

## Pharmacotechnical development and characterization of gel based on *Anacardium occidentale* L.

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### SUMMARY

**Introduction:** Among the many plants used in folk medicine, *Anacardium occidentale* L. stands out as a plant belonging to the Anacardiaceae family, commonly known as cashew tree. Several pharmacological properties are known, such as anti-tussive, antisyphilitic, diuretic, wound-healing, and antimicrobial actions. The stem bark is attributed with various pharmacological actions, with notable emphasis on its wound-healing activity. **Objective:** The present study aimed to develop a gel containing *Anacardium occidentale* L. glycolic extract with wound-healing activity, evaluating its physicochemical and microbiological characterization. **Materials and methods:** Two gels, Gel 1 and Gel 2, were prepared, composed of Carbopol® 940, propylene glycol, glycerin, EDTA, nipagin, with the glycolic extract of *Anacardium occidentale* L. incorporated into the gel base. The gels were evaluated on days 1, 20, 25, and 35. The physicochemical quality control was conducted by determining the pH and verifying physical and visual aspects, such as changes in color or precipitation, and spreadability test. **Results:** The formulations presented pH values between 6.0 and 8.0, respectively, normal and homogeneous appearance, and characteristic odor, with attention drawn to the color change in Gel 2 after 20 days of study. Gel 2 exhibited superior and more homogeneous spreadability. Regarding the viable microbial count assay, conducted for microbiological quality control, it was confirmed that the formulations were within acceptable microbial limits. **Conclusion:** Based on the results of this study, the formulations demonstrated acceptable physicochemical and microbiological characteristics, ruling out the need for reformulation.

*Keywords:* Wound healing, Cashew tree, *Anacardium occidentale* L. Gel.

## RESUMEN

### Desarrollo farmacotécnico y caracterización de un gel a base de *Anacardium occidentale* L.

**Introducción:** Entre las muchas plantas utilizadas en la medicina popular, *Anacardium occidentale* L. destaca como una planta perteneciente a la familia Anacardiaceae, comúnmente conocida como árbol de anacardo. Se conocen varias propiedades farmacológicas, como acciones antitusivas, antisifilíticas, diuréticas, cicatrizantes y antimicrobianas. A la corteza del tallo se le atribuyen diversas acciones farmacológicas, con énfasis notable en su actividad cicatrizante. **Objetivo:** El presente estudio tuvo como objetivo desarrollar un gel que contenga extracto glicólico de *Anacardium occidentale* L. con actividad cicatrizante, evaluando su caracterización fisicoquímica y microbiológica. **Materiales y métodos:** Se prepararon dos geles, Gel 1 y Gel2, compuestos por Carbopol 940, propilenglicol, glicerina, EDTA, nipagin, con el extracto glicólico de *Anacardium occidentale* L. incorporado en la base del gel. Los geles se evaluaron en los días 1, 20, 25 y 35. El control de calidad fisicoquímico se llevó a cabo mediante la determinación del pH y la verificación de aspectos físicos y visuales, como cambios de color o precipitación, y la prueba de esparcimiento. **Resultados:** Las formulaciones presentaron valores de pH entre 6,0 y 8,0, respectivamente, apariencia normal y homogénea, y olor característico, prestando atención al cambio de color en el Gel2 después de 20 días de estudio. El Gel 2 mostró una esparcibilidad superior y más homogénea. En cuanto al ensayo de recuento microbiano viable, realizado para el control de calidad microbiológica, se confirmó que las formulaciones se encontraban dentro de los límites microbianos aceptables. **Conclusiones:** Basándonos en los resultados de este estudio, las formulaciones demostraron características fisicoquímicas y microbiológicas aceptables, descartando la necesidad de reformulación.

*Palabras clave:* Cicatrización de heridas, árbol de anacardo, gel de *Anacardium occidentale* L.

## RESUMO

### Desenvolvimento farmacotécnico e caracterização de gel à base de *Anacardium occidentale* L.

**Resumo:** Dentre as muitas plantas utilizadas na medicina popular, destaca-se *Anacardium occidentale* L., pertencente à família Anacardiaceae, comumente conhecida como cajueiro. São conhecidas diversas propriedades farmacológicas, tais como ação antitussígena, anti-sifilítica, diurética, cicatrizante e antimicrobiana. A casca do caule é atribuída a diversas ações farmacológicas, com destaque para sua atividade cicatrizante. **Objetivos:** O presente estudo teve como objetivo desenvolver um gel contendo extrato glicólico de *Anacardium occidentale* L. com atividade cicatrizante, avaliando sua caracterização físico-química e microbiológica. **Materiais e métodos:** Dois géis, Gel 1 e Gel 2 foram preparados, compostos por Carbopol 940, propileno-glicol, glicerina, EDTA, nipagin, com o extrato glicólico de *Anacardium occidentale* L. incorporado à base do gel. Os géis foram avaliados nos dias 1, 20, 25 e 35. O controle de qualidade físico-químico foi realizado através da determinação do pH e verificação de aspectos físicos e visuais, como alterações de cor ou precipitação, além do teste de espalhabilidade. Resultados: As formulações apresentaram valores de pH entre 6,0 e 8,0, respectivamente, aparência normal e homogênea, e odor característico, com atenção voltada para a alteração de cor do Gel 2 após 20 dias de estudo. O Gel 2 apresentou espalhabilidade superior e mais homogênea. Em relação ao ensaio de contagem microbiana viável, realizado para controle de qualidade microbiológica, confirmou-se que as formulações estavam dentro dos limites microbianos aceitáveis. Conclusão: Com base nos resultados deste estudo, as formulações demonstraram características físico-químicas e microbiológicas aceitáveis, não havendo necessidade de reformulação.

*Palavras chave:* Cicatrização de feridas, Cajueiro, Gel de *Anacardium occidentale* L.

## INTRODUCTION

*Anacardium occidentale* L., a perennial plant belonging to the Anacardiaceae family, is commonly known as cashew tree [1]. Native to the northeastern region of Brazil, this plant thrives in regions ranging from sea level to an altitude of 1,000 m. It has expanded into South American countries, was introduced to India and Africa by the Portuguese, and has spread throughout Southeast Asia [1, 2].

Several pharmacological studies have demonstrated the potential of the genus, particularly in terms of its anti-inflammatory activity [3], wound healing properties [4], antifungal effects [5], and broad-spectrum antimicrobial activity [6]. These pharmacological effects have been associated with the presence of metabolites such as flavonoids, terpenes, steroids, xanthenes, and primarily phenolic lipids and derivatives, as well as saponins and essential oils. Additionally, carbohydrates, tannins, catechins, glycosides, resins, alkaloids, and sterols have also been identified in association with these pharmacological effects [7].

In addition to driving the food industry by providing raw materials for the juice and cashew nut-derived products [1], The *Anacardium occidentale L*, with the application of new technologies, stands out as an important source for the extraction of phytotherapeutics and other compounds, thus offering greater opportunities, scientific progress, and technological development to the region and the country. Isolated compounds from the cashew tree have been associated with wound healing activity [4], gastroprotective effects, anti-inflammatory activity, antimicrobial properties, and analgesic effects [8, 9]. Therefore, the literature highlights several procedures involving the use of *A. occidentale* for improving the wound healing process and maintaining cutaneous-membrane integrity.

Wound healing is a complex process. Wound dressings are therapeutic tools that aid in the healing of skin injuries and wounds. Among the numerous studied practices involving dressings, the use of gel has proven to be highly effective due to its hydroactive properties, low cost, and simple and safe manufacturing process [10, 11]. In order to enhance the overall functions of dressings, the incorporation of bioactives, drugs, nanoparticles, and/or other wound healing enhancers has been investigated. These can be incorporated into polymeric matrix wound dressings primarily to improve the quality and accelerate the healing of lesions [11].

Among the pharmacologically active parts of the cashew tree, the bark deserves attention as it is used as an astringent, tonic in various asthenias, appetite stimulant, abortifacient, contraceptive, vaginal antiseptic, and effective in the treatment of aphthae, asthma, bronchitis, intestinal colic, muscle weakness, diabetes, diarrhea, dysentery, skin diseases, sterility, fever, hypertension, throat inflammation, leishmaniasis, malaria, burns, syphilis, cough, peptic ulcer, impotence, genital problems, wound healing activity, gastroprotective activity, among others [12, 13].

The use of natural extract from *A. occidentale* is considered a great promise in the biomedical field. It is abundantly found in nature and easily available in the market. It is popularly known for its wound healing, antibacterial, anti-inflammatory, and anti-

oxidant properties. Therefore, considering the reports on the various pharmacological actions of cashew bark and the characteristics of the wound healing process, the present thesis aims to develop a gel formulation containing *A. occidentale* extract for wound healing, thus contributing to new alternatives in wound treatment and biotechnological development.

The primary goal of this study was to develop a gel formulation containing cashew tree glycolic extract, aiming at the wound healing action described in the literature, in order to provide benefits and treatment alternatives for society.

## METHODS

### Cashew tree bark collection

The sample of the barks were obtained by collecting a sawn branch of the *A. occidentale* plant at Gamelões site (Figure 1), located in Cuité-PB municipality, on February 20th.



**Figure 1:** Species of *A. occidentale*, Cuité-PB.

The branch was cleaned with soap and water to remove residues and contaminants, and the barks were then removed using a machete. The barks were subjected to a drying process in a circulating air oven at 28 °C for two days, and subsequently, they were ground into powder using a knife mill resulting in 138 g of powder.

### Preparation of *A. occidentale* glycolic extract

The obtained powder from *A. occidentale* bark was added to a wide-mouthed flask. Separately, in a graduated cylinder, the 50% water/ethanol solution containing propylene glycol (VETEC) was prepared according to Table 1. The solution was added to the flask containing the *A. occidentale* powder, and maceration was carried out for eight

days with alternating agitation. At the end of maceration, filtration was performed using a Buchner funnel, a Kitasato flask, and filter paper with the aid of a vacuum pump (Primatec 131). The amount of solution (50% hydroalcoholic solution + propylene glycol) specified in the Brazilian Pharmacopoeia Formulary, 2011, was passed over the filtered extract. After filtration, the plant material was subjected to maceration again for eight days, followed by filtration. The extracts from both macerations were mixed at the end of the process.

**Table 1.** Composition of glycolic extract of *A. occidentale*.

Components	Amount
Powder from the bark of <i>A. occidentale</i>	138 g
propylene glycol	13.79 mL
Water/Ethanol (1:1)	258 mL

#### Preparation of *A. occidentale* gel

Table 2 presents the components used for the formulation preparation and their respective functions. Two gel formulations with Carbopol<sup>®</sup> 940 (Carbomer 940) as the base were prepared, containing glycerin, propylene glycol, EDTA (ethylene diamine tetraacetic acid), nipagin (methylparaben), and triethanolamine in their formula. Table 2 describes the composition of the gels containing different amount of *A. occidentale* glycolic extract.

**Table 2.** Composition of healing gel from *Anacardium occidentale L.*

Components	Gel 1	Gel 2
Carbopol	1.5 g	1.5 g
Glycerin	7.5 g	7.5 g
EDTA	0.15 g	0.15 g
Propylene glycol	4.05 g	4.05 g
Nipagin	0.3 g	0.3 g
Triethanolamine	q.s.p	q.s.p
<i>Anacardium occidentale L</i> extract	4 g	8 g
Water	133 g	129 g

After weighing all the components of the base gel formulation, manipulation was carried out as follows: Phase A consisted of propylene glycol and nipagin, with nipagin

dissolved in propylene glycol. Phase B consisted of EDTA and glycerin, with EDTA dissolved in water and dispersed in glycerin. Subsequently, Phase A was incorporated into Phase B.

The Carbopol was pulverized, dissolved in the resulting mixture of Phase A+B, and set aside for 24 hours to allow polymer hydration. After that, triethanolamine was added with agitation. In the next step, the incorporation of *A. occidentale* L. extract into the gel base was performed, and the pH was checked and adjusted.

### Physical-chemical quality control

The gel samples were evaluated on days 1, 20, 25, and 35, and certain parameters such as pH, color change, and precipitation were observed. pH determination was performed using indicator strips (MQuant®), while parameters such as color change and precipitation were assessed through visual analysis.

### Determination of spreadability

To determine the spreadability, a technique proposed by Knorst was used [14], which involves using glass plates on a millimeter paper scale to determine the surface area covered by the sample by measuring the perpendicular diameters and subsequently calculating the mean diameter. One gram of the sample was placed in the central space of the plate, and then a glass plate of known weight was placed on top of the sample. After three minutes, the diameters covered by the sample in a horizontal position were measured using the millimeter paper, and the mean diameter was calculated. This procedure was repeated by incrementally adding weights of 250 g, 500 g, and 750 g at three-minute intervals from one weight to another. This spreadability assay were conducted at room temperature, which was maintained between 21 – 25 °C

The spreadability of the samples was determined based on the added weight, according to:  $Ei = (d^2 \times \pi)/4$ , where:  $Ei$  is the spreadability of the sample for a specific weight in square millimeters (mm<sup>2</sup>) and  $d$  is the mean diameter in millimeters (mm) [15]. The procedure was performed in triplicate for gel 1 and gel 2, and the mean and standard deviation were calculated.

### Microbiological control

Microbiological control was performed through the viable microbial count assay. In the assay, 1 mL of each sample diluted in universal neutralizer was used. The analyses for each dilution were carried out in duplicate. The samples were seeded in depth (Pour Plate) for the enumeration of bacteria and fungi, respectively. The viable microbial count assay involves counting the population of microorganisms that show visible growth

within 5 days on Casein-Soy Agar at  $32.5 (\pm 2.5) ^\circ\text{C}$  and within 7 days on Sabouraud Dextrose Agar at  $22.5 (\pm 2.5) ^\circ\text{C}$  for bacteria and fungi counting, respectively [16].

## RESULTS AND DISCUSSION

### Physicochemical quality control

#### *Organoleptic characteristics*

The organoleptic characteristics were analyzed in terms of appearance, color, and odor. In the evaluation of appearance, visual observation was made to determine if any changes occurred in the analyzed formulations, such as phase separation and formulation precipitation. Color analysis was performed visually, while odor evaluation was conducted directly through olfaction [17].

As a result, the gel formulations containing the *A. occidentale* glycolic extract showed positive results, exhibiting a homogeneous appearance and pleasant odor. Gel 2 only exhibited a slight color alteration, acquiring a darker shade after 20 days of the study. However, this change indicates that it is not due to instability but rather the interaction between the glycolic extract and the formulation during the study. The appearances of the gels remained unchanged throughout the testing period, with no observed phase separation or component separation, clumping, or precipitation (Figure 2). Similarly, no odor modification was observed at the end of the study, as the samples retained their characteristic odor. These data indicate that the formulation demonstrated a good ability to interact with the *A. occidentale* glycolic extract, which was confirmed by monitoring the physicochemical characteristics of the samples under the three evaluated conditions.

The formulations did not exhibit phenomena such as precipitation, syneresis, or phase separation, and their appearance was considered normal without any changes. In the formulation of gel 2, a change in color was observed, shifting from a reddish hue to a brownish color, as shown in Figure 3.

Sing *et al.* (2007) developed three herbal gels using three different polymeric bases: Carbopol<sup>®</sup>, carboxymethyl cellulose (CMC), and hydroxypropyl methylcellulose (HPMC), and monitored their stability. The stability study conducted on the three different formulations yielded different and relevant results at the end of the study. The authors observed a significant decrease in the pH of the CMC gel, along with a change in physical appearance, resulting in a loss of semi-solid consistency. Physical changes were also observed in the HPMC gel. Variations in color, appearing darker, were observed in the Carbopol<sup>®</sup> and



HPMC gels. Based on these results, the authors selected the Carbopol® gel as the most stable for the development of herbal formulations.

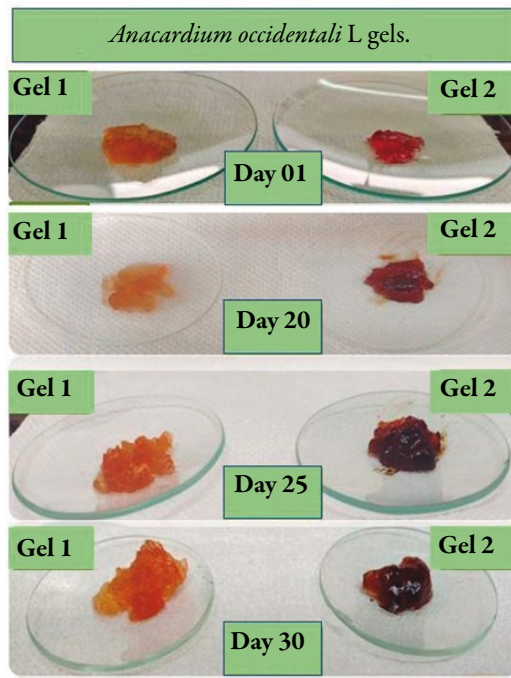


Figure 2. Gels containing *A. occidentale* extract and the analysis of day 1, 20, 25 and 35.

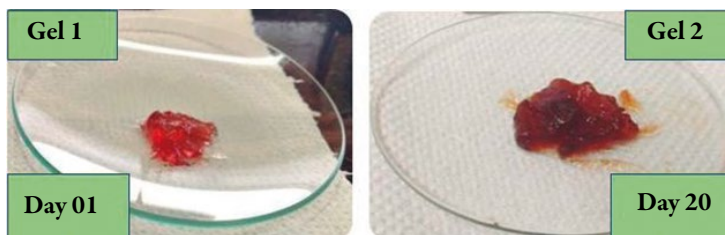


Figure 3. Aspect of Gel 2 on the 1st and 20th day

The color and odor variations in herbal formulations may not be considered significant, as high temperature can interfere with the organoleptic characteristics of semi-solid formulations. Therefore, it is necessary to provide guidance to the patients regarding temperature and appropriate storage conditions based on the type of formulation [18].

### pH determination

The pH values determined using indicator strips on days 1, 20, 25, and 35 are presented in Table 3.

**Table 3.** pH values on days 1, 20, 25, 35 of Gel 1 and Gel 2.

Gel	pH	Day
1	6.0	1
	6.0	20
	6.0	25
	6.0	35
2	9.0	1
	8.0	20
	8.0	25
	8.0	35

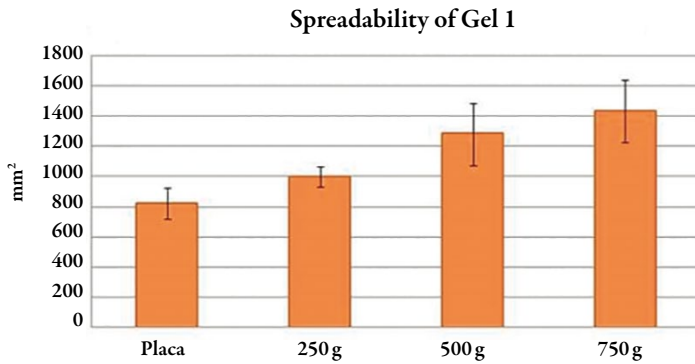
The pH of a formulation is standardized based on the stability pH range of active components and the biological tolerance range for topical products (5.5 to 8.0). The gel formulations developed in this research showed a pH compatible with the skin (6.0 and 8.0, respectively) and no significant changes were observed at the end of the study.

The determination of pH is a critical factor in the study of stability, as changes in pH value can occur due to various factors such as impurities, hydrolysis, decomposition, and process error. These instabilities can also occur due to storage time and/or improper transportation and storage conditions [19].

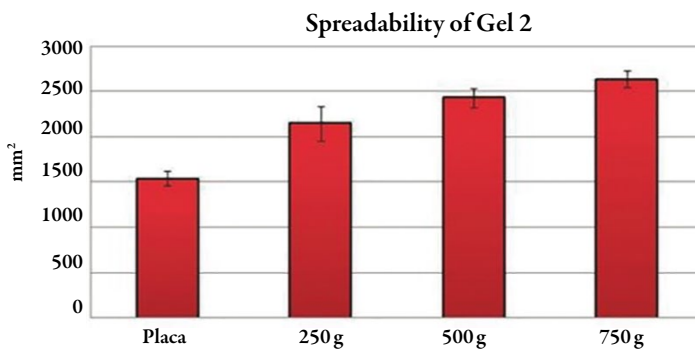
### Spreadability determination

Figures 4 and 5 present the results of gel spreadability expressed in  $\text{mm}^2$ , showing the spreadability indices ( $y$ ) and the weights applied to the sample ( $x$ ). This test aimed to evaluate the time taken for the formulation to spread over the applied surface, thus identifying any changes in the product's consistency.

By observing Figures 4 and 5, it is possible to evaluate that gel 2 exhibited superior spreadability, with a more homogeneous distribution and a low standard deviation when compared to gel 1.



**Figure 4.** Spreadability of Gel 1



**Figure 5.** Spreadability of Gel 2

The spreadability test of the topical gel allows for the evaluation of product changes and can indicate ease or difficulty in its application [20]. Spreadability is explicitly demonstrated by the amplification of formulations intended for topical applications over a specific period at targeted sites, making it an essential attribute in pharmaceutical forms. In semi-solid formulations for topical use, quantifying this parameter is important to monitor changes in the formulation's ability to spread in a specific area, which can either facilitate or hinder its application, distribution, and/or absorption through the skin [15].

## Microbiological Quality Control

### *Viable Microorganism Count*

In the viable microorganism count assay using agar casein soy culture medium for bacteria, the plates showed low colony growth as shown in table 4, not exceeding the limits allowed by the Brazilian Pharmacopoeia, 6th edition; 2019, which sets a maximum limit of  $10^2$  CFU of non-pathogenic bacteria for non-sterile products. There was also low fungal growth in the samples cultured on Sabouraud medium, complying with the limits specified by the Brazilian Pharmacopoeia, 6th edition; 2019, which sets a maximum limit of  $10^1$  CFU per plate.

**Table 4.** Viable Microorganism Count

Bacteria (Soy Casein Agar)		
Sample	Bacteria (Soy Casein Agar)	Fungi (Sabouraud Dextrose Agar)
Gel 1	3.3 UFC/mL	6.6 UFC/mL
Gel 2	20 UFC/mL	10 UFC/mL

Microbiological evaluation allows verifying whether the choice of the preservation system is adequate or if interactions between formulation components may compromise its efficacy [17].

Microbial contamination of a product can cause changes in its physical and chemical properties and also pose a risk of infection to the user. Therefore, orally and topically used pharmaceutical products (capsules, tablets, suspensions, creams, patches, etc.) that are not intended to be sterile should be subject to microbial contamination control. Quality assurance and manufacturing control provided by good practices should ensure that the product meets the specified requirements, including acceptable limits for microorganisms, among other parameters [16].

Other criteria that should also be considered include the microbial load of raw materials, the manufacturing process, the product formulation, and the results of water activity determination, when applicable. Low water activity results (equal to or less than 0.75 measured at 25 °C), as well as low or high pH, absence of nutrients, and the addition of preservatives, help prevent microbial contamination [16].

## CONCLUSION

The gel base formulations of Carbopol® 940 gel and *A. occidentale* glycolic extract demonstrated acceptable physicochemical characteristics after manipulation. This work

contributed to clarifying important aspects in the field of compounding, as the pharmaceutical development and characterization study allows for a better understanding of the physicochemical nature of the vehicle and quality control of raw materials and finished products. Based on the results of this study, it can be stated that Gel 2 exhibited relevant and positive characteristics when compared to Gel 1, resulting in a homogeneous appearance and pleasant odor, as well as superior spreadability. Therefore, it can be suggested that the presented gel formulation is stable, with the composition of the gel considered appropriate, thus ruling out the need for reformulation.

## CONFLICTS OF INTEREST

The authors have reported no conflicts of interest.

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