

FEDERATION OF INTERNATIONAL PHARMACY

MEDICINAL AND AROMATIC PLANT SECTION

-oOo-

"Plants and today's products - an overview"

Anthony C. Dweck

Research Director

Peter Black Toiletries, Cradle Bridge, Mortimer Street,
Trowbridge, Wiltshire, UK. SP4 6DF

-oOo-

INTRODUCTION

[SLIDE 1]

Good afternoon, Ladies, Gentlemen and fellow scientists. My lecture today will concentrate on the development of skin care products, which contain active medicinal plant materials and examine the concept that because skin relies on a number of processes to remain healthy, that a formulation requires numerous plant actives in order to satisfy those various functions.

I do not know what your perception of a cosmetic chemist or cosmetologist (as we are sometimes called) is likely to be. Perhaps we are seen as crackpots like this,

[SLIDE 2]

working in laboratories that look like this

[SLIDE3]

...but I can assure you that this is not the case, we are more like this

[SLIDE 4]

when compared to our wealthy colleagues in the pharmaceutical industry!

DIFFERENCES BETWEEN THE COSMETIC AND PHARMACEUTICAL

So what are the differences between our two industries? Well, I think that this question is very simple to answer. The skin care product protects healthy skin, whereas the pharmaceutical product treats unhealthy or diseased skin. On paper that sounds extremely simple, but in reality there is a very thin line between us, for instance, we can quite happily sell a product for dry skin, but at what stage does dry skin become a medical condition, say eczematous?

[SLIDE5]

This slide shows the way in which our two industries overlap.

The law tries to be helpful, but in many cases we are very close to infringement of the Medicines Act, so we need to look at the definitions very closely.

DEFINITIONS

[SLIDE 6]

The cosmetic industry and the medicinal industry agree quite closely with their definition of a cosmetic.

Here is ours.....

The Consumer Products (Safety) Regulations 1989 SI 2233

Cosmetic product means any substance or preparation intended to be applied to any part of the external surfaces of the human body (that is to say, the epidermis, hair system, nails, lips and external genital organs), or to the teeth or buccal mucosa wholly or mainly for the purpose of cleaning, perfuming or protecting them, or keeping them in good condition or changing their appearance or combating body odour or perspiration except where such cleaning, perfuming, protecting, keeping, changing or combating is wholly for the purpose of treating or preventing disease.

"Cosmetic products intended to come into contact with the mucous membranes" means a cosmetic product intended to be applied in the vicinity of the eyes, on the lips, in the oral cavity or to the external genital organs, and does not include any cosmetic product which is intended to come into only brief contact with the skin;

and here is yours.....

[SLIDE 7]

The Royal Pharmaceutical Society of Great Britain. Number 12, April 1994. "Medicines, Ethics and Practice - a guide for pharmacists".

Cosmetic means any substance or preparation intended to be applied to the various surfaces of the human body including epidermis, pilary system and hair, nails, lips and external genital organs, or the teeth and buccal mucosa wholly or mainly for the purpose of perfuming them, cleansing them, protecting them, caring for them or keeping them in condition, modifying their appearance (whether for aesthetic purposes or otherwise) or combating body odours or normal body perspiration.

I think you will agree that they are almost identical word for word. This is the definition of a medicinal product, which I am sure you are perfectly familiar with.....

[SLIDE 8]

Medicinal product means any substance or article (not being an instrument, apparatus or appliance) which is manufactured, sold, supplied, imported or exported for use wholly or mainly in either or both of the following ways, that is to say:

(a) use by being administered to one or more human beings or animals for a medicinal purpose;

(b) use as an ingredient, by a practitioner or in a pharmacy or in a hospital or in a business comprising the sale of herbal remedies, in the preparation of a substance or article which is to be administered to one or more human beings or animals for a medicinal purpose.

Medicinal purpose means any one or more of the following purposes, that is to say:

(a) treating or preventing disease;

(b) diagnosing disease or ascertaining the existence, degree or extent of a physiological condition;

(c) contraception;

(d) inducing anaesthesia

(e) otherwise preventing or interfering with the normal operation of a physiological function, whether permanently or temporarily, and whether by way of terminating, reducing or postponing, or increasing or accelerating, the operation of that function or in any other way.

CAUTIONS

So before we look at the development of natural products let me give a few words of caution. Natural does not mean safe, indeed, natural can mean poisonous. The pharmaceutical industry calls on a number of plants for their drug use, and they must not be used in cosmetic products. Do not assume because a plant is not regulated, that it is automatically safe, there are many quite toxic plants from obscure regions of the world that are potentially dangerous. I have appended the **legally** forbidden plants in my session paper. However, the right plant, using the correct part, at the appropriate concentration, of the prescribed form, for the specific indication is, in all likelihood, safe and beneficial. The cosmetic legislation does not restrict the use of the permitted plants at all.

I do not intend to talk any more about cosmetics, but will now switch my attention to pharmaceutical skin care. What on earth is pharmaceutical skin care I hear you ask? This is skin care that has pharmaceutical applications; that is, it is intended for post operative patient care and is specifically designed to assist in the treatment of the physiological and the psychological trauma following surgery. Depending on the claims it may or may not hold a pharmaceutical license.

POTENTIAL PROBLEMS

[SLIDE 9]

Assuming that it is to be licensed, there is a distinct lack of understanding with the medical authorities when it comes to herbal preparations, though medical practitioners seem to be keeping an open mind and have derived many benefits from using plant derived products for the treatment of skin problems.

If you are thinking of licensing a "natural" product, then these are the types of problems that the licensing authorities will have. I take the side of the Devil's Advocate in this discussion, and so you must forgive the strong views.

1. The plant chemical composition may vary season to season
2. The chemicals within a plant or mixture of plants might react synergistically
3. Including more than three plants in a formula constitutes "polypharmacy".
4. Because some historical plant trials have failed, there is a feeling that all future trials will fail. It is hardly surprising that some studies have not been successful, since some trials have been conducted with the wrong species of the plant, the wrong part of the plant, the wrong age of the plant, the wrong extract of the plant and so on.
5. A single chemical is not usually responsible for a single effect, so that the reason for that effect cannot be specifically assigned.
6. A major stumbling block is that the plant does not appear in the British Pharmacopoeia, though it may appear in other Pharmacopoeias, which are not recognised by the authorities.

SKIN TISSUE

[SLIDE 10]

The idea that all stages of healing can be treated with one product containing one active ingredient is idealistic and simplistic.

There are many processes that occur within the skin as it heals, and for each of those mechanisms there is a plant that will encourage or maintain each function.

In order to simplify my discussion I have reduced these processes to just three, namely granulation, re-epithelialisation and cicatrisation, and I know that we could include a dozen other stages in skin healing, such as fibroblast activity, neutrophil involvement, formation of the collagen 3 mat, and so forth, but I really do want to try and keep things simple.

The healing process

First stage - granulation

[SLIDE 11]

This is the stage where the scab is formed and this process is usually accompanied by swelling, redness and often there is pain and heat at the site of injury. So what causes these conditions? The damaged cells trigger the release of chemicals (amongst them histamine) which cause the blood vessels to expand, so allowing more blood into the affected area, and it is this increase in blood flow beneath the surface of the skin that causes the redness. There is also a change in the permeability of the vessels, which allows serum or plasma to leak into the surrounding tissue. Now this is a normal process, and in healthy subjects this leakage is quite happily drained away by the lymph glands. However, in the case of injury, the lymph glands cannot cope with the

rate of leakage, so that swelling and inflammation occurs.

The next stage is the removal of irreparable cell debris, which is achieved by the white blood cells. These cells are summoned during the inflammation process, and can collect in such large numbers that they increase the swelling. More than that, where there is infection, this build up and swelling can eventually rupture the skin surface to be discharged as pus. This process of inflammation and pain is, to a certain extent, a protective process that immobilises the area and helps localise the infection and damage to surrounding tissue.

Second stage - re-epithelialisation

[SLIDE 12]

The second stage is vital, since it forms the new tissue under the protective scab, and this process normally follows soon after the inflammatory stage, once the cell debris has been removed. The repair of tissue is a continuous process, however, the body has a mechanism which is able to put the system into overdrive, when that tissue has been compromised or damaged. This cellular activity needs to have near perfect conditions to function properly.

As we get older, this process can start to break down or function poorly, so we start to see the appearance of pigmentation and irregular skin profile caused by uneven skin cell activity.

Third stage - resolution of scar tissue.

[SLIDE 13]

Having formed the initial, fragile underlying tissue, the cells continue to rebuild the epithelium, refining the tissue and re-establishing the stratum corneum and the infrastructure of the underlying tissue. Failure of this cellular regenerative process can lead to permanent scarring.

This is not a new concept and the Chinese have been employing 'polypharmacy' for thousands of years.

1. AN HISTORICAL FORMULATION

[SLIDE 14]

Chinese formulation

So having had a quick look at the background, let us take a Traditional Chinese remedy as an example. This formula has been tried, tested and has been refined by the process of trial and error, so I make absolutely no apologies for using it. The base in which it is used can be adapted to form the ideal environment for skin healing, and this is an easy task for any chemist.

It is useful to first view the structure of the formula from the Chinese perspective. In China, a formula is viewed in a different way to Western medicine.

[SLIDE 15]

Chinese medicine is based on the principle that every recipe consists of an Emperor herb, which is the main beneficial in the recipe; the Ministers, which support the Emperor herb in its action; the Assistants, which provide a complimentary action; the Harmonisers which help hold the blend together; and finally, a Directional herb, which acts to support the function of the Meridians.

This representation of the formula is not too dissimilar to a modern herbalist's view, who will have one major herb to tackle the key problem, and then perhaps include additional herbs to address related problems and less urgent issues.

The names are in Taiwanese pin yin, but I have included the Mandarin names in Appendix II of the preprint. The Linnean names avoid all ambiguity and should always be used.

[SLIDE 16]

HSIAO FENG SAN

Formula for skin diseases with internal heat, copious secretions and pruritis.

TANG KUEI	ROOT	<i>ANGELICA SINENSIS</i>	TANG KUEI
REHMANNIA	RHIZOME	<i>REHMANNIA GLUTINOSA</i>	TI HUANG
GYPNUM	MINERAL		SHIH KAO
ANEMARRHENA	RHIZOME	<i>ANEMARRHENA</i>	CHIH MU
SESAME	SEED	<i>SESAMUM INDICUM</i>	HU MA TZU
ATRACTYLODES	RHIZOME	<i>ATRACTYLODES OVATA</i>	TSANG CHU
ARCTIUM	FRUIT	<i>ARCTIUM LAPPA</i>	NIU PANG TZU
SILER	ROOT	<i>SILER DIVARICATUM</i>	FANG FENG
AKEBIA	STEM	<i>AKEBIA QUINATA</i>	MU TUNG
LICORICE	ROOT	<i>GLYCYRRHIZA URALENSIS</i>	KAN TSAO
CICADA	EXUVIAE	<i>CRYPTOTYMPANA ATRATA</i>	CHAN SHUI
SOPHORA	ROOT	<i>SOPHORA FLAVESCENS</i>	KU SHENG
SCHIZONEPETA	WHOLE	<i>SCHIZONEPETA TENUIFOLIA</i>	CHING CHI

As you will notice, it is an extremely complex blend of herbs, with some mineral and insect elements, which could be omitted. This blend is made to a 25% concentration and used at about 6% in the final formula. All the materials are made from dried ingredients, so that in the final formula the fresh plant equivalent is between 8 to 10%. This level would be prescribed for a protective role, and the concentration increased for a healing activity, say to 20% fresh plant equivalent.

[SLIDE 17]

THE EMPEROR

BURDOCK SEEDS

Arctium lappa

[SLIDE 18] The plant that we all know

[SLIDE 19] The seeds used by the Chinese

Arctium lappa is the major player in the formula, and there is considerable data to support the use of the plant for chronic skin diseases, skin disorders such as acne, boils, skin sores, abscesses and eczema. And recent studies suggest that the plant may contain compounds that play a role in suppressing cell mutation and chromosomal aberrations.

Terpenoids: the sesquiterpenes arctiol (= 8-hydroxyeudesmol), fukinone, dehydrofukinone, fukinanolide (a lactone), eremophilene, petasitolone and β -eudesmol, and the triterpene taraxasterol with its acetate and palmitate esters. Also arctiopicrin, a sesquiterpene ester-lactone of germacranolide structure.

The seeds in particular have been reported to contain lignans lappaol A, B, C, D and E; arctiin, arctigenin and metaresinol. Roots contain gamma-guanidobutyric acid and 14-polyacetylene compounds with trideca-1,11-dien-3,5,7,9-tetrayne (50%) and tridec-1-en-3,5,7,9,11-pentayne together with trideca-1,3,11-trien-5,7,9-triayne (30%) as the main components. Inulin (about 50%), arctic acid, germacrolide, and chlorogenic acid are also present.

THE MINISTERS

[SLIDE 20]

[SLIDE 21]

LIQUORICE

Glycyrrhiza uralensis

What a wonderful herb liquorice or *Glycyrrhiza uralensis* makes in this formula. It could easily be the Emperor, it is so beneficial. It is widely used herbs by practitioners of western herbal medicine, Kanpo and Ayurvedic traditions, as well as having a long history in ancient Egyptian and Greek prescriptions.

Its major role is as an anti-inflammatory, which is similar in activity to hydrocortisone.

It is used in France for rheumatoid arthritis, and will reduce and sooth the feeling of heat that often accompanies inflammation. A recent Russian study has shown an anti-inflammatory action of the extract on the skin was similar to a 0.5% prednisolone liniment and they also found that the dried powder was good for eczema.

It contains 2-9% of an intensely sweet saponin known as glycyrrhizin, glycyrrhetic acid, the aglycone of glycyrrhizin is also present in the root at levels of 0.5-0.9%. Liquorice also contains a large quantity of flavonoids which impart the characteristic yellow colour to the root. Liquiritin is the main flavanoid glycoside naturally present in the root, but on heating is converted to isoliquoritigenin.

THE ASSISTANTS

[SLIDE 22]

[SLIDE 23]

CHINESE ANGELICA

Angelica sinensis

Chinese Angelica or *Angelica sinensis* is vasodilatory, anti-inflammatory, is said to invigorate and nourish the blood. It removes skin blemishes (such as liver spots and melanin pigment deposits, where the melanosis process has basically failed), and is good for chapped skin. These properties are not dissimilar to our own Angelica which is *Angelica archangelica*.

[SLIDE 24]

REHMANNIA

Rehmannia glutinosa

Rehmannia glutinosa is also used for removing dark spots on the skin, but is also haemostatic.

The major components are β -sitosterol and β -mannitol are identified. Catalpol, an iridoid glycoside is also present.

It also contains eight types of sugars, amino acids like mannitol, arginine etc., and phosphoric acid.

[SLIDE 25]

ANEMARRHENA

Anemarrhena asphodeloides Bunge

The root-like stem of the perennial herb *Anemarrhena asphodeloides* one of the lily family is used. Its chemical components are saponin, asphonin, sarsapogenin, maykogenin, neogitogenin, and timosaponin. These components give the plant its anti-inflammatory and sedative effects.

[SLIDE 26]
ATRACTYLIS

Atractylis macrocephala or *Atractylodes macrocephala*

Atractylis macrocephala or *Atractylodes macrocephala* is used for aching joints and muscles, swelling and pain in feet and legs, weakness and sluggishness.

[SLIDE 27]

AKEBIA

Akebia quinata

Akebia quinata is a creeping woody vine. The plant contains the crystalline alkaloid akebin, which hydrolyses to yield hederagenin, rhamnose and oleanolic acid; as well as various potassium salts. Prescribed as an antiphlogistic, for the treatment of abscesses and to reduce oedema and associated swelling.

DIRECTIONAL HERBS

[SLIDE 28]

[SLIDE 29]

SILER

Siler divaricatum Benth. et Hook

The roots of *Siler divaricatum* are used medicinally for their antipyretic and analgesic effects.

CICADA

Cryptotympana pustulata (Cicadidae)

Cryptotympana pustulata is an insect, from which the moulting are used, and these are also used for their antipyretic and calming effects.

[SLIDE 30]

SOPHORA

Sophora flavescens

The root of *Sophora flavescens* is used to produce an extract that is antibacterial, antipyretic, antipruritic and used externally for eczema, skin sores or parasitic dermal lesions. It is also useful for preventing spots and freckles.

It contains matrine, oxymatrine, sophoranol, anagyrene, lupin alkaloids (e.g. matrin, oxymatrine etc.) which are marked as the main pharmacologically active constituents.

HARMONISING HERB

[SLIDE 31]

[SLIDE 32]

SCHIZONEPETA

Schizonopeta tenuifolia (Benth)

Schizonopeta tenuifolia is useful in skin complaints, and especially in nettle-rash (urticaria), scrofulous or painful swellings, and weeping pustules of infected scores. It is a herb widely used in Traditional Chinese Medicine.

[SLIDE 33]

SESAME

Sesamum indicum

Sesamum indicum seeds are used, which are demulcent, and applied externally are rich in mucilage and so soothing for ophthalmic and cutaneous complaints.

The seeds contain 45-58% fatty oil (comprising 47% olein, 35% linolein, 9% palmitin, 6% stearin, myristin), a resinous principle sesamin, sesamol, pentosan, phytin, lecithin, choline, 1% calcium oxalate, chlorogenic acid, vitamins A and B.

In the West, sesame oil is employed externally to soften the skin, as well as a dressing for burns, and a vehicle for liniments.

REASONS FOR SUCCESS

The reasons for the success of this ancient remedy are many. It can be seen that the various plants have a proliferation of activities that would address many aspects of the healing process, all of which are stimulated by a broad range of different actives contained within the plants. It is highly likely, that these plants act synergistically.

Thus, looking through the key words mentioned for each plant one finds demulcent, antipyretic, antitoxic, antiphlogistic, anti-inflammatory, antipruritic, antiulcer, haemostatic, antispasmodic, antibacterial and other skin regulating activities.

2. ANOTHER HISTORICAL FORMULATION

[SLIDE 34]

If we go back in time to our own history, then we can find our own examples of polypharmacy.

Formula from Physicians of Myddvai

The Physicians of Myddvai were 12th Century healers from Wales and here is one of their recipes for "any type of wounded integument".

"Take avens, violet, daisy, bugle, ribwort plantain and feverfew; pound and boil them well with fresh butter, and strain. keep it for it is useful."

Avens (*Geum urbanum*) or Colewort is anti-inflammatory, astringent and traditionally used for skin problems. Violet (*Viola tricolor*) [SLIDE 35] used traditionally for eczema and other cutaneous disorders, relieves inflammation, antipruritic and anodyne (soothes pain). [SLIDE 36] Daisy (*Bellis perennis*) or Bruisewort reduces bruising and swelling, used for suppurating wounds, furuncles and boils etc. Bugle (*Ajuga reptans*) or Sickwort is a haemostatic and was used to stop bleeding caused by cuts. [SLIDE 37] Ribwort Plantain (*Plantago lanceolata*) is antipruritic, haemostatic, anti-inflammatory and anodyne. [SLIDE 38] Feverfew (*Tanacetum parthenium*) soothes swellings, anti-inflammatory and soothing on insect bites.

A modern herbalist would not be at all uncomfortable with this herb and it is well cited for the treatment of problem skin conditions.

3. A MODERN FORMULATION REGIME

[SLIDE 39]

Returning our thoughts to the various stages of healing, it did not seem unreasonable to propose that the use of a regime of products that would cater for each of those stages could be developed. It also occurred to us that it did not seem unreasonable to propose that a single product could be developed which contained all the medicinal plant elements necessary to address each of the functions required for a particular stage to be successful.

[SLIDE 40]

You may recall these stages were:

Granulation
Re-epithelialisation
Cicatrisation

The three products in one particular suite are not intended as skin care products, but are intended as post mastectomy surgical cosmetics.

[SLIDE 41]

The complications are:-

Pruritis,
Pain, tenderness, soreness
Skin dryness, cracking
Discomfort
Inflammation
Slow speed of recovery

[SLIDE 42]

The desired product benefits are:-

Hydration
Environment for healthy cell growth
Healthy bacterial flora
Establishment of correct level of occlusion/skin respiration
Optimisation of numerous physiological processes

[SLIDE 43]

From the patients point of view there is tremendous psychological trauma, a lack of self esteem and feeling that her body has been defaced. For her there is no specific product for her specific condition.

The experimental product

This product is a cooling and soothing gel to improve the comfort of the skin, to relieve inflammation and to help in the healing process. It helps maintain the normal moisture balance in the skin, whilst providing an ideal environment for skin healing during granulation.

[SLIDE 44]

Granulation stage

[SLIDE 45] A special form of *Aloe barbadensis* Miller (100%)
Sanguinaria canadensis

[SLIDE 46] *Ruscus aculeatus*

[SLIDE 47] *Viola tricolor*

Re-epithelialisation

[SLIDE 48] *Oenothera biennis*

[SLIDE 49] *Matricaria chamomilla*
Tocopherol acetate

Cicatrisation

Rosa aff. rubignosa

Alpha bisabolol

Ruscus aculeatus

Allantoin

Mimosa tenuiflora

Patient response to these products

How do patients respond to these products? Well, they seem to like them, and though I am not keen on anecdotal evidence, I am pleased with the early responses.

[SLIDE 50]

[SLIDE 51]

[SLIDE 52]

[SLIDE 53]

These spontaneous responses were summarised as follows:-

[SLIDE 54]

scar fading	20%
moisturising	20%
softening	60%
skin comfort	20%
relief of itching	25%
soothing	25%
pleasing, pleasant	65%
suppleness	25%
smoothness	40%

We have also carried out cutometer measurements to measure the improvement in skin elasticity, corneometer measurements to measure the improvement in the skin moisture, and these figures will be in the published proceedings.

Finally, we hope to be able to present the findings of our clinical trials due to start by the end of the year at St. Bartholomew's Hospital and Christie's Hospital at a later date.

Conclusion

I hope that I have demonstrated that there is a very promising future for the use of medicinal plants both in cosmetics and toiletries, but also in the closely related area of Pharmaceutical Cosmetics.

[SLIDE 55]

However I will leave you with one formula from the 15th century ascribed to Alberticus Anglicus Take a very fat puppy dog and skin him; then take the juice of cucumber, rue and pellitory; berries of ivy and juniper; fat of vulture, fox and bear in equal parts; stuff the puppy therewith and boil him. Add wax to the grease that floats on the surface and make therefrom an ointment.

I think you will agree that we have all developed quite substantially. I would like to thank you all for listening to me today