Supplementary Materials

1 Extraction of AC-EVs

Due to the complex composition of plant-derived materials, more rigorous impurity removal and purification procedures are required compared with those used for mammalian extracellular vesicles to ensure adequate purity. Based on previously reported isolation and purification protocols for PDEVs, [1-4] the following extraction procedure was established: Fresh purple onions purchased locally were washed with ultrapure water, air-dried, and weighed (total mass:150 - 200 g). The onions were then cut into small pieces and processed using a juicer. A defined amount of onion pieces was added into the juicer along with an equal volume of PBS and homogenized at 12,000 rpm to obtain an onion juice mixture. The homogenate was subsequently filtered through gauze and a funnel to remove debris, yielding a filtrate. The filtrate was transferred into 50 mL centrifuge tubes, balanced, and centrifuged at 1,000 × g for 10 min at 4 ℃. The supernatant was collected and centrifuged at 3,000 × g for 20 min, followed by centrifugation at 10,000 × g for 2 h. The resulting supernatant was filtered through a 0.45 μm membrane to obtain crude extracellular vesicles. Sucrose solutions at concentrations of 5%, 10%, 30%, and 45% were then prepared and sequentially layered into ultracentrifuge tubes from high to low density. The volumes of the gradient solutions were 3 mL (5%), 3 mL (10%), 2 mL (30%), and 2 mL (45%), respectively. Finally, 1 mL of PBS-diluted crude extracellular vesicles was added to the top layer, followed by ultracentrifugation at 150,000 × g for 2 h. A distinct band containing onion-derived components was observed, primarily distributed between the 10% and 30% layers. This band was carefully collected using a pipette. The collected fraction was transferred into a new ultracentrifuge tube, mixed with 10 mL PBS, and centrifuged at 100,000 × g for 2 h. The supernatant was discarded, and the pellet was resuspended and filtered through a 0.22 μm membrane to obtain purified AC-EVs, which were immediately stored at -80 ℃ for subsequent use.

2 Preparation of ACEV@CEL

In this study, celecoxib was loaded into AC-EVs using an ultrasonication method. Briefly, AC-EVs (1 mg/mL) were mixed with a celecoxib solution to obtain a homogeneous mixture. The mixture was subjected to ultrasonication (200 W, 5 s on/10 s off cycles, for a total of 6 cycles), with a 1 min cooling interval on ice between cycles before the next round of sonication. Following ultrasonication, the mixture was incubated at 37 ℃ for 1 h to restore the stability of the vesicle membrane. Subsequently, the mixture was transferred into a 100 kDa ultrafiltration tube and centrifuged at 4 ℃ and 4,500 × g for 15 min to remove unbound celecoxib, thereby obtaining ACEV@CEL.

3 Determination of Drug Loading in ACEV@CEL

3.1 Construction of the Celecoxib Standard Curve

First, 25 mg of celecoxib was accurately weighed, dissolved in 1 mL of DMSO, and transferred into a 10 mL amber volumetric flask. The solution was then brought to volume with PBS and thoroughly mixed to obtain a stock solution. Subsequently, a series of standard solutions with concentrations of 0.4 μg/μL, 0.6 μg/μL, 0.8 μg/μL, 1.0 μg/μL, 1.2 μg/μL, and 1.4 μg/μL were prepared using PBS. The absorbance of celecoxib at 252 nm was measured stepwise for each concentration using a microvolume spectrophotometer, following the manufacturer's instructions, with PBS serving as the blank control. Linear regression analysis was then performed by plotting mass concentration (μg/μL) against absorbance (Abs).

3.2 Determination of Encapsulation Efficiency (EE%) of ACEV@CEL

The absorbance of ACEV@CEL after ultrafiltration was measured at 252 nm using a microvolume spectrophotometer. The corresponding mass concentration of celecoxib was calculated based on the standard curve equation. The encapsulation efficiency of ACEV@CEL was then calculated using the following formula:

Encapsulation efficiency (EE%) = (mass of celecoxib in ACEV@CEL / total mass of added celecoxib) × 100%.

4 Determination of the Concentrations of AC-EVs and ACEV@CEL

In this study, the concentrations of AC-EVs and ACEV@CEL were determined using the BCA assay. RIPA buffer and PMSF were mixed at a volume ratio of 99:1 to prepare the lysis buffer. A total of 7 μL of AC-EVs or ACEV@CEL was mixed with 63 μL of lysis buffer and thoroughly homogenized on ice. For the preparation of the standard curve, PBS and a protein standard solution (0.5 mg/mL) were added to a 96-well plate in the following volumes: PBS at 20, 18, 16, 12, 8, and 0 μL, and protein standard at 0, 2, 4, 8, 12, and 20 μL, respectively. Subsequently, 20 μL of each sample was added to the wells, with three replicates per sample. Finally, BCA working solution A and B were mixed at a volume ratio of 50:1, and 200 μL of the mixture was added to each well. After incubation at 37 ℃ for 30 min, the absorbance of each sample was measured at 562 nm using a microplate reader. A standard curve was generated, and sample concentrations were calculated by interpolating their absorbance values against the standard curve.

5 Characterization of AC-EVs and ACEV@CEL

5.1 NTA

The NTA instrument and computer were first powered on, and the system was initialized. The tubing was flushed with ultrapure water and cleaning solution to ensure the absence of air bubbles and impurities. Quality control beads were then loaded to optimize the instrument settings, followed by particle size standard beads, concentration standard beads, and PBS solution, and the corresponding data were recorded. Purified AC-EVs and ACEV@CEL were serially diluted tenfold with PBS until reaching a final dilution of 1000-fold relative to the original solution. The diluted samples were then loaded into the instrument to obtain particle size distribution data.

5.2 TEM

The morphological characteristics of AC-EVs and ACEV@CEL were observed using the floating negative staining method. Briefly, 10 μL of PBS-resuspended sample was gently dropped onto a carbon-coated copper grid and allowed to stand at room temperature for 1 min. Excess sample was removed using filter paper. The grid was then negatively stained with uranyl acetate for 30 s, and excess staining solution was

carefully wicked off from the edge using filter paper. After rapid rinsing with ultrapure water, the grid was air-dried at room temperature for 10 min. Once completely dried, the samples were examined under a transmission electron microscope (80 kV), and images were acquired.

6 Establishment of the Rat Periodontitis Model and Grouping

A total of 30 SPF-grade male rats (6 weeks old, weighing approximately 180–200 g) were used in this study. All animals were subjected to a one-week acclimatization period prior to any experimental procedures. Before treatment, each rat was anesthetized with isoflurane inhalation. During the induction phase, rats were placed in a sealed anesthesia chamber and exposed to a mixture of 3%–4% isoflurane with pure oxygen; anesthesia was maintained via a nose cone delivering 1.5%–2.0% isoflurane. Adequate anesthesia was confirmed by the loss of pedal reflex and stable respiratory rate, and body temperature was maintained using a heating pad. All procedures were conducted in accordance with animal ethical guidelines (Approval No.: CMU20241371).

The 30 rats were randomly divided into five groups (n = 6 per group), and body weight was recorded weekly:

(1) **Control group (CON):** PBS was injected into the gingival sulcus of the bilateral maxillary first molars every 2 days. Rats were provided with sufficient clean water and food ad libitum postoperatively.

(2) **Periodontitis group (PD):** After anesthesia, rats were fixed on a heating pad. The oral cavity was exposed using a mouth opener, and the tongue was retracted to one side. A 0.25 mm orthodontic stainless steel ligature wire was inserted from the palatal side between the first and second maxillary molars and passed through to the buccal side. The wire was looped around the cervical region of the first molar and tied at the mesial cervical area, with the depth of ligation reaching the gingival sulcus. Care was taken to ensure that the ligature did not interfere with normal feeding or oral activity. Meanwhile, 10 μg/μL *P. gingivalis* LPS was injected into the gingival sulcus. The ligature was checked every 2 days, and PBS was injected into the gingival sulcus of the first molar.

(3) **AC-EVs group (AC-EVs):** Ligature placement was performed as described in (2). Subsequently, AC-EVs (20 μg/mL) were injected into the gingival sulcus of the bilateral maxillary first molars every 2 days.

(4) **Celecoxib group (CEL):** Ligature placement was performed as described in (2). Subsequently, celecoxib (2 mg/mL) was injected into the gingival sulcus of the bilateral maxillary first molars every 2 days.

(5) **ACEV@CEL group (ACEV@CEL):** Ligature placement was performed as described in (2). Subsequently, ACEV@CEL was injected into the gingival sulcus of the bilateral maxillary first molars every 2 days, with the concentration adjusted such that the celecoxib content was equivalent to that in the CEL group.

After 4 weeks of ligation, the experiment was terminated. Following 12 h of fasting, rats were euthanized by CO_2 overdose. Cardiac perfusion was then performed using physiological saline until organ blanching was observed, followed by perfusion with 4% paraformaldehyde. The heart, liver, spleen, lungs, and kidneys were harvested and fixed in 4% paraformaldehyde. Bilateral maxillary alveolar bone tissues were collected, surrounding soft tissues were removed, and the samples were fixed in 4% paraformaldehyde.

7 Micro-CT Evaluation

After fixation at 4 ℃ for 48 h, the rat maxillae were thoroughly rinsed with PBS and subsequently stored in PBS. Prior to scanning, the samples were secured within plastic tubes using foam to ensure stability and consistent orientation within the scanning chamber, thereby minimizing motion artifacts during image acquisition. The specimens were scanned using a Micro-CT system, followed by three-dimensional reconstruction and analysis. The scanning parameters were set as follows: voltage 70 kV, current 114 μA, and voxel resolution 17.5 μm. After scanning, the raw data were reconstructed into two-dimensional and three-dimensional images using Mimics 21 software. On the reconstructed three-dimensional models, the distance from the CEJ to the ABC between the maxillary first and second molars (CEJ–ABC) was measured. The mean value of this distance was used to quantify alveolar bone loss.

8 Decalcification

All tissues were fixed in 4% paraformaldehyde for 48 h, followed by rinsing under running water for 24 h to remove residual fixative. The alveolar bone samples were then decalcified in 10% EDTA solution, with the volume of EDTA maintained at approximately 5–7 times that of the tissue. The decalcification solution was replaced daily, and the process was continued for 4 weeks. After decalcification, the tissues were dehydrated, embedded, and sectioned into slices with a thickness of 2 μm. The sections were baked for 4 h and subsequently stored at 4 ℃ for further staining.

9 Histological Staining

9.1 H&E Staining

Paraffin-embedded sections were baked at 60 ℃ for 1 h, followed by deparaffinization in xylene twice for 10 min each. The sections were then rehydrated through a graded ethanol series (100%, 95%, 90%, 80%, and 70%) and finally rinsed in distilled water. The sections were stained with hematoxylin for 3–5 min, rinsed under running water, and differentiated using 1% hydrochloric acid alcohol. Subsequently, the sections were blued under running water or in a weak alkaline solution. After bluing, the sections were counterstained with eosin for 1–3 min to visualize the cytoplasm and extracellular matrix. Following staining, the sections were dehydrated through graded ethanol, cleared in xylene, and mounted with neutral resin. The sections were then observed under a light microscope to evaluate alveolar bone resorption, trabecular structure, periodontal ligament integrity, and inflammatory cell infiltration.

9.2 TRAP Staining

(1) Preheat an adequate volume of deionized water to 37 ℃, and allow the fixation solution to equilibrate to room temperature. Immerse the cell coverslips for 30 s and rinse thoroughly with deionized water, avoiding excessive drying.

(2) Wash once with PBS, taking care during aspiration to avoid detaching cells.

(3) Prepare two 1.5 mL EP tubes, adding Fast Garnet GBC base solution and sodium nitrite solution, respectively. Gently mix for 30 s and incubate at room temperature for 2 min. The combined solution constitutes the mixture used in the next step.

(4) Label another tube as A (B) and prepare the staining solution by mixing the above solution with Naphthol AS-BI phosphate solution, acetate solution, prewarmed (37 ℃) deionized water, and tartrate solution according to the specified proportions.

(5) Transfer the prepared staining solution into an appropriate staining container. Incubate in a water bath at 37 ℃ in the dark (e.g., wrapped in aluminum foil) and ensure the solution reaches 37 ℃ before adding the slides.

(6) Place the coverslips into the staining solution and incubate at 37 ℃ in the dark for 1 h.

(7) After incubation, thoroughly rinse the coverslips with deionized water.

(8) Counterstain with Hematoxylin Gill No. 3 for 2 min.

(9) Rinse with alkaline tap water for 5 min until blue-stained nuclei are observed.

(10) Allow the samples to air dry naturally, mount with glycerol gelatin, and observe under a microscope. For each sample, five random fields were selected, and the number of osteoclasts in each field was recorded for subsequent statistical analysis.

10 Biosafety Evaluation

The biosafety of the treatments was assessed by performing H&E staining on major organs of the rats to evaluate potential toxic effects. The heart, liver, spleen, lungs, and kidneys were processed for sectioning and H&E staining according to the method described in Section 9.1. Histological examination was then conducted to assess inflammatory cell infiltration and tissue damage in these organs, thereby determining whether AC-EVs induced any adverse effects on major organs.

11 Culture of RAW264.7 Cells

11.1 Cell Thawing

Frozen cells were retrieved from liquid nitrogen and immediately transferred into a 37 ℃ water bath for rapid thawing. Once completely thawed, the cell suspension was transferred into a centrifuge tube and supplemented with 4 mL of culture medium (DMEM + 20% fetal bovine serum + 1% penicillin–streptomycin). The cells were centrifuged at 800 rpm for 3 min, the supernatant was discarded, and the cell pellet was resuspended in 1 mL of medium. The cells were then transferred into a culture flask,

supplemented with 4 mL of complete medium, and incubated at 37 ℃ in a humidified atmosphere containing 5% CO_2.

11.2 Cell Passaging

Cell morphology was observed under an inverted microscope to determine whether passaging was required. The culture medium in the T25 flask was gently discarded, and 2 mL of fresh medium (DMEM + 10% fetal bovine serum + 1% penicillin–streptomycin) was added. The cells were detached by gentle pipetting, followed by centrifugation at 800 rpm for 3 min. The cell pellet was resuspended in fresh medium and subsequently seeded into new culture flasks containing fresh medium.

11.3 Cell Cryopreservation

Cells were harvested as described above and centrifuged at 800 rpm for 3 min. The cell pellet was then resuspended in 1 mL of serum-free freezing medium. The cell suspension was subjected to stepwise freezing by sequential storage at −20 ℃ and −80 ℃. For long-term preservation, the cells were finally stored in liquid nitrogen.

12 Evaluation of the Internalization of AC-EVs and ACEV@CEL by RAW264.7 Cells

12.1 Labeling of AC-EVs and ACEV@CEL with Dil Dye

A total of 10 mg of Dil was dissolved in 1 mL of DMSO by thorough pipetting, followed by further dilution in 9.7 mL of DMSO to ensure complete dissolution. The solution was stored at −20 ℃ in the dark. For labeling, 1 μL of the Dil solution was added to 99 μL of AC-EVs or ACEV@CEL and incubated at 37 ℃ for 30 min. Meanwhile, 1 μL of Dil was added to 99 μL of PBS as a control.

12.2 Removal of Excess Unbound Dye

The cap of the exosome spin column was opened, and the storage buffer was carefully removed from the top of the column using a micropipette and discarded. The bottom plug was then removed, and the next step was performed immediately. A total of 200 μL of sterile PBS was added to the column and centrifuged at 100 × g for 90 s. Subsequently, 100 μL of the labeled extracellular vesicle sample was carefully loaded onto the column and centrifuged again at 100 × g for 90 s. The eluate was discarded.

The column was then placed into a new 1.5 mL light-protected microcentrifuge tube, 200 μL PBS was added, and centrifugation at 100 × g for 90 s was performed to obtain 200 μL of purified, labeled extracellular vesicles.

12.3 Determination of the Concentration of Labeled AC-EVs and ACEV@CEL

The concentration of the labeled samples was determined as described in Section 4 ("Determination of the Concentrations of AC-EVs and ACEV@CEL").

12.4 Co-incubation of Labeled AC-EVs and ACEV@CEL with Cells

The labeled AC-EVs and ACEV@CEL were added to the culture medium at the determined concentrations, mixed thoroughly, and then applied to the cells. An equal volume of labeled PBS was added to the control group following the same procedure. After 6 h of incubation, the cells were washed three times with PBS, fixed with 4% paraformaldehyde for 10 min, and washed again three times with PBS.

12.5 Cytoskeleton Staining with Phalloidin and Nuclear Staining with DAPI

Cells were washed twice with PBS for 10 min each. They were then fixed with 3.7%–4% formaldehyde or paraformaldehyde for 20 min, followed by two additional PBS washes. Cells were stained with 5 μg/mL FITC-phalloidin at room temperature for 30–60 min and washed twice with PBS. Nuclear staining was performed using DAPI for 10 min, followed by two additional PBS washes.

12.6 Confocal Microscopy Observation

The internalization of AC-EVs and ACEV@CEL by RAW264.7 cells was observed using a confocal laser scanning microscope.

13 CCK-8 Assay for Cell Viability

Cells were collected, and the cell suspension was adjusted to an appropriate concentration. The cells were seeded into 96-well plates at a density of 3×10^3 cells per well in 100 μL medium and incubated overnight at 37 ℃ in a humidified atmosphere with 5% CO_2 to allow cell attachment. A blank group (medium only, without cells) and a negative control group (cells with medium, treated with PBS only) were included. In the experimental groups, RAW264.7 cells were co-incubated with different concentrations of AC-EVs, celecoxib, and ACEV@CEL (AC-EVs: 5, 10, 20, 50, and

100 μg/mL; celecoxib: 1, 5, 10, 20, and 50 μmol/L; ACEV@CEL: the concentration of celecoxib encapsulated in ACEV@CEL was determined as described above, and ACEV@CEL was added at corresponding concentrations to achieve final celecoxib concentrations of 1, 5, 10, 20, and 50 μmol/L). Each group was set up with five replicates. After 48 h of incubation, the culture plate was removed, and 10 μL of CCK-8 solution was added to each well, followed by an additional 4 h of incubation. The absorbance (Abs) of each well was then measured at 450 nm using a microplate reader. Cell viability was calculated relative to the negative control group, followed by statistical analysis. Each group included five technical replicates. During analysis, the wells with the highest and lowest absorbance values were excluded, and the remaining three wells were used for subsequent statistical analysis.

Cell viability (%) = (Absorbance of experimental group − absorbance of blank group) / (absorbance of negative control group − absorbance of blank group) × 100%.

14 TRAP Staining to Evaluate the Effects of Different Treatments on Osteoclast Differentiation

This part of the experiment was divided into four groups: CON, AC-EVs, CEL, and ACEV@CEL. After seeding, RAW264.7 cells were cultured overnight to allow adherence(6-well plate, 1×10^5 cells per well). Subsequently, all groups were treated with 50 ng/mL M-CSF and 100 ng/mL sRANKL. Meanwhile, cells in the AC-EVs group were additionally treated with 20 μg/mL AC-EVs, the CEL group received 10 μmol/L celecoxib, and the ACEV@CEL group was treated with ACEV@CEL at a concentration equivalent to 10 μmol/L celecoxib. The CON group received an equal volume of PBS. After 2 days, the culture medium was replaced, and M-CSF was substituted with *P. gingivalis* LPS (10 ng/mL), while sRANKL and the respective treatment concentrations remained unchanged. The cells were continuously cultured with medium replacement every 2 days. At Day 6, treatment was terminated, and TRAP staining was performed according to the method described in Section 9.2. The number of TRAP-positive cells in each group was counted and subjected to statistical analysis.

15 Western Blotting

15.1 Sample Preparation

Cells were grouped and treated as described in the previous section. At the experimental endpoint, the culture medium was discarded, and cells were washed three times with pre-cooled PBS. Then, 150 μL of lysis buffer was added to each well of a six-well plate. Cells were scraped on ice using a cell scraper and transferred into EP tubes, followed by lysis on ice for 10 min with intermittent sonication. After lysis, samples were centrifuged at 4 ℃ and 12,000 rpm for 15 min. The supernatant was collected, and 7 μL was taken and diluted with 63 μL PBS for protein concentration determination. Subsequently, 5× loading buffer was added to the remaining supernatant at a volume ratio of 1:4. After mixing, the samples were denatured by boiling at 95 ℃ for 10 min in a metal bath and stored at −80 ℃.

15.2 Western Blot Analysis

(1) Glass plates were cleaned with deionized water and air-dried. The plates were assembled into the casting frame and secured in the stand. Deionized water was added between the plates and left for 20 min to check for leakage. Separating and stacking gels were prepared in 50 mL centrifuge tubes according to the kit instructions. After adding the polymerization catalyst and mixing thoroughly, the gel solution was poured between the plates.

(2) The deionized water was removed and residual moisture was wiped off. The separating gel was slowly poured between the plates to approximately 1.5 cm below the top edge. Deionized water was gently layered on top of the separating gel to ensure a flat interface and prevent disturbance. After polymerization at room temperature for 30 min, the water was removed and the stacking gel was poured evenly. A 10-well comb was carefully inserted vertically without introducing bubbles. The gel was allowed to polymerize for 20 min at room temperature.

(3) During gel polymerization, electrophoresis buffer and transfer buffer were prepared (transfer buffer can be stored at 4 ℃). After polymerization, the gel assembly was mounted in the electrophoresis tank, and both the inner and outer chambers were filled with running buffer. The comb was carefully removed vertically to avoid damaging the gel.

(4) The protein molecular weight marker was taken from −20 ℃ and the protein samples from −80 ℃, heated at 95 ℃ for 10 min, briefly centrifuged, and kept on ice. A total of 2.5 μL marker was loaded into both ends of the gel, and 10 μL protein samples were loaded into the remaining wells. Loading was performed carefully to avoid overflow. The running buffer level was adjusted appropriately.

(5) Electrophoresis was conducted under constant voltage. After confirming correct electrode connections, proteins were separated at 80 V until the marker migrated through the stacking gel, followed by 120 V until the bromophenol blue dye front reached the bottom of the gel.

(6) For protein transfer, a transfer cassette was prepared with the black side facing down, and filter papers and sponges were soaked in transfer buffer. A PVDF membrane was cut to the size of the gel, marked at the upper left corner, activated in methanol for 30 s, and equilibrated in transfer buffer. The gel was carefully removed and placed on filter paper, and the PVDF membrane was placed on top. Air bubbles between the gel and membrane were carefully removed. The assembly was completed with three layers of filter paper and sponges, clamped, and placed in the transfer tank.

(7) Protein transfer was performed under constant current at 200 mA, with transfer time calculated as 1 min per kDa. The temperature of the transfer buffer was monitored, and ice packs were added if necessary to prevent overheating.

(8) After transfer, the PVDF membrane was removed and immersed in pre-prepared TBST buffer. The membrane was cut according to the molecular weight of the target proteins and marked. It was then blocked with protein-free blocking solution at room temperature for 30 min.

(9) Primary antibodies were prepared according to the manufacturer's recommended dilution and added to incubation boxes. The blocked membranes were washed with TBST and incubated with primary antibodies overnight at 4 ℃ on a shaker.

(10) After primary antibody incubation, membranes were washed in TBST three times for 10 min each with shaking.

(11) Appropriate HRP-conjugated secondary antibodies were selected based on the host species of the primary antibodies and diluted 1:10,000 in TBST. Membranes were incubated with secondary antibodies for 60 min with gentle shaking.

(12) Membranes were washed again in TBST three times for 10 min each.

(13) Enhanced chemiluminescence (ECL) substrate was prepared according to the instructions under light-protected conditions. The imaging system was set up, and membranes were placed on the imaging platform. Excess buffer was removed, and ECL substrate was evenly applied to the membrane surface and incubated for 2 min. Optimal exposure time was determined, and images were captured and saved. Densitometric analysis was performed using ImageJ (version 1.53, National Institutes of Health, USA), and target protein expression levels were normalized to the corresponding internal controls.

16 Statistical Analysis

All quantitative data are presented as the mean ± standard deviation (SD). Statistical analyses were conducted using SPSS Statistics 26.0 (IBM Corp., Armonk, NY, USA) . For comparisons among multiple groups, one-way analysis of variance (ANOVA) followed by Tukey's multiple comparisons test was applied. At least three biological replicates were included in each group. A p value < 0.05 was considered statistically significant.

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