

Theraflax in the improvement of psoriatic symptoms.
Application of ω 3/ ω 6 essential fatty acids in psoriatic patients

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Theraflax, a product of Crede Natural Oils (RSA), is used as a food supplement for patients with different forms of psoriasis. Theraflax is a well-balanced combination of essential fatty acids (EFA) and other fatty acids, derived from different plant species: *Borago officinalis*, *Nigella sativa*, *Linum usitatissimum*. According to the producers the content of polyunsaturated fatty acids (Tabl.1) is considered optimal.

Tabl.1 The fatty acid content of Theraflax

Fatty acid content	%
Alpha-Linolenic	45.3
Linoleic	23.6
Oleic	17.9
Gamma-Linolenic	2.2
Palmitic	5.6
Other fatty acids	2.1
Total fatty acids	99.7
Aromatic oils	0.3

Psoriasis is one of the most often occurring dermatological disorders, affecting more than 2% of the world population. Psoriasis is a chronic relapsing skin disease, sometimes involving the nails and joints, based on genetic predisposition and exogenous provocation. It is characterized by dysfunction of keratinization, clinically presented with erythemo-papulo-squamous lesions, disseminated on different body areas.

The etiology of the disease is still unknown. Viral, immune and metabolic theories are widely discussed, however in recent studies the scientific attention is focused on the genetic predisposition. According to this theory psoriasis is a polygenetic disease, in close correlation to hypertension, podagra, diabetes mellitus and dyslipidemia. The wide extension of the disease, family history and greater incidence in monosygotic twins with the priority of HLA B13/B17 haplotypes and ABH erythrocyte antigens could verify this hypothesis. HLA Bw6 haplotype proves to be a 10-fold greater incident risk and together with HLA B57 leads to higher incidence in the twenties and thirties. HLA B27 is related with psoriasis arthropathica, which usually affects middle aged people.

Many exogenous factors could induce or trigger the disease. They can be summarized in four main groups: physical (mechanical, thermal, electromagnetic, etc), chemical, infectious (viral, bacterial, etc.), medicamentous (tetracyclines, anti malarial drugs, ACE inhibitors, Lithium, etc.). Emotional stress, especially in association with hormonal disturbance, is an endogenous triggering factor.

The histopathology of psoriasis is characterized by dysfunction of keratopoesis. The major pathological features are parakeratosis, Munro abscesses and an increased number of mitoses. Acantosis and spongiosis are often seen. The dermal-epidermal border is well marked. The upper derma shows papillomatosis and dilation of capillaries with excess of perivascular neutrophilic infiltration. The nerve fibers are dystrophic, with enlarged neurolema and central cylinder.

Two major metabolic dysfunction routes accentuate the **pathogenesis**:

1. Impaired keratinization

2. Impaired cell differentiation

The increased epidermopoesis, characterized by a three times greater number of cells/1mm² in the basal layer and multiple DNA syntheses, leads to a seven times lower rate of regeneration and a 12fold shortening of transition time. The smaller number of epidermal desmosomes and tonofillaments can demonstrate the impaired cell differentiation.

The intimate **pathogenetic mechanisms** can be considered as follows:

- **cAMP deficiency.** cAMP is a nucleotide, which plays an important role in the processes of cell differentiation, hormonal synthesis and stimulation of glucogenolysis. The cAMP deficiency in the inflamed skin lesions increases the cell permeability and distribution

of lysosome enzymes in the corneal layer. The level of cGMP and the cGMP/cAMP ratio is significantly higher in the psoriatic lesions.

➤ **Decreased synthesis of chalone.** The chalone are proteins restricting cell division rate. Their effect can be regulated by adrenaline with which they activate adenylatecyclase, thus increasing the level of cAMP. The reduced quantity of chalone in the psoriatic lesion leads to accelerated cell proliferation and regeneration time reduction.

➤ **Arachidonic acid.** The enzyme- phospholipase A₂ -separates arachidonic acid from membrane cell phospholipids. The metabolism of arachidonic acid proceeds in two major pathways and ends with the synthesis of leukotrienes and prostaglandines, which act as mediators of inflammation and cell-to-cell modulators. The lipoxygenase pathway of arachidonic acid metabolism is accelerated in psoriasis and leukotriene metabolism is increased in such patients. Leukotriene B₄ has a leading role among the leukotriene substances thus explaining the neutrophil hemotaxis and Munro abscesses in the inflamed epidermis. Meanwhile the limited cyclooxygenase metabolism proves the lower level of prostaglandine E₂, which inhibits the adenylatecyclase activity and reduces the content of cAMP.

At the same time the arachidonic acid acts as a second messenger, activating proteinkinase C, whose main metabolic product –phosphatidil-inositol-biphosphate (PIP₂)-is a modulator of cell proliferation and differentiation, and its lower content in the psoriatic lesions explains the hyperproliferation and lack of maturation of the affected epiderma.

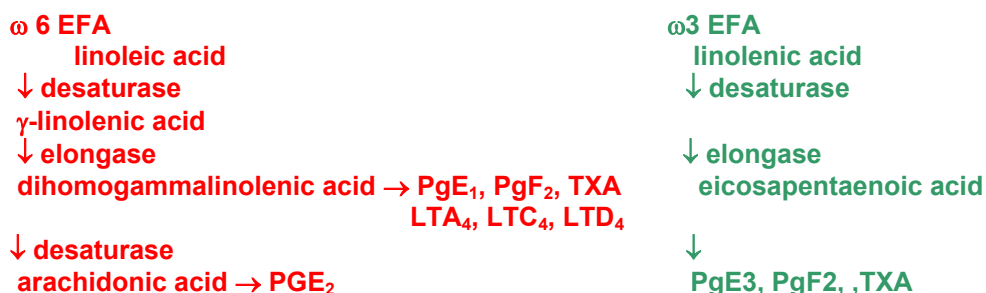
➤ **Immunological mechanisms.** The pathologic process of skin and joint lesions in psoriatic arthritis is an inflammatory reaction, and evidence also exists for autoimmune reactions, perhaps mediated by complement activation. However, synovial-lining hyperplasia is less, macrophages are fewer, and vascularity is greater in psoriatic arthritis compared with rheumatoid arthritis synovium.

Antiepidermal keratin and anticytokeratin-18 antibodies have been found in the sera of patients with psoriasis and psoriatic arthritis. Several studies have shown a significant reduction in the number and percentage of CD4+ T cells in the peripheral blood, whereas they are found throughout the skin lesions and synovium. Dendritic cells have been found in the synovial fluid of patients with psoriatic arthritis and are reactive in the mixed leukocyte reaction; the inference is that the dendritic cells present an unknown antigen to CD4+ cells within the joints and skin of patients with psoriatic arthritis, leading to T-cell activation. Fibroblasts from the skin and synovia of patients with psoriatic arthritis have an increased proliferative activity and the capability to secrete increased amounts of interleukin-1, interleukin-6, and platelet-derived growth factors. Several studies suggest that cytokines secreted from activated T cells and other mononuclear proinflammatory cells induce proliferation and activation of synovial and epidermal fibroblasts.

Psoriatic plaques have increased levels of leukotriene B₄. Injections of leukotriene B₄ cause intraepidermal microabscesses, suggesting a role for this compound in the development of psoriasis. Psoriatic arthritis is an autoimmune disorder affecting 4% of the patients with psoriasis. It involves the joints but also the ligaments, tendons, fascia, and insertions.

➤ **Metabolic changes.** The saturated fatty acids (SFA) – palmitine and stearine- are highly increased in the blood samples of psoriatic patients in comparison to the levels of polyunsaturated fatty acids (EFA)- linoleic and arachidonic, which play an important role as structural compounds of membrane cell phospholipids. EFAs play an important role in different metabolic pathways as it is shown on Fig. 1.

Fig.1 Metabolism of essential fatty acids (EFA)

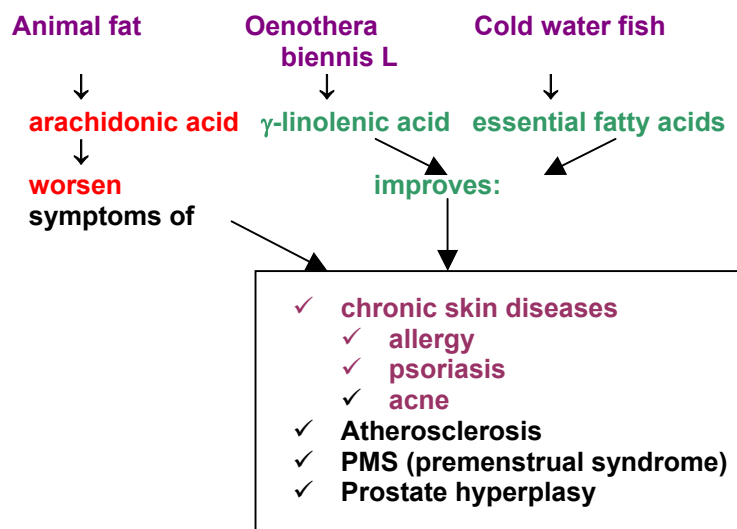


It is suggested that membrane phospholipid compounds differ in patients suffering from psoriasis combined with a lower content of essential fatty acids compared to saturated fatty acids. This leads to changes in the lipid surroundings of membrane proteins, which are mainly receptors and enzymes. The changes refer to the tertiary and 4th structure of the proteins, which explains the altered activity of certain receptors which on their part influence the activity of phospholipase A₂ and phospholipase C. Those are the main enzymes involved in the metabolism of the phospholipids and their different metabolite pathways. The authors of this hypothesis believe that either the reduced intake of essential polyunsaturated fatty acids or the impaired EFA/SFA ratio intake in genetically predisposed individuals cause increased synthesis of arachidonic acid and its inflammatory metabolite substances, respectively. However, the correction of the polyunsaturated fatty acid intake to proper quantities could have formed anti-inflammatory mediators- PG E₁ and PG E₃, for example.

The idea of the introduction of polyunsaturated fatty acids in everyday diet as a psoriasis therapy is based on the epidemiological characteristics of the disease and particularly on the low incidence in Eskimo population. Obviously, the rich content of polyunsaturated fatty acids in fish- the most common food product in Eskimo diet- can be determined as a preventing factor. Surely, the proper everyday intake of essential fatty acids could change the lipid surrounding of membrane proteins, thus modulating their conformation and activity. Avoiding the oversupply of arachidonic acid, and reaching appropriate balance in the EFA/SFA ratio, proper synthesis of anti-inflammatory mediators can be obtained. The proper EFA/ SFA intake harmonizes the impaired Th₁/Th₂ balance and increases the resistance towards exogeneous inflammatory factors (bacterial, viral, etc.) that often trigger certain chronic relapsing dermatoses including psoriasis.

The essential polyunsaturated fatty acids influence the skin metabolism as well as the function of other human organs and systems. Fig 2 represents the contents of polyunsaturated fatty acids in different food products and their activity towards various pathological conditions:

Fig.2 Impact of EFA over different pathological conditions



It is confirmed experimentally that polyunsaturated fatty acids reduce the relative cancer risk and increase the life expectancy in cancer patients. They decelerate skin aging and limit the frequency of migraine attacks thanks to their vasoprotective activity.

It is hypothesized that polyunsaturated fatty acids could restrict the synthesis of leukotriene metabolites of arachidonic acid thus reducing the symptoms of inflammation and pain in different chronic conditions including psoriasis and psoriatic arthritis.

The polyunsaturated fatty acid deficiency especially the lack of ω3 EFA and the improper EFA/SFA ratio can cause various pathological processes, which are summarized as followed:

- **Immune reactivity disorders** originating in accentuated susceptibility to infections, especially dermatological.
- **Low wound healing rate**
- **Damaged skin barrier**
- **Hair loss**
- **Dry scaly skin**
- **Lowered visual sharpness**
- **Cardiac rhythm and conduction abnormalities**
- **Hypertension**
- **Impaired liver function**
- **Neuro-psychiatric problems-** lower concentration ability, emotional instability, parenthesis, etc.
- **Fertility dysfunction**
- **Renal problems**
- **Damaged RBC(red blood cell) function**
- **Physical retardation**

Nutritiology gives standardized doses for the daily intake of polyunsaturated and saturated fatty acids, as follows (Tabl.2).

Tabl.2 EFA and SFA recommended daily doses

Linoleic acid	7-10% of energy supply
αLinolenic acid	2-3% of energy supply
γ Linolenic acid	1-4 g/ daily
Ω 3 EFA(EPS and DHS)	1-5 g/ daily

The content of polyunsaturated fatty acids differs in the various food products. The richest amount of EFA is found in plant and marine oils (Tabl.3).

Tabl.3 Content of EFA in various food products

Linoleic acid	Maize, Soya and Sunflower oils
αLinolenic acid	Soya, Semen Lini
γ Linolenic acid	Oenothera biennis, Borrago officinalis
Ω 3 EFA	Fish, shells

The content of Ω 3 polyunsaturated fatty acids predominates in fish and marine delicatessen and is shown on Tabl.4.

Tabl.4 Content of Ω 3 polyunsaturated fatty acids in marine food products (mg/100g)

Food products	EPS	DHS
Herring	2700	450
Calmar	1070	2280
Salmon	700	2140
Trout	150	335
Sea crab	280	130
Shrimp	215	150
Clam fish	50	100

The overdose application of polyunsaturated fatty acids has several negative characteristics that need to be considered.

- **immune system function disorder**
- **Fertility problems** due to the depletion of Vit E depots. Therefore additional supply of Vit E is needed.
- Reduction of **insulin activity**
- Increased susceptibility to **bleeding**
- **Vit B3, Vit B6 and Vit C** as well as **microelements Mg and Zn** stimulate the transformation of linoleic acid into γlinolenic. Their deficiency, together with the high blood glucose level, alcohol and saturated fatty acid excess inhibit this process.

Tabl.5 Interference of different substances into EFA metabolism

EFA	Promotor	Inhibitor
Linoleic acid	Vit B6 Mg Zn	Alcohol and saturated fatty acids excess
γLinolenic acid	Vit B6 Vit B3 Vit C	Acetysal Corticosteroids

Based on the preliminary observations and theoretical presumptions it was assumed that Theraflax might have a beneficial effect on psoriatic symptoms. According to the instructions given by the producer Crede Natural Oils (RSA) Theraflax should be taken every day, in a dosis of 20 ml, divided in two administrations, for at least 6 months. On achieving improvement the dose can be reduced according to the individual threshold of each patient.

The clinical observation of Theraflax was done at the Dermatological department of the Medical Faculty- Sofia, for the period from 01.06.2001 to 01.09.2002. The observation objective presumed a beneficial effect of Theraflax on patients with different forms of psoriasis, who were instructed to take only the supplement for a duration of a minimum of 6 months. They were allowed to apply indifferent emollients as well (Linola Fett- Dr Wolff; Excipial Hydrolotio- Spirig; ex tempore prepared cold crème containing vaselin, lanolin and aqua calcis in equal quantities). The criteria were patients with chronic relapsing psoriasis, psoriatic arthritis or erythrodermia psoriatica and history of psoriasis for at least 2 years. All patients took 20 ml Theraflax daily, divided into two equal doses in the morning and in the evening. The follow-up period extended for 6 months as the patients underwent three obligatory clinical examinations – on the 30th, 90th day and at the end of the 6th month. At the beginning of the observation and at the end of the third month routine blood analyses and biochemistry samples (including blood glucose and liver tests) were taken. cAMP and cGMP parameters were worked out for 35 patients.

The observation included 73 patients, 24 among whom noted slight dyspepsy and gastric discomfort on taking the supplement. Twentyone of the patients were excluded from the observation. Severe vomiting occurred in two female patients that had undergone cholecystectomy in the past. Intolerance of the same kind was observed in one male patient who had complicated internal status- morbus hypertonicus, diabetes mellitus, and chronic bronchitis. Six women and one man were excluded for concomitant intake and application of minerals, vitamins and antipsoriatic drugs. A male patient with comorbidity of psoriasis and acne vulgaris who announced exacerbation of the acne symptoms towards acne congloba during the observation belonged to this group. Despite the good therapeutical response he was forced to discontinue the intake of Theraflax for the need of treating his acne with different medications. Eight patients were excluded from the observation for irregular intake of Theraflax, and three other patients have not attended the obligatory follow-up visits.

Fifty-two patients (40 male and 12 female) underwent the entire course of observation for at least 6 months. The forms of psoriasis affecting the patients were 28- psoriasis vulgaris, 19- psoriasis arthropathica and 5- erythroderma (Tabl.6).

Tabl.6 Clinical forms of psoriasis

Clinical form	Number of patients
Chronic relapsing psoriasis vulgaris	28
Psoriasis arthropathica	19
Erythroderma psoriatica	5

Fluctuation in patient dermatological status was observed as clinical improvement was sometimes followed by a relapse of the disease despite the continuation of Theraflax. A female patient with verrucous psoriatic lesions on both hands, who had undergone 5 sessions of Xray therapy before the initiation of Theraflax, showed good improvement in her clinical status.

The routine blood analyses and liver enzymes at the beginning and the end of the study were not significantly influenced.

Evaluation scoring and the assessment method used in analyzing the patient response before and after Theraflax intake was PASI (psoriasis area and severity index). The four main anatomic sites assessed were: head (h), upper extremities (u), trunk(t), lower extremities(l), corresponding approximately to 10, 20, 30 and 40% of the body surface area(BSA).

The PASI score was calculated from:

$$\text{PASI} = 0.1(E_h + I_h + D_h) \times A_h + 0.2(E_u + I_u + D_u) \times A_u + 0.3(E_t + I_t + D_t) \times A_t + 0.4(E_l + I_l + D_l) \times A_l$$

E- erythema, I-induration, D- desquamation, A- area.

E, I, D were evaluated to a 4-point scale where: 0=no symptom; 1= slight, 2=moderate, 3=marked, 4=very marked.

A was assigned a numerical value based on the extent of lesions in a given anatomic site: 1=<10%, 2=10-29%, 3=30-49%, 4=50-69%, 5=70-89%, 6=90-100%. PASI varied in steps of 0.1 units from 0.0 to 72.0. The highest score stayed for complete erythroderma.

The results were statistically based on SYSTAT VERSION 7. The statistical analysis showed great improvement of patient psoriatic status at the end of the study (t= 5.395, p=0.000).

Tabl.7 Statistical analysis-PASI

Paired samples t test	PASI 0	PASI 1
Mean	10.654	6.301
Standard Deviation	7.748	5.331
Mean Difference /95%/	4.135	

The values of cAMP and cGMP were determined at the beginning and approximately in the 3rd month of Theraflax treatment in 35 patients. The statistical evaluation of these values showed significant increase of cAMP (t=-2.742; p=0.001, Tabl.8) with no difference in the cGMP (t=0.481, p=0.633, Tabl.9). These results supported the hypothesis of the beneficial effect of Theraflax over the psoriatic pathobiochemistry and especially over the reduction of joint inflammation in psoriasis arthropathica which was characterized by impaired Th₁/ Th₂ balance and predominance of IL-1, IL-10 synthesis. However, further evaluation is needed.

Tabl.8 Statistical analysis- cAMP

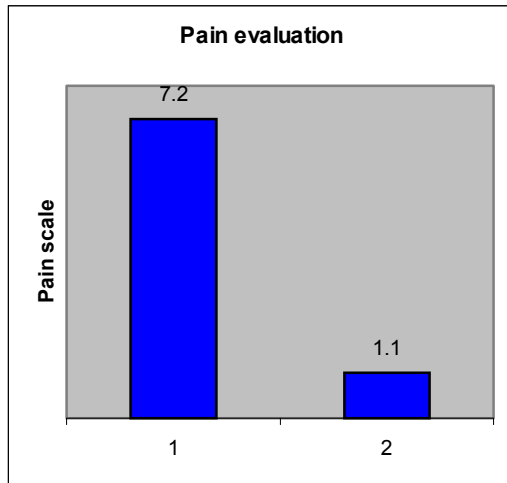
Paired samples t test	cAMP 0	cAMP 1
Mean	13,188	14,249
Standard Deviation	3,423	2,599
Mean Difference /95%/	-1,061	

Tabl.9 Statistical analysis- cGMP

Paired samples t test	cGMP 0	cGMP 1
Mean	4,493	4,381
Standard Deviation	1,814	1,239
Mean Difference /95%/	0,112	

There was a significant reduction of the pain symptoms in the patients with psoriasis arthropathica, which occurred between the 7th and 21th day of the initiation of the treatment. Evaluated at the beginning of the observation as 7.2 (based on 10grade scale), the arthralgia was estimated as 1.1 at the end. Only one patient out of 19 did not report a reduction of pain intensity (Fig. 3).

Fig.3 Evaluation of joint pain before and after Theraflax intake



None of the patients were completely cured.

Conclusions

1. The observation proved an excellent effect of Theraflax on the pain symptoms in patients with psoriasis arthropathica. Most of the patients claimed effective beneficial response in the first 10 days of the initiation of the treatment. This result confirms the prediction that Theraflax as a natural well-balanced product, may be one of the best methods for alleviating the pain symptoms compared with the multiple adverse effects of the antiinflammatory and immunomodulating drugs used nowadays.
2. The statistically significant reduction of PASI (especially of induration and desquamation of the plaques) defines the food supplement Theraflax as an essential part of the everyday menu of psoriatic patients.
3. The significant decrease of cAMP suggests the possible effect of Theraflax to interfere with the complicated pathobiochemistry of psoriasis thus effectively altering the impaired metabolic pathways.
4. The most important side effect of Theraflax proves to be dyspepsy and gastric discomfort that were observed in 24 (out of 73) patients, three of whom discontinued the intake for this reason.
5. The greatest defect of Theraflax was suggested to be the short expiry date (6 months only).
6. Theraflax alone does not cure psoriasis but it should be considered an important concomitant agent in the combined antipsoriatic regimen.

Recommendations

1. Theraflax should be administered together with Vit B₃, B₆, Vit C and microelements Mg and Zn, which exert synergetic effect on its metabolism.
2. Alcohol, sugar and saturated fatty acid excess could reduce the utilization of polyunsaturated fatty acids, therefore their concomitant intake should be avoided.

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