicity.

A search on potential carcinogenicity showed no evidence available.

NTP7:	none
IARC Monograph:	none
OSHA regulated	none

Fan et al.⁹ studied the protective effect of extracts from Aloe vera L. var. chinensis (Haw.) Berg. on experimental hepatic lesions and a primary clinical study on the injection of in patients with hepatitis. When dogs were given in with Aloe injection of 0.1 ml/kg/d x 180, no toxicity was noted.

Winters et al.¹⁰ studied the effects of aloe extracts on human normal and tumour cells in vitro. Treatment of monolayer cultures of both cells with fractions of a 'stabilized' commercial A vera gel caused marked cellular granularity and inhibition of attachment of cells within 2 days. These cytotoxic responses prevented the completion of cell attachment and growth experiments using A vera gel fractions.

Parry et al.¹¹ showed the effects of crude extracts (500 mg/kg IP and 500-1000 mg/kg PO) of three species of aloes in rats and mice particularly as regards their abortifacient actions. The LD50 values were as follows: A. globuligemma < 250 mg/kg IP; A. chabaudii 250-500 mg/kg IP; A. cryptopoda > 1500 mg/kg IP Thus the most toxic was A. globuligemma. Their most visibly striking toxic effects in rats were CNS depression, and post mortem investigations showed widespread haemorrhagic lesions. Administration of the aloes to pregnant mice and rats did not cause expulsion or resorption of the foetuses. Rats which survived the treatment delivered normal sized, healthy litters at term. It was suggested that the aloe species tested did not possess abortifacient activity.

Spoerke and Ekins¹² reports aloe vera as harmless and non-toxic.

However, Morrow et al.¹³ reports that a few people might have experienced an adverse reaction. A single case is described.

Imanishi et al.¹⁴ report that the aloe is not cytotoxic.

Solar et al.¹⁵ found that neither bactericide nor bacteriostatic activity has been detected in Aloe extract, though mice were protected against the infection caused by the Klebsiella, a pneumonia vector to man, giving rise to an experimental septicaemia in the mouse.

Ajabnoor¹⁶ found in alloxan-diabetic mice, a single oral dose (500 mg/kg) of the exudate of Aloe barbadensis leaves had no significant effect on serum glucose level. However, intraperitoneal administration of the bitter principle (5 mg/kg) had a highly significant effect. In chronic studies in which aloes was given twice daily or the bitter principle was given once daily for 4 days, the maximum decrease in plasma glucose level was observed on the 5th day in both cases.

Krumbiegel et al.¹⁷ Therapeutic doses of two laxatives (Agiolax and Sennatin) were repeatedly administered to 10 healthy volunteers in a two-way change-over design. Blood samples were collected up to 96 h after the first dose, and plasma levels of total aloe-emodin and rhein were determined simultaneously with a sensitive (lower limit of quantification: 0.5 ng aloe-emodin and 2.5 ng rhein per

millilitre plasma) and specific fluorometric HPLC method. Aloe-emodin was not detectable in any plasma sample of any subject. Rhein concentration time courses showed highest levels of 150-160 ng/ml and peak maxima at 3-5 h and 10-11 h after dosing probably according to absorption of free rhein and rhein released from prodrugs (e.g. sennosides) by bacterial metabolism, respectively.

Hunter et al.¹⁸ Three women and one man aged forty-one to sixty-five years experienced a severe burning sensation following the application of aloe vera or vitamin E preparations to a skin area that had been subjected to a chemical peel or dermabrasion. Subsequently, a severe dermatitis occurred that required hospitalization of one patient and intravenous administration of steroids. The dermatitis abated very slowly in all patients: full recovery took three months or more. One patient resumed the use of vitamin E creams two years after the episode of dermatitis and experienced no adverse effect. Patients undergoing dermabrasion or chemical peel procedures should be cautioned specifically against the use of aloe vera or vitamin E topically in the first weeks after surgery.

Lang¹⁹ reported that after oral administration of 4.5 mg/kg ¹⁴C-aloe emodin (AE) to rats 20-30% of the dose was excreted in urine and the rest in feces. AE was quickly metabolized to rhein, to an unknown metabolite and to conjugates of all three. In the plasma about 10% of ¹⁴C-activity was identified as free AE. Maximum plasma values were reached 1.5-3 h p.a. with 248 (male) and 441 (female) ng equivalents AE/ml. Maximum concentrations in plasma were about 3 times higher than those in ovaries and 10 times higher than those in testes. Only liver, kidney and intestinal tract showed higher concentrations than plasma. Terminal half-life (for radioactivity) in blood was about 50 h.

Agarwal²⁰ reported on five thousand patients of atheromatous heart disease, presented as angina pectoris, were studied over a period of five years. After adding the 'Husk of Isabgol' and 'aloe vera' (an indigenous plant known as ghee-guar-ka-paththa) to the diet, a marked reduction in total serum cholesterol, serum triglycerides, fasting and post prandial blood sugar level in diabetic patients, total lipids and also increase in HDL were noted. Simultaneously the clinical profile of these patients showed reduction in the frequency of anginal attacks and Gradually, the drugs, like verapamil, nifedipine, beta-blockers and nitrates, were tapered. The patients, most benefitted, were diabetics (without adding any antidiabetic drug). The exact mechanism of the action of the above two substances is not known, but it appears, that probably they act by their high fibre contents. Both these substances need further evaluation. The most interesting aspect of the study was that no untoward side effect was noted and all the five thousand patients are surviving till date.

Hogan²¹ reports an adverse event of widespread dermatitis after topical treatment of chronic leg ulcers and stasis dermatitis.

Ishii²² The mechanism of action of aloe-emodin-9-anthrone, a decomposition product of barbaloin, in causing a significant increase in the water content of the rat large intestine, was investigated. Aloe-emodin-9-anthrone inhibited rat colonic Na⁺, K⁽⁺⁾-adenosine triphosphatase (ATPase) in vitro, and increased the paracellular permeability across the rat colonic mucosa in vivo. Therefore, it seemed that the increase in water content of the rat large intestine produced by aloe-emodin-9-anthrone was due to both inhibition of absorption and stimulation of secretion without stimulation of peristalsis. Furthermore, pretreatment with loperamide, an antidiarrheal agent, completely prevented the increase of paracellular permeability induced by aloe-emodin-9-anthrone but did not completely reduce the concomitant increase in residual fluid volume. These findings suggest that aloe-emodin-9-anthrone has multiple mechanisms of action involved in the increase of water content in the rat large intestine.

Ishii²³ reports that Charcoal transport, as an indicator of the degree of peristalsis, and water content in the large intestine after the intracaecal administration of barbaloin, were measured simultaneously in the same rat. Charcoal transport was significantly accelerated at both 3.5 and 6.5 h after the administration of barbaloin. At 6.5 h, diarrhea instead of normal faeces was observed. Moreover, at 1 h before the

acceleration of charcoal transport, a marked increase in the relative water content of the large intestine was observed. It appears that the increase in water content of the large intestine induced by barbaloin precedes the stimulation of peristalsis, attended by diarrhea. Therefore, it is suggested that the increase in water content is a more important factor than the stimulation of peristalsis in the diarrhea induced by barbaloin.

Ishii²⁴ Aloe-emodin-9-anthrone(AE-anthrone), produced from barbaloin in the rat large intestine, caused not only an increase in the intestinal water content but also stimulated mucus secretion. This might play an important role in the occurrence of diarrhea. It was demonstrated that the amount of AE-anthrone produced in the rat large intestine(maximal amount: 568 micrograms/rat at 4 h after injection) was enough to cause both of these effects, which were observed following intracecal administration of barbaloin (31.1 mg/kg). These results together with our previous data, which showed a relationship between increase in the intestinal water content and the stimulation of peristalsis, confirm that AE-anthrone is the principal agent responsible for the cathartic effect of barbaloin. We also propose that the increase in water content is a more important factor than stimulation of peristalsis in the induction of diarrhea by barbaloin.

Nakamura²⁵ and Shoji²⁶ report on two cases of contact dermatitis

Hirata et al²⁷. Aloenin has been established to be 4-methoxy-6-(2-beta-D-glucopyranosyloxy-4-hydroxy-6-methylphenyl)-2-pyrone; it shows an inhibitory activity for gastric juice secretion. Rats metabolized it to 4-methoxy-6-(2,4-dihydroxy-6-methylphenyl)-2-pyrone, 2,5-dimethyl-7-hydroxychromone and glucose, which were excreted in the feces and the urine. The distribution of the radioactivity originating from ¹⁴C-labeled aloenin was studied. The tracer found in the kidney and the liver reached 60% of the amount administered 24 h after feeding and decreased rapidly in the next 24 h.

Ghannam et al.²⁸ investigated the property that the dried sap of the aloe plant (aloes) has an ability to lower the blood glucose was studied in 5 patients with non-insulin-dependent diabetes and in Swiss albino mice made diabetic using alloxan. During the ingestion of aloes, half a teaspoonful daily for 4-14 weeks, the fasting serum glucose level fell in every patient from a mean of 273 +/- 25 (SE) to 151 +/- 23 mg/dl (p less than 0.05) with no change in body weight. In normal mice, both glibenclamide (10 mg/kg twice daily) and aloes (500 mg/kg twice daily) induced hypoglycaemia after 5 days, 71 +/- 6.2 and 91 +/- 7.6 mg/dl, respectively, versus 130 +/- 7 mg/dl in control animals (p less than 0.01); only glibenclamide was effective after 3 days. In the diabetic mice, fasting plasma glucose was significantly reduced by glibenclamide and aloes after 3 days. Thereafter only aloes was effective and by day 7 the plasma glucose was 394 +/- 22.0 versus 646 +/- 35.9 mg/dl, in the controls and 726 +/- 30.9 mg/dl in the glibenclamide treated group (p less than 0.01). We conclude that aloes contains a hypoglycaemic agent which lowers the blood glucose by as yet unknown mechanisms.

Siegers²⁹. In a model of dimethylhydrazine-induced colorectal tumors in male mice aloin- or sennoside-enriched diets (0.03%) did not promote incidence and growth of adenomas and carcinomas after 20 weeks. Furthermore, in anthranoid-fed mice no significant changes in serum electrolytes as well as parameters of hepato- and nephrotoxicity were observed.

Kim³⁰. In order to investigate chemopreventive effect of Aloe (*Aloe barbadensis*), benzo(a)pyrene (B(a)P; 500 mg/kg) was orally administered to male ICR mice and B(a)P diol epoxide-I-DNA (BPDE-I-DNA) adducts were quantitated for 16 days following daily treatment of Aloe (2500 mg/kg) by ELISA (enzyme linked immunosorbent assay) using monoclonal antibody 8E11. BPDE-I-DNA adduct formation was significantly inhibited and DNA repair was enhanced in various organs (liver, kidney, stomach, lung) (p less than 0.001) from ICR mice daily treated with Aloe. When mice were pretreated with Aloe for 16 days before B(a)P treatment, inhibition of BPDE-I-DNA adduct formation and DNA

repair were more efficiently carried out. These data suggest that Aloe have a significant effect on the inhibition of BPDE-I-DNA adduct formation and DNA repair in ICR mice and it may have a possible role in chemoprevention of human cancer.

APPENDIX V

REFERENCES

UNCARIA

Uncaria sinensis

Uncaria rhynchophylla

Uncaria spp.

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The investigation on steroidal fraction of *Uncaria tomentosa*, commonly called Una de gato, showed the presence of beta-sitosterol (60%), stigmasterol, and campesterol. The percentage of sterols have been carried out by GLC. The spectroscopic data 1H-NMR and MS of the three compounds are also reported, with the beta-sitosterol as the main sterol. Preliminary pharmacological investigations prove a moderate antiinflammatory activity.
5. Harada M Ozaki Y Ohno H: Effects of indole alkaloids from *Gardneria nutans* Sieb. et Zucc. and *Uncaria rhynchophylla* Miq. on a guinea pig urinary bladder preparation in situ. Chem Pharm Bull (Tokyo) (1979 May) 27(5):1069-74. [No abstract available]
6. Harada M Ozaki Y: Effect of indole alkaloids from *Gardneria* genus and *Uncaria* genus on neuromuscular transmission in the rat limb in situ. Chem Pharm Bull (Tokyo) (1976 Feb) 24(2):211-4. [No Abstract Available]
7. Harada M Ozaki Y Sato M: Ganglion blocking effect of indole alkaloids contained in *Uncaria* genus and *Amsonia* genus and related synthetic compounds on the rat superior cervical ganglion in situ. Chem Pharm Bull (Tokyo) (1974 Jun) 22(6):1372-7. [No Abstract Available]
8. Qin CL Liu JY Cheng ZM Jiao Y: [Experimental studies on *Uncaria sinensis* (Oliv.) Havil and *Achyranthes bidentata* Blume and their compacity]. Chung Kuo Chung Yao Tsa Chih (1994 Jun) 19(6):371-3, 384 (Published in Chinese).

Pharmacological studies were conducted on *Uncaria sinensis* and *Achyranthes bidentata* both separately and combined. Comparison was made on the hypotensive effect on normal and renal-type hypertensive rats as well anti-spasmodic and sedative effects in mice. The results showed that *Uncaria sinensis* and *Achyranthes bidentata* have obvious synergic action in compatibility.

9. Liu GX Huang XN Peng Y: [Hemodynamic effects of total alkaloids of *Uncaria macrophylla* in anesthetized dogs] Chung Kuo Yao Li Hsueh Pao (1983 Jun) 4(2):114-6. (Published in Chinese). [No Abstract Available].

10. de Matta SM Monache FD Ferrari F Marini-Bettolo GB: Alkaloids and procyanidins of an *Uncaria* sp. from Peru. *Farmaco [Sci]* (1976 Jul) 31(7):527-35.

The alkaloid and procyanidin composition of *Uncaria* sp. from eastern Peru, used in folk medicine was studied. Five alkaloids have been separated and identified as pteropodine, speciophylline, isopteropodine, uncarine F and isomytraphylline, all belonging to the oxindole group characteristic of the Rubiaceae. Moreover (--) epicatechin and four dimeric procyanidins A1, B1, B2 and B4 have been shown to constitute the polyphenolic fraction of the plant extract.

11. Chan KC Morsingh F Yeoh GB: Alkaloids of *Uncaria pteropoda*. Isolation and structures of pteropodine and isopteropodine. *J Chem Soc [Perkin 1]* (1966) 24:2245-9. [No Abstract Available].

12. Phillipson JD Hemingway SR: Chromatographic and spectroscopic methods for the identification of alkaloids from herbarium samples of the genus *Uncaria*. *J Chromatogr* (1975 Feb 19) 105(1):163-78.

A combination of thin-layer chromatography, gas-liquid-chromatography, ultraviolet spectroscopy and mass spectrometry techniques for the alkaloid screening of herbarium samples of the genus *Uncaria* (Rubiaceae) is described. Some sixty alkaloids are distinguished by the screening procedure, and they represent heteroyohimbine, oxindole, roxburghine, simple beta-carboline, pyridino-indolo-quinolizidinone and gambirtannine types.

13. Chang P Koh YK Geh SL Soepadmo E Goh SH Wong AK: Cardiovascular effects in the rat of dihydrocorynantheine isolated from *Uncaria callophylla*. *J Ethnopharmacol* (1989 Apr) 25(2):213-5. [No Abstract Available].

14. Rizzi R Re F Bianchi A De Feo V de Simone F Bianchi, L: Stivala LA Mutagenic and antimutagenic activities of *Uncaria tomentosa* and its extracts. *J Ethnopharmacol* (1993 Jan) 38(1):63-77.

Mutagenic and antimutagenic activities of extracts and chromatographic fractions of *Uncaria tomentosa* bark are reported. The plant extracts and fractions show no mutagenic effect in different strains of *Salmonella typhimurium* with and without metabolic activation. However, the plant extracts and fractions show a protective antimutagenic effect in vitro against photomutagenesis induced by 8-methoxy-psoralen (8-MOP) plus UVA in *S. typhimurium* TA 102. A decoction of *U. tomentosa* ingested daily for 15 days by a smoker decreased the mutagenicity induced in *S. typhimurium* TA98 and TA100 by the subject's urine.

15. Mok JS Chang P Lee KH Kam TS Goh SH:

Cardiovascular responses in the normotensive rat produced by intravenous injection of gambirine isolated from *Uncaria callophylla* B1. ex Korth. *J Ethnopharmacol* (1992 Jun) 36(3):219-23.

Among several alkaloids, including dimeric indoles, isolated from *Uncaria callophylla*, gambirine which is an alkaloid unique to this plant, has been found to be another hypotensive principle from the plant. Intravenous injections of gambirine in the dose range of 0.2 to 10.0 mg/kg caused a dose-related fall in both systolic and diastolic blood pressures as well as heart rate. At all doses gambirine showed a prompt onset of action and at the higher doses (5.0-10 mg/kg), marked persistence of hypotension accompanied by severe bradycardia were observed. In addition, higher doses of gambirine produced a more marked decrease in diastolic than systolic pressure while at lower doses both decreased equally. It is suggested that the hypotensive effect of gambirine may be peripheral in origin and is associated, at least in part, with a cardiac action.

16. Aquino R De Feo V De Simone F Pizza C Cirino G: Plant metabolites. New compounds and anti-inflammatory activity of *Uncaria tomentosa*. *J Nat Prod* (1991 Mar-Apr) 54(2):453-9.

Bioassay-directed fractionation of the anti-inflammatory extracts of *Uncaria tomentosa*, using the carrageenan-induced edema in rat paw, has led to the isolation of a new quinovic acid glycoside 7 as one of the active principles. Furthermore, a new triterpene 8 was isolated as its methyl ester. The structures were elucidated by spectral and chemical studies.

17. Aquino R De Simone F Vincieri FF Pizza C Gacs-Baitz E: New polyhydroxylated triterpenes from *Uncaria tomentosa*. *J Nat Prod* (1990 May-Jun) 53(3):559-64.

Three novel polyhydroxylated triterpenes have been isolated from *Uncaria tomentosa*. Their structures were established as 1, 2, and 3 by detailed spectral studies including ¹H-¹³C correlations via long range couplings using the INAPT pulse sequence, nOeds, and 2D ¹H-¹³C direct chemical shift correlation (HETCOR) nmr techniques.

18. Aquino R De Simone F Pizza C Conti C Stein ML
Plant metabolites. Structure and in vitro antiviral activity of quinovic acid glycosides from *Uncaria tomentosa* and *Guettarda platypoda*. *J Nat Prod* (1989 Jul-Aug) 52(4):679-85.

A reinvestigation of the bark of *Uncaria tomentosa* afforded, in addition to the major quinovic acid glycosides 1-3, three further glycosides 4-6. The structures were elucidated by spectral and chemical studies. Furthermore, a series of antiviral tests were performed on all these glycosides and on the related glycosides 7-9, previously isolated from *Guettarda platypoda*.

19. Hemingway SR Phillipson JD: Proceedings: Alkaloids from S. American species of *Uncaria* (Rubiaceae). *J Pharm Pharmacol* (1974 Dec) 26 Suppl:113P. [No Abstract Available]

20. Phillipson JD Hemingway SR: Proceedings: *Uncaria* species as sources of the alkaloids gambirine and the roxburghines. *J. Pharm Pharmacol* (1973 Dec) 25:Suppl:143P. [No Abstract Available].

21. Hemingway SR Phillipson JD: N-oxides isolated during the alkaloid screening of *Uncaria* species. *J Pharm Pharmacol* (1972 Dec) 24:Suppl:169P-170. [No Abstract Available].

22. Kanatani H Kohda H Yamasaki K Hotta I Nakata Y Segawa T Yamanaka E Aimi N Sakai S: The active principles of the branchlet and hook of *Uncaria sinensis* Oliv. examined with a 5-hydroxytryptamine receptor binding assay. *J Pharm Pharmacol* (1985 Jun) 37(6):401-4.

Of the alkaloids obtained from *Uncaria sinensis* Oliv., geissoschizine methyl ether, corynantheine and dihydrocorynantheine decreased specific [³H]5-HT binding to membrane preparations from rat brain and from in-vitro experiments on guinea-pig ileum, these alkaloids were found to be partial agonists for 5-HT receptors. Therefore, they might be useful in the treatment of diseases resulting from disorders of 5-HT metabolism.

23. Kuramoto M Ishimura Y Lu W Morimoto J Yamasaki Y: Proceedings: Effect of the extract of *Uncaria kawakamii* of Formosa origin in dissolving artificial bladder calculi. *Jpn J Pharmacol* (1974) 24(0):s:37. [No Abstract Available].

24. Horie S Yano S Aimi N Sakai S Watanabe K: Effects of hirsutine, an antihypertensive indole alkaloid from *Uncaria rhynchophylla*, on intracellular calcium in rat thoracic aorta. In: *Life Sci* (1992) 50(7):491-8.

The effects of hirsutine, an indole alkaloid from *Uncaria rhynchophylla* (MIQ.) Jackson, on cytosolic Ca²⁺ level ([Ca²⁺]_{cyt}) were studied by using fura-2-Ca²⁺ fluorescence in smooth muscle of the isolated rat aorta. Noradrenaline and high K⁺ solution produced a sustained increase in [Ca²⁺]_{cyt}. Application of hirsutine after the increases in [Ca²⁺]_{cyt} induced by noradrenaline and high K⁺ notably decreased [Ca²⁺]_{cyt}, suggesting that hirsutine inhibits Ca²⁺ influx mainly through a voltage-dependent Ca²⁺ channel. Furthermore, the effect of hirsutine on intracellular Ca²⁺ store was studied by using contractile responses to caffeine under the

Ca²⁺-free nutrient condition in the rat aorta. When hirsutine was added at 30 microM before caffeine treatment, the agent slightly but significantly reduced the caffeine-induced contraction. When added during Ca²⁺ loading, hirsutine definitely augmented the contractile response to caffeine. These results suggest that hirsutine inhibits Ca²⁺ release from the Ca²⁺ store and increases Ca²⁺ uptake into the Ca²⁺ store, leading to a reduction of intracellular Ca²⁺ level. It is concluded that hirsutine reduces intracellular Ca²⁺ level through its effect on the Ca²⁺ store as well as through its effect on the voltage-dependent Ca²⁺ channel.

25. Kuramochi T Chu J Suga T: Gou-teng (from *Uncaria rhynchophylla* Miquel)-induced endothelium-dependent and independent relaxations in the isolated rat aorta. In: *Life Sci* (1994) 54(26):2061-9.

Gou-teng is a drug used for treatment of hypertension in Chinese medicine. Its antihypertensive action has been previously confirmed in the spontaneously hypertensive rat (SHR). Here, its vasorelaxing effect and the mechanisms of actions were studied in vitro. Gou-teng extract (GTE) relaxed the norepinephrine (NE)-precontracted aortic ring preparations isolated from Wistar Kyoto rats (WKY) with and without intact endothelium; the latter was significantly less sensitive than the former. The GTE-induced endothelium-dependent relaxation was significantly inhibited by NG-monomethyl-L-arginine (NMMA) in a dose-dependent manner while indomethacin did not affect the relaxation. Atropine inhibited the acetylcholine (ACh)-induced endothelium-dependent relaxation but did not the GTE-induced one. Furthermore, once GTE was applied, the following NE-induced contraction was significantly reduced even after repeated washout. NMMA effectively reduced and rather reversed this residual effect of GTE. From these results, it is concluded that GTE relaxes the NEprecontracted rat aorta through endothelium-dependent and, to lesser extent, -independent mechanisms. The endothelium-dependent component would be mediated by EDRF/NO pathway in which the muscarinic cholinceptors were not involved. Thus, GTE appears to be a potent and long-lasting vasodilator mainly through EDRF/NO release.

26. Liu J Mori A: Antioxidant and free radical scavenging activities of *Gastrodia elata* Bl. and *Uncaria rhynchophylla* (Miq.) Jacks. *Neuropharmacology* (1992 Dec) 31(12):1287-98.

Gastrodia elata Bl. (GE) and *Uncaria rhynchophylla* (Miq.) Jacks (UR) are two traditional Chinese medicinal herbal drugs, used for the treatment of convulsions and epilepsy. Their antioxidant effects in vivo and their free radical scavenging effects in vitro were investigated. Epileptogenic foci in the lateral brain of the rat were induced by the injection of ferric chloride into the lateral cortex. Both extracts significantly inhibited the increase in levels of lipid peroxide in the ipsilateral cortex, at all times observed. In addition, the two extracts also induced an early increase of activity of superoxide dismutase in the mitochondrial fraction of the ipsilateral cortex. In in vitro experiments, the two extracts exhibited significant dose-dependent scavenging effects on free radicals, using electron spin resonance spectroscopy. These results suggest that the proposed antiepileptic effects of GE and UR may be attributable to the antioxidant activity of the active components in these two medicinal herbs.

27. Ozaki Y: [Vasodilative effects of indole alkaloids obtained from domestic plants, *Uncaria rhynchophylla* Miq. and *Amsonia elliptica* Roem. et Schult]. *Nippon Yakurigaku Zasshi* (1990 Feb) 95(2):47-54. (Published in Japanese)

Vasodilative effects of hirsutine (HS) and hirsuteine (HST) which were isolated from the domestic plant *Uncaria rhynchophylla* Miq. and beta-yohimbine (beta-Y) which was isolated from the domestic plant *Amsonia elliptica* Roem. et Schult. were carried out. In the hind-limb artery of anesthetized dogs, intra-arterial administration of HS, HST and beta-Y caused a vasodilatation. The vasodilative potency of HS was somewhat stronger than that of HST, and the potency of both alkaloids was approximately equal to that of papaverine. The vasodilative effect of beta-Y was similar to that of yohimbine, which is considered to be derived from its alpha-adrenoceptor blocking effect, and the potency of both alkaloids was approximately the same, while the effect of beta-Y was stronger than that of papaverine. In the coronary artery, HS showed a vasodilatation and its potency was weaker than that of papaverine. Also, HS showed the same effect in the cerebral artery, and the potency of HS was approximately the same as that of papaverine. These results suggest that the mode of the vasodilative effect induced by HS may partly differ from that of papaverine.

28. Ozaki Y: [Pharmacological studies of indole alkaloids obtained from domestic plants, *Uncaria rhynchophylla* Miq. and *Amsonia elliptica* Roem. et Schult]. *Nippon Yakurigaku Zasshi* (1989 Jul) 94(1):17-26. (Published in Japanese).

Pharmacological studies on hirsutine (HS), hirsuteine (HST), rhynchophylline (RP), isorhynchophylline (IRP) and dihydrocorynantheine (DCT) which were isolated from the domestic plant *Uncaria rhynchophylla* Miq. and beta-yohimbine (beta-Y) which was isolated from the domestic plant *Amsonia elliptica* Roem. et Schult. were carried out. These alkaloids showed a mild central depressive effect in mice, a weak non-competitive anti-spasmodic action in the mouse intestine, and a hypotensive effect in rats. Since beta-Y showed alpha-adrenoceptor blocking action, the hypotensive effect of beta-Y may be partly due to the vasodilative effect induced by its alpha-adrenoceptor blocking action. HS and beta-Y showed a preventive effect on the development of gastric erosions in mice. HS had antiarrhythmic effects on both aconitine-induced arrhythmias in mice and ouabain-induced arrhythmias in guinea pigs. The potency of the antiarrhythmic effects induced by HS was approximately the same as that of ajmaline, an indole alkaloid. Since HS did not show beta-adrenoceptor blocking action, the antiarrhythmic effects of HS would not be due to its beta-adrenoceptor blocking effect.

29. Yano S Horiuchi H Horie S Aimi N Sakai S Watanabe K
Ca²⁺ channel blocking effects of hirsutine, an indole alkaloid from *Uncaria* genus, in the isolated rat aorta. *Planta Med* (1991 Oct) 57(5):403-5.

Ca²⁺ channel blocking activity of hirsutine and its pharmacological features were studied. Hirsutine (10⁻⁶ to 3 x 10⁻⁵ M) produced a dose-dependent relaxation of the isolated rat aorta contracted by norepinephrine and high K⁺ concentration. This effect was exhibited in the aorta strips with or without the endothelium, suggesting an involvement of vasodilative mechanisms not dependent on the endothelium. Hirsutine also inhibited the contractions induced by serotonin and Ca²⁺ channel activator YC-170, but not by Ca²⁺ ionophore A23187. The pA₂ value of hirsutine was 6.6 +/- 0.1 (mean +/- S.E.; n = 4) in antagonizing cumulative dose-response curve for Ca²⁺ in the depolarized aorta strips. It is concluded that hirsutine apparently exhibits Ca²⁺ channel blocking activity mainly through inhibition of the voltage-dependent Ca²⁺ influx.

30. Endo K Oshima Y Kikuchi H Koshihara Y Hikino H: Hypotensive principles of *Uncaria hooks*. *Planta Med* (1983 Nov) 49(3):188-90. [No Abstract Available].

31. Balz JP Das NP: *Uncaria elliptica* a major source of rutin. *Planta Med* (1979 Jun) 36(2):174-7. [No Abstract Available].

32. Ponglux D Tantivatana P Pummangura S: Alkaloids from the leaves of *Uncaria homomalla*. *Planta Med* (1977 Feb) 31(1):26-30. [No Abstract Available].

33. Aisaka K Hattori Y Kihara T Ishihara T Endo K Hikino H: Hypotensive action of 3 alpha-dihydrocadambine, an indole alkaloid glycoside of *Uncaria hooks*. *Planta Med* (1985 Oct)(5):424-7. [No Abstract Available].

34. Wagner H Kreutzkamp B Jurcic K: [The alkaloids of *Uncaria tomentosa* and their phagocytosis-stimulating action] Die Alkaloide von *Uncaria tomentosa* und ihre Phagozytose steigernde Wirkung. *Planta Med* (1985 Oct)(5):419-23. (Published in German). [No Abstract Available]

35. Law KH Das NP; Initiation and maintenance of callus tissue culture of *Uncaria elliptica* for flavonoid production. In: *Prog Clin Biol Res* (1988) 280:67-70. [No Abstract Available].

36. Wu CC Chang CC Chen RL: [The antihypertensive effect of *Uncaria rhynchophylla* in essential hypertension (author's transl)]. Taiwan I Hsueh Hui Tsa Chih (1980 Sep) 79(9):749-52. (Published in Chinese). [No Abstract Available].
37. Chang CC Tung LH Chen RR Chiueh CC: A study on the antihypertensive action of uncarine A, an alkaloid of *Uncaria formosana* used in Chinese herb medicine. Taiwan I Hsueh Hui Tsa Chih (1979 Feb) 78(2):61-9. [No Abstract Available].
38. Merlini L Mondelli R Nasini G Hesse M: The structure of roxburghines A-E, new indole alkaloids from an *Uncaria* Sp. Tetrahedron (1970 May) 26(10):2259-79. [No Abstract Available].
39. Chan KC: Gambirdine and isogambirdine, the alkaloids from *Uncaria gambir* Hunt) Roxb. Tetrahedron Lett (1968 Jun) 30:3403-6. [No Abstract Available].
40. Merlini L Mendelli R Nasini G Hesse M: Gambirine, a new indole alkaloid from *Uncaria gambier* Roxb. Tetrahedron Lett (1967 Apr) 16:1571-4. [No Abstract Available].
41. Yamanaka E Kimizuka Y Aimi N Sakai S Haginiwa J: [Studies of plants containing indole alkaloids. IX. Quantitative analysis of tertiary alkaloids in various parts of *Uncaria rhynchophylla* MIQ]. Yakugaku Zasshi (1983 Oct) 103(10):1028-33 (Published in Japanese). [No Abstract Available].
42. Nozoye T Shibamura Y Shigehisa A: [Studies on *Uncaria* alkaloid. XXI. Separation of rhynchophylline and corynoxine (author's transl)]. Yakugaku Zasshi (1975 Jun) 95(6):758-9 . (Published in Japanese). [No Abstract Available].
43. Haginiwa J Sakai S Aimi N Yamanaka E Shinma N: [Studies of plants containing indole alkaloids. 2. On the alkaloids of *Uncaria rhynchophylla* Miq]. Yakugaku Zasshi (1973 Apr) 93(4):448-52 (Published in Japanese). [No Abstract Available].
44. Haginiwa J Sakai S Takahashi K Taguchi M Shujiro S: [Studies of plants containing indole alkaloids. I. Alkaloids in *Uncaria* genus]. Yakugaku Zasshi (1971 May) 91(5):575-8. (Published in Japanese). [No Abstract Available].
45. Liu HM Jiang Z Feng XZ: [New oxindole alkaloid glycosides from *Uncaria sinensis*]. Yao Hsueh Hsueh Pao (1993) 28(11):849-53 (Published in Chinese).

Two 16-carboxy derivatives of pentacyclic oxindole alkaloids and its glucopyranosyl esters have been isolated from the ethanolic extract of the leaves of *Uncaria sinensis* (Olive.) Havil. These structures were deduced on the basis of spectroscopic evidences and chemical correlations, and named mitraphyllic acid (I), isomitraphyllic acid (II), isomitraphyllic acid (16-1)-beta-D-glucopyranosyl ester (III) and mitraphyllic acid (16-1)-beta-D-glucopyranosyl ester (IV).

46. From the Internet. CAT'S CLAW or *Uncaria tomentosa* (WILD) DC.

Peruvian native natural plant located in the Peruvian jungle. It's a shrub, climber, located in the secondary forest that grows up to 20mts high. The stem has spines (Claw) 2 cms long. The leaves have an oval form and membranous consistency, are approximately 9 - 17 cms long, and are green to amber in colour. The characteristic downiness of the veins in the leaves is the main reason for the name "Tomentosa". The bark is used. The Cat's Claw - *Uncaria Tomentosa*(Wild) DC according to the chemical and pharmacological studies done, two Oxindolic Alkaloids have been identified: Rincophiline, and Isorincophiline jointly with N - Oxides. Secondary alkaloids have been identified: Pteropodine, Speciophiline, Isopteropodine, Mitraphilineo, Uncarine F, Hirsuteine, Hirsutin, Dihydrocorynantheine and Isomitrafiline. Because of the above mentioned features Cat's Claw *Uncaria tomentosa* (Wild) DC is considered worldwide as miracle of nature because of its high anti-inflammatory effects and powerful stimulation of the immune system. Product

zone: Peru (in the rainforest). Annual production: 100 - 120 MT (raw material). Uses: for use in the pharmaceutical, botanical, herbal supplement, teas & beverage industries. The process of Lyophilised eliminates the water and impurities by sublimation at low pressures and temperatures, maintaining all the active contents, eliminating the toxic residues not assimilative by the human organism.

Universidad Nacional Mayor de San Marcos, (Universidad del Peru, Decana de America), Department of Pharmacology and Biochemistry, Institute of Organic Chemistry Applied on Pharmacology, "Juan de Dios Guevara Romero". Analysis Bulletin No. 060.

Origin: Peruvian Imports Ltd.

Sample received: Bark of Cat's Claw (*Uncaria tomentosa*)

Date received: May 18, 1995

Analysis requested:

1. (Marcha Fitoquimica completa)
2. Value of total alkaloids
3. (Espectrofotometria)

(MARCHA FITOQUIMICA COMPLETA)

The analysis established the presence of :

Glycosides, Saponins, (Taninos), Oxindole Alkaloids

VALUE OF TOTAL ALKALOIDS

0.354% of total alkaloids expressed as (Mitrafilina)

3.(ESPECTROFOTOMETRIA ULTRAVIOLETA/VISIBLE)

maxim (lambos) of absorption: 202nm, 276 nm

solvent: distilled water

Conclusions

1.The presence of oxindole alkaloids and glycosides establishes (fitoquimicamente) that the sample received is Cat's Claw extract (*Uncaria tomentosa*).

2. The concentration of total alkaloids is 0.354%. Lima. May 25, 1995. (signed) Dr. Enrique Leon Sorta. Director, Institute of Organic Chemistry Applied on Pharmacology "Juan de Dios Guevara Romero". From Health Foods Business, June 1995

CAT'S CLAW

By Steven Foster

...Cat's Claw as it is known in English, or una de gato as it is called in Spanish, is a tropical member of the madder family (Rubiaceae) that can be placed in the "hot herb" category. Botanists know it as *Uncaria tomentosa*. The genus *Uncaria* is a group found throughout the tropics, primarily in Southeast Asia, as well as the Asian continent, Africa and South America. Two species are found in South America, including *Uncaria tomentosa* DC as well as *Uncaria guianensis* (Aubl) Gmel. In all there are 34 species of *Uncaria*. The South American species are lianas or high climbing, twining woody vines. *Uncaria guianensis* has been used as a folk medicine for intestinal ailments and to promote healing of wounds.

Folk Medicine Origins

According to Dr. James A. Duke of USDA's Germplasm Resources Laboratory, the acknowledged guru of medicinal plants in the US government, and South American ethnobotanist colleague Rodolfo Vasquez, both *Uncaria tomentosa* and *Uncaria guianensis* are used as folk medicines in the Amazon. In their *Amazonian Ethnobotanical Dictionary* (CRC Press 1994), *Uncaria Guianensis* is collected in large quantities in South

America for shipment to the European market. Most American supplies seem to favour *Uncaria tomentosa*. According to Duke and Vasquez, a bark decoction of *Uncaria guianensis* is used in Peru as an anti-inflammatory, anti-rheumatic, as well as a contraceptive. It is used for treating gastric ulcers and tumours. The Boras use the bark for the treatment of gonorrhoea. In Columbia and Guiana, Indian groups use it for the treatment of dysentery. The plant also has a reputation as a folk cancer remedy for cancers of the urinary tract, particularly in females.

Uses of *Uncaria tomentosa* from Peru, the centre of the plant's range, are similar to the above uses. It is also used for the treatment of gastric ulcers, arthritis, intestinal disorders, certain skin disorders as well as various tumours. The National Cancer Institute was finding some preliminary encouraging results in researching its tumour inhibiting properties when funding for the project was cut in 1980. Formal research in the US came to an end at that time. Reports of success as a folk cancer remedy, especially in South America continued, leading to further scientific research on the plant group on the 1980s and 1990s. Now the Nation Cancer Institute's screening programme for anti-cancer compounds from plants has been re-instituted using new and sophisticated *** methods.

... One study identified alkaloids unique to *Uncaria Tomentosa* making it possible to differentiate between samples of the bark of this and other *Uncaria* species. They then studied the immunostimulatory effects of the individual alkaloids and found that with the exception of two (mitraphylline and rychophylline), all alkaloids had a pronounced effect on enhancing phagocytosis, as determined by two laboratory tests as well as the carbon clearance test in mice, (which measures the phagocytic activity of white blood cells on carbon particles injected into the body cavity of mice). This research provided a pharmacological basis for the various reports of effectiveness of the plant in various disease conditions.

47. In a reference from Floraceutical we read of *Uncaria tomentosa* (Willd.) D.C. Rubiaceae, also called locally Una de gato.

History: The highland Peruvians have long valued decoctions of this herb for a variety of internal and external ailments

Folk lore uses: Used by the Peruvian Indians for stomach ailments and as an anti-inflammatory. Used on external scrapes and cuts.

Cosmetic uses: Useful as an anti-inflammatory for cuts and bruises. Use at 3-5%;

Constituents: alkaloids, tannins and saponins. The bark is used.

48. Direct Source Home Page

Cat's Claw is a herb found in the upper Rain Forest in Peru. Its botanical name is *Uncaria Tomentosa*. It has been gaining popularity world wide as an effective multi-purpose nutritional supplement. Research shows that Cat's Claw contains several "Oxindole Alkaloids having properties stimulating the immunologic system" as referenced under U.S. Patent Numbers 4,844,901 and 4,940,725. In addition to this herb's immunologic properties, available research indicates that *Uncaria Tomentosa* has antiviral, antioxidant, anti-inflammatory, and anti-tumor properties.

There has been much research and documentation completed on Cat's Claw from the mid 1970's to present, unfortunately much of the European and Peruvian research has not been widely distributed in the U.S. Direct Source has been created specifically to provide a source for individuals and practitioners to obtain this type of documentation and research on Cat's Claw. Cat's Claw, sometimes referred to by its Latin name, *Uncaria Tomentosa*, has also been referred to as "Una de Gato," its Peruvian name. Cat's Claw is a vine that grows between 400 and 800 meters above sea level in the Amazon jungle and grows up and around other trees sometimes reaching 100 feet high and more. It gets its name from the small sharp thorns, two at the base of each pair of leaves, which look like a cat's claw.

Research began on Cat's Claw in the early 1970's when a story about an amazing recovery by an individual with cancer who was treated with Cat's Claw was related to an Austrian, Mr. Klaus Keplinger. Mr Keplinger

informed a group of scientists in Innsbruck and Graz. From then on, other scientists in Germany and in Italy began researching the Peruvian plant. Mr. Keplinger filed the first patent in the U.S. on *Uncaria Tomentosa* in 1989 when the plant's alkaloids were isolated and tested, mainly consisting of six oxindole alkaloids most prevalent in the Cat's Claw bark. This patent has fueled additional research since 1989 and research is ongoing today. It is important to understand that most of the clinical research, trials and reports completed to date (and included in the research book offered by Direct Source) which show the alkaloids to be antiviral, anti-inflammatory, immunostimulating, antimutagenic, antioxidant and have other benefits, are tests determining the alkaloid's active principals "in-vitro". This means they have been proven in the test tube - not "in-vivo", or in the human body. While these in-vitro tests are very promising, many more in-vivo tests will be needed to determine the true efficacy of this plant for specific diseases in humans.

Included in the Research book are the only three trials we've found and included that could be considered in-vivo, which were in fact, human studies. Two were performed using "Krallendorf" which is a Cat's Claw extract produced by a German company called Immodal. One of these documents is termed a "therapy observation" and spans a ten year period with 78 patients suffering from brain tumors treated with Krallendorf. Another is a summary of a trial with 32 HIV-infected patients treated with Krallendorf from 1987 to 1991. The third in-vivo test was performed by an Italian group studying the plant's antimutagenic properties on smokers and non-smokers.

In-vivo tests and trials are currently underway at several institutions in several countries and some preliminary results look promising, but the final results are not in yet. Cat's Claw has not been clinically proven to cure AIDS or cancer.

One of the best sources located on Cat's Claw is a book titled, "The Saga of the Cat's Claw" by Dr. Fernando Cabieses. Dr. Cabieses is a well known neurologist and neurosurgeon with residency in Lima, Peru. He is Professor Emeritus at the Universidad Mayor de San Marcos and Honorary Professor at the Universities of Trujillo, Piura, Cajamarca, Chiclayo, Cusco, Arequipa and Garcilaso de la Vega. He is also Clinical Professor of Neurosurgery at the University of Miami, Florida, a member of the World Health Organization Committee for Traditional Medicine and is the Chairman of the Instituto Nacional de Medicina Tradicional of Peru, a branch of the Ministry of Health (The National Institute of Traditional Medicine of Peru). He has studied Cat's Claw extensively, as well as all available clinical research reports and trials. In his book, he gives a clear and easily understood translation of each of the clinical in-vitro studies and what they mean. We would like to share his views on Cat's Claw concerning AIDS in his book, because they reflect our own:

Therefore, "in-vitro", we already know that the alkaloids of our plant stimulate the immune mechanisms. This is excellent. It opens a promising avenue of research "in-vivo" in order to determine whether these substances are active in conditions where the immune system is depressed. None of us is unaware of AIDS, the horrible monster stalking humanity, and much hue and cry has been raised about *U.tomentosa's* effects as a miracle cure for this cursed condition. But so far, no such cure exists. Most of the alleged successes are the works of quacks, adventurers and outright swindlers. Some of the noise comes from a few bona-fide but ignorant physicians or others influenced by cases which are certainly interesting but, unfortunately, poorly documented. The subject demands much more study, and to speak now of "cures" when the evaluation is still under way cruelly raises false hopes in desperate people. Several Peruvian groups, among them Professor Eduardo Gotuzzo and Doctor Rosario Rojas, are currently conducting topnotch studies which should soon give us more reliable information.

Dr. Cabieses' closing statements in *The Saga of the Cat's Claw* are the following:

The proper design of research protocols for human application in neoplastic diseases and in severe problems of immune deficiency (AIDS) is not child's play, and the limits between the possible and the desirable are frequently cloudy and diffuse. A link between "in vitro" and "in vivo" is now being designed in Peruvian medical institutions of great prestige like the University Cayetano Heredia and Instituto Nacional de Enfermedades Neoplasicas, as well as under the direction of experts in alternative medicines like natural medicine (Father Edmundo Szeliga, Doctor Mirez, Doctor Lida Obregon) and homeopathy (Dr. F.P. Iaccarino).

The following are quotes that have been extracted from the compilation of many documents from around the world that are included in the Cat's Claw Documentation Book. Once again, these are the opinions and claims of each individual author:

Excerpted from the book: Herbs of the Amazon - Traditional and Common Uses, By Dr. Donna Schwontkowski, Doctor of Chiropractic Medicine:

"Una de Gato is considered one of the most important botanicals in the rainforest. In Peru, Una de Gato tea is used as a medicinal herb with almost unlimited curative properties. This herb is a powerful cellular rejuvenator. It has been used for the treatment of gastritis (inflammation of the stomach), ulcers, cancer, arthritis, rheumatism, irregularities of the female cycle, and acne. It is also used to treat organic depression. External applications of Una de Gato include the treatment of wounds, fungus, fistulas and hemorrhoids. European research shows that Una de Gato activates the immune system by increasing lymphocytic (white blood cell) activity."

Excerpted from the book: Traditional Uses of Rainforest Botanicals by John Easterling:

It is considered one of the most important botanicals in the Rainforest. By supporting and enhancing immune system function, Una de Gato is indicated in a broad spectrum of conditions including all types of infections. Urarina tribesman of Peru tell stories of Una de Gato curing tumors. Una de Gato was one of the plants researched by the National Institute for Health as an anti-cancer agent. Studies from various laboratories indicate it normalizes the immunoglobins by activating T-lymphocytes and macrophages.

Excerpted from the book: Powerful and Unusual Herbs from the Amazon and China, Published by the World Preservation Society:

Una de Gato from the Peruvian rainforest is a favorite for stimulating the immune system. World wide research done on this powerful herb has led scientists to patent many of the single chemicals found in it for use in healing cancer, arthritis, AIDS, and other diseases. However, traditional wisdom shows that using the whole plant can be far more powerful than any one isolated ingredient.

Excerpted from The Herb Quarterly, Winter 1994, in an article titled "Cat's Claw (Una de Gato) A Wondrous Herb From the Amazon Rain Forest" by Phillip Steinberg: In July 1989, U.S. Patent No 4,844,901 was issued to an Austrian scientist named Klaus Keplinger, and a second patent, No. 4,940,725, was issued to him in July 1990. These patents explain how Dr. Keplinger isolated six oxindole alkaloids from the root of *Uncaria tomentosa* and that four of these alkaloids have been proven to be "suitable for the unspecified stimulation of the immunologic system". According to Keplinger's research, these four alkaloids have been shown to have a pronounced enhancement effect on phagocytosis (the ability of the white blood cells and macrophages to attack, engulf and digest harmful micro-organisms, foreign matter, and debris.) According to both patents, the most immunologically active alkaloid is isopteropodine or isomer A. Besides isomer A and the other three immuno-stimulating alkaloids, there exists another alkaloid known as rynchophylline. This alkaloid has been studied at the Shanghai College of Traditional Medicine. According to their findings, rynchophylline has demonstrated an ability to inhibit platelet aggregation and Thrombosis, which suggests that rynchophylline may be useful in preventing strokes and reducing the risk of heart attack by lowering blood pressure, increasing circulation, and inhibiting both the formation of plaque on the arterial walls and the formation of blood clots in the brain, heart, and arteries.

The research book contains everything that could be found concerning Cat's Claw, including copyrighted articles. Much effort was expended in tracking down authors and publishers of copyrighted articles to obtain permission to include the document in the compiled research documents.

One important article written by Brent W. Davis, D.C. was published in the "Collected Papers of the International College of Applied Kinesiology - Summer 1992". This article was copyrighted by Mr. Davis and we have been unable to reach him to obtain his permission to include his article in the compiled research book. If you know where to reach him, we would appreciate your input by email.

The following direct quotes have been excerpted from the Brent W. Davis, D.C. article copyrighted in 1992, titled <cite>A "New" World Class Herb for A.K. Practice: *Uncaria tomentosa* - a.k.a. Una de Gato (UDG): Abstract of the article: "Abstract: Background information is provided on one of the Amazon's most valuable medicinal plants. The author describes his original field research and specimen collection of *Uncaria tomentosa* (UDG) in the Amazon beginning in 1988, and his subsequent A.K. clinical evaluation of that herb continuing to the present. The pharmacology and therapeutics of UDG are presented. Its profound healing ability is outlined. In important therapeutic areas, UDG far surpasses other world class herbs (such as *Astragalus*, *Echinacea*, *Ganoderma*, *Goldenseal*, *Artemisia annua*, Siberian "Ginseng", *Panax*, et al.), as well as potent over-the-counter products such as undecylenic acid, "citrus seed extract", caprylic and lauric acids."

I took six weeks to attend the International Congress on Traditional Medicines in Peru, and to do long awaited herbal research in Brazil. Many of the presenters at the congress on traditional medicines were holistic medical physicians who had used herbs in clinical practice for years. UDG was discussed as one of about a dozen herbs which are used consistently to cure cancer and other serious disorders. Since 1988 I have been clinically evaluating many of the great South American herbs mentioned at the congress (and from other avenues as well) in terms of their applications in general practice - not for their oncolytic properties. In some profoundly important areas, *Uncaria tomentosa* stands out above many others.

UDG was brought to the attention of European practitioners in the early 1980's. A few years before, the modern rediscovery of Una de Gato took place. Apparently in the early 70's an Austrian journalist traveling in Peru happened upon the herb which he gave to an ailing relative who took it and subsequently was cured of cancer. The journalist then invested a great deal of time and effort researching *Uncaria tomentosa*, and he came to the conclusion that the central woody portion of the plant is the useful part. He developed this opinion on the basis of chemical analyses and clinical evaluation done in Germany and Austria which showed that a very active alkaloid is in the highest concentration in that part of the plant. He and other collaborators filed for international patents on this "active ingredient" which may appear in the marketplace in the near future.

Pharmacology: The first published chemical analysis of *Uncaria tomentosa* appeared in 1974(1). Two primary alkaloids were chromatographically identified as Rynchophyllin and Isorynchophyllin, as well as 5 secondary alkaloids. In 1985, Dr. B. Kreutzkamp and co-workers in Germany undertook more extensive analysis of UDG and came up with a classification of 6 alkaloids, the most immunologically active one being Isopteropodin(2). It has been reported in the literature that several color variations of fresh *Uncaria tomentosa* wood correspond with different concentrations of alkaloids, the darker colored wood being the richest in Isopteropodin.

Different of the alkaloids have been experimentally shown (2) to be:

1. Immunostimulating by way of enhancing phagocytosis.
2. Ganglion-blocking with an enhancing effect on parasympathetic tone.
3. Inhibitory to striated muscle contraction;
4. Hypotensive, uterostimulant and antipyretic;
5. Diuretic.

Italian researchers took a different approach from their German and Austrian colleagues. They found chemical and biological activity in the bark of the UDG vine. They reported quinovic acid glycosides and triterpenes to be active ingredients with anti-viral and anti-inflammatory activity (3). Another group of Italian researchers found a steroidal fraction of UDG bark to be anti-inflammatory (4). A very good recent article of Italian researchers' work discusses cytotoxicity, mutagenicity, and anti-mutagenicity tests performed with a special alcoholic extract of the bark of UDG(5). The researchers found that "All the *Uncaria tomentosa* extracts exerted a protective action against photomutagenesis induced by 8-MOP + UVA. The values ranged from a minimum of about 30% to a maximum of about 70%". The authors concluded, "The anti-mutagenic effect of the extract employed in these series of oxidative reactions is probably attributable to the quinovic acid glycosides from *Uncaria tomentosa*. This plant shows anti-mutagenic activity in-vivo in smokers, confirming its high anti-oxidant potential".

European Application of UDG Therapy

In a presentation to heilpraktikers in Europe, German doctor of medicine, Iwan Diehl, summarized well the therapeutic usage of the wood of UDG by German and Austrian physicians:

Effectiveness: Because of the mode of action of Uncaria extract, side-effects do not appear if the recommended dose is taken. In association with individuals who have frequently used laxatives, there may be temporary disorders of intestinal peristalsis, which disappear spontaneously after a few days. For the alkaloids of Uncaria extract, the following effects have been proven:

Stimulation of the non-specific immune system with activation of macrophages and granulocytes to eliminate non-physiological substances; Enhancement of the sensitivity and reactivity of the immune system to seize and to eliminate very weak antigens; Inhibition of inflammation by a repairing incorporation of lipids into the lipid matrix of damaged cell membranes; Selective inhibition of growth of malignant cells by simultaneous improvement of erythrocyte and macrophage function; Enhancement of the growth inhibitory effect of (pharmaceutical) cytostatics by an intact immune system; Selective growth inhibition of virus transformed cells. Indications: A positive influence has been observed on the following disorders: Dermatological disorders, Allergic disorders, Rheumatic disorders, Chronic inflammation, Viral diseases (herpes zoster), Malignant diseases (cytostasis and radiotherapy are more efficient under a concomitant therapy with Uncaria)

Uncaria is contraindicated for transplant carriers, because of a possible graft rejection. During pregnancy, Uncaria should not be used. In cases of treatment with H2-antagonists (e.g. anti-ulcer medication), a potentiation of the H2-antagonist might be expected. In my experience on approximately 150 patients during the last four years (who have received adjunctive monotherapy with UDG), I have seen Uncaria tomentosa break through severe intestinal derangements that no other available products can touch, including the strong & very useful undecylenic acid. Administration UDG wood is administered as a tea, or in tablets, in the amount of 3 to 25 grams per day, or that equivalent if a concentrate is used. Sensitive individuals may require less than 3 g. I generally do not use over 5 grams per day-more commonly 3 grams/day. One phase of treatment normally lasts 10-14 days. Then other formulations can be used, cycling back to UDG in tough cases in perhaps 7-10 days. Individuals who treat advanced stages of pathology might routinely use between 10-20 grams per day for several weeks at a time."

Care with UDG

Possible contraindication. Peruvian and European practitioners say there are no side-effects from UDG use. In my experience, that is not entirely true. What I find interesting is that the appearance of what seems to be an undesirable side-effect, is generally an indication that UDG is working well. The undesirable side-effect is diarrhea. In the patients who have benefited most from UDG wood, the herb tends to progressively alter bowel consistency from hard or normal to loose. It's kind of like the ascorbic acid advocates "take it til it runs and then back off" phenomenon. In rare cases UDG causes what appears to be full blown dysentery. I am hypothesizing that in the latter, actual encystment of some other type of sequestration of parasites has occurred in the patient's past, and that UDG breaks open the encystment, and that is why the previously intractable problem finally moves toward resolution. After a positive pre-administration clinical screening which shows compatibility with Uncaria tomentosa, there is no substitute for trial. As you are learning about UDG, try monitoring its effects as a monotherapy for 7 to 14 days on several well chosen cases. It can be impressive.

GAMBIR

Uncaria gambir

1. In a data sheet from Maruzen Pharmaceuticals (through K&K Greeff) we read that the leaves and twigs are used as an astringent and haemostat.

2. Phelps Brown (B161) refers to *Uncaria gambir* as Gambir Plant, where the extract of the leaves and young shoots are used medicinally. Gambir is a stout climbing shrub with round branches. Leaves ovate, lanceolate, acute, smooth, and have short petioles. Flowers in loose heads, green and pink; calyx short, corolla funnel-shaped; stamens five, and the fruit a two-celled capsule. It is an inhabitant of the East Indian Archipelago, where it is extensively cultivated. On the island of Bingtang alone there are 60,000 Gambir plantations. It affords what is known as 'pale catechu'. It is chiefly imported from Singapore. It is found in cubes which float on water, externally brown, internally pale brick red, breaking easily. Taste bitter, very astringent, and mucilaginous. Boiling water almost completely dissolves it. It is used in the arts for tanning.

Properties and uses

It is employed as an astringent. In various affections of the mouth it is an efficacious astringent. It is also excellent as a stomachic in dyspeptic complaints, especially when accompanied with pyrosis. It should be used just before taking food. It is an excellent astringent in chronic diarrhoea and dysentery. Dose from 10-40 grains.

Nauclea sinensis Oliv.

1. Keys (B115) says that it is a shrub, the branches small, bearing compressed, curved spines occasionally. It has white flowers. Central China. The stems and spines are officinal. The taste is bitter and astringent. The drug contains the alkaloid rynchophylline, which lowers blood pressure and paralyzes sympathetic nerve ending. Employed as a sedative, antispasmodic in infantile nervous disorders. Dose 5-10g. (In Japan, *Nauclea rynchophylla* Miq. [Syn. *Uncaria rynchophylla* Miq., *Ourouparia rynchophylla* Miq.] is used.)

2. Abbiw (B136) recommends the plant for wounds, cuts and sores. *Nauclea latifolia* - African Peach (Sukisia), application of powdered, ground roots or root-bark used.

3. Trees, shrubs and climbers of the Bijilo Forest Park. *Nauclea latifolia* or Batio or Guinea Peach

Climbing shrub with large (18 cm by 10cm), elliptic, shiny, opposite leaves and stout long branches. Flowers clustered in pendulous, spherical heads at the ends of the branches. Individual flowers are small tubular, white and fragrant. Fruit is a round brown agglomeration like a large strawberry, eaten by monkeys and birds.

Nauclea rynchophylla

1. Tang and Palmer (B81) say that it is also known as *Uncaria macrophylla* or *Uncaria sessilifructus*. The thorn is the part used. The meridians are the heart and liver. The taste is sweet. To stop convulsions, spasms and tics, this herb is given with *Gastrodia elata*. For the treatment of reddened eyes caused by headache, it is prescribed together with *Chrysanthemum morifolium*, mulberry leaves (*Morus alba*) and menthol. It does not need boiling. Dosage: 6-12 g.

2. Reid (B191) refers to the plant as *Uncaria rynchophylla* or Morning Star or Gou Teng in Chinese. It is a member of the Rubiaceae family, and found in Central China. The stems and spines are used. Nature: Sweet; slightly cold. Affinity: Liver; pericardium Effects: Sedative to liver; antipyretic; antispasmodic in children's nervous disorders. Indications: Ailments of liver-yang ascending: pressure and pain in head, dizziness, blurry vision; body heat due to excess heat; convulsions and spasms in children; fainting and convulsions during the 6th, 7th and 8th month of pregnancy. Dosage: 5-10 g. Remarks: The drug dilates the capillaries and other blood vessels and is now used to lower blood pressure as well.

3. Guo-Qing Liu, Dept of Pharmacology, China Pharmaceutical University, Nanjing 210009, China: Chinese Natural Products and New drugs. *Pharmaceutical News*, Vol.2, No.2, 1995. Drugs affecting the Cardiovascular System. Rynchophylline (Rhy) is an active constituent from *Uncaria rynchophylla* and is an antihypertensive and antiarrhythmic agent with potent antiplatelet aggregation (PAF) properties. The antiarrhythmic properties may be due to inhibition of potassium currents.

