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Clinical Evaluation of Indian Sandalwood Oil and Its Protective Effect on the Skin against the Detrimental Effect of Exposome

Vimi Lutchmanen Kolanthan [1], Andrew Brown [2], Vitisha Soobramaney [1], Evans Georges Philibert [1], Veronique Francois Newton [1], Muzzammil Hosenally [3], Bibi Nusayha Sokeechand [1], Gitanjali Petkar [1], Alain Moga [4], Philippe Andres [5], Madiiha Bibi Mandary [1,*] and Dhanushka Hettiarachchi [2,*]

1 Centre International de Développement Pharmaceutique (CIDP), BioPark, Socota Phoenicia, Sayed Hossen Road, Phoenix 73408, Mauritius; v.kolanthan@cidp-cro.com (V.L.K.); v.soobramaney@cidp-cro.com (V.S.); e.philibert@cidp-cro.com (E.G.P.); v.newton@cidp-cro.com (V.F.N.); n.sokeechand@cidp-cro.com (B.N.S.); g.petkar@cidp-cro.com (G.P.)
2 Quintis Pty Ltd. Level 1, 87 Colin Street, West Perth 6005, Australia; andrewb@quintis.com.au
3 Department of Economics and Statistics, University of Mauritius, Réduit 80837, Mauritius; m.hosenally@uom.ac.mu
4 Prologue Biotech, 516 Rue Pierre et Marie Curie, 31670 Labège, France; alain.moga@qima.com
5 Clipeum Pharma, 06530 Peymeinade, France; philippe.andres@clipeumpharma.fr
* Correspondence: m.mandary@cidp-cro.com (M.B.M.); danny@quintis.com.au (D.H.)

Abstract: The skin is constantly subject to external stressors (the exposome), including particulate matter and blue light. These can penetrate the deeper layers of the skin, inducing the release of free radicals and triggering an inflammatory cascade of events contributing to cutaneous aging and exacerbating inflammatory skin conditions. This study demonstrates the clinical efficacy of Indian sandalwood oil of varying concentrations against oxidative stress induced by urban dust and blue light. Twenty-two healthy human subjects entered and completed the study of 11 days. Test products containing 0.1%, 1% and 10% of sandalwood oil, as well as a placebo and a comparator control (α-tocopherol), were applied on the different investigational zones of the upper back of each subject. Exposure ensued on day 7, using a controlled pollution exposure system (CPES) and blue light at a wavelength of 412 nm. Sebum was sampled on each investigational zone following the last exposure. The level of squalene monohydroperoxide (SQOOH) was the primary endpoint. A dose-dependent decrease in SQOOH on the zones treated with 10%, 1% and 0.1% of the sandalwood oil formulation compared to the untreated zones was observed. The zone treated with the 10% sandalwood-containing formula demonstrated the highest protective efficacy with the lowest amount of SQOOH. Increasing the concentration of the sandalwood oil increased its protective antioxidant activity. The results collected from this intraindividual comparative is the first clinical trial to suggest that sandalwood oil at a concentration between 1% and 10% protects the skin against the oxidative stress induced by urban dust and blue light exposure.

Keywords: oxidative stress; blue light; pollution; in vivo; Indian sandalwood oil; squalene

Citation: Lutchmanen Kolanthan, V.; Brown, A.; Soobramaney, V.; Philibert, E.G.; Francois Newton, V.; Hosenally, M.; Sokeechand, B.N.; Petkar, G.; Moga, A.; Andres, P.; et al. Clinical Evaluation of Indian Sandalwood Oil and Its Protective Effect on the Skin against the Detrimental Effect of Exposome. *Cosmetics* **2022**, *9*, 35. https://doi.org/10.3390/cosmetics9020035

Academic Editor: Enzo Berardesca

Received: 4 February 2022
Accepted: 18 March 2022
Published: 23 March 2022

1. Introduction

The skin, being the outermost barrier of the body, is very sensitive to the exposome to which it is frequently exposed in our daily life. This is of major consequence, as the main function of the skin is to protect against these detrimental effects. Routine daily activities have greatly increased our exposure to toxic pollutants [1]. Among those toxic pollutants, the constituents of air pollutants such as polycyclic aromatic hydrocarbons (PAHs), volatile organic compounds (VOCs) and particulate matter (PM) can considerably damage the skin. Additionally, the action of these harmful agents is usually amplified with the interaction of UV light, leading to oxidative skin damage [2]. PAHs, the most harmful component of air pollution, emerge from the combustion of all organic matter and can generate reactive

oxygen species. Its association with UV light induces the proliferation of melanocyte and provokes melanogenesis [3,4].

It has been previously demonstrated that the different wavelengths of the visible light spectrum each have a different impact on the skin [5]. Being a major target of oxidative stress by blue light, the skin has been reported to undergo significant and lasting hyperpigmentation, inflammation, and cell death [6]. Nowadays, the population of people with urban lifestyles continues to expand. As this urban lifestyle grows, more and more people are directly exposed to pollution caused by vehicle fumes, industries, cigarette smoke and others [7]. To a certain degree, the skin can protect itself against pollutants through the pathways of the immune system's cells. However, persistent regular exposure to high levels of pollutants impacts this protective mechanism significantly [8]. To this end, frequent application of skincare products that act as an effective shield against the exposome, such as blue light and pollution, is crucial. For instance, a cosmetic formulation comprising of ingredients that can protect the skin by physically shielding it and scavenging oxidative pollutants simultaneously is greatly desired.

Indian sandalwood oils are produced mainly by steam distillation of heartwood from the species *Santalum album* L. and is one of the oldest raw materials used for perfumery [9]. Indian sandalwood oil from the *S. album* L. is considered as the gold standard to use as an ingredient in cosmetics, medicine and for aromatherapy [10,11]. Previous studies have demonstrated that, at different pharmacological doses, sandalwood oil demonstrated a protective effect of varying degrees, and was capable of attenuating the damages induced by the generation of reactive oxygen species (ROS) in vitro [12–16].

Most recently, we investigated the antiaging and antioxidant properties of Indian sandalwood oil as a protective active ingredient in vitro on the human keratinocyte cell line (HaCaT) and ex vivo on human skin explants [12]. Through this study, it was revealed that there was a protective efficacy against oxidative stress in vitro, whereby it was capable of protecting HaCaT cells against blue light and cigarette smoke. Notably, Indian sandalwood oil demonstrated the ability to decrease the level of matrix metalloproteinase-1 (MMP-1) by a significant amount in human skin explants, thus attesting to its antiaging properties ex vivo [12]. While the pharmacological attributes of Indian sandalwood oil have been extensively researched in vitro and ex vivo, no in vivo clinical assessment of its efficacy against both blue light and pollution has been reported thus far.

As a continuation of our previous work, we investigate for the first time the in vivo protective effect of Indian sandalwood oil applied to the skin in a contemporary skin care format against the oxidative stress induced by particulate matter (ambient dust NIST SRM 1649b) and blue light at 412 nm through the assessment of sebum lipid peroxidation. We made use of the Controlled Pollution Exposure System (CPES), which allowed for the quantified administration of pollutants on human test subjects and the analysis of the direct impact of the pollutant in conjecture with blue light at 412 nm [17]. Data collected from this study would give an accurate description of the benefit of Indian sandalwood oil on the skin in a real-life scenario as compared to an artificial lab environment.

2. Materials and Methods

2.1. Study Design and Ethical Aspects

This study was conducted as a monocentric, controlled, randomized, double-blinded, intraindividual comparative trial. The study was conducted in compliance with the protocol, current internal procedures and in the spirit of ICH Topic E6 (R2). The investigation was in full compliance with the principles outlined in the Declaration of Helsinki and with the national regulations of Mauritius. A written informed consent was received from all volunteers. This study was submitted to the Fortis-Darné Clinique Independent Ethics Committee (IEC) with the study code 2021CMCL059 and was approved on the 29 January 2021.

2.2. Study Participants

A total of 22 healthy subjects between 18 and 65 years old were recruited as subjects for this study. The main exclusion criteria were as follows: pregnancy, breastfeeding or planning a pregnancy, any hypersensitivity or known allergies to dust, any major systemic conditions and the onset of diseases including atopic dermatitis, contact dermatitis, eczema, vitiligo, skin cancer or any other photo-dermatological problems that may affect measurements. The subjects were instructed to maintain their current hygiene and cosmetic routine and not to do any sunbathing, which may interfere with the study assessments.

2.3. Study Schedule

The study duration was eleven days, where subjects attended a baseline visit at D0 for acclimatization and the application of the product on seven demarcated investigational zones of 3 cm × 4 cm on the upper back (Figure 1). From D1 to D6, the subjects returned to the investigation center for the application of 2 mg/cm^2 of the product on the investigational zones. On D7, D8 and D9, the application of the product was carried out on the defined zones, followed by an adaptation period of 15 min at 22–23 °C with a humidity of 50–60%. An exposure of the exposed zones to ambient dust (NIST SRM 1649b) was done using the CPES, followed by the exposure to blue light at a wavelength of 412 nm. The study ended on D10, whereby product application and exposure were carried out, followed by a sebum sampling of the seven zones one hour after the exposure.

Figure 1. Schematic illustration of the seven demarcation zones, whereby each zone was of 3 cm × 4 cm on the upper back of the subjects. The different test products were applied on the zones according to a randomization list. Each zone was then exposed to ambient dust followed by blue light. After the last exposure, sebum sampling was performed on each investigational zone.

2.4. Investigational Products

The investigational products consisted of five different formulae, notably 10% *w*/*w*, 1% *w*/*w* and 0.1% *w*/*w* Indian sandalwood oil in caprylic triglycerides, a vehicle control caprylic triglycerides and a positive control α-tocopherol (0.5% *w*/*w*) in caprylic triglycerides. Indian sandalwood oil was supplied by Quintis Sandalwood Pty Ltd. (West Perth, Australia) and α-tocopherol was supplied by Sigma-Aldrich (St. Louis, MO, USA).

The selection of Indian sandalwood oil concentration ranges for testing was based on the concentration ranges that are likely to be used in a cosmetic presentation. Indian sandalwood oil used in this experiment was obtained by steam distillation of the aromatic heartwood from Santalum album grown in the Ord River Irrigation Area, Kununurra, Western Australia. The oil complied with the ISO standard 3518-2002 and the use-by date on the Indian sandalwood oil used was well within its limit with 4 years remaining. Table 1 showed the major constituents of the Indian sandalwood oil used in this investigation.

Table 1. Major constituents and characteristics of Indian sandalwood oil used in this study.

Constituent	Concentration (% *w*/*w*)
Z α-santalol	48.2
Z β-santalol	20.5
trans α-bergamotol	5.9
epi β-santalol	4.0

2.5. Medical Examination

A clinical examination of the back of each subject was performed by the investigator at the baseline D0, and on each subsequent visit for the assessment of local tolerance (functional signs and assessments of erythema, skin dryness, edema, desquamation or papules) and the reporting of adverse events.

2.6. Ambient Dust Exposure

Particulate matter (NIST SRM 1649b) was exposed to subjects' skin on the upper back at a specific concentration of 100 µg/m^3 for a duration of 2 h within specially designed cylindrical cups (Ø: 5 cm; height: 3 cm) fitted onto the skin by double-sided tapes. Each cup had one inlet for the incoming particulate matter, at a flow rate of 500 mL/min, and for two other outlets. The first outlet enabled the evacuation of the particulate matter through filters to ensure that there was none remaining in the air exhaust, and the second outlet was connected to a particle detector. This detector displayed the particle size distribution (PM1, PM2.5, PM10 and others) as well as the total particle count in the air mixture.

2.7. Blue Light Exposure

The 412 nm blue light lamp consisted of 10 identical LEDs (Honglitronic, Guangzhou, PRC) emitting continuous visible radiation embedded in a reflector, which was covered by a transparent glass window. A single peak with a maximum wavelength of 412 $\pm$ 5 nm could be observed for the lamps. The aperture on the light source was 4.5 cm $\times$ 4.5 cm. A thermopile detector (Gentec-EO USA Inc., Lake Oswego, OR, USA) was used to measure the precise intensity of the light source in watt/cm^2 at the level of the investigational site. The distance between the blue light lamps and the exposed zones was adjusted to ensure that volunteers were exposed to 60 J/cm^2 of blue light for 30 minutes

2.8. Swabbing and Sampling

The zone of interest is well demarcated with an area of 3 cm^2. A swab is dipped into a cocktail solution prior to swabbing the demarcated zone for 45 s. The swab is then collected in the cocktail solution and stored at -20 °C prior to analysis of the squalene monohydroperoxide by Synelvia Laboratories (Labège, France).

The swab homogenates were centrifuged at 10,000$\times$ *g* for 5 min. Samples were extracted using a double liquid/liquid extraction method, evaporated under nitrogen at 60 °C, and the residue was dissolved in 50 µL of ethanol. An UltiMate 3000 (Dionex, Sunnyvale, CA, USA) liquid chromatography system coupled to an ISQ detector (Fisher Scientific, Waltman, MA, USA) was used for the detection of SQOOH. Atmospheric pressure chemical ionization was used as the ion source for mass spectrometry, where the positive ion spectra were recorded in the range 50–450 *m*/*z*.

2.9. Statistical Analysis

Qualitative variables were described as the number and percentage of the different response modalities, while the quantitative measurements were summarized using the mean, median, minimum, maximum and the standard deviation. For the variable of interest, 95% confidence intervals (CI) were computed and presented in bar charts of the means by treatment. Formal zone (treatment) comparison was conducted using an ANOVA procedure, with treatments and subjects as fixed factors. All statistical analyses were performed at a 5% significance level using 2-sided tests, except normality tests, conducted at 1% (Shapiro–Wilk test). The SPSS 19.0 (SPSS Inc., Chicago, IL, USA) program was used for statistical analysis purposes.

3. Results

3.1. Panel Description

The study panel (Table 2) comprised of 22 healthy adults aged between 18 and 65 years old.

Table 2. Characteristics of the subjects included in the study.

Required Age Range?	Yes	22	100.0%
	No	0	0.0%
Gender	Female	15	68.0%
	Male	7	32.0%

3.2. Protective Effect of Sandalwood Oil

To evaluate the protective effect of the products, the level of the oxidized form of squalene (squalene monohydroperoxide; SQOOH) was monitored. Table 3 reported that the amount of SQOOH collected on the non-treated and exposed zones were significantly higher than the nontreated and nonexposed zones. A four-fold increase in the level of SQOOH was reported in the nontreated exposed zone when compared to the nontreated nonexposed zone. The level of SQOOH collected by the vehicle control following an exposure to the stress was as high as the nontreated and exposed zone, which indicated that the vehicle control does not offer a level of protection against the oxidative stress induced by blue light at 412 nm and ambient dust. The zones treated with the positive control, 0.5% α-tocopherol, and exposed showed a lower amount of SQOOH when compared to the exposed zones that were either left untreated or treated with the vehicle control.

Table 3. Descriptive statistics for the levels of SQOOH (ng/mg prot) collected at D10 for 22 subjects.

	Nonexposed	**Exposed**					
Zone	**Nontreated**	**Nontreated**	**Placebo**	**0.1% Sandalwood Oil**	**1% Sandalwood Oil**	**10% Sandalwood Oil**	**α-Tocopherol (0.5%)**
Mean	138.75	549.46	495.13	470.80	378.75	343.66	398.23
Median	100.69	494.54	483.77	463.11	353.07	309.92	380.73
Minimum	44.71	213.36	189.84	102.36	139.94	68.78	126.62
Maximum	459.63	1078.65	823.29	794.50	740.94	577.97	843.50
SD	116.25	248.16	170.74	177.30	144.54	149.38	157.77

Table 3 illustrates the descriptive statistical analysis obtained following exposure to the different environmental stressors. A dose-dependent decrease in the levels of SQOOH was reported on the zones treated with the sandalwood formulations. The highest concentration of sandalwood at 10% exhibited the lowest amount of SQOOH of 343.66 ng/mg protein compared to 549.46 ng/mg protein on the nontreated and exposed area (Table 3). This difference translates into a 37% significant decrease when compared to the nontreated/exposed

zones and a 31% decrease when compared to the placebo control. The 1% sandalwood oil also showed a 31% and a 24% decrease in the levels of SQOOH when compared to the untreated/exposed zone and the vehicle control zone, respectively. The 0.1% sandalwood displayed the lowest protective efficacy, whereby a 14% and 5% decrease was reported when compared to the untreated/exposed zone and the placebo control, respectively (Figure 2).

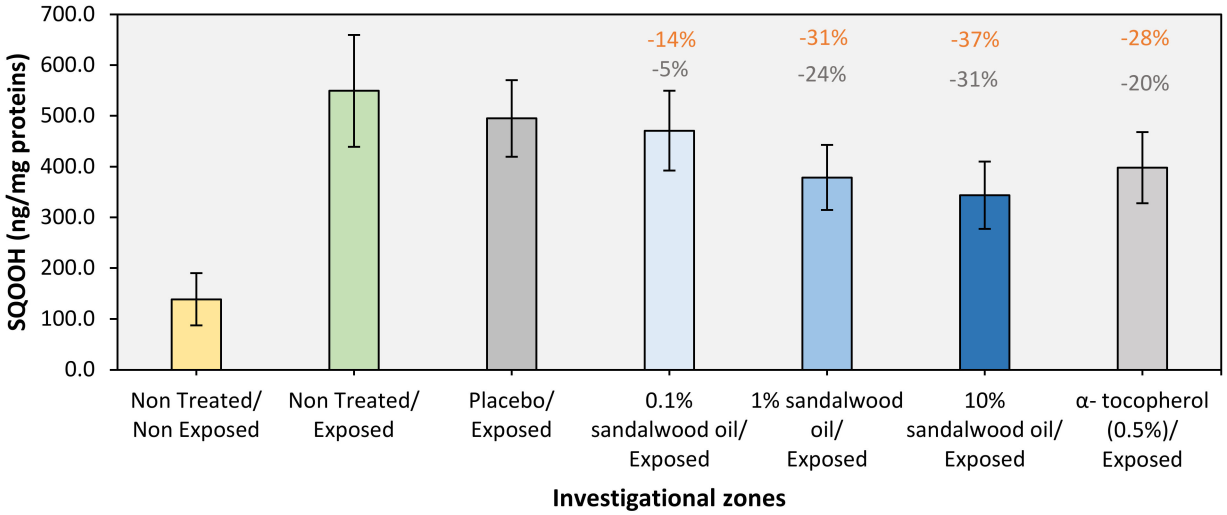

Figure 2. The level of SQOOH (ng/mg proteins) collected on each zone. The error bars represent 95% confidence intervals (CI). The percentage variation w.r.t to the exposed vehicle control is denoted in gray. The percentage variation w.r.t to the nontreated and exposed control is denoted in orange.

Zone comparison also revealed significant differences when the nontreated exposed zone was compared to the 1% and 10% sandalwood and the 0.5% α-tocopherol (Table 4). A significant decrease was obtained for the 1% and 10% sandalwood and the 0.5% α-tocopherol when compared to the vehicle control. No significant change in the level of SQOOH was reported in the zone treated with the placebo compared to the exposed untreated zone.

Table 4. Selected pairwise comparisons based on SQOOH at D10 (n = 22 subjects).

Investigational Zone (I)	Zone of Comparison (J)	Mean (%) Change	Mean Difference (I-J)	*p*-Value
Nontreated/Exposed	Nontreated/Nonexposed	296	410.706	<0.001
Placebo/Exposed	Nontreated/Exposed	−10	−54.332	0.586
α-Tocopherol (0.5%)/Exposed		−28	−151.234	<0.001
0.1% Sandalwood oil/Exposed		−14	−78.658	0.158
1% Sandalwood oil/Exposed		−31	−170.713	<0.001
10% Sandalwood oil/Exposed		−37	−205.803	<0.001
0.1% Sandalwood oil/Exposed	Placebo/Exposed	−5	−24.326	0.986
1% Sandalwood oil/Exposed		−24	−116.381	0.005
10% Sandalwood oil/Exposed		−31	−151.470	<0.001
1% Sandalwood oil/Exposed	0.1% Sandalwood oil/Exposed	−20	−92.055	0.055
10% Sandalwood oil/Exposed	1% Sandalwood oil/Exposed	−9	−35.089	0.918

4. Discussion

It is well documented that pollutants negatively impact the skin, leading to a variety of drawbacks such as hyperpigmentation, extrinsic ageing, increased skin roughness and

the disruption of the skin barrier function [17]. Therefore, cosmetic products for the skin are engineered to possess properties capable of counteracting the effects of pollutants and other environmental exposomes. Here, the protective effect of different concentrations of Indian sandalwood oil was evaluated against a placebo and a positive control (α-tocopherol) by monitoring the level of squalene in its oxidized form. Reminiscent to previously published data, the induction of SQOOH reported in the zones exposed to the real-life conditions of the exposome compared to the nonexposed zones indicated that ambient dust and blue light is capable of inducing a rise in the oxidation levels basally [17].

This clinical study confirms the benefits of Indian sandalwood oil on human subjects. The investigation began with the analysis of Indian sandalwood oil in vitro and ex vivo using human skin explants [12]. In order to confirm these previous findings, we attempted to explore the impact of Indian sandalwood oil in vivo in this study. The gap between the lab environment and clinical trials is ever so present in the preclinical and clinical spheres. Indeed, about 30% of topical drugs fail in human clinical trials due to adverse reactions, despite promising preclinical studies, and another 60% fail due to a lack of efficacy [18]. This is the first study that put forth the positive effects of sandalwood oil against key environmental stressors in simple models, such as in vitro and ex vivo models, all the way up to more complex models, such as in vivo clinical trials, on human test subjects. This, in turn, attests to the robustness of this study.

Thus, we have taken the step to fill a scientific gap, as no previous in vivo studies have explored the potential of Indian sandalwood oil against the combined effects of blue light at a wavelength of 412 nm and pollution. The dose-dependent nature of these in vivo findings calls to the high repeatability of the effect of the oil.

Squalene is an intermediate in the cholesterol biosynthesis pathway [19] and is the main component of skin surface polyunsaturated lipids, where it acts as an emollient and antioxidant [20]. Being highly sensitive towards these reactive oxygen species (ROS) makes them capable of functioning as a quencher of free oxygen radicals, which leads to the formation of different peroxidized byproducts such as squalene monohydroperoxides (SQOOH). Indeed, this antioxidant property of squalene has been previously reported in vitro, whereby it was reported to effectively scavenge ROS as a result of stress such as sunlight exposure. Its ability to quench singlet oxygen also prevents corresponding lipid peroxidation at the level of the skin surface [19]. In this connection, the evaluation of SQOOH was chosen as a suitable endpoint to draw sufficient conclusions pertaining to the protective effect of Indian sandalwood oil.

To date, there has been a lack of research on the effects of particulate matter such as ambient dust on the skin. A previous study has shown the impact of ambient dust on ex vivo and in vitro models [21], but the effect of particulate pollutants in in vivo human models remain largely unexplored. A standardized method (CPES) to substantiate the efficacy of antipollution products on the skin was utilized. The CPES allows for the exposure of ambient dust particles to healthy volunteers in vivo in a controlled environment [17] The dust particles are constantly vaporized onto the skin using an aerosol generator which mimics a real-life scenario. Together with an exposure to blue light at 412 nm, this clinical trial accurately depicted a realistic occurrence of being in contact with these two environmental stressors.

Alpha-tocopherol (α-tocopherol) used at 0.5% is a known antioxidant found in cosmetic products which has been used in this study as positive control [22]. The antioxidant ability of α-tocopherol stems from its ability to react with peroxyl radicals and singlet oxygens which favor lipid peroxidation [23]. Thus, by extension, it is capable of decreasing the amount of SQOOH produced compared to the vehicle study. Since no changes were reported in the levels of SQOOH between the exposed vehicle treated zone and the exposed untreated zone, it was implied that the protective activity exhibited by the sandalwood oil on the other treated zones were not due to mechanical or optical influence.

This study also highlighted that 10% and 1% of the sandalwood oil formulation both displayed better protective efficacy against the environmental exposomes when compared

to the 0.5% of α-tocopherol. This in vivo study confirmed for the first time the superior protective effect of the sandalwood oil formulations against the oxidative stress induced by environmental stressors or the exposome.

This investigation was assessed using sandalwood oil naturally produced and distilled from Indian sandalwood grown in a sustainable manner under strict monitoring in plantations. The resulting test oil is recognized as a complex blend of naturally sourced molecules exhibiting chirality. Indian sandalwood oil is an ideal natural product for use as an active cosmetic ingredient as readily defined by ISO 3518 and the British Pharmacopoeia [24]. The experimental group was also conscious of the sustainability of the materials used in the test and the ongoing sustainability of the supply. The recent availability of Indian sandalwood was from reputable suppliers who grew the product sustainably in Northern Australia, controlled the quality of the product and the absence of pesticide and herbicide residues. The protective efficacy observed against different environmental exposomes was attributed to the whole oil and the complex nature of the botanical substance. It is important to recognize that the result was obtained is from the whole oil and not a particular isolate or part of the oil. As a result, the test material needed to be complete and free from any constituents that may have been added after extraction. The suppliers' end-to-end chain of custody was able to guarantee this.

Indian sandalwood oil has shown the ability to protect the skin and act as an extracellular and intracellular buffer against oxidative stress. Indeed, through the in vitro and ex vivo data previously reported, and the current in vivo data, Indian sandalwood oil showed significant antioxidant and antiaging properties against the environmental exposome, as well as the ability to decrease the level of SQOOH, which offered added protection to the skin barrier. Thus, Indian sandalwood oil was capable of exerting a protecting effect across all layers of the skin.

Cosmetic ingredients are known to act as a barrier by limiting the contact time between the skin and the exposome, or by triggering intracellular or extracellular biochemical processes that slow the formation of primary oxidative products. In this connection, an ideal cosmetic formulation would possess both of these aforementioned properties [7]. These clinical and previous in vitro and ex vivo findings strongly support that Indian sandalwood oil possess both the desired characteristics in improving the overall defenses of the skin.

5. Conclusions

The study aimed at evaluating the protective effect of a cosmetic product containing Indian sandalwood oil against cutaneous oxidative stress induced by particulate matter (ambient dust, NIST SRM 1649b) and blue light at a wavelength of 412 nm. These results suggests that Indian sandalwood oil at a concentration between 1% and 10% protects the skin against the oxidative stress induced by ambient dust and blue light exposure. These results also confirm our previous studies, whereby sandalwood oil was reported to protect against oxidative stress in vitro. This effect in vivo appears as numerically superior to the protective effect seen with 0.5% α-tocopherol.

Author Contributions: Conceptualization, P.A., V.F.N., D.H. and A.B.; methodology, V.L.K., V.F.N. and A.B.; formal analysis, M.H., B.N.S. and A.M.; investigation, V.L.K., E.G.P., V.S. and G.P.; resources, V.L.K., V.F.N. and D.H.; data curation, M.H. and B.N.S.; writing—original draft preparation, M.B.M.; writing—review and editing, M.B.M. and V.F.N.; supervision, V.F.N.; project administration, V.L.K.; funding acquisition, V.L.K. and D.H. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Quintis Sandalwood Pty Ltd. (West Perth, Australia), funding both the study and providing the test material.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki and OECD Good laboratory Practices (GLP). This study was submitted to the Fortis-Darné Clinique Independent Ethics Committee (IEC) with the study code 2021CMCL059 and was approved on 29 January 2021.

Informed Consent Statement: Consent was acquired from the surgical patients.

Data Availability Statement: The data presented in this study are available on request from the corresponding authors. The data are not publicly available due to privacy reasons.

Acknowledgments: Authors acknowledge Bill Harrison and Vanessa Ligovich of Quintis Sandalwood Pty Ltd. (West Perth, Australia) for their critical and valuable input.

Conflicts of Interest: The authors declare no conflict of interest.

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