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Evidence for antioxidant and anti-inflammatory potential of mango (*Mangifera indica* L.) in naproxen-induced gastric lesions in rat

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Abstract

This study investigated the anti-inflammatory and antioxidant effects of hydroalcoholic extracts of mango peel and pulp on oxidative damage in a naproxen-induced gastric injury rat model. The extracts were assessed for antioxidant activity (ABTS and FRAP methods), and the phenolic profile was investigated with UPLC-QToF-MS^E. Gastric damage was evaluated in vivo by assessing the membrane lipid peroxidation (malondialdehyde (MDA) content), myeloperoxidase (MPO) enzyme activity, and glutathione (GSH) content. Mango peel and pulp contained high contents of bioactive compounds, particularly phenolics (69.50–5.287.70 mg gallic acid equivalents/100 g), carotenoids (651.30–665.50 μg/100 g), and vitamin C (21.59–108.19 mg/100 g). UPLC-QToF-MSE analysis identified 17 phenol compounds, including gallotannins, glycosylated flavonoids, and xanthone. The hydroalcoholic extracts of mango peel and pulp (LPe and LPu, respectively) significantly reduced the MPO activity and MDA content. In addition to preventing naproxen-induced GSH decline, LPe (30 mg/kg) and LPu (10 mg/kg) restored its content to normal levels. LPe and LPu neutralized the oxidizing agents triggered by naproxen and reduced the severity of gastric lesions owing to their antioxidant properties.

1 | INTRODUCTION

Oxidative stress strongly contributes to the progression of numerous chronic diseases and is also considered an important factor for triggering chronic inflammation through the activation of numerous transcription factors (Zhang & Tsao, 2016). It is also related to the overproduction of reactive oxygen species (ROS) and reactive nitrogen species (RNS) during inflammatory processes (Wang et al., 2014).

Although various synthetic substances can help to minimize oxidative stress and are used to treat inflammation-associated chronic diseases, all have some side effects (Islam et al., 2016). These side effects mainly occur in the gastrointestinal tract and range from dyspepsia to serious life-threatening conditions, such as erosions, hemorrhages, perforations, and gastric and duodenal ulcers (Repetto & Llesuy, 2002).

Several studies have shown that a diet rich in compounds with high antioxidant activity can potentially alleviate many chronic degenerative diseases triggered by oxidative stress (Barbagallo et al., 2015; Liguori et al., 2018; Pisoschi & Pop, 2015). Fruit is noted for its quality and quantity of antioxidant compounds, such as carotenoids, phenolic compounds, and vitamins C and E, which play an important role in controlling ROS production and increasing its elimination under non-stress conditions, thereby protecting cells

against oxidative damage (Zhang & Tsao, 2016). In this way, fruit consumption can contribute to the maintenance of health and disease prevention (Du et al., 2016).

Mango (*Mangifera indica* L.) is one of the most highly consumed tropical fruits and is an economically important crop in Brazil, mainly in the northeast region. Its high consumption and popularity are due to its excellent sensory attributes, such as its flavor, aroma, and color; it is also a good source of bioactive compounds. In addition to being consumed without processing, mango is industrially processed for its juice, nectar, and pulp, and this process generates waste peels and seeds (Matharu et al., 2016). Studies have shown that these by-products contain high levels of antioxidant activity due to their high concentration of phenolic compounds, carotenoids, tocopherols, and sterols (Gómez-Caravaca et al., 2016).

Gastrointestinal disorders such as peptic ulcers are due to oxidative processes induced by ROS. However, to understand the physiological responses resulting from the disease, it is necessary to elucidate their pathogenesis and to seek alternative therapies to alleviate or even reverse the harmful effects of oxidative and inflammatory processes in damaged tissues. Studies have shown a close association between antioxidant activity and an antiulcerogenic effect (Repetto & Llesuy, 2002; Wu et al., 2018). In this context, mango can be considered pharmacologically promising because it has a high content of antioxidants, mainly phenols (flavonoids, xanthones, and phenolic acids), which contributes to its notable antioxidant properties (Ajila & Prasada-Rao, 2013; Araujo et al., 2014; Barnes et al., 2015; Berardini et al., 2004; Dorta et al., 2014; Hewavitharana et al., 2013; Oliveira et al., 2016).

Few studies have investigated the use of antioxidant compounds from mango for the treatment of diseases resulting from oxidative processes. This study evaluated the ability of hydroalcoholic extracts of mango peel and pulp to manage ulcerogenic damage triggered by oxidative stress using a rat model of gastric injury induced by naproxen.

2 | MATERIALS AND METHODS

2.1 | Plant material, chemicals, and reagents

Ripe mango fruit (*M. indica* L. cv Tommy Atkins) was purchased from the State Food Supply Central (CEASA-Ceará, Brazil). MTT [3-(4,5-dimethylthiazol, 2-yl)-2,5-diphenyl-212 tetrazolium bromide], ABTS (2,2'-azino-bis(3-ethylbenzo-thiazoline-6-sulfonic acid)); TPTZ (2,4,6-tripyridyl-*s*-triazine), Trolox (6-hydroxy-2,5,7,8-tetramethyl-chroman-2-carboxylic acid), Folin–Ciocalteu reagent, and gallic acid (98%) were purchased from Sigma–Aldrich (Buchs, Switzerland). Methanol, ethanol, phosphoric acid, acetonitrile, and hydrochloric acid (analytical and HPLC grade) were acquired from Fisher Scientific (Leicestershire, UK). All other reagents were of analytical grade.

2.2 | Sample preparation

The mango fruits were selected according to integrity, absence of physical damage and disease, washed individually under running water, sanitized by immersion in sodium hypochlorite solution (200 ppm) for 15 min, and then dried on filter paper. The pulp was then manually separated from the peel using cleaned knives, and the seeds were discarded. The peel and pulp were cut into pieces (0.5 × 1 cm), weighed, and lyophilized (96 hr at 7 mm/Hg) to obtain a fine powder (12% peel relative humidity (RH) and 26% pulp RH). These samples were stored in a freezer (−20°C) until extraction and characterization analysis.

The extractions were obtained according to Dorta et al. (2012). In hermetically sealed tubes, the powder of peel (0.5 g) or pulp (1.0 g) was added to 25 ml of 50% ethanol (1:1, v/v) and homogenized using a magnetic stirrer (model Q261, Quimis) at 325 rpm for 1 min. The tubes were then placed in a 50°C water bath for 60 min, followed by centrifugation (Jouan CR-312 centrifuge, Thermo Electron Corp.) at 3,000*g* for 20 min. Subsequently, the supernatant was collected by filtration, and the solvent was removed through a rotary evaporator under vacuum. The mango pulp (LPu) or peel (LPe) extract was lyophilized for later in vitro and in vivo analyses.

2.3 | Antioxidant capacity

2.3.1 | Antioxidant compounds

Total carotenoids were determined as in Nagata and Yamashita (1992). One gram of the freeze-dried pulp or peel was suspended in 10 ml of extraction solution (2:3 acetone: hexane), homogenized for 1 min, and then filtered through qualitative filter paper (80 g/m^2). The optical density of the filtrate was measured at 663 nm, 645 nm, 505 nm, and 453 nm by a spectrophotometer (UV-1800, Shimadzu). The results are expressed as μg β-carotene/100 g dry weight (DW).

The vitamin C content was quantified according to Cox and Pearson (1976), with some modifications. Freeze-dried pulp (2 g) or peel (1 g) was added to 40 ml of oxalic acid (0.4%) and stirred for 5 min. Next, a 1 ml aliquot of each sample was reacted with 9 ml of DFI solution (0.02% 2,6-dichlorophenol-indophenol). The vitamin C content was quantified at 520 nm using a spectrophotometer. The results are expressed as mg ascorbic acid/100 g DW.

The method described by Francis (1982) was used to determine total anthocyanins and yellow flavonoids. Briefly, 1 g of hydroalcoholic extract (pulp or peel) was suspended in 30 ml of extraction solution (95% ethanol:1.5 M HCl, 85:15 v/v) and homogenized in a tissue homogenizer (Turrax T-25 digital, IKA®, Staufen, Germany) for 2 min. The samples were then transferred to a 50 ml amber volumetric vial and refrigerated for 12 hr in the dark. Next, the samples were filtered and the absorbance at 535 nm was measured by a spectrophotometer to obtain the total anthocyanin content and at 374 nm to obtain the yellow flavonoid content. The results are expressed as mg/100 g DW.

The total phenolics content was obtained using the Folin–Ciocalteu method as described by Obanda et al. (1997). Hydroalcoholic extracts (1 ml) from the pulp (LPu) and peel (LPe) of mango were homogenized in 1 ml of Folin–Ciocalteu reagent, 2 ml of 20% sodium carbonate, and 2 ml of distilled water. After homogenization, the solutions were allowed to stand for 30 min in the dark, after which the absorbance at 700 nm was measured. A standard curve of gallic acid (0–500 mg/L) was used to obtain the final result, which was expressed as mg of gallic acid equivalents/100 g of DW.

2.3.2 | $ABTS^{\bullet+}$ assay

The total antioxidant activity (TAA) was obtained using two methods. The first was the $ABTS^{\bullet+}$ free radical capture method of Re et al. (1999) and modified by Rufino et al. (2010). The $ABTS^{\bullet+}$ radical was generated by reacting the ABTS solution (7 mM) with potassium persulfate (140 mM). This reaction was allowed to proceed in the dark at room temperature for 16 hr before use. Ethanol was used to dilute the $ABTS^{\bullet+}$ radical to an absorbance of 0.70 ± 0.05 at 734 nm. A 30 μl aliquot of each hydroalcoholic extract (LPu and LPe) was mixed with 3 ml of the radical. Spectrophotometric readings were made after exactly 6 min of reaction. A Trolox calibration curve (100–2,000 μM) was prepared and used to obtain the results. The results are expressed in μM Trolox/g DW.

2.3.3 | Ferric reducing antioxidant power (FRAP) assay

The second method used to determine the TAA was FRAP, which was carried out following the procedures described by Benzie and Strain (1999), with modifications. In the absence of light, 2.7 ml of FRAP reagent, 90 μl of extract, and 270 μl of distilled water were mixed in test tubes. The mixtures were homogenized in a tube shaker (Vortex mixer model VX-200, Labnet) and then incubated in a 37°C water bath for 30 min. After this period, the absorbance at 595 nm was measured on a spectrophotometer (Shimadzu model UV 1,800). The TAA was calculated based on an aqueous ferrous sulfate (Fe_2SO_4) solution calibration curve (500–1,500 μM) following the same procedure. The results are expressed as the antioxidant activity equivalent to ferrous sulfate (μM Fe_2SO_4/g of each extract).

2.4 | Phenolic profile of mango peel and pulp by ultra-performance liquid chromatography-quadrupole time-of-flight mass spectrometry (UPLC-QToF-MS^E)

LPe and LPu were solubilized in 1:1 H2O/MeOH (2 ml), filtered through a PTFE filter (0.22 μm), and stored at −80°C in glass vials prior to analysis. The analyses were performed on an Acquity UPLC (Waters) coupled to a Xevo quadrupole time-of-flight mass spectrometer (QTOF, Waters). The chromatographic runs were executed on a Waters Acquity BEH UPLC column (150 mm × 2.1 mm i.d., 1.7 μm) at 40°C. The mobile phase was water containing 0.1% formic acid (A) and acetonitrile containing 0.1% formic acid (B). The elution profile was 2% B (0–1.5 min), 2%–95% B (1.6–15 min), 100% B (15.1–17 min), followed by equilibration with 2% B (17.1–19 min). The flow rate was 0.3 ml/min and the injection volume was 5.0 μl. Ionization was accomplished with an electrospray ionization source (negative mode), and collection was from 110 to 1,180 Da, with a source temperature of 120°C, a desolvation temperature of 350°C, a desolvation gas flow rate of 500 L/hr, an extraction cone of 0.5 V, and a capillary voltage of 2.6 kV. Leucine enkephalin was used as a reference standard. MS^E was used as the mode of acquisition. Masslynx 4.1 software (Waters Corporation) was used to control the instrument. All the samples were injected in triplicate.

2.5 | Cell viability analysis by in vitro MTT assay

This cytotoxicity test assesses the lethal or sublethal effects of a substance or product at the cellular level. The IEC-6 cell line (normal intestinal epithelial cells of *Rattus norvegicus*) was provided by the Morphology Department of the Federal University of Ceará Faculty of Medicine and used for the MTT (3-(4,5-dimethylthiazol-2-yl)-2 ,5 diphenyltetrazolium bromide) cytotoxicity assay according to Mosmann (1983). Lyophilized LPu and LPe were solubilized in pure water to obtain concentrations of 0.5 and 1.0 g/ml, and the absorbance was measured at 570 nm. Cytotoxin A from *Clostridium difficile* was used as a positive control, while cells in culture medium were used as a negative control, with its absorbance considered proportional to 100% cell viability. The absorbances of cell cultures in the presence of each extract at both concentrations were compared with the positive and negative controls. The results are expressed as a percentage of cell viability.

2.6 | Anti-inflammatory and antioxidant activities of the hydroalcoholic extracts of mango peel and pulp

All experiments in this study were approved by the Ethics Committee for Animal Care of the Federal University of Ceará (UFC; CEUA 6185090320).

2.6.1 | Naproxen-induced gastric mucosal damage

Wistar rats (48 animals) of both sexes weighing between 180 and 220 g, were supplied by the Central Animal Facility of UFC and by the Animal Facility of the Department of Physiology and

Pharmacology, UFC. The rats were separated into 8 groups of 6 animals each and maintained in cages with raised floors and wide mesh (to prevent coprophagy) in a separate animal room under standard conditions of temperature (22 ± 2°C) and a 12 hr light/dark cycle. After an 18 hr fast, groups of rats orally received naproxen (NAP; 300 mg/kg) or carboxymethylcellulose (CMC; 0.5%). They were sacrificed 6 hr later by cervical dislocation. The stomachs were quickly removed, opened along the greater curvature, washed with water, and extended on a board. They were photographed with a digital camera for further analysis of macroscopic changes. Planimetry was used to measure the mucosal lesion area (mm^2), along with the ImageJ program. The stomachs were then weighed, frozen, and stored at −70°C until they were used for glutathione (GSH), malondialdehyde (MDA), and myeloperoxidase activity (MPO) assays.

2.6.2 | Effect of mango extracts on naproxen-induced gastrointestinal lesion

After an 18-hr fast, CMC (0.5%; control) or three concentrations (10, 30, and 100 mg/kg) of LPu and LPe were administered by gavage to the rats. After 30 min, NAP (300 mg/kg) was administered by gavage. After an additional 6 hr, the animals were sacrificed and the stomachs were prepared for the next assays following the procedures described above.

2.6.3 | Glutathione concentrations

GSH is an endogenous antioxidant molecule that maintains cellular function by protecting cells from oxidative damage (Marí et al., 2009). The GSH concentrations in stomach tissue samples were measured to assess cellular oxidative stress. The procedures were performed in accordance with Sedlak and Hanus (1982), which is based on the reaction of DTNB [5,5-dithio-bis-(2-nitrobenzoic acid)] with the free thiol. This reaction generates a mixed disulfide acid (2-nitro-5-benzoic acid), which is then used to determine the content of non-protein sulfhydryl groups (NP-SH). A piece of stomach tissue treated with CMC (control), NAP (300 mg/kg), LPu, or LPe (10, 30, or 100 mg/kg) was homogenized in 5 ml of cold 0.02 M EDTA (1 ml per 100 mg/tissue). Aliquots (400 ml) of the tissue homogenate were mixed with 320 ml of distilled water and 80 ml of 50% (w/v) trichloroacetic acid in glass tubes and centrifuged at 1000*g* for 15 min. Next, 800 µl of Tris buffer (0.4 M, pH 8.9) and 20 ml of 0.01 M 5,5-dithio-bis (2-nitrobenzoic acid) was added to each 400 ml supernatant and stirred for 3 min. The absorbance was then measured at 412 nm. A standard curve of reduced glutathione, similarly processed in parallel, was used to determine the GSH concentration, and the results are expressed as micrograms of NP-SH/g tissue.

2.6.4 | Malondialdehyde concentrations

MDA is an oxidative indicator and a marker of damage in lipid peroxidation induced by free radicals. MDA concentrations were determined using the method of Mihara and Uchiyama (1978), which is based on the reaction with thiobarbituric acid. In short, 250 µl of 10% stomach tissue homogenate of rats treated with CMC (control), NAP (300 mg/kg), or 10, 30, or 100 mg/kg LPu or LPe were mixed with 1.5 ml of 1% H_3PO_4 and 0.5 ml of 0.6% thiobarbituric acid aqueous solution and then stirred and heated in boiling water for 45 min, followed by cooling. Next, 2 ml of n-butanol was added, and the mixture was stirred for 40 s in a vortex mixer, followed by centrifuging at 1,200*g* for 10 min. The butanol layer was separated, and the difference between the optical density at 535 and 520 nm was measured to calculate the MDA concentration, expressed as nanomoles of MDA/g of stomach tissue.

2.6.5 | Gastric myeloperoxidase activity

MPO is an enzyme secreted by neutrophils and indicates inflammatory reactions related to oxidizing species. The MPO activity assay was performed according to Bradley et al. (1982). Gastric tissue (50 mg) was mixed in potassium buffer containing 0.5% hexadecyltrimethylammonium bromide (pH 6.0; 50 mg tissue per ml) and subsequently homogenized in a Polytron homogenizer. The homogenate was centrifuged at 11000*g* for 20 min. The MPO activity per mg of tissue was measured using 0.0005% nitrogen peroxide as a substrate for MPO. The unit of MPO activity was defined as that capable of converting 1 mmol of nitrogen peroxide into water in 1 min.

2.6.6 | Histological assessment and microscopy scoring of gastric damage

The tissue samples underwent histopathological evaluation to assess disease. The stomach tissue samples were fixed in 10% formaldehyde for 24 hr, followed by transfer to 70% ethanol, where they remained until the histological procedures were performed. They were finally examined by optical microscopy. The samples were evaluated according to the criteria of Laine and Weinstein (1988) for the following attributes: loss of epithelial cells (score of 0–3), edema on the mucosa surface (score of 0–4), hemorrhagic injury (score of 0–4), and infiltration of inflammatory cells (score of 0–3), with 14 being the maximum score.

2.7 | Statistical analysis

In this study, a fully randomized design was used for the in vitro analysis, with two treatments (mango peel and pulp extracts), three replicates per treatment, and triplicate analyses. For statistical

analysis, the data were subjected to analysis of variance (ANOVA) using Sisvar (version 7.7), and the averages were compared by the Tukey test at 5% probability ($\alpha = 5\%$). *p* values below this value were considered significant.

GraphPad Prism (version 6.0) was used to perform the statistical analysis of the in vivo data, in which the statistical tests (ANOVA or Kruskal–Wallis) were carried out according to the characteristics of the variables. The Bonferroni multiple comparisons test was performed for groups that presented significant differences. The significance level adopted was 0.05 ($\alpha = 5\%$), and *p* values below this value were considered significant.

3 | RESULTS AND DISCUSSION

3.1 | Bioactive compounds

The quantification of total anthocyanins showed a higher amount in LPe than in LPu (Table 1). Indeed, these compounds are commonly found at higher concentrations in fruit and vegetable peels than in the pulp because pigments are synthesized in cells close to the surface and act as ultraviolet radiation filters They also improve and regulate the rate of photosynthesis (Gorinstein et al., 2001; Mazza & Miniati, 1993). For yellow flavonoids, LPu had ~14% less content than LPe (Table 1). Similar to anthocyanin biosynthesis, flavonol biosynthesis in plant tissues is influenced by sunlight; therefore, it is reasonable that yellow flavonoids would be found in higher quantities in the peel than in the pulp (Lopes et al., 2016; Spayd et al., 2002). Higher vitamin C concentrations were also found in LPe than in LPu, which is similarly explained owing to the strong sun exposure of tropical fruits. The parts of the fruit most exposed to sunlight have the highest vitamin C content (Gurgel et al., 1951). There was a high content of total carotenoids in both of the mango extracts, corroborating Silva et al. (2014); however, there was no significant difference between the two fruit parts.

The highest content of phenolic compounds was obtained from LPe (Table 1). The content of these bioactive compounds varies among the different fruit tissues, with peels and seeds containing higher amounts of phenolic compounds compared with the edible tissues (Gorinstein et al., 2001, 2002; Soong & Barlow, 2004).

The TAA was measured by the ABTS and FRAP methods (Table 1); however, the ABTS method was more suitable for the study. The ABTS method revealed a significant difference in TAA between the two extracts, with LPe having significantly higher TAA than LPu, although LPu also had high antioxidant activity. These results might be associated with the high content of phenolics and other antioxidant compounds quantified in both extracts. As yet, previous studies have only identified strong positive correlations between the total antioxidant activity and total phenolic content; however, it is possible that non-phenolic substances may also contribute to the total antioxidant activity in some way (Oliveira et al., 2012; Parikh & Patel, 2018).

3.2 | Phenolic profile by UPLC-QToF-MS^E

In this study, a total of 17 compounds were identified in the mango pulp and peel extracts. Peak identification was performed based on the relative retention time values, UV–Vis spectra, and mass spectra obtained using qTOF-MS, along with data documented in previous studies. Table 2 summarizes the compounds identified in the extracts, along with the retention time (min), molecular formula, experimental and calculated *m/z*, fragments, error (ppm), and the presence of the compounds in each extract type. Figure 1 shows the peak chromatograms for the identified phenolic compounds. Peak **1** shows an $[M\text{-}H]^-$ ion at *m/z* 341 ($C_{12}H_{21}O_{11}$) with a fragment of glucose at *m/z* 179 and was tentatively identified as sucrose (Michodjehoun-Mestres et al., 2009). Sucrose is present in mango pulp and peel (Chidan et al., 2012). Peaks **2** and **3** were identified as quinic acid isomers by their molecular ions at *m/z* 191 ($C_7H_{11}O_6$). These compounds were previously identified in mango peel, pulp, seed, and bark (Gómez-Caravaca et al., 2016). Peak **4** presented an $[M\text{-}H]^-$ ion at *m/z* 493 ($C_{19}H_{25}O_{15}$), with fragmentation partners indicating loss of dihexose and gallic acid at *m/z* 331 and 169, respectively.

TABLE 1 Antioxidant compounds and total antioxidant activity (TAA) from mango pulp and peel (cv Tommy Atkins)

	Samples	
Antioxidant capacity	**Pulp**	**Peel**
Total polyphenol (mg EAG/100 g)	69.50 ± 4.80^b	5,287.70 ± 14.10^a
Total anthocyanin (mg/100 g)	1.10 ± 0.05^b	6.20 ± 0.40^a
Yellow flavonoid (mg/100 g)	1.10 ± 0.05^b	85.40 ± 5.90^a
Total carotenoid (μg/100 g)	665.50 ± 4.60^a	651.30 ± 8.20^a
Vitamin C (mg/100 g)	21.59 ± 2.60^b	108.19 ± 7.80^a
ABTS (μM Trolox/g)	24.75 ± 0.17^b	144.40 ± 1.23^a
FRAP (μM ferrous sulphate/g)	15.03 ± 0.06^a	20.62 ± 0.11^a

Abbreviations: ABTS, (2,2'-azino-bis (3-ethylbenzo-thiazoline-6-sulfonic acid)); EAG, equivalent gallic acid; FRAP, ferric reducing antioxidant power.

Means followed by different letters in horizontal differ from each other at the 5% significance level by Tukey's test.

TABLE 2 Identification of compounds in *Mangifera indica* peel and pulp by UPLC-QToF-MS^E

Peak no	Rt min	$[M-H]^-$ Observed	$[M-H]^-$ Calculated	Product Ions (MS/MS)	Empirical Formula	ppm (error)	Putative name	Reference	LPe	LPu
1	2.36	341.1083	341.1084	179	$C_{12}H_{21}O_{11}$	−0.3	Sucrose[b]	Chidan et al. (2012)	x	x
2	2.53	191.0555	191.0556	—	$C_7H_{11}O_6$	−0.5	Quinic acid[a]	Gómez-Caravaca et al. (2016)	x	x
3	3.61	191.0555	191.0556	—	$C_7H_{11}O_6$	−0.5	Quinic acid isomer[b]	Gómez-Caravaca et al. (2016)	—	**x**
4	3.63	493.1203	493.1193	331, 313, 169, 125	$C_{19}H_{25}O_{15}$	2.0	Galloyl-*O*-sucrose[b]	Li et al. (2016)	—	**x**
5	3.70	169.0134	169.0137	125	$C_7H_5O_5$	−1.8	Gallic acid[a]	Gómez-Caravaca et al. (2016)	**x**	**x**
6	3.95	575.1039	575.1037	423, 303, 261	$C_{26}H_{23}O_{15}$	0.3	Maclurin mono-*O*-galloyl-glucoside[b]	Berardini et al. (2004)	—	x
7	4.04	421.0772	421.0771	331, 301	$C_{19}H_{17}O_{11}$	0.2	Mangiferin[a]	Dorta et al. (2014)	—	x
8	4.12	727.1160	727.1147	576, 575, 557, 466, 465, 303, 261	$C_{33}H_{27}O_{19}$	1.8	Maclurin di-*O*-galloyl-glucoside[b]	Berardini et al. (2004)	—	**x**
9	4.25	573.0886	573.0880	421, 301, 169	$C_{26}H_{21}O_{15}$	1.0	Mangiferin-*O*-gallate[b]	Berardini et al. (2004)	—	**x**
10	4.27	787.0997	787.0994	635, 617, 465, 313, 169	$C_{34}H_{27}O_{22}$	0.4	Tetra-*O*-galloylglucoside[b]	Dorta et al. (2014)	—	**x**
11	4.33	939.1101	939.1104	787, 769, 635, 617, 169	$C_{41}H_{31}O_{26}$	−0.3	Penta-*O*-galloylglucoside[b]	Gómez-Caravaca et al. (2016); Dorta et al. (2014); Berardini et al. (2004)	—	x
12	4.38	463.0884	463.0877	301.0332	$C_{21}H_{19}O_{12}$	1.5	Quercetin-*O*-hexoside[b]	Brito et al. (2007), Michodjehoun-Mestres et al. (2009)	—	x
13	4.39	1,091.1210	1,091.1213	939, 787,769, 635, 617 169	$C_{48}H_{35}O_{30}$	−0.3	Hexa-*O*-galloylglucoside[b]	Gómez-Caravaca et al. (2016); Berardini et al. (2004)	—	**x**
14	4.51	433.0762	433.0771	301, 300	$C_{20}H_{17}O_{11}$	−2.1	Quercetin-*O*-pentoside[b]	Brito et al. (2007), Michodjehoun-Mestres et al. (2009)	—	**x**
15	4.71	447.0919	447.0927	301, 300	$C_{21}H_{19}O_{11}$	−1.8	Quercetin-*O*-rhamnoside[b]	Dorta et al. (2014)	—	**x**
16	4.84	317.0290	317.0297	179, 151, 137, 107	$C_{15}H_9O_8$	−2.2	Myricetin[a]	Std	**x**	—
17	4.86	477.1024	477.1033	315, 314	$C_{22}H_{21}O_{12}$	−1.9	Rhamnetin-*O*-hexoside[b]	Dorta et al. (2014)	—	**x**

Note: Classification according to Sumner et al. (2007):

[a]Compounds identified using authentic analytical standards.

[b]Identified by spectral similarity.

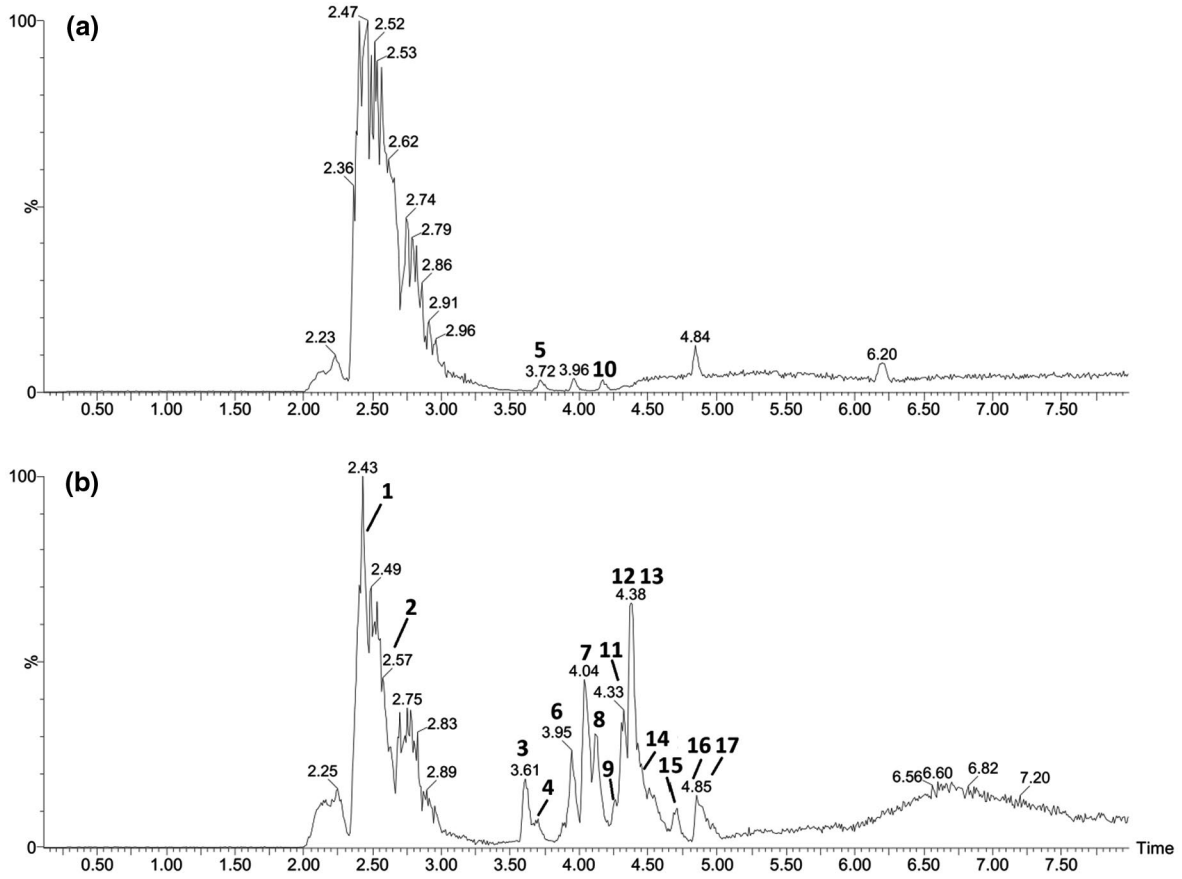

FIGURE 1 Chromatogram profile of pulp (a) and peel (b) of mango fruit (*Mangifera indica M.*)

Thus, this peak was identified as galloyl-*O*-sucrose (Li et al., 2016). Peak **5** was identified as gallic acid by the precursor ion at *m/z* 169 ($C_7H_5O_5$) and authentic standard comparison. Gallic acid and gallotannins are the main polyphenols in mango bark (Ajila & Prasada-Rao, 2013; Dorta et al., 2014; Kim et al., 2009). Peaks **6** and **8** were characterized as maclurin derivatives. In peak **6,** the product ion at *m/z* 303 resulted from cross-ring cleavage of C-glycoside after the loss of a galloyl moiety ([M-H-120-152]). The fragment at *m/z* 261 was identified as a maclurin aglycone ion. Therefore, peak 6 was identified as maclurin mono-*O*-galloyl-glucoside, and peak 8 at *m/z* 727 ($C_{33}H_{27}O_{19}$) was identified as maclurin di-*O*-galloyl-glucoside because it contained one galloyl moiety more than peak 6 (Berardini et al., 2004). Peaks 7 and 9 exhibited precursor ions at *m/z* 421 ($C_{19}H_{17}O_{11}$) and 573 ($C_{26}H_{21}O_{15}$), respectively. Peak 7 showed a product ion at *m/z* 331 ([M-H-90]) and *m/z* 301 ([M-H-120]), which are typical of a *C*-glycoside. Based on the fragmentation partners and on the occurrence of this compound in *M. indica*, peak 7 was identified as mangiferin (Dorta et al., 2014). Peak 9 showed 152 *u* (galloyl moiety) more than peak 7 and was identified as mangiferin-*O*-gallate (Berardini et al., 2004; Dorta et al., 2014). Peaks 10, 11, and 13 showed precursor ions at *m/z* 787 ($C_{34}H_{27}O_{22}$), 939 ($C_{41}H_{31}O_{26}$), and 1,091 ($C_{48}H_{35}O_{30}$), respectively, with sequential fragmentation loss in MS^2 of 152 Da (galloyl moiety); this is characteristic of ellagitannins. Comparing the fragmentation partners with literature data, these compounds were identified as tetra-*O*-galloyl glucoside (peak 10), penta-*O*-galloyl glucoside (peak 11), and hexa-*O*-galloyl glucoside (peak 13; Berardini et al., 2004; Dorta et al., 2014; Gómez-Caravaca et al., 2016). Peaks 12, 14, and 15 produced deprotonated ions at *m/z* 463 ($C_{21}H_{19}O_{12}$), 433 ($C_{20}H_{17}O_{11}$), and 447 ($C_{21}H_{19}O_{11}$), respectively, and were identified as quercetin derivatives by the product ion at *m/z* 301 of the quercetin ion. Furthermore, the main fragments were characteristic of the loss of

TABLE 3 Cell viability assay (IEC-6 cell culture) of mango peel extract (LPe) expressed as optical density (OD) using MTT test (tetrazolium salt reduction)

Concentration of mango peel extract (LPe)	DO (A_{570}/A_{630})
Control (100 μl culture medium)	0.509 ± 0.022
20 mg/kg	0.444 ± 0.025
10 mg/kg	0.507 ± 0.095
5.0 mg/kg	0.295 ± 0.007[a]
2.5 mg/kg	0.154 ± 0.055[a]
1.25 mg/kg	0.302 ± 0.317[a]
0.625 mg/kg	0.415 ± 0.444

Abbreviations: A_{570}, absorbance at 570 nm; A_{630}, absorbance at 630 nm; DO, optical density.

[a]Significant difference ($p < .05$) when compared to the carboxymethylcellulose group (Control).

hexose (162 Da), pentose (132 Da), and rhamnose (146 Da) moieties; according to the fragmentation partners, they were identified as quercetin-*O*-hexoside, quercetin-*O*-pentoside, and quercetin-*O*-rhamnoside, respectively (Brito et al., 2007; Chagas et al., 2020; Dorta et al., 2012; Michodjehoun-Mestres et al., 2009). Peak 16 showed a precursor ion at *m/z* 317 ($C_{15}H_9O_8$). Comparison with the authentic standard led to its identification as myricetin. Peak 17 exhibited a precursor ion at *m/z* 477 ($C_{22}H_{21}O_{12}$) with the loss of a hexose unit (162 Da), giving a rhamnetin unit product at *m/z* 315. Based on the product ion, peak **17** was identified as rhamnetin-*O*-hexoside (Dorta et al., 2014).

3.3 | Cell viability test

The cell viability assay showed that LPe did not promote cell death, and cell proliferation occurred at the 20, 10, and 0.625 mg/kg concentrations (Table 3). For LPu, cell proliferation occurred at the 20, 10, 5, 2.5, and 0.625 mg/kg concentrations, and cell toxicity was not observed (Table 4). However, despite the low optical density value observed in response to the 1.25 mg/kg concentration, suggesting that there was no cell proliferation, this LPu concentration did not promote cell death. The amount of formazan produced is directly proportional to the number of living cells; when cells die, they lose the ability to form formazan from MTT. Color formation is a useful and convenient marker for viable cells only and is, therefore, a sensitive, quantitative and robust colorimetric method for measuring cell viability and proliferation (Vega & Pugsley, 2011).

3.4 | Effects of mango hydroalcoholic extracts on naproxen-induced gastropathy

The group that received only NAP (300 mg/kg) presented lesions in the gastric mucosa (42.05 $mm^2 \pm 6.88$), while the group that received only the CMC vehicle (control) did not develop lesions (Figure 2). However, LPu and LPe at the three concentrations were able to attenuate the gastric damage in a dose-dependent manner. For LPu, reductions of 81% (8.00 $mm^2 \pm 1.93$), 86% (5.71 $mm^2 \pm 4.73$), and 64% (15.21 $mm^2 \pm 4.78$) were found for the 10, 30, and 100 mg/kg doses, respectively, while for LPe these reductions were 61% (16.46 $mm^2 \pm 5.51$), 65% (14.78 $mm^2 \pm 9.93$), and 74% (10.79 $mm^2 \pm 0.84$; Figure 2). Naproxen is a non-selective and non-steroidal anti-inflammatory drug extensively prescribed for chronic arthritis treatment. However, this drug can cause dyspepsia, stomach and duodenum bleeding, the activation of inflammatory bowel disease, and tissue damage (ulcers) in the gastrointestinal tract, which increases ROS production (Tanaka et al., 2001). Together with the increase in MPO, increased ROS releases superoxide and hydroxyl radicals, which are extremely harmful to the gastric mucosa (Wallace & Granger, 1996). Thus, it is likely that the efficacy of both extracts may be due to their antioxidant properties provided by their rich range of antioxidant compounds—mainly the phenolic content (Table 2). These compounds play an important role in free radical scavenging and can reduce ROS released as a result of naproxen.

TABLE 4 Cell viability assay (IEC-6 cell culture) of mango pulp extract (LPu) expressed as optical density (OD) using MTT test (tetrazolium salt reduction)

Concentration of mango pulp extract (LPu)	DO (A_{570}/A_{630})
Control (100 μl culture medium)	0.509 ± 0.022
20 mg/kg	0.531 ± 0.164
10 mg/kg	0.848 ± 0.010[a]
5.0 mg/kg	1.112 ± 0.177[a]
2.5 mg/kg	0.866 ± 0.412[a]
1.25 mg/kg	0.338 ± 0.376[a]
0.625 mg/kg	0.689 ± 0.013[a]

Abbreviations: A_{570}, absorbance at 570 nm; A_{630}, absorbance at 630 nm; DO, optical density.

[a]Significant difference ($p < .05$) when compared to the carboxymethylcellulose group (Control).

3.5 | Histological assessment

Histological analysis revealed that the administration of naproxen (300 mg/kg) provoked lesions in the rat stomach gastric wall. These lesions were characterized by gastric gland disruption with epithelial cell loss, edema, hemorrhage, and intense infiltration of inflammatory cells when compared with the control group (Table 5, Figures 3 and 4a,b), as previously noted by Carvalho et al. (2015). However, the administration of LPu (10, 30, and 100 mg/kg) and LPe (10, 30, and 100 mg/kg) preserved the integrity of the mucosa without injury to the epithelium, keeping the glandular structure organized and significantly reducing the infiltration of inflammatory cells, edema formation, and naproxen-induced hemorrhagic damage. The results suggest that both extracts exerted a gastroprotective effect (Table 5, Figures 3 and 4c-h). Thus, considering the reduction of all inflammation parameters measured in this study, it is suggested that both mango extracts may have gastroprotective properties associated with their antioxidant activity, which can be attributed to their rich composition of antioxidant compounds (Table 2). According to Repetto and Llesuy (2002) and Carvalho et al. (2007), clinical and experimental evidence suggest that oxidative stress is closely related to the etiopathology of peptic ulcer disease. In addition, studies have found that fruits and vegetables have a gastroprotective effect due to their bioactive chemical constituents (mainly phenolic compounds; Morikawa et al., 2006; Santos & Rao, 2001).

3.6 | Effect of mango hydroalcoholic extracts on malondialdehyde and glutathione concentrations

Figure 5 shows that the MDA concentrations in the naproxen-treated gastric tissue were significantly higher (5.44 μmol MDA/mg

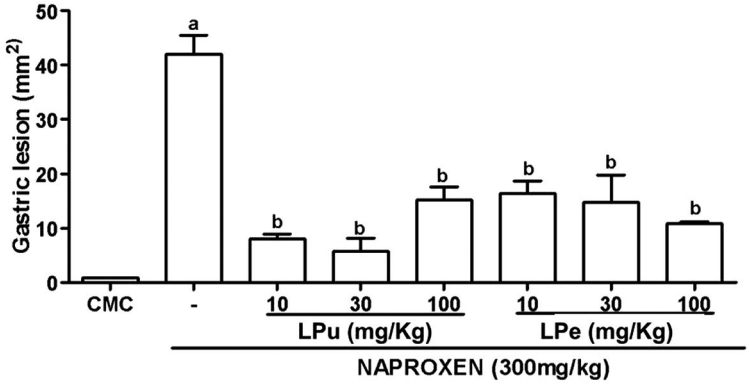

FIGURE 2 Evaluation of the protective effect of mango pulp extract (LPu) and mango peel extract (LPe) at different concentrations (10, 30 and 100 mg/kg), in the naproxen-induced gastric lesion model. The result was expressed as mean ± SEM for group of six animals per group. (a) $p < .05$ when compared to the NAP group; (b) $p < .05$, when compared with the CMC group (control). Statistical analysis was performed using ANOVA, followed by Bonferronis test. The total area of macroscopic gastric lesions was determined 6 hr after naproxen administration

TABLE 5 Protective effect of mango peel (LPe) and pulp (LPu) hydroalcoholic extract in Naproxan-induced microscopic gastric damage according Laine and Weinstein (1988)

Experimental group ($N = 5$)	Hemorrhagic lesion (score 0–4)	Oedema (score 0–4)	Erosion (loss of cell architecture) (SCORE 0–3)	Cell infiltrate (score 0–3)	Total (score 14)
CMC	0	0	0	0	0
NAP	1 (1–2)[a]	2.5 (1–4)[a]	3 (2–3)[a]	2 (1–3)[a]	7.5 (5–12)[a]
LPe (10 mg/kg)	0 (0–0)[b]	1 (1–2)	0 (0–1)[b]	0 (0–2)[b]	1 (1–5)[b]
LPe (30 mg/kg)	0 (0–0)[b]	1 (0–3)	2 (0–2)	1 (0–2)	4 (0–7)
LPe (100 mg/kg)	0 (0–1)	1 (0–2)[b]	1 (0–2)[b]	1 (1–2)	3 (1–7)
LPu (10 mg/kg)	0.5 (0–2)	1 (0–2)[b]	2 (0–2)	1 (0–1)	4.5 (0–7)
LPu (30 mg/kg)	1 (0–2)	1 (1–2)	1 (0–1)[b]	0 (0–2)[b]	3 (1–7)
LPu (100 mg/kg)	0 (0–1)[b]	0 (0–1)[b]	1 (0–2)[b]	1 (0–1)[b]	2 (0–5)[b]

Note: Values denote median with minimum and maximum, respectively, by Kruskal-Wallis test.

Abbreviations CMC, Group Carboxymethylcellulose 0.5%; LPe, mango peel hydroalcoholic extract; LPu, mango pulp hydroalcoholic extract; NAP, animal treated with Naproxen (300 mg/Kg).

[a]$p < .05$ versus Group NAP (animals treated with Naproxen).

[b]$p < .05$ versus Group Carboxymethylcellulose 0.5%.

tissue ±0.93) than in the CMC group (4.04 μmol MDA/mg tissue ±0.93) and that LPu and LPe at all doses significantly reduced MDA formation. Treatment with LPu led to an 80% reduction of MDA (1.07 μmol MDA/mg tissue ±0.14) at the lowest dose (10 mg/kg). For LPe, the highest dose (100 mg/kg) led to the greatest reduction (40%; 3.25 μmol MDA/mg tissue ±0.40).

Regarding GSH, naproxen treatment led to a significant decrease in GSH concentration (33.17 μg NP-SH/g tissue ±4.60) when compared to the CMC treatment (109.90 μg NP-SH/g tissue ±21.93), demonstrating its oxidative action (Figure 6). LPu and LPe pretreatment effectively maintained the GSH concentration compared with the naproxen group. For both LPu and LPe, there were no significant differences from the CMC group at all doses (10, 30, and 100 mg/kg, respectively): LPu: 79.37 μg NP-SH/g ± 25.5, 82.55 μg NP-SH/g ± 16.96, and 90.03 μg NP-SH/g ± 23.40; LPe: 79.29 μg NP-SH/g ± 10.0, 78.48 μg NP-SH/g ± 18.25, and 78.17 μg NP-SH/g ± 31.22.

Antioxidant compounds have been associated with gastroprotective effects that occur through different mechanisms, such as iron-chelating properties, free radical scavenging potential, and the inhibition of ROS and RNS production, where they can provide protection to the membrane lipids and even heal the gastric mucosa (Ali Khan et al., 2017; Alvarez-Suarez et al., 2011; Boots et al., 2008; Carullo et al., 2017; de Jesus et al., 2012; Miyazaki et al., 2018; Pal et al., 2010; Rodeiro et al., 2007; Sen et al., 2013; Serafim et al., 2020). Thus, the increased GSH concentrations and decreased MDA concentrations after treatment with the mango extracts can be attributed to their bioactive antioxidant properties (Table 2). These extracts contained compounds such as gallic acid, quercetin derivatives, gallotannins, myricetin, and mangiferin. The

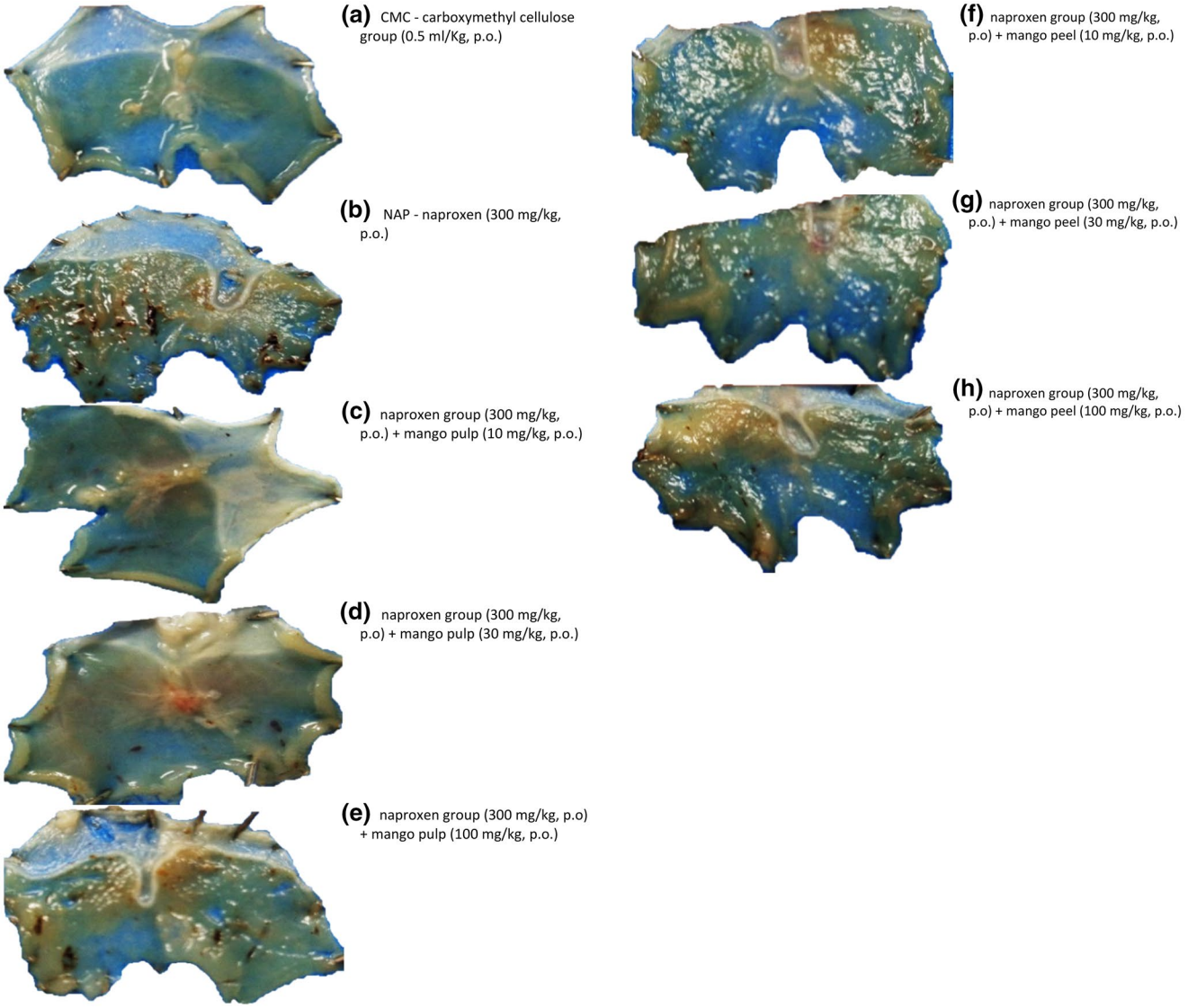

FIGURE 3 Macroscopy of the mice gastric wall pretreated with mango (*Mangifera indica* L.) pulp extract (LPu) or peel extract (LPe) at different concentrations (10, 30 and 100 mg/kg) in naproxen-induced lesion. Gastric wall photomicrographs of mice pretreated with: (a) CMC group (0.5% carboxymethylcellulose, p.o.); (b) CMC group (0.5% carboxymethylcellulose, p.o.) + NAP (naproxen 300 mg/kg, p.o.); (c) LPu group (10 mg/kg, p.o.) + NAP (naproxen 300 mg/kg, p.o.); (d) LPu group (30 mg/kg, p.o.) + NAP (naproxen 300 mg/kg, p.o.); (e) LPu group (100 mg/kg, p.o.) + NAP (naproxen 300 mg/kg, p.o.); (f) LPe group (10 mg/kg, p.o.) + NAP (naproxen 300 mg/kg, p.o.); (g) LPe group (30 mg/kg, p.o.) + NAP (naproxen 300 mg/kg, p.o.); (h) LPe group (100 mg/kg, p.o.) + NAP (naproxen 300 mg/kg, p.o.)

latter is a xanthone that has a gastroprotective effect owing to its antioxidant mechanism of action; it also modulates the activation and functionality of macrophages and confers membrane lipid peroxidation protection (Andreu et al., 2005; Carvalho et al., 2015; García et al., 2002; Leiro et al., 2003).

3.7 | Myeloperoxidase activity

Another important consequence of naproxen-induced gastrointestinal injury is the increased concentration and activity of MPO, which is associated with increased neutrophil infiltration in damaged tissues. Therefore, MPO is considered to be a marker of inflammation and neutrophil infiltration in ulcerated conditions, and reduction in its levels occurs during the healing process (Higuchi et al., 2009; Souza et al., 2004). At all doses, LPu and LPe treatment reduced the MPO activity compared to the naproxen-treated group (4.147 U/g tissue ±1.38). The MPO activities after treatment with the extracts were close to that of the CMC group (0.1264 U/g tissue ±0.25), as shown in Figure 7.

The suppression of infiltration and the inhibition of neutrophil migration (Figure 4), evidenced by the decreased MPO activity, suggests that mango peel and pulp extracts have an anti-inflammatory effect, which might be attributed to their rich composition of antioxidant compounds (Table 2).

Many studies report that bioactive compounds have anti-inflammatory effects that are exerted through antioxidant

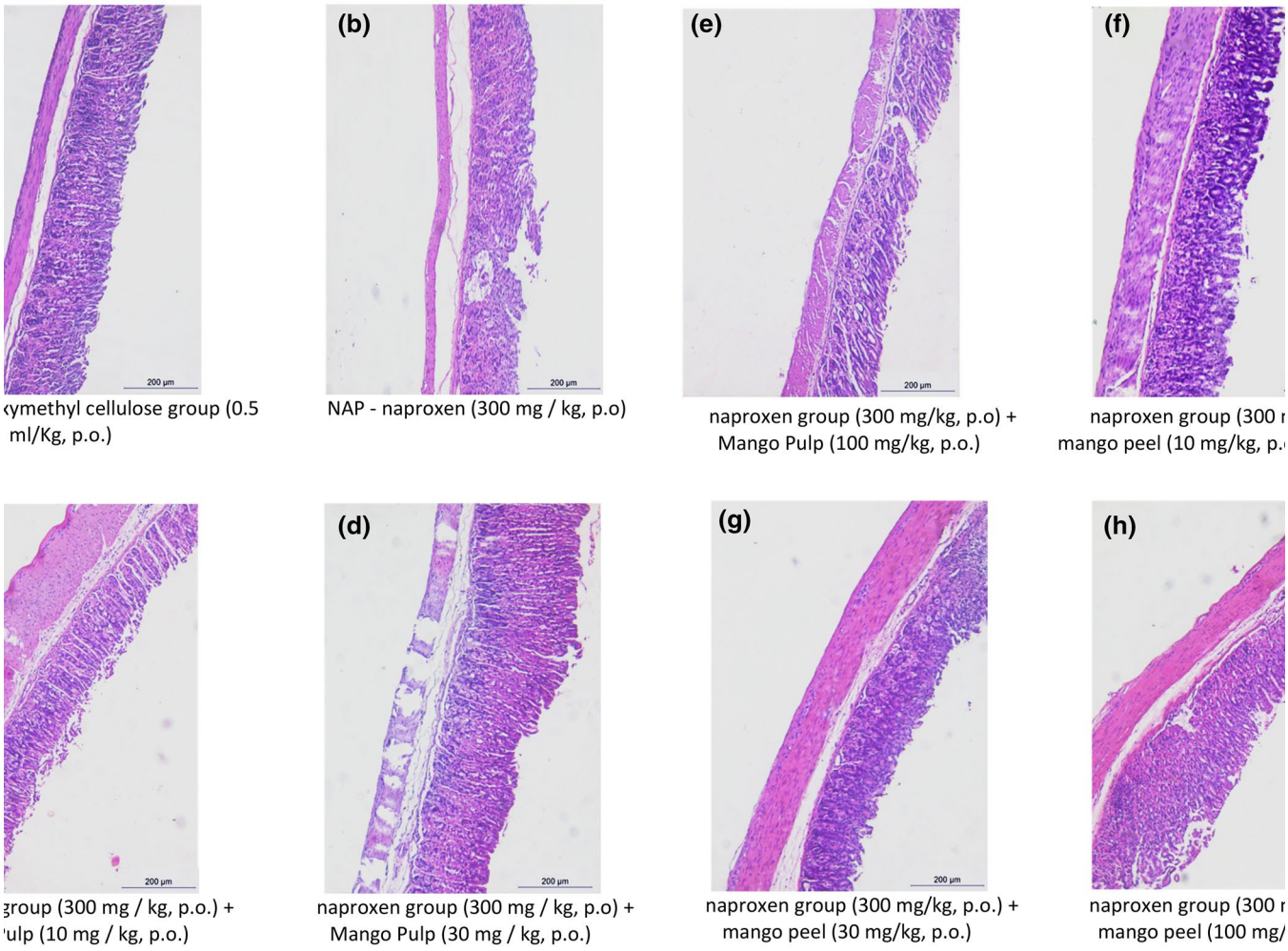

FIGURE 4 Histological evaluation of the naproxen-induced gastric damage in mice pretreated with mango (*Mangifera indica* L.) pulp extract (LPu) or peel extract (LPe) at different concentrations (10, 30 and 100 mg/kg) in naproxen-induced lesion. (a) Control stomach: intact gastric epithelium with organized glandular structure and normal submucosa could be seen; (b–e) naproxen-induced damage. (b) mice pre-treated with vehicle presented damaged mucosal epithelium with disrupted glandular structure and edema of submucosa and inflammatory infiltrate of mucosa; (c) LPu 10 mg/kg; (d) LPu 30 mg/kg; (e) LPu 100 mg/kg. (c–e) depict a recovery in mucosa epithelium and reorganized glandular structure, as well as improvement of edema by LPu. (H&E staining; magnification 100); (f) LPe 10 mg/kg; (g) LPe 30 mg/kg; (h) LPe 100 mg/kg. (f–h) depict a recovery in mucosa epithelium and reorganized glandular structure, as well as improvement of edema by LPe. (H&E staining; magnification 100)

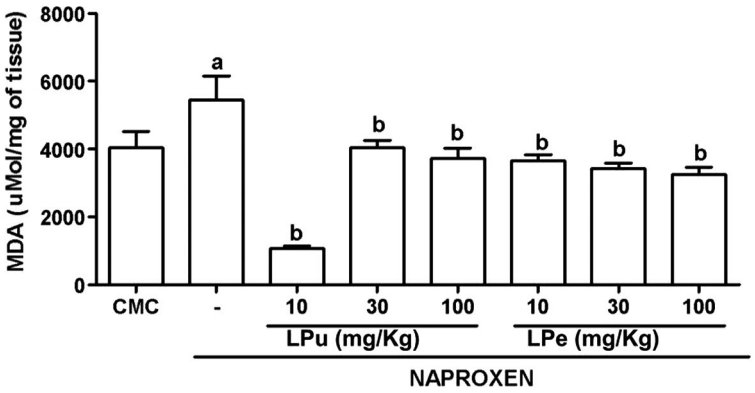

FIGURE 5 Malondialdehyde (MDA) concentration in the gastric wall of mice previously treated with mango peel extract (LPe) and mango pulp extract (LPu) in naproxen-induced gastropathy (300 mg/kg). The result was expressed as mean ± SEM for group of six animals per group. (a) $p < .05$ when compared to the NAP group; (b) $p < .05$, when compared with the CMC group (control). Statistical analysis was performed using ANOVA, followed by Bonferronis test

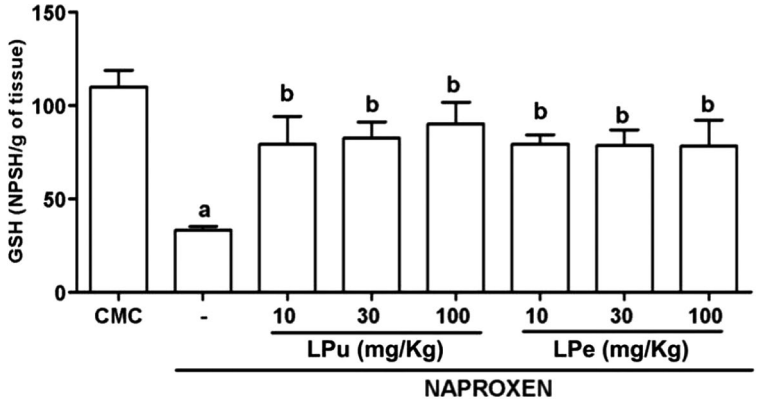

FIGURE 6 Determination of glutathione (GSH) levels in the gastric wall of mice previously treated with mango peel extract (LPe) and mango pulp extract (LPu) in naproxen-induced gastropathy (300mg/kg). The result was expressed as mean ± SEM for group of six animals per group. (a) $p < .05$ when compared to the NAP group; (b) $p < .05$, when compared with the CMC group (control). Statistical analysis was performed using ANOVA, followed by Bonferronis test

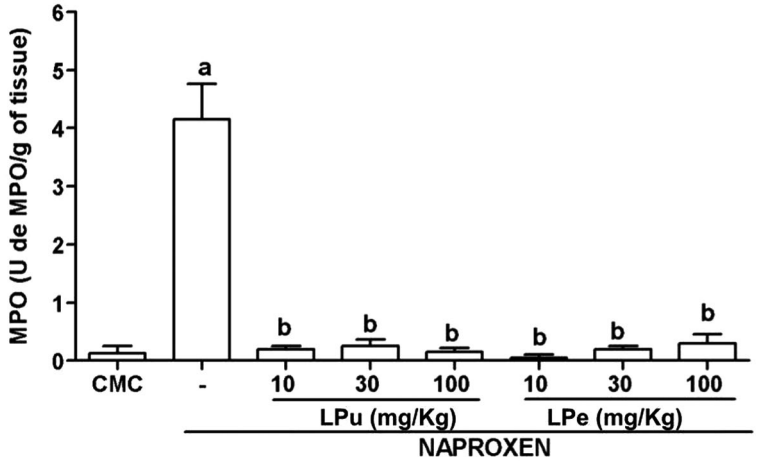

FIGURE 7 Determination of myeloperoxidase (MPO) activity in the gastric wall of mice previously treated with mango peel extract (LPe) and mango pulp extract (LPu) in naproxen-induced gastropathy (300 mg/kg). The result was expressed as mean ± SEM for group of six animals per group. (a) $p < .05$ when compared to the NAP group; (b) $p < .05$, when compared with the CMC group (control). Statistical analysis was performed using ANOVA, followed by Bonferronis test

mechanisms, inhibiting the initiation of oxidative reactions or stopping their spread to prevent inflammation. These compounds can also limit the oxidation of lipids, proteins, and lipoproteins during ulcerative conditions (Arnhold & Flemmig, 2010; Nimse & Pal, 2015; Reichlin et al., 2010). These effects contribute to the modulation and reduction of MPO activity and other inflammatory factors (Boots et al., 2008; Carullo et al., 2017; Farzaei et al., 2015; de Jesus et al., 2012; Pal et al., 2010; Sen et al., 2013).

4 | CONCLUSION

The hydroalcoholic extracts of mango pulp and peel were effective in preventing oxidative damage in gastric tissue triggered by naproxen in a rat gastropathy model. This was evidenced by significantly reduced myeloperoxidase activity and malondialdehyde content. Furthermore, the glutathione concentration was maintained close to that of the control treatment. These results can be attributed to the antioxidant capacity of the extracts, which had high contents of antioxidant compounds (mainly phenolics), such as mangiferin, quercetin derivatives, and gallic acid, as identified in the UPLC-QToF-MS^E analysis.

There are several opportunities for future related work, such as the encapsulation of extracts within polymeric matrices to increase their bioaccessibility. Other extraction methods could be investigated in order to obtain higher concentrations of the desired compounds. These compounds could be incorporated into food matrices to develop a nutraceutical able to inhibit oxidative processes. This study can also be a basis for the investigation of compounds derived from plants that can promote the alleviation or prevention of gastrointestinal disorders, such as gastric ulcers.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Carla Ferreira Gomes: Data curation; Formal analysis; Investigation; Writing-original draft; Writing-review & editing. **Luciana de Siqueira Oliveira:** Investigation; Methodology; Supervision; Writing-original draft; Writing-review & editing. **Delane Rodrigues:** Writing-original draft. **Paulo Ribeiro:** Formal analysis; Methodology; Validation. **Kirley Canuto:** Methodology; Writing-review & editing. **Antoniella Duarte:** Formal analysis; Methodology; Validation; Writing-review & editing. **Kaliana Eça:** Writing-review & editing. **Raimundo Figueiredo:** Resources; Supervision.

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