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Oral Supplementation with *Rosa damascena* Extract Improves Skin Antioxidant Status: Exploratory Clinical Studies

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Abstract

Rosa damascena has long been cultivated for its essential oil and consumed as an edible flower. It is a rich source of phytochemicals including phenolic acids and flavonoids exhibiting strong antioxidant properties, making it a promising candidate for mitigating the adverse effects of exposome-related oxidative stress. This study evaluated the antioxidant potential of dietary supplementation with an upcycled *Rosa damascena* extract (RE) derived from a by-product of fresh rose hydrodistillation, used alone or in combination. Its composition and antioxidant activity were assessed using the Folin-Ciocalteu assay, HPLC methods and the total antioxidant power assay both *in vitro* (PAOT Liquid®) and *in vivo* (PAOT Skin®). Two exploratory clinical studies were conducted: in study 1, volunteers received a single oral dose of 40 or 140 mg of RE; in study 2, volunteers took a blend of RE and melon concentrate, standardized in Superoxide Dismutase, daily for 8 weeks. Both the single oral dose of RE and the 8-week daily supplementation with the combined formulation significantly improved skin antioxidant status. These findings suggest that RE, either alone or in combination, offers a promising strategy for protecting the skin against oxidative stress and preventing its associated consequences.

Keywords

Antioxidants, Food Supplement, Polyphenols, *Rosa damascena*, Superoxyde Dismutase, Skin Protection

1. Introduction

The skin is the largest human body organ, accounting for approximately 15% of the total body weight. It is a complex, flexible, and resistant tissue that serves as the body's external protective barrier. The skin barrier plays several critical roles, including protecting against external agents and maintaining homeostasis [1] [2].

Oxidative stress refers to an imbalance between the production of free radicals, particularly reactive oxygen species (ROS), and the body's capacity to neutralize them using antioxidants. This imbalance leads to cellular damage, affecting lipids, proteins and DNA [3]. In the skin, oxidative stress accelerates skin aging by degrading collagen and elastin, two essential proteins for firmness and elasticity [4] [5]. Oxidative stress also promotes the appearance of wrinkles, pigmented areas, and the loss of natural radiance. Furthermore, it compromises the skin barrier, leading to increased dryness, dullness, and a higher susceptibility to inflammation and blemishes, ultimately diminishing the skin's vitality and youthful appearance [6]-[8].

Antioxidant properties of plant-based dietary supplements have been researched for their role in neutralizing free radicals. They prevent cellular damage and support body defenses and well aging. More recent studies have highlighted the benefits of antioxidant supplementation for improving skin elasticity, reducing fine lines and wrinkles, and restoring a radiant, even skin tone [9] [10]. Research on supplementation with specific plant-based ingredients is a new approach for maintaining and even improving skin condition. Indeed, while cosmetic and topical products are extensively used by consumers, food supplements represent another complementary way to maintain skin health and beauty from within with a more global approach.

Roses are widely recognized for their longstanding applications in traditional uses. Derivative products such as essential oil, concrete, absolute, and rose water are widely employed in perfumery, pharmaceuticals, and the food industry for their fragrant, gustatory, and health-enhancing properties [11]. Moreover, rose petals are edible and have long been used in the preparation of jams, teas, cakes, flavorings, and candies in various cultures. Among rose species, the damask rose (*Rosa damascena* Mill.), often referred to as the "Queen of Flowers", is one of the most important members of the *Rosaceae* family, with a long history of global consumption. The abundance of phytochemicals—particularly phenolic compounds and flavonoids—makes rose flowers a highly bioactive ingredient. Traditionally, damask roses have been used to treat inflammation, depression, cough, fever, and hypertension. It is also employed in the management of skin diseases, allergies, and conjunctivitis, and is known for its tonic and astringent effects on the skin's capillaries [12] [13].

The leading producers of rose essential oil—Bulgaria, Turkey, and Iran—account for more than 90% of global production, reflecting deep-rooted expertise and specialized cultivation techniques in these regions. Their know-how in producing high quality rose essential oil and rose water has solidified their dominance in the industry, highlighting both the commercial importance of *Rosa damascena* and its profound cultural value in traditional medicine [14] [15]. While essential oil and rose water are the primary products, rose hydrodistillation generates tons of wastewater every year. This non-distillated by-product is usually discarded although rich in highly valuable active polar phenolic compounds [16].

To valorize this underutilized resource, a novel *Rosa damascena* extract (RE) was developed from hydrodistillation wastewater. It harnesses its bioactive potential for the cosmetics and nutraceutical industries and allows a reduction of the environmental impact. RE contains high levels of bioactive compounds, including polyphenols particularly flavonoids and phenolic acids, all known for their strong antioxidant and anti-inflammatory properties [11] [15] [17]-[21]. To enhance its efficacy, RE was combined with a specific melon concentrate rich in superoxide dismutase (SOD) and an extract of *Malpighia glabra*, commonly known as acerola, a natural source of vitamin C. This formulation, named Rose Extract Melon Concentrate (REMC), aims to provide a synergistic approach to skin health. Oral supplementation with melon concentrate has been shown to increase endogenous antioxidant defenses and reduce oxidative stress [22]-[25]. A clinical study indicated that daily supplementation with melon concentrate, standardized to provide 280 U of SOD, enhanced skin protection by reducing the oxidative load and protecting against the damages caused by free radicals [25]. Vitamin C is well known for its role in skin health thanks to its potent antioxidant properties and its ability to stimulate collagen synthesis. It protects the skin from environmental damage and supports the skin's natural repair mechanisms [19] [26] [27]. In the REMC formulation, the combined mechanisms of RE, SOD-rich melon concentrate, and vitamin C offer a comprehensive strategy to enhance skin resilience and provide protection from environmental damage to prevent premature aging.

This study investigated the potential benefits of RE, administered either alone or as part of the REMC formulation, for improving skin health and mitigating oxidative stress. First, the composition of RE and REMC was analyzed using the Folin-Ciocalteu assay and High-Performance Liquid Chromatography (HPLC), and their antioxidant capacities were assessed *in vitro* using Pouvoir AntiOxidant Total (PAOT) Liquid® technology [28]. Then, two exploratory clinical studies were conducted. A first clinical study evaluated the antioxidant effect of a single administration of RE at two doses on the skin. In a second 8-week randomized clinical study, the antioxidant effect of REMC daily supplementation was measured versus placebo. In both studies, the assessment of the oxidative state of the skin was carried out using PAOT Skin® Technology, enabling precise and direct assessment of skin oxidation level and underlying the benefits of RE and REMC [29]-[31].

2. Materials and Methods

2.1. Chemicals and Reagent

Folin-Ciocalteu's phenol reagent, 3,4,5-trihydroxybenzoic acid (Gallic acid) were purchased from Merck (Darmstadt, Germany). All HPLC-MS grade solvent (Acetonitrile, water and formic acid) and anhydrous disodium carbonate were purchased from CARLO ERBA Reagents (Val de Reuil, France). Electrocardiogram conductive gel was provided by Dermedics (Veauche, France).

2.2. Plant Material and Extraction

In this research work, *Rosa damascena* extract (RE) was the main active ingredient. This upcycled ingredient is a fresh rose flower water extract. It's a non-distillated by-product of the hydrodistillation of fresh *Rosa damascena* petals according to the patent N˚ PCT/EP2024/059606_FR2307532. A composition combining this RE with melon concentrate rich in SOD (Robertet, Grasse, France) and acerola, referred to as REMC was formulated. Detailed information about the antioxidant content of this melon concentrate has been previously published [32]. In this study, it contains 14 U SOD/mg powder (280 U of SOD in 300 mg of REMC) measured according to the method of Zhou and Prognon [33]. Dehydrated juice from Acerola (*Malpighia glabra* L.) was used in powder form.

2.3. Physicochemical Characterization

2.3.1. Total Phenolic Compounds (TPC)

The determination of total polyphenols was carried out according to the Folin-Ciocalteu method. Briefly, samples were prepared at 0.5 g/L in distillated water and centrifugated. Then, 5 mL of the diluted sample were mixed with 37.5 mL of distillated water, 1.5 mL of Folin-Ciocalteu reagent and 1.5 mL of saturated disodium carbonate 30% (w/v) solution and incubated for 1 hour. The absorbance of the mixture was measured at 675 nm using a Spectrophotometer UV-Vis Perkin-Elmer Lambda 20 against a blank of 1.5 mL of Folin-Ciocalteu reagent and 1.5 mL of saturated disodium carbonate 30% (w/v) solution in 42.5 mL distillated water. The polyphenol concentrations were calculated from a calibration curve established with standard solutions of Gallic acid (concentration ranging from 0 to 20 mg/mL). Results were expressed as mg Gallic acid equivalents per gram of dry sample (mg GAE/g), thus providing a quantitative measure of the polyphenol content in the sample.

2.3.2. HPLC-DAD-ELSD-MS Analysis

The phenolic compounds of RE were also characterized by High-Performance Liquid Chromatography (HPLC) analysis coupled with diode detection (DAD), Evaporative light scattering detector (ELSD) and electrospray ionization mass spectrometry (MS-ESI) in positive and negative modes. The analysis was carried out on an Agilent Poroshell 120 S-C18 column (4.6 × 150 mm × 2.7 µm) with a mobile phase composed of water (A) and acetonitrile (B) containing both 0.15% formic acid, at a flow rate of 1 mL/min. The elution program includes an isocratic phase at 5% B (0 - 5 min), followed by a linear gradient up to 60% B (5 - 35 min), then 60% to 85% B (35 - 50 min) and finally 85% to 95% B (50 - 55 min). The system remains in an isocratic phase at 95% B for up to 60 min. System delay volume is 1.04 ml. The column is maintained at 30˚C and 20 µL of a 1% (w/w) rose extract solution in MeOH/water (1/9 w/w) is injected. The compounds were identified by comparing retention times as well as UV spectra, obtained at 280 and 330 nm with a DAD detection, and mass spectra with the one of pure molecules. Mass spectra were acquired by performing MS-ESI detection with a scan of m/z from 100 to 1000 under the specified conditions: drying gas temperature at 3550˚C and flow at 10.0 L/min, nebulization pressure at 50 psi, and capillary voltage at 3000 V.

2.3.3. Total Antioxidant Power Measurement (PAOT® Score)

The PAOT Liquid® Technology is a patented technology (WO 2020/109736A1) allowing total antioxidant capacity determination in various matrices, such as raw materials and processed food products, cosmetic and medicinal preparations, biological fluids or plant extract [28] [34]. To evaluate RE and REMC antioxidant effectiveness, 1 g of extract was used in each PAOT Liquid® measurement. Two microelectrodes, the working and the reference electrode, were used to record the electrochemical changes following addition of extracts. These variations are triggered by changes in the concentrations of oxidized/reduced forms of a molecule in a state of free radicals called mediator (M•) in the presence of antioxidants. The PAOT Liquid® activity was estimated by measuring a decrease in the solution electrochemical potential and a PAOT Liquid® score was determined. Thus, PAOT Liquid® technology is suitable for assessing non-enzymatic antioxidants, but because it relies on chemical redox reactions, it seems not appropriate for measuring enzymatic antioxidants such as SOD.

2.4. Exploratory Clinical Studies

2.4.1. Subjects Consent

For each study, the trial objectives, study design, risks, and benefits were explained to the subjects. The study was authorized by "Comité de Protection des Personnes of CHU Liège" under N˚ 177/2021. The study was conducted in accordance with the 1964 Declaration of Helsinki and the European guidelines for good clinical practice. Before inclusion in the study, subjects received an information sheet and an informed consent form. The investigator explained the study procedures and allowed ample time for subjects to decide before collecting the signed consent forms. Subjects were informed of their right to withdraw from the study at any time. Written informed consent was obtained from all subjects.

2.4.2. Subjects and Eligibility Criteria

Both exploratory studies had the same inclusion and exclusion criteria. The inclusion criteria required subjects to be healthy women between 40 - 60 years old, non-smokers or occasional smokers. The subjects provided written informed consent, agreeing to follow specific study requirements to limit potential bias in the analysis. These included avoiding medications, dietary supplements, and topical products on the forearms before and during the study, as well as ensuring they were not fatigued or recently tanned. In the first study, a maximum baseline PAOT Skin® score ≤ 40 was also part of the selection criteria to ensure similar antioxidant status between groups.

According to literature [30], the distribution of PAOT Skin® Scores among the population of 263 healthy volunteers followed a typical Gaussian curve. A mean value of 31.09 with 16.25 as standard deviation (SD) were found. Due to normal distribution, we could apply the formula Mean value $\pm 1.96 \times SD$ which allowed to determine normal reference values for PAOT skin® Score ranging from 0 to 62.94. The PAOT skin® score is inversely proportional to oxidative stress status.

For both studies, the exclusion criteria were: having taken a nutritional supplement and/or medication during the last month preceding the start of the study (*i.e.* analgesic, anti-inflammatory, antibiotic), having used any product with anti-aging/wrinkle or antioxidant action in addition to the consumption of any fruit/fruit juice or alcohol in the 24 hours preceding the start of the study, or to have allergies, scars or sunburn. To be a postmenopausal, pregnant and/or breast-feeding woman, with systemic diseases or dermatological diseases, medical treatment, or medical or surgical history that could affect and compromise the result of the study were also exclusion criteria. Both studies were conducted double blind.

2.4.3. Protocol Details and Study Organization

Following the evaluation of the antioxidant effectiveness of RE and REMC using PAOT Liquid® Technology, two double-blind, randomized exploratory clinical studies were conducted. The main objective of the first exploratory clinical study (study 1) was to evaluate and compare the bioavailability and antioxidant effectiveness of two doses of RE following a single oral intake. In contrast, the second exploratory study (study 2) involved an 8-week daily supplementation period, comparing a formulation containing REMC to a placebo.

1) Single intake supplementation: Study 1

In study 1, two quantities of RE were tested: 40 mg for RE1 and 140 mg for RE2, respectively. At T0, a PAOT skin® measurement was performed on the forearm of all 36 subjects. They were then randomized into two groups of 18 subjects to receive a single oral administration of either RE1 or RE2 (**Figure 1**). Additional PAOT skin® measurements were performed at 2 hours, 4 hours, 6 hours and 8 hours after RE supplementation. For this study, the dosage was one capsule taken with a glass of water immediately after the T0 measurement. After the measurement taken 4 hours after supplementation, a standardized meal was provided to subjects.

2) Two months Supplementation Trial: Study 2

In study 2, subjects were randomly assigned to two groups of 20 individuals each. Subjects took either a placebo or REMC supplement daily (one capsule before breakfast) over an 8-week period. The REMC formulation was composed of 140 mg RE, 140mg of acerola extract and 20 mg of melon concentrate, corresponding to 280 U of SOD. REMC was standardized in polyphenols (>24 mg) and vitamin C (>12 mg). PAOT skin® measurements were conducted in both groups at baseline (W0), Week 4 (W4) and Week 8 (W8). Subjects took their supplement under usual condition in the morning prior to the measurements. The schematic design of the clinical study is illustrated in Figure 1.

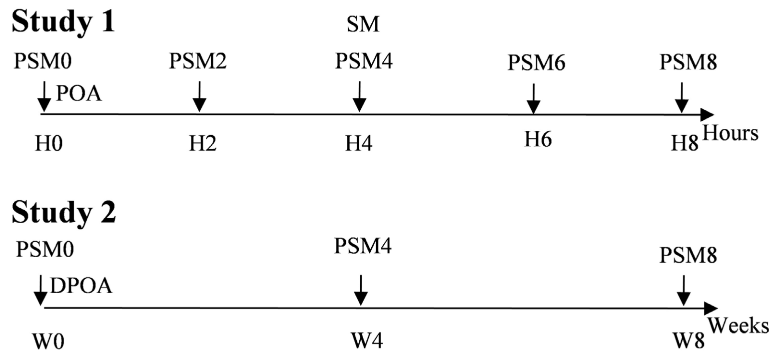

Figure 1. Schematic representation of clinical study designs. Study 1: H: Hours post oral administration; POA: Product Oral Administration; PSM: PAOT skin® measurements; SM: Standardized Meal. Study 2: W: Weeks of daily oral supplementation; DPOA: Daily Product Oral Administration; PSM: PAOT Skin® Measurements.

2.4.4. Skin Antioxidant Activity Measurements

The PAOT Skin® measurements were analyzed using the method described in literature [29]-[31], which employs a patch system (gel mediator) involving an electron giver (antioxidant) and acceptor (oxidant). Prior to analysis, the skin of subjects was meticulously cleaned and dried using absorbent paper. This patch was applied to specified areas of the skin, ensuring secure connections to both working and reference microelectrodes attached to the forearms. Over a 10-minute period, the shift in electrochemical potential within the gel mixture was recorded to estimate the Skin Oxidative Stress Status (SOSS). This shift reflects interactions between the oxidized and reduced forms of the gel mediator with skin antioxidants and oxidants, respectively. Results were calculated using the following formula:

$$\text{Antioxidant Efficiency (\%)} = ((\text{PAOT}_{tn} - \text{PAOT}_{t0})/\text{PAOT}_{t0}) \times 100$$

where PAOT_{tn}: Total antioxidant Power of skin at tn of supplements intakes, PAOT_{t0}: Total antioxidant Power of skin at baseline (before supplements intakes).

PAOT Skin® measures the total antioxidant activity of the skin, indicating the effectiveness of a product in reducing skin oxidative stress. This method effectively validates the bioavailability and the biological activity of the active ingredients present in the formulation. For the daily kinetics, the maximum antioxidant efficiency value was selected for each participant. Since individual responses vary, each participant may reach peak antioxidant efficiency at different rates and time following supplementation. This variation depends on pharmacokinetics which defines how a live organism affects the absorption, distribution, metabolism and excretion of active molecules [35].

2.4.5. Descriptive Analysis

A descriptive analysis was performed on the demographic data and the assessments data. Quantitative variables were evaluated by calculating the mean antioxidant efficiency, the standard deviation, the standard error of mean (SEM).

2.4.6. Statistical Analysis

In the first clinical study, maximum antioxidant efficiency was compared to the T0 in both RE1 and RE2 groups. In the second study, antioxidant efficiency was measured at week 4 and week 8. The results were compared with the T0 and intergroup comparisons were made versus placebo group. To assess product efficiency, one-factor ANOVA was employed for each group in study 1 and Wilcoxon and Mann-Whitney tests were used for intragroup comparison and to compare REMC to placebo at T4 and T8. Statistical analyses were conducted with Excel and Prism software with a significant threshold set at 5% and results expressed as means of values.

3. Results

3.1. Phytochemical Composition and Antioxidant Activity

The TPC of RE and REMC has been evaluated by Folin-Ciocalteu method (Table 1) and accounted for about one-seventh of the dry extract. RE contained a higher level of total phenolics than REMC with respectively 148 mg GAE/g and 129 mg GAE/g highlighting the importance of RE's polyphenols in REMC.

HPLC-DAD-ELSD-MS analysis of RE has led to the identification of 19 compounds including flavonoids and phenolic acids as summarized in Table 2. Among them, 13 flavonols namely glycosides of kaempferol and quercetin and their aglycones, were identified. Beside flavonols, RE also contained organic acids such as quinic acid and phenolic acids mainly derived from gallic acid and ellagic acid.

REMC composition was very close to RE except for the presence of ascorbic acid due to the addition of acerola. The amount of the main phenolic compounds of RE and the REMC formulation has been evaluated by HPLC-DAD as shown in Table 1.

Table 1. Phenolic contents of RE and REMC formulation by Folin Ciocalteu (FC) and HPLC methods and antioxidant capacity obtained via the PAOT Liquid® Technology.

	Extract	
	RE	REMC
Total phenolic content (mg GAE/g DW)[a]	148	129
Phenolic compounds amount (mg/g DW)[b]		
Gallic acid	44	21
Ellagic acid	10	6
Astragalin	6	3
Ascorbic acid content	-	53
PAOT Liquid® Scores (unit ×10/g)	3551.46	2943.45

[a]mg gallic acid equivalent per gram of dried extract determined by Folin Ciocalteu method.
[b]mg per gram of dried extract determined by HPLC-DAD method.

Table 2. Compounds identified by HPLC-DAD-ELSD-MS in Rose Extract (RE). MW: molecular weight; Rt: retention time.

Peak no.	Rt (min)	MW	Identified compounds	Synonym	CAS no.
1	1.63	192	Quinic acid		77-95-2
2	3.45	170	3,4,5-Trihydroxybenzoic acid	Gallic acid	149-91-7
3	7.01	154	3,4-Dihydroxybenzoic acid	Protocatechuic acid	99-50-3
4	15.37	284	2-Phenylethyl-glucoside		18997-54-1
5	16.55	610	Quercetin-3-O-rutinoside	Rutin	153-18-4
6	16.69	302	Ellagic acid		476-66-4
7	17.02	464	Quercetin-3-O-galactoside	Hyperoside	482-36-0
8	17.09	464	Quercetin-3-O-glucoside	Isoquercitrin	482-35-9
9	17.74	594	Kaempferol-3-O-rutinoside	Nicotiflorin	17650-84-9
10	17.89	448	Kaempferol-7-O-glucoside	Populnin	16290-07-6
11	18.33	448	Kaempferol-3-O-glucoside	Astragalin	480-10-4
12	18.46	448	Quercetin-3-O-rhamnoside	Quercitrin	522-12-3
13	19.11	436	2-phenylethanol-O-(6-O-galloyl) glucoside		1007865-86-2
14	19.12	418	Kaempferol-3-O-arabinoside	Juglalin	99882-10-7
15	19.27	594	Kaempferol-3-O-glucosylrhamnoside	Multiflorin B	52657-01-9
16	19.94	432	Kaempferol-3-O-rhamnoside	Afzelin	482-39-3
17	22.28	617	Kaempferol-3-O-(6”-O-trans-p-coumaroyl) glucoside	Tiliroside	20316-62-5
18	22.46	302	Quercetin		117-39-5
19	25.20	286	Kaempferol		520-18-3

Results showed that phenolic acids concentration was significantly higher than that of flavonoid derivatives. Gallic acid, in particular, seems to be the most abundant phenolic compound in RE with 44 mg/g DW followed by ellagic acid with 10 mg/g DW. Among the flavonols, astragalin (Kaempferol-3-O-glucoside) was predominant in RE and REMC with 6 mg/g and 3 mg/g DW respectively.

The analytical study of RE and REMC has shown a relatively high amount of phenolics known for their antioxidant capacity. This was assessed *in vitro* by the PAOT Liquid® test (Table 1). Products with a PAOT Liquid® score higher than 1000 are considered to have very effective antioxidant efficacy. RE and REMC have shown very high antioxidant levels almost 3 times higher than the upper limit of the PAOT Liquid® scale. As for the previous dosage of phenolic content, RE, in particular, had a very high PAOT Liquid Score® (3551.46 ± 150.5). Both showing promising *in vitro* antioxidant activities, formulations containing *Rosa damascena* were incorporated into oral supplements aimed at improving skin health and combating oxidative stress and were tested on human subjects.

3.2. Evaluation of Oxidative Stress Level

3.2.1. Study of Antioxidant Efficiency of RE: Single Intake Supplementation

Thirty-six subjects aged between 44 and 60 years (mean 49.4) were recruited and randomly assigned into two groups of 18 subjects. As shown in Figure 2, the RE1 group achieved a significant increase of 27.1% in maximum antioxidant efficacy relative to baseline (p-values ≤ 0.01). The group supplemented with RE2 exhibited a significant increase in maximum antioxidant efficiency, reaching 74.0% (p-values ≤ 0.01) after a single intake compared to baseline. These findings indicate that a low dose of RE (40 mg) has already a significant antioxidant efficacy while a higher dose of RE (140 mg) induces a greater antioxidant efficacy than a lower dose. The difference between the two doses was approaching significance with p-value = 0.078.

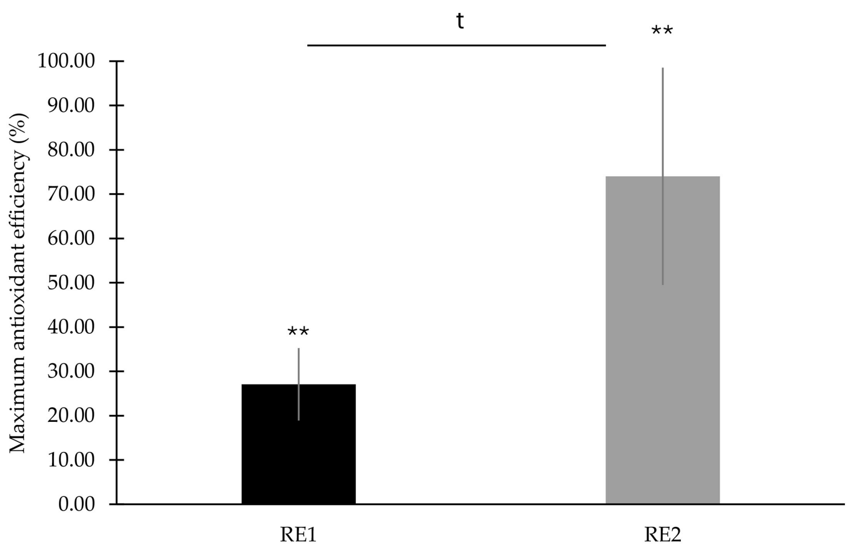

Figure 2. Influence of RE at two doses on maximum antioxidant efficiency. The results are expressed in maximum antioxidant efficiency (%) as mean ± SEM. Antioxidant Efficiency (%) = $((PAOT_{tn} - PAOT_{t0})/PAOT_{t0}) \times 100$, **p-values < 0.01 compared to the time 0, t p-value < 0.1 compared with RE1.

3.2.2. Evolution of Antioxidant Efficiency during an Eight-Week Supplementation

Forty subjects aged between 40 and 60 years (mean 51.4) were recruited and randomly assigned into two groups of 20 subjects.

Antioxidant efficiency is represented in Figure 3. After 4 weeks of supplementation, the REMC group exhibited a 137.4% significant increase ($p < 0.0001$) in antioxidant efficiency (versus baseline), compared to a 29.1% non-significant increase in the placebo group. After 8 weeks of daily supplementation, the REMC group maintained a significant positive antioxidant response throughout the study with a 91.4% significant increase in antioxidant efficiency versus baseline. In contrast, the placebo group showed a 7.2% non-significant antioxidant efficiency versus baseline over the same period. At both time points, REMC demonstrated significantly greater antioxidant efficiency compared to the placebo.

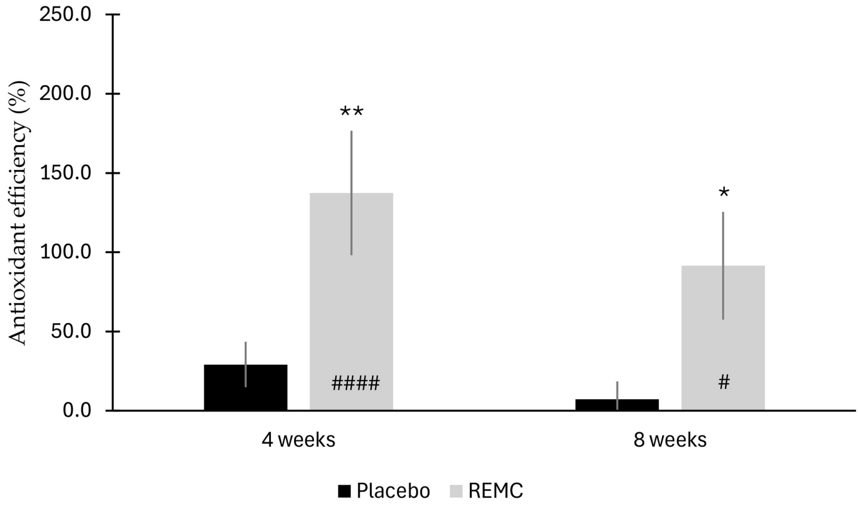

Figure 3. Antioxidant efficiency of REMC and placebo after 4 and 8 weeks of supplementation. The results are expressed in antioxidant efficiency (%) as mean ± SEM. Antioxidant Efficiency (%) = $((PAOT_{tn} - PAOT_{t0})/PAOT_{t0}) \times 100$, ####p-values ≤ 0.0001 and #p-values ≤ 0.05 compared to the time 0, **p-values ≤ 0.01 and *p-values ≤ 0.05 compared to the placebo group.

4. Discussion

This study first assessed the phytochemical composition of RE and REMC by evaluating the TPC by UV-vis spectrophotometry, identifying and quantifying molecules by HPLC. The TPC of RE and REMC results highlight that RE seems to be the main source of polyphenol in REMC. RE and REMC contain a relatively high amount of total phenolics and the dosages of the present study are in concordance with Sabahi and al, 2020 and Dina and al, 2021 [36] [37], where wastewater of *Rosa damascena*, shown a TPC of 167.76 ± 0.29 mg GAE/g of extract and 170.0 mg GAE/g of extract respectively. Liu *et al.* (2020) [38] studied the *Rosa damascena* pulverized flower residue (DRFR) extracted three times with water (10 min each time) by using smashing tissue extraction at room temperature. DRFR TPC was quantified 386.4 ± 6.5 mg GAE/g meaning that other by-products of Rose hydro-distillation could also be valuable [39].

According to literature, *Rosa damascena* primarily contains flavonol glycosides, especially glycosylated derivatives of quercetin (notably hyperoside, isoquercitrin, rutin, quercitrin) and kaempferol (mainly nicotiflorin, afzelin, astragalin, and trifolin) [14]-[16] [18]. Additionally, phenolic acids, primarily gallic acid, as well as some gallotannins, ellagic acid derivatives, phenylethyl alcohol derivatives, and anthocyanins are present, contributing significatively to the extract's antioxidant and anti-inflammatory properties [37] [38] [40]-[42]. HPLC-DAD-ELSD-MS results in **Table 1** corroborate with previous reports on *Rosa damascena* wastewater [15] [16] [37] [43] and other rose by-product extracts [14] [18] [38]. The composition of RE was especially similar to wastewater of *Rosa damascena* from Bulgaria, as described by Solimine *et al.* 2016 [16]. However, one flavonol, namely Kaempferol-7-glucoside (Populnin), seems to be identified here for the first time in rose wastewater. Gallic acid has not been identified in Solimine *et al.* 2016 study of the Bulgarian *Rosa damascena* wastewater although its composition was very similar to RE [16]. Nevertheless, Osman *et al.* 2023 [43] reported the presence of gallic acid in wastewater and Rusanov *et al.* 2014 and Solimine *et al.* 2016 noted the presence of ellagic acid in this by-product [15] [16]. The predominance of gallic acid in *Rosa damascena* extracts has been reported by some authors [41] [44]. Mohsen *et al.* 2020 also reported the preponderance of gallic and ellagic acid in a methanol extract of Egyptian *Rosa damascena* [45]. Furthermore, ellagic acid was identified in rose wastewater, along with kaempferol and quercetin, as tyrosinase inhibitor *in vitro* [16]. Glycoside of kaempferol has been identified by many authors in rose wastewater [15] [16] [37] and other rose by-product extracts [18] [38]. Schieber *et al.* also found that astragalin was the most abundant flavonol quantified in an acetone/water extract of distilled rose petals with a similar amount than in RE (4.1 mg/g). Furthermore, a study of 24 Iranian *Rosa damascena* genotype revealed that astragalin (6.1 - 12.9 mg/g DW) was among the main flavonoids along with isoquercitin and quercetin 7-(6"-galloylglucoside) in methanolic extracts of dried petals [40].

Many authors acknowledged the *in vitro* antioxidant capacity of rose byproducts including wastewater and other extracts, but the comparison of results is hazardous in reason of the different methods and units used [14] [37] [38] [43]. PAOT Liquid® was used in this study because it provides a more accurate and comprehensive measurement of antioxidant molecules present in the extract, offering a higher level of precision compared to traditional methods. Unlike conventional tests, PAOT Liquid® considers the nature and specificity of antioxidants, as well as the interaction between the solvent and the extract, ensuring more reliable results. RE and REMC have a PAOT Liquid® score 3 times higher than the upper limit of 1000 of the PAOT Liquid® scale, they are considered to have a very effective antioxidant efficacy. In REMC, both complementary primary antioxidants (SOD) and secondary antioxidants, such as the polyphenols of RE and vitamin C, are associated to potentiate the effect. However, the PAOT Liquid® score of REMC was lower than the one of RE. This is linked to the fact that PAOT Liquid® technology is not adapted to SOD present in REMC as it is an enzymatic antioxidant. In real-life conditions, certain physiological mechanisms in the skin and body can trigger the production of endogenous antioxidants through the stimulation of exogenous antioxidant molecules, via processes such as adaptive oxidative stress or hormesis [30] [31]. To more accurately assess the effectiveness and bioavailability of REMC, an *in vivo* assay considering both primary and secondary antioxidant activity such as PAOT Skin®, was conducted.

The first exploratory clinical study allowed to demonstrate the antioxidant activity and fast bioavailability of RE after only one oral intake. This is consistent with studies from the literature, where *Rosa damascena* extracts have demonstrated antioxidant activity *in vitro* [37] [46]. Besides, a dose effect was observed as the higher dose of 140 mg had a stronger effect than the lower dose of 40 mg. The antioxidant effectiveness of polyphenols on the skin depends on several key factors, including dose, bioavailability, type of polyphenols, and interactions with other compounds [47]. Greater amount of available polyphenols increase the ability to neutralize free radicals [48]. Meanwhile, the concentration of polyphenols in blood after ingestion, directly affects their availability to skin tissues [49]. Higher doses of RE increase blood concentration, thus improving antioxidant effectiveness. In addition, S. Grether-Beck *et al.* 2016 [50] have shown that polyphenols such as lycopene and lutein improve skin parameters like roughness and density. Polyphenols neutralize ROS by direct reactions with free radicals, inhibit or enhance the action of numerous enzymes, and chelate pro-oxidant metal ions. Additionally, they can boost the effectiveness of other antioxidants [51]. Based on these preliminary results and data from the literature, it was hypothesized that combining the highest RE dose (140 mg) with other well-known antioxidants: melon concentrate standardized in SOD and acerola containing vitamin C could enhance antioxidant efficiency.

The second clinical study confirmed the antioxidant efficacy of REMC after 4 and 8 weeks of supplementation. This effect can be attributed to the presence of antioxidant molecules and the complementarity between primary and secondary antioxidants provided by REMC. Non-enzymatic antioxidants, including polyphenols, scavenge free radicals and modulate signaling pathways involved in oxidative stress. In contrast, enzymatic antioxidants, such as SOD, play a crucial role in neutralizing ROS by catalyzing their conversion into less harmful molecules [52] [53]. Vitamin C acts synergistically with these compounds by directly reducing ROS and regenerating other antioxidants, such as vitamin E, thereby reinforcing the overall antioxidant network [54] [55]. Individual variability in antioxidant responses can be influenced by environmental and lifestyle factors, including diet, stress levels, physical activity and overall health status [56] [57]. These variables may modulate the effectiveness of antioxidant supplements over time. These findings align with numerous studies that emphasize the potential of plant natural ingredients in the field of natural care [58]-[61]. Oral administration of REMC offers several advantages over topical administration, including more uniform systemic distribution, which may enhance the effectiveness of active compounds at the skin level.

The approach based on food supplementation of natural ingredients offers an in-depth and efficient way to address skin needs [9] [25] [62]-[65]. The selection of ingredients is not only crucial, but their combination also plays a key role in overall efficacy. In these studies, REMC was demonstrated as an effective antioxidant allowing to reduce skin oxidative stress.

Given the central role of oxidative balance in maintaining skin health, future investigations should aim to explore the broader skin benefits of REMC supplementation. In particular, alternative methods to measure the oxidative status of the skin could be explored. In addition, the bioactive compounds identified in the RE extract, such as ellagic acid, exhibits tyrosinase-inhibiting properties and may contribute to improved pigmentation and overall skin luminosity [16]. Therefore, benefits of the supplementation on skin conditions such as tone, brightness and pigmentation would provide valuable insights into its potential as a holistic approach to skin care.

5. Conclusions

The study emphasized the often-overlooked value of co-products rich in flavonoids and polyphenols obtained from rose hydrodistillation. Upcycling those co-products contributed to both environmental sustainability and the development of innovative nutraceutical solutions. Indeed, RE significantly supported antioxidant defense, with dose-dependent effects. When combined with melon concentrate rich in SOD, the association between primary and secondary antioxidants allowed to enhance skin antioxidant efficiency and prevent oxidative stress and its associated consequences.

Further studies are needed to confirm those preliminary results and should investigate deeper the composition and the broader benefits of REMC on skin parameters such as skin luminosity, skin tone uniformity or pigmentation disorders. These additional skin benefits are crucial for assessing the full impact of REMC on skin health.

Author Contributions

Conception and design, acquisition of data, or analysis and interpretation of data: M.H., S.K., I.L., A.G., M.K., S.M. Drafting the article or revising it: M.K., S.M., S.K., A.G., M.H., I.L. Final approval of the version to be published: All authors. Agreement to act as guarantor of the work: A.G., M.H., S.M.

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Conflicts of Interest

The authors declare no conflict of interest.

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Abbreviations

The following abbreviations are used in this manuscript:

DAD	Diode Array Detector
DW	Dry Weight
ELSD	Evaporative light scattering detector
FC	Folin Ciocalteu
GAE	Gallic Acid equivalents
HPLC	High-Performance Liquid Chromatography
MS-ESI	Mass Spectrometry ElectroSpray Ionization
MS	Mass Spectrometry
MW	Molecular Weight
PAOT	Pouvoir AntiOxidant Total
POA	Product Oral Administration
PSM	PAOT Skin® Measurements
RE	Rose Extract
REMC	Rose Extract Melon Concentrate
ROS	Reactive Oxygen Species
Rt	Retention time
SD	Standard Deviation
SEM	Standard Error of the Mean
SM	Standardized Meal
SOD	SuperOxide Dismutase
SOSS	Skin Oxidative Stress Status
TPC	Total Polyphenol Compounds
UV-Vis	UltraViolet-visible light