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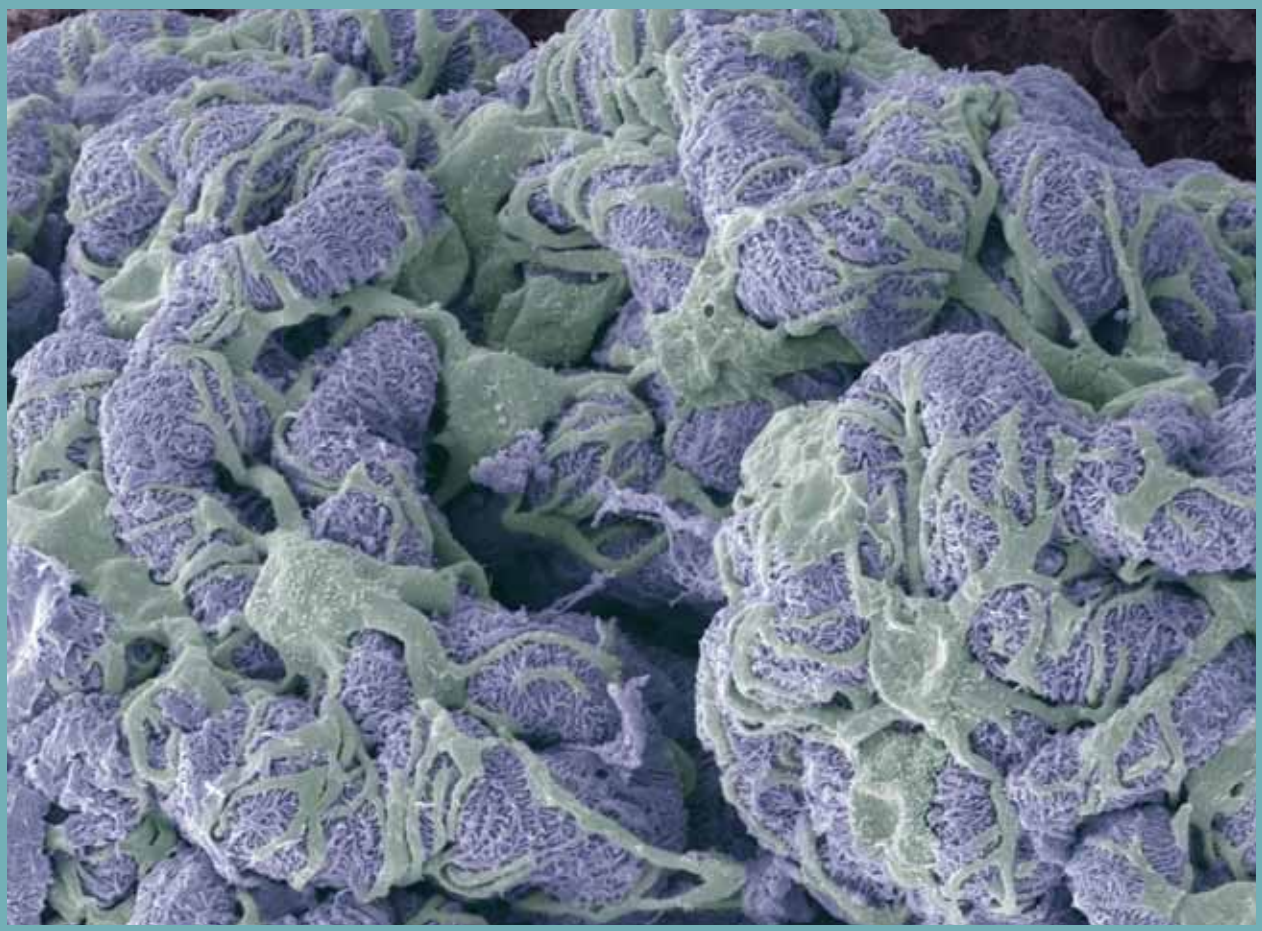

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Application of the Essential Oil from Copaiba (*Copaifera langsdorffii* Desf.) for Acne Vulgaris: a Double-Blind, Placebo Controlled Clinical Trial

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Abstract

Copaiba oil-resin is widely used in traditional medicine due to its anti-inflammatory, healing, and antiseptic activities. This research aims to extract and evaluate the qualitative and quantitative composition of copaiba essential oil from the oil-resin, and test its effects, after incorporation in a gel applied in volunteers with acne, in a double-blind placebo controlled clinical trial. The essential oil was extracted by steam distillation, and purified by freezing to remove the residual remnant water. The density of the essential oil was gravimetrically determined by weighing 1 mL of liquid at 20°C. The identification of the essential oil components was carried out through high-resolution gas chromatography analysis, coupled with mass spectrometry. The essential oil has a density of 0.9175 mg/mL and was composed of 48 substances, 14 of which were the major components representing 95.80% of total essential oil composition. Cis-thujopsene was the main component (46.96% of total essential oil composition). The surface affected with acne decreased when treated with placebo ($F = 13.931$, $p = 0.001$, $r = 0.518$; $r^2 = 0.268$), but the linear model could explain only 26.8% of total variance in original data matrix. There was a highly significant decrease in the surface affected with acne in the areas treated with the 1.0% copaiba essential oil preparation ($F = 86.494$, $p = 0.000$, $r = 0.834$; $r^2 = 0.695$).

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Introduction

The first European settlers of Central and South America reported that the indigenous American Indians applied the oil-resin of copaiba to the navels of newborn and the wounds of warriors after battle, and used this plant as an anti-inflammatory and healing agent. This traditional use came from the observation that injured animals rubbed their bodies on the stems of copaiba trees to heal their wounds.[1]

Copaiba oil-resin is widely used in folk medicine, especially in northern Brazil. The plant is an important commercial product in areas where it grows, because its oil is exported for use in the cosmetics industry. The oil-resin is used medicinally as a component of products such as ointments and syrups. It is administered topically and orally.[2,3]

Copaiba trees belong to the family Leguminosae, sub-family Caesalpinoideae. They are a slow growing tree, which can reach a height of 25 to 40 meters tall and can live for up to 400 years. The stem is rough, with dark brown bark, and with a diameter of 0.4 to 4 meters.[4] The oil-resin, in biological terms, is a product of excretion or detoxification of the plant organism, and acts as a defense against microorganisms, such as fungi and bacteria.[5]

Copaiba oil-resin is used medicinally in all regions of Brazil.[1] Its original folk use was as an anti-blenorragic agent (i.e., a medicine used to treat vaginal mucus discharge). It is now used externally as a skin-healing agent and for anti-inflammatory purposes. It is used internally as a diuretic, expectorant, and antimicrobial agent (primarily for urinary disorders). When used internally, it is often mixed with honey and lemon juice.[6]

Key words: acne, copaiba, anti-inflammatory, essential oil, antiseptic, phytocosmetic

Chromatographic analysis of copaiba oil-resin has revealed that it is comprised of sesqui- and diterpenes. The main diterpene skeletons described in copaiba oil-resins are of the kaurane-, labdane-, and cleorodane-type. The most commonly detected structures by spectrophotometry of each of those diterpene skeletons are copalic, carenoic, and hardwickiic acids, with the copalic acid constituent found in all copaiba oil-resins analyzed.[7]

Most of the therapeutic properties of copaiba are attributed to diterpenes. These plant compounds are considered to be a biological defense against predators, phytophagous insects and organisms, and pathogens, as well as a response to mechanical damage. Some of the identified sesquiterpenes have been reported to have antiulcer, antiviral, and anti-rhinovirus activity.[4] Concentrations and nature of sesquiterpenes and diterpenes can vary, but these two classes of compounds, and no other, must be present in copaiba oil-resins for use in commercial products.[8]

Despite its wide empirical use, there have been few studies on the biological activity of the essential oil of *Copaifera langsdorffii* Desf. This study aims to extract and evaluate the qualitative and quantitative centesimal composition of the essential oil from copaiba oil-resin, and, when used in a cosmetic base, test its clinical effectiveness in acne vulgaris.

Materials and Methods

Extraction and purification of the essential oil

Copaiba oil-resin was obtained from trees grown on a legal reserve in a private rural property at Santa Teresa (19°55'37"S; 40°35'16"W). Steam distillation was used to extract the essential oil from the oil-resin. The essential oil was then separated from the water effluent produced in the steam distillation extraction process by a combination of purification and freezing.

The density of the essential oil was gravimetrically determined by weighing 1 mL of liquid at 20°C, using a temperature-controlled water bath. The essential oil was weighed in an analytical balance with an accuracy of 1.0 mg. Extraction, purification, and density determination of the essential oil were made in the Laboratory of Chemical Sciences at Centro Universitário Vila Velha (UVV).

Study Design

This study was carried out at the Polyclinic UVV, located in the municipality of Vila Velha, Espírito Santo, Brazil. Volunteers with acne vulgaris were recruited from the local population. Subjects were treated with either active treatment or placebo, with clinical follow-up conducted by a physical therapist specializing in dermatological therapy, Prof. Valeria Rossetto Lemos, CEFITO 2-4163-F, Professor of Physical Therapy and Aesthetics of UVV.

Preparation of placebo and test gels

Preparation of placebo and active test gels was conducted in the laboratory of Pharmaceutical Production at UVV. The test-gel was made by incorporating 1.0 percent (weight/weight) of copaiba essential oil in natrozol gel, using 0.5 percent Tween 80 as a surfactant. A solution of parabens and sorbic acid were used as a preservative. The finished products were stored in opaque aluminum tubes, internally covered with a plastic surface, and closed with screw cap. Preparation and packing of placebo gel followed the same steps.[9] After packing, gel tubes received different color codes that identified the tubes as having either a concentration of 1.0 percent copaiba oil or placebo. These codes were only known by the researchers.

Inclusion criteria

All volunteers underwent a dermatological screening. Only subjects with a clinical diagnosis of type 1 acne lesions (e.g., mild acne consisting mostly of non-inflamed comedones) were included in the study. All participating volunteers signed a consent form and terms of commitment to voluntary participation in research. A parental or legal representative's permission was required for all volunteers under the age of 18 years old.

Exclusion criteria

Exclusion criteria for this study included (1) physical and/or mental development conditions that precluded an ability to execute the homecare demanded by the study design, (2) pregnancy, (3) acne that was incompatible with a diagnosis of type 1 acne vulgaris, and (4) use of other medications for the treatment of acne.

Research procedures

After a preliminary screening, ten volunteers were selected to receive 100 ml of neutral liquid soap for cleaning the site of acne prior to the application of active gel and placebo. The active gel and placebo preparations were marked with stripes of different colors on the labels of the tubes. These gels were applied to two distinct regions, always starting the application with the active gel, to help

prevent volunteers from noticing the difference between the odorless placebo gel and the characteristic odor produced by copaiba essential oil in the active test gel.

The application of placebo and active gel were carried out in double-blind trial. Volunteers did not know which of the two gels they were applying in a given region and the evaluators did not perform the application of the gels to the volunteers. The gels were applied twice a day for 21 days, with directions given to spread gels manually until a uniform cover of the affected area was produced.

Since application of active gel and placebo were to be done in a homecare environment, volunteers signed a commitment form to comply faithfully with the recommended procedures. Furthermore, to monitor compliance with the applications, gel tubes were weighed and sealed before starting treatment, and were weighed weekly using a portable balance with an accuracy of 10 mg to ensure that there were steadily decreasing tube weights.

Evaluation of the evolution of surface affected with acne

The areas affected with acne were photographed with a 2 cm scale in an average area of 12.25 cm^2. These pictures were then analyzed using ImageTool for Windows, release 3.0,[10] which was used to determine the total area occupied by acne pustules in each photograph. In order to correct for scale effects produced by different sizes of the pustules, the affected surfaces obtained for each volunteer were standardized by their respective percentages, calculated in relation to the larger affected area detected, and subsequently subjected to arcsine transformation. Thus, the assumption of normality of data distribution was satisfied, and it was possible to use simple linear regression to determine the effect of exposure time to the proposed treatment on the development of pustules and inflamed surfaces in the treated areas.[11]

The null hypothesis tested was that the gel with copaiba essential oil produced no change in the acne evolution. The significance level used to reject the null hypothesis was p values equal to or less than 0.05, and coefficient of line determination (r^2) equal to or greater than 0.5, which expresses an explanation power for the estimated linear model of at least 50 percent in relation to the variance present in the original data set. Linear regression and the line determination coefficients allowed evaluation of the data set for consistency, and as a means for detecting potential disagreement between results obtained and the established coding of the application gels.

In order to test the null hypothesis, a simple linear regression analysis was performed. It considered the time in weeks of exposure to active or placebo gel treatments as the independent variable, and the evolution of the area affected by acne as a dependent variable.[11] Statistical analysis was performed using SYSTAT program, version 11.0.

Chromatographic analysis

The identification of the essential oil components was carried out by high-resolution gas chromatography analysis, coupled with mass spectrometry, at the Fine Chemistry Laboratory in Tommasi Analítica. The injection volume was 2µL, composed of 1.6 mL of a solution of essential oil (30mg/ml) and 0.4 mL of a solution of hydrocarbon series of C7-C30, as internal standard, both using *n*-hexane as the solvent.

The gas chromatography coupled with mass spectrometry (GC-MS) system used consisted of a gas chromatograph, Thermo Scientific® Ultra GC coupled to a mass spectrometer, Thermo Scientific®. The fused silica capillary column used was a DB-5 J & W Scientific (30m x 0.25 mm x 0.25 mm). Helium was the carrier gas, and the column temperature program was increased by 3º C per minute between 60°-240° C. The mass spectra were obtained at 70eV at a scan rate of 0.84 scan/sec, at the range m/z 40-500.[12]

The retention times of sample components and a mixture of *n*-alkanes from C7-C30, co-injected into the GC-MS system under the same temperature program were used for the calculation of the Arithmetic Index (AI) of van der Dool and Kratz, and of the Kovats Retention Index (KI).[12] Identification of essential oil components was based on the calculated KI compared with the available literature,[12] and mass spectra with the GC-MS spectral library.

Results

Density and phytochemical profile of copaiba essential oil

The essential oil obtained from copaiba had a density of 0.9175 mg/mL. Chromatographic analysis identified 48 substances, 14 of which were considered the major components. The 14 major components represented 95.80 percent of the total essential oil composition, with cis-thujopsene accounting for 46.96 percent of the total essential oil. The relative amounts of the major compounds are listed in table 1. The remaining 34 substances

Table 1. Major components of the essential oil of *Copaifera langsdorffii*

Arithmetic Index		Kovats Index			
Calculated	Adams, 2009	Calculated	Adams, 2009	Identification	%
1426	1429	1427	1431	cis-thujopsene	46.96
1444	1444	1446	1446	seychelene	8.04
1376	1374	1377	1376	α-copaene	7.75
1525	1521	1526	1522	β-sesquiphellandrene	7.34
1466	1464	1467	1466	caryophyllene	6.71
1391	1389	1392	1390	β-elemene	3.91
1536	1537	1538	1538	α-cadinene	3.27
1517	1514	1518	1515	geranyl isobutanoate	2.27
1530	1532	1532	1533	γ-cuprenene	2.26
1585	1586	1586	1587	α-thujopsan-2-ol	2.26
1504	1509	1505	1509	α -bulnesene	2.15
1512	1514	1513	1515	cubebol	1.24
1349	1348	1352	1351	α-cubebene	0.91
1338	1339	1340	1341	3-hydroxy-benzenemethanol	0.81

detected only comprised 4.2 percent of the total essential oil, with concentrations ranging between 0.01 and 0.6 percent.

Qualitative aspects of clinical cases

Ongoing qualitative analysis of the volunteers resulted in no signs or symptoms that disturbed the continuity of treatment. Table 2 lists the surface areas affected by acne before treatment and at 7-day intervals for each individual. There were no significant differences between the placebo and active gel-treated areas before starting treatment (*U*-Mann-Whitney = 30.0; p = 0.13; df = 1). After 21 days of treatment, there was a highly significant decrease in the extent of area affected by acne, both in the region treated with placebo gel and with the active gel. Evidence of a positive clinical effect were (1) cessation in the eruption of new pustules, (2) healing of pre-existing pustules, and (3) diminishing of erythematous area.

Table 3 summarizes the statistical analysis data. Although linear regression indicated a highly significant decrease in the surface affected with acne in the region treated with placebo gel (i.e., the slope of the calculated area was negative [see bottom chart in figure 1]), the determination coefficient of the estimated line (r^2) could not explain more than 26.8 percent of the total variance of original data set, which did not allow for the acceptance of this estimated line with placebo treatment as being of biological significance. Because of this, the apparent decrease in the surface affected with acne subsequent to placebo application was not accepted, since at least 73 percent of the effect could not be explained. In the areas treated with placebo, aggravations affecting both men and women occurred in most volunteers during the 21 days of treatment (Table 2).

There was a decrease in the surface area affected with acne with the active gel, evidenced by a regression line (see top chart in figure 1) with a highly significant negative slope (table 3). This suggests an attenuation of the surface area affected with acne (t = -9.300, p < 0.01) with the statistical

Table 2. Surface area (mm^2) affected by acne

		Surface area affected with acne (mm^2)							
		Placebo				Copaiba Essential Oil (1.0%)			
Volunteer	Sex	Day 0	Day 7	Day 14	Day 21	Day 0	Day 7	Day 14	Day 21
1	F	101.11	45.02	17.81	2.54	46.62	46.49	28.9	20.22
2	M	66.48	95.86	75.03	32.73	128.91	70.14	70.4	73.57
3	F	46.44	15.62	28.5	11.97	123.5	21.46	40.67	10.64
4	F	75.76	21.43	35.64	35.85	52.2	28.6	9.59	6.31
5	M	25.96	31.23	27.17	27.19	85.62	47.87	36.48	37.36
6	F	44.41	19.43	25.94	27.21	36.14	21.09	18.26	14.63
7	F	15.61	8.4	15.91	17.35	51.05	39.08	11.25	10.99
8	M	41.91	32.04	16.74	8.91	59.51	15.32	9.69	8.69
9	F	23.75	12.03	5.36	19.39	46.53	17.34	11.33	11.2
10	F	38.85	6.37	16.8	20.64	27.01	23.73	10.58	2.65

Table 3. Estimated parameters for the simple linear regression of the evolution of surfaces affected with acne submitted to treatments with the placebo gel and active gel with copaiba essential oil at 1.0 percent (w/w).

Parameter	Placebo	Copaiba Essential Oil (1.0%)
Constant ± SE	1.280 ± 0.095	1.408 ± 0.067
Angular Coefficient ± SE	-0.027 ± 0.007	-0.048 ± 0.005
t	-3.732	-9.300
F	13.931	86.494
p	0.001	0.000
r	0.518	0.834
r^2	0.268 (26.8%)	0.695 (69.5%)
Auto-correlation	0.145	0.189

SE: Mean Standard Error; *t*: *t*-Statistics; *F*: Fischer's ratio; *p*: significance level; r: multiple linear correlation coefficient; r^2: squared multiple correlation coefficient.

model explaining at least 69.6 percent of total variation of the data set ($r^2 = 0.696$).]

Discussion

Since the available reports have focused on analyzing the oil-resin, there has been no specific information about the composition of copaiba essential oil. The oil-resin is a natural dispersion of diterpene acids in a mixture of mono- and sesquiterpenes,[7,13] which are the main components of the essential oil.[13] The most common sesquiterpenes reported are caryophyllene, copaene, zingiberene, bisabolene, and bergamotene, while the main diterpenes are kaurenoic, hardwichiic, kovalenic, polyalthic, and copalic acids, the last of which is considered a characteristic diterpene from the genus *Copaifera*.[14] Previously reported studies showed similarity in sesquiterpene compounds in the profile of the oil-resin from *Copaifera duckei* Dwyer, *Copaifera multijuga* Hayne, and *Copaifera reticulata* Ducke: Caryophyllene has been reported as the main substance in the latter two oils.[15]

The main compounds of the oils from *C. multijuga*, *Copaifera cearensis* Huber ex Ducke and *C. reticulata* were β-caryophyllene, followed by α-humulene, α-copaene, α-bergamotene, and γ-cadinene with differing amounts of each of these compounds found in the them in the oils from the various copaiba oil-resins.

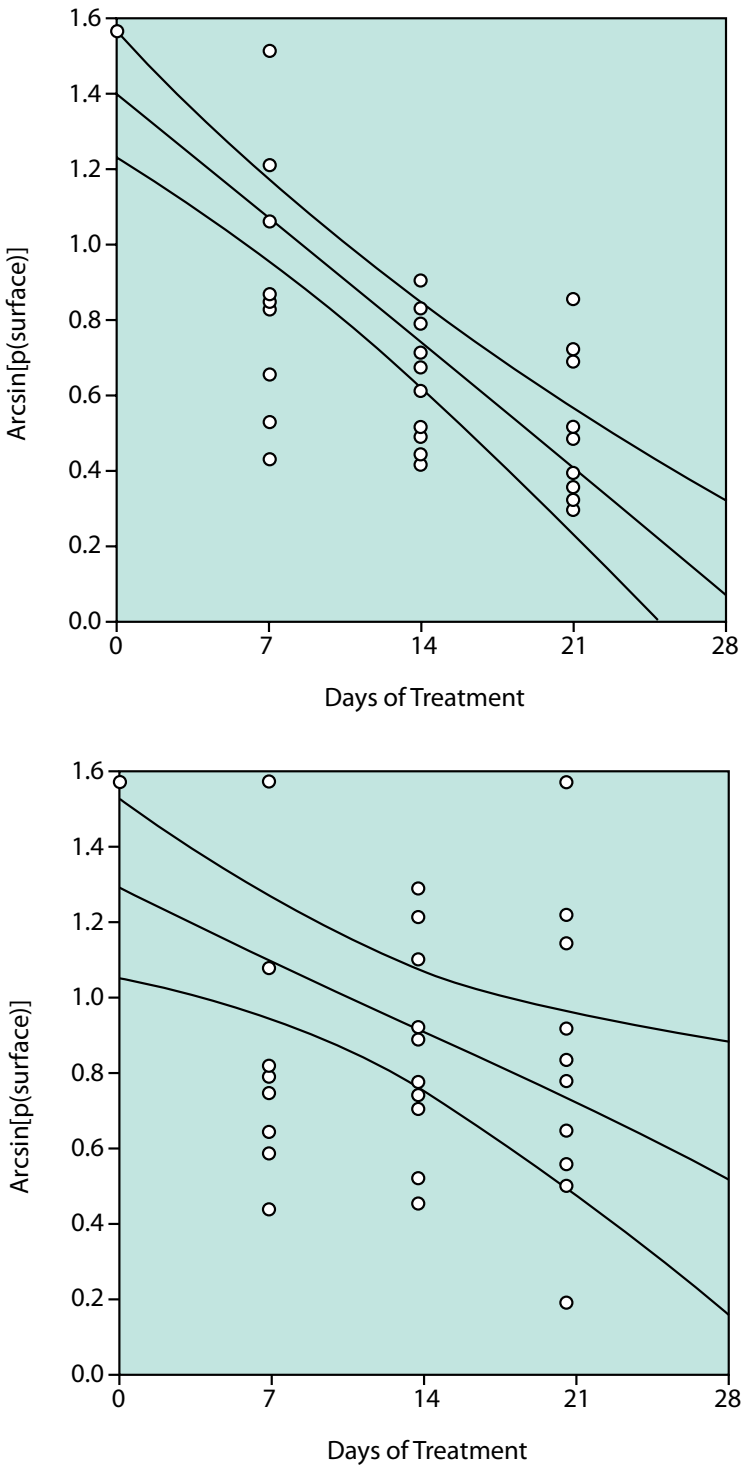
The anti-inflammatory activity of oil-resin from *C. langsdorffii* has usually been attributed to the diterpene kaurenoic acid, since this acid inhibits the transcriptional activities of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), an important molecule involved in the activation of macrophages.[16] However, in our trial, an anti-inflammatory action of the essential oil was observed despite the lack of this compound in the copaiba essential oil sample used. This suggests that other substances might also have anti-inflammatory actions. Among the major sesquiterpenes detected in the essential oil, β-caryophyllene has been mentioned in previous studies as having anti-inflammatory, anti-edema, local anesthetic, antimicrobial, and antioxidant actions.[14]

While the apparent decrease of surface area affected with acne in the areas treated with placebo (and so by virtue some degree of the response to active gel treatment) could possibly be related to the hygiene of the skin performed with the liquid soap, we do not believe that this alone explains the results. Personal hygiene is of minor relevance to acne, and, in fact, excessive skin cleaning may exacerbate acne symptoms.[17] The purpose of washing the skin is not the treatment of acne; instead, the purpose is to clean and prepare the skin to receive and tolerate the topical formulation that will be applied.[18]

Most dermatologists agree that the choice of agents used to treat acne involves the integration of multiple factors such as severity of injury, disease history, tendency to scarring, and post-inflammatory pigmentation. The therapy must be, therefore, adapted to each patient, depending on the nature and severity of acne.[19] Topical therapy is considered first-line treatment of acne and is recommended for patients with acne comedones and inflammation of a mild to moderate degree. However, for patients with moderate to severe acne inflammation resistant to current topical therapies, systemic medications are the treatment of choice.[20]

Our results suggest that the copaiba essential oil treatment had only a topical, instead of a systemic effect. The rationale for this conclusion

Figure 1. Simple linear regression of the effect of the gels applied in the areas affected with acne during 21 day of treatment in the volunteers studied (top graph is active treatment; bottom graph is placebo)



was that, since both of the gels (active and placebo) were applied at the same time in the same volunteers, and the effect in the areas treated with the active gel were significantly greater, the main effect appeared to be specific to the location where the active test gel was applied.

Conclusion

Although copaiba essential oil had not previously been tested in the treatment of acne, some investigations on the essential oils of ten other plant species had demonstrated promising *in vitro* results for inhibiting the growth of *Propionibacterium acnes*, in protecting against free radicals, and in modulation of the inflammatory response subsequent to its infection.[21] This suggested the possibility that copaiba essential oil would be efficacious for acne vulgaris. Our results indicate that the essential oil from copaiba might have utility as a topical treatment for mild acne. Larger studies are warranted to further assess its efficacy in this clinical condition, and to determine whether it would have any utility for more severe acne vulgaris or might synergize with other existing acne therapies.

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