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Production and Characterization of a β-Cyclodextrin Inclusion Complex with *Platonia insignis* Seed Extract as a Proposal for a Gastroprotective System

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Abstract: *Platonia insignis* Mart, Clusiaceae, known as *bacuri*, is a species native to Brazil that, in studies with extract of the seed of its fruit, showed antioxidant activity against free radicals. Products with such properties may be of great importance in the treatment of peptic ulcers since this pathology may be associated with the inflammatory process caused by the action of free radicals. Cyclodextrins are molecules capable of forming inclusion complexes with other molecules, affecting their physicochemical properties and improving their pharmacokinetic characteristics. Thus, this work aimed to produce, characterize, and evaluate the gastroprotective effect of the inclusion complex of β-cyclodextrin (β-CD) with the *bacuri* seeds hexanic extract (BSHE). In the characterization of the inclusion complex, an apparent stability constant (Kc) of 416 mol/L was obtained in the solubility study; the BSHE:β-CD m/m (g) complexation ratios at 1:9, 2:8, and 3:7 were 5.51%, 21.46%, and 20.11%, respectively. The formation of the BSHE:β-CD inclusion complex was observed by FTIR technique, indicating the disappearance of bands characteristic of BSHE (2960 cm^{-1} and 1755 cm^{-1}) when in the complex, compared to the spectra of pure BSHE or in physical mixture with β-CD, and by X-ray diffraction, which indicated a loss of crystallinity, typical signals of pure β-CD, and presentation of intense amorphization, characteristic of BSHE, incorporated in the β-CD pockets. In the evaluation of gastroprotective activity, through absolute ethanol-induced gastric lesions in mice, both BSHE and BSHE:β-CD reduced gastric lesions, with 100 mg/kg dose of the complex having the greatest gastroprotective effect. BSHE:β-CD was also able to reduce gastric lesions from ischemia and reperfusion, with the 50 mg/kg dose being the most effective. BSHE:β-CD, also at this dose, reduced the MDA levels of the gastric mucosa, indicating a possible antioxidant activity in its gastroprotective effect. Thus, it was concluded that inclusion complex formation between β-CD and BSHE is possible, and that this formulation enhanced the gastric protective activity.

Keywords: *Platonia insignis* Mart; *bacuri*; β-cyclodextrin; ulcer; gastroprotection

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1. Introduction

Natural products have been used as the main source of compounds for medicines, cosmetics, and food, being an important resource for technological development and

health maintenance [1–3]. Environmental, ecological, food resources, and health benefits are strictly linked under biodiversity perspectives: studies on the taxonomy of plants, increasing species variety, tracking species' biochemistry, intra-species biodiversity, or environmental influences and how these affect food quality and health advantages have become key issues [4]. Brazilian biodiversity represents a promising source for research on new active pharmacological compounds [1,5,6]. Despite Brazil being responsible for up to 20% of the living species known in the world, part of the Brazilian biological and chemical biodiversity remains unexplored [1].

Among the plant species native to Brazil, *Platonia insignis* Mart. (Clusiaceae), popularly known as *bacuri*, has been the subject of many studies. Studies have revealed that *bacuri* seeds have the following constituents: unsaturated fatty acids (oleic, stearic, and linoleic), diterpenes, and prenylated benzophenones, such as garcinielliptone (about 10–12% of the fatty extracts from *bacuri* seeds), diterpenes, alcohols, and long-chain hydrocarbons [7–9]. Pharmacological investigations of the extract of the seeds of *P. insignis* fruits report some activities, such as antioxidant [10,11], leishmanicidal [12], and anticonvulsant [13]. In addition, the decoction of fruit seeds is popularly used to treat diarrhea [14].

The gastric mucosa is often exposed to different harmful agents, endogenous (hydrochloric acid and pepsin) or exogenous (*Helicobacter pylori*, smoking, alcohol intake, use of NSAIDs, stress) that can trigger gastric ulcers and even tumors [15–18]. Peptide ulcers, for example, have some treatment models that can promote the healing of mucosal damage [18]. The antioxidant activity already proven for the extract of *bacuri* seeds may be important for the gastroprotective action of this vegetable derivative since free radicals can cause the appearance of ulcers and inflammatory processes in the gastrointestinal tract [19–23]. Several antioxidant compounds control the production of free radicals, which may have an endogenous origin or come from the diet and other sources (e.g., ascorbic acid, β-carotene, vitamin E, unsaturated fatty acids, and selenium) [19–22,24–27]. Antioxidants have the ability to stabilize or even deactivate such radicals before biological targets in cells are reached [28]. In general, the more hydroxyl substitutions, the stronger the antioxidant and prooxidant activities [29,30].

Cyclodextrins are organic molecules with a hydrophobic internal cavity and, therefore, capable of forming inclusion complexes with a wide variety of organic molecules, which can affect the physicochemical properties of the target molecule, such as antioxidant activity, water solubility, and stability [30,31]. Encapsulation can also increase dissolution rate, membrane permeability and bioavailability, mask flavor and increase product shelf life, providing protection against degradation of light or heat [32–35] also in the perspective of nanopharmaceutical and nanonutraceutical area, interesting in both pharmaceutical and food industries by possibility to control their properties using different types of raw materials [36–38].

Therefore, the present paper proposed the production and characterization of an inclusion complex β-cyclodextrin and hexanic extract of bacuri seeds and the evaluation of its gastroprotective effect in a gastric ulcer model.

2. Material and Methods

2.1. Drugs and Reagents

Garcinielliptone was isolated by silica gel column chromatography of the hexanic extract of the seeds of *P. insignis* Mart. and identified by hydrogen and carbon nuclear magnetic resonance and mass spectrometry [9,39]. For the extraction of raw materials, hexane (Labsynth, Diadema, SP, Brazil) was used, and in the preparation of the analysis solutions, methanol and absolute ethanol (Labsynth, Diadema, SP, Brazil). Commercially purchased were: β-cyclodextrin (Sigma-Aldrich, St. Louis, MO, USA), carbenoxolone, N-acetylcysteine (Eurofarma, Itapevi, SP, Brazil), Tween 80 (Sigma-Aldrich, St. Louis, MO, USA), sodium thiopental (Cristália, Itapira, SP, Brazil), 10% ketamine chloridate (Syntec), 2.0% chloridate xylasin (Syntec, Santana de Parnaíba, SP, Brazil), acetic acid (Labsynth,

Diadema, SP, Brazil), and thiobarbituric acid (TBA) and sodium duodecyl sulfate (SDS) from Sigma-Aldrich, St. Louis, MO, USA.

2.2. Extract Preparation and Procedures for Production and Characterization of a β-Cyclodextrin Inclusion Complex with Platonia Insignis Seed Extract

2.2.1. Hexane Extract from Platonia Insignis Seeds

The *bacuri* seed was obtained at the Piauí Supply Center—CEAPI, and a desiccant was deposited at the Herbarium Graziella Barroso of the Federal University of Piauí, Brazil (under number: ICNTEPB27164). The seeds of the fruits were dried and powdered, following by extraction with hexane in Soxhlet for 8 h. The evaporation of the solvent was followed by a total extraction yield of 42.98% (Figure 1). The chromatographic profile of the *bacuri* seed hexane extract (BSHE) was obtained by high-resolution gas chromatography coupled to a mass spectrometer (HRCG/MS), using an Agilent chromatograph with a DB5 capillary column (J&W) (30 m × 0.25 mm × 0.25 m) in split mode (10:1). The chemical constituents were identified by the characteristic fragmentation and by comparison of the mass spectra obtained with the records of the NIST 2.0 computational library.

2.2.2. Phase Solubility Studies

The investigation of phase solubility was conducted according to Higuchi and Connors (1965) [40], in triplicate, adding the excess extract to test tubes containing aqueous solutions of β-cyclodextrin (Figure 1), in increasing concentrations (0–10 mmol/L). The solutions were heated to 50 °C for 10 min to solubilize the extract. The samples were kept in a water bath at 37 °C, under agitation, for two days. After the suspension reached equilibrium, aliquots were removed, filtered through filter paper, and diluted in methanol.

To carry out the quantification of the BSHE in the tests, a stock solution of this substance at a concentration of 0.2 g/L in methanol was scanned, from which a series of dilutions was prepared to obtain concentrations from 1 to 35 mg/L, with absorbance measurements at a wavelength of 280 nm. Equation (1) was used to calculate the apparent stability constant (Ks) of the BSHE:β-CD inclusion complexes from the slope of the phase solubility diagram and the solubility of BSHE in the absence of CD (S_0).

$$\mathrm{Ks} = \frac{\text{slope}}{S_0\,(1 - \text{slope})} \tag{1}$$

2.2.3. Production of BSHE:β-CD Inclusion Complexes

The inclusion complexes between the hexanic extract and β-CD were prepared by two methodologies [41] (Figure 1). In the first method, the mass refers to the extract being dissolved in 20 mL of ethanol, under heating and continuous agitation, and the mass referring to β-CD was dissolved in 250 mL of an ethanol:water mixture (1:4), under heating and agitation. The two solutions remained under stirring and heating at 70 °C for 35 to 40 min. Complexes were prepared in 1:9 proportions, 2:8; 3:7 BSHE:β-CD m/m (g). The solution was injected into the bench-top spray dryer, BUCHI B-290, with an inlet pressure of 0.9 Bar, with a sample flow of 7 mL/min, inlet temperature of 105 °C, outlet temperature of 62 °C, and sample temperature of 60 °C. The other methodology used was that of BSHE:β-CD by physical mixing, where the referent mass of the extract was mixed with the referent mass of β-cyclodextrin using grade and pistil.

2.2.4. Determination of Garcinielliptone FC by UV-Vis in BSHE and BSHE:β-CD Inclusion Complexes

The garcinielliptone FC analytical curve was prepared using concentrations from 5 to 40 mg/L, for which absorbance measurements were read at a wavelength (ʎ max) of 280 nm, using a Varian Cary 300 double-beam spectrophotometer UV/Vis [42]. The reading wavelength was identified by scanning the garcinielliptone in methanol in the range of 200 to 400 nm. The analysis of the hexane extract by high-performance gas chromatography (HPGC-MS) allowed verifying 16 chemical constituents in the total ion

chromatogram. The hexane extract has a composition rich in fatty acid esters, obtaining the following constituents with the respective contents (Table 1). It should be noted that peak 12 represents the major constituent of the extract, which is a prenylated benzophenone.

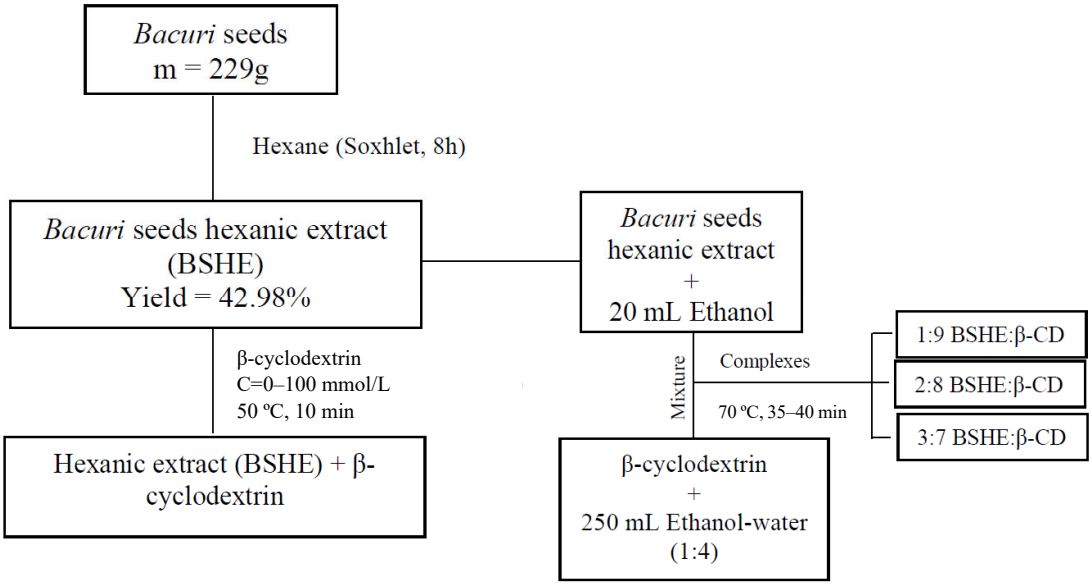

Figure 1. Graphical scheme of extract preparation (BSHE) and procedures for the production of a β-cyclodextrin inclusion complex with *Platonia insignis* seed extract.

Table 1. Chemical constituents (%) hexanic extract of the seeds of *P. insignis* Mart.

Peak	Constituents	Tr (min)	Area (%)
1	Methyl ester of palmitoleic acid C16:1 cis 9	19.131	0.44
2	Palmitic acid methyl ester C16:0	19.934	4.66
3	Palmitic acid ethyl ester C16:0	22.033	0.42
4	Linolenic acid methyl ester C18:3 cis, cis, cis 9,12,15	24.596	0.13
5	Linoleic acid methyl ester C18:2 cis, cis 9.12	24.747	0.17
6	Oleic acid methyl ester C18:1 cis 9	24.93	3.57
8	Stearic acid methyl ester C18:0	25.647	0.49
9	Gadoleic acid methyl ester C20:1 cis 9	26.599	0.18
10	Squalene	39.48	0.52
11	GFC (garcinielliptone FC)	41.037	0.50
12	Prenylated benzophenone (γ-mangostine)	43.754	77.35
13	Campesterol	46.122	0.74
14	Stigmasterol	46.506	1.14
15	Sitosterol	47.447	1.06
16	Lanosterol	47.93	3.45

Through the analytical curve of garcinielliptone FC produced, it was determined that the concentration of garcinielliptone in the hexane extract was 7.71% ± 0.47, which has anti-inflammatory activity [13,43,44].

To determine the garcinielliptone content in the complexes, the garcinielliptone analytical curve was used, and the non-complexed extract was removed from the β-cyclodextrin molecules by washing the complexes formed with hexane. For this, 8 mL of hexane was added and dissolved for a few seconds in the ultrasound; the supernatant liquid was slowly aspirated with a dropper, performing this procedure in triplicate for each complex until only complexed extract was left. Then, the complexes were stored in a desiccator until drying and UV/Vis analysis. The washed complexes removed from the desiccator were dissolved in methanol, and the volume was made up to 10 mL, being analyzed at 280 nm in triplicate.

2.2.5. Characterization of BSHE:β-CD Inclusion Complexes

The FT-IR spectra of samples were recorded using an FT-IR spectrometer (Varian 660-IR) equipped with a diamond crystal cell for attenuated total reflection (ATR). The spectra were obtained (32 scans per sample or background) in the range of 400–4000 cm^{-1} range with a nominal resolution of 4 cm^{-1} at room temperature. The air as a background spectrum was used to adjust the spectra. A lyophilized/powder sample was applied to the ATR crystal surface for the measurements. The ATR crystal was meticulously cleaned using wet cellulose tissue before being dried with a flow of nitrogen gas. To make sure that no residue from the prior sample was left on the cleaned crystal, it was spectrally inspected. Each sample spectrum was captured five times in order to assess its reproducibility and perform statistical analysis. A Shimadzu model XRD-6000 X-ray diffractometer with Cu radiation was used to conduct the XRD experiments. At a scan rate of 2°/min, the samples were scanned from 2θ = 10–55°. To maintain a flat sample plane, the powder sample was spread out on a glass plate, and measurements were taken.

2.3. In Vivo Study by Animal Model: Performance as Gastroprotective System

2.3.1. Animal Models

Mice (*Mus musculus*, Swiss variety) were used, weighing between 25 and 30 g, and rats (*Ratus norvegicus*, Wistar lineage), weighing 180 to 220 g, were supplied by the Animal Facility from Research Center for Medicinal Plants from the University Federal of Piauí (Teresina, Brazil). The animals were maintained in standard cages at a controlled temperature (24 ± 1 °C) and a 12 h light/dark cycle, with free access to water and food. They fasted for a period of 18 h and were acclimatized to the test environment for 2 h before each experiment. In all experiments, the animals were kept in raised cages with a wide mesh floor to avoid coprophagy. After the experimental procedures, the animals were euthanized with an overdose of sodium thiopental (100 mg/kg, i.p.). The experimental protocols were approved by the Ethics Committee on the Use of Animals of Universidade Federal do Piauí (Teresina, Brazil) under approbation no. CEEA-PI 008/12.

2.3.2. Ethanol-Induced Gastric Ulcer

After an 18 h fasting period, mice were randomly divided into groups of six animals. Acute gastric lesions were induced by intragastric administration of absolute ethanol in a volume of 0.2 mL per animal [45]. According to the division of the animal groups, 1 h before the application of the ulcerogenic agent, it was administered orally: BSHE (25, 50, and 100 mg/kg), BSHE:βCD (25, 50, and 100 mg/kg), saline (negative control) or carbenoxolone (100 mg/kg). After 30 min, The stomach was taken out and opened along the point of greatest curvature after the animals were euthanized. The stomachs were scanned, and the percentage (%) of the ulcerated region in relation to the overall stomach area was determined using the Image J software (Figure 2) [46]. A glandular part of the stomach was used for malondialdehyde assay.

2.3.3. Gastric Lesions Induced by Ischemia and Reperfusion in Rats

Wistar rats (n = 6/group) were treated orally with saline, N-acetylcysteine (200 mg/kg), BSHE (25; 50 and 100 mg/kg), or BSHE:β-CD inclusion complexes (25, 50, and 100 mg/kg). After 30 min, the animals were anesthetized (ketamine 30 mg/kg and xylazine 0.3 mg/kg) by intraperitoneal injection (Figure 2). An incision was made in the abdomen, and after the location of the celiac artery, the animals were subjected to 30 min of ischemia induced by the occlusion of the artery by a microvascular clamp and followed by reperfusion of 1 h according to the adapted method by Ueda and Okada [47]. Then, the animals were euthanized, and their stomachs were removed and prepared for analysis, as mentioned above.

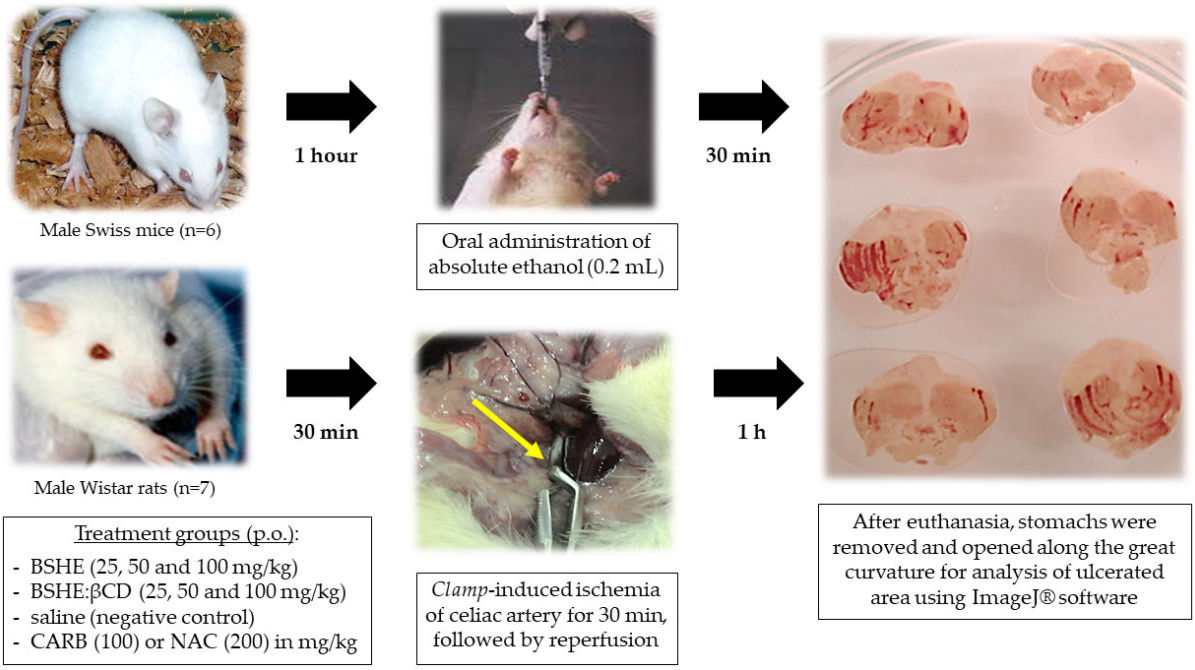

Figure 2. General scheme of ethanol and ischemia/reperfusion-induced gastric ulcers in rodents. Legend: CARB = carbenoxolone; NAC = N-acetylcysteine.

2.3.4. Dosage of Malonaldehyde (MDA)

A total of 100 mg of the glandular part of the stomach was weighed and cut into small pieces and stored at −70 °C. Then, 1 mL of phosphate buffer was added and homogenized in a tissue crusher. It was centrifuged at 10,000× *g* rpm at 4 °C for 5 min. A total of 300 µL of the supernatant was pipetted, and a mixture of 350 mL of acetic acid (pH 3.5) and 600 mL of diluted thiobarbituric acid (TBA) at 0.5% was added. The tubes were shaken every 15 min while they were held in a water bath at 85 °C for 1 h, followed by a freezing bath for 15 min. Afterward, each tube received 50 µL of 8.1% sodium duodecyl sulfate (SDS). The tubes were then centrifuged for 15 min at 12,000× *g* rpm and 25 °C. After removing the supernatant, the spectrophotometer was read at 510, 532, and 560 nm [48].

2.4. Statistical Analysis

The results were presented as mean ± S.E.M. (standard error of the mean). The data obtained were evaluated using analysis of variance (ANOVA) followed by the Tukey test using GraphPad Prism version 5.0. The differences were considered significant when values of $p < 0.05$.

3. Results and Discussion

3.1. Characterization of the BSHE:β-CD Inclusion Complexes

Cyclodextrins (CDs) are water-soluble cyclic oligomers derived from starch used to improve the solubility, stability, and bioavailability of drugs [49–52]. In addition, some studies have reported that the formation of the inclusion complex can prolong and increase the duration and intensity of medications [49–53]. Cyclodextrins can be found in more than 35 commercially available drugs, including pills, parenteral solutions, eye drops, ointments, and suppositories [54–57].

The formation of the inclusion complex is facilitated by the removal of water molecules from the inside of the DC cavity, partially hydrophobic, and their replacement by nonpolar molecules spontaneously, being, therefore, an energetically viable process [49]. This process is facilitated by the action of several forces of interactions, such as the formation of hydrogen bonds, van der Waals interactions, the very change in the surface tension of the medium,

and the reduction of the tension of the cyclodextrin ring, which, combined, strongly influence the formation of the inclusion complex [53,55–57].

Figure 3 corresponds to the concentration of BSHE versus the concentration of cyclodextrin. In order to calculate the stability constant (Kc) and the stoichiometry of the complex formation from the intrinsic solubility of the substrate (So) and the slope of the straight line resulting from the solubility diagram, the complexation study allows for the analysis of the solubility results of the guest molecule in solutions with increasing concentrations of CDs [55,56,58–60].

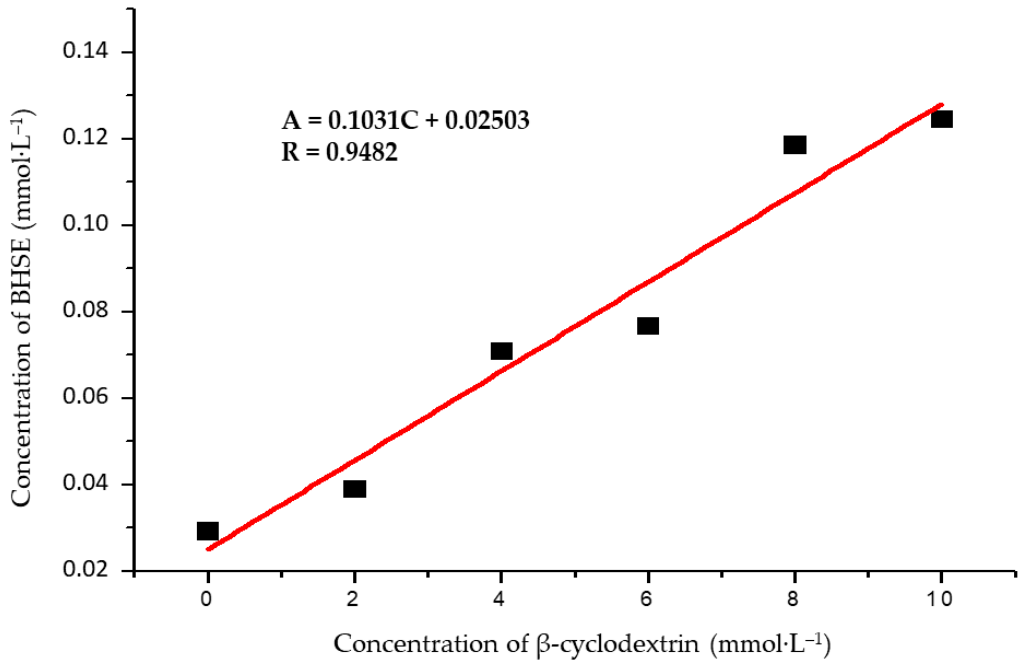

Figure 3. Solubility diagram of the BSHE:β-CD inclusion complexes.

The average molar mass of the BSHE, necessary for the realization of the diagram, was obtained through the analysis of the chemical constituents of the hexanic extract and their respective contents, obtained through the total ion chromatogram of the fraction of this extract, as shown in Table 1. The diagram obtained from β-CD is of the increasing linear type because its solubility increases in direct proportion to the concentration of the complexing agent. From the diagram, the angular coefficient was obtained, with a result of less than 1 (0.01031), indicating the stoichiometry of the 1:1 complex [61–63].

From the straight-line equation obtained from the β-CD solubility diagram, the stability constant (Kc) was calculated based on the equations created by adapting Higuchi and Connors (1965), which assesses the mechanism by which the solution containing cyclodextrin (CD) and drug (F), forms the complex (CD.F), and complexation efficiency (Ec) [62–65], described below (Equations (2)–(4)):

$$K_{C1:1} = \frac{\text{Angular coefficient}}{S0\ (1 - \text{Angular coefficient})} \tag{2}$$

$$Ec = \frac{\text{Angular coefficient}}{(1 - \text{Angular coefficient})} \tag{3}$$

$$CD + F \overset{Kc}{\Leftrightarrow} CD.F \tag{4}$$

The higher the (Kc) value obtained, the easier it is to form an inclusion complex. In the inclusion complex formed between the hexanic extract of bacuri seeds and the β-CD molecule, a constant value (Kc) of 416 mol/L was obtained. In pharmaceutical terms, it is desirable to use formation complexes whose constant is between 100 and 1000 M^{-1}.

Drugs having a lower formation constant form unstable complexes, while those with high formation constants are too stable to release the drug into the body [66]. Therefore, Figure 1 shows that EHSB complexation is feasible and can improve the solubility of the system in view of the characteristics of cyclodextrin. For the aspect ratio 1:9, 2:8, and 3:7 of EHSB:β-CD (w/w), complexation yields were, respectively, 5.51%, 21.46%, and 20.11%. Possessing a better complexation ratio, the BSHE:β-CD 3:7 formulation was chosen in the gastroprotection protocols for its higher content of the marker garcinielliptone and better antioxidant activity [67].

This could be related to the fact that during the complexation process, not all molecules are able to penetrate the cyclodextrin cavity, either due to their size, their weak affinity, or even the excessive amount of drug compared to the amount of cyclodextrins for complexation [62,63,65,66]. Therefore, in a complexation process, there will be free drug, complex drug, and free cyclodextrin, in balance [58,59,62,63]. The challenges for complexation processes include nonpolar molecules (or functional groups of molecules) whose dimensions are smaller than those of the cyclodextrin cavity that can be included in that cavity [68,69]. The dynamic balance between free drug molecules and complexed drug molecules is quantitatively described by the stability or association constant, where there is the existence of complex drug, free drug, and free CD [70–72].

Figure 4 shows the FT-IR spectra of the BSHE:β-CD inclusion complexes. By comparing the infrared spectra of the pure drug, cyclodextrin, and the solid complexes obtained by various production methods [59,69–73], one may assess the formation of inclusion complexes in the solid phase. The vibrational spectrum of the various functional groups of the complexed or free drug molecules is used to detect substantial changes in the shape and location of the absorption bands, hence verifying interactions at the molecular level [74–77]. FT-IR spectroscopy can be viewed as a "fingerprint analytical technique" that allows the structural identification of compounds, considering that two chemical structures will not provide the same FT-IR spectrum [78]. By highlighting their molecular vibrations, or the stretching, bending, and torsion of the chemical bonds, in specific infrared areas, FT-IR provides typical characteristics of chemical or biochemical components in the samples.

Even though cyclodextrin and BSHE's interactions in the inclusion complex are not particularly strong, since they are non-covalent electrostatic bonds (Van der Waals, hydrophobic interactions, hydrogen bonds) [79–82], deviations and changes in the intensity of several bands are observed when we compare the isolated spectra of BSHE and β-cyclodextrin molecule. In the spectrum of β-cyclodextrin (Figure 4A), a broadband of medium intensity in 3250 cm^{-1} is observed, attributed to the stretching of the O-H bonds, and a strong band in 1030 cm^{-1}, attributed to the stretching of the simple C-O bond. The BSHE's infrared spectrum shows a marked absorption in 2960 cm^{-1} as main bands, related to the asymmetric stretch C-H of alkanes; in 1755 cm^{-1}, it also has a strong band related to the stretching of the C=O bond of esters and/or ketone and in 1100 cm^{-1} plus a strong absorption band, related to the simple CO bond stretching of esters (Figure 4B).

Figure 4C shows an overlap of the patterns of the physical mixture BSHE:β-CD. The characteristic bands of BSHE and β-CD (2915 cm^{-1}, 1734 cm^{-1}, and 1020 cm^{-1}) were identified, demonstrating that there was a weak interaction between the extract and β-CD. In the formation of the inclusion complex BSHE:β-CD (Figure 4D), it shows that the bands in 2960 cm^{-1} and in 1755 cm^{-1} decreased a lot in intensity, reaching almost the disappearance. These phenomena are associated with the insertion of a molecule into the β-CD cavity, which causes a conformational restriction, reducing the free movement of encapsulated molecules and contributing to the reduction of the intensity of their signals. The band 1030 cm^{-1} shifted to 1023 cm^{-1} and increased in intensity, indicating a convolution of peaks.

The spectra of inclusion complexes in different proportions of BSHE:β-CD were also analyzed (Supplementary 1). The three proportions of 2:8, 3:7, and 1:9 m/m (g) of BSHE:β-CD demonstrate that there was a suitable complexation between the molecule BSHE and β-CD, as there was an intense decrease in the characteristic peaks of BSHE, without significant differences between the complexes.

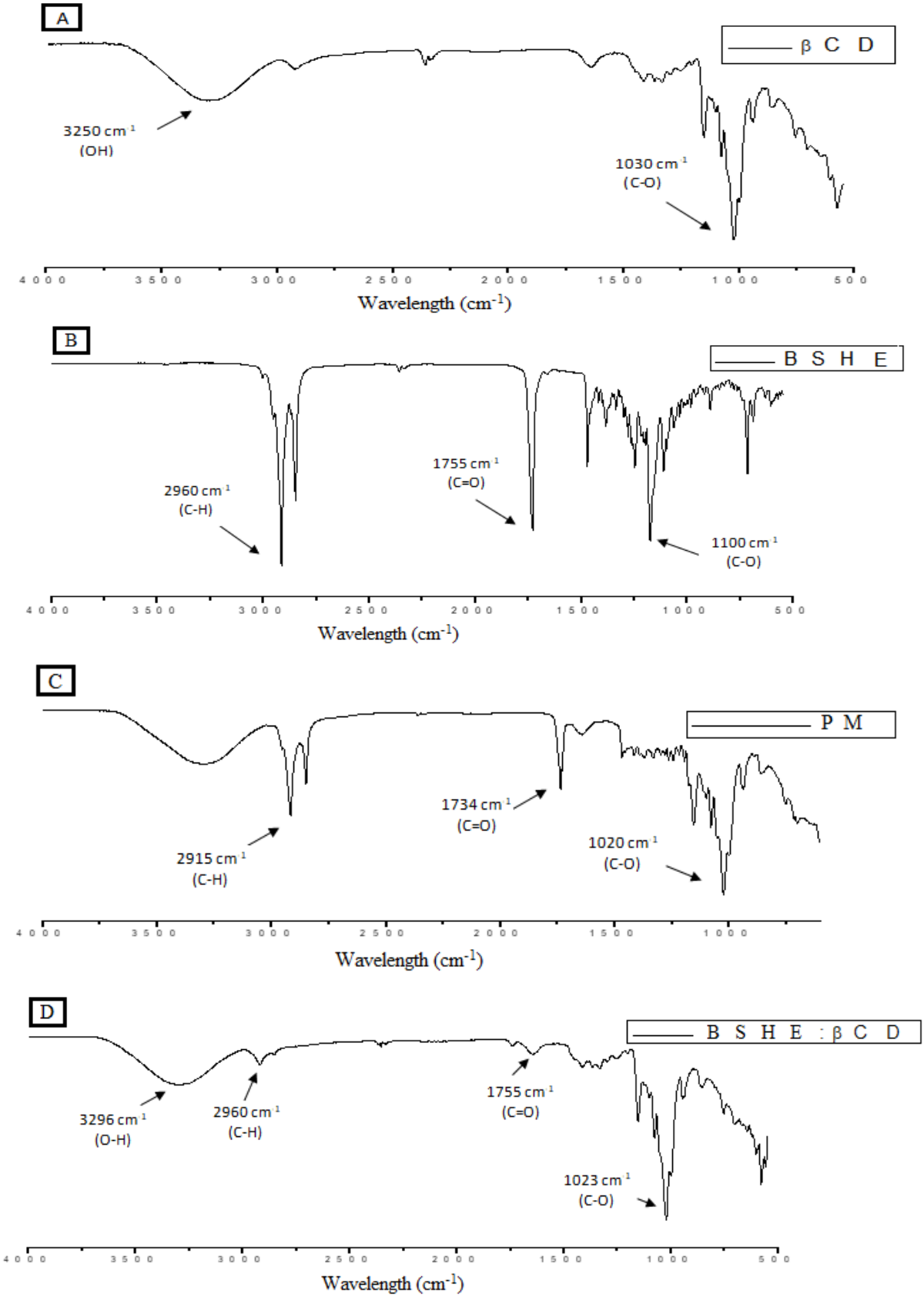

Figure 4. Infrared spectrum of samples containing BSHE and β-CD. (**A**) β-cyclodextrin molecule, (**B**) bacuri seed hexane extract (BSHE), (**C**) physical mixture between BSHE:β-CD, and (**D**) BSHE:β-CD inclusion complexes.

The formation of the inclusion complex was also verified by the P-XRD spectrum [83,84]. X-ray diffraction (XRD) is one of the best techniques for the characterization of inclusion complexes due to its simplicity and speed because it allows a morphological study of the substances and their structures and/or crystalline fractions [85–89]. The guest molecules replace the enthalpy-rich water molecules from the inner cavity during the development of an inclusion complex. This results in modifications to the crystal lattice, which alter the inclusion complex's XRD pattern [90]. When compared to the pattern of the complexes, they exhibit stronger crystallinity. The diffraction pattern of a physical mixture often involves the overlapping of the patterns of the guest molecule and the β-CD with peaks of smaller intensity [91]. When the formation of inclusion complexes occurs, changes in the characteristic peaks of the host molecule can form new peaks, which indicate a new solid phase, which corresponds to the drug-β-CD complex [92].

The analysis of the β-CD molecule by XRD (Figure 5) shows that there is the formation of several diffraction peaks, presenting itself as a high crystalline compound. The β-CD diffractogram showed characteristic peaks at 2θ = 9.30°, 10.72°, 12.88°, 15.50°, 17.20°, 22.81°, 27.23°, and 32.01°. The BSHE has an amorphous characteristic, with some characteristic peaks at 2θ = 19.24°, 22.70°, and 23.22°. The physical mixture BSHE:β-CD shows a diffraction pattern similar to that of β-CD, but with some changes in the baseline, either due to the decrease and/or displacement of peaks very characteristic of β-CD at 2θ = 9.19°, 10.71°, 12.70°, 15.50°, and 17.21°. This indicates the presence of BSHE (by decreasing the peaks) and a small interaction between BSHE and β-CD.

In the inclusion complex BSHE:β-CD, alterations in the diffraction patterns referring to β-CD and BSHE alone were observed. The number and intensity of the signals were reduced, characterizing loss of crystallinity and presenting intense amorphization with the observation of only two broad bands of low intensity, at 2θ = 12.84° and 18.49°. Obtaining a diffractogram that resembles an amorphous material, that is, one without clearly defined fine peaks may be a sign that complexation has occurred [93].

3.2. Gastroprotective effect of BSHE:β-CD Inclusion Complexes

The loss of crucial defense mechanisms, such as a reduction in the activity of antioxidant enzymes, the destruction of the gastric mucus barrier, the production of reactive oxygen species (ROSs), which causes oxidative stress, and the activation of the innate immune system, are characteristics of the gastric lesion caused by ethanol [94]. In the present study, gastric ulcers were induced in mice to assess the gastroprotective effect of BSHE:β-CD inclusion complexes (Figure 6). The administration of oral ethanol (96%, 0.2 mL/animal) to mice treated with saline (negative control) caused severe damage to the gastric mucosa, clearly producing the expected characteristic zone of necrotizing lesions of the mucosa, generally parallel along the stomach body axis (Figure 6A). As marked in Figure 6A, the lesions can be seen by the white arrows that point to formed stretches. BSHE (Figure 6B), BSHE:β-CD (Figure 6C), and carbenoxolone (Figure 6D) decreased the effect of stretch marks, suggesting the gastroprotective effect.

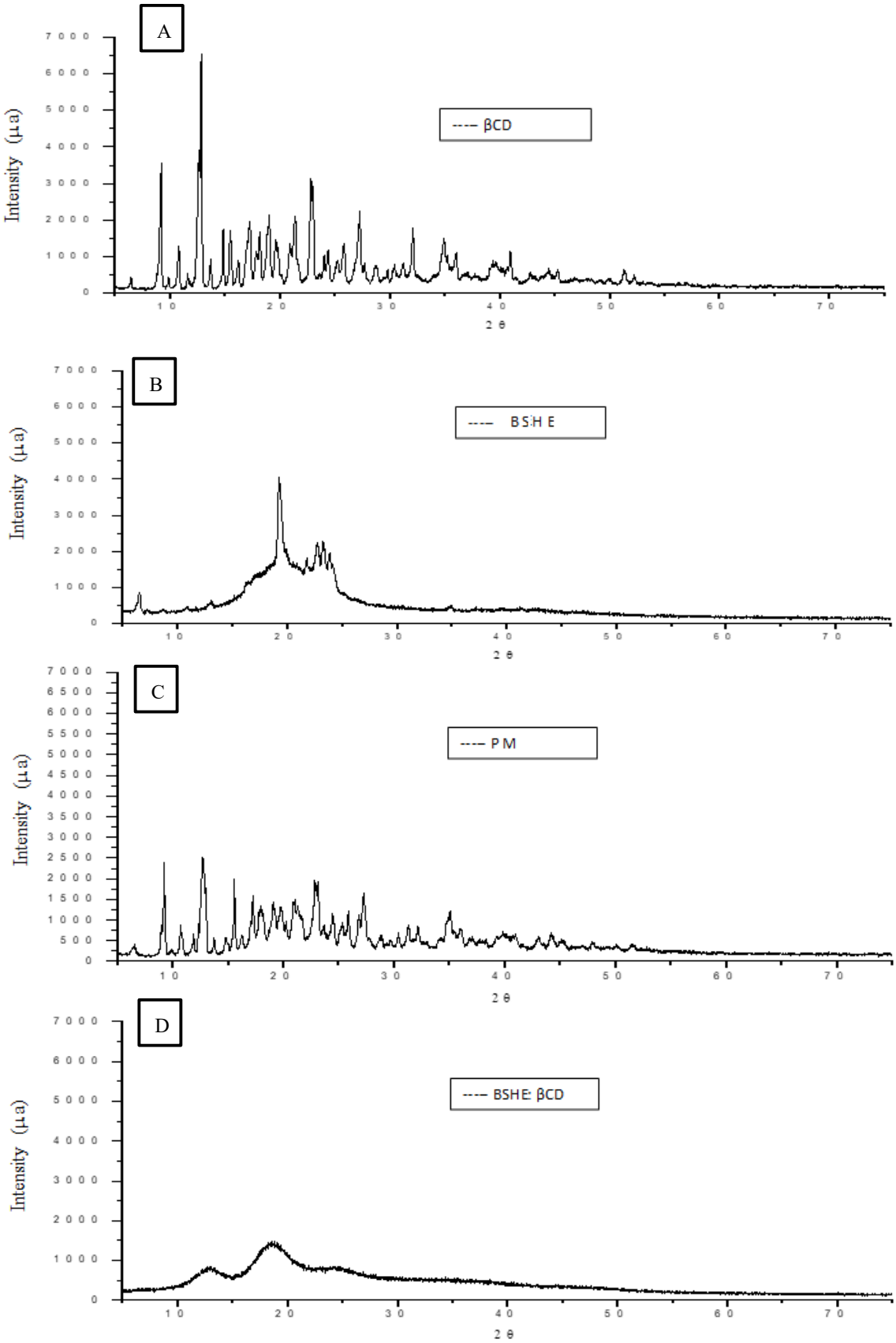

Figure 5. X-ray diffraction (XRD) of samples containing BSHE and β-CD. (**A**) β-cyclodextrin molecule, (**B**) bacuri seed hexane extract (BSHE), (**C**) physical mixture between BSHE:β-CD, and (**D**) BSHE:β-CD inclusion complexes.

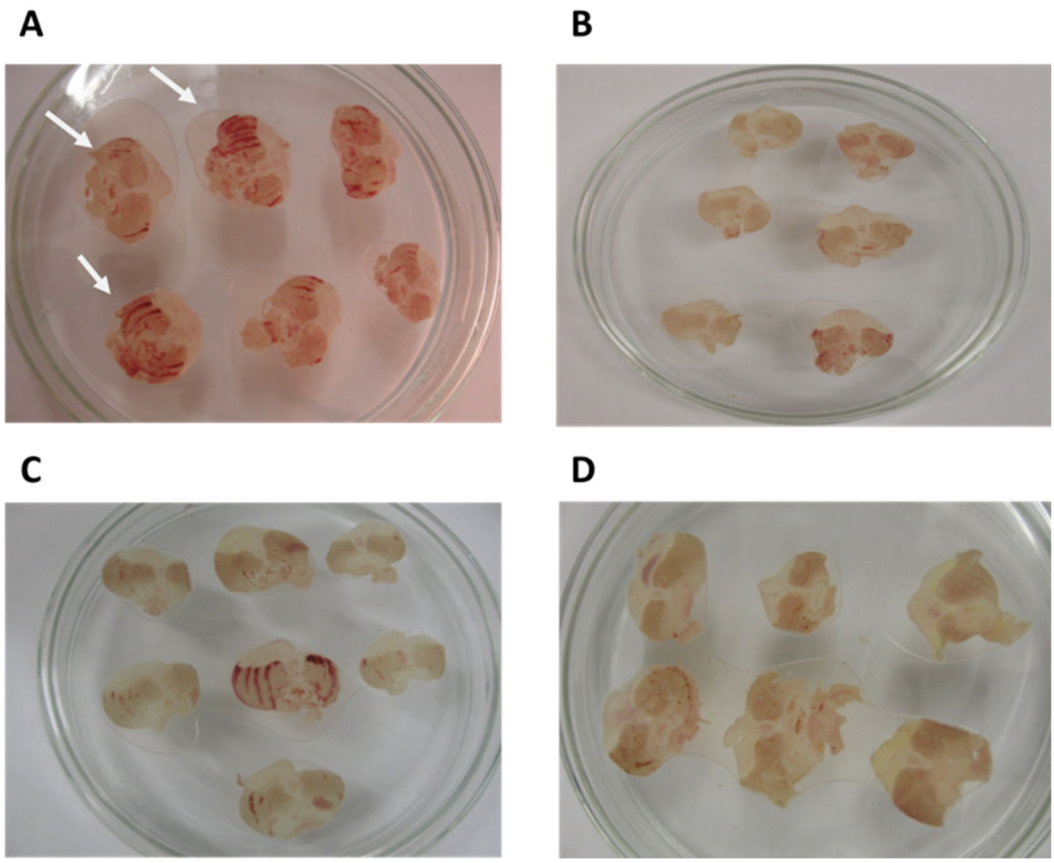

Figure 6. Injury area of the gastric mucosa of the stomachs in mice. (**A**) Negative control treated with saline, (**B**) BSHE administered in the proportion of 100 mg/kg, (**C**) BSHE:β-CD inclusion complexes in the proportion of 100 mg/kg, (**D**) positive control: carbenoxolone (100 mg/kg). (The white arrows signal the stretches).

Figure 7 shows the analysis of gastroprotective activity BSHE:β-CD inclusion complexes in gastric lesions induced by absolute ethanol in mice. Through the lesion area analysis, it can be confirmed that both BSHE and BSHE:β-CD show gastroprotective activity in this assay (Figure 7). The gastric lesion observed in the control group (saline) was 26.70 mm^2 (±2.56) of the mucosa area. When compared with the negative control, the animals treated with BSHE and BSHE:β-CD inclusion complex showed a significant reduction in the area of gastric lesions. BSHE at doses of 25 and 50 mg/kg reduced lesion area to 10.50 $mm^2 \pm 2.48$ (60.70%) and 8.72 $mm^2 \pm 1.68$ (67.40%), respectively; for BSHE:β-CD, the same doses reduced it to 8.53 $mm^2 \pm 1.55$ (68.10%) and 9.6 $mm^2 \pm 1.10$ (64.10%), respectively, showing significant lesion area reduction compared with the negative control, but without significance between them.

The BSHE:β-CD inclusion complex at a dose of 100 mg/kg had the same effect as carbenoxolone and was more effective than BSHE (Figure 7). Animals treated with carbenoxolone (positive control) at a dose of 100 mg/kg had a decrease in ulcerative lesions of 2.34 mm^2, promoting 91.20% inhibition of the ulcerative lesion. The animals treated with BSHE:β-CD inclusion complexes at a dose of 100 mg/kg had a decrease in ulcerative lesions of around 89.5% (area equivalent to 2.8 mm^2) when compared with carbenoxolone. These results justify the complexation to obtain better effects of a possible phytomedication obtained from the extract of the seeds of *Platonia insignis* since BSHE:β-CD inclusion complexes in the proportion of 100 mg/kg proved to be more effective than the EHSB. It should be noted that the BSHE:β-CD inclusion complexes are in the proportion of 3:7 (BSHE:β-CD), that is, only 30% of the pure BSHE.

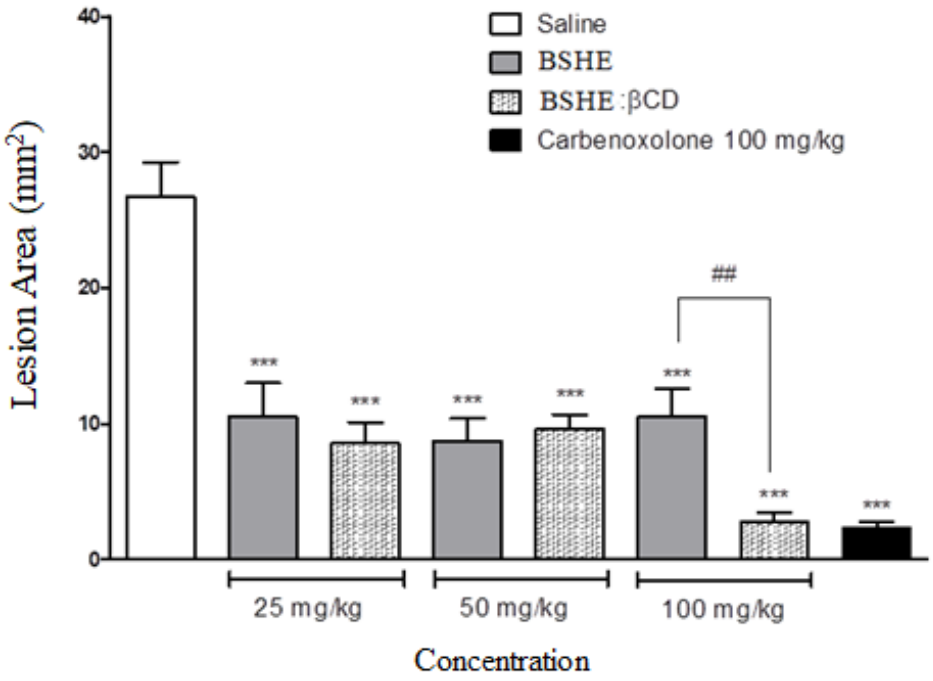

Figure 7. Analysis of gastroprotective activity BSHE:β-CD inclusion complexes in gastric lesions induced by absolute ethanol in mice. BSHE and BSHE:β-CD inclusion complexes were used at doses of 25, 50, and 100 mg/kg. For negative control, saline was used, and for positive control, carbenoxolone (100 mg/kg) was used. Data are expressed as mean ± E.P.M., *** $p < 0.001$, compared to control (ANOVA, followed by Tukey's test), ## $p < 0.01$ comparing BSHE with BSHE:β-CD inclusion complexes.

The presence of terpenes and flavonoids in the BSHE may justify the inhibitory activity on gastric ulceration [95,96]. Phenolic compounds have an antiulcerogenic effect related to cytoprotective activity [97]. The *Platonia insignis* Mart. has a high content of flavonoids and sesquiterpenes [98–100].

Figure 8 shows the results of the protective effect in an ischemia and reperfusion (RI) ulcer model. The saline group presented 10.34 mm^2 ± 1.05 of gastric lesion area. The BSHE showed a significant decrease in gastric injuries areas at doses of 25, 50, and 100 mg/kg, which was of 5.12 mm^2 ± 0.52, 3.76 mm^2 ± 0.85, and 2.68 mm^2 ± 0.39, respectively, showing a gastroprotection percentage of 50.50%, 63.60%, and 74.10%, respectively, when compared to the negative control group. Furthermore, the BSHE:β-CD inclusion complex also showed a decrease in lesions area of 3.97 mm^2 ± 0.82, 2.70 mm^2 ± 0.52, and 2.48 mm^2 ± 0.41 at concentrations of 25, 50, and 100 mg/kg, respectively, leading to a reduction percentage in 61.60%, 73.90%, and 76.10% when compared to saline group. The positive control (N-acetylcysteine) reduced the lesions by 79.40% (area equivalent to 2.13 mm^2). These results demonstrate that the BSHE and BSHE:β-CD inclusion complex have excellent gastroprotective activity, with an inhibition statistically similar to the positive control, which is a derivative of the natural amino acid cysteine and acts as a precursor to the reducing agent glutathione, an endogenous molecule with a crucial role in the defense mechanism of toxic agents and gastric ulcers [101–104].

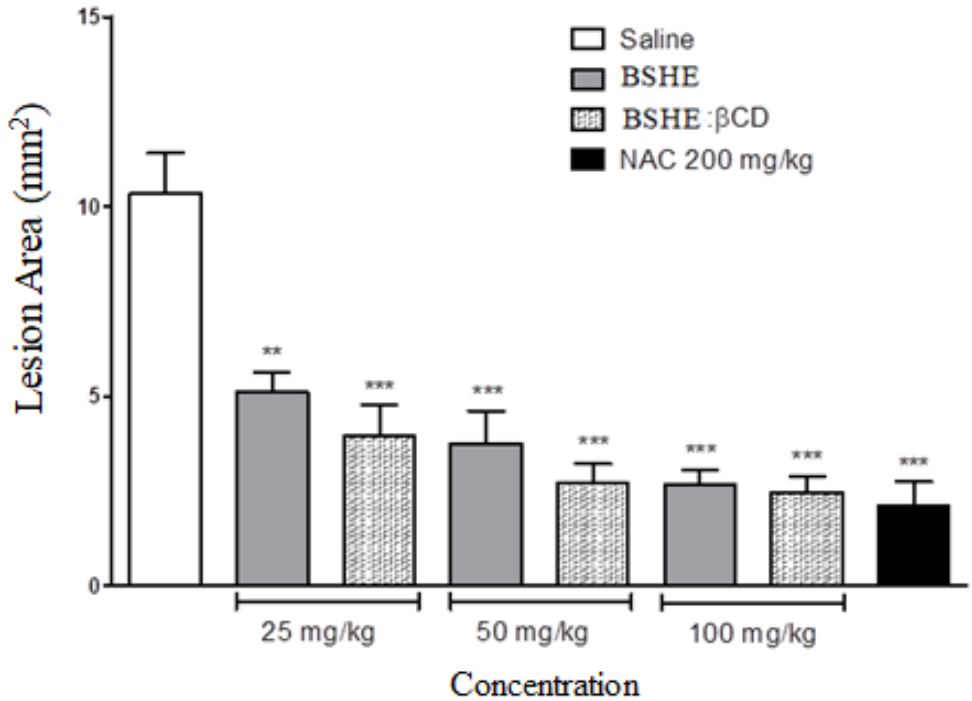

Figure 8. Analysis of gastroprotective activity BSHE:β-CD inclusion complexes in gastric lesions induced by I/R in rats. BSHE and BSHE:β-CD inclusion complexes were used at doses of 25, 50, and 100 mg/kg. For negative control, saline was used, and for positive control, N-acetylcysteine (200 mg/kg) was used. Data are expressed as mean ± E.P.M., ** $p < 0.01$ and *** $p < 0.001$, compared to control (ANOVA, followed by Tukey's test).

The ischemia and reperfusion (IR) ulcer model is used to assess drug response in an ulcerogenesis process without the use of chemical agents, pathogens, or somatic stress, as in the ethanol, *H. pylori* and cold and containment models, isolating ulcerative factors related to free radicals formed by inflammatory and vascular processes [105–108]. The perfusion of the gastric mucosa is an essential factor in the ability of the mucosa to protect itself against injuries, and its defense is reduced in ischemic conditions, resulting in cell death and damage to the mucosa [109–113]. Ischemia is able to induce lesions in the gastric tissue; however, after reperfusion, there are the main damaging events that can increase by about three times in relation to those caused in the ischemia process [114]. The results of gastroprotection activity by I/R (Figure 8) suggest that the protection of the lesions may be related to the antioxidant activity of the bacuri extract.

Figure 9 shows the evaluation of malonaldehyde (MDA) production in gastric tissues. MDA is a biomarker of the damage caused by reactive oxygen and nitrogen species (EROs and ERNs) derived from the lipid peroxidation of cell membranes [115–118]. In the present study, a reduction in malonaldehyde levels after treatment with BSHE, BSHE:β-CD inclusion complexes, and carbenoxolone was observed. The chemical components of *Platonia insignis*, such as xanthones and benzophenones, have antioxidant activity similar to the activities catalyzed by superoxide dismutase [99,100]. Thus, the results indicate that BSHE:β-CD inclusion complexes may carry this compound types, which has promising potential application for gastroprotection.

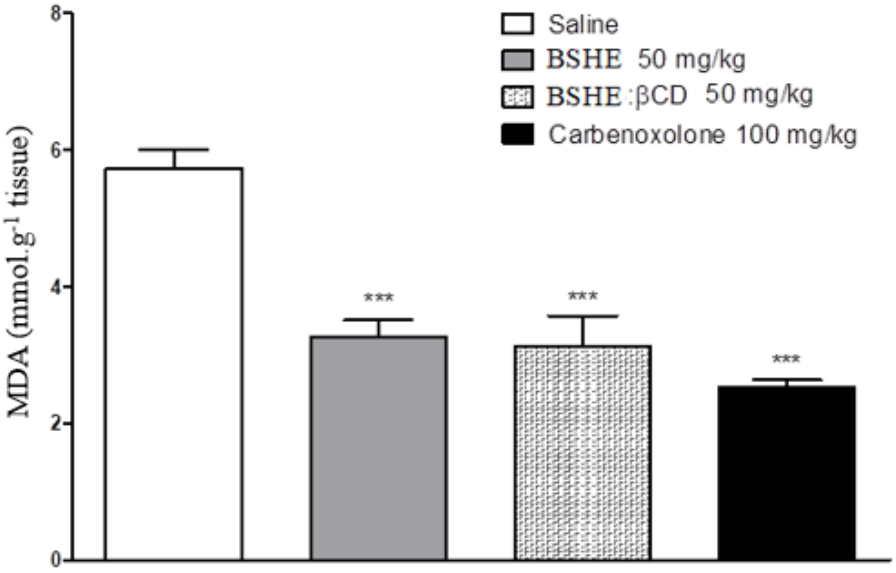

Figure 9. Detection of MDA in gastric tissue with gastric ulcer. BSHE, BSHE:β-CD inclusion complexes, and carbenoxolone (positive control) were used in concentrations of 50 mg/kg, 50 mg/kg, and 100 mg/kg, respectively. For negative control, saline was used. Data are expressed as mean ± E.P.M., *** $p < 0.001$, compared to control (ANOVA, followed by Tukey's test).

4. Conclusions

In the context of plant resources as a promising source of natural products, the exploration of *Platonia insignis* features and the new formulation is here focused. The present study demonstrated success in the process of construction of the BSHE:β-CD inclusion complexes allied to the nanonutraceutical area. Moreover, this product was capable of preserving and enhancing the gastroprotective effect of BSHE against gastric lesion models once it reduces injured areas with less amount of this vegetal derivative inside the β-CD complexes. Furthermore, this study opens for the further development of nanoformulations using fruits byproducts as biomass, as achieved for seeds of *P. insignis* in this work. In this sense, toxicological studies are additionally recommended to ensure safety allied to a wide possibility of pharmacological and nutraceutical applications.

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