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Brief Report

The Skinny on Moisturizers: A Brief Report

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ABSTRACT

Objective
To compare the effectiveness of 5 different skin moisturizers using JELL-O® as a model for the human skin.

Methods
In this study five different moisturizers (Equate®, Burt's Bees®, Suave®, Aveeno® and Vaseline®) were applied to equivalent samples of JELL-O®. Observations were made over a 12-day period and data was collected at 15 different time intervals. The primary outcome was the height (cm) and weight (g) of the JELL-O® sample at each time interval. The study was an *ex vivo* experiment conducted in a home laboratory. No Institutional Review Board (IRB) approval was required since the research does not involve living organisms.

Results
Overall, the JELL-O® sample that had the Vaseline® applied on it had the lowest loss of height and weight. The height stayed at 100% of its original value and the weight only decreased to 97.2% of the original value by the end of the observation period. In contrast, the sample which had Suave® applied to the surface its height and weight decrease the most (42% and 28% respectively). The other moisturizers had effects intermediate between these two extremes.

Conclusion
Based on this *ex vivo* head to head study using JELL-O® as a model for the human skin the 5 moisturizers examined had widely differing levels of effectiveness with Vaseline® appearing to be the most protective against evaporative losses and Suave® appearing to be the least.

Keywords
Moisturizers; Dry skin; Different moisturizers; Skin lotions; Vaseline® effectiveness.

INTRODUCTION

The skin consists of three distinctive layers.[1] These are the epidermis, dermis, and hypodermis. The epidermis is the outermost layer of the skin, and it provides a waterproof barrier and creates our skin tone.[2] The epidermis consists of further layers: stratum basale, stratum spinosum, stratum granulosum, stratum lucidum, and stratum corneum.

It is the water content of the outermost layer of skin that makes the difference between normal skin and dry skin.[2-4] Normally, the stratum corneum has the same surface area as the skin layers beneath it. When its water content is low, however, this layer shrinks in volume and surface area. As it tightens against the skin below, it eventually cracks, producing that flaky or scaly appearance that is recognized as the dry skin. The stratum corneum is always losing water through evaporation, but factors such as extreme heat and dry weather can increase this evaporation.[5] The skin produces natural oils to help seal the water, but bathing, as well as harsh soaps and detergents, deplete these natural oils. One of the things that can be done to help prevent dry skin is to use moisturizers.

Often doctors recommend treating dry skin with moisturizers (which helps keep the skin moist), such as ointments, creams, and lotions. Dry skin may be lacking water or important oils that help keep the skin moist. Moisturizers contain many ingredients that work to add, or retain oils and water in the skin.

The primary aim of this study was to directly compare 5 common moisturizers on the market in terms of their effectiveness in preventing dry skin due to evaporative losses.

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MATERIALS AND METHODS

Study Design

During the study, JELL-O® in petri dishes were used as the skin model. The petri dishes used were empty containers filled with JELL-O® to act as the base. The height (cm) and weight (g) of the JELL-O® was noted at each time point. In order to make things more standardized, the height and weight were expressed as a percentage. This was an *ex vivo* experiment comparing the aforementioned 5 moisturizers. Repeated measurements were taken at 15 different time points over 12 days. During the study, the constant variables were the temperature (°F) and the environment that the petri dishes were kept in, the JELL-O® (in terms of brand and color, which was yellow), weight scale (the petri dishes were measured on the same scale), metric ruler the petri dishes were measured with the same ruler, the amount of JELL-O® i.e. 30 ml that was kept in the refrigerator with a temperature around 37 °F for 4 hours once it was made.

Skin Model

The skin model used during the study was JELL-O® in petri dishes. JELL-O® is a gelatin dessert mostly made from water and gelatin, which is a substance derived from collagen. Collagen is a group of fibrous proteins found in many tissues in humans and other animals, where it helps to connect and support tissues. It is commonly found in the skin and is particularly important in the dermis layer.

Exposure Groups

In this study, there were 5 different exposure groups: Vaseline®, Equate®, Aveeno®, Burt's Bees®, and Suave®. These five moisturizers were chosen because their specific ingredients make them different from each other.

Control Group

During the study, the controls were the three petri dishes that had only JELL-O® on the dish.

Primary Outcome Variables

The primary outcome variables were the height and weight of the JELL-O® at each time point. To make things more standardized we expressed height and weight as a percentage of the starting height and weight of each JELL-O® sample.

Research Methods

Following the instructions on the JELL-O® box, the sample was prepared. Fifty milliliter of the sample was placed in each petri dish prior to refrigeration. The samples were refrigerated for four hours.

The height and weight of each JELL-O® sample was measured before adding the moisturizers. Two tablespoons (30 ml) each of moisturizer was added to each of the three petri dishes assigned to that moisturizer. Using a plastic knife, the moisturizer was evenly spread across the entire surface. Lastly, one set of measurements were taken. An hour later, another set of measurements were made. Measurements were taken on a daily basis for 12-days following this . Each moisturizer was applied to three samples. This created a total of 45 data points for each moisturizer and the control for a total of 270 data points.

Data Management and Statistical Analysis

Microsoft Excel® was used for data management and in generating descriptive statistics as well as basic graphs.

Table 1. *Change in Height (centimeters) of JELL-O® Sample Over Time (hours) After Application of Various Topical Moisturizers*

	Height (in centimeters)																	
Time (in hours)	Equate®			Burts Bee's®			Suave®			Aveeno®			Vaseline®			JELL-O®		
	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3
JELL-O*	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60
0	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60
1	0.60	0.60	0.60	0.50	0.50	0.50	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.55	0.55	0.55
24	0.59	0.60	0.60	0.50	0.50	0.49	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.50	0.50	0.50
48	0.55	0.55	0.55	0.45	0.45	0.45	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.60	0.49	0.49	0.49
72	0.54	0.54	0.54	0.42	0.42	0.42	0.50	0.50	0.50	0.60	0.60	0.60	0.60	0.60	0.60	0.40	0.40	0.40
96	0.53	0.52	0.53	0.39	0.38	0.39	0.50	0.49	0.50	0.55	0.55	0.55	0.60	0.60	0.60	0.35	0.35	0.35
120	0.50	0.50	0.50	0.31	0.32	0.32	0.48	0.48	0.48	0.55	0.54	0.55	0.60	0.60	0.60	0.30	0.30	0.30
144	0.50	0.50	0.50	0.29	0.30	0.30	0.39	0.40	0.40	0.54	0.54	0.54	0.60	0.60	0.60	0.20	0.20	0.20
168	0.50	0.50	0.50	0.29	0.29	0.29	0.30	0.30	0.30	0.53	0.53	0.53	0.60	0.60	0.60	0.18	0.18	0.18
192	0.50	0.49	0.50	0.27	0.26	0.27	0.22	0.22	0.21	0.51	0.51	0.51	0.60	0.60	0.60	0.17	0.17	0.17
216	0.50	0.49	0.50	0.26	0.26	0.25	0.20	0.20	0.20	0.50	0.50	0.50	0.60	0.60	0.60	0.15	0.15	0.15
240	0.49	0.49	0.49	0.25	0.24	0.25	0.19	0.18	0.19	0.50	0.50	0.50	0.60	0.60	0.60	0.11	0.11	0.11
264	0.49	0.49	0.49	0.24	0.23	0.24	0.18	0.18	0.18	0.50	0.50	0.50	0.60	0.60	0.60	0.10	0.10	0.10
288	0.49	0.49	0.49	0.23	0.23	0.23	0.17	0.17	0.17	0.50	0.50	0.50	0.60	0.60	0.60	0.09	0.09	0.09

JELL-O- Jell-O alone before adding moisturizer; and T-Trail*

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Table 2. *Change in Percent of Initial Height (centimeters) of JELL-O® Sample Over Time (hours) After Application of Various Topical Moisturizers*

	Percent of Initial Height					
Hours	Equate®	Burts Bee's®	Suave®	Aveeno®	Vaseline®	JELL-O®
0	100%	100%	100%	100%	100%	100%
1	100%	83.3%	100%	100%	100%	91.7%
24	100%	83.3%	100%	100%	100%	83.3%
48	91.7%	75.0%	100%	100%	100%	81.7%
72	90.0%	70.0%	83.3%	100%	100%	66.7%
96	88.3%	65.0%	83.3%	91.7%	100%	58.3%
120	83.3%	53.3%	80.0%	91.7%	100%	50.0%
144	83.3%	50.0%	66.7%	90.0%	100%	33.3%
168	83.3%	48..3%	50.0%	88.3%	100%	30.0%
192	83.3%	45.0%	36.7%	85.0%	100%	28.3%
216	83.3%	43.3%	33.3%	83.3%	100%	25.0%
240	81.7%	41.7%	31.7%	83.3%	100%	18.3%
264	81.7%	40.0%	30.0%	83.3%	100%	16.7%
288	81.7%	38.3%	28.3%	83.3%	100%	15.0%

Table 3. *Change in Weight (grams) of JELL-O® Sample Over Time (hours) After Application of Various Topical Moisturizers*

	Weight (in Grams)																	
Time (in hours)	Equate®			Burts Bee's®			Suave®			Aveeno®			Vaseline®			JELL-O®		
	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3
JELL-O*	62.50	62.50	62.50	62.50	62.50	62.50	62.50	62.50	62.50	62.50	62.50	62.50	62.50	62.50	62.50	62.50	62.50	62.50
0	76.30	76.30	76.30	74.57	74.43	74.50	81.30	81.30	81.30	80.70	80.70	80.70	87.20	87.20	87.21	62.50	62.50	62.50
1	76.31	76.30	76.29	74.55	74.45	74.50	81.24	81.33	81.32	80.69	80.70	80.70	87.20	87.21	87.20	59.00	59.00	59.00
24	76.20	76.19	76.21	73.32	73.30	73.28	80.19	80.20	80.20	79.00	79.00	79.00	87.00	87.00	87.00	51.30	51.30	51.30
48	76.10	76.10	76.10	69.70	69.64	69.76	78.31	78.26	78.32	75.31	75.25	75.25	86.90	86.91	86.90	44.40	44.40	44.40
72	76.10	76.09	76.10	67.20	66.90	66.90	69.30	69.30	69.30	73.10	73.10	73.10	86.81	86.80	86.80	37.90	37.90	37.90
96	76.00	76.00	76.00	64.69	64.71	64.70	61.29	61.30	61.30	71.70	71.69	71.69	86.69	86.72	86.70	32.90	32.90	32.90
120	76.00	76.00	76.00	62.40	62.40	62.40	55.89	55.90	55.90	70.60	70.60	70.60	86.50	86.51	86.50	27.90	27.90	27.90
144	75.90	75.90	75.90	60.17	60.20	60.23	51.33	51.44	51.42	69.49	69.50	69.50	86.30	86.31	86.30	25.70	25.70	25.70
168	75.80	75.80	75.80	58.26	58.34	58.30	47.60	47.60	47.60	68.52	68.45	68.45	86.29	86.30	86.30	24.90	24.90	24.90
192	75.79	75.80	75.80	56.80	56.80	56.80	41.87	41.89	41.95	67.70	67.70	67.70	86.22	86.17	86.22	24.70	24.70	24.70
216	75.71	75.70	75.69	55.22	55.36	55.32	37.81	37.78	37.80	66.90	66.90	66.90	86.22	86.15	86.22	24.60	24.60	24.60
240	75.71	75.70	75.69	53.60	53.60	53.59	36.69	36.70	36.70	66.30	66.30	66.30	85.20	85.20	85.20	24.60	24.60	24.60
264	75.60	75.60	75.60	52.00	52.00	52.00	35.67	35.67	35.77	65.80	65.79	65.79	84.90	84.91	84.90	24.50	24.50	24.50
288	75.60	75.60	75.60	50.50	50.51	50.50	34.80	34.80	34.80	68.10	65.10	65.10	84.81	84.80	84.80	24.50	24.50	24.50

JELL-O- Jell-O alone before adding moisturizer; and T-Trail*

RESULTS

Overall, the JELL-O® sample that had the Vaseline® applied on it had the lowest loss of height and weight. The height stayed at 100% of its original value and the weight only decreased to 97.2% of the original value by the end of the observation period. In contrast, the sample which had Suave® applied to the surface saw its height and weight decrease the most (42% and 28% respectively). The other moisturizers had effects intermediate between these two extremes. The results of the experiment are shown in Tables 1 (change in height of JELL-O® over time), 2 (change in percent of initial height of JELL-O® over time), 3 (change in weight of JELL-O® over time), and 4 (change in percent of initial weight of JELL-O® over time) and in Figures 1 (change in percent of weight over time) and 2 (change in percent of height over time).

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Table 4. *Change in Percent of Initial Weight (grams) of JELL-O® Sample Over Time (hours) After Application of Various Topical Moisturizers*

Percent of Weight in Petri Dishes						
Time (in Hours)	Equate®	Burts Bee's®	Suave®	Aveeno®	Vaseline®	JELL-O®
0	100%	100%	100%	100%	100%	100%
1	100%	100%	100%	100%	100%	94.4%
24	99.9%	98.4%	98.6%	97.9%	99.8%	82.1%
48	99.7%	93.6%	96.3%	93.3%	99.7%	71.0%
72	99.7%	89.9%	85.2%	90.6%	99.5%	60.6%
96	99.6%	86.8%	75.4%	88.8%	99.4%	52.6%
120	99.6%	83.8%	68.8%	87.5%	99.2%	44.6%
144	99.5%	80.8%	63.2%	86.1%	99.0%	41.1%
168	99.3%	78.3%	58.5%	84.9%	99.0%	39.8%
192	99.3%	76.2%	51.5%	83.9%	98.9%	39.5%
216	99.2%	74.2%	46.5%	82.9%	98.9%	39.4%
240	99.2%	71.9%	45.1%	82.5%	97.7%	39.4%
264	99.1%	69.8%	43.9%	81.5%	97.4%	39.2%
288	99.1%	67.8%	42.8%	80.7%	97.2%	32.8%

Figure 1. *Change in Percent of Weight (grams) Over Time (hours) After Application of Moisturizer to Petri Dish with JELL-O®*

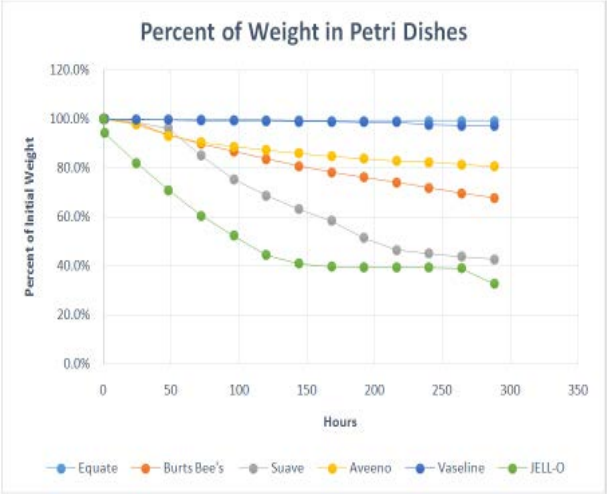
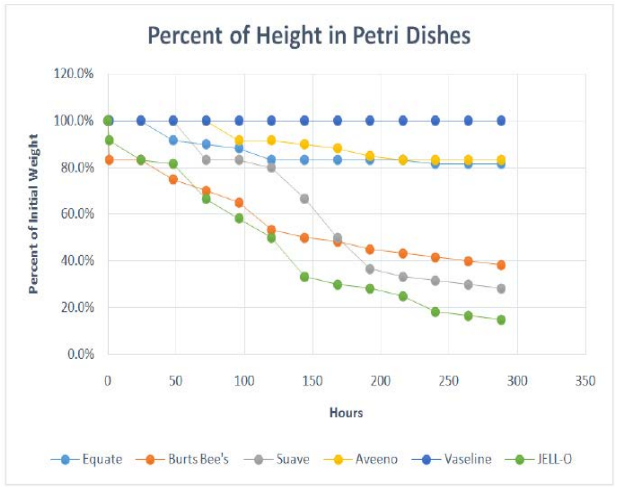


Figure 2. *Change in Percent of Height (centimeters) Over Time (hours) After Application of Moisturizer to Petri Dish with JELL-O®*



DISCUSSION

This study describes a novel *ex vivo* experiment to assess the effectiveness of five different skin moisturizers. Loss of height and weight of the JELL-O® samples was used to simulate trans epidermal water loss in the human skin. Vaseline® seemed to have the highest effectiveness while Suave® appeared to have the least.

Our results are broadly consistent with prior studies though we could not find a head to head study that compared multiple moisturizers due to how we carried out this experiment. A prior study argued that Vaseline® petroleum jelly, in a minimum concentration of 5% is the most effective occlusive as it reduces transepidermal water loss by as much as 98%.[5] Vaseline® is thought to primarily work by acting as an occlusive. One study showed that Vaseline® petroleum jelly actually accelerated skin recovery after artificial disruption using acetone.[6] The study found that Vaseline® permeates through the stratum corneum interstices allowing recovery of the skin despite its occlusive properties.

Measuring the effect of topical moisturizers on changes in stratum corneum thickness *in vivo* requires expensive techniques such as confocal Raman spectroscopy.[7] We demonstrate a low cost *ex vivo* alternative way of assessing the effect of different topical moisturizers in terms of their effectiveness in preventing or reducing water loss.

STRENGTHS AND LIMITATIONS

It is believes that the technique used in this study was both a strength and a limitation. It was a strength because it were non-

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invasive and allowed the experiment to be repeated multiple times with strict quality control. At the same time, because this was an *ex vivo* study, we cannot surely say that the results would have been the same if performed on human beings. This is due to humans having various skin types, like dry and oily skin, which could lead to an alteration in which products best suit them. Therefore, further research is warranted in order to improvised the results.

CONCLUSION

In conclusion, based on this *ex vivo* head to head study using JELL-O® as a model for the human skin the 5 moisturizers examined had widely differing levels of effectiveness with Vaseline® appearing to be the most protective against evaporative losses and Suave® appearing to be the least.

NOTE

The author is a scholar at Townview Talented and Gifted (TAG) Magnet School in Dallas, Texas which is constantly rated as a top high school in the United States (currently ranked #11 as per U.S. News). At the age of 12, she became one of the youngest authors within and outside of the United States by publishing a novel, "Ancient Dynasty Chronicles: The Untold Truth," which is available on Amazon and many other locations. She donated the book's proceeds to her previous school, Uplift North Hills Preparatory (50%) and the St. Jude Children's Cancer Research Hospital (50%). Currently, she is preparing to publish her second book in the end of 2019. Additionally, she is a recipient of multiple piano awards, a person who strives to help the people around her through kind acts, and a straight "A" student at school.

Last year, during the science fair conducted by University of Texas (UT) Southwestern in Dallas, this study/research on "The Skinny on Moisturizers" received the prestigious UT Southwestern STARS award. The same study has been extended as an academic journal. The author wished to publish her research work to the academic world, as she believes that she will not only learn from this experience, perhaps even inspire the people around her to feel enthusiastic about the scientific area.

EIC's Comments: "This work is done by a high school student and we are publishing this as it fits into our mission of promoting and encouraging studies in science, technology, engineering and mathematics (STEM) field for our next generation".

DISCLOSURE

I certify that no funding has been received for the conduct of this study and/or preparation of this manuscript. I certify that the study does not promote any commercial product and I haven't received any compensation from the companies for the study or publication.

REFERENCES

1. Proksch E, Brandner JM, Jensen JM. The skin: An indispensable barrier. *Exp Dermatol.* 2008; 17(12): 1063-1072. doi: 10.1111/j.1600-0625.2008.00786.x

2. Lee T, Friedman A. Skin barrier health: Regulation and repair of the stratum corneum and the role of over-the-counter skin care. *J Drugs Dermatol.* 2016; 15(9): 1047-1051.

3. Nolan K, Marmur E. Moisturizers: Reality and the skin benefits. *Dermatol Ther.* 2012; 25(3): 229-233. doi: 10.1111/j.1529-8019.2012.01504.x

4. Madison KC. Barrier function of the skin: "la raison d'etre" of the epidermis. *J Invest Dermatol.* 2003; 121(2): 231-241. doi: 10.1046/j.1523-1747.2003.12359.x

5. Kraft JN, Lynde CW. Moisturizers: What they are and a practical approach to product selection. *Skin Therapy Lett.* 2005; 10(5): 1-8.

6. Ghadially R, Halkier-Sorensen L, Elias PM. Effects of petrolatum on stratum corneum structure and function. *J Am Acad Dermatol.* 1992; 26(3 Pt 2): 387-396. doi: 10.1016/0190-9622(92)70060-s

7. Crowther JM, Sieg A, Blenkiron P, et al. Measuring the effects of topical moisturizers on changes in stratum corneum thickness, water gradients and hydration *in vivo*. *Br J Dermatol.* 2008; 159(3): 567-577. doi: 10.1111/j.1365-2133.2008.08703.x

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Letter to the Editor

Squamous Melanocytic Tumour at an Unusual Site: An Uncommon Case and Literature Review

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ABSTRACT

We herein present a case report of a 60-year-old male patient diagnosed with squamous-melanocytic tumour (SMT) in his anal region, comprised of two intermingled different phenotypic lesions. This dual tumour is quite uncommon and could potentially be challenging on both diagnose and also management. It is the first case reported on this location, moreover, the lack of consensus for these lesions makes it difficult to classify them. We reviewed the literature of similar SMT's and discussed its histogenesis. As they are rare, their biological behavior and potential metastasis remain unclear. Therefore, close follow-up is advised.

Keywords
Combined neoplasia; Squamous-melanocytic tumour; Uncertain; Anal canal.

INTRODUCTION

Anal squamous cell carcinoma is a rare condition. Of all cancers of the lower gastrointestinal tract, anal squamous cell carcinoma accounts for 4% of the total.[1] Likewise, primary malignant melanoma of the anorectal area are quite infrequent and only represents 0.4%-1.6% of all melanomas and less than 1% of anal canal tumours.[2] Not surprisingly, a combination of both (squamous cell and melanocytic lesions) is an exceeding rare tumour. Our case is the first SMT case reported in the anorectal region. The literature review shows nineteen SMT reported cases. Most of them located on the head and neck[3] and none in the perineal or genital areas. The biological behaviour remains unclear and albeit eighteen cases have not shown any further malignant report there is one case with SMT metastasis5. There is no definitive risk factor for SMT lesions although some of them have been linked to previous burn and solar conditions.[3-5]

CASE REPORT

A 60-year-old male patient presented a dark pigmented nodule on his anal canal. No other clinical information was provided. The clinical hypothesis was either a malignant or benign pigmented lesion. The lesion was excised through a shave biopsy and sent to histopathological analysis.

Histopathological Findings

Histological examination showed on low-power magnification a fairly well-circumscribed epidermal tumour with endophytic proliferation displaying striking dark pigment within it. The neoplasia surrounded adnexal structures such as hair follicles occupying superficial dermis, infiltrating into the deep dermis. High-power magnification showed a focal ulcerated area and a combined population. The first population was characterised by mild atypical eosinophilic epithelial cells. Admixed with the later, there was a second type of cells represented by pigmented epithelioid to stellated shaped within the same stroma. The tumour was confined to the basal membrane (*in situ*). There was no evidence of invasive malignancy.

The histological differential diagnosis in this case include melanoacanthoma, squamous cell carcinoma (SCC) colonised by atypical melanocytes, collision tumours of malignant melanoma (MM) and SCC, pigmented SCC, MM with adnexal extension (Figures 1 and 2).

Immunohistochemistry was performed to better identify

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Figure 1. *Hematoxylin and Eosin Stain (H&E) of a Heavily Pigmented Squamous Cell Proliferation at Low Power (x2)*

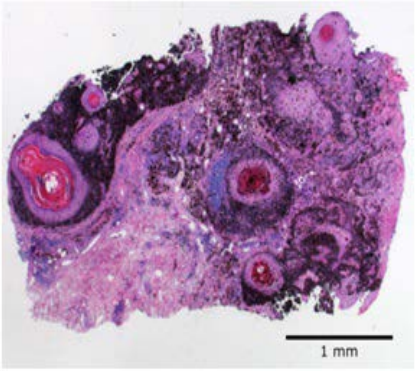


Figure 2. *A Higher Magnification (x 20) Showing the Intermingled Proliferation of Pigmented Cells (melanocytes) and Squamous Cells with Keratin Formation*

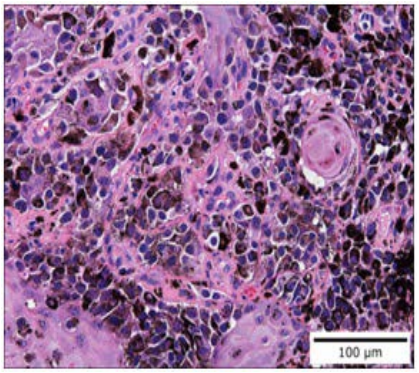


Figure 3. *Combined Immunohisto Chemistry: S100 (black) Highlighting Melanocytes Together with CK5/6 (red) Staining Squamous Cell with Keratin Formation*

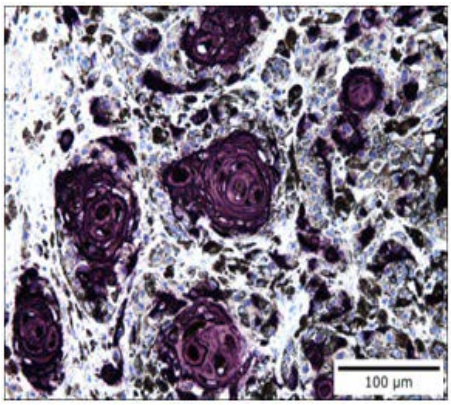
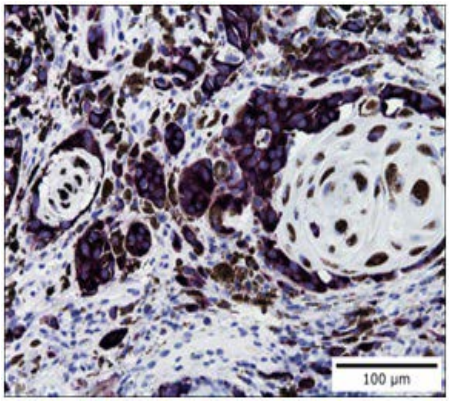


Figure 4. *Melan A Marker: Highlighting Melanocytes. Note that the Squamous Cells are Not Staining*



the nature of the cells. Figure 3 shows a combined immunohistochemistry. Due to the heavy brown pigment CK5/6 marker was performed in red colour showing cytoplasmic positivity for squamous cells. Together with that, there was a strong nuclear and cytoplasmic positivity for S100 (black colour), highlighting the melanocytes within the keratin formation. Another melanocytic marker (Melan A) was performed, showing strong cytoplasmic positivity which stained negative in the squamous cells (Figure 4). The presence of markers for both types of cells confirms the squamous and the melanocytic components, therefore supporting a diagnosis of a squamous-melanocytic tumour (SMT).

DISCUSSION

Squamous-melanocytic tumours are an uncommon and rare cutaneous neoplasia. There are only eighteen reported cases in the literature (Table 1) and none of them located in the anal canal. The squamous melanocytic lesion was first described by Rosen et al[6] and further restudied and classified as SMT by Pool et al.[8]

A literature review by Pool et al,[8] Satter et al[11] and Wang et al[3] who had evaluated tumour sites, age, gender and metastasis follow-up can be seen in the table below (Table 1). The great majority of those tumours are located in the head and neck region[3,8,10,12-14] and just one case was showed metastasis.[4] No gender predilection were seen as reported by Boyd et al[17] and the average age varied from 30s to 90s according to Wang et al.[3]

The theories for the tumoural histogenesis have been debated and there are four believed categories[8,12,14]: colonization tumour, combined tumour, collision tumour and biphenotypic tumour. Our case can be placed on the combined tumour classification.

Overall, we have presented a rare tumour with unusual location, since the most common location is head and neck and yet none of them occurred on the anal region. Although histogenesis remains unclear,[5,14] some papers support sun exposure and scarring process as a main tumorigenesis factor.[7] Our findings go against the sun exposure theory in as much as anal region usually is not a sun exposed area.

To sum up, we reported a rare neoplasia with dual component, composed of both malignant squamous and malignant melanocytic cells, known as squamous-melanocytic neoplasia. This case is the first to report the lesion on the area and is important to illustrate and to alert how it can easily be mistaken by its dif-

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Table 1. *SMT Location and Outcome in the Literature*

SMT	Age	Gender	Location	Metastasis
Muhlemann et al[5]	59	M	Trunk	Unknown
Rosen et al[6]	Unknown	Unknown	Unknown	Unknown
Walker and Walker[7]	78	F	Tigh	Unknown
Akiyama et al[4]	55	M	Right lower leg	Yes
Pool et al[8]	44	M	Head & Neck	No
	47	F	Head & Neck	No
	50	M	Head & Neck	No
	70	M	Head & Neck	No
Cutlan et al[9]	72	F	Shoulder	No
Dorić et al[10]	61	F	Head& Neck	No
Satter et al[11]	63	F	Left leg	No
	73	F	Left forearm	No
Rongioletti et al[12]	94	M	Back	No3
Pouryazdanparast et al[13]	62	M	Head & Neck	No
Leonard et al[14]	68	M	Head & Neck	No
Miteva et al[15]	82	M	Head & Neck	No
Amerio et al[16]	32	F	Right arm	No
Wang et al[3]	63	F	Head & Neck	No
Present study	60	M	Anal canal	No

SMT: Squamous-melanocytic tumour; M: Male; F: Female

ferentials. This is a neoplasia with uncertain biological potential and prognosis, with treatment relying on complete excision and observation. Due to the uncertain behaviour of these lesions, close follow-up is strongly advised.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

1. Wietfeldt ED, Thiele J. Malignancies of the anal margin and perianal skin. *Clin Colon Rectal Surg.* 2009; 22(2): 127-135. doi: 10.1055/s-0029-1223845

2. Belli F, Gallino GF, Lo Vullo S, Mariani L, Poiasina E, Leo E. Melanoma of the anorectal region: The experience of the National Cancer Institute of Milano. *Eur J Surg Oncol.* 2009; 35: 757-762. doi: 10.1016/j.ejso.2008.05.001

3. Wang HY, Zhang XB, Su RJ, Wang CB, Liu X. An uncommon malignant cutaneous squamomelanocytic tumor. *Exp Ther Med.* 2013; 5: 897-901. doi: 10.3892/etm.2013.882

4. Akiyama M, Inamoto N, Nakamura K. Malignant melanoma and squamous cell carcinoma forming one tumor in a burn scar. *Dermatology.* 1997; 194: 157-161. doi: 10.1159/000246086

5. Muhlemann MR, Griffiths RW, Briggs JC. Malignant melanoma and squamous cell carcinoma arising in a burn scar. *Br J Plast Surg.* 1982; 35: 474-477. doi: 10.1016/0007-1226(82)90048-0

6. Rosen LB, Williams WD, Benson J, Rywlin AM. A malignant neoplasm with features of both squamous cell carcinoma and malignant melanoma. *Am J Dermatopathol.* 1984; (6 Suppl): 213-219.

7. Walker AN, Walker GK. Scar-associated malignant melanoma and squamous carcinoma in situ. *South Med J.* 1989; 82: 1419 -1421. doi: 10.1097/00007611-198911000-00020

8. Pool SE, Manieei F, Clark WH Jr, Harrist TJ. Dermal squamomelanocytic tumor: A unique biphenotypic neoplasm of uncertain biological potential. *Hum Pathol.* 1999; 30: 525-529. doi: 10.1016/s0046-8177(99)90195-8

9. Cutlan RT, Wesche WA, Chesney TM. A cutaneous neoplasm with histopathological and immunohistochemical features of both malignant melanoma and squamous cell carcinoma. *J Cutan Pathol.* 2000; 27: 551.

10. Dorić M, Radović S, Kuskunović S, et al. Dermal squamomelano-cytic tumor: Neoplasm of uncertain biological potential. *Bosn J Basic Med Sci.* 2008; 8(2): 152-155. doi: 10.17305/bjbms.2008.2972

11. Satter EK, Metcalf J, Lountzis N and Elston DM. Tumors composed of malignant epithelial and melanocytic populations: A case series and review of the literature. *J Cutan Pathol.* 2009; 36: 211-219. doi: 10.1111/j.1600-0560.2008.01000.x

Dermatol Open J. 2020; 5(1): 6-9. doi: 10.17140/DRMTOJ-5-139

12. Rongioletti F, Baldari M, Carli C, Fiocca R. Squamomelanocytic tumor: A new case of a unique biphenotypic neoplasm of uncertain biological potential. *J Cutan Pathol*. 2009; 36: 477-481. doi: 10.1111/j.1600-0560.2008.01061.x

13. Pouryazdanparast P, Yu L, Johnson T, Fullen T. An unusual squamo-melanocytic tumor of uncertain biologic behavior: A variant of melanoma? *Am J Dermatopathol*. 2009; 31: 457-461. doi: 10.1097/DAD.0b013e318182c7dc

14. Leonard N, Wilson N, Calonje JE. Squamomelanocytic tumor: an unusual and distinctive entity of uncertain biological potential. *Am J Dermatopathol*. 2009; 31: 495-498. doi: 10.1097/DAD.0b013e31819b4077

15. Miteva M, Hershthal D, Ricotti C, Kerl H, Romanelli P. A rare case of cutaneous squamousmelanocytic tumour: Revisiting the histogenesis of combined neoplasms. *Am J Dermatopathol*. 2009; 31(6): 599-603. doi: 10.1097/DAD.0b013e3181a88116

16. Amerio P, Carbone A, Auriemma M, Tracanna M, Di Rollo D, Angelucci D. Metastasizing dermal squamomelanocytic tumour: More evidences. *J Eur Acad Dermatol Venereol*. 2011; 25: 734-735. doi: 10.1111/j.1468-3083.2011.03999.x

17. Boyd AS, Rapini PR. Cutaneous collision tumors. An analysis of 69 cases and review of the literature. *Am J Dermatopathol*. 1994; 16: 253-257.

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Case Illustration

Hidradenoma Papilliferum

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A 45-year-old female patient presented with an asymptomatic nodule of 6-months duration in the vulva. On examination, a well-circumscribed nodule of size 1 cm was seen on inner aspect of left labium majus (Figure 1). The nodule was firm and non-tender. Dermoscopy showed pink and white structures with curvilinear vessels (Figures 2 and 3). Differential diagnoses considered were hidradenoma papilliferum or some other adnexal tumor, pyogenic granuloma, and a remote possibility of donovaniosis or amelanotic melanoma. The nodule was excised and sent for histopathological examination, which showed a dermal tumor with cells in papillary folds, tubules, and cystically dilated spaces. These findings were those of hidradenoma papilliferum.

Figure 1. *Hidradenoma Papilliferum-Nodule of 1 cm on Inner Aspect of Left Labium Majus*

Hidradenoma papilliferum is an uncommon benign neoplasm arising from apocrine glands, seen in middle-aged females, commonly between the ages of 30-49-years. It usually presents as a firm, flesh to red-coloured nodule in the anogenital area.[1]

The tumor has a good prognosis and malignant transformation is extremely rare.[2]

Figure 2. *Hidradenoma Papilliferum: Pink and White Structures with Curvilinear Vessels*

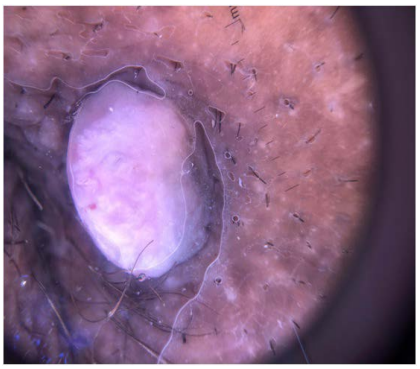
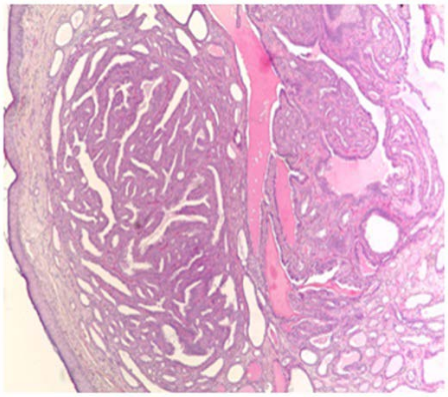


Figure 3. *Hidradenoma Papilliferum: An Epithelial Proliferation of Tubular and Acinar Structures Coated by a Double Layer of Abundant Ductal Cells and Myoepithelial Cells on the Outer Layer*



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CONSENT

The authors have received written informed consent from the patient.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

1. Daniel F, Mahmoudi A, de Parades V, Flejou JF, Atienza P. An uncommon perianal nodule: Hidradenoma papilliferum. *Gastroenterol Clin Biol.* 2007; 31: 166-168. doi: 10.1016/s0399-8320(07)89349-3

2. Nirmala D, Rajnish K, Sunita S, Nidhi R. Hidradenoma papilliferum of the vulva: case report and review of literature. *Arch Gynecol Obstet.* 2011; 284: 1015-1017. doi: 10.1007/s00404-010-1784-7

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Review

Photobiomodulation in Cells' Repair

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ABSTRACT

Photobiomodulation is a non-invasive treatment modality acting at different biological levels through the non-thermal transfer of photons to the living matter *via* a photoelectric effect, inducing photochemical reactions in treated cells. The objective of this article is to review the literature on Photobiomodulation, its different fields of application and mechanisms of action, for establishing a comprehensive summary of evidence. The search strategy initially run searches in scientific databases MEDLINE, PubMed, EMBASE and Cochrane registries from 1990 up to March 2020, with entries Photobiomodulation, LLLT-LEDT, PDT, Photobiology, Cytochrome c Oxidase. Selection criteria was based on preferably inclusion of randomized clinical trials (RCTs), systematic reviews (SR) and studies providing qualitative and quantitative data with the best consistency, in a field where heterogeneity of light parameters is often a difficulty to comparison of findings. Publised expert opinions were also considered. A total of 80 publications were reviewed out of a thousand obtained from databases, among which were retained 9 RCTs, 6 systematic reviews, 3 meta-analysis and 2 case-reports. Differences were found in treatment parameters as wavelength, dosage, energy output, treatment length, performances of light-sources, quantity of diodes and single power of these, which may explain the paucity of high-level body of evidence in Cochrane databases. However, numerous state-of-the- art researches are also found, led by dedicated research teams paving the way to standardized methods of evaluation and comprehension of light-biological-tissues interaction and optimization of outcomes in a promising field.

Keywords
PhotoBioModulation; Low-Level-Laser-Therapy (LLLT); Light emitting diodes (LED); Biophotons-mitochondria; Adenosine-triphosphate (ATP); Inflammation-pain-skin rejuvenation; Photo dynamic therapy (PDT); Photobiology.

INTRODUCTION

Photobiomodulation (PBM) is defined as the use of low-level-lasers or light-emitting-diodes (LED) of low-intensity and non-ionizing radiation, emitting visible light from 400 nm to 700 nm and near-infrared (NIR) from 700 nm to 1100 nm in the electromagnetic spectrum, aiming at a biostimulation of exposed tissues.[1,2] PBM has mostly been studied for pain reduction, mitigation of inflammation and stimulation of wound healing. In the settings of a dermatological or aesthetic medicine practice, PBM has also demonstrated to be a useful tool, assisting practitioners to better address adverse events and recovery time in the aftermath of surgical and non-surgical procedures. Potential side-effects of any intervention, even when minor and temporary, remain anxiogenic for both patient and practitioner, when they can be significantly improved with PBM. These therapeutic effects of photonic energy have been applied since the beginning of humanity with the use of sunlight, as a photomedicine, for the treatment of a variety of diseases and skin disorders.[3] With the progress of sciences and technologies, a more comprehensive understanding of the nature of light, its interaction with matter and particularly with biological tissues, improving wound healing, was achieved.[4] The decoding of the mechanisms of action of PBM, revealed the role of the cytochrome-c-oxidase as photo-acceptor (CCO) but also the importance of interfacial water layers (IWL) interacting with photons and participating in adenosine-triphosphate (ATP) upregulation.[5,6] National Aeronautics and Space Administration (NASA), US Navy and UK military, with their own therapeutic experiments in the 1990s, demonstrated faster recovery post-injuries, enhanced wound healing, angiogenesis and cytoprotection.[7,8] Since three decades, research has demonstrated the efficacy, tolerability and high safety profile of low-level-light-therapies—light-emitting-

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diodes-therapies (LLLT-LEDT), alone or in combined protocols, in numerous domains which will be reviewed, as dermatology, rheumatology, sports medicine, gynecology, dentistry, oncology and infectiology.[9] Supporting tissues to self-repair, energizing cells' metabolism for a faster return to homeostasis, this non-invasive, non-ablative, biostimulative therapy has also shown that cohesion was not an absolute requirement for PBM, introducing the labelling of LLLT.[10]

THE NATURE OF LIGHT

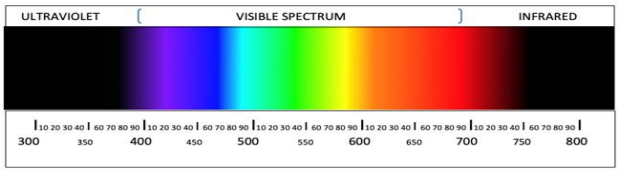
Light

Light is a periodic phenomenon, characterized by its frequency (ν) defined into Hertz (Hz), periodicity (T) and wavelength (λ) measured by meter and nanometer (nm) and, the interplay between these parameters participating in the manifestation of light.[11] The contact between light and matter generates interaction. Light is absorbed, reflected, deviated or emitted by matter. Absorption occurs when matter retains light without emitting it back, usually transforming light energy into thermal energy; scattering when light is absorbed and re-emitted; reflection when light bounces back on a planar surface with a straightforward, predictable trajectory or multiple trajectories on uneven surface; deviation or refraction when light crosses different propagation mediums and, emission when excited atoms land back from higher orbital levels to their basal level producing radiation in quantifiable emission or luminescence in the visible or non-visible spectrum.[4,12] Additional properties of the electromagnetic waves are polarization and interference. Hence, light is a wave constituted of a herd of particles or photons behaving wave-like, defined also as light quanta.[13] Light is carried into waves comprising perpendicular electric and magnetic fields in motion and superposition. Although extremely fast, the speed of light (c) is not infinite, it is considered a universal constant: c=299,792 458 m/s in vacuum, with differences according to the medium it travels.[14]

Light Spectrum

The various radiations of the electromagnetic spectrum are differentiated according to their wavelength.[1] A smaller segment of this field is observed when white light passes through a prism and refracts separated colored components, known as the light spectrum, constituted of a range from 400 nm to 700 nm of different wavelengths of light visible to the human eye. Infrared (IR) corresponds to wavelengths above the 700 nm nominal edge of red up to 1 millimeter and frequency beneath 400 THz (Figure 1). The sources, as lasers, emitting light with a sole wavelength and optical frequency are monochromatic, whereas sources emitting with more than one wavelength and frequency are polychromatic, as is the sun.[15]

Figure 1. *The Segment of Visible Light in the Electromagnetic Spectrum*



Interaction Light and Matter

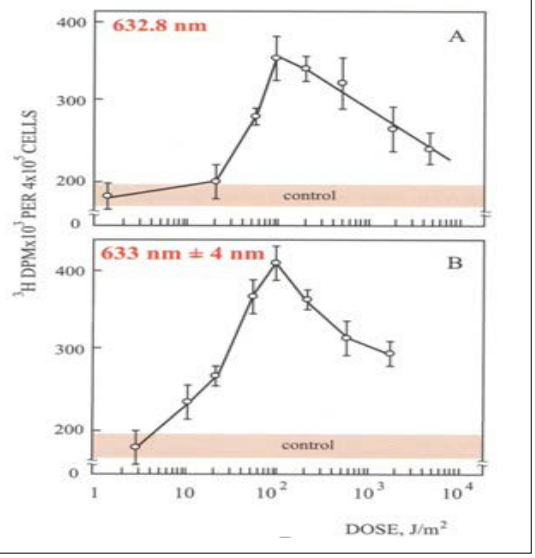
Light interacts with matter by phenomena of absorption, scattering, reflection or refraction. When applied to biological tissues, rays of light constituted of trillions of photons will interact in regard to the optical qualities of the recipient. This communication is the response of biological tissues. The settings and parameters of all light-devices appreciate this response of biological tissues to the light stimuli for optimizing their therapeutic effects. PBM focuses on light absorption by biological tissues, interplay between the photon and its target, also called chromophore or receptor, capturing the energy of light.[16]

COHERENCE *VS* NON-COHERENCE

Distinct Interactions

In 1917, Einstein initiated the concept of monochromatic light in which all photons were to be aligned in a row, leading to the creation of the first laser source in 1960 and later the development of non-coherent light-sources too (Figure 2).[2,17] Two technologies appeared: the high frequency thermal lasers, applying to targeted chromophores a higher energy than their repairing capacity and, the low frequency non-thermal LLLT or LEDs-sources, applying to chromophores energy levels optimizing cells' repairing capacities[18] Photobiomodulation was born.

Figure 2. *Effects of Coherent 632,8 nm Red Light (A) and Non-coherent 633 nm Red Light (B) on the Integration of Thymidine Radio-marked in Culture of Cells: Coherence is Not Essential to Biostimulation, Karu et al*[18]



Light interacts with human multi-layered and heterogeneous biological tissues through an array of mechanisms. Depending on the thermal or non-thermal character of light-tissue interaction, the effects induced are either photophysical, photochemical

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or photobiomodulative.[18-20]

Lasers

The thermal effects of coherent lasers characterized by their monochromaticity and single wavelength, produce, depending on the degree and duration of the heating of tissues, either hyperthermia (41-44°), coagulation (50-100°), vaporization (100°) or the melting of tissues (above 300°), thoroughly described by Ansari et al.[4] These thermal modifications, also influenced by the distribution of temperature in targeted tissues, result into different applications from dermatological surgery, ophthalmology, odontology, gynecology, gastroenterology, arthroscopy with the use of endoscopes, angioplasty and radiological monitoring.[4]

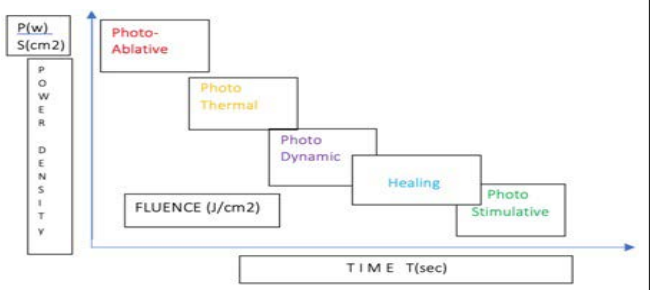
Low-Level-Light and LED

The non-thermal effects of LLLT and LEDs are related to the biophysiological properties of wavelengths, defined as the distance between two consecutive peaks, the chromophore they target and their depth of penetration. Mester et al[9] demonstrated in 1973 in a study on murines, that He-Neon laser emitting in red 632,8nm had visible effects on cytochromes, accelerating wound healing, evidenced by following studies.[11] NASA experimented the influence of light on astronauts' metabolism, weakened in space in the absence of gravity, evidencing improved wound healing post minor injuries[7] and leading to the equippement of its spaceships with LED panels.[8]

Low Level Lasers are non-thermal lasers, known as soft lasers, emitting a coherent, monochromatic polarized light penetrating deeply into tissues, ranging from 400nm to 800nm and 900nm to 940nm for Near-Infrared (NIR).[2] As a comparison, the Helium Neon laser (He-Neon), emitting red at 632nm, has a power output between 1 and 25 milliwatts, whereas the Nd:YAG (neodymium-doped yttrium aluminum garnet) laser, used in cataract surgery, delivers up to 10 watts. Low-Level-Lasers have a significant lower power output requiring longer treatment sessions, ranging in minutes rather than seconds yet, energizing tissues they penetrate rather than cutting or burning them.[20]

Light emitting diodes (LEDs) are electroluminescent diodes producing narrow-band light through the motion of electrons in high-efficiency semi-conducting materials as germanium (Ge) or gallium (Ga) resulting into a specific colored component or wavelength of red (633 nm), yellow (590 nm), blue (415 nm) and their combinations in the visible spectrum. Therapeutic LEDs (247 nm-1300 nm) are non-coherent, monochromatic lights, transferred to tissues for absorption through a photoelectric effect in a non-thermal fashion.[19,21,22] The infrared wavelengths are absorbed by cell membranes inducing photophysical reactions.[21,23] Up to date, the therapeutic properties are evidenced for a portion of this scale, although research in luminotherapy is found back to the 19th century when Finsen (1903) demonstrated that red light increases the metabolic level of cells' mitochondria.[3] His intensive research on the activity of red light on smallpox and measles, published under the title Phototherapy awarded him a Nobel prize in Physiology and led to the establishment of the first sanatoriums across Europe treating tuberculosis with sunlight.[3] Since then, the therapeutic capacities of light have been studied in many fields of medicine. A multi-center research initiated by the Institute of Cellular and Integrative Neurosciences in Strasbourg, France, led by Tsai et al (CNRS)[24] studied the role of the photopigments melanopsin, encoded by *OPN4* gene, on sleep control patterns in humans. Light reaching human eye transmits to the brain two types of information, a visual one analyzed by retinal rods and cones photoreceptors and, a non-image-forming one regulated by melanopsin able to detect the intensity and quality of the light emission.[24] Haltaufderhyde et al[25] demonstrated that photons absorbed through opsins are converted into a cellular response by phototransduction. The authors observed in cell culture that OPN1-SW, OPN2, OPN3 and OPN5 were also expressed at epidermal level in melanocytes and keratinocytes.[25] In cultured primary human epidermal melanocytes (HEMs) and primary human keratinocytes (KERs), the authors found opsin receptors, suggesting that they may function as epidermal photoreceptors, which is of interest when considering the application of PBM to the skin (Figure 3).[25]

Figure 3. *Thermal and Non-thermal Photo-effects of Lasers and LEDs*



MECHANISMS OF ACTION

The Mitochondrial Respiratory Chain

Cellular respiration is achieved *via* the glycolysis and the citric acid cycles, producing the essential energy-carrier adenosine triphosphate (ATP).[26] An additional pathway also generates ATP *via* the respiratory electron transport chain and its redox reactions during the aerobic glucose catabolism.[26] Karu et al[5] demonstrated that the mitochondrial protein cytochrome c oxidase (CCO), a terminal enzyme in this mitochondrial respiration in charge of molecular oxygen reduction and ultimately ATP synthesis, was a photo-active acceptor. This major finding enlightened how much communication between the extra-cellular matrix and other cells was fundamental for cells' integrity, growth and differentiation.[27] By catching the stimuli of light through the CCO enzyme, cells respond through a signaling pathway, matching together as key and keyhole.[5,22] In vegetable kingdom, this transformation of light,or photosynthesis, into photochemical energy triggering biochemical modifications is a process well-documented.[28] Karu et al[18] demonstrated, while evaluating the effects of wavelengths in the optical band 570 nm-650 nm on deoxyribonucleic acid (DNA) and ribonucleic

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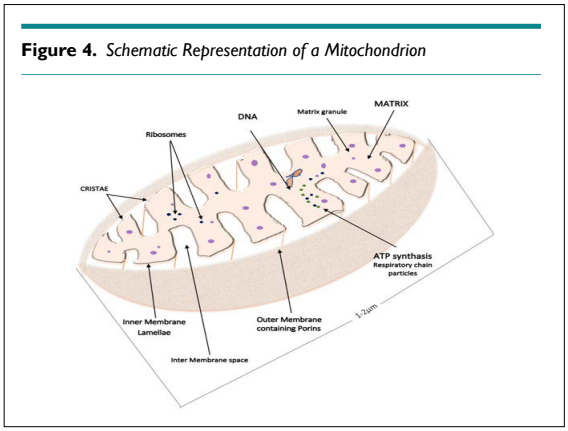
acid (RNA,) that light coherence was not an absolute necessity for igniting a biostimulative activity. The authors showed that similar results can be achieved with non-coherent LED-sources.[18] The mitochondria within cells is receptive to visible light, inducing a photochemical response *via* the CCO or a photophysical response when stimulated by NIR (Figure 2).[23,29] This photoactivation is also related to the redox-sensitive status of the photoreceptor: damaged cells with lower redox potential are more sensitive to light stimuli.[23] In many studies, the repairing and rejuvenating outcomes obtained with LEDT are related to the mitochondria, the CCO and the ATP upregulation,[10] as well as the synthesis in the cytosol of the nicotinamide adenine dinucleotide reduced form (NADH).[6] The use of appropriate wavelengths, pulsed wave (PW) or continuous wave (CW) modes generated a different impact on the reduction of free radicals, a higher tissues stimulation was observed with pulsed modes in specific contexts. This was also described by Barol et al[30] in a case-control study on limited cutaneous systemic sclerosis where significant improvement of osteo-articular symptoms severity was reported in cases treated with (PW) mode at 940nm LLLT, while the augmentation of microcirculation and catabolism may also have participated in the *in situ* calcinosis and overall functional improvement.[30] Better and faster wound healing with (PW) was also reported with 810 nm diode laser at 10 Hz, evidencing a significant decrease of inflammation, increase of cellular proliferation, epithelization, neovascularization, enhanced CCO and ATP performance.[31]

The benefits of LLLT-LEDs could be comprehended as a mitochondrial therapy, care and micronutrition, mitochondrial protection from dysfunction, oxidative stress and molecular degradation and, a photo prophylaxis too.[26,32,33]

Adenosine Triphosphate Production

Adenosine triphosphate production represents the core energy supply to cellular activity, an inner currency for cells' exchanges synthesized under aerobic conditions in the mitochondria, the organelles containing the respiratory electron transport chain. As seen above, CCO being the end enzyme of the electron transport chain, it combines oxygen and NADH for hydrogen ions synthesis.[6] The hydrogen ions once increased in number, diffuse out of the matrix space, participating into the phosphorylation of adenosine diphosphate (ADP) into ATP.[34] However, this respiration is compromised when mitochondria start generating nitric oxide (NO), binding to the CCO in place of oxygen, resulting into less ATP and more oxidative stress and, potentially more inflammation. He et al[34] described that PBM helps recover the binding of CCO with oxygen inducing quantifiable changes in the mitochondrial membrane potential (MMP) and in the ATP content. Therefore, the primary mechanism of action of PBM takes place within the mitochondria, the CCO absorbing the emitted light and water achieving less density, more fluidity.[5,34] A resonance takes place between cells and light wavelengths, inducing metabolic processes of repair and regeneration. It is now established that at DNA level, cells emit biophotons, which may explain their affinity with light.[34] The interest of LLLT and LEDT lies in this capacity to increase MMP and ATP synthesis in various types of cells, protecting them from oxidative stress, modulating reactive oxygen species (ROS) production, in a dose-dependent way.[10] More recently, Sommer[6] suggested that the causal relation between CCO, as a primary photo-acceptor, and the extra-ATP synthesis was not necessarily the only hypothesis in red-to-NIR (R-NIR) exposure. The author evaluated that two more aspects have to be considered in the ATP synthesis: the mitochondrial inner membrane and the role of the CCO in reducing molecular oxygen to water. For Sommers, the interaction light-tissues between photons and interfacial water layers (IWL) was causal to ATP upregulation in R-NIR therapies (Figure 4).[6]

Figure 4. *Schematic Representation of a Mitochondrion*



Dosing the Stimulation

Dosimetry is to phototherapy what dosage is to medicine; it depends of the anciency, the depth and the surface of the target. It also depends of the physiological or pathological condition of the tissues. Karu et al[5,35] described that PBM induces a higher stimulation in weaker, stressed or damaged cells, up to the maximum of their biological activity. As is the case for all energy-based therapies, setting the parameters acknowledging this dose-response is primordial for optimizing patient-centered outcomes.[35] Biostimulation and cellular effects are modulated by critical parameters: the power density or irradiance or intensity measured in mW/cm^2, the energy density or fluence, dose or radiant exposure measured in J/cm^2 and the treatment/irradiation time in seconds.[36] Biostimulation is supported by an equation between intensity, surface, total irradiation time and energy density, if not, the result is absence of biostimulation. A similar rule was reported with lasers: under 4 mW, no biological effect was observed, whatever the irradiation time.[37] A physiological response can be initiated with a minimal irradiance. On the contrary, a too long exposure with low irradiance will not induce the expected physiological effect, while a too long exposure with too high irradiance may inhibit PBM benefits or lead to cells' exhaustion. The World Association for Laster Therapy (WALT) has provided dosage recommendations in LLLT.[38] Treatment frequency, intervals between sessions and correct coverage of the treatment target are also parameters to be considered as light can be reflected, refracted or scattered depending on the treated tissues.[4,12] The relationship between these parameters is usually adopted with the equation described by Jagdeo et al.[29]

Power density (W/cm^2)×time (seconds)=fluence (J/cm^2)

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Dosing the stimulation is particularly of prime essence in photo dynamic therapy (PDT) where irradiance source, total light dose and power output in milliwatt, are game changers in treatment protocols and performance.[38,39]

FIELDS OF APPLICATION

Cells respond to the biostimulation of light during and post PBM, through cellular and molecular mechanisms seen above, particularly with oxygen re-binding with CCO, enhancing cellular respiration and augmentation of ATP synthesis. Restoring the respiratory electron transport chain is essential in the context of inflammatory reactions as an impaired cells' repiration, when NO is also increased and competing with oxygen, endangers the innate immune system and homeostasis.[29,34]

Dermatology

Non-coherent wavelengths of LLLT-LED-sources applied in PBM target chromophores as the CCO or the endogenous protoporphyrin, as a monotherapy for skin conditions and diseases or associated to systemic or topical therapies. These light-sources have a modulating action on the intrinsic cellular activity, either inhibiting or stimulating it and a biphasic dose-dependent response, demonstrated in wound healing and mitigation of inflammation.[40] The applications in dermatology are vast and thoroughly studied by authors as Pelletier.[41] Recently, Jagdeo et al[39] performed a systematic review of 31 RCTs studying dermatological conditions treated with LED-PBM. According to criteria of the Oxford Centre for Evidence-based Medicine-Levels of Evidence,[42] the authors attributed a grade B of recommendation for the Food and Drug Administration (FDA)-approved treatment of Acne vulgaris, Herpes complex and zoster and, a grade C of recommendation for skin rejuvenation with LED-PBM. Non-FDA-cleared LED procedures were attributed a grade B of recommendation for the treatment of acute wound healing, grade C for psoriasis and grade D for atopic dermatitis, chronic wound healing, oral mucositis and radiation dermatitis.[39]

Dermatological conditions are characterized by the suffering of cells depleted from the energy necessary for self-repair. It is particularly the case in the healing of wounds and ischemic tissues lacking trophicity, ulcers or compressed nerves. PBM may be comprehended as an energy supplementation improving DNA and RNA synthesis, as well as cells' adhesion. Wound healing is maybe the most widely spread application of PBM in dermatology, its effects having been demonstrated at all stages of the healing process.[7-9,43,44] A normal wound healing undergoes three distinct phases. At first inflammatory signs in tissues, secretions from lymph and blood vessels, followed by coagulation by thrombokinases activation and fibrin production start the exudation and detersion phase of wound healing. Increased capillary permeability brings antibodies, leucocytes and macrophages towards the wounded area.[45] Stimulated fibroblasts generate from approximatively Day 4 a muco-polysaccharides matrix for collagen fibers synthesis necessary in the gradual restoration of the wound from the inside out. In this proliferative phase, neo-angiogenesis assures nutrition to growing tissues. Approximatively from Day 6, myofibroblasts contract to progressively close the wound borders; less irrigated, granulation tissues become tighter and ultimately form scar tissues in this differentiation phase which will stop with the re-epithelialization by migration of epidermal cells at wound surface.[45] Studies have also shown that PBM improves post-operative wound healing at the first stages.[46] NASA[7,8] experimental studies monitoring injuries in spaceships reported wound healing improved by 50% in cases receiving LED treatments compared to those not treated. Similarly, the Naval Special Warfare (Norfolk, USA)[7] evaluated wound healing in the conditions of submarines where there is no light, lower oxygen and higher CO_2 levels, concluding in 50% improvement of muscularskeletal injuries in cases treated with LLLT-LEDs 670 nm, 720 nm and 880 nm. Accelerated healing of burn injuries and systemic effect of PBM were also observed on mice models.[43] In a preliminary study Min et al[44] evaluated the faster healing of ischemic wounds and recalcitrant diabetic ulcers, reporting increased fibroblasts proliferation, growth factors synthesis, collagen production and angiogenesis. without neoplastic transformation, tissues' growth stops once the wound is healed. The treatment of ophthalmic herpes zoster with PBM was evaluated by Park et al[47] in a pilot study on 28 individuals all receiving antiviral agents and half receiving 830 nm LED-PBM additionally. The authors concluded in significantly faster healing and lower mean visual analogue scale (VAS) scores in the group who received LED-therapy compared to control groups. Kleinpenning et al[48] evaluated the treatment of inflammatory skin diseases as psoriasis and atopic dermatitis in a double-blind, randomized comparative study between red and blue wavelengths activity targeting the endogenous photosensitizer protoporphyrin IX. Clinical improvement of psoriasis erythematous plaques was observed in both groups yet, was significantly higher with blue light therapy.[48] Comprehensive studies have also evaluated the treatment of acne with blue-red therapies, particularly with pulsed wavelengths.[49,50] Tsoukas et al[51] described the activity of red light in inflammatory processes of acne modulating cytokine release from macrophages while blue light, once absorbed at a peak of 415 nm by the natural porphyrins secreted by Propionibacterium acnes colonizing sebaceous glands, was releasing singlet oxygen and ROS with significant bactericidal action.[52-54] With the emergence of bacterial resistance to antibiotics, blue-red therapy is estimated a safe and efficient tool for treating inflamed lesions in mild to moderate acne.[49] Many studies have also demonstrated the accelerated healing of edema, erythema and inflammation post-surgical and non-surgical aesthetic procedures as intense pulsed light (IPL) and fractional lasers.[55,56]

The stimulation of the mitochondria has also substantial effects on the aging process, increasing collagen production and decreasing collagenase activity. Boisnic et al[57] observed in a hospital-setting study the repairing action of LEDs on connective tissues, directly stimulating the metabolic activity of dermal fibroblasts, inducting new dermal papilla, with synthesis of endogenous collagen and elastin. Fouque-Parachini et al[58] demonstrated in an *in vivo* study assessed by vivascope confocal microscopy, the benefits of a LED-source (Triwings®, Biophoton) on skin rejuvenation at epidermal and basal layers, improving lentigos and stimulating neocollagenesis. The authors findings demonstrated cells' membranes repolarization, modification of the free-water/bound-water ratio,

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improvement of microcirculation, emergence and increase of vascularized dermal papillae count and, tissular hydration resulting in an overall rejuvenation of the skin. The authors also observed decrease and homogenization of melanin in treated areas.[58]

Barolet[59] and Weiss et al[60] described a photo prophylaxis role of LLLT-LED therapies in prevention of post-inflammatory hyperpigmentation, solar lentigines and ultraviolet (UV)-induced erythema, concomitant to proper use of broad-spectrum sun care. In a prospective, randomized, placebo-controlled, double-blinded, split-face clinical study Lee et al[61] evaluated with histologic, ultrastructural, profilometric and biochemical analysis the effects of 633 nm and 830 nm LEDT on skin rejuvenation. Their findings demonstrated significant reduction of wrinkles, activation of fibroblasts and increase of collagen and elastin, also observed in a study of Calderhead et al.[23]

Another major application of monochromatic lights in dermatology is the treatment with photo dynamic therapy (PDT) of non-melanoma skin cancer (NMSC) and cancerization fields, particularly superficial basal cell carcinoma (sBCC) and *in-situ* squamous cell carcinoma (in-SCC) not exceeding 2 mm thickness according to the international guidelines.[62] The therapeutic fundaments of topical PDT for NMSC imply a photosensitizer-precursor of protoporphyrin IX (PpIX), light in the absorption spectrum of the photosensitizer and oxygen.[63] More recently, Alam[64] described the conversion of lipophilic methyl-aminolevulinate (MAL) or 5-aminolevulinic acid (5-ALA) into photoactive porphyrins at lesion site once exposed to light at 37 J/cm^2, as advised by the industry leader.[65] MAL-PDT is reported for good neoplastic cells selectivity, tissue penetration and intracellular PpIX accumulation in a diffuse uptake fashion. PDT induces a type II photooxidation generating ROS affecting cells' membranes, improving dermic echogenicity and reducing lesional vascularization.[66] PDT is also applied to non-malignant skin diseases and pre-cancerous lesions, experiments are proposed with lower-irradiance red wavelengths for lessening the pain in actinic keratosis[67] and for treating acne and infections.[53,54,68] Researchers are also working on the incorporation of light for PDT in a novel fabric.[69]

Since paradoxical hair growth has been observed post-laser and IPL-assisted hair reduction, researchers investigated the use of light to promote hair growth.[70] Trelles et al[71] first described in 1984 hair re-growth in alopecia areata cases treated with an HeNe laser at 632,8 nm and 4 J/cm^2 weekly, while daily application resulted in cells' exhaustion and hair thinning, evidencing the biphasic dose-dependent response in PBM.[40] The authors described hair shafts showing increased keratin number in medulla at microscopic analysis.[71] In a systematic review of LLLT at R-NIR 635 nm and 810 nm in adult androgenic alopecia, the authors described that the upregulation of ATP production may reverse bulbs miniaturization and maintain hair follicles longer in their anagen phase.[72] In a double-blinded randomized controlled trial (RCT), Lanzafame et al[73] evaluated the efficacy and safety of 655 nm LLLT-LED *vs* placebo in 47 females with androgenic alopecia. Their findings showed a change in hair count over baseline of 100.3-53.4 (N=24) (p<0.0001) in the treated cases group and a percentage of hair increased by 11.05-48.30 (N=18) in placebo controls while 48.07-17.61 (N=24) (p<0.001) in the treated cases, with an overall hair growth over the study time increased by 37% in the treatment group.[73] The stimulative activity of LLLT-LED on epidermal stem cells in hair follicle bulges when applied at 90 mW/cm^2 R-NIR is estimated to down regulate inflammatory mediators and to shift hair follicles into the anagen phase, enhancing also hair tensile strength and scalp health.[74] In another recent study, Buscone et al[75] provided evidence that *OPN2* and *OPN3* are expressed in human hair follicle and interact with blue light at 453 nm resulting in hair growth *ex vivo*. Further research is required in this application, with well-controlled studies. However, LLLT-LED therapies for male and female androgenic alopecia are FDA-approved since 2007 on a safety basis, they may also represent a promising prospective solution for other forms of non-cicatricial alopecia.[76]

Body contouring with the application of LLLT as a non-invasive modality has also been evaluated in a retrospective study entailing 689 individuals, concluding in significant mean circumferential reduction recorded at different measurement points with 3.27 in. (p<0,0001) and overall mean reduction of 5.17 in. (p<0,0001) not related to fluid loss, demonstrating adipocytes' apoptosis and influence of LLLT on systemic lipid metabolism.[77]

Rheumatology, Traumatology and Sports Therapies

PBM for the management of acute and chronic pains has been thoroughly evidenced since decades in scientific literature.[78] Efficacy, tolerability and safety of treatments require appropriate wavelengths in the optical window between 633 nm and 905 nm in R-NIR and appropriate intensity on elected anatomical site. Beneficial treatment of musculoskeletal pains, orthopedic injuries and post-surgical conditions, in humans and animals, is largely reported in literature.[78-82]

Particularly, Konstantinović et al[83] in a double-blind, randomized, placebo-controlled study on 60 individuals with acute neck pain with radiculopathy treated with 905 nm LLLT, demonstrated statistically significant pain reduction on VAS measurement in cases against controls (p=0.003, accounting high effect size d=0.92). The mechanism of action of PBM in pain control entails the anti-inflammatory activity of R-NIR wavelengths decreasing also edema, the blockade of the nociceptor transfer along A and C fibers and the mitigation of neurotransmitters.[78] Overall good reduction of pain induced by masseter muscle fatigue and tinnitus condition have also been reported,[84] making PBM a cost-effective and evidence-based therapeutic modality in chronic and acute pain.

In sports medicine, PBM for the treatment of injury-related pain has demonstrated significant reduction of all-pain, enhanced tissues' repair and faster recovery, by improvement of inflammation, micro-circulation and tissues' oxygenation[85,86] PBM in tendinopathy, golfer or tennis elbow and injuries influencing knee or wrist mobility and ankle stability, impacting the return-to-play of athletes has demonstrated significant results.[87] Additionally, by increasing mitochondrial respiration and ATP production mediated by MMP at muscle levels, PBM is considered a preventive

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measure for muscle conditioning prior to physical performance, in men and women.[88,89] In a systematic review with meta-analysis, Leal-Junior et al,[87] evaluated 12 RCTs in which LLL-LED therapies where applied in the course of exercise with 50 to 200 mW, 5J per spot. Findings demonstrated significant improvement of athletes' performance up by 5.47 (95 % CI 2.35-8.59, $p<0.0006$) and increase of time until exhaustion up by 4.12 (95 % CI 1.21-7.02, $p<0.005$) against placebo. The authors reported that the improvement of muscle metabolism was dose-dependent and they evaluated a time-response of 3-6 h,[87] confirmed in other studies.[10,40] PBM is an evidence-based therapeutic option for optimizing the return-to-play of athletes.[87]

Neurology

Hamblin[90] first reviewed the interest of transcranial-photobiomodulation (t-PBM) in brain disorders, including trauma, degenerative diseases and psychiatric disorders and, the existing evidence on light applied to the prefrontal cortex. The global aging of the population and the augmentation of lifespan may involve higher occurrence rates of neurodegenerative diseases as dementia, Alzheimer or Parkinson, burdening public health policies. Hamblin[90] also initiated a current of thoughts for future hypothesis of research on t-PBM, focusing on neurodevelopmental disorders as autism and depression and, how attention bias and ischemia risk can be improved. The question of light penetration to the cerebral cortex has been addressed by many researchers, the debate being still on in regard of optimal light-source, laser or non-coherent LED, wavelength range and power density for achieving the best biological effects.[91,92] The outcomes observed in these studies have enlightened significant improvement of cognitive function in individuals with long-standing traumatic brain injury, which unfortunately, faded away once treatment was stopped. Furthermore, Gordon et al[93] have discussed that the effects of PBM were not restricted to the sole area illuminated and that a remote, indirect benefit is to be explored in the future. The interest of t-PBM on healthy individuals as a cognitive capacity improvement light-therapy, enhancing capacity to stay focused, is also in the pipeline of research.[90,94]

A few authors have described a mood-enhancement and regulation of sleep patterns effect following PBM, it is known that pro-inflammatory cytokines participate to mood disorders. In a recent review, Askalsky et al[95] consider that t-PBM in range of 808-835 nm NIR at higher powers outputs could be a novel neuromodulating strategy for major depressive disorders (MDD). In previous research, the mechanism of action of t-PBM was estimated to stimulate the respiratory chain and ATP production at the mitochondrion as well as the regional blood circulation.[96] Current knowledge stimulates further research, evidencing if coherent lights are mandatory or if non-coherent lights can be a more practical and cost-effective alternative. Also, demonstrating if (PW) mode would be superior to (CW) mode as anti-depressor application of t-PBM.[90,95]

Oncology

Photo dynamic therapy has a strongly evidenced background in the treatment of superficial skin cancers but has also limitations in the capacity of light to penetrate tissues deeply, depending on the elected photosensitizers and *in-situ* dosimetry.[97] Expanding this therapeutic modality from superficial to deep-seated diseases and malignant tumors has raised interest in research in the past years. Scientific reflections have focused on different light-sources for exciting a mono-photosensitizer, two-photon photosensitizers or conjugated with nanosystems for achieving synergetic action.[98,99] Research evolves towards a NIR-activated PDT allowing deeper tissues penetration with longer wavelengths and less off-targeting or normal tissues damaging.[98] This interstitial PDT challenges scientists with barriers to overcome as the non-homogeneity and three dimensions (3D) shape particular to solid tumors.[100] Clinical translation requires this new modality to be approved and light and photosensitizers parameters to be consolidated in well-designed trials before expanding treatment options.[101]

Bensadoun et al[102] have also thoroughly described the relieving effects of PBM in mucositis reduction. A research followed in 2017 by a clinical trial for establishing a treatment protocol reducing chemo and radio-induced oral mucositis in children applied LLLT-LED 635 nm (Oncolase) every other day at doses of 4 J/cm^2 in a sweeping fashion in cheeks, tongue dorsum, lateral and belly, palate, superior and inferior gums.[103] The findings demonstrated significant reduction in recovery time, in pain and inflammation associated to the condition and no aggravation towards a higher grade of mucositis.[103] Improvement of quality of life was also assessed with the recovery of chew and swallow capacity.

Gynecology

The gynecological internal applications of lasers originated from applications in cancerology as described above and from applications in odontology as will be reviewed below.

PBM in gynecology can be applied with LED or laser sources, internally and externally according to the indication, for alleviating inflammation, sanitizing the tissues, enhancing the healing of gynecological and obstetrical wounds,[104] improving functional disorders of the vulvar-vaginal and uro-genital regions[105] and, decreasing low-grade inflammation and endometriosis-related pelvic pain.[106] PBM alone or combined to other therapies is reported in the treatment of genital cutaneous diseases as lichen, herpes or eczema.[107] Lanzafame et al[108] recently discussed the application of PBM for relieving genitourinary syndrome in menopausal women, concluding in high efficacy and tolerability of this option. Morphological and physiological changes occurring in menopausal women, particularly with the decrease of intra-mucous microcirculation leading to vaginal dryness, lack of trophicity, atrophy and irritation are syndromes well-treated with PBM with intravaginal probes and external light-exposure. Red and NIR have showed interesting effect by stimulating collagen production[109] and angiogenesis.[110]

Dentistry

The LLLT-LEDT have been reported since three decades in Rus-

sian[111] and Japanese[112] scientific literature in fields of dentistry and oral diseases, for hard and soft tissues, triggering biochemical exchanges for the healing of wounds in the oral cavity, the reduction of pain with endorphins'release, the enhancement of bone and nerves repair after oral surgery.[113] In a systematic review Shukla et al[114] analyzed findings of 13 studies in which LLLT-LED was applied in temporomandibular (TMD) or craniomandibular disorders. The reduction of pain in individuals suffering from TMD was effective in the majority of these studies, with the hypothesis proposed of modulation of inflammation at the TMD joint capsule.[115] However, the discrepancies in trials standards call further research for consensus on light dosage. PDT with toluidine blue patch has also been described as a useful tool for disrupting the adherence of bacterial biofilms at root canal.[116,117] As seen in previous chapter Dermatology, the stimulative action of PBM on fibroblasts was mainly evidenced with cultured dermal fibroblasts yet, it is estimated that similar analgesic, anti-inflammatory and regenerative effects on buccal and gingival fibroblasts is possible in reason of their close response profile. PBM is a relevant option for optimizing wound healing, alleviating pain, as trigeminal neuralgia or in TMD and repairing tissues by biostimulation.[118]

Infectiology

We have seen in the treatment of acne and cutaneous superficial or deep-seated malignant lesions, the antibacterial and anticarcinoma activity triggered by PDT with ROS and singlet oxygen generation.[52-54]

Another field of application of the antimicrobial effect of visible violet-blue light at 405-470 nm has been researched for the decontamination of hospitals and healthcare premises.[68,119] Disinfection policies for risk control of hospital-acquired infections are a major public health concern, aggravating with antimicrobial resistance.[120] Therefore, PDT has been explored as an alternative solution with demonstrated efficacy on bacteria and fungi but also on viruses.[121,122] Gram-positive, sensible to major photosensitizers, respond to anionic types, while Gram-negative bacteria to cationic photosensitizer.[123] Viruses also have shown sensitivity to PDT, according to their nucleic acid and capsid type, whereas fungi require higher doses of light and photosensitizer.[124,125] The photodisinfection of environmental surfaces with blue light is also of interest in clinical practice for sanitizing and reducing the risk of pathogens proliferation, in adjunction of asepsis rules, by application of LEDs on facial and body areas immediately after aesthetic procedures, when not contraindicated.[126]

Addressing the field of photobiomodulation, the blue light hazards shall be mentioned. Blue wavelengths are shorter yet, intense, while retinal tissues are rich in chromophores. The retinal mitochondria are susceptible to potential photochemical damage in case of prolonged and unprotected exposure,[127] which implies proper knowledge and training of healthcare professionals for adopting preventive measures against this public concern.

Interest of Photobiomodulation in Acute Pulmonary Disorder

As discussed in the previous section, visible light in the blue spectrum demonstrated substantial antimicrobial activity and capacity to inactivate certain viruses. This could possibly be of interest in the fight for jugulating pandemics, a fortiori in viruses having host pathways replicating in humans.[128]

Photobiomodulation has also a potential role in the prevention of respiratory complications in coronavirus disease-2019 (COVID-19) pandemic through its capacity to modulate the inflammatory response in individuals. A recent review of Enwemeka et al[129] evaluated the evidence-based data on the effects of PBM concluding that light-therapies at 660 nm may alleviate pulmonary inflammation, down regulate pro-inflammatory and pro-fibrotic cytokines, reduce collagen deposits in murine lungs and improve airways edema.[130,131] Furthermore, a protective role on cardiomyocytes from hypoxia with R-NIR wavelengths has also been demonstrated supporting that PBM, when individuals are in need for extra mitochondrial ATP, may play an important role, improving also cutaneous manifestations.[132]

Finally, in the prevention of infectious diseases, the respect of individual's microbiome is a principle now largely integrated and, the interaction light-microbiome recently researched by Libert et al[133] may have a natural role for maintaining individual's integrity towards a better health.

CONCLUSION

The efficacy of PBM is not always easy to understand, particularly when the outcomes of this therapy have sometimes a certain latency. However, PBM and more specifically LEDT may be considered as an homeopathic counterpart, assisting aesthetic interventions, inducing a regeneration, rejuvenation and foremost, a repair at organelles, cells and organs levels with a dynamic flux of biophotons.[134] A better understanding of the life of underlying tissues, their interplay with light and the mechanisms of action of PBM at cellular level will enable clinicians to define parameters optimizing benefits of light therapies. There is also the necessity for rigorous methodology, randomized controlled clinical trials enabling further research to achieve higher statistical power and overpass any further controversy in a very promising therapeutic modality with arrays of indications, deeply revolutionizing healing concepts and healthcare professions.

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REFERENCES

1. Zwinkels J. *Light, Electromagnetic Spectrum, Encyclopedia of Color Science and Technology*. Heidelberg, Germany: Springer, Berlin, Heidelberg; 2015. doi: 10.1007/978-3-642-27851-8

2. Karu TI. Molecular mechanisms of therapeutic effect of low intensity laser radiation. *Lasers Life Sci.* 1988; 2(1): 53-74.

3. Finsen NR. La Photothérapie. Paris: du Finsen's Medicinske Lysinstitut de Copenhague; 1903.

4. Ansari MA, Erfanzadeh M, Mohajerani E. Mechanisms of laser-tissue interaction: II. tissue thermal properties. *J Lasers Med Sci.* 2013; 4(3): 99-106.

5. Karu T, Pyatibrat LV, Kalendo GS. Photobiological modulation of cell attachment via cytochrome C oxidase. *Photochem Photobiol Sci.* 2004; 3(2): 211-216. doi: 10.1039/b306126d

6. Sommer AP. Mitochondrial cytochrome c oxidase is not the primary acceptor for near infrared light-it is mitochondrial bound water: the principles of low-level light therapy. *Annals of Translational Medicine.* 2019; 7(Suppl 1): S13. doi: 10.21037/atm.2019.01.43

7. Whelan HT, Buchmannla EV, Whelan NT, Turner SG, Cevenini V, Stinson H, et al. NASA light emitting diode medical applications from deep space to deep sea. 2001; 552: 35-45. doi: 10.1063/1.1357902

8. Whelan H, Smits RL, Buchman EV, Whelan NT, Turner SG, Margolis DA, et al. Effect of NASA light-emitting diode irradiation on wound healing. *J Clin Laser Med Surg.* 2001; 19(6): 305-314. doi: 10.1089/104454701753342758

9. Mester E, Korenyi-Both A, Spiry T, Scher A, Tisza S. Stimulation of wound healing by means of laser rays, clinical and electron microscopical study. *Acta Chir Acad Sci Hung.* 1973; 14(4): 347-456.

10. Ferraresi C, Kaippert B, Avci P, Huang YY, de Sousa MV, Bagnato VS, et al. Low-level laser (light) therapy increases mitochondrial membrane potential and ATP synthesis in C2C12 myotubes with a peak response at 3-6 hours. *Photochem Photobiol.* 2015; 91(2): 411-416. doi: 10.1111/php.12397

11. Farivar S, Malekshahabi T, Shiari R. Biological effects of low-level laser therapy. *J Lasers Med Sci.* 2014; 5(2): 58-62.

12. Schmitt M, Mayerhöfer T, Popp J, Kleppe I, Weisshart K. Light–matter interaction. In: Popp J, Tuchin VV, Chiou A, eds. *Heinemann Handbook of Biophotonics.* 2013; doi: 10.1002/9783527643981.bphot003

13. Santana-Blank L, Rodríguez-Santana E, Santana-Rodríguez KE, Reyes H. "Quantum Leap" in photobiomodulation therapy ushers in a new generation of light-based treatments for cancer and other complex diseases: Perspective and mini-review. *Photomed Laser Surg.* 2016; 34(3): 93-101. doi: 10.1089/pho.2015.4015

14. Kondakci HE, Abouraddy AF. Optical space-time wave packets having arbitrary group velocities in free space. *Nat Communications.* 2019; 10: 929. doi: 10.1038/s41467-019-08735-8

15. Revell VL, Barrett DC, Schlangen LJ, Skene DJ. Predicting human nocturnal nonvisual responses to monochromatic and polychromatic light with a melanopsin photosensitivity function. *Chronobiol Int.* 2010; 27(9-10): 1762-1777. doi: 10.3109/07420528.2010.516048

16. Jacques SL. Optical properties of biological tissues: A review. *Physics in Medicine and Biology.* 2013; 58(11): R37-R61. doi: 10.1088/0031-9155/58/11/R37

17. Karu TI. Photobiology of low power laser effects. *Health Phys.* 1989; 56(5): 691-704. doi: 10.1097/00004032-198905000-00015

18. Karu TI. Photochemical effects upon the cornea, skin and other tissues. Photobiology of low-level lasers effects. Laser Technology Centre, Moscow, USSR: Academy of Sciences; 1982.

19. Noé C, Pelletier-Aouizerate M, Cartier H. LED in dermatology. *Annales de Dermatologie et de Vénéréologie.* 2017; 144(4): 301-314. doi: 10.1016/j.annder.2016.10.009

20. Barolet D, Boucher A. Thérapie LED non ablative et non thermique. Principes de photobiologie cutanée. Indications - Perspectives futures. *Nouv Dermatol.* 2007; 26 (Suppl): 10-15.

21. Karu TI, Kolyakov SF. Exact action spectra for cellular responses relevant to phototherapy. *Photomed Laser Surg.* 2005; 23: 355-361. doi: 10.1089/pho.2005.23.355

22. Karu TI, Pyatibrat LV, Afanasyeva NI. A novel mitochondrial signaling pathway activated by visible-to-near infrared radiation. *Photochem Photobiol.* 2004; 80(2): 366-372. doi: 10.1562/2004-03-25-RA-123

23. Calderhead RG, Vasily DB. Low level light therapy with light-emitting diodes for the aging face. *Clin Plast Surg.* 2016; 43: 541-550. doi: doi: 10.1016/j.cps.2016.03.011

24. Tsai JW, Bourgin P, Hannibal J, Hagiwara G, Colas D, Ruppert E, et al. Melanopsin as a sleep modulator: Circadian gating of the direct effects of light on sleep and altered sleep homeostasis in Opn4−/− mice. *PLoS Biol.* 2009. doi: 10.1371/journal.pbio.1000125

25. Haltaufderhyde K, Ozdeslik RN, Wicks NL, Najera JA, Oancea E. Opsin expression in human epidermal skin. *Photochem Photobiol.* 2015; 91: 117-123. doi: 10.1111/php.12354

26. Ryan MT, Hoogenraad NJ. Mitochondrial-nuclear communications. *Ann Rev Biochem.* 2007; 76: 701-722. doi: 10.1146/annurev.biochem.76.052305.091720

27. Lubart R, Wollman Y, Friedmann H, Rochkind S, Laulicht I. Effects of visible and near-infrared lasers on cells culture. J *Photochem Photobiol.* 1992; 12: 305-310. doi: 10.1016/1011-1344(92)85032-p

28. Choules L, Govindjee. Stories and photographs of William A. Arnold (1904–2001), a pioneer of photosynthesis and a wonderful

friend. *Photosynth Res.* 2014; 122: 87-95. doi: 10.1007/s11120-014-0013-9

29. Karu TI. Multiple roles of cytochrome c oxidase in mammalian cells under action of red and IR-A radiation. *IUBMB Life.* 2010; 62(8): 607-610. doi: 10.1002/iub.359

30. Barolet D. Pulsed versus continuous wave low-level light therapy on osteoarticular signs and symptoms in limited scleroderma (CREST syndrome): A case report. *J Biomed Opt.* 2014; 19(11): 118001. doi: 10.1117/1.JBO.19.11.118001

31. Keshri GK, Gupta A, Yadav A, Sharma SK, Singh SB. Photobiomodulation with pulsed and continuous wave near-infrared laser (810 nm, Al-Ga-As) augments dermal wound healing in immunosuppressed rats. *PLoS One.* 2016; 11(11): e0166705. doi: 10.1371/journal.pone.0166705

32. Barolet D, Boucher A. LED photoprotection: Reduced MED response following LED therapy. *Lasers Surg Med.* 2007; 40(2): 106-112. doi: 10.1002/lsm.20615

33. He J, Ford HC, Carroll J, Douglas C, Gonzales E, Ding S, et al. Assembly of the membrane domain of ATP synthase in human mitochondria. *PNAS license.* 2018; 115(12): 2988-2993. doi: 10.1073/pnas.1722086115

34. Sun Y, Wang C, Dai J. Biophotons as neural communication signals demonstrated by in situ biophoton autography. *Photochem Photobiol Sci.* 2010; 9(3): 315-322. doi: 10.1039/b9pp00125e

35. Karu T, Tiphlovaa O, Esenaliev R, Letokhov V. Two different mechanisms of low-intensity laser photobiological effects on Escherichia coli. *J Photochem Photobiol B.* 1994; 24(3): 155-161. doi: 10.1016/1011-1344(94)07016-4

36. Sommer AP, Pinheiro AL, Mester AR, Franke R-P, Whelan HT. Biostimulatory windows in low-intensity laser activation: lasers, scanners, and NASA's light-emitting diode array system. *J Clin Laser Med Surg.* 2001; 19(1): 29-33.

37. Gross AJ, Wolfgang J. Helium-neon laser irradiation inhibits the growth of kidney epithelial cells in culture. *Lasers Surg Med.* 1990; 10(1): 40-44. doi: 10.1002/lsm.1900100110

38. Bjordal JM. Low level laser therapy (LLLT) and world association for laser therapy (WALT) dosage recommendations. *Photomed Laser Surg.* 2012; 30(2): 61-62. doi: 10.1089/pho.2012.9893

39. Jagdeo J, Austin E, Mamalis A, Wong C, Ho D, Siegel D. Light-emitting diodes in dermatology: A systematic review of randomized controlled trials. *Lasers Surg Med.* 2018; 50(6): 613-628. doi: 10.1002/lsm.22791

40. Huang YY, Sharma SK, Carroll J, Hamblin MR. Biphasic dose response in low level light therapy - an update. *International Dose-Response Society.* 2011; 9(4): 602-618. doi: 10.2203/dose-response.11-009.Hamblin

41. Pelletier-Aouizerate. Photobiomodulation and light emitting diodes in aesthetic therapy. In: *Series in Cosmetic and Laser Therapy.* FL, USA: Taylor & Francis Inc; 2016.

42. Centre for Evidence-Based Medicine. Oxford Centre for Evidence-based Medicine - Levels of Evidence (March 2009). cebm Web site. https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/. Accessed June 17, 2019.

43. Lee GY, Kim WS. The systemic effect of 830-nm LED phototherapy on the wound healing of burn injuries: A controlled study in mouse and rat models. *J Cosmet Laser Ther.* 2012; 14(2): 107-110. doi: 10.3109/14764172.2011.649762

44. Min PK, Goo BL. 830 nm light-emitting diode low level light therapy (LED-LLLT) enhances wound healing: A preliminary study. *Laser Therapy.* 2013; 22(1): 43-49. doi: 10.5978/islsm.13-OR-06

45. Otterço AN, Andrade AL, Brassolatti P, Pinto K, Araújo H, Parizotto NA. Photobiomodulation mechanisms in the kinetics of the wound healing process in rats. *J Photochem Photobiol B.* 2018; 183: 22-29. doi: 10.1016/j.jphotobiol.2018.04.010

46. Ramos RM, Burland M, Silva JB, Burman LM, Gelain MS, Debom LM, et al. Photobiomodulation improved the first stages of wound healing process after abdominoplasty: An experimental, double-blinded, non-randomized clinical trial. *Aesthetic Plastic Surgery.* 2019; 43(1): 147-154. doi: 10.1007/s00266-018-1271-2

47. Park KY, Han TY, Kim IS, Yeo IK, Kim BJ, Kim MN. The effects of 830 nm light-emitting diode therapy on acute herpes zoster ophthalmicus: A pilot study. *Ann Dermatol.* 2013; 25(2): 163-167. doi: 10.5021/ad.2013.25.2.163

48. Kleinpenning MM, Otero ME, van Erp PEJ, Gerritsen MJP, Kerkhof PCM. Efficacy of blue light vs. red light in the treatment of psoriasis: A double-blind, randomized comparative study. *J Eur Acad Dermatol Venereol.* 2012; 26(2): 219-225. doi: 10.1111/j.1468-3083.2011.04039.x

49. Morton CA, Scholefield R, Whitehurst C, Birch J. An open study to determine the efficacy of blue light in the treatment of mild to moderate acne. *The Journal of Dermatological Treatment.* 2005; 16: 219-223. doi: 10.1080/09546630500283664

50. Bumah VV, Masson-Meyers DS, Tong W, Castel C, Enwemeka CS. Optimizing the bactericidal effect of pulsed blue light on Propionibacterium acnes - A correlative fluorescence spectroscopy study. *J Photochem Photobiol B.* 2020; 202: 111701. doi: 10.1016/j.jphotobiol.2019.111701

51. Tsoukas M, Keshavmurthy A, Inamadar A, Pei S. Light-based therapies in acne treatment. *Indian Dermatology Online Journal.* 2015; 6: 145. doi: 10.4103/2229-5178.156379

52. Tzung TY, Wu K-H, Huang M-L. Blue light phototherapy in the treatment of acne. *Photodermatol Photoimmunol Photomed.* 2004; 20(5): 266-269. doi: 10.1111/j.1600-0781.2004.00109.x

53. Papageorgiou P, Katsambas A, Chu A. Phototherapy with blue (415nm) and red light in the treatment of acne vulgaris. *Br J Dermatol.* 2000; 142(5): 973-978. doi: 10.1046/j.1365-2133.2000.03481.x

54. Yamada FR, Da Silva MM, Scasni KR. The use of LED for acne treatment. *J Cosmetol.* 2018; 2(1): 000107.

55. Alster TS, Wanitphakdeedech R. Improvement of post fractional laser erythema with light-emitting diode photo modulation. *Dermatol Surg.* 2009; 35(5): 813-815. doi: 10.1111/j.1524-4725.2009.01137.x

56. Khoury JG, Goldman J. Use of light-emitting diode photomodulation to reduce erythema and discomfort after intense pulsed light treatment or photodamage. *J Cosmet Dermatol.* 2008; 7(1): 30-34. doi: 10.1111/j.1473-2165.2008.00358.x

57. Boisnic S, Branchet MC, Bénichou L. Intérêt d'un nouveau traitement par exposition a des sources lumineuses monochromatiques. *Journal de Médecine Esthétique et de Chirurgie Dermatologique.* 2006; 33(131): 181-186.

58. Fouque-Parachini L, Guérif-Ferreira Y, Oberto G, Berghi A, Domloge N. Photorejuvenating effect of LED Triwings® on the skin. In vivo study by confocal microscopy VivaScope®. 2011.

59. Barolet D. Light emitting diodes (LEDs) in dermatology. *Seminars of Cutaneous Medicine and Surgery.* 2008; 27(4): 227-238. doi: 10.1016/j.sder.2008.08.003

60. Weiss R, McDaniel D, Geronemus R, Weiss M, Beasley K, Munavalli G, Bellew S. Clinical experience with light emitting diode (LED) photomodulation. *Dermatol Surg.* 2005; 31(9 Pt 2): 1199-1205. doi: 10.1111/j.1524-4725.2005.31926

61. Lee SY, Park KH, Choi JW, Kwon JK, Lee DR, Shin MS, et al. A prospective, randomized, placebo-controlled, double-blinded, and split-face clinical study on LED phototherapy for skin rejuvenation: Clinical, profilometric, histologic, ultrastructural, and biochemical evaluations and comparison of three different treatment settings. *J Photochem Photobiology B.* 2007; 88(1): 51-67. doi: 10.1016/j.jphotobiol.2007.04.008

62. Braathen LR, Szeimies RM, Basset-Seguin N, Bissonnette R, Foley P, Pariser D, et al. Guidelines on the use of photodynamic therapy for nonmelanoma skin cancer: An international consensus, International Society for Photodynamic Therapy in Dermatology. *J Am Acad Dermatol.* 2007; 56(1): 125-143. doi: 10.1016/j.jaad.2006.06.006

63. Roozeboom MH, Arits A, Mosterd K, Sommer A, Essers B, de Rooij M, et al. Three-year follow-up results of photodynamic therapy vs. imiquimod vs. fluorouracil for treatment of superficial basal cell carcinoma: A single-blind, noninferiority, randomized controlled trial. *Journal Investigat Dermatol.* 2016; 136(8): 1568-1574. doi: 10.1016/j.jid.2016.03.043

64. Alam M. *Evidence-Based Procedural Dermatology.* NY, USA: Springer International Publishing; 2019: doi: 10.1007/978-3-030-02023-1

65. Galderma. Product Monograph: PrMetvix. Galderma Web site. https://www.galderma.com/sites/g/files/jcdfhc196/files/inline-files/Metvix-PM-E.pdf. Accessed June 17, 2019.

66. Lupu M, Caruntu C, Popa MI, Voiculescu VM, Zurac S, Boda D. Vascular patterns in basal cell carcinoma: Dermoscopic, confocal and histopathological perspectives. *Oncol Lett.* 2019; 17(5): 4112-4125. doi: 10.3892/ol.2019.10070

67. Mordon S, Vignion-Dewalle AS. Low-irradiance red light compared to conventional red light in photodynamic therapy of actinic keratosis: A way to reduce pain during treatment. *Dermatol Ther.* 2019; 32(3): e12913. doi: 10.1111/dth.12913

68. Halstead DF, Thwaite JE, Burt R, Laws TR, Raguse M, Moeller R, et al. Antibacterial activity of blue light against nosocomial wound pathogens growing planktonically and as mature biofilms. *Appl Environment Microbiol.* 2016; 82(13): 4006-4016. doi: 10.1128/AEM.00756-16

69. Vignion-Dewalle AS, Abi Rached H, Thecua E, Lecomte F, Deleporte P, Béhal H, et al. A new light-emitting, fabric-based device for photodynamic therapy of actinic keratosis: Protocol for a randomized, controlled, multicenter, intra-individual, phase II noninferiority study (the phosistos study). *JMIR Research Protocols.* 2019; 8(4): e12990. doi: 10.2196/12990

70. Mester E, Szende B, Tota JG. Effect of laser on hair growth in mice. *Kiserl Orvostud.* 19: 628-631.

71. Trelles MA, Mayayo E, Cisneros JL. Tratamiento de la alopecia areata con laser HeNe. *Investigacion Y Clinica Laser.* 1984; 1: 15-17.

72. Delaney SW, Zhang P. Systematic review of low-level laser therapy for adult androgenic alopecia. *Journal of Cosmetic Laser Therapy.* 2018; 20(4): 229-236. doi: 10.1080/14764172.2017.1400170

73. Lanzafame R, Blanche R, Chiacchierini R, Kazmirek E, Sklar J. The growth of human scalp hair in females using visible red light laser and LED sources. *Lasers Surg Med.* 2014; 46(8): 601-607. doi: 10.1002/lsm.22277

74. Avci P, Gupta GK, Clark J, Wikonkal N, Hamblin MR. Low-level laser (light) therapy (LLLT) for treatment of hair loss. *Lasers*

Surg Med. 2014; 46(2): 144-151. doi: 10.1002/lsm.22170

75. Buscone S, Mardaryev AN, Raafs B, Bikker JW, Sticht C, Norbert Gretz, et al. A new path in defining light parameters for hair growth: Discovery and modulation of photoreceptors in human hair follicle. *Lasers Surg Med.* 2017; 49(7): 705-718. doi: 10.1002/lsm.22673

76. Jimenez JJ, Wikramanayake TC, Bergfeld W, Hordinsky M, Hickman JG, Hamblin MR, et al. Efficacy and safety of a Low-level Laser device in the treatment of male and female pattern hair loss: A multicentre, randomized, sham device-controlled, double-blind study. *Am J Clin Dermatol.* 2014; 15(2): 115-127. doi: 10.1007/s40257-013-0060-6

77. Jackson RF, Stern FA, Neira R, Ortiz-Neira CL, Maloney J. Application of low-level laser therapy for noninvasive body contouring. *Lasers Surg Med.* 2012; 44(3): 211-217. doi: 10.1002/lsm.22007

78. Cotler HB, Chow RT, Hamblin MR, Carroll J. The use of Low Level Laser Therapy (LLLT) for musculoskeletal pain. *MOJ Orthopedics and Rheumatology.* 2015; 2(5): 00068. doi: 10.15406/mojor.2015.02.00068

79. Stergioulas A. Low-level laser treatment can reduce edema in second degree ankle sprains. *J Clin Laser Med Surg.* 2004; 22(2): 125-128. doi: 10.1089/104454704774076181

80. Tumilty S, Munn J, McDonough S, Hurley DA, Basford JR, Baxter GD. Low level laser treatment of tendinopathy: A systematic review with meta-analysis. *Photomed Laser Surg.* 2010; 28(1): 3-16. doi: 10.1089/pho.2008.2470

81. Lopes-Martins RA. Tendinitis, an open avenue for low-level laser therapy. *Photomed Laser Surg.* 2014; 32(7): 369-370. doi: 10.1089/pho.2014.9859

82. Chow RT, Johnson MI, Lopes-Martins RA, Bjordal JM. Efficacy of low-level laser therapy in the management of neck pain: A systematic review and meta-analysis of randomised placebo or active-treatment controlled trials. *Lancet.* 2009; 374(9705): 1897-1908. doi: 10.1016/S0140-6736(09)61522-1

83. Konstantinovic LM, Cutovic MR, Milovanovic AN, Jovic SJ, Dragin AS, Letic, M, et al. Low-level laser therapy for acute neck pain with radiculopathy: A double-blind placebo-controlled randomized study. *Pain Med.* 2010; 11(8): 1169-1178. doi: 10.1111/j.1526-4637.2010.00907.x

84. Wilden L. The different response of the main symptoms of inner ear exhaustion to a specific high-dosage low-level laser therapy. *Med Laser Appl.* 2009; 24(2): 133. doi: 10.1016/j.mla.2009.02.027

85. Foley J, Vasily DB, Bradle J, Rudio C, Calderhead RG. 830 nm light-emitting diode (led) phototherapy significantly reduced return-to-play in injured university athletes: A pilot study. *Laser Therapy.* 2016; 25(1): 35-42.

86. Simunovic Z, Ivankovich AD, Depolo A. Wound healing of animal and human body sport and traffic accident injuries using low-level laser therapy treatment: A randomized clinical study of seventy-four patients with control group. *J Clin Laser Med Surg.* 2000; 18(2): 67-73. doi: 10.1089/clm.2000.18.67

87. Leal-Junior ECP, Vanin AA, Miranda EF, de Carvalho PTC, Corso SD, Bjordal JM. Effect of phototherapy (low-level laser therapy and light-emitting diode therapyon exercise performance and markers of exercise recovery: A systematic review with meta-analysis. *Lasers Med Sci.* 2015; 30: 925-939. doi: 10.1007/s10103-013-1465-4

88. de Almeida P, Lopes-Martins RÁ, Tomazoni SS, Silva JA, de Carvalho P, Bjordal JM, et al. Low-level laser therapy improves skeletal muscle performance, decreases skeletal muscle damage and modulates mRNA expression of COX-1 and COX-2 in a dose-dependent manner. *Photochem Photobiol.* 2011; 87(5): 1159-1163. doi: 10.1111/j.1751-1097.2011.00968.x

89. Paolillo FR, Corazza AV, Borghi-Silva A, Parizotto NA, Kurachi C, Bagnato VS. Infrared LED irradiation applied during high-intensity treadmill training improves maximal exercise tolerance in postmenopausal women: A 6-month longitudinal study. *Lasers Med Sci.* 2013; 28: 415-422. doi: 10.1007/s10103-012-1062-y

90. Hamblin MR. Shining light on the head: Photobiomodulation for brain disorders. *BBA Clinical.* 2016; 6: 113-124. doi: 10.1016/j.bbacli.2016.09.002

91. Tedford CE, DeLapp S, Jacques S, Anders J. Quantitative analysis of transcranial and intraparenchymal light penetration in human cadaver brain tissue. *Lasers Surg Med.* 2015; 47(4): 312-322. doi: 10.1002/lsm.22377

92. Yaroslavsky AN, Schulze PC, Yaroslavsky IV, Schober R, Ulrich F, Schwarzmaier HJ. Optical properties of selected native and coagulated human brain tissues in vitro in the visible and near infrared spectral range. *Physics Med Biol.* 2002; 47(12): 2059-2073. doi: 10.1088/0031-9155/47/12/305

93. Gordon LC, Johnstone DM. Remote photobiomodulation: An emerging strategy for neuroprotection. *Neural Regen Res.* 2019; 14: 2086-2087. doi: 10.4103/1673-5374.262573

94. Naeser MA, Saltmarche AE, Krengel MH, Hamblin MR, Knight JA. Improved cognitive function after transcranial, light-emitting diode treatments in chronic, traumatic brain injury: Two case reports. *Photomed Laser Surg.* 2011; 29(5): 351-358. doi: 10.1089/pho.2010.2814

95. Askalsky P, Iosifescu DV. Transcranial photobiomodulation for the management of depression: Current perspectives. *Neuropsychiatric Disease and Treatment.* 2019; 15: 3255-3272. doi: 10.2147/NDT.S188906

96. Mintzopoulos D, Gillis TE, Tedford CE, Kaufman MJ. Effects of near-infrared light on cerebral bioenergetics measured with phosphorus magnetic resonance spectroscopy. *Photomed Laser Surg*. 2017; 35(8): 395-400. doi: 10.1089/pho.2016.4238

97. Sivasubramanian M. Chuang YC, Lo LW. Evolution of Nanoparticle-Mediated Photodynamic Therapy: From Superficial to Deep-Seated Cancers. *Molecules*. 2019; 24(3): 520. doi: 10.3390/molecules24030520

98. Deng K, Li C, Huang S, Xing B, Jin D, Zeng Q, et al. Recent progress in near infrared light triggered photodynamic therapy. *Smal*. 2017; 13(44): 1702299. doi: 10.1002/smll.201702299

99. Bolze F, Jenni S, Sour A, Heitz V. Molecular photosensitisers for two-photon photodynamic therapy. *Chem Comm*. 2017; 53(96): 12857-12877. doi: 10.1039/c7cc06133a

100. Yang M, Yang T, Mao C. Enhancement of photodynamic cancer therapy by physical and chemical factors. *Angewandte Chemie*. 2019; 58(40): 14066-14080. doi: 10.1002/anie.201814098

101. Zein R, Selting W, Hamblin M. Review of light parameters and photobiomodulation efficacy: Dive into complexity. *J Biomed Opt*. 2018; 23: 1. doi: 10.1117/1.JBO.23.12.120901

102. Bensadoun R, Franquin JC, Ciais G, Darcourt V, Schubert MM, Viot M, et al. Low-energy He/Ne laser in the prevention of radiation-induced mucositis. A multicenter phase III randomized study in patients with head and neck cancer. *Support Care Cancer*. 1999; 7(4):244-252. doi: 10.1007/s005200050256

103. University Hospital of Toulouse. Feasibility study of a protocol to treat pediatric oral mucositis by Low-level Laser Therapy (PEDIALASE). ClinicalTrials Web site. https://clinicaltrials.gov/ct2/show/NCT02604329. Accessed June 17, 2019.

104. Shallal MM, Hajim KI. Enhancement of surgical vaginal mucosal wound healing using he-ne laser of 632.8 nm with topical application of tolidine blue. *Iraqi J Comm Med*. 2010.

105. Botez M, Anton C, Mircea R, Anton E. Noninvasive laser therapy for outpatients with chronic inflammatory disorders of cervix. *Rev Med Chir Soc de Med si Nat Iasi*. 2012; 116(4): 1131-1135.

106. El Faham DA, Elnoury MAH, Morsy MI, El Shaer MA, Eldin GMN, Mahmou O, et al. Has the time come to include low-level laser photobiomodulation as an adjuvant therapy in the treatment of impaired endometrial receptivity? *Lasers Med Sci*. 2018; 33: 1105-1114. doi: 10.1007/s10103-018-2476-y

107. Wasson CJ, Zourelias JL, Aardsma NA, Eells JT, Ganger MT, Schober JM, et al. Inhibitory effects of 405 nm irradiation on Chlamydia trachomatis growth and characterization of the ensuing inflammatory response in HeLa cells. *BMC Microbiol*. 2012; 12: 176. doi: 10.1186/1471-2180-12-176

108. Lanzafame RJ, de la Torre S, Leibaschoff GH. The Rationale for photobiomodulation therapy of vaginal tissue for treatment of genitourinary syndrome of menopause: An analysis of its mechanism of action, and current clinical outcomes. *Photobiomodulation, Photomedicine, and Laser Surgery*. 2019; 37(7): 395-407. doi: 10.1089/photob.2019.4618

109. Marques AC, Albertini R, Serra AJ, da Silva EA, de Oliveira VL, Silva LM, et al. (2016), Photobiomodulation therapy on collagen type I and III, vascular endothelial growth factor, and metalloproteinase in experimentally induced tendinopathy in aged rats. *Lasers Med Sci*. 2016; 31(9): 1915-1923. doi: 10.1007/s10103-016-2070-0

110. Fortuna T, Gonzalez AC, Sa MF, Andrade ZA, Reis SRA, Medrado ARAP. Effect of 670nm laser photobiomodulation on vascular density and fibroplasia in late stages of tissue repair. *Int Wound J*. 2018; 15(2): 274-282. doi: 10.1111/iwj.12861

111. Prokhonchukov AA. 30-letniĭ opytprimeneniialazerov v stomatologii. [In: Russian]. [30 years of experience in using lasers in dentistry]. *Stomatologiia*. 1995; 74(4): 68-73.

112. Nanami T, Shiba H, Ikeuchi S, Nagai T, Asanami S, Shibata T. Clinical applications and basic studies of laser in dentistry and oral surgery. *Keio J Med*. 1993; 42(4): 199-201.

113. Holder MJ, Milward MR, Palin WM, Hadis MA, Cooper PR. Effects of red light-emitting diode irradiation on dental pulp cells. *J Dental Res*. 2012; 91(10): 961-966. doi: 10.1177/0022034512456040

114. Shukla D, Muthusekhar MR. Efficacy of low-level laser therapy in temporomandibular disorders: A systematic review. *Natl J Maxillofac Surg*. 2016; 7(1): 62-66. doi: 10.4103/0975-5950.196127

115. Chang, WD, Lee CL, Lin HY, Hsu YC, Wang CJ, Lai PT. A meta-analysis of clinical effects of low-level laser therapy on temporomandibular joint pain. *Journal of Physical Therapy Science*. 2014; 26(8): 1297-1300. doi: 10.1589/jpts.26.1297

116. Garcez AS, Núñez SC, Azambuja N, Fregnani ER, Rodriguez HMH, Hamblin MR, et al. Effects of photodynamic therapy on gram-positive and gram-negative bacterial biofilms by bioluminescence imaging and scanning electron microscopic analysis. *Photomed Laser Surg*. 2013; 31(11): 519-525. doi: 10.1089/pho.2012.3341

117. Donnelly RF, McCarron PA, Tunney MM, Woolfson AD. Potential of photodynamic therapy in treatment of fungal infections of the mouth. Design and characterisation of a mucoadhesive patch containing toluidine blue O. *J Photochem Photobiol B*. 2007; 86(1): 59-69. doi: 10.1016/j.jphotobiol.2006.07.011

118. Nadhreen AA, Alamoudi NM, Elkhodary HM. Low-level laser therapy in dentistry: Extra-oral applications. *Nigerian J Clin Practice*. 2019; 22(10): 1313-1318. doi: 10.4103/njcp.njcp_53_19

119. Maclean M, Macgregor SJ, Anderson JG, Woolsey GA, Coia JE, Hamilton K, et al. Environmental decontamination of a hospital isolation room using high-intensity narrow-spectrum light. *The Journal of Hospital Infection*. 2010; 76(3): 247-251. doi: 10.1016/j.jhin.2010.07.010

120. Enwemeka CS. Antimicrobial blue light: An emerging alternative to antibiotics. *Photomed Laser Surg*. 2013; 31(11): 509-511. doi: 10.1089/pho.2013.9871

121. Mesquita, MQ, Dias CJ, Neves MGPMS, Almeida A, MG, Faustino MAF. Revisiting current photoactive materials for antimicrobial photodynamic therapy. *Molecules*. 2018; 23(10): 2424. doi: 10.3390/molecules23102424

122. Cabral J, Ag R. Blue light disinfection in hospital infection control: Advantages, drawbacks, and pitfalls. *Antibiotics*. 2019; 8(2): 58. doi: 10.3390/antibiotics8020058

123. Hamblin MR, O'Donnell DA, Murthy N, Rajagopalan K, Michaud N, Sherwood ME, et al. Polycationic photosensitizer conjugates: Effects of chain length and Gram classification on the photodynamic inactivation of bacteria. *The Journal of Antimicrobial Chemotherapy*. 2002; 49(6): 941-951. doi: 10.1093/jac/dkf053

124. Hamblin MR, Hasan T. Photodynamic therapy: a new antimicrobial approach to infectious disease? *Photochem Photobiol Sci*. 2004; 3(5): 436-450. doi: 10.1039/b311900a

125. Costa L, Tomé JP, Neves MG, Tomé AC, Cavaleiro JA, Cunha A, et al. Susceptibility of non-enveloped DNA- and RNA-type viruses to photodynamic inactivation. *Photochem Photobiol Sci*. 2012; 11(10): 1520-1523. doi: 10.1039/c2pp25156f

126. Kharkwal GB, Sharma SK, Huang YY, Dai T, Hamblin MR. Photodynamic therapy for infections: Clinical applications. *Lasers Surg Med*. 2011; 43(7): 755-767. doi: 10.1002/lsm.21080

127. Tao J-X, Zhou W-C, Zhu X-G. Mitochondria as potential targets and initiators of the blue light hazard to the retina. *Oxid Med Cell Longev*. 2019; 2019: 6435364. doi: 10.1155/2019/6435364

128. Guo Y-R, Cao Q-D, Hong Z-S, Tan Y-Y, Chen S-D, Jin H-J, et al. The origin, transmission and clinical therapies on coronavirus disease (COVID-19) outbreak – an update on the status. *Military Med Res*. 2019; 7: 11. doi: 10.1186/s40779-020-00240-0

129. Enwemeka CS, Bumah VV, Masson-Meyers SD. Light as a potential treatment for pandemic coronavirus infections: A perspective. *J Photochem Photobiol*. 2020; 111891. doi: 10.1016/j.jphotobiol.2020.111891

130. Brochetti, R.A., Leal, M.P., Rodrigues, R. da Palma RK, de Oliveira LVF, Horliana ACRT, et al. Photobiomodulation therapy improves both inflammatory and fibrotic parameters in experimental model of lung fibrosis in mice. *Lasers Med Sci*. 2017; 32: 1825-1834. doi: 10.1007/s10103-017-2281-z

131. De Brito AA, da Silveira EC, Rigonato-Oliveira NC, Soares SS, Brandao-Rangel M, Soares CR, et al. Low-level laser therapy attenuates lung inflammation and airway remodeling in a murine model of idiopathic pulmonary fibrosis: Relevance to cytokines secretion from lung structural cells. *J Photochem Photobiol B*. 2020; 203: 111731. doi: 10.1016/j.jphotobiol.2019.111731

132. Zhang R, Mio Y, Pratt PF, Lohr N, Warltier D, Whelan HT, et al. NIR light protects cardiomyocytes from hypoxia and reoxygenation injury by a nitric oxide dependent mechanism. *J Mol Cell Cardiol*. 2009; 46(1): 4-14. doi: 10.1016/j.yjmcc.2008.09.707

133. Liebert A, Bicknell B, Johnstone DM, Gordon LC, Kiat H, Hamblin MR. "Photobiomics": Can light, including photobiomodulation, alter the microbiome? *Photobiomodul Photomed Laser Surg*. 2019; 37(11): 681-693. doi: 10.1089/photob.2019.4628

134. Bischof M. *Integrative Biophysics Biophotonics*. NY, USA: Kluwer Academic Publishers; 1995.

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Case Report

Lupus Erythematosus Affecting the Genitalia: An Unusual Site

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ABSTRACT

Cutaneous lupus erythematosus classically affects sun-exposed areas. It's rarely affects the genitalia, and there are few cases reported in the literature. Thus, we report the different genital manifestations observed in a patient with lupus erythematosus affecting the genital area.

Keywords
Genitalia; Cutaneous lupus erythematosus; Systemic lupus.

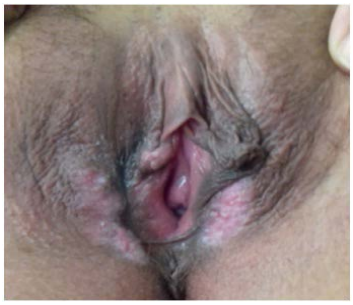
INTRODUCTION

In lupus erythematosus (LE), involvement of the genital area is uncommon, with few cases described in the literature.[1] We report a case of a 23-year-old woman, with history of lupus erythematosus, who presented with a genital lesion during an acute flare of her disease.

OBSERVATION

A 23-year-old woman, with history of lupus erythematosus, treated with hydroxychloroquine and external photoprotection, was admitted for an acute flare of her disease, with joint and cutaneous manifestations. Clinical examination found erythematous plaques diffusly on the face and extremities and multiple alopecic plaques. In addition to this typical finding, painless white erosive plaques, which were bilateral and roughly symmetrical, were noted on both labia majora (Figure 1). Laboratory studies revealed the anti-native deoxyribonucleic acid (DNA) antibodies were highly positive at 44 (normal range ≤5), elevated erythrocyte sedimentation rate at 38 in the first hour (normal must be ≤22 in the first hour), anemia at 10 (normal ≥12.5 g/dL) , lymphopenia at 250 g/dL (normal ≥500 g/dL) and a high 24-hour urine protein at 3.5 g/24 h (normal ≤0.5 g/24 h). Hence a renal biopsy was performed, which confirmed the diagnosis of lupus glomerulopathy grade II. Therefore, the diagnosis of a genital involvement of systemic lupus erythematosus was retained. Treatment included intravenous methylprednisolone therapy at the dose of 500-1000 mg over 1-hour once a day for 3-days followed by oral prednisolone 0.5-1 mg/kg/d for 4-weeks and topical clobetasol for skin and genital lesions, plus hydroxychloroquine (200 mg/j), resulting in an improvement of her skin and genital lesions, joint and nephritis disease as well.

Figure 1. *White Erosive Plaques, Bilateral and Roughly Symmetrical, on Both Labia Majora*



DISCUSSION

The genital manifestations of lupus erythematosus have been described sporadically in the literature. They occur in approximately 5% of patients with chronic cutaneous lupus erythematosus, and have been described rarely in patients with systemic lupus erythematosus.[1] At our knowledge, the first case was reported in 1994 by

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Biasi et al.[2] Then, two others cases, which reported a discoid lupus at the genitalia associated to systemic lupus erythematosus (SLE), were described.[3-5] Moreover, two cases of genital involvement of systemic lupus erythematosus was reported by Del Alcázar-Viladomiu et al and Wester and Al, in 2018 and 2019, respectively.[6,7] In addition, there are few studies which describe this entity. Clinically, lesions may be ulcers, erosions, or atrophic erythematous plaques with the characteristic scarring alopecia of discoid lupus erythematosus.[8] Typical discoid lupus erythematosus ulcers and plaques may occur in patients with systemic lupus erythematosus or discoid lupus erythematosus. In our patient, we had founded bilateral erosions. Typically, these cutaneous lesions are asymptomatic.[9] That it was similar in our patient. The treatment is the same as for other manifestations of lupus, with a short corse of potent topical corticosteroids combined with systemic hydroxychloroquine or chloroquine.[1,5,9]

CONCLUSION

Genital involvement is rare in LE and it is perhaps under diagnosed. Our case suggests that, although ultraviolet light may be the most important environmental factor in inducing skin lesions, other intrinsic immune mechanisms may be similar in non-exposed skin, especially, in the genitalia. In addition, other precipitating factors, such as the Köebner phenomenon, may impact this localization.

CONSENT

The authors have received written informed consent from the patient.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

1. Burge SM. Mucosal involvement in systemic and chronic cutaneous lupus erythematosus. *Br J Dermatol*. 1989; 121: 727-741. doi: 10.1111/j.1365-2133.1989.tb08215.x

2. Biasi D, Carletto A, Caramaschi P, Bambara LM. Vulvar lesion in a patient affected systemic lupus erythematosus. *Lupus*. 1994; 3(1): 69. doi: 10.1177/096120339400300115

3. Romiti R, Anzai A, Nico MM. Genital discoid lupus: A rare manifestation of cutaneous lupus erythematosus. *Lupus*. 2014; 23: 707-710. doi: 10.1177/0961203314522336

4. Bilenchi R, Pisani C, Poggiali S, Andreassi A, de Padova LA, di Perrit T. Discoid lupus erythematosus of the vulva. *Lupus*. 2004; 13: 815-816. doi: 10.1191/0961203304lu1062cr

5. Jolly M, Patel P. Looking beyond the ordinary: Genital lupus. *Arthritis Rheum*. 2006; 55(5): 821-822. doi: 10.1002/art.22233

6. Del Alcázar-Viladomiu E, López-Pestaña A, Tuneu-Valls A. Lupus erythematosus affecting the Genitalia: An unusual site. *Actas DermoSifiliográficas*. 2018; 109(1): 78-80. doi: 10.1016/j.ad.2017.05.010

7. Wester A. Genital plaques in a patient with SLE. *Journal of the American Academic of Dermatology*. 2019; 81(4): AB216. doi: 10.1016/j.jaad.2019.06.793

8. Nico MM, Vilela MA, Rivitti EA, Lourenc¸o SV. Oral lesions in lupus erythematosus: Correlation with cutaneous lesions. *Eur J Dermatol*. 2008; 18: 376-381. doi: 10.1684/ejd.2008.0388

9. Darwish. T. Medical image. Genital lupus. *N Z Med J*. 2008; 121(1277). 86-87.