Flaxseed oil, a fish oil challenger?

Abstract: The too low level of omega-3 intake in the modern diet is a fact which is worrying health professionals and authorities. Among the “traditional” recommendation for a safe and equilibrated diet, recommending food containing omega-3, is there, out of the inescapable fish oil leading to some digestive discomforts, any alternative? Two human clinical trials conducted to verify the effective efficiency of this re equilibrated diet on various skin parameters (hydration, surface evaluation, inflammation) are reviewed here. The results of the clinical trials on various skin parameters (hydration, transepidermal water loss, roughness, scaling, superficial inflammation and blood flow) were quite convincing about the interest of such a supplementation.

Key words: PUFA, skin, hydration, inflammation, blood flow

The fatty acids of the omega-6/omega-3 families

Fatty acids (FA), in general, are long chain molecules. If they have more than a single bound they are called polyunsaturated fatty acids (PUFAs).

Roughly, PUFAs from the omega-6 series is starting with the linoleic acid (LA) (C18:2 n-6), an essential FA coming from the diet, metabolized through desaturation and elongations by other PUFAs, such as C18:3 n-6: γ-linolenic acid (GLA) and C20:4 n-6, arachidonic acid (AA).

In the normal diet the long chain PUFAs, such as AA are supplied by animal foods (meat, eggs, breast milk...). Omega-6 are also widely present in vegetal oils (borage, evening primrose, black current, sunflower...).

In parallel to the omega-6 family, the omega-3 fatty acids (PUFAs).

Among this wide range of activities, omega-3 has a great impact on skin physiology. Basic skin functions such as the barrier function, temperature regulation, photo protection, water homeostasis are impacted by supplementary or dietary intervention [12, 13]. The modulation of these functions is generally coupled with changes in skin structure which produce some changes in skin appearance.

Linoleic acid (AA), γ-linolenic acid (GLA) or α-linolenic acid (ALA) play a role in cellular signaling interfering with eicosanoids pathways or influencing the regulation of gene expression [13, 14].

Further, epidermal lipids are known to play a crucial role in the mediation of desquamation and the deficiency of essential fatty acids seems to be involved in cutaneous scaling disorders (xerosis, psoriasis, atopic dermatitis) [15].

Two recent orientation studies were performed in dermatology, focusing on skin hydration and skin sensitivity. They were successively designed and performed in order to verify under real conditions of use whether or not the oral administration of ALA (through flaxseed oil, 55% ALA) have any influence on these skin conditions.

In other words, among the general properties of PUFAs, is it possible to determine some concrete facts showing the interest of consuming reasonable amounts of omega-3 and to see an improvement of skin health conditions. This is the aim of the two study performed which conditions and results will be described in this paper [16, 17].

Physiological activity of flaxseed oil: two clinical trials in dermatology.

Skin sensitivity I

Study design

This first study was carried out as a monocentric, double-blind, randomized and placebo controlled application test on 26 healthy volunteers with dry (Corneometer value < 40 au1 [18]) and sensitive skin. Subjects were divided into two subgroups of 13 (1 verum – 1 reference group).

Verum was composed of 555.32 mg of flaxseed oil (i.e. ≥ 289 mg ALA/capsule) associated with stabilizing antioxidants (D-α-tocopherol and Rosemary extract). The daily dose of ALA was of at least 1,153 mg. Reference was composed of 560 mg safflower oil, with a minimum LA content of 70% (i.e. ≥ 392 mg/capsule). The study lasted for 12 weeks, dosage regimen being 4 capsules/day (2 at breakfast, 2 at diner). Parameters of the study were measured before supplementation and at weeks 6 and 12 (end point).

Methods

Skin parameters were evaluated by measurement of skin hydration (Corneometer CM825® – Courage & Khazaka), transepidermal water loss (TEWL, barrier function of the skin) (Tewameter TM 300® – Courage & Khazaka) [18, 19] and skin surface structure (SELS, Visioscan® – Courage & Khazaka) for the evaluation of the following items: roughness, scaling, smoothness and wrinkles [20].

The sensitivity of the skin was assessed by the Nicotinide irritation test according to Primavera & Berardesca [21]. Measurements were...
performed on the inner forearm of the volunteers. After application of nicotinate (0.25%, 5 μL/cm²), inducing a local inflammation, reddening of the skin was measured by chromammetry as “a” value (Minolta CR 300®). Additionally, capillary surface blood flow was measured by Laser-Doppler-Flowmetry (O2C-System, Lea Instruments, Giessen, Germany).

Statistics
For all parameters and all time points (week 0, week 6, week 12) descriptive statistics (mean, standard deviation, minimum, lower quartile, median, upper quartile and maximum) were calculated. For all parameters pre-post differences were calculated and analyzed descriptively. For the pre-post differences the two treatment groups were compared using the Wilcoxon rank-sum test.

Within the two treatment groups each combination of two time points was compared using the Wilcoxon signed-rank test.

Results
In summary this orientation study clearly demonstrates the effect of the supplementation by ALA (1.15 g/day on the average) on skin parameters and inflammation induced by the nicotinate test as shown in Table 1. The following results were observed.

Treatment A: Flaxseed oil
After 6 weeks of treatment:
– For treatment A, statistically significant changes (p < 0.05) for the parameters “Blood Flow” (decrease) and “SELS: roughness” (increase) were observed, compared to baseline.
– For treatment B a statistically significant increase (p < 0.05) for the parameter “SELS: roughness” was observed compared to week 0.

After 12 weeks of treatment:
– For treatment A a statistically significant increase (p < 0.05) for the parameters skin hydration and smoothness was observed after twelve weeks compared to week 0.
– A statistically significant decrease (p < 0.05) for the parameters TEWL, roughness, scaling, redness a-value and blood flow, was observed after twelve weeks compared to week 0.

Treatment B: Safflower oil
After 6 weeks of treatment:
– Treatment B showed a statistically significant increase (p < 0.05) for the parameter “skin hydration” (+13%) compared to week 0.

After 12 weeks of treatment:
– A statistically significant decrease (p < 0.05) for the parameter roughness was observed after twelve weeks compared to week 0.

Comparison within groups (A vs B)
For the pre-post differences “week 0 – week 6” the comparison of the two treatment groups showed statistically significant differences (p < 0.05) in favor of treatment A for the parameter blood flow.
ences (p < 0.05) in favor of treatment A for the comparison of the two treatments or any photosensitizing disorder. BMI of the patients was (0.25%; 5 L/cm²) allowed during the whole study. Nicotinate test was applied inducing an inflammation of the skin; reddening was measured by chromametry (Minolta CR 300, Ahrnsburg, Germany) as “a-value” before and after treatment. Erythema intensity is given as Δa-value; a-value after treatment minus a-value before treatment. Additionally, capillary blood flow was determined by Laser-Doppler-Flowmetry (O2C-System, Lea Instruments, Giessen, Germany) in the irritated area.

Statistics

For all parameters and all time points (week 0, week 6, week 12) descriptive statistics (mean, standard deviation, minimum, lower quartile, median, upper quartile and maximum) were calculated. For all parameters pre-post differences were calculated and analyzed descriptively. For the pre-post differences the two treatment groups were compared using the Wilcoxon rank-sum test. Within the two treatment groups each combination of two time points was compared using the Wilcoxon signed-rank test. In addition, the two pre-post differences Week 6/Week 0 and Week 12/Week 0 were compared by an ANOVA with parameter treatment as the independent variable. The least square means for the pre-post differences and the respective 95% confidence intervals were calculated. These confidence intervals were used to assess whether the pre-post difference was significantly different from [17].

Results

The effects of the supplementation by ALA or GLA on skin parameters and inflammation induced by the nicotinate test are shown in table 2. One can see that the results of this second study are consistent with the ones of the Skin

Table 1. Percentual changes vs T0 after 6 and 12 weeks.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Flaxseed oil (Omega-3) – A</th>
<th>Safflower oil (Omega-6) – B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 6</td>
<td>Week 12</td>
<td>Week 6</td>
</tr>
<tr>
<td>Hydration</td>
<td>++7% (ns)</td>
<td>+39%&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>TEWL</td>
<td>--21%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>--31%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>SELS</td>
<td>--22%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>--30%&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Roughness</td>
<td>+3% (ns)</td>
<td>+7%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Wrinkles</td>
<td>--0.4% (ns)</td>
<td>+2% (ns)</td>
</tr>
<tr>
<td>Nicotinate test</td>
<td>--22% (ns)</td>
<td>--48%&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Blood flow</td>
<td>--34%&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>--66%&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

ns: not significant.

<sup>a</sup> Significant (p < 0.05, Wilcoxon Rank sum Test).

<sup>b</sup> A significantly different from B (p < 0.05, Wilcoxon signed rank test).

For the pre-post differences “week 0 – week 12” the comparison of the two treatment groups showed statistically significant differences (p < 0.05) in favor of treatment A for the parameters skin hydration, roughness, redness a-value, blood flow. For all the other parameters, on the pre-post differences, no statistically significant differences can be shown.

Skin sensitivity II

In the second study the effects of flaxseed oil were compared with the one of a reference product, the borage oil, known to have hydrating properties on the skin [22]. It seemed interesting to have an idea of the performances of both oils on the previously studied parameters as described in the Sensitive Skin I study.

Study design

The study was carried out as a monocentric, randomized, double-blind, placebo-controlled application test in three parallel groups of fifteen subjects each (45 healthy non-smoking women, between 18 and 65 years) with dry skin (Corneometer value < 40 au [18] and sensitive skin). The study lasted for 12 weeks, dosage regimen being 4 capsules/day: 2 at breakfast; 2 at diner. The study lasted for 12 weeks, dosage regimen as described in the Sensitivity study are consistent with the ones of the Skin

The study lasted for 12 weeks, dosage regimen being 4 capsules/day: 2 at breakfast; 2 at diner.

Methods

Parameters of the study were measured before supplementation and at weeks 6 and 12 (end point): Skin hydration in arbitrary units (Corneometer C285®), TEWL in g/h per m² (TEWA-Meter TM 300 – Courage & Khazaka Electronics [18, 19]), SELS (Visioscan – Courage & Khazaka) [20] for the evaluation of the following items: roughness, scaling, smoothness and wrinkles. Nicotinate irritation was used to test the sensitivity of the skin according to Primavera et al. [21]. Measurements were performed on the inner forearm of the volunteers. No treatment with any ointment on the tested areas was allowed during the whole study. Nicotinate (0.25%; 5 µL/cm²) was applied inducing an inflammation of the skin; reddening was measured by chromametry (Minolta CR 300, Ahrnsburg, Germany) as “a-value” before and after treatment. Erythema intensity is given as Δa-value; a-value after treatment minus a-value before treatment. Additionally, capillary blood flow was determined by Laser-Doppler-Flowmetry (O2C-System, Lea Instruments, Giessen, Germany) in the irritated area.

Statistics

For all parameters and all time points (week 0, week 6, week 12) descriptive statistics (mean, standard deviation, minimum, lower quartile, median, upper quartile and maximum) were calculated. For all parameters pre-post differences were calculated and analyzed descriptively. For the pre-post differences the two treatment groups were compared using the Wilcoxon rank-sum test. Within the two treatment groups each combination of two time points was compared using the Wilcoxon signed-rank test. In addition, the two pre-post differences Week 6/Week 0 and Week 12/Week 0 were compared by an ANOVA with parameter treatment as the independent variable. The least square means for the pre-post differences and the respective 95% confidence intervals were calculated. These confidence intervals were used to assess whether the pre-post difference was significantly different from [17].

Results

The effects of the supplementation by ALA or GLA on skin parameters and inflammation induced by the nicotinate test are shown in table 2. One can see that the results of this second study are consistent with the ones of the Skin

Table 2. Percentual changes vs T0 after 6 and 12 weeks.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Flaxseed oil (Omega-3) – A</th>
<th>Borage oil (Omega-6) – B</th>
<th>Placebo - C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 6</td>
<td>Week 12</td>
<td>Week 6</td>
<td>Week 12</td>
</tr>
<tr>
<td>Hydration</td>
<td>+12%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>+19%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>+7.9% (ns)</td>
</tr>
<tr>
<td>TEWL</td>
<td>--8%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>--26%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>--9%&lt;sup&gt;a,d&lt;/sup&gt;</td>
</tr>
<tr>
<td>SELS</td>
<td>--15%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>--34%&lt;sup&gt;a,b,c&lt;/sup&gt;</td>
<td>--7.6% (ns)</td>
</tr>
<tr>
<td>Roughness</td>
<td>--29%&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>--35%&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>--25.1% (ns)</td>
</tr>
<tr>
<td>Scaling</td>
<td>+5% (ns)</td>
<td>+4%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>--0.2% (ns)</td>
</tr>
<tr>
<td>Wrinkles</td>
<td>--1% (ns)</td>
<td>0% (ns)</td>
<td>+0.8% (ns)</td>
</tr>
<tr>
<td>Nicotinate test</td>
<td>Redness (a-values)</td>
<td>--32%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>--45%&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Blood flow</td>
<td>--34%&lt;sup&gt;a&lt;/sup&gt;</td>
<td>--81%&lt;sup&gt;a,b,c&lt;/sup&gt;</td>
<td>--28%&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

ns: not significant.

<sup>a</sup> Significant (p < 0.05, Wilcoxon Rank sum Test).

<sup>b</sup> A significantly different from C (p < 0.05, Wilcoxon signed rank test).

<sup>c</sup> A significantly different from B (p < 0.05, Wilcoxon signed rank test).

<sup>d</sup> B significantly different from C (p < 0.05, Wilcoxon signed rank test).
Sensitivity I study despite the limited number of healthy volunteers in each study. The data are of the same order of magnitude for the parameters TEWL, SELS, redness and blood flow for both flaxseed oil groups. The results on hydration were in both cases significantly different from time 0 inside of each group. However, in this second study, hydration was not significantly different from the corresponding placebo group after 12 weeks of treatment (+19% vs. +9%). It is also interesting to note that significant effects are seen already at week 6 (hydration, TEWL, roughness, scaling, redness and blood flow) which was less clear for study I were significant differences from time 0 at 6 weeks.

It has been shown (unpublished data) a significant bioconversion of ALA into EPA in Sensitive Skin I for the flaxseed oil group at week 12, compared to the reference group (safflower oil). The two studies presented in this article confirm this concept in showing interesting results of improving the balance omega-6/omega-3 ratio. However, dietary ALA failed to increase DHA, but decreased AA. The authors concluded that dietary supply of ALA was a very efficient means of improving the balance omega-6/omega-3 (AA/EPA) in Red Blood Cells and cardiomyocytes.

As shown by A. Morise et al. [25], absorption and storage of ALA is very efficient in the hamster. It powerfully increased EPA. However, TEWL, roughness, scaling, redness and blood flow only.

Discussion

Flaxseed oil, cold pressed from the seeds of the flax plant (Linum usitatissimum), is one of the richest sources of n-3 fatty acids (FA) in the vegetable world. With more than 50% of total FA, ALA is predominant in the oil which also contains the n-6 Linoleic acid (16%) and the monounsaturated oleic acid (20%) as major constituents (table 3). The flaxseed oil supplement used in the present study is typical with respect to its composition of fatty acids [23]. Borage oil is pressed from the seeds of the borage plant (Borago officinalis) and rich in the n-6 fatty acids GLA (22%) and LA (39%); oleic acid (15%) is also present in quite high amounts (table 3). Its composition is also typical regarding its FA pattern [23].

Facing the lack of omega-3 consumption in the modern diet as shown by N. Combe et al. (2001) [24], it was interesting to see if oils of vegetable origin may have a significant impact on human health with a special focus to skin physiology, via ALA supplementation. Fish oils were traditionally used as the “ideal” tool to restore omega-6/omega-3 ratio and contribute to body homeostasis. However, fish oils, in the current “modern life” are not anymore really used either crude or through fatty fishes diets, despite their great interest in health benefits. Due to the lack of omega-3 in the western food, to find another way to consume Omega 3 from natural origin may have sense, nutrition wise.

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The use of flaxseed oil may also contribute to restore a better ratio Omega 3/Omega 6 and further studies would be necessary with greater populations and on a longer period to appreciate the full benefits suggested in these two orientation studies. However, it should be pointed out that flaxseed oil, despite its interest as shown in this paper, cannot be a substitute to a healthy and equilibrated diet.

Table 3. Fatty acid composition (% of total fatty acids) (From De Spirt et al. 2008 [17]).

<table>
<thead>
<tr>
<th>Fatty acid</th>
<th>Flaxseed oil</th>
<th>Borage oil</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:0</td>
<td>0.00</td>
<td>0.00</td>
<td>36.9</td>
</tr>
<tr>
<td>10:0</td>
<td>0.00</td>
<td>0.00</td>
<td>21.8</td>
</tr>
<tr>
<td>14:0</td>
<td>4.73</td>
<td>1.87</td>
<td>0.24</td>
</tr>
<tr>
<td>16:0</td>
<td>4.12</td>
<td>2.82</td>
<td>0.00</td>
</tr>
<tr>
<td>18:3n-9</td>
<td>19.6</td>
<td>15.0</td>
<td>0.00</td>
</tr>
<tr>
<td>18:2n-6</td>
<td>16.0</td>
<td>38.7</td>
<td>0.00</td>
</tr>
<tr>
<td>18:3n-6</td>
<td>0.00</td>
<td>21.6</td>
<td>0.18</td>
</tr>
<tr>
<td>18:3n-3</td>
<td>52.8</td>
<td>0.38</td>
<td>0.00</td>
</tr>
<tr>
<td>20:0</td>
<td>0.16</td>
<td>0.21</td>
<td>0.00</td>
</tr>
<tr>
<td>20:1</td>
<td>0.20</td>
<td>3.95</td>
<td>0.00</td>
</tr>
<tr>
<td>20:2</td>
<td>0.00</td>
<td>0.23</td>
<td>0.00</td>
</tr>
<tr>
<td>22:1</td>
<td>0.00</td>
<td>2.23</td>
<td>0.00</td>
</tr>
<tr>
<td>24:0</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>24:1</td>
<td>0.00</td>
<td>1.30</td>
<td>0.00</td>
</tr>
<tr>
<td>Non-identified fatty acids</td>
<td>2.39</td>
<td>11.7</td>
<td>38.3</td>
</tr>
</tbody>
</table>

REFERENCES

8. MUSIEK ES, ET AL. Electrophilic cyclopenteno- one neuroprostanes are anti-inflammatory mediators formed from the peroxidation of the Omega-3 polyunsaturated fatty acid docosahexaenoic acid. J Biol Chem 2008; [Epub ahead of print].


