The Topical Use of

AZELAIC ACID

in Dermatology

ESSAY

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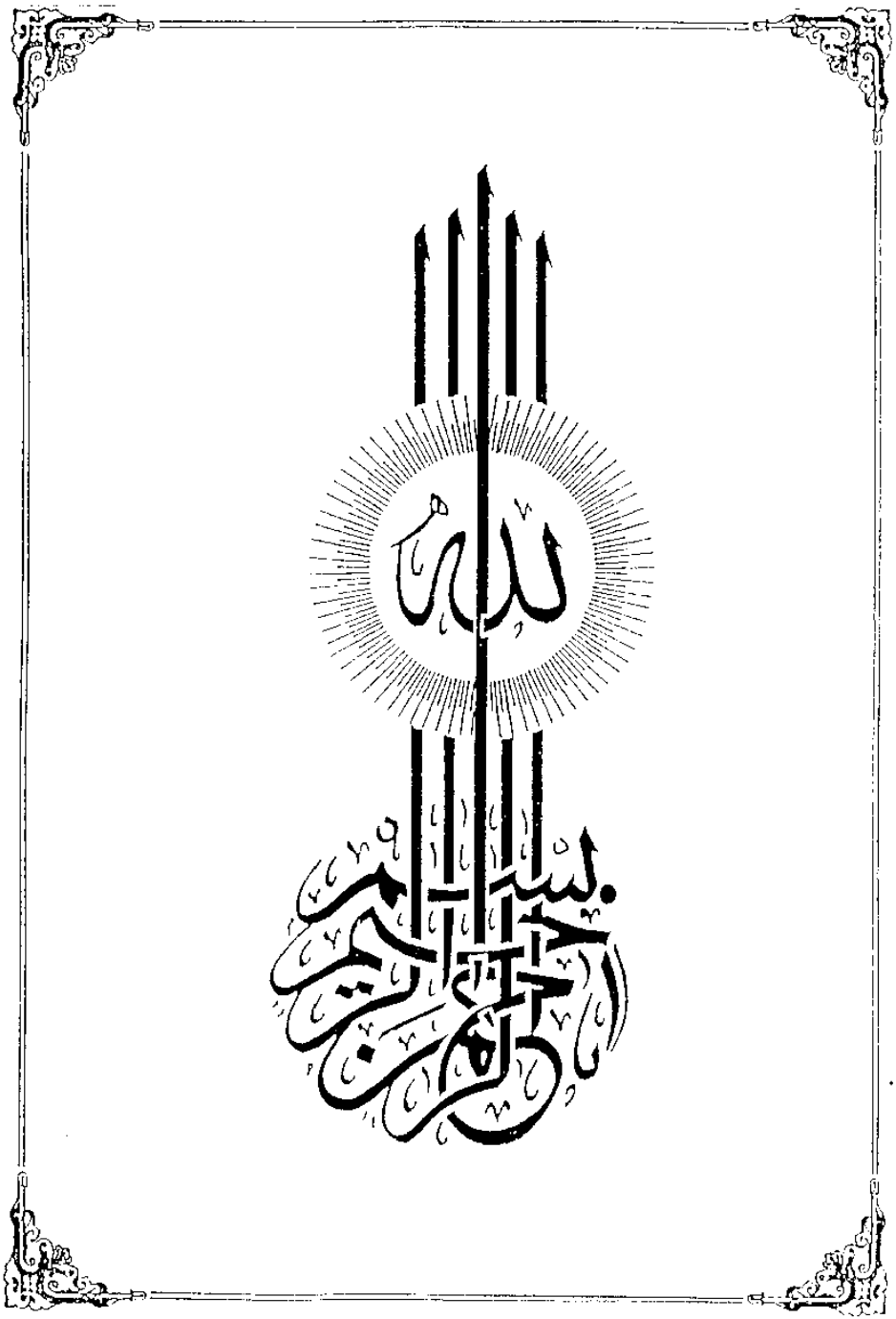
بسم الله الرحمن الرحيم

سُبْحَانَكَ لَا عِلْمَ لَنَآ إِلَّا مَا عَلَّمْتَنَآ

إِنَّكَ أَنتَ الْعَلِيمُ الْحَكِيمُ

صدق الله العظيم

سورة البقرة آيه رقم (٣١)



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AIM OF THE WORK

The aim of this work is to evaluate and report the up-to-date and recent advances in the use of azalaic acid as a practical clinical therapeutic agent.

ABBREVIATIONS

AA	Azelaic Acid
Ca^{++}	Calcium
Co	Coenzyme
K^{+}	potassium
LD_{50}	Lethal Dose 50
Na^{+}	sodium
NAD	Nicotinamide Adenine Dinucleotide
NADP	Nicotinamide Adenine Dinucleotide Phosphate
NADPH	Nicotinamide Adenine Dinucleotide Phosphate (reduced)

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INTRODUCTION

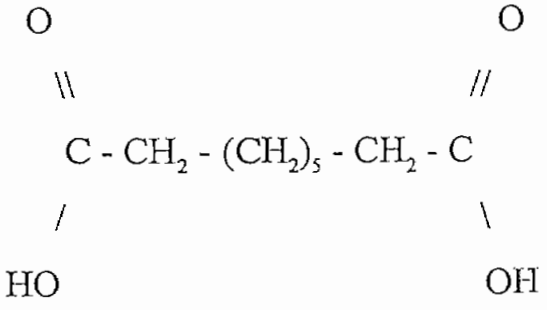
The initial discovery and recognition of the biological properties and therapeutic potential of AZELAIC ACID (AA) lies firmly to the credit of Marcella Nazzaro-Porro, Siro Passi and their associates of the San Gallicano dermatological institute of ROME *(Breathnach, 1989c).*

Their starting-point was an academic interest in skin surface lipids and the pathogenesis of hypopigmentation in pityriasis versicolor (*Nazzaro-Porro and Passi,* 1978a). It had been generally thought that the hypopigmentation in pityriasis versicolor was due to the filtering out of the ultraviolet irradiation by the fungus in the stratum corneum, but ultrastructural examination of the biopsies revealed damage to melanocytes ranging from swelling and vacuolation of mitochondria to extensive degeneration of some cells (*Breathnach et al.,* 1975). The lipophilic and lipid-dependent nature of pityrosporum and the highly modified pattern of skin surface lipids associated with its presence suggested that some metabolic products of lipid nature might be the cause of this damage (*Breathnach et al.,* 1984).

This hypothesis seemed to be confirmed when pityrosporum was shown to be able to oxidize unsaturated fatty acids, in cultures of the fungus supplemented with unsaturated fatty acids with double bond in the 6-12 position it was observed that dicarboxylic acids of chain lengths C_6-C_{12} were formed and that these dicarboxylic acids exhibited an ascending gradient of competitive tyrosinase inhibition in vitro *(Nazzaro-Porro et al.,* 1979*).*

It seemed reasonable to assume that the hypochromia in pityriasis versicolor might be due to the antityrosinase activity of these diacids, and the possibility arose that they might be beneficially applied to the treatment of hyperpigmentary disorders and set to test one of the reasonably soluble dicarboxylic acids with an intermediate range of antityrosinase activity (*Nazzaro-Porro and Passi,* 1978a).

AZELAIC ACID is a naturally occurring saturated dicarboxylic acid, [1,7-heptanedicarboxylic acid $HO_2.C(CH_2)_7.CO_2H$], straight chained contains 9 carbon atoms (C_9). With a molecular weight of 188.22, and melting point of 105.5 degrees centigrade. It can be prepared by oxidation of oleic acid by nitric acid, and occurs in rancid oleic acid.(*Breathnach*,1989b)



AZELAIC ACID

Chemical formula

(Gollnick, 1993)

Among dicarboxylic acids AA (C_9 dicarboxylic acid) was originally chosen in preference to other diacids (such as; for instance, dodecanedioic acid, $C_{12,}$ which has similar effects) because: it is much cheaper than othe dicarboxylic acids, and it has no toxic, teratogenic, or mutagenic effect. Also it is relatively easier to be incorporated into creams for topical applications and when administered orally to humans, at the same concentrations as the other dicarboxylic acids it reaches much higher serum and urinary concentrations (*Passi et al.*, 1989).

A cream containing 15-20 % of AA was prepared and when applied topically, proved effective in the treatment of melasma and post-inflammatory melanosis leaving no residual hypochromia (*Nazzaro-Porro and Passi* 1978b).

A positive beneficial effect was also observed following application of the cream to cases of lentigo maligna (*Nazzaro-Porro et al.*, 1979). This beneficial effect of topical AA on lentigo maligna provides a most satisfactory form of therapy especially in early cases and for extensive long standing lesions in older patients (Nazzaro-Porro *et al.*, 1982).

Breathnach et al., in 1984, stated "though we are aware of the body of opinion that maintains surgery to be the only justifiable treatment for lentigo maligna, however surgical treatment may be inapplicable, and its results can be cosmetically unacceptable. Those who would advocate it as the only treatment must take into account that lentigo maligna is a relapsing condition and that surgery, by its very nature, can be extremely difficult to apply a second time".

The beneficial effect of AA on acne was first observed when a number of patients who where treated for melasma reported a coincidental improvement in their "spots". *Nazzaro-Porro et al., (1983)* following it up, performed an open study on a 100 patients with acne vulgaris at three centers, the results where encouraging.

In controlled studies topical AA 20% demonstrated comparable anti-acne efficacy to topical tretinoin, benzoyl peroxide, erythromycin and oral tetracycline (*Gollnick and Graupe*, 1989).

While in patients with melasma AA 20% proved clearly superior to 2% hydroquinone - the drug most frequently used in melasma (*Verallo-Rowell et al.*, 1989).

On topical application AA is well tolerated with adverse effects apparently limited to a generally mild and transient local cutaneous irritation which may make AA useful in those patients with a more sensitive skin type (*Gollnick*, 1990).

While the mechanism of action of AA in dermatological conditions is unclear, it may possibly be related to its inhibition of mitochondrial oxidoreductase activity and DNA synthesis (Picardo *et al.*, 1983).

Thus topical AA, employed either as mono therapy or in combination with other treatment, is likely to prove of value in the management of acne and several hyperpigmentary disorders.

PHARMACODYNAMIC PROPERTIES

THE EFFECT OF AA ON CUTANEOUS MICROFLORA

Normally there are large numbers of the skin surface commensals these include, Diphtheroides, Non-haemolytic staph.(Epidermidis), anthracoids, streptococcus faecalis, E.coli, fungi, yeast and Saprophytic acid fast bacilli. Under normal conditions they are unlikely to cause any significant pathological effects (*Stewart,* 1974).

Some of these skin surface commensals are found in the sebaceous follicles - under normal conditions - such as propionibacterium acnes, propionibacterium granulosum, staphylococcus species and pityrosporum ovale (*Leeming et al.*, 1985).

There is a strong opinion that propionibacterium acnes is of prime importance in acne, several pieces of evidence support this view:

* Firstly, the onset of acne occurs at puberty with the enlargement of the sebaceous glands, an increase in sebum excretion rate and an increase in follicular colonization by propionibacterium (*Leyden et al.*, 1975a).

* Secondly, successful antibiotic treatment is accompanied by a reduction in the propionibacterial density on the skin (Marples et al., 1974).

* Finally, animals even hairless bred strains, do not induce acne as their skin is devoid of propionibacteria. (Webster *et al., 1981*).

While acne is not a bacterial disease, the follicular bacterial population plays a major role in the generation of the extracellular inflammatory substances. Propionibacterium acnes organisms are found deep in the sebaceous follicles, while the more superficial follicular flora consist of staphylococcal species and lipophilic pityrosporum yeast. Propionibacterium acnes has been shown to produce a low molecular weight peptide that is chemotactic for polymorphonuclear leukocytes, the chemotactic activity of this peptide will attract the polymorphonuclear leukocytes to the intrafollicular site. Subsequent events can lead to further follicle damage and dermal inflammation from the release of extracellular and intracellular hydrolytic leukocytic enzymes. the action of the extracellular enzymes of propionibacterium acnes, including lipases, proteases and hyaluronidases, also contribute to the inflammatory response. Thus while acne is not a bacterial disease per Se, it is clear that propionibacterium acnes acts as a source of pro-inflammatory substances. (*Strauss,* 1989)

Breathnach et al., (1984) reported that skin areas treated with AA cream showed a marked reduction (about 60%) of the free fatty acid fraction as compared with the control areas, indicating an inhibition of bacterial lipase activity. While these effects are suggestive of a direct antibacterial (bacteriostatic or bactericidal) action of AA in vivo the possibility that they might be mediated indirectly through AA-induced alteration to the cutaneous microenvironment cannot be excluded.

Bladon et al., (1986) compared oral tetracycline and AA for treatment of acne vulgaris. Using one gram oral tetracycline and 20% AA cream topically. They found a reduction in the numbers of staphylococci of 224-fold (99.6%),

and a 30-fold decrease in the density of propionibacterium acnes on the skin (96.7%), while tetracycline had no significant effect on the density of micrococcaceae or the propionibacterium .

Mayer-da-Silva, (1989) in an electron microscopic study for acne bearing skin before and after treatment with AA found that comedones obtained before treatment were always filled with abundant fat droplets with varying electron density, horny material, multitudes of bacteria and clusters of ovoid yeast spores. In comedones obtained after treatment the follicular channel still contained abundant fat droplets and a little horny material, but the number of bacteria and spores were dramatically decreased. Which supports the in vivo anti-microbial activity of AA.

Using AA 20% cream or its base alone (as control) applied twice daily, confirmed that AA reduces the cutaneous bacterial flora and has established that those bacteria located in the pilosebaceous follicles are affected as these on the skin surface. There was a reduction of 97.7% after two months of treatment of the follicular micrococcaceae compared with the pre-treatment levels. The propionibacterium densities were not reduced after one month of treatment, but were so after a further one month (99.9% reduction) (*Cunliffe and Holland,* 1989).

Nazzaro-porro et al.,(1985) showed that AA at 0.5 mmol/L concentration fully inhibited the growth of aerobic bacteria (proteus mirabilis, staphylococcus aureus, escherichia coli, pseudomonia aeruginosa, cornybacterium) and also the growth of the anaerobic propionibacterium acnes at 0.1 mmol/L.