Original Articles

The benefits of using a compound containing Polypodium leucotomos extract for reducing erythema and pigmentation resulting from ultraviolet radiation

Benefícios do uso de um composto contendo extrato de polypodium loucotomos na redução da pigmentação e do eritema decorrentes da radiação ultravioleta

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ABSTRACT

Introduction: Solar radiation can produce erythema and pigmentation in the skin, interfering with pigmentary dermatoses such as melasma. Photoprotection is essential in the treatment or prevention of hyperpigmentation. The use of Polypodium leucotomos extract was effective in reducing the damage resulting from solar radiation, through antioxidant and immunomodulatory mechanisms.

Objective: To evaluate the efficacy of Polypodium leucotomos extract in reducing the erythema and pigmentation following exposure to solar radiation.

Methods: Twenty volunteers were exposed to UVB and UVA radiation emitted by a solar simulator. The reading of the minimum pigmentary and erythema doses were performed after two and 24 hours of exposure, respectively. After seven, 14 and 28 days use of Polypodium leucotomos extract (1,000 mg daily), the minimum pigmentary erythema doses were re-assessed.

Results: There was an increase in mean values for the minimum pigmentary and erythema doses in all visits, with a statistical significance of ($p < 0.05$) after 28 days for the minimum pigmentary dose and after 14 and 28 days for the minimum erythema dose.

Conclusions: The continued use of a compound containing Polypodium leucotomos extract was effective in increasing individual resistance to pigmentation and erythema resulting from UV radiation, meaning it can contribute to the treatment of skin pigmentation disorders such as melasma.

Keywords: chemexfoliation; antioxidants; cosmetics; efficacy; shikimic acid.

RESUMO

Introdução: *A radiação solar é capaz de produzir eritema e pigmentação na pele, interferindo em dermatoses pigmentares como o melasma. A fotoproteção é essencial no tratamento ou prevenção da hiperpigmentação. A utilização do extrato de Polypodium leucotomos demonstrou ser efetiva na redução dos danos decorrentes da radiação solar, através de mecanismos antioxidantes e imunomoduladores.*

Objetivo: *Avaliar a eficácia do uso de extrato de Polypodium leucotomos na redução do eritema e pigmentação após exposição à radiação solar.*

Métodos: *20 voluntários foram expostos à radiação UVB e UVA, através do uso de simulador solar. A leitura da dose pigmentária mínima e da dose eritematosa mínima foram realizadas após duas e 24 horas da exposição, respectivamente. Após o uso durante sete, 14 e 28 dias do extrato de Polypodium leucotomos (1000mg ao dia), novas determinações da dose pigmentária mínima e dose eritematosa mínima foram realizadas.*

Resultados: *Observou-se aumento das médias da dose pigmentária mínima e dose eritematosa mínima em todas as visitas, com significância estatística ($p<0,05$) após 28 dias para a dose pigmentária mínima e após 14 e 28 dias para a dose eritematosa mínima.*

Conclusões: *O uso continuado de um composto contendo extrato de Polypodium leucotomos foi eficaz no aumento da resistência individual à pigmentação e eritema decorrente da radiação UV, podendo cooperar no tratamento de transtornos pigmentares da pele, como o melasma.*

Palavras-chave: *raios ultravioleta; queimadura solar; pigmentação da pele; substâncias protetoras.*

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INTRODUCTION

With a more intense or prolonged exposure to ultraviolet radiation, cutaneous tissue will react – to a greater or lesser extent, depending on individual's susceptibility – [1] presenting a clinical picture of erythema and pigmentation, as seen in Table 1.

Erythema – or sunburn – is more evident in fair-skinned individuals, beginning after a period of two to four hours of exposure to sunlight, and reaches its greatest intensity after around 24 hours. Its onset results from vasodilation and the subsequent migration of polymorphonuclear leukocytes, characterizing an acute inflammatory reaction. UVB radiation is the main determinant of the onset of erythema.[1]

Solar pigmentation can be immediate, persistent, or late. Immediate and persistent pigmentations are due to the action of UVA radiation. Resulting from photo-oxidation of the preformed melanin and from melanin transfer from the melanocytes to keratinocytes, these pigmentations are more apparent in darker skinned individuals, arising a few minutes after exposure to sunlight, reaching their peak in two hours and regressing around 72 hours after the exposure.

On the other hand, late pigmentation results from the increased production of melanin due to the action of UVB and UVA, and also affects darker or dark-skinned individuals. Its onset begins three days after exposure to sunlight and can last for months.

The ability to respond to solar radiation through skin pigmentation (tanning) or the production of erythema (sunburn) is genetically determined by ethnic characteristics of individuals.[2]

Fairer-skinned individuals respond predominantly with sunburn, while darker-skinned individuals willexperience a more intense pigmentation rather than erythema.[1]

To quantify an individual's susceptibility to erythema and/or pigmentation, visual measurements, such as the minimal erythemal dose (MED) and the minimum pigmentary dose (MPD), can be used.

The MED can be defined as the smallest amount of effective erythematogenic energy, enough to produce the first perceptible erythema reaction with clearly defined borders.[3] For its determination, an individual must be exposed to increasing doses of UV radiation (through a device called solar simulator, whose radiation spectrum is similar to that of the sun). The reading of the erythema and MED are carried out 24 hours after.[3]

Similarly, Moyal et al.[4,5] described the MPD as the lowest UV dose required for producing an area of persistent pigmentation. For this determination, an individual must be exposed only to UVA radiation in the solar simulator, with the reading of the MPD being carried out after 2 hours.

The greater the MED or MPD, the greater the resistance of an individual to the production of erythema or pigmentation, respectively.

Prevention of erythema is desirable for individuals with acute exposure to the sun, due to the evident discomfort it causes during leisure or work activities. It was in search of a solution for this problem that the first sunscreens were developed early in the last century.

Conversely, prevention of pigmentation is particularly relevant for individuals predisposed to develop pigmentary dermatosis, such as melasma and post-inflammatory hyperchromia. In these situations, the use of topical sunscreens is also recommended, specifically those that have protection against UVA.

In addition to topical sunscreens, some oral use agents with photoprotective action have been developed more recently, with an aim at interfering with the molecular and cellular mechanisms linked to the development of acute and chronic actinic damage.

Among these agents, the Polypodium leucotomos extract (PLE), rich in phenolic derivatives, enjoys an extensive bibliography demonstrating its benefits as a photoimmunomodulator agent capable of reducing acute and chronic actinic damage.[6]

The effect created by the aqueous extract of Polypodium leucotomos leaves is intrinsically related to its antioxidant and anti-inflammatory activity, reducing the erythematogenic response triggered by solar radiation and the phototoxic reaction triggered by the use of psoralen associated with the exposure to UVA radiation-emitting devices.[7]

Furthermore, there is evidence that the systemic use of PLE is capable of preventing the depletion of epidermal antigen presenting cells (Langerhans cells).[7]

The combination of these effects has demonstrated the extract's photoprotective capacity for the prevention of the erythematogenic and phototoxic response to solar radiation.

A study by González et al.[8] was considered a milestone in the establishment of the mechanisms of action of that phytoextract. The authors evaluated a group of 21 volunteers who received topical or oral PLE and were exposed to varying doses of natural solar radiation, with or without psoralen ingestion for triggering a phototoxic reaction. Twelve patients were treated orally with PLE, four of which had received psoralens and eight who had not. The results showed that the use of topical and sys-

Table 1: Características dos principais efeitos agudos da radiação solar

	Erythema (sunburn)	Immediate + persistent pigmentation	Late pigmentation
Responsible wavelength	UVB	UVA	UVB + UVA
More frequently affected individuals	(I a III) = Lower phototypes (I to III)	Higher phototypes * (III to VI)	Higher phototypes * (III to VI)
Etiopathogenic mechanisms	Acute inflammatory reaction	Photooxidation of preformed melanin	Increased production of melanin
Onset	2 to 4 hours	Minutes	From 72 hours
Peak	24 hours	2 hours	
Duration	48 hours	72 hours	From days to weeks

*Phototype classification according to the Fitzpatrick scale.[2]

temic PLE promoted in their respective groups a statistically significant increase in MED and MPD in the non-sensitized group and a significant increase in the minimum phototoxic dose (MFD) in the photosensitized group.

Other studies published subsequently[9,10] have demonstrated that the use of oral PLE in varied doses and administered in an acute fashion a few hours before exposure to UV radiation, was capable of raising the MED, increasing the volunteers' individual resistance to UV-induced erythema.

Moreover, the effect of PLE's in the treatment of pigmentary dermatosis – such as melasma – has been proposed through antioxidant mechanisms (bearing in mind that the pigment is derived from the photo-oxidative process of melanin) and anti-inflammatory mechanisms.

Two studies[11,12] have demonstrated that patients with melasma showed clinical and colorimetric improvement of lesions with continued use of PLE after 12 weeks of treatment.

OBJECTIVES

Primary Objective: To evaluate, by determining the MPD, the effectiveness of the continued use of a formulation containing Polypodium leucotomos extract in reducing pigmentation.

Secondary objectives: To evaluate, by determining the MED, the effectiveness of the continued use of a formulation containing Polypodium leucotomos extract in reducing sunburn.

To evaluate the tolerability to the product after continued use.

METHODS

Study design

Clinical, open, monocentric study with clinical evaluations.

Study population

After having been granted approval by the Research Ethics Committee (REC), the study took place in the period from June to August 2013. Twenty female volunteers were initially recruited and included in the study (ages between 18 and 60 years old, skin phototypes II and III, absence of active skin condition, absence of continuing use of systemic medication). All volunteers signed the Free and Informed Term of Consent (FITC) before undergoing any procedures described in the study's protocol.

In addition to the required characteristics of the population and in order to ensure the eligibility of each of the volunteer, none of the following criteria could be met: pregnancy or potential risk of pregnancy, lactation, use of anti-inflammatory medications and/or topical or systemic immunosuppressants, use of antihistamines for up to 15 days before the beginning of the study, atopic or allergic history, active skin conditions (local and/or disseminated) that could impact the results of the study, conditions that could cause immune suppression, intense exposure to sunlight up to 15 days prior to the inclusion in the study, and other conditions considered to be reasonable for disqualification by the investigator.

Methodological procedures

After initial clinical evaluation for verification of eligibility criteria, each volunteer was referred to the demarcation of test areas and subsequent irradiation. One of the demarcated areas received UVA irradiation, and the other, UVB irradiation.

In the irradiated areas, UV radiation exposures were performed in six subsites (six gates) with areas of 50cm² each. The irradiations emitted by the solar simulator were delivered with progressive doses.

For the UVA irradiated area, these doses were predetermined by a UVA radiation detector, with each being 25% higher than the previous one, according to a geometric progression – the series of six UVA irradiation doses should cover the range 8J / cm² to 25J / cm².

For the UVB irradiated area, the doses were predetermined by a UVB radiation detector, with each dose being 12% higher than the previous one, according to a geometric progression.

After the exposure, each volunteer had to wait for 15 additional minutes in order that any immediate reaction to the UV radiation, such as tanning, reflection erythema, and vesicant eruption could be observed. Any possible reaction was recorded in the medical record accordingly.

After 2 and 24 hours of the irradiation, readings of the areas irradiated with UVA and UVB were carried out with an aim at determining the MPD and the MED, respectively.

MPD's values are expressed in joules per square centimeter (J / cm²).

MED is defined as the amount of radiant energy required to produce the first perceptible erythematous reaction with clearly defined borders, observed at between 16 and 24 hours after the exposure to UV radiation. It is expressed in millijoules per square centimeter (mJ / cm²).

After determining the pre-treatment MPD and MED, the volunteers were released to start the treatment.

During a 28-day period the volunteers made use of the compound containing PLE (Fernblock®, Melora, São Paulo, Brazil), with a daily dose of 4 capsules of 250 mg each (1,000 mg / day) – 2 capsules taken at 9:00 and 2 capsules taken at 13:00.

After 7, 14, and 28 days of medication use, the volunteers returned to the study center for new measurements of the MPD and MED.

On the days of the intermediate exposures (D7 and D14), the volunteers came to the study center and received the UVA and UVB doses before taking the first capsule of the day (at 9:00). This ensured that the last ingestion of the complex had taken place at least 19 hours prior to exposure to the UVR.

These procedures were repeated in new areas of each volunteer's dorsum.

The results were tabulated and the statistical analysis performed using the Student's t-test for paired samples.

RESULTS

All of the 20 included volunteers completed the study, with none having presented a picture characterized by a serious adverse event. Notwithstanding, one volunteer had an adverse

event with mild abdominal colic, which regressed spontaneously and did not require early withdrawal from the study.

MPD PROGRESSION THROUGHOUT THE VISITS

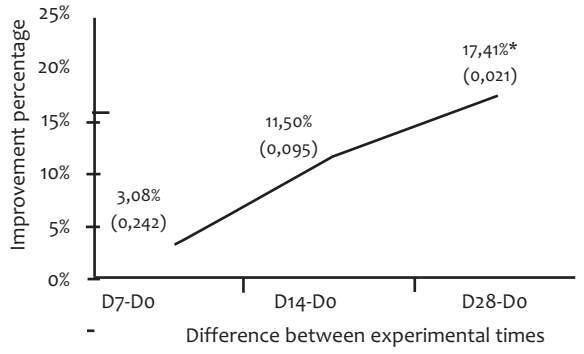
Graph 1 shows the percentage change between the mean values of MPD at the experimental times D0, D7, D14, and D28. It is possible to notice that the studied product provided a statistically significant increase ($p = 0.021$) on MPD values after 28 days of continuous use, suggesting preventive action against UVA-caused photodamage. In particular there was preventive action by stimulation of production of persistent solar pigmentation.

The percentage change shows a gain of up to 17.41% in the MPD, i.e. an increase in the individual resistance to the production of pigmentation.

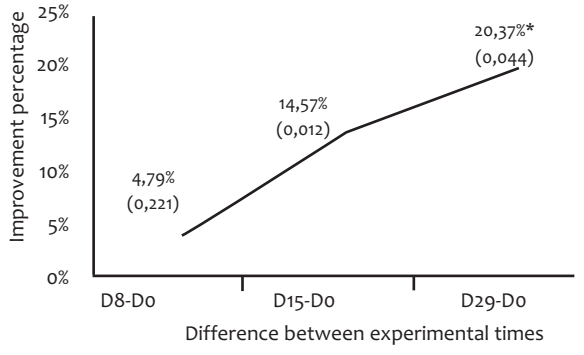
MED PROGRESSION THROUGHOUT THE VISITS

Graph 2 shows that the studied drugs provided a statistically significant increase in MED values, after 15 days ($p = 0.012$) and 29 days ($p = 0.044$) of continuous use, thus demonstrating the presence of a preventive action against photodamage caused by UVB, particularly in preventing solar erythema.

The percentage change indicates a gain of up to 20.37% in MED, meaning increased individual resistance to the production of solar erythema.



Graph 1: Percentage change in MED at different experimental times regarding the baseline (p-value) * statistical significance ($p < 0.05$)



Graph 2: depicts the percentage change between mean values of MED at the experimental times D1, D8, D15 and D29

DISCUSSION

Photoprotection can be conceptualized as a set of measures aimed at reducing or minimizing the harmful effects of solar radiation on the skin.

Of these harmful effects, the development of sunburn and pigmentation has the most acute onset and usually becomes the primary motivation for the establishment of photoprotection measures.[1,4,5]

Among pigmentary dermatoses, melasma is the most common, and is a frequent complaint in dermatologic practices, constituting one of the main motivations for prescribing photoprotective measures.

It is known that immediate and persistent pigmentation results from the photo-oxidation of the preformed melanin, making it therefore an oxidative phenomena triggered by UVA radiation and visible light, that has an intrinsic correlation with the etiopathogeny of the melasma.[1]

Thus, the introduction of new oral photoprotective active principles, capable of providing a reduction in UV-caused pigmentation through antioxidant and immunomodulatory action, is desirable.

PLE was proven to have significant antioxidant and immunomodulatory capacity in laboratory experiments.[6] In addition, previous clinical studies have indicated that intense use of PLE can produce an increase in MED, showing a clear photoprotective effect.[7-10]

More recently, two clinical studies with melasma patients indicated that the continued use of PLE can produce clinical and colorimetric reduction of lesions, confirming its effectiveness as a therapeutic option in the treatment of this condition.[11,12]

A study evaluating the effect of the continued use of PLE in preventing solar pigmentation (i.e. in the increase of MPD) had not been published to date, and the experimental model employed in the present study is widely used in photobiology to demonstrate the photoprotective efficacy of sunscreen against UVA radiation. Also, there is an absence of studies proving the effectiveness of continued use of PLE in the prevention of solar erythema (i.e. in the increase of MED).

The present study was aimed at evaluating the effects of the continued use of PLE in reducing solar pigmentation, by evaluating the MPD, and the reduction of solar erythema by evaluating the MED changes between experimental times.

The findings have demonstrated that the continued use of a compound containing PLE, at 1,000 mg / day dose produced a positive effect on the increase of MPD, leading to an improved resistance to pigment production due to exposure to solar radiation.

The authors observed a positive effect already at the evaluation on D14, with an improvement greater than 11%. Nevertheless, it was at the evaluation on D28 that the best result was observed, with a statistically significant improvement in excess of 17%.

As already mentioned, the increase in MPD produced by the use of PLE generates a higher resistance to pigmentation and, therefore, a greater photoprotective action against pigmen-

tation – a development that is particularly desirable in patients suffering from pigmentary dermatoses, such as melasma.

It was also possible to note that continued use produces better effects, which reinforces the observation of previous clinical studies showing results in the treatment of melasma within 12 weeks of use.[11,12] Regarding the production of erythema, the authors of the present study observed a similar behavior, though with different numbers.

In the evaluation after 15 days of use, the authors observed a statistically significant increase of roughly 15% in MED, which increased to the even higher level of 20% (with statistical significance) after 29 days of use.

Prior studies to evaluate protection against erythema by determining the MED were aimed at verifying the effect of the intensive use of PLE.[8-10]

Middelkamp-Hup MA et al.[10] carried out a study with clinical assessments of erythema and histological evaluations in volunteers irradiated with solar simulator before and after receiving acute doses of PLE up to a maximum of 24 hours prior to exposure.

The assessment of erythema was not based on the determination of MED, but on the use of a scale to evaluate erythema, which makes comparisons with the results of the present study difficult. It is, however worth noting that the authors found a statistically significant reduction in erythema in irradiated sites after taking PLE up to 2 hours after the ingestion of the last dose of the extract. In the present study, the objective was not to identify the acute effect linked to the ingestion of PLE, but rather to identify some continued benefit regardless of the time of ingestion of the doses (as mentioned above, the volunteers received UVA and UVB doses after at least 19 hours had passed since the last ingestion of the investigated product), which is of particular interest for the understanding of the benefits found in patients with chronic photodermatoses, such as melasma.

The results found in the present study demonstrate that the continued use of PLE provides a slow and gradual increase of MPD and basal MED. This is not exactly a cumulative effect, but a gradual increase in the individual's tolerance to pigmentation and erythema triggered by UV.

CONCLUSION

The continued use of a compound containing PLE produced a significant reduction in MED within 14 days of use, and a significant reduction of MPD within 28 days of use, after exposure to solar simulator irradiation. This has demonstrated the presence of the positive effect in the anti-erythematogenic and anti-pigmentary actions following ultraviolet exposure. This compound can provide benefits to users who bear photodermatoses or dermatoses that may be exacerbated by exposure to UV radiation, such as melasma.●

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