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Development and Characterization of *Aloe vera* Mucilaginous-Based Hydrogels for Psoriasis Treatment

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Abstract: The *Aloe vera* (L.) Burman f. pulp extract (AE), obtained from the inner parts of *Aloe vera* leaves, is rich in polysaccharides, including glucomannans, acemannans, pectic compounds, cellulose, and hemicelluloses; acemannan and glucomannan are considered the two main components responsible for most of the plant's therapeutical properties. Besides having anti-inflammatory activity, these polysaccharides accelerate wound healing and promote skin regeneration, thus they can be utilized in healing products. The objective of this study was to develop *Aloe vera* mucilaginous-based hydrogels for topical use in psoriasis treatment. The hydrogels were prepared with 80% *w/w* of *A. vera* mucilaginous gel, evaluating two distinct polymers as the gelling agent: 1% carbopol 940 (FC1 and FC2) or 2% hydroxyethylcellulose (FH3 and FH4). FC1, FC2, FH3 and FH4 were evaluated for their organoleptic characteristics, rheological properties, pH and glucomannan content. Polysaccharide fractions (PFs) were extracted from the AE and used as a group of chemical markers and characterized by infrared (IR) spectroscopy and 1H nuclear magnetic resonance ($_1$H NMR). The quantification of these markers in the raw material (AE) and in the hydrogels was carried out using spectrophotometric techniques in the UV-VIS region. The hydrogels-based hydroxyethylcellulose (FH3 and FH4) had glucomannan contents of 6.76 and 4.01 mg/g, respectively. Formulations with carbopol, FC1 and FC2, had glucomannan contents of 8.69 and 9.17 mg/g, respectively, an ideal pH for application on psoriasis, in addition to good spreadability and pseudoplastic and thixotropic behavior. Considering these results, hydrogel FC1 was evaluated for its keratolytic activity in a murine model of hyperkeratinization. For that, 0.5 mL of test formulations FC1 and FPC (0.05% clobetasol propionate cream) were topically applied to the proximal region of adult rats daily for 13 days. After euthanasia, approximately 2.5 cm of the proximal portion of each animal's tail was cut and placed in 10% buffered formalin. Then, each tail fragment was processed and stained with hematoxylin and eosin (HE), and the results obtained from the histological sections indicated a 61% reduction in stratum corneum for animals treated with the *A. vera* hydrogel (FC1G) and 66% for animals treated with clobetasol propionate (PCG), compared to the group of animals that did not receive treatment (WTG). This study led to the conclusion that compared to the classic treatment (clobetasol propionate), the 80% *A. vera* hydrogel showed no significant difference, being effective in controlling hyperkeratinization.

Keywords: *Aloe vera*; glucomannan; hydrogel; psoriasis

1. Introduction

Aloe vera (L.) Burman f. (*Aloe barbadensis* Miller) is a medicinal plant belonging to the Liliaceae family, currently known as Asphodelaceae, by the Angiosperm Phylogeny Group III System (APG III 2009) [1]. Among over 300 species of Aloe, *A. vera* is the most widely used in medicines, cosmetics, and food products. Most of its therapeutic properties (antiviral, antibacterial, healing, antioxidant, anti-inflammatory, anticancer, antidiabetic, antiallergic, immunostimulant and UV protection) are attributed to the presence of polysaccharides [2–10]. Acemannan alone was used in wound care pharmaceuticals and alveolar osteitis patients as Acemannan Hydrogel™ [7,11] and Acemannan immunostimulant™ was applied in fibrosarcoma treatment in cats and dogs [7,12], in addition to other products such as Immuno-10 [13,14], Alcortin® [13] and Mole-Cure® [15].

The mucilaginous gel of *A. vera* consists mostly of water (>98%) and its remaining solid content is rich in polysaccharides (60%) such as pectin, cellulose, hemicellulose, mannose derivatives, acemannan and glucomannan, with the last two being considered the main components responsible for the majority of biological and functional activities of Aloe [6,16]. Research has shown positive effects on wound healing of products derived from *A. vera*. Those are attributed to nutrient maintenance, humidity, oxygenation, inflammation control, immunoactivity, epithelialization and fibroblast proliferation [17–21].

Psoriasis is classified as a non-contagious, chronic inflammatory systemic disease with a cutaneous, nail, and joint manifestations. In addition, it has variable clinical features and a relapsing course. Recently, Leng and co-authors (2018) showed the pharmacological activity of *A. vera* mucilage in psoriasis [22,23]. In addition, in a recent review article, Yadav et al. (2021) [24] described the topical therapeutic approach of polymeric formulations in the treatment of psoriasis, highlighting the use of Carbopol® 940, chitosan, hydroxypropylmethylcellulose, Poly-(lactic-co-glycolic acid) (PLGA) and polyethylene glycol in hydrogels, emulsions, nanogels, and scaffolds.

Psoriasis is an autoimmune chronic inflammatory disease that affects about 2% of the world's population. This disease, besides causing physical suffering, also affects the psychosocial aspects of the patient. Epidermal changes are primarily characterized as being due to keratinocyte hyperproliferation, which leads to abnormal differentiation and impaired barrier function. In addition, the histopathological findings of the lesions of patients with psoriasis can be characterized by hyperkeratosis (thickening of the stratum corneum-SC) and parakeratosis (abnormal SC maturation), and epithelial acanthosis, associated with the infiltration of inflammatory cells in the dermis and epidermis, and elongation of the dermal papillae with dilated capillaries. However, since the 1980s, T lymphocytes, macrophages, T-Helper-17, T-Helper-22, regulatory T cells, dendritic cells, and new cytokines, including interleukins (IL) IL-22, IL-23, IL-17 e IL-20 have been identified in dermal inflammatory infiltrates, allowing the pathogenesis of psoriasis to be defined as an autoimmune disease [25–29].

The treatment of mild psoriasis consists of drugs applied topically, but moderate to severe clinical conditions are treated systemically. The systemic treatments can include phototherapy, methotrexate, acitretin, cyclosporine and biological medicines such as adalimumab, etanercept, risanquizumab, ustequinumab and secuquinumab [22].

Topical keratolytics, emollients, corticosteroids (clobetasol and dexamethasone) and calcineurin inhibitors are among the recommended drugs. Alternatively, drugs or fractions extracted from plants, such as *A. vera*, have shown satisfactory results in the treatment of psoriasis [30–33]. Topical treatments may also be applied as adjuvants to systemic therapy and maintaining treatment after a dose reduction or discontinuation [34].

In the last two decades, alternative medicine has become extremely popular, and the topical use of herbal drugs has become one of the most used complementary therapies

in treating skin lesions or diseases such as psoriasis [35]. In this context, an *A. vera*-based herbal product shows promise due to its safety and tolerability [23,30]. Dhanabal et al. (2012) [36] evaluated an ethanolic extract of *A. vera* mucilage for antipsoriatic activity using a mouse tail psoriasis model described by Vogel (2008) [37]. They reported activity of 81.95% of *A. vera* extract compared to 87.94% for tarazotene (a topical retinoid indicated for the treatment of plaque psoriasis).

In 1996, Syed and co-authors [33] showed clinical studies performed with patients diagnosed with mild to moderate psoriasis using hydrophilic cream with 0.5% *A. vera*. The treatment was analyzed for eight months and showed significant improvement compared to the placebo group. Another work published by Choonhkarn et al., 2009 [30] also showed satisfactory results for treating psoriasis using a cream with 70% of *A. vera* mucilaginous gel in sick volunteers. Additionally, one group was treated with a cream containing 0.1% triamcinolone acetonide. Both treatments observed excellent PASI (Psoriasis Area and Severity Index) rates.

Recently, Leng et al. 2018 [23] evaluated markers of the inflammatory response of psoriasis using HaCaT cells to better understand the molecular bases involved in the action of the polysaccharide extracted from *A. vera*. The results showed that by stimulating the cells with TNF-α and exposing them to the polysaccharide, a significant reduction in keratinocyte proliferation and NF-κB signaling was observed. Therefore, the effectiveness of the administration of *A. vera* polysaccharides for treating patients with psoriasis seems to depend on its anti-inflammatory activity. Consequently, it has been considered a promising drug candidate for the treatment of psoriasis due to its potential clinical applications.

It is known that topical corticosteroids are the clinician's first choice for treating psoriasis disease: clobetasol propionate and dexamethasone in a topical application of corticosteroids 1–3 times a day per less than 30 days. However, while clobetasol has very high potency and can be used in most psoriasis lesions, it cannot be used in certain regions due to the risk of skin atrophy and telangiectasia, such as on the face, flexural and genital areas, where there is still tachyphylaxis [22].

The present work aimed to develop and characterize an *A. vera* hydrogel due to the importance of polysaccharides for its biological activity in psoriasis treatment. For this purpose, the hydrogels were prepared from the AE and evaluated for their organoleptic characteristics, rheological properties, pH, glucomannan content and antipsoriatic activity by the evaluation of the hyperkeratinization process in a murine model and in comparison with a pharmaceutic market product (clobetasol 0.05%).

2. Materials and Methods

2.1. Materials

The leaves of *A. vera* (L.) Burman f. were collected from the Institute for Research in Drugs and Medicines-IPEFARM/UFPB (lat: -7.11499977111816 long: -34.8630981445312). The voucher specimen of the plant was deposited at the Herbarium Professor Lauro Pires Xavier/UFPB (registration JPB0063909), located in João Pessoa, Paraíba, Brazil. The raw materials used in this study were as follows: Ethyl alcohol 92.8° GL (Toscano, João Pessoal/Brazil), imidazolidinyl urea (Akema, Coriano/Italy), disodium EDTA (Dow, Pittsburg/PA/USA), anhydrous citric acid (Cofco Biochemical, Nong Bua/Thailand), methylparaben (Ueno fine, Bang Rak/Thailand), aminomethyl propanol (Angus Chemical, Sterlington/LA/USA), propylene glycol (Anidrol, Diadema/Brazil), carbopol (Vetec, Duque de Caxias/Brazil), hydroxyethylcellulose (Dow, Pittsburg/PA/USA) and sodium metabisulfite (Sigma-Aldrich, St. Louis/MI/USA). All other chemicals were of analytical grade and were used without any further chemical modification.

2.2. Methods

2.2.1. Preparation of AE

A. vera leaves about 5–6 years old were used in the preparation of mucilaginous gel. All collected material was washed, cut at the basal end, and left upright for 30 min to

remove excess exudate. After a second washing process, the green epidermis was removed from the plant material to obtain the *A. vera* pulp in fillets. The fillets were homogenized in a mixer (Mallory, Robot 250, Maranguape, Brazil) for 1 min and exhaustively filtered under vacuum using a polyester membrane to remove fibrous material. The extraction process was performed to obtain crude AE, which was used as the raw material and to extract the polysaccharide fraction, used as a phytochemical marker.

2.2.2. Polysaccharide Fraction Extraction and Characterization

The PF was prepared by adding 1000 mL of ethyl alcohol to 200 mL of the AE (5:1, *v/v*) obtained as previously described. The mixture was kept at 4 °C for 24 h for flocculation of the high molecular weight alcohol-insoluble polysaccharide fraction (PF), which was separated using sieves and left in Petri dishes for evaporation of residual alcohol. Subsequently, PF was resuspended in 400 mL of distilled water, frozen at −20 °C and dried for 54 h in a lyophilizer (Labconco Brand Freeze Dryer, model FREEZONE 4.5, Kansas City, MI, USA). The lyophilized PF was characterized by Fourier transform infrared (FT-IR) and proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy and was used to obtain the calibration curve in the UV/VIS glucomannan quantification method.

The FT-IR spectrum of the isolated standard glucomannan was obtained by preparing KBr cells containing the samples and was carried out in a Rayleigh FT-IR Spectrometer, on a wavelength range from 4000 to 400 cm^{-1}. The 1H NMR spectra of PF was performed at 400 MHz using a JEOL Eclipse 400 NMR Spectrophotometer (JEOL–Pleasanton, CA, USA), at 25 °C and MNOVA (Mestrelab Research, San Diego, CA, USA) software. For this purpose, 5 mg of sample were solubilized in 1.0 mL of deuterium oxide 99.9%.

2.2.3. Hydrogel Based on *A. vera* Extract

All hydrogel samples were prepared under mechanical agitation (IKA, RW20, Staufen, Germany) by adding the gelling polymer to the AE. The composition of each prepared hydrogel is described in Table 1.

Table 1. Qualitative and quantitative composition of formulation of *A. vera* hydrogels.

Ingredients (g)	FC1	FC2	FH3	FH4	Function
A. vera (L.) extract	80.0	80.0	80.0	80.0	API *
Carbopol 940	1.0	1.0	-	-	Gelling
Hydroxyethylcellulose	-	-	2.0	2.0	Gelling
Citric acid	0.5	-	-	0.5	Acidulant
Aminomethylpropanol	qs.	qs.	-	-	Alkalizing
Methylparaben	0.2	0.2	0.2	0.2	Preservative
Imidazolidinyl urea	0.3	0.3	0.3	0.3	Preservative
Propylene glycol	5.0	5.0	5.0	5.0	Humectant
Disodium edetate	0.1	0.1	0.1	0.1	Chelator
Sodium metabisulphite	0.05	0.05	0.05	0.05	Antioxidant
Distilled water q.s.p.	100.0	100.0	100.0	100.0	Vehicle

* API Active pharmaceutical ingredient.

Formulations FC1 and FC2 were prepared by dispersing the carbopol 940 as the anionic gelling agent in 40.0 g of the AE and kept at rest for 2 h. Then, another 40 g of the AE were slowly added under continuous stirring. Samples FH3 and FH4 were prepared by preheating 80 g of the mucilaginous gel at 60 °C and slowly adding hydroxyethylcellulose, non-ionic gelling agent, under mechanical stirring. All samples were added of imidazolidinyl urea and methylparaben, previously solubilized in propylene glycol under heating at 60 °C and then cooled down. Disodium edetate and sodium metabisulfite aqueous solution were also added to all samples. For FC1 and FC2 samples, it was necessary to add aminomethylpropanol for the final pH adjustment (6.0–7.0), stirring for 10 min. FH3 and FH4 samples were kept under continuous stirring for 1 h.

Organoleptic characteristics were evaluated by odor perception and macroscopic visual parameters such as color, appearance, absence of precipitates or aggregates, turbidity, and color change [38]. Hydrogel formation was also evaluated by the tube inversion method through the property of not flowing nor being deformed due to its own weight [39,40]. The pH of the formulations was determined in samples previously dispersed in distilled water (10% *w/v*), with a potentiometer (Digimed, model DM-20, São Paulo, Brazil). The result is the average of three determinations [41].

2.2.4. Characterization

Spreadability

Exactly 1 mL of each sample was applied to the center of a millimeter plate, on which a glass plate of known weight was added. After one minute, the diameters covered by the sample were read in the vertical and horizontal positions and then the average diameter was calculated. This procedure was repeated by adding, one by one, six more plates of increasing weight and recording the diameters of the corresponding sample 1 min after each plate was added. Results were expressed as the spreadability of the sample as a function of the added cumulative weight according to Equation (1) [42,43].

$$Ei = d^2.\frac{\pi}{4} \quad (1)$$

where:

Ei = sample spreadability for a given weight (mm^2);

d = average diameter (mm).

The results were represented by the mean ± standard deviation (SD), n = 3.

Rheological Properties

Rheological measurements were determined at 25 °C by rheometer type HAAKE (MARS II Rheometer®, Thermo Scientific™, Waltham, MA, USA), coupled to a thermal controller (HAAKE DC50, Thermo Scientific™, Waltham, MA, USA) using PP20 Ti sensor (plate/plate, diameter 20 mm) for hydrogels and for comparative purposes measurements of mucilaginous gel were made using sensor C60/2 (cone/plate, diameter 60 mm). The parameters were established using the Rheowin 4 Job Manager software (Thermo Scientific, Waltham, MA, USA) from 0.1 to 1000 1 s^{-1} [44]. Hydrogel formulations were evaluated for apparent viscosity versus shear rate curves, and rheological behavior was evaluated using the hysteresis curve. Therefore, during the analysis, a sample of the mucilaginous gel and each hydrogel was initially submitted to increasing shear rates and, subsequently, to decreasing rates. The samples FC1, FC2 and AE were evaluated for viscoelastic behavior, and the response variables were the elastic and viscous modulus. Analysis was performed on the linear viscoelastic regime at 25 °C. The tension used was 1 Pa and the frequency ranged from 0.1 to 10 Hz. The mechanical spectra were characterized by values of G′ and G″ (Pa) as a function of frequency (f). G′ is the storage modulus, related to the solid response of the material and G″ is the loss modulus, related to the fluid response of the material. The results are represented by the mean ± standard deviation (SD), n = 3.

Determination of Glucomannan from AE and Hydrogels

A UV/VIS spectrophotometric technique (Thermo Scientific, Evolution 300T, Waltham, MA, USA) described by Eberendu [45,46] was used to quantify the glucomannans present in the AE used as raw material, as well as for the analysis of the obtained hydrogels.

Glucomannan calibration curve: For this purpose, a 5000 µg/mL aqueous solution of lyophilized glucomannan (PF) was prepared under magnetic stirring for 3 h. Successive dilutions were made using distilled water to prepare solutions at 1000, 1250, 2000, 2500, 3000, 3750, 4000 and 4500 µg/mL. Subsequently, 400 µL aliquots of each of these concentrations were transferred (in triplicate) to 1mL Eppendorf tubes. Each tube received 500 µL of potassium hydroxide solution (0.28 M KOH) and 100 µL of congo red reagent

(2×10^{-4} M). At the end, final concentrations between 400 and 2000 μg/mL were obtained in the complexation reaction. The mixtures were kept at room temperature for 20 min and glucomannan contents quantified by spectrophotometry at 540 nm.

Determination of glucomannan content: For the quantification of glucomannan content in AE and in the hydrogels exactly 1 g of AE and each hydrogel was transferred to 10 mL volumetric flasks, and their volumes completed with distilled water. These solutions were kept under magnetic stirring for 1 h for complete solubilization. Subsequently, 400 μL aliquots of AE and of each hydrogel solution were transferred in triplicate to 1 mL Eppendorf tubes. Then, 500 μL of KOH solution and 100 μL of congo red reagent were added to each tube. The mixtures were kept at room temperature for 20 min then absorbance reading at 540 nm was performed. The glucomannan contents were determined using the calibration curve equation described. The results were represented by the mean ± standard deviation (SD), n = 3.

2.2.5. In Vivo Antipsoriatic Activity

In vivo assays were carried out in the vivarium of the IPeFarM/UFPB in Federal University of Paraíba (UFPB), after prior approval (CEUA nº 9373270420) by the Ethics Committee on Animal Experimentation of the same university. All experiments followed the norms of the National Council for the Control of Animal Experimentation (CONCEA). The histopathological evaluations were carried out at the General Pathology Laboratory of the Department of Physiology and Pathology at UFPB.

The antipsoriatic activity was assessed by mouse tail test for psoriasis following Vogel (2008) [37] with some modifications. The comparative analysis of hyperkeratinization process was made using *A. vera* hydrogel and clobetasol 0.05% (pharmaceutic market product). For this, 18 adult Wistar rats with an average weight of 330 g were used, kept in individual cages with food and water *ad libitum*, and under standard lighting conditions (light/dark cycle 12/12 h) and temperature (22 ± 2 °C). The animals were randomized into three groups: 1. no treatment group (negative control, WTG, n = 6); 2. group treated with 0.05% clobetasol propionate (positive control, PCG, n = 6), and 3. group with 80% of *A. vera* hydrogel (FC1G, n = 6). Both FC1G and PCG groups were submitted to the application of drugs once a day for 13 consecutive days.

The amount of 0.5 mL of the formulation was topically applied to the proximal part of the tail, and contact was maintained for 24 h. Twenty-four hours after the last treatment, the animals were euthanized, the proximal parts of their tails were cut, and their fragments were stored in containers containing 10% buffered formalin. In addition to the inflammatory evaluation, Hematoxylin-eosin (HE) staining was used for the evaluation of keratinocytes and their extracts. For this, the samples of the fragments included in paraffin were cut in a microtome at a thickness of 3μm, mounted on histological slides, dewaxed in xylene for 30 min, and hydrated in alcohol in decreasing concentrations for 25 min. They were then washed in running water for 25 min and then washed in distilled water for five minutes. The samples were then treated with Harris' hematoxylin for 1 min, washed in distilled water for 5 min, stained with eosin for 3 min, and washed in running water for another 30 s. Finally, the slides were dehydrated in increasing concentrations of alcohol, cleared in xylene, and mounted with Entellan®.

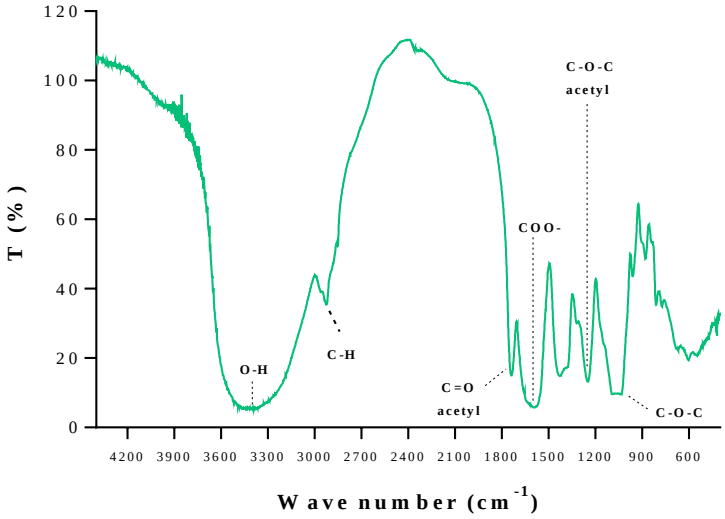
2.3. Statistical Analysis

For statistical analysis of pH and spreadability results, Student's *t*-test was performed, $p < 0.05$, and for glucomannan content determination tests, the ANOVA/Tukey test was performed, $p < 0.05$, both using GraphPad Prism program 6.01 (GraphPad software, San Diego, CA, USA). Kolmogorov–Smirnov test, analysis of variance (ANOVA) for multiple comparisons and post Tukey test, using a 5% significance level, were used to evaluate biological data with the GraphPadPrism 5® program (GraphPad Software Inc. La Lola, San Diego, CA, USA).

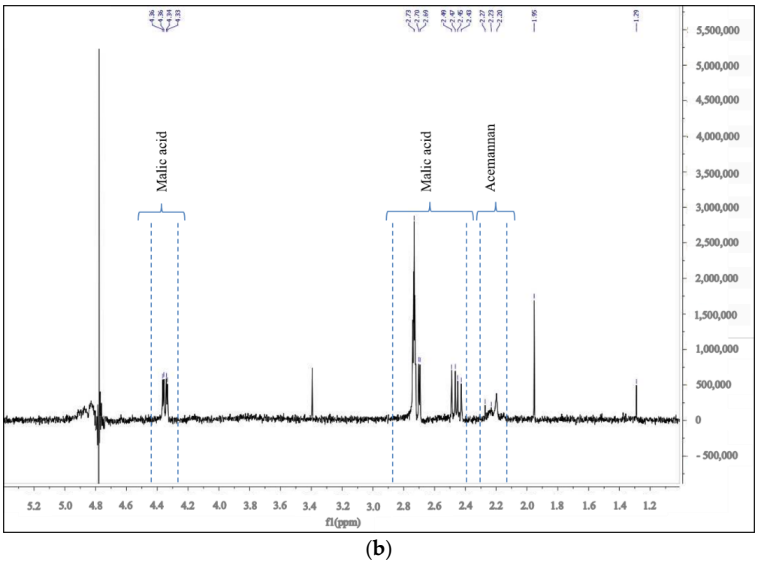
3. Results and Discussions

3.1. Identification of Glucomannan by FTIR and ^{1}H-NMR

The FTIR spectrum of the polysaccharide fraction (PF) showed the presence of -OH groups (3420 cm^{-1}), -CH asymmetrical stretch (2923 cm^{-1}), C=O stretches of acetyl groups (1760–1740 cm^{-1}), COO- asymmetric stretching (1598 cm^{-1}), CH_3 and COO- symmetric stretching (1428 cm^{-1}), C-O-C stretching vibrations of acetyl groups (1248 cm^{-1}) and ether C-O-C in sugar (1091–1030 cm^{-1}) (Figure 1a), suggestive of storage polysaccharides such as acemannan and other glucomannans. These results support the findings of bioactive acetylated polysaccharides by other authors and represent the *A. vera* mucilage and its derivatives' fingerprint [1,4,10,39,40,47,48].



(**a**)



(**b**)

Figure 1. FTIR (**a**) and ^{1}H-NMR (**b**) spectra for polysaccharide fraction.

The hydroxyl and ether (C-O-C) group signals in sugar units showed high intensity between 3420 cm^{-1} and 1050 cm^{-1}, respectively. A band emerged in 1066 cm^{-1} due to the presence of mannose components, galactose and glucan units [39,49]. The comparison between the bands found in the spectrum also enabled the correlation of those found by other authors for acemannan, which supports the evidence of an efficient extraction process.

The spectra of PF confirmed that the fractions contained acetylated glucomannan, since they exhibited two characteristic bands of acetyl groups in 1746 cm^{-1} and 1248 cm^{-1}.

The ^{1}H-NMR spectrum of the PF (Figure 1b) showed signals at 2.2, 2.23 and 2.24 ppm corresponding to acetyl groups. These signals matched those characteristic of the *A. vera* species found by other authors [13,50,51]. Diehl and Teichmuller (1998) [50] proved that the ^{1}H-NMR is an essential tool for the evaluation of the identity and quality of plant mucilage from *A. vera*. Acemannan is a β-(1→4) partially acetylated mannan in positions 2, 3 or 6 and exhibits a characteristic signal at 2.00–2.26 ppm, which corresponds to the hydrogen present on the acetyl groups, which is considered a fingerprint for the *A. vera* species. Additionally, malic acid signals were observed at 4.45 ppm, which corroborates with other results found for the same polysaccharide fractions by Bozzi et al. (2007) [16] and Minjares-Fuentes et al. (2017) [51]. By examining the ^{1}H-NMR spectra of the PF extracted from the AE, it is possible to suggest that it contains acemannan.

3.2. Aloe vera Hydrogel Characterization

The preparation of the formulations was satisfactory using a simple method, capable of scaling-up. Using prior industry knowledge of *A. vera* products, citric acid was also used in this work to adjust the pH of mucilaginous gel to values below 4.6 to prevent possible enzymatic or microbiological degradation [52]. FC1 and FH4 samples were obtained with AE added with citric acid. The gelation of FC1 and FC2 hydrogels samples was observed after the addition of aminomethyl propanol, since these formulations were prepared with the anionic polymer Carbopol, whose viscosity is pH dependent, with no difficulty to disperse it in the mucilaginous gel. The obtained hydrogel proved to be soft to the touch and less viscous than hydroxyethylcellulose hydrogels. During the preparation of the formulations with hydroxyethylcellulose (FH3 and FH4), it was observed that upon heating to 60 °C the polymer was more easily dispersed in the mucilaginous gel, followed by gradual gelation.

AE has a light-yellow color, which was not significantly altered after incorporation of the excipients. All developed hydrogels were viscous and yellow, without deformation or flow when the tube was inverted. In addition, the formulations were also homogeneous, without precipitates or lumps, and with a characteristic odor (Table 2).

Table 2. Physical and sensorial parameters of *A. vera* hydrogels.

Parameters	FC1	FC2	FH3	FH4
Odor	typical	Typical	typical	typical
Color	Yellow	light Yellow	light Yellow	light Yellow
Aspect	Homogeneous	Homogeneous	Homogeneous	Homogeneous
Opacity	Opaque	Opaque	Opaque	Opaque
Fluidity	Absent	Absent	Absent	Absent
pH	6.70 ± 0.03	7.18 ± 0.19	6.31 ± 0.14	4.67 ± 0.11

A. vera hydrogels presented pH values between 4.67 and 7.18. Formulations FH3 and FH4 showed significant differences ($p < 0.05$), justified by the addition of citric acid to the AE in the FH4 formulation. FC1 and FC2 formulations also differed significantly in pH values ($p < 0.05$). Carbopol hydrogel thickening was obtained after neutralization of the polymer with inorganic bases or low molecular weight amines.

The pH of the hydrogel FC2 was higher than FC1, yet it is recommended for use in certain skin conditions characterized by increased acidity, such as psoriasis, where the application of higher pH products is preferable [53].

Khan et al. (2013) [17] developed formulations containing *A. vera* gel with carbopol 934, sodium carboxymethylcellulose and hydroxypropyl methylcellulose gelling agents and found pH values for the gels at 6.6 ± 0.5, close to neutral pH. The authors reported skin safety formulations. Powar et al. (2016) [54] incorporated meloxicam in *A. vera* hydrogels prepared by dispersing in different concentrations of gelling agents such as

hydroxypropyl methylcellulose, carboxymethyl cellulose and carpobol 934. However, pHs of all developed formulations were between 6.2 and 7.3, compatible with skin pH. Therefore, the formulations FC1, FC2 and FH3, due to their pH closer to neutrality, are the most suitable for application in skin conditions, considering the pathophysiological aspect of psoriasis, which is intended to be treated with this hydrogel.

Carbopol-based hydrogels showed superior spreadability than formulations made from hydroxyethylcellulose. FC1 and FC2 carbopol hydrogels presented initial spreadability with a weight of 380 g of 3036.9 and 3134.5 mm^2, respectively, with maximum spreadability values of around ~5200 mm^2 after adding 2705 g, while FH3 and FH4 hydrogels showed maximum values of spreadability of 3421.7 and 3614.0 mm^2, respectively. Thus, it was found that spreading carbopol formulations at the application site will require less effort than hydroxyethylcellulose formulations. These hydrogels (FH3 and FH4) require more effort, but in contrast, have a smaller application area than those achieved with the formulations with carbopol (Figure 2).

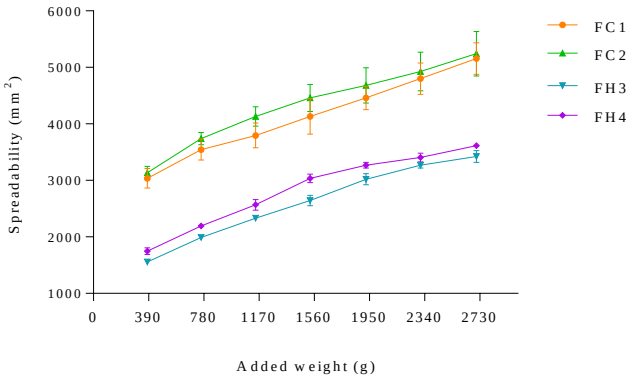
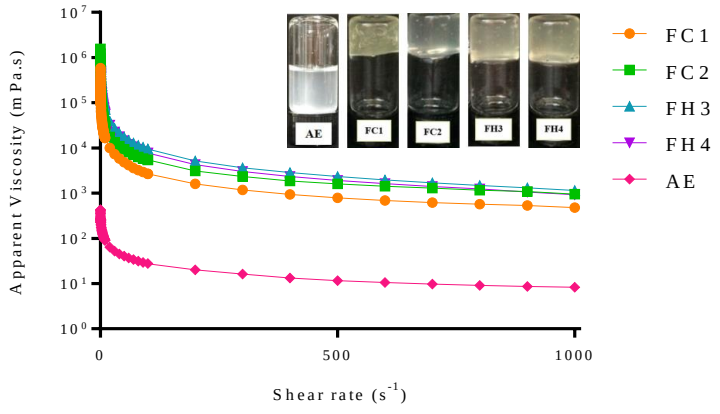


Figure 2. Spreadability of *A. vera* hydrogels containing carbopol 940 (FC1; FC2) and hydroxyethylcellulose (FH3; FH4) as a function of added weight.

The therapeutic effectiveness of topical gels depends on their spreadability. A uniform application of the gel to the skin is essential and a requirement of quality for topical products, besides favored patient compliance with treatment [55].

The rheological behavior of the formulations was evaluated to observe the influence of the polymers used. Figure 3 shows the results of apparent viscosity as a function of shear rate for an aliquot of AE, as well as for hydrogel formulations containing *A. vera* extract. The data revealed a pseudoplastic rheological behavior; that is, there was a gradual decrease in apparent viscosity as the shear rate was increased.



(**a**)

Figure 3. *Cont.*

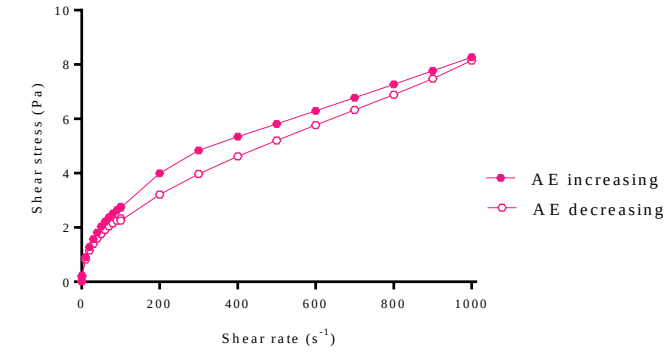
AE and Hydrogels	Shear stress (Pa)				Apparent viscosity (mPa.s)			
	Shear rate (s^{-1})							
	1	10	100	1000	1	10	100	1000
AE	0.23	0.91	2.76	8.27	229	91	28	8
FC1	93.20	165.08	269.09	482.53	93,191	16,506	2,691	482
FC2	203.37	298.98	544.31	950.29	203,374	29,898	5,443	950
FH3	540.42	708.25	949.92	1150.89	540,174	70,792	9,499	1,151
FH4	354.39	555.91	776.47	921.79	354,342	55,590	7,764	922

(**b**)

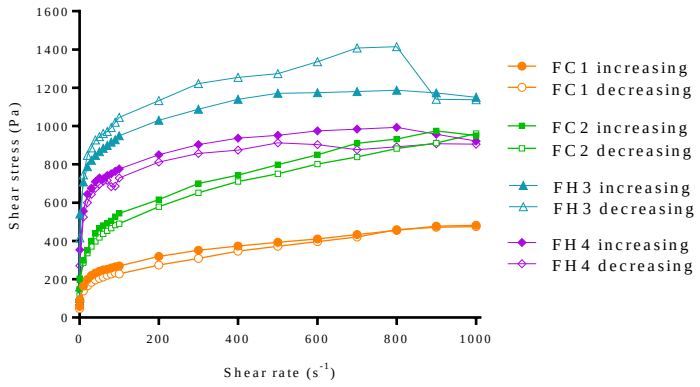
Figure 3. (**a**) Apparent viscosity as function of shear rate for AE and *A. vera* hydrogels FC1, FC2, FH3 and FH4), at 25 °C. (**b**) information about numerical values of apparent viscosity of tested hydrogels at 1, 10, 100 and 1000 s^{-1} and yield stress.

In general, hydrophilic gels have pseudoplastic rheological behavior, becoming fluid during the application of shear stress, facilitating the spreading, but recovering the initial viscosity when ceasing the application of force, allowing proper administration of the product. Similar data for mucilaginous gel were found by Medina-Torres and colleagues (2016) [56] when analyzing fresh *A. vera* mucilaginous gel, solutions of *A. vera* freeze-dried mucilaginous gel and xanthan gum.

The rheograms of all evaluated samples showed no linear relationship between the values of shear stress and shear rate, denoting their non-Newtonian character (Figure 4). Moreover, the data obtained were thixotropic for the FC1, FC2 and FH4 formulations (Figure 4b) due to the visible shift in the curves in the increasing-decreasing cycles (descending curves shifted to lower positions). This phenomenon indicates the alignment of polymeric chains when subjected to external pressure and, consequently, easier spreading in the region where they will be applied, attracting special interest in topical gel technology (Table 3).



(**a**)



(**b**)

Figure 4. Rheological behavior of (**a**) AE and (**b**) *A. vera* hydrogels.

Table 3. Spreadability, rheological behavior and glucomannan content of *A. vera* hydrogels.

Parameters	FC1	FC2	FH3	FH4
Maximum spreadability (mm^2)	5155.5 ± 279.3	5243.1 ± 394.2	3421.7 ± 103.7	3614.0 ± 30.7
Rheological behavior	Thixotropic	Thixotropic	Rheopectic	Thixotropic
Glucomannan content of AE (mg/g) * and (*w/w*)	13.87 ± 0.53(1.4%)			
Glucomannan content of hydrogels (mg/g) ** and (*w/w*)	8.69 ± 0.24 (0.87%)	9.17 ± 0.20 (0.92%)	6.76 ± 1.06 (0.67%)	4.01 ± 0.51 (0.40%)

* mg glucomannan/g Aloe extract ** mg glucomannan/g hydrogel.

Figure 4b presents the FH3 formulation as a rheopectic system. This is observed by the behavior of the sample with an increase in viscosity during shear and the return of their original viscosity at the end of the analysis. Rheopectic systems can remain in an infinite cycle between shear time-dependent viscosity increase and rest time-related viscosity decrease [57].

According to the data, FC1 and FC2 formulations showed better results regarding pH, spreadability and rheological behavior. It should be noted that FH3 showed rheopectic behavior and FH4 showed inadequate pH for topical treatment. Therefore, additional analysis of the viscoelastic behavior of the hydrogels FC1 and FC2, as well as in the AE, were made for comparative purposes (Figure 5).

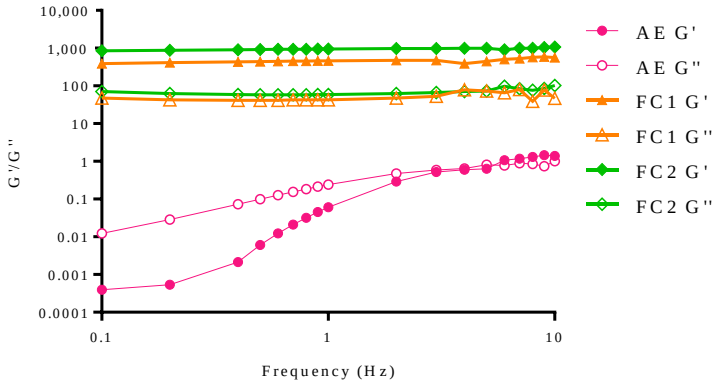


Figure 5. Frequency sweeps of AE, FC1 and FC2 hydrogels, at 25 °C. G′, elastic modulus; G″, viscous modulus.

The data obtained for storage modulus (G′) and loss modulus (G″) for FC1 and FC2 samples showed that these are gel behavior formulations, G′ > G″ (Figure 5). It is noteworthy that the values obtained for G′ are much higher than those obtained for G″, regardless of the frequency range studied. In contrast, the fraction extracted from the plant, AE, showed the lower magnitude of elastic modulus, and a higher frequency dependence, since there is a crossing point at 4 Hz and an inversion of elastic modulus.

In a recent study, Medina-Torres and co-authors (2016) [56] presented viscoelastic properties of different concentrations of mucilaginous gel extracted from *A. vera*. The authors reported that with the increase in the mucilaginous gel concentration, G″ becomes more prominent than G′, favoring increased elasticity. The explanation is the formation of a macromolecular network.

Ni et al. (2004) [7] suggested that glucomannan is responsible for the viscoelastic property of *A. vera* products, according to the observed rheological behavior for the polysaccharide fraction, a partially acetylated glucomannan which is rich in mannose.

Quantification of glucomannan content was obtained using the method described by Eberendu (2005) [46], y = 0.00025x − 0.008, with a correlation coefficient (R^2) of 0.9955, suitable for pharmaceutical products analysis. The glucomannan content of AE used in the

hydrogel formulations (FC1, FC2, FH1 and FH2) was 13.87 ± 0.53 mg glucomannan per g AE, i.e., 1.4% (Table 3).

Regarding the formulations, the glucomannan content was found between 0.4 and 0.92% (*w/w*). Preparations formulated with carbopol (FC1 = 8.69 ± 0.24) and FC2 = 9.17 ± 414 0.24) showed no significant difference in glucomannan values ($p > 0.05$), but those formulated with hydroxypropylcellulose, FH3 and FH4 obtained values around 6.76 ± 1.06 and 4.01 ± 0.51 mg glucomannan per g hydrogel, respectively, with significant differences between them ($p < 0.05$). This greater reduction in the glucomannan content of hydrogels FH3 and FH4 can be explained by the use of heating at 60 °C during the preparation of the formulations, which may have structurally modified the polysaccharides. The results corroborate Femenia et al. (2003) [58], who reports that *A. vera* polysaccharides are affected physically and chemically when subjected to temperatures between 30 and 80 °C.

3.3. In Vivo Antipsoriatic Activity

The histological sections of the skin of the rat's tail (Figure 6), showing Dermis and Epidermis (EP), highlight the stratum corneum of the epidermis (SC). In the animals of the negative control group without treatment (WTG), it was observed that the SC remained with a fibrillar and lacy aspect with a thickness of 234.7 μm^2. On the contrary, the animals from the other experimental conditions, treated with *A. vera* hydrogel (FC1G) and clobetasol propionate (PCG), had a reduction of 145.3 μm^2 and 156.1 μm^2, respectively, in thickness of SC when compared to the negative control group.

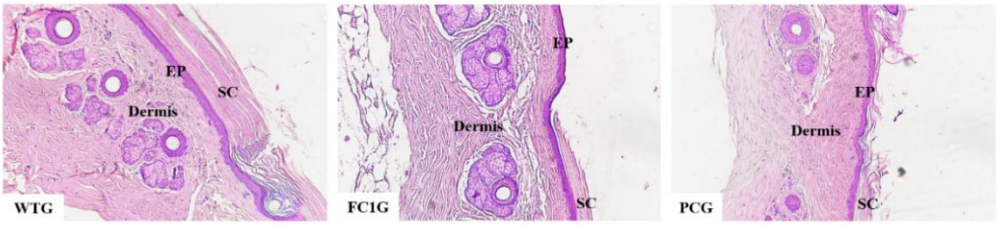


Figure 6. Histological skin section stained in hematoxylin and eosin (HE). Control group without treatment (WTG), group treated with *A. vera* hydrogel (FC1G), and group treated with Clobetazol (PCG). SC: Stratum Corneum. EP: Epidermis.

In the rat tail test, FC1G and PCG decreased the stratum corneum compared to the negative control (WTG) (Figure 7), as they showed a significant decrease in the stratum corneum thickness. There were more than 60% reductions in the stratum corneum for both FC1G and PCG, the main parameter evaluated in the effectiveness of the hydrogel, and there was no significant differences between them.

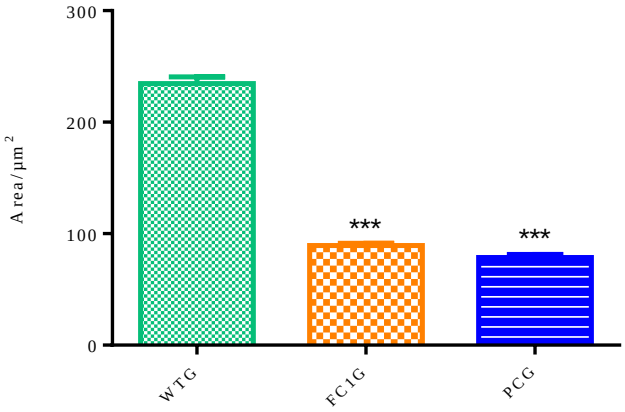


Figure 7. Morphometric analysis of the stratum corneum area under different experimental conditions. Results are displayed as mean ± standard error of mean, with n of 6 animals for each group. *** $p < 0.001$ when compared to the control group. One-way ANOVA followed by the tukey test.

4. Conclusions

In this study, AE-based hydrogels were obtained and evaluated for pH values, spreadability, rheological behavior and glucomannan content. Glucomannan, obtained by the precipitation in ethyl alcohol from the *A. vera* extract, was identified by ^{1}H-NMR and FT-IR experiments and used as a phytochemical marker for quantification in the AE (raw material) and in the obtained hydrogels. All hydrogels (FC1, FC2, FH3 and FH4) showed good spreadability, but only hydrogels FC1, FC2 and FH3 showed adequate pH for skin application. The hydrogels showed pseudoplastic and thixotropic behavior, except hydrogel FH3, which showed rheopectic behavior. The evaluation of viscoelastic behavior of hydrogels FC1 e FC2 confirmed the obtained formulations with adequate characteristics for topical application and higher glucomanann contents. These results show that the gelling agent carbopol, as well as the hydrogel obtention processes, improved the rheological properties of the Aloe extract, confirming the promising use of *A. vera* hydrogel for psoriasis treatment. Histological sections from the in vivo assays showed a reduction in approximately 61% and 66% in the stratum corneum (SC) thickness after treatment with the *A. vera* hydrogel and clobetasol propionate, respectively, when compared to the control group (without treatment). The results show the great potential of *A. vera* hydrogel with keratolytic action that can be used in psoriasis treatment. Although the data obtained are promising, further studies are needed to ensure the efficacy and safety of *A. vera* mucilaginous-based hydrogel products.

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