HOLIMEL®, PHOTO-PROTECTION ALL YEAR ROUND WITH A NEW IN & OUT SOLUTION

In the last decades, rising awareness about UV toxicological aspects has clearly been driving the global sun care market. Besides the growing incidence of UV-induced disorders, repercussions of sun exposure on premature aging are also of concern. And yet, with only 15% to 30% of people making use of sun care solutions in case of UV exposure, large market shares are still to be acquired. With consumers looking for both higher and beyond sun protection, there is a real enthusiasm for products able to provide a more natural and holistic approach of daily protection.

Unique melon juice concentrate, naturally rich in antioxidants, HOLIMEL®, recently gave evidence of its potential on photo-protection. Conducted in 2017, the clinical study was assessed on 88 healthy men and women, administered with HOLIMEL® orally and/or topically for 4 days to 1 month. Results highlighted a significant increase in Minimal Erythema Dose going from 16% to 27%, with an efficacy observed after just 4 days.

100% natural solution, in line with today's market and consumer's expectations HOLIMEL® is a promising alternative on a vibrant market.

ROBERTET
HEALTH & BEAUTY

SUN PROTECTION, A CHANGING MARKETPLACE

In the last 40 years, the incidence of melanoma in the US increased over 15-fold [1]. Additionally, the relationship between UV and skin aging is now clearly recognized: UV exposure would be responsible for 80% of the visible changes commonly attributed to aging [2]. This stated situation currently goes along with a wider communication regarding the importance of sun protection and a rising awareness of the population. And yet, the awareness raising work has not yet born all its fruits: in a study published in 2015, the American Centers for Disease Control and Prevention emphasized that despite consumer's education, only 15% of men and 30% of women regularly make use of sunscreen in case of skin exposure [3].

From a market point of view, this effort is logically reflected in a vibrant market, with large shares still to be acquired. A dynamism illustrated in particular in the development of natural ingredients and emerging economies in Latin America and Asia Pacific. This renewal however comes with an increasing segmentation of the market and the emergence of contrasting trends within those segments.

Mature vs emerging markets

In 2015, 70% of the global demand was concentrated within 10 countries, led by the United States. In 2020, although North America will remain the largest market, it should have lost about 6% of its market shares in favor of emerging countries [4]. If the sun care market is globally projected to experience a 5.8% CAGR[1] by 2020, it is, in fact, a two-tier development. While mature markets, including US or Western Europe, should undergo between 1 and 5% annual growth, emerging markets in Asia Pacific and Latin America will experience soaring growth rates, reaching 11% CAGR for China and Brazil [5].

Among these emerging markets, Asia in particular is characterized by specific consumer needs and preferences, as reflected in:

- A step ahead in the area of mineral filters. When organic filters represent 90% of market shares in the US and Western Europe, 35% of UV filters used in Asian products currently are inorganic.

- A fragmented market. While in the US, 80% of UV protection ingredients are still dedicated to sun care products (10% to skin care, 5% to hair care), in Asia, only 55% go in traditional sun care products (35% in skin care, 10% in hair care) [5].

Sun-care vs skincare

On this market, another noteworthy trend emerges, driven by changing consumer habits on both mature and younger markets. While the classic sunscreen market seems under pressure, oscillating in recent years between slight decline and small increase (-3% in 2013, +2% in 2015) [5] [6], the market of photo-protective skincare experiences an expansion. Lying behind this tendency, a growing interest for multi-task products and for a holistic approach of daily protection.

The pursuit of multipurpose solutions

Introduced on the market in the 2000s with the concept of BB cream, multifunction solutions grew in popularity in recent years. Looking for more time efficient but still effective beauty routine, consumers attempt to simplify their daily habits and increasingly opt for products offering several benefits at once. Face mask/exfoliator, cleanser/toner, moisturizing/anti-aging/mattifying day cream,

[1] Compound Annual Growth Rate

there is a clear demand for multi-claim products and ingredients.

Among consumer's expectations, one of the leading trend relates to protection against every day environmental threats. Air contaminants, infrared and blue light, and of course UV radiations, this growing concern for both indoor and outdoor pollutants is driven by the increase of urban pollution in emerging markets and an awareness of their harmful effects not only on health but more importantly on skin aging. As a case in point, almost 20% of skincare products launched globally in 2015 carried an UV-protection claim while 8% of the ones launched in Australia in 2016 were positioned as "anti-pollution" [7].

On the other side, sun-care products are not spared either by the multipurpose trend. If day creams play sunscreens, brands are also working hard to make sun-care products more relevant to current needs. Anti-aging, moisturizing or anti-pollution, the purpose is to give consumers better reasons to use sunscreen on a regular basis.

With consumers looking for both higher sun protection and beyond sun protection, the border is slowly blurring between sun and skin care.

The natural challenge

Finally, major trend on the global market of personal care, the lean toward plant-based ingredients is widely represented on the segment of photo-protection. Associated with a strong desire for healthier products, the trend is also driven by a growing awareness of the use of synthetic chemicals whose safety for both people and their environment is the subject of frequent debates.

As an example, in 2015, 75% of adults using sun protection expressed their preference for natural ingredients, while nearly 25% of women with young children claimed to be concerned about the safety of sun protection ingredients [6]. From a market point of view this is expected to result in a 19% growth of natural ingredients by 2020 [5]. According to Mintel, the trend should be particularly upward in North America and Western Europe, as well as through younger consumers [5].

HOLIMEL®, A HOLISTIC SOLUTION FOR PHOTO-PROTECTION

Last born of Bionov's SOD B® range of product, HOLIMEL® is a 100% natural melon juice concentrate, obtained from a unique proprietary and non-GMO variety of Cantaloupe melon. Original composition and high source of natural and protected Superoxide Dismutase (SOD), an essential antioxidant enzyme, HOLIMEL® acts by boosting the body's natural antioxidant defenses (SOD, Catalase, and Glutathione Peroxidase) thus preventing oxidative stress and inflammation. 100% bioactive, HOLIMEL® benefits from a proven efficacy against UV radiation side effects, demonstrated through both oral and topical route.

Antioxidant property of Bionov's ingredients has been confirmed several times. Years of researches conducted on both human and animal models enabled not only to highlight a strong potential on various oxidative stress-related disorders, but also to elucidate the complex way of action behind that. These scientific evidences are today supported by 3 gold standard clinical studies and more than 25 scientific publications.

HOLIMEL®, an in and out clinically proven efficacy

Already recognized on the market of stress (Extramel®) and cellulite (Dimpless®), Bionov® today puts its patented melon juice concentrate at the service of skin care. The potential of HOLIMEL® on UV side effects has

in this way been investigated in a randomized, double blind and placebo-controlled clinical study, during 32 days, using Minimal Erythema Dose (MED) as primary outcome. Determined as the threshold dose of UV that will produce sunburn or redness, MED is thus directly correlated to skin UV protection.

Recently completed and still unpublished, the study was assessed on a total of 88 healthy male and female subjects (18 to 50 years old) with phototype II and III (from fair skin to darker white skin). The population was divided into 4 groups, all supplemented both orally and topically, and randomized as follow:

Table 1. *Distribution of Verum and Placebo among the subjects*

Group	Number of subjects	Dietary supplement	Cream
"Active cream"	22	Placebo	Verum
"Active supplement	22	Verum	Placebo
"Double active"	22	Verum	Verum
"Double placebo"	22	Placebo	Placebo

The oral supplement was administered during 32 days and consisted in:
-One capsule of HOLIMEL® per day, corresponding to a daily dose of 20mg or 280 IU of SOD, in the Verum groups,
-One capsule of Placebo per day, containing excipients only, in the Placebo groups.

The cream was administered once a day during 4 days, directly at the study site and consisted in:
-A neutral base with 0,1% of HOLIMEL® standardized at 6IU/g, in the Verum groups,
-A neutral base in the Placebo groups.
(The topical administration was assessed twice during the study, on different areas, between D0 and D3 and between D28 and D31.)

This factorial design enables, through an inter and intra-subject comparison, to assess all at once efficacy of the dietary supplement, of the cream, and finally efficacy of the combination of both.

HOLIMEL® improves skin resistance to photo-damages

The measure of MED was performed on the buttock of each subject, 20 ± 4 hours after exposure to controlled dose of UV with a solar simulator (wavelength 280-400 nm); at D0, D5 and D33. The efficacy of the product was thus assessed for 4 days of topical administration, 32 days of oral supplementation and for the combo of both.

Reported in Figure 1, the results highlight a significant increase of MED, occurring in all the groups supplemented with the Verum:

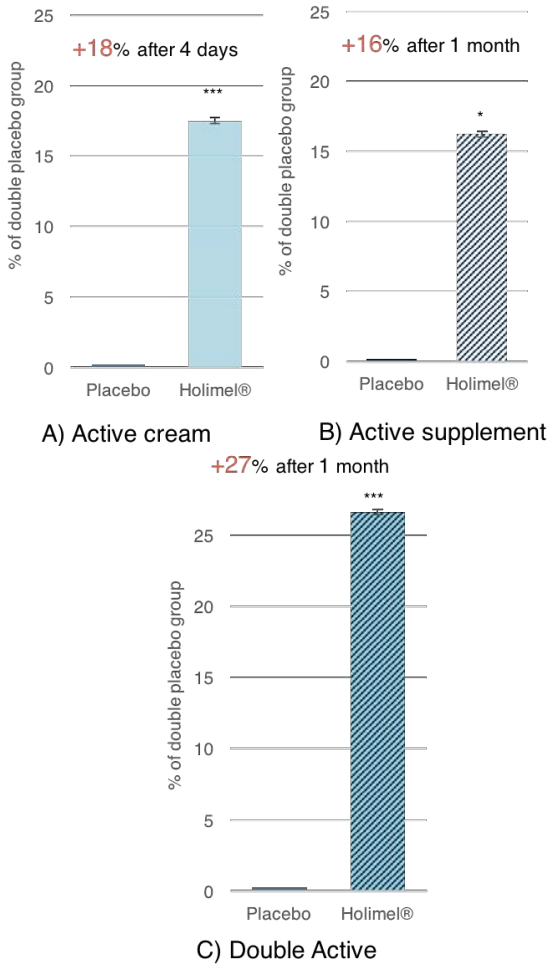

Figure 1. *MED evaluation after oral supplementation and topical administration with Verum or Placebo. A) Results after 4 days of Verum cream and Placebo*

*supplement. B) Results after 1 month of Verum supplement and Placebo cream. C) Results after 1 month of double Verum. Values are % of placebo ± SEM. (*p<0.05, *** p<0.001)*

-A significant increase of **18%** (A) after **4 days** of **topical** application of HOLIMEL®,

-A significant increases of **16%** (B) after **32 days** of **oral** supplementation with HOLIMEL®,

-Finally, a significant increase of **27%** (C) after **32 days of oral** supplementation and **4 days of topical** administration.

-On the other side, no difference could be observed in the double placebo group.

Whether administrated orally or topically, HOLIMEL® is thus able to improve resistance of the skin to UV irradiations and associated damages. Results observed in the "Double active" group even suggest that its efficacy could be fostered when used both orally and topically. It could thus be interesting to observe the effect of an entire month of combined use.

HOLIMEL® boosts endogenous antioxidant expression

Those substantiating data are not the first ones encouraging Bionov®'s melon juice concentrate in UV protection. Conducted in 2016 as preliminary research, an experiment on human skin explants demonstrated that a topical administration of HOLIMEL® was able to stimulate the expression of endogenous antioxidants, in the same way as already observed after oral administration.

In this study, the explants were placed on culture medium and HOLIMEL® applied to their surface once a day during 4 days. Untreated explants were used as a negative control and sunscreen (FPS30) treated explants as a positive one. After 4 days of treatment, a natural light simulator was used to irradiate the explants (1.5 J/cm2 of UVB + 22 J/cm2 of UVA). The quantification of endogenous antioxidant defenses in the skin was assessed after 24 more hours of incubation, through western blotting.

Results reported in Figure 2 confirm that topical administration of HOLIMEL® leads to an increase in the expression of endogenous antioxidant enzymes, with a 63%, 39% and 13% increase for SOD, CAT and GPx respectively.

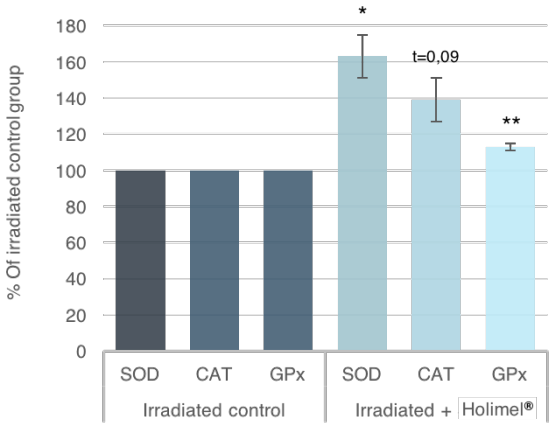

Figure 2. *Skin antioxidant enzymes expression in irradiated human explants treated (Holimel®) or not (control) with Holimel®. Values are % of irradiated control ± SEM. (*p<0.05; **p<0.01)*

HOLIMEL® prevents UV-related skin alterations

Marker for UV irradiation harmful effects, occurrence of sunburn cells was assessed on the same irradiated human explants than already noted.

Arising in reaction to UVB dose exceeding a threshold damage response, sunburn cells are none other than irreparably and severely damaged keratinocytes. Being potentially mutagenic, they exhibit then the capacity to release a tumor necrosis factor marking them for destruction by apoptosis.

Characterized by pyknotic nucleus and eosinophilic cytoplasm, sunburn cells where quantified through histologic staining.

Presented in Figure 3, the results show that HOLIMEL® was able to prevent UV radiations side effects, with a 74% decrease in sunburn

cells occurrence between untreated and HOLIMEL® treated irradiated explants.

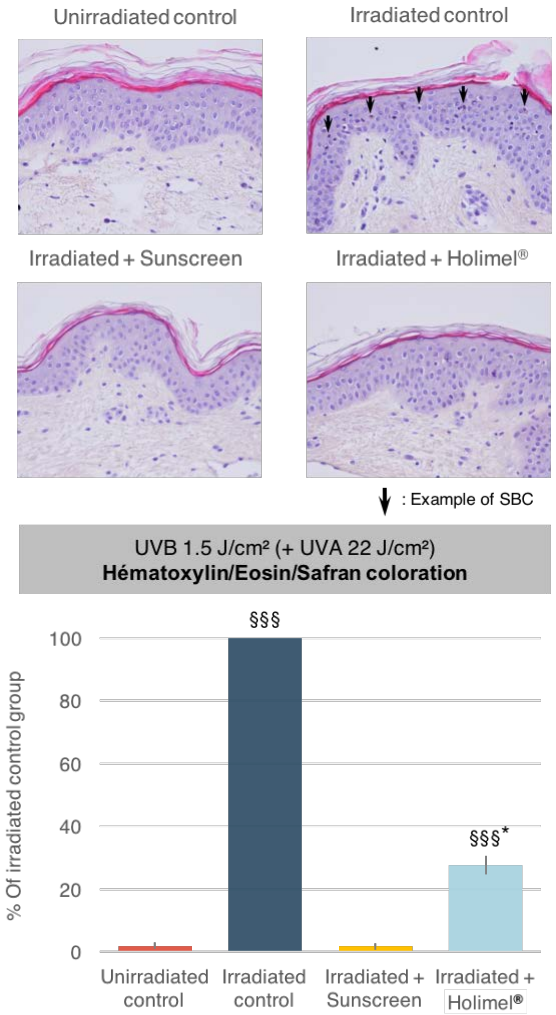

Figure 3. *Sunburn cells detection in irradiated human skin explants treated (Holimel®) or not (Control) with Holimel® through histologic staining. Values are % of irradiated control ± SEM. (§§§p<0,001 compared with unirradiated control; *p<0.05 effect of Holimel® compared with Irradiated control)*

Through its antioxidant property and its ability to increase the expression of the body's own antioxidant defenses, HOLIMEL® is thus able to improve skin resistance to UV irradiations and associated harmful effects.

UV RAYS, OXIDATIVE STRESS AND ASSOCIATED DAMAGES

Because of its role of dynamic interface between internal and external environment, skin is particularly exposed to both endogenous and exogenous factors. Largest body organ and first line of defense it hence appears as a major target for exogenous toxic threats, such as UV radiations (UVR). Besides the incontestable positive effects of solar exposure on human health, UV have been widely investigated for toxicology aspects. Capable of altering both skin structure and function, UV are today regarded as the most important risk factor for skin disorders, going from sunburns to skin cancers [8]. In addition, UV would be responsible for 80% of the visible changes commonly attributed to skin aging, including pigmentation disorders, wrinkles and texture [2].

Within the skin, solar radiations behave differently depending on their wavelength:

- If the whole solar spectrum participates in skin cell damages, **shorter wavelength UVB (280-315 nm)** are considered to be the most noxious. With a limited ability to penetrate skin layers, UVB are almost completely absorbed by the epidermis; they are however **directly** absorbed by DNA and thus highly mutagenic [8]. UVB have the primary responsibility for skin reddening and sunburn and play a key role in the development of skin cancer.

- Accounting for 95% of UVR reaching the earth surface, **longer wavelengths UVA (315-400 nm)** penetrate deeply into the dermis. Responsible for reactive oxygen species (ROS) overproduction, they cause damages through **indirect** photosensitizing reactions. UVA play the major part in tanning and photo-aging and, although at a lower level, contribute to significant epidermis damages, including skin cancers.

Whether acting directly or indirectly, UVR affect skin physiology in different manners (Figure 4):

- **DNA damages.** The effects of UVR on DNA are mostly caused by the formation of dimeric photoproducts between adjacent pyrimidine

bases on the same strand, which are directly involved in mutations in the epidermal cells and in the development of cancer cells. DNA damages also occur indirectly via interaction of ROS with intracellular chromophores and photosensitizers. The resulting oxidative imbalance is then responsible for transient and permanent genetic damages. In the epidermis, UVB act primarily on keratinocytes, which react to dose exceeding a threshold damage response, by the occurrence of sunburn cells, irreparably damaged keratinocytes marked for apoptosis;

- **Inflammation** is one of the most obvious effects of UVR on the skin. UV induce a cascade of cytokines, vasoactive and neuroactive mediators in the skin that together result in an inflammatory response and causes erythema and sunburn [8];

- **Modulation of signal transduction pathways.** Because ROS are normally involved in cellular signaling, UV-induced ROS imbalance results in a dysregulation of multiple genes expression. In the skin, these signaling pathways converge to stimulate transcription factor AP-1, leading to enhanced matrix and collagen degradation as well as decreased collagen synthesis [2]. These modifications in connective tissue are directly involved in photo-aging;

- Protein oxidation and lipid peroxidation. Direct consequence of oxidative stress, oxidation of proteins and lipids alters their structure and interferes with their function.

As reflected in Figure 4, oxidative stress is thus strongly involved in UV-induced damages, going from photo-aging and skin disorders to skin cancers. Firstly responsible for ROS overproduction, several studies highlight that UVR would additionally be able to induce an impairment of the epidermal antioxidant defense system [9]. Although highly effective, our endogenous defenses hence rapidly become overwhelmed in case of repeated and prolonged UV exposure.

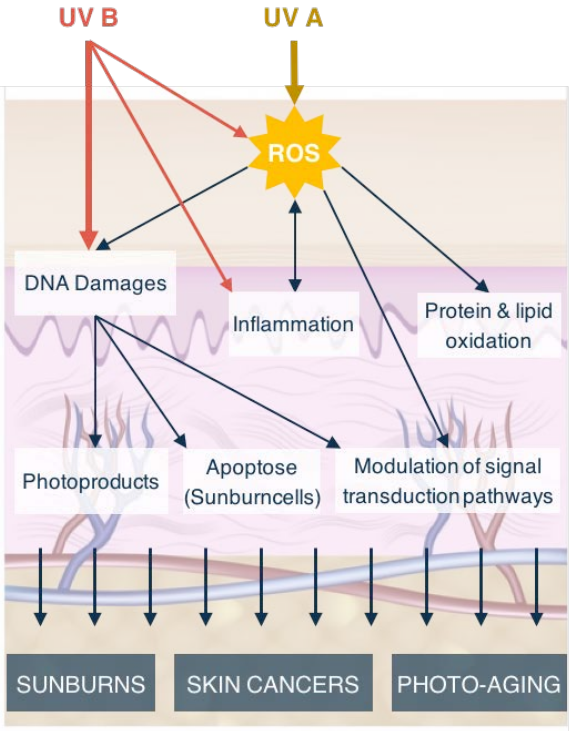

***Figure 4**. Mechanism of UVA and UVB-associated skin photo-damages and photo-aging.*

Already well recognized for its antioxidant property, HOLIMEL® has been shown not only to decrease markers for oxidative stress but to induce the body's own defense mechanism [10] [11] [12]. This antioxidant capacity has also been proven to secondly act on inflammation, as already evidenced several times [10] [13], and today confirmed clinically through a increase of MED. Finally, HOLIMEL® demonstrated a strong capacity to prevent sunburn cells occurrence, a well-known marker for UVB side effects.

With its clinically proven efficacy against UV-induced oxidative stress, inflammation and sunburn cells, HOLIMEL® contributes to skin resistance to both UVA and UVB damages. It thus represents a relevant solution for an effective photo-protection.

Clinically proven to protect skin against both UVA and UVB-associated damages, HOLIMEL® is a unique and effective solution for photo-protection. Natural, low-dose and efficient both in & out, HOLIMEL® appears as a promising alternative, on a market looking for holistic and plant-based solutions.

HEALTH BENEFITS

100% natural antioxidant
Boosts endogenous antioxidant defenses
Increases skin resistance to UV irradiations
Reduces UVA & UVB-related skin damages
Fast-acting (Oral: 1 month, Topic: 4 days)

CONSUMER ORIENTED

Oral and/or topical
Low dose
Allergen free
Vegan
Kosher & Halal

PROVEN EFFICACY

1 clinical trial
1 preclinical trial on human explants
Demonstrated way of action
Demonstrated bioactivity
Protective coating

NATURAL PROCESS

Patented
Green & gentle on environment
Solvent free
Additive free
Made in France

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