UV Filters, Ingredients with a Recognized Anti-Inflammatory Effect

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Abstract

Background: To explain observed differences during SPF determination using either an in vivo or in vitro method, we hypothesized on the presence of ingredients having anti-inflammatory properties.

Methodology/Principal Findings: To research our hypothesis, we studied the 21 UV filters both available on the market and authorized by European regulations and subjected these filters to the phorbol-myristate-acetate test using mice. We then catalogued the 13 filters demonstrating a significant anti-inflammatory effect with edema inhibition percentages of more than 70%. The filters are: diethylhexyl butamido triazone (92%), benzophenone-3 and titanium dioxide (90%), benzophenone-3 (83%), octocrylene and isomethyl p-methoxycinnamate (82%), PEG-25 PABA and homosalate (80%), octyl triazine and phenylbenzimidazole sulfonic acid (78%), octyl dimethyl PABA (75%), bis-ethylhexyloxyphenyl methoxyphenyl triazine and diethylamino hydroxybenzyl hexylbenzoate (70%). These filters were tested at various concentrations, including their maximum authorized dose. We detected a dose-response relationship.

Conclusions/Significance: The anti-inflammatory effect of a sunscreen ingredient may affect the in vivo SPF value.

Introduction

The effectiveness of sunscreen products is quantifiable using two indicators, the SPF (Sun Protection Factor) and the UVA-PAF (UVA-Protection Factor). For many years, these two indicators were determined in vivo using volunteers [1,2]. For ethical reasons, in vivo methods have been more recently proposed in order to spare humans from excessive sun exposure [3-6]. While these two methods are perfectly correlated in a great number of situations, it has been demonstrated that with respect to SPF determination for many products, the in vivo values are higher than those obtained for in vitro method. This difference can be explained by the use of certain ingredients having anti-inflammatory properties to formulate these products, such as α-bisabolol and 18 β-glycyrrhetinic acid [7-10]. Thus, the goal of our research was to determine the intrinsic anti-inflammatory properties of the UV filters currently authorized for use in Europe.

Materials and Methods

Paraffinum liquidum, Cetiol® HE, stearic acid, glycerin, parabens and triethanolamin (TEA) were purchased from Cooper (Melun, France). Xanthan gum (Rhodicare® T) was obtained from Rhodia (Paris, France). Polyvinylmethylacrylate (PMMA) plates were purchased from Europlast (Aubervilliers, France). The standard (reference) molecules Phorbol 12-Myristate 13-Acetate (PMA), niflumic acid, hydrocortisone 17-butyrate, diclofenac and ketoprofen were purchased from Sigma Aldrich (Saint Quentin Fallavier, France). The filters we tested are presented in Table 1. Note that we also studied zinc oxide (Tegosun® Z500, Goldschmidt, Montigny-le-Bretonneux), an ingredient that is not included in the list of Europe-authorized filters but traditionally used in sunscreen products. We tested thirteen commercial sunscreen products, with varying levels of protection (weak, medium and very high) (Table 2).

Swiss mice, male, weighing 14–16 grams, were purchased from Janvier (St Berthevin, France). The mice were bred in the animal facility of the department of Pharmacology. The mice were caged individually and were fed standard laboratory chow and water ad libitum under standard conditions of temperature and light.

An O/W emulsion placebo was prepared in the laboratory as previously described [11]. The different filters and standard (reference) molecules were incorporated into the formulation in order to study their anti-inflammatory properties. Concerning the incorporation percentages, for the anti-inflammatory reference molecules, we followed the dose commonly found in medicinal preparations that use them; for the filters, we decided to use the maximum authorized dose with respect to current European regulations. However, for the filters that demonstrated a noteworthy anti-inflammatory effect by inhibiting the edema more than 70%, the dose-response relationship was also studied via other concentrations such as 0.50, 1.25, 2.50 and 5.00%. For titanium dioxide, which is authorized up to 25.00%, we also tested formulas containing 2.5, 5.0, 10.0 and 15.0% of this ingredient. Hydrophilic phase and oil-phase were heated separately to 78 to
### Table 1. Characteristics of UV-filters tested.

| INCI Name                                | Trade name (Suppliers)                                      |
|------------------------------------------|-------------------------------------------------------------|
| Homosalate                               | Neoheliopan HMS (Symrise, Puteaux, France)                  |
| Oxybenzone                               | Neoheliopan BB (Symrise, Puteaux, France)                   |
| Phenylbenzimidazole sulfonic acid        | Eusolex 232 (Merck, Fontenay sous Bois, France)             |
| Butylmethoxydibenzoylmethane             | Eusolex 9020 (Merck, Fontenay sous Bois, France)            |
| Octocrylene                              | Parsol 340 (Roche vitamines, Neuilly/Seine, France)         |
| Ethyl hexyl methoxycinnamate             | Escalol 557 (International speciality products, Köln, Germany) |
| PEG-25 PABA                               | Uvinul P25 (Laserson, Etampes, France)                      |
| Isoamyl p-methoxycinnamate               | Neoheliopan E1000 (Symrise, Puteaux, France)                |
| Octyl triazone                           | Uvinul T150 (Laserson, Etampes, France)                     |
| Diethylhexylbutamidotriazone             | Uvasorb HEB (3 V Sigma, Bergamo, Italy)                      |
| 4-methylbenzylidene camphor              | Neoheliopan MBC (Symrise, Puteaux, France)                  |
| Ethylhexylsalicylate                     | Eusolex OS (Merck, Fontenay/Bois, France)                   |
| Octyldimethyl PABA                        | Escalol 507 (International speciality products, Köln, Germany) |
| Benzophenone-5                           | Uvinil MS 40 (Laserson, Etampes, France)                    |
| Methylene bis-benzotriazolyl tetramethylbutylphenol | Tinosorb M (Ciba, Saint-Fons, France)                      |
| Disodium phenyl dibenzimidazole tetrasulfonate | Neoheliopan AP (Symrise, Puteaux, France)                  |
| Bis-Ethylhexylxylophenol methoxyphenyl triazine | Tinosorb S (Ciba, Saint-Fons, France)                      |
| Polysilicone 15                          | Parsol SLX (Roche vitamines, Neullly/Seine, France)         |
| Diethylamin hydroxybenzoyl hexyl benzoate | Uvinul A+ (Laserson, Etampes, France)                       |
| Titanium dioxide, Butylene glycol dicaprylate/dicaprate, Silica, Polyglyceryl-2 dipolyhydroxystearate | Eusolex T-Oleo (Merck, Fontenay/Bois, France)              |
| Zinc oxide                               | Tegosun Z 500 (Degussa, Essen, Germany)                     |

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### Table 2. Sunscreen products tested.

| Trade name/labelled SPF | UV-filters                                                                                                         |
|-------------------------|-------------------------------------------------------------------------------------------------------------------|
| Nivea Sun 50+            | Octocrylene, Butylmethoxydibenzoylmethane, Bis-ethylhexylxylophenol methoxyphenyl triazine, Homosalate, Titanium dioxide, Sodium phenylbenzimidazole sulfate, Diethylhexyl butamido triazone, Ethylhexylmethoxycinnamate |
| Vichy Capital soleil® lotion 50+ | Octocrylene, Ethylhexylsalicylate, Butylmethoxydibenzoylmethane, Titanium dioxide, Ethylhexyltriazone, Terephaldehyde diacapram sulfonic acid, | |
| Bioderma Photoderm bronz spray 15 | Octocrylene, Butylmethoxydibenzoylmethane, Methylene bis-benzotriazolyl tetramethylbutylphenol |
| La Roche Posay spray lotion 20 | Octocrylene, Butylmethoxydibenzoylmethane, Ethylhexyltriazone, Drometrisole trisiloxane, Terephaldehyde diacapram sulfonic acid, Titanium dioxide |
| Roc soleil protexion® lotion spray 30 | Ethylhexylsalicylate, Octocrylene, Butylmethoxydibenzoylmethane, Bis-ethylhexylxylophenol methoxyphenyl triazine, Diethylamin hydroxybenzoyl hexyl benzoate, Methylene bis-benzotriazolyl tetramethylbutylphenol |
| Avene spray sensitive skin 50+ | Methylene bis-benzotriazolyl tetramethylbutylphenol, Titanium dioxide, Titanium dioxide, Butylmethoxydibenzoylmethane, Bis-Ethylhexylxylophenol methoxyphenyl triazine |
| Lancaster Oil-free milky spray 6 | Bis-ethylhexylxylophenol methoxyphenyl triazine, Butylmethoxibenzoylmethane, Octocrylene, Ethylhexylmethoxycinnamate |
| Soleil Biofine® sun lotion spray 30 | Octocrylene, Methylene bis-benzotriazolyl tetramethylbutylphenol, Butylmethoxydibenzoylmethane, Diethylamin hydroxybenzoyl hexyl benzoate, Bis-Ethylhexylxylophenol methoxyphenyl triazine |
| Polysianes milky spray 30 | Ethylhexylmethoxycinnamate, Octocrylene, Methylene bis-benzotriazolyl tetramethylbutylphenol, Bis-Ethylhexylxylophenol methoxyphenyl triazine |
| Sun lotion kids Carrefour 50+ | Octocrylene, Titanium dioxide, Butylmethoxydibenzoylmethane, Bis-Ethylhexylxylophenol methoxyphenyl triazine, Phenylbenzimidazole sulfonic acid, Diethylhexyl butamidotriazone |
| Vea scudo SPF 5            | Titanium dioxide, Zinc oxide |
| Solei® Boots SPF 15        | Octocrylene, Butyl methoxydibenzoylmethane, Ethylhexyl salicylate, Diethylhexylbutamidotriazone, Bis-ethylhexylxylophenol methoxyphenyl triazine, Titanium oxide |
| Hello Kitty SPF 30         | Homosalate, Ethylhexylsalicylate, Benzophenone-3, Butyl methoxydibenzoylmethane |

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Table 3. SPF of sunscreen products using in vitro method.

| Trade name/labelled SPF | SPF (Mean ± SD) |
|-------------------------|-----------------|
| Nivea Sun 50+           | 76±8            |
| Vichy Capital soleil® lotion 50+ | 44±4          |
| Bioderma Photoderm bronz spray 15 | 17±2          |
| La Roche Posay spray lotion 20 | 19±2          |
| Roc Soleil protection® lotion spray 30 | 18±2          |
| Avene spray 50+         | 41±4            |
| Lancaster 6             | 11±1            |
| Soleil Blaine® lotion spray solaire 30 | 24±2          |
| Polysianes milky spray 30 | 48±4            |
| Sun lotion kids Carrefour 50+ | 57±3          |
| Vea® Boots SPF 15       | 15±1            |
| Hello Kitty SPF 30      | 17±1            |

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Table 4. Anti-inflammatory effect of references.

| References            | (% w/w) | Edema inhibition (%) Mean ± SD |
|-----------------------|---------|--------------------------------|
| Niflumic acid         | 2.5     | 99±2                           |
| Hydrocortisone 17-butyrate | 0.1     | 99±2                           |
| Diclofenac            | 1.0     | 100±0                          |
| Ketoprofen            | 2.5     | 93±2                           |

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Table 5. Anti-inflammatory effect of UV-filters tested at the maximum authorized concentration.

| Filters                              | (% w/w) | Edema inhibition (%) Mean ± SD |
|--------------------------------------|---------|--------------------------------|
| Homosalate                           | 10      | 83±4                           |
| Benzophenone-3                       | 10      | 90±4                           |
| Phenylbenzimidazole sulfonic acid    | 8       | 80±2                           |
| Butylmethoxydibenzoylmethane         | 5       | 58±5                           |
| Octocrylene                          | 10      | 83±4                           |
| Ethyl hexyl methoxycinnamate         | 10      | 56±3                           |
| PEG-25 PABA                           | 10      | 82±3                           |
| Isomyl p-methoxycinnamate            | 10      | 83±4                           |
| Octyl triazone                       | 5       | 81±6                           |
| Diethylhexylbutamidotriazone         | 10      | 95±4                           |
| 6-methylbenzilidene camphor          | 4       | 65±2                           |
| Ethylhexylsalicylate                 | 5       | 59±4                           |
| Octylidimethyl PABA                   | 8       | 78±3                           |
| Benzophenone-5                       | 5       | 92±3                           |
| Methylene bis-benzotriazolyl tetrathymethylbutylphenol | 10 | 56±2                       |
| Disodium phenyl dibenzimidazole tetrasulfonate | 10 | 69±7                       |
| Bis-Ethylhexyloxyphenol methoxyphenyl triazine | 10 | 76±3                       |
| Polysilicone 15                      | 10      | 69±2                           |
| Diethylamino hydroxybenzoxyl hexyl benzoate | 10 | 70±4                       |
| Titanium dioxide, Butylene glycol dicaprylate/dicaprate, Silica, Polyglyceryl-2 dipolyhydroxystearate | 25 | 92±3                       |
| Zinc oxide                           | 25      | 63±5                           |

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where \( E_0 \) is the CIE erythemal spectral effectiveness, \( S_i \) is the solar spectral irradiance and \( T_s \) is the spectral transmittance of the sample [3].

We determined the anti-inflammatory effects of the emulsions formulated in the laboratory and the commercial sunscreen products using a Phorbol 12-Myristate 13-Acetate (PMA) test. The mouse ear edema was provoked according to the method described by Carlson et al. with some modifications [12–14]. First, the thickness of the mouse ears was measured using a model micrometer gauge (Oditest®, Kroeplin, Schlüchtern, Germany). 10 µL of sunscreen product or preparation with standard (reference) molecule or filter was applied using a ripette genix electro dispenser (Fisher scientific, Illkirch, France), to the mice’s right ears, twice at 5 minute intervals. 10 µL of placebo emulsion was applied, following the same protocol, to the mice’s left ears. Thirty minutes later, 10 µL of a hydro-alcoholic solution of Phorbol-12-Myristate-13-Acetate (250 µg.mL\(^{-1}\)) was then applied to each ear, in order to provoke an edema. After three and a half hours, the Oditest® was performed again to determine the thickness of the ears. Ear edema, calculated by subtracting the thickness of the left ear (vehicle) from the thickness of the right ear (PMA), was expressed as an increase in ear thickness. We determined the percentage that the inflammatory reaction was inhibited for each mouse by comparing the ear edema in treated

82°C, until the contents of each part were solubilized. Then, the oily preparation was added slowly to the hydrophilic preparation while stirring (Yellow line OST basic mixer, IKA, Staufen, Germany). It was necessary to continue stirring until the emulsion formed was cooled to room temperature (20°C).

The SPF of the commercial sunscreen products was determined using an in vitro method according to a previously described protocol (Couteau et al., 2007a). 30 mg of product was weighed and then spread across the entire surface of PMMA plates (25 cm\(^2\)) using a finger cot. 15 mg remained on the finger cot. Three plates were prepared for each product to be tested and 9 measures were performed on each plate. Transmission measurements between 290 and 400 nm were taken using a spectrophotometer equipped with a xenon arc lamp and an integrating sphere (UV Transmittance Analyzer UV1000S, Labsphere, North Sutton, US). The standard used was the 8% homosalate standard mandated by the US Food and Drug Administration Sunscreen Monograph. The calculations for either term used the same relationship:

\[
SPF = \frac{\sum_{i=1}^{400} E_i S_i d_i}{\sum_{i=1}^{290} E_i S_i T_i d_i}
\]
and untreated animals. Five mice were used for each product tested.

Results and Discussion

The SPF values \((\text{in vitro determination})\) of the commercially-available sunscreen products are presented in Table 3. Six products presented an \textit{in vitro} SPF value inferior to the labeled value.

The anti-inflammatory effect of the 4 standard molecules and the 21 UV filters (all substances applied topically to the mice) was studied. Note that the large majority of the filters demonstrated a significant anti-inflammatory effect (Tables 4 and 5). Two filters stood out from the rest: diethylhexyl butamido triazole and benzophenone-5. These two demonstrated the greatest anti-inflammatory properties, showing an effectiveness similar to ketoprofen. Titanium dioxide also revealed itself to be quite anti-inflammatory. However, it should be remembered that we tested this substance at its highest incorporation dose—25\%, a level that is never attained in practice because of the problematic consistency of a product formulated with this percentage.

The activity of homosalate (Fig. 1) (Table 5) is not surprising as this filter belongs to the salicylate family, which are well-known non-steroidal anti-inflammatory substances (NSAIs) and some of
which occur naturally [15]. The same is true for the benzophenones. Note that ketoprofen is a derivative of benzophenone (Fig. 1) and that numerous synthetic benzophenone substitutes have shown anti-inflammatory properties [16–19]. A structure-activity relationship of benzophenones as a novel class of MAP kinase inhibitors with high anti-inflammatory properties has been reported [20].

The anti-inflammatory effect of cinnamic acid derivatives (Fig. 1) such as caffeic acid is well known [21–23]. This would explain the results obtained with octyl methoxycinnamate and isoamyl p-methoxybenzoinamide. Furthermore, it would appear that benzimidazole type molecules also have an anti-inflammatory effect [24,25].

Table 6. Anti-inflammatory effect of sunscreens.

| Trade name                                | Edema inhibition (%) | Mean ± SD |
|-------------------------------------------|----------------------|----------|
| Nivea Sun 50+                              | 76±3                 |
| Vichy capital soleil® lotion 50+           | 48±3                 |
| Bioderma Photoderm bronz spray 15          | 44±3                 |
| La Roche Posay spray lotion 20             | 85±6                 |
| Roc soleil protection® lotion spray 30     | 80±1                 |
| Avene spray sensitive skin 50+             | 76±4                 |
| Lancaster oily-free milky spray 6          | 48±1                 |
| Soleil Bioline® sun lotion spray 30        | 48±4                 |
| Polysiane milky spray 30                   | 71±5                 |
| Sun lotion kids Carrefour 50+              | 54±2                 |
| Veau scudo SPF 5                           | 56±7                 |
| Soleil® Boots SPF 15                      | 74±2                 |
| Hello Kitty SPF 30                         | 46±3                 |

Certain triazines demonstrated an inhibitory effect of the MAP kinases [26].

We can clearly state that there exists a dose-response relationship (Fig. 2, 3, 4, 5 and 6). At a lower dose we observed a reduced anti-inflammatory effect. Only two filters (isoamyl p-methoxybenzoinamide and diethylhexyl butamido triazone), even at a low dose, inhibited the edema by about 70%.

We observed an anti-inflammatory effect with the commercial sunscreen products (Table 6). For half the products (six products on the thirteen studied), the effect was quite significant, with an edema inhibition upper to 70%.

All of this has consequences in terms of determining the effectiveness of the final product. In Europe, it is difficult to determine whether a product is anti-inflammatory or not simply by reading the ingredients on the label because we do not know at what percentage these filters have been incorporated. The effect is not linked to the indicated protection factor, but to the specific filters and their concentrations. Certain sunscreen products, even with a medium protection level, like La Roche Posay® SPF 20 and Soleil® Boots® SPF 15, for example, demonstrate a significant anti-inflammatory effect when compared to Vichy Capital soleil® Lait 50+. Besides, the anti-inflammatory effects can be modified when sunscreen is UV-exposed, as many UV-filters are known to be photo-unstable [11].

It is important to note that the in vitro method of SPF testing takes the anti-inflammatory effect of the products tested into consideration while the in vitro method does not. It remains to be shown how the biological response of the human UV-irradiated skin might vary with inclusion of specific anti-inflammatory ingredients in the sunscreens.

Author Contributions

Conceived and designed the experiments: LC C. Couteau. Performed the experiments: C. Chauvet EP. Analyzed the data: LC C. Couteau. Contributed reagents/materials/analysis tools: C. Chauvet EP. Wrote the paper: LC C. Couteau.

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