Corryocactus brevistylus (K. Schum. ex Vaupel) Britton & Rose (Cactaceae): Antioxidant, Gastroprotective Effects, and Metabolomic Profiling by Ultrahigh-Pressure Liquid Chromatography and Electrospray High Resolution Orbitrap Tandem Mass Spectrometry

Carlos Areche 1, Marco Hernandez 1, Teresa Cano 2, Juana Ticona 2, Carmen Cortes 3, Mario Simirgiotis 3, Fátima Caceres 4, Jorge Borquez 5, Javier Echeverría 6* and Beatriz Sepulveda 7*

1 Departamento de Química, Facultad de Ciencias, Universidad de Chile, Santiago, Chile, 2 Departamento de Química, Facultad de Ciencias Naturales y Formales, Universidad Nacional de San Agustín, Arequipa, Perú, 3 Instituto de Farmacia, Facultad de Ciencias, Universidad Austral de Chile, Valdivia, Chile, 4 Laboratorio de Botánica, Departamento de Biología, Facultad de Ciencias Básicas, Universidad Nacional de San Agustín, Arequipa, Perú, 5 Departamento de Química, Facultad de Ciencias Básicas, Universidad de Antofagasta, Antofagasta, Chile, 6 Departamento de Ciencias del Ambiente, Facultad de Química y Biología, Universidad de Santiago de Chile, Santiago, Chile, 7 Departamento de Ciencias Químicas, Universidad Andrés Bello, Viña del Mar, Chile

Corryocactus brevistylus (K. Schum. ex Vaupel) Britton & Rose (Cactaceae) is a shrubby or often arborescent cactus popularly known as “sancayo” and produce an edible fruit known as “Sanky” which is consumed in Arequipa-Perú. The purpose of this study was to report the gastroprotective activity and relate this activity to the antioxidant capacity and presence of phenolic compounds for the first time. A metabolomic profiling based on Ultrahigh-pressure liquid chromatography and electrospray high resolution mass spectrometry, and the antioxidant activities (DPPH, ABTS, and FRAP), ascorbic acid content, total phenolics and flavonoids contents, and the mode of gastroprotective action of the Sanky fruit including the involvement of prostaglandins, nitric oxide, and sulfhydryl compounds is reported. Thirty-eight compounds were detected in the ethanolic extract including 12 organic acids, nine hydroxycinnamic acids, three isoamericanol derivatives, six flavonoids, five fatty acids, and two sterols. The results of the biological tests showed that the ethanolic extract had antioxidant capacity and gastroprotective activity on the model of HCl/EtOH-induced gastric lesions in mice (at 10, 25, 50, and 100 mg/kg). The effect elicited by the extract at 50 mg/kg was reversed by indometacin and N-ethylmaleimide but not by NG-nitro-L-arginine methyl ester suggesting that sulfhydryl groups and prostaglandins are involved in the mode of gastroprotective action.
conclusion, our study proves that *C. brevistylus* pears have some gastroprotective and antioxidant capacities and consumption is recommended for the presence of several bioactive compounds.

**Keywords**: Cactaceae, *Corryocactus brevistylus*, sancayo, flavonoids, phenolics compounds, gastroprotective, gastric ulcer

## INTRODUCTION

Today, fruits are considered the healthiest food in human health. Several native edible plants have played a significant role in all geographical regions of the world in human history and many local fruits are commercially available as juice, jam, or manufactured products (cookies, ice cream, yogurt, or dried fruits) due to the endemic knowledge of their health beneficial properties supported by their content of fiber, vitamins, and minerals plus bioactive compounds (Dreher, 2018; Pepin et al., 2019). Indeed, there is growing interest on the identification, composition, and nutritional properties of endemic edible fruits by the population and the scientific community (Yeung et al., 2018). In this sense, many foods have been studied and the technological progress each day finds new biological applications on fruits and fruit products. Among endemic South American edible fruits, we can find *Opuntia* prickly pear (Aruwa et al., 2019; Smeriglio et al., 2019), chayote pear (Díaz-de-Cerio et al., 2019), cherimola pulp (Albuquerque et al., 2016), strawberry (Baby et al., 2018), maqui (Rivera-Tovar et al., 2019), and murta (Rivera-Tovar et al., 2019) among others.

The Cactaceae family in Perú comprises 43 genera including 250 species where almost 80% of these species are endemic (Ostolaza Nano, 2014). The tribe Notocacteae include 10 genera, and only four genera have been found in Perú including *Corryocactus*, *Eulychnia*, *Isla ya*, and *Neowerdermannia*. In Perú, *Corryocactus brevistylus* (K. Schum. ex Vaupel) Britton & Rose (Cactaceae, Figure 1) is a shrubby or often arborescent cactus popularly known as “sancayo”, which is distributed in South America from Yura in Arequipa-Perú to Iquique in Northern Chile. According to Ostolaza;2014, *C. brevistylus* is a source of edible fruits known as “Sanky” which are consumed and marketed by peasants in Arequipa for its high ascorbic acid content (Ostolaza Nano, 2014). It is considered effective to prevent liver diseases and gastritis. According to the information provided by the residents of Arequipa-Perú, the peel of the fruit is used to strengthen the scalp and it was never seriously considered as a crop for a rational exploitation [neglected and underutilized species (NUS)]. In Chile, this cactus is very abundant in the Andes of Iquique (Quebrada de Chusmiza, Mamiña, and Chiapa) and the Chapiquiña-Belén, where it is called, *cardon verde, guacalla*, and *tacaysiña*. Its edible fruit is acidic and receives several vernacular names (*maksa, kontumela, kontumila, kontoksa, kontuksa, romba, or rumba*) and has various medicinal properties. It is consumed in the morning, with empty stomach, for gallbladder problems, stomach pain, liver, kidney stones, and as a laxative (Villagrán and Castro, 2003; Echeverría et al., 2020). *C. brevistylus* grows at about 4,000 meters above the sea level and their stems reach up to 2–5 m tall, forming large groups of dark green to light yellowish-green, with thorns of up to 24 cm long. Its flowers are yellow between 5–6 cm long x 10 cm wide. *Corryocactus brevistylus* fruit is green-yellowish, juicy, 12 cm long with abundant thorns and are found in saline soils and having a neutral acid flavor (Rispoli and Chipana, 2018). This edible fruit was used since ancient times by the Incas as a natural energizer to support their long Andean trips (Ostolaza Nano, 2014). Almost nothing is known on the chemistry and biological effect of Sanky (*C. brevistylus* fruits). Therefore, no information on the presence of their metabolites has been informed to date.

High performance liquid chromatography (HPLC) or ultrahigh-pressure liquid chromatography (UHPLC) coupled to high resolution-mass spectrometry is today a fundamental tool for the identification of phenolic compounds in edible fruits. Among the instruments offered in the market, the Q-Exactive Focus uses a very rapid high-resolution mass spectrometer for

![FIGURE 1 | Corryocactus brevistylus fruits.](image-url)
the detection of organic molecules equipped with an orbital trap, a quadrupole (Q) plus an HCD cell (High-Resolution Collision), producing parent ions and daughter fragments at high-resolution and good sensitivity. The hyphenated UHPLC-MS approach is suitable for the analysis of small organic compounds up to 2,000 Daltons, including fruit pigments, organic acids, flavonoids, pesticides, toxins, and terpenes (Perez et al., 2016).

In the course of our investigation on NUS Andean plants with potentiality as new crops, we now report the gastroprotective and antioxidant capacities, phenolic and flavonoid contents, and phenolic profiling based on Ultra HPLC electrospray high resolution mass spectrometry (UHPLC/ESI/HR-MS) plus the mode of gastroprotective action of *C. brevistylus* fruits including the mechanism of action [involvement of nitric oxide (NO), prostaglandins (PGs), and sulphydryls (SHs)].

**MATERIALS AND METHODS**

**Plant Material**

Ripe fruits from *C. brevistylus* (K. Schumann ex Vaupel) Britton et Rose were collected by hands in January 2016, in Chiguata (16° 24′ 09″ S, 71° 24′ 56″ W), Arequipa (Perú). The fruits were transported to the laboratory under refrigeration until processing. The species was identified by Dr. Fatima Caceres, Biology Department, San Agustín National University, Arequipa, Perú. A voucher specimen (N° CB-15012016) was deposited at the Herbarium of the San Agustín National University.

**Fruit Processing**

*Coryocactus brevistylus* fruits were divided into epicarp (peel) and pulp. The pulp was frozen (465 g) and then lyophilized obtaining 50 g of dried fruit powder. This powder (40 g) was extracted three times with ethanol (500 mL each time) at room temperature under sonication (15 min each). The solutions were filtered, combined and evaporated under reduced pressure below 40°C to obtain 8 g of crude ethanolic extract (CEX).

**Identification of Phenolic Compounds by UHPLC-ESI-HR-MS/MS**

Equipment: A Thermo Scientific Dionex Ultimate 3000 UHPLC system operated by Chromeleon 7.2 Software (Thermo Fisher Scientific, Bremen, Germany) hyphenated with a Thermo high resolution Q Exactive focus mass spectrometer (Thermo, Bremen, Germany) were employed for analysis. Nitrogen obtained from a generator (Ciantecnologica, Seville, Spain) was recorded. Mobile phases were 1% formic aqueous solution (A) system operated by Chromeleon 7.2 Software (Thermo Fisher 320, 254, 280, and 440 nm, and 800–200 nm in the PDA was recorded. Mobile phases were 1% formic aqueous solution (A) and acetonitrile with 1% formic aqueous solution (B). The gradient program was: (0.00, min, 5% B); (5.00 min, 5% B); (10.00 min, 30% B); (15.00 min, 30% B); (20.00 min, 70% B); (25.00 min, 70% B); (35.00 min, 5%B); and 12 minutes before each injection for equilibration. The flow rate was set at 1.00 mL min⁻¹, and the injection volume was 10 µL.

MS parameters: The HESI II and other parameters were optimized as previously reported (Simirgiotis et al., 2016).

**Chemicals**

Ultra-pure water [< 5 µg/L TOC, (total organic carbon)] was obtained from a water purification system Arium 126 61316-RO, plus an Arium 611 UV unit (Sartorius, Göttingen, Germany). Methanol (HPLC grade), ethanol, formalin, and formic acid (puriss. p.a. for mass spectrometry) from J. T. Baker (Phillipsburg, NJ, USA) were obtained. Folin-Ciocalteu reagent, sodium nitrite, trolox, sulfuric acid, copper sulfate, and aluminum chloride were from Merck (Santiago, Chile). DPPH reagent, (2,2-diphenyl-1-picrylhydrazyl), lansoprazole, ferric chloride hexahydrate, 2,4,6-tris(2-pyridyl)-s-triazine, N-ethylmaleimide (NEM), Indomethacin (IND), N-nitro-L-arginine methyl ester (L-NAME), oxalic acid, trolox, ascorbic acid, quercetin, gallic acid, DMSO, and HPLC standards (rutin, rhapamnetin, and isorhamnetin, all standards with purity higher than 95% by HPLC) were purchased from Sigma-Aldrich Chem. Co. (St Louis, MO, USA) or Extrasynthèse (Genay, France).

**Mice**

Animals were bought from the Institute of Public Health of Chile, Santiago. Swiss albino mice in metabolism cages were fasted for 24 h. Mice were weighed (30 ± 3 g) before the experiments. Mice were fed using certified diet (Champion) with free access to water under standard conditions (50% relative humidity, 12 h dark-light period, and 22°C room temperature). These protocols were approved by the Animal Use and Care Committee of the Universidad de Chile that follows the recommendations of the Canadian Council on Animal Care (Olfert et al., 1993). Such certificate was approved in July 2014 by Dr. Nicolas Giuliani with number AUCC-02072010.

**HCl/Ethanol-Induced Lesions**

The gastroprotective effect of the CEX was evaluated in the HCl/Ethanol-induced lesion model (Matsuda et al., 2002; Parra et al., 2015). Mice were randomly placed into groups of seven animals each and fasted for 24 h with free water access prior to the experiments. Fifty min after oral administration of CEX (10, 25, 50, and 100 mg/kg), lansoprazole (30 mg/kg) or 10% Acacia gum (vehicle), all groups were orally dispensed with 0.2 mL of a solution containing 0.3 M HCl/60% ethanol (HCl/EtOH) for gastric lesion induction. The CEX was administered at 50 mg/kg in a second experiment to evaluate its possible mode of gastroprotective action using carbenoxolone (100 mg/kg) as a positive control. Mice were sacrificed 60 min after the administration of HCl/EtOH, and the stomachs were excised and inflated by injection of saline solution (1 mL). The ulcerated stomachs were fixed in 5% formalin for 30 min and opened along the greater curvature. Gastric damage was observed in the gastric mucosa as elongated black-red lines, parallel to the long axis of the
Antioxidant and Gastroprotective Effects of *Coryocactus brevistylus*

**DPPH Test**

The capturing capacity of the DPPH• radical was measured by the decolorization method (Brito et al., 2014; Ramírez et al., 2014). Briefly, 9 µL of CEX extract (2 mg/mL), plus 341 µL of methanol DPPH solution (400 µM) were adjusted with methanol to an absorbance of 1.10 ± 0.02 at 517 nm. The mixture was homogenized, allowed to react in the dark at room temperature for 20 min, after which time absorbance was measured at 517 nm. The percentage of discoloration of the DPPH radical was obtained by measuring the change in absorbance at 517 nm, the values obtained converted to percent inhibition of the DPPH moiety. A curve was performed with different dilutions of the extract, (5–50 mg/L; r² = 0.9998) and the results were expressed as half maximal inhibitory concentration (IC₅₀) in µg/mL.

**ABTS•⁺ Radical Scavenging Assay**

The capturing capacity of the ABTS•⁺ radical was performed as reported previously (Brito et al., 2014; Ramírez et al., 2014). The ABTS⁺ radical is generated by the oxidation of ABTS with potassium persulfate after 16 h of incubation at room temperature in the dark. Briefly, 27 µL of the CEX extract to be measured, (2 mg/mL), was added to 273 µL of the previously prepared ABTS•⁺ solution (adjusted with 80% methanol to obtain an absorbance of 0.70 ± 0.02 at 734 nm), to the well of the microplate (Synergy HTX, Biotek USA) and subsequently allowed to react in darkness at room temperature for 6 min. The absorbance was then measured at 765 nm and the values obtained converted to % inhibition of the ABTS•⁺ radical and the results were expressed as IC₅₀ in µg/mL.

**Ferric Reducing Antioxidant Power Test (FRAP)**

For the FRAP assay, the methodology was performed as published with slight modifications (Brito et al., 2014; Ramírez et al., 2014). Briefly, to 10 µL of the dissolved extract (2 mg/mL), 290 µL of the FRAP solution was added and mixed in the well of the microplate, allowed to react in the dark at room temperature for 5 min. The absorbance measurement of the colored Fe-TPTZ complex was done at 595 nm. Absorbance data were replaced in the Trolox standard curve equation (µmol/L). The results were obtained as equivalents of Trolox (TE), in Trolox micromoles per gram of dry weight (µmol Trolox/g dry weight).

**Statistical Analysis**

Results were expressed as the mean ± S.D. In all experiments, statistical differences between treatments and controls were determined by one-way analysis of variance (ANOVA) followed by Dunnett’s test. The level of significance was set at P < 0.01. All statistical analyses were performed using the software GraphPad Prism 6 for Windows.

**RESULTS**

**Identification of Phenolic Compounds**

In this study, 38 compounds were detected by UHPLC/PDA and electrospray high resolution orbitrap tandem mass spectrometry.
(UHPLC-ESI-HR-MS) in CEX of *Corryocactus brevistylus* fruits (Figure 2). Those compounds contained in the CEX were detected on a UHPLC and identified or tentatively characterized based on UV spectra and full HR-MS spectra plus diagnostic fragmentations (Table 1) in electrospray negative mode, since negative mode is the best mode of ionization for phenolic compounds. (The phenols loose easily a proton and the charge are delocalized, so it is the normal way of ionization for those compounds). A total of 37 peaks including 13 organic acids (peaks 1–8, 10–11, and 19–21), nine hydroxycinnamic acids (peaks 9, 12–14, 16, 19, and 22–24), three isoamericanol derivatives (25–27), six flavonoids (peaks 15, 17–18, 28–30), five fatty acids (peaks 31–33 and 35–36), and two sterols (peak 34 and 38) were identified taking into account their elution order and comparing their MS data with respect to plant metabolites reported in the literature and spiking experiments using standards (Gómez-Romero et al., 2011; Simirgiotis, 2013; Brito et al., 2014; Ramirez et al., 2014; Makita et al., 2016; Simirgiotis et al., 2016; Su et al., 2016; Guerrero-Castillo et al., 2019). Peak 37 is considered unknown.

### Organic Acids and Other Phenolic Derivatives

Peaks 1–6 with deprotonated molecules at \( m/z \): 133.01357, 191.01907, 147.02913, 205.03491, and 137.02357 were identified as malic, citric, and hydroxyglutaric acid (Schor et al., 2002) and its isomer, homo(iso)citric and hydroxybenzoic acids (Mocan et al., 2018) respectively. Peak 7 was assigned tentatively as a dehydro-shikimic acid \((C_7H_{11}O_5)^{-}\) while peak 8 with a parent ion at \( m/z \): 175.0243 MS\(^2\) ions at \( m/z \): 115.0071; 113.01269; and 87.00942, was identified as ascorbic acid \((C_6H_7O_6)^{-}\) (Boonpangrak et al., 2016). Peak 10, 11, and 20 were tentatively identified as benzoyl aspartic acid derivatives whose molecular ions [M-H]- were at \( m/z \) 236.0561, 236.0562, and 262.0562 (Nakazaki et al., 1963). Finally, peak 21 was identified as nonanodioc acid and azelaic acid (187.0972, \( C_{9}H_{15}O_4^- \)) (Garelnabi et al., 2010). All these compounds were previously described exhibiting a similar fragmentation pattern and to the best of our knowledge have so far not been identified in Sancayo fruits. L-Malic acid is the naturally occurring form found in fruits as apple, blueberries, grapes, apricots, peaches, pears, and maqui except in cactus fruits. Isocitric acid is an organic acid very common in fruits and vegetables which is mainly found at high concentrations in citrus fruits (El-Mostafa et al., 2014; Aragona et al., 2018).

### Hydroxycinnamic Acids

Peak 9 was identified as caffeoyl-O-hexoside \((C_{15}H_{17}O_9)^{-}\), while two compounds (peak 12 and 13) had similar deprotonated molecules [M-H]- at \( m/z \) 353.0513. MS/MS fragmentation pattern of peak 12 (\( m/z \) 191.0191; 173.0085; 154.9978; 111.0078) indicated the presence of caffeoyl-(iso) citric acid while peak 13 was identified as its isomer (Masike et al., 2017). In similar manners, peaks 14 and 16 with ions [M-H]- at \( m/z \) 337.0564 and 337.0563 were identified as two coumaroyl-(iso) citric acids \((C_{15}H_{13}O_{10})^-\) (Masike et al., 2017). Peak 19 was detected at 11.90 min and identified as feruloyl-(iso) citric acid based on its deprotonated molecule [M-H]- at \( m/z \) 367.0671 \((C_{16}H_{15}O_{10})^-\), diagnostic MS/MS fragmentations (193.0506; 159.0457; 131.0308; 103.0160) indicated the presence of feruloyl-(iso) citric acid while peak 20 was identified as feruloyl-(iso) citric acid based on its deprotonated molecule [M-H]- at \( m/z \) 367.0671 \((C_{16}H_{15}O_{10})^-\), diagnostic MS/MS fragmentations (193.0506; 159.0457; 131.0308; 103.0160) indicated the presence of feruloyl-(iso) citric acid.
| Peaks | UV Max (nm) | Tentative identification | [M-H]⁻ | RT (min) | Theoretical Mass (m/z) | Measured Mass (m/z) | Accuracy (ppm) | MSⁿ ions (m/z) |
|-------|-------------|--------------------------|--------|---------|-----------------------|---------------------|----------------|----------------|
| 1     | –           | Malic acid C₄H₅O₅⁻      | 1.46   | 133.0132 | 133.0136              | 2.1                 | 115.0030       |
| 2     | –           | (iso) citric acid C₆H₇O₇⁻ | 1.82   | 191.0197 | 191.0190              | 3.7                 | 173.0080; 111.0078 |
| 3     | –           | Hydroxylutaric acid C₈H₆O₅⁻ | 2.10   | 147.0288 | 147.0291              | 2.0                 | 129.0184; 111.0078 |
| 4     | –           | Hydroxyglutaric acid isomer C₈H₆O₅⁻ | 2.39   | 147.0288 | 147.0291              | 2.0                 | 129.0184; 111.0078 |
| 5     | –           | Homo (iso) citric acid C₈H₆O₇⁻ | 2.86   | 205.0342 | 205.0349              | 3.4                 | 187.0245; 161.0451; 111.0078 |
| 6     | 280, 211   | Hydroxybenzoic acid C₆H₈O₇⁻ | 8.66   | 137.0244 | 137.0237              | 5.1                 | 93.1205        |
| 7     | 211        | Ascorbic acid C₆H₆O₃⁻      | 1.94   | 93.0361  | 93.0361               | 0.0                 | 111.0078       |
| 8     | 211        | Ascorbic acid C₆H₆O₃⁻      | 1.94   | 93.0361  | 93.0361               | 0.0                 | 111.0078       |
| 9     | 213, 287, 326 | Caffeoyl-O-hexoside C₁₀H₁₀O₆⁻ | 2.07   | 303.0514 | 303.0510              | 0.4                 | 192.0600       |
| 10    | 217, 288   | Benzoyl aspartic acid derivative C₁₄H₁₄O₆N⁻ | 2.07   | 303.0514 | 303.0510              | 0.4                 | 192.0600       |
| 11    | 217, 290, 323 | Benzoyl aspartic acid derivative C₁₄H₁₄O₆N⁻ | 2.07   | 303.0514 | 303.0510              | 0.4                 | 192.0600       |
| 12    | 221, 255, 342 | Caffeoyl (iso) citric acid C₁₀H₁₀O₆⁻ | 2.07   | 303.0514 | 303.0510              | 0.4                 | 192.0600       |
| 13    | 221, 266, 331 | Caffeoyl (iso) citric acid C₁₀H₁₀O₆⁻ | 2.07   | 303.0514 | 303.0510              | 0.4                 | 192.0600       |
| 14    | 221, 268, 318 | Coumaroyl (iso) citric acid C₁₀H₁₀O₆⁻ | 2.07   | 303.0514 | 303.0510              | 0.4                 | 192.0600       |
| 15    | 254, 345   | Rutin* C₁₄H₁₀O₆⁻ | 2.07   | 303.0514 | 303.0510              | 0.4                 | 192.0600       |
| 16    | 225, 288, 327 | Coumaroyl (iso) citric acid C₁₀H₁₀O₆⁻ | 2.07   | 303.0514 | 303.0510              | 0.4                 | 192.0600       |
| 17    | 255, 350   | Isorhamnetin-O-rutinoside C₁₄H₁₀O₆⁻ | 2.07   | 303.0514 | 303.0510              | 0.4                 | 192.0600       |
| 18    | 228, 290   | Taxifolin C₁₀H₁₀O₆⁻ | 2.07   | 303.0514 | 303.0510              | 0.4                 | 192.0600       |
| 19    | 227, 288, 327 | Feruloyl (iso) citric acid C₁₄H₁₀O₆⁻ | 2.07   | 303.0514 | 303.0510              | 0.4                 | 192.0600       |
| 20    | 223, 290, 321 | Benzoyl aspartic acid derivative C₁₄H₁₀O₆⁻ | 2.07   | 303.0514 | 303.0510              | 0.4                 | 192.0600       |
| 21    | 224        | Azelaic acid C₉H₁₀O₅⁻ | 1.72   | 262.0553 | 262.0562              | 3.5                 | 169.0859; 157.1228; 125.0964 |
| 22    | 225, 312   | Methylcoumaroyl(iso)citric acid C₁₄H₁₀O₆⁻ | 1.72   | 262.0553 | 262.0562              | 3.5                 | 169.0859; 157.1228; 125.0964 |
| 23    | 226, 311   | Methylcoumaroyl (iso) citric acid C₁₄H₁₀O₆⁻ | 1.72   | 262.0553 | 262.0562              | 3.5                 | 169.0859; 157.1228; 125.0964 |
| 24    | 225, 314   | Methylferuloyl (iso) citric acid C₁₄H₁₀O₆⁻ | 1.72   | 262.0553 | 262.0562              | 3.5                 | 169.0859; 157.1228; 125.0964 |
| 25    | 223, 283   | Unknown (possibly isoamericanol C₁₄H₁₀O₆⁻ | 1.72   | 262.0553 | 262.0562              | 3.5                 | 169.0859; 157.1228; 125.0964 |
| 26    | 223, 285, 328 | Unknown (possibly isoamericanol fragment or derivative) C₁₄H₁₀O₆⁻ | 1.72   | 262.0553 | 262.0562              | 3.5                 | 169.0859; 157.1228; 125.0964 |
| 27    | 195, 223, 283 | Unknown (possibly isoamericanol B1 or its isomer C₁₁H₈O₆⁻ | 1.72   | 262.0553 | 262.0562              | 3.5                 | 169.0859; 157.1228; 125.0964 |
| 28    | 254, 381   | Quercetin* C₁₀H₁₀O₆⁻ | 1.72   | 301.0314 | 301.0315              | 0.3                 | 179.0502; 178.9986; 177.0193; 151.0036; 107.0129 |
| 29    | 254, 354   | Isorhamnetin* C₁₀H₁₀O₆⁻ | 1.72   | 301.0314 | 301.0315              | 0.3                 | 179.0502; 178.9986; 177.0193; 151.0036; 107.0129 |

(Continued)
Peaks 22 and 23 were identified as isomers of the derivative methylocoumaroyl(iso) citric acid (C16H15O9−), and finally peak 24 as methylferuloyl (iso) citric acid (C17H17O10−).

**Flavonoids**

Several metabolites were detected as flavonoids (UV max 254–354 nm). Thus, peak 15 with a deprotonated molecule at m/z 609.14508 was identified as rutin (C27H29O16−) (Mocan et al., 2018) and peak 17 with a deprotonated molecule at m/z:623.16071 and MS fragments at 315.0509, 301.0353, as rhamnetin/isorhamnetin-3-O-rutinose (C28H31O16−) (Brito et al., 2014) or rhamnetin/isorhamnetin-O-neohesperidose (since isorhamnetin aglycone was found using standard). Peak 18 was identified as the flavanonol taxifolin (C15H11O7−) (dihydroquercetin) that is a bioactive flavanonol commonly found in grapes (Yang et al., 2016). Peak 28 with an anion at m/z:301.03140, was assigned as quercetin (C15H9O7−) using authentic standard, and peaks 29 and 30 as two isomers of methyl quercetin (C18H33O5−), producing flavone diagnostic fragments at m/z: 301.0353, 179.0502, and 151.0035; 107.0129 isorhamnetin and rhamnetin, respectively (El-Mostafa et al., 2014; Aragona et al., 2018). Spiking experiments using some available standards (rutin, quercetin, rhamnetin, and isorhamnetin) were performed.

**Fatty Acids**

Peaks 35 and 36 with ions at m/z:411.23883 were tentatively identified as isomers of the fatty acid pentahydroxy-oxodocosanoic acid (C22H35O7−) while peaks 31 and 32 with ions at m/z:329.2331 and 329.2330 were tentatively identified as trihydroxy-octadecenoic acid and its positional isomer (C18H33O5−) (Toomik et al., 2012).

**Sterols**

Peak 34 at m/z: 481.3171 was tentatively identified as peniocerol derivative (C27H45O7−), while peak 38 as its demethylated derivative (C25H40O7−). Peniocerol is a sterol isolated and reported from *Myrtillocactus geometrizans* (Mart. ex Pfeiff.) Console (Cactaceae) (Céspedes et al., 2005).

**Unknown**

Peak 25, 26, and 27 with parent ions at m/z: 493.1493, 327.08740, and 493.1493 were unknown compounds tentatively identified as hydroxycinnamic acid derivatives (163.0938, C9H7O3−) possibly isoamericanol B1, C1 derivatives (CAS 77879-90) a constituent of *Phytolacca dioica* L., a dioxin which has the coumaroyl moiety in its structure (Di Petrillo et al., 2019).

**Biological Activity**

**Antioxidant Activity**

DPPH, FRAP, and ABTS (TEAC) tests were used to measure the antioxidant activity of *C. brevistylus* fruits for the first time (see Table 2). These capacities were compared to other fruits previously reported by us including other South American fruits (Céspedes et al., 2010; Ramirez et al., 2014; Simirgiotis et al., 2010; Areche et al., 2012, 2014).
et al., 2016; Guerrero-Castillo et al., 2019). In addition, three main types of metabolites were tentatively identified in this work, organic acids, hydroxycinnamic acids, and flavonoids, besides polyunsaturated fatty acids (Table 1), that could be responsible for the antioxidant power. However, the ascorbic acid content of C. brevistylus fruits (38.46 ± 3.72 mg/100 g) was higher than that reported for another south American Cactaceae: Copao pears (Eulychnia acida Phil.), 35.7 mg/100 g (Jiménez-Aspee et al., 2014). Furthermore, the total phenolic values of C. brevistylus fruits, TPC: 24.34 ± 3.67 mg GAE/g dry weight, (Table 2) together with total flavonoids (TPC: 13.33 ± 1.88 mg quercetin/g dry weight, Table 2) were higher to those published for the green variety and flavonoids: 2.45 to 3.07 mg G/AE/g dry weight for the green variety and flavonoids: 2.45 to 3.07 mg G/AE/g dry weight for the same variety, respectively (El-Mostafa et al., 2014), and were higher to those reported for Copao pears, (47.42 mg GAE/100 g MeOH extract and 0.10 mg quercetin/100 g MeOH extract (Jiménez-Aspee et al., 2014); also the TPC was half to those published for the Opuntia ficus-indica (L.) Mill. pears (from 9.64 mg GAE/g dry weight for the red variety to 12.28 mg GAE/g dry weight for the green variety and flavonoids: 2.45 to 3.07 mg G/AE/g dry weight, for the same varieties, respectively (El-Mostafa et al., 2014), and were higher to those reported for Copao pears, (47.42 mg GAE/100 g MeOH extract and 0.10 mg quercetin/100 g MeOH extract (Jiménez-Aspee et al., 2014); also the TPC was half to that of the Chilean guava fruits Ugni molinae Turcz., (50 mg GAE/g dry weight) which is situated in the average of antioxidant edible fruits (Balasundram et al., 2006; Pinto et al., 2009; Rodriguez-Roque et al., 2014). Also, the TPC were half lower to those measured for Chilean blueberries (45.86 ± 3.46 mg GAE/g) (Ramirez et al., 2015) and TFC nearly half to that of the Luma apiculata (DC.) Burret berries (29 mg G Quercetin/g) (Simirgiotis et al., 2013). In the DPPH assay, C. brevistylus fruit extract (47.45 ± 0.23 µg/mL) was closer to that published for lemon fruits, TPC: 24.34 ± 3.67 mg GAE/g dry weight, (Table 2) and higher to those published for the Antioxidant and Gastroprotective Effects of Corryocactus brevistylus. These data can classify C. brevistylus fruit extracts with moderate to high antioxidant activity, such as plum, cherries, and strawberries (Gironés-Vilaplana et al., 2014; Ramirez et al., 2015; Simirgiotis et al., 2016).

Gastroprotective Activity

The effects of the CEX on the model of HCl/EtOH in mice are presented in Table 3. An oral administration of CEX at 10, 25, 50, and 100 mg/kg inhibited the formation of gastric lesions compared with control group (P < 0.01). It is also clear that the inhibition by CEX did not display a dose-response relationship. The inhibition displayed by CEX at 50 and 100 mg/kg, p.o. (63% and 73%) was similar to that obtained with lansoprazole (67%). In the second experiment, we decided to evaluate the possible mechanism of gastroprotective action of CEX at a single oral dose of 50 mg/kg. Table 4 shows the results of CEX on the gastric lesions induced by HCl/EtOH in mice pretreated with indomethacin (IND, 10 mg/kg, s.c.), NEM (10 mg/kg, s.c.), or L-NAME (70 mg/kg, i.p.).

Regarding mode of gastroprotective action, pretreatment with NEM (an SH blocker) reduced the gastroprotective activity of CEX, suggesting that the protective effect of this extract is through the participation of endogenous SHs (Table 4).

| Species               | DPPH | ABTS | FRAP  | TPC   | TFC   | AA   |
|-----------------------|------|------|-------|-------|-------|------|
| Sanky pulp            | 47.45 ± 0.23 | 225.12 ± 2.42 | 155.34 ± 3.67 | 24.34 ± 3.67 | 13.33 ± 1.88 | 38.46 ± 3.72 |
| Gallic acid*           | 5.47 ± 0.25  | –     | –     | –     | –     | –    |
| Quercetin*            | 7.08 ± 0.65  | –     | –     | –     | –     | –    |

*Antiradical DPPH and ABTS activities are expressed as IC50 in µg/mL for extracts and compounds; †Expressed as µM TE/g dry weight. ‡TPC expressed as mg gallic acid/g dry weight; ¶Total flavonoid content (TFC) expressed as mg quercetin/g dry weight; ‡Expressed as mg per 100 g. *Used as standard antioxidants. Values in the same column are significantly different (P ≤ 0.05).

AA, ascorbic acid content; FRAP, ferric reducing antioxidant power test; TPC, total phenolic content; TFC, total flavonoid content.

Table 2 | DPPH assay, ABTS antioxidant activity (ABTS), ferric reducing antioxidant activity (FRAP), total phenolic content (TPC), total flavonoid content (TFC), and ascorbic acid content (AA) of Corryocactus brevistylus edible fruit extract (n = 5).

| Compound             | n | Lesion index (mm) | % Lesion reduction | Dose (mg/kg) |
|----------------------|---|-------------------|--------------------|--------------|
| CEX-10               | 7 | 36.6 ± 4.7* | 18**             | 10            |
| CEX-25               | 7 | 29.7 ± 3.3* | 34**             | 25            |
| CEX-50               | 7 | 16.7 ± 3.9* | 63                | 50            |
| CEX-100              | 7 | 12.0 ± 3.4* | 73                | 100           |
| Lansoprazole         | 7 | 15.7 ± 2.9* | 67                | 30            |
| Control              | 7 | 45.3 ± 5.3* | –                 | –             |

The results are expressed as mean ± SD. *P < 0.01 compared with the control and **P < 0.01 compared with lansoprazole (ANOVA followed by Dunnett’s test). n = number of mice.

Table 3 | Gastroprotective activity of CEX on HCl/EtOH-induced gastric lesions in mice.

| Treatment           | Dose (mg/kg) | Lesion index (mm) |
|---------------------|--------------|-------------------|
| Control             | –            | 41.6 ± 4.9        |
| IND                 | 10           | 36.0 ± 3.8        |
| NEM                 | 10           | 38.6 ± 4.4        |
| L-NAME              | 70           | 40.7 ± 5.1        |
| CEX                 | 50           | 16.7 ± 3.5*       |
| IND + CEX           | 10 + 50      | 35.9 ± 2.8        |
| NEM + CEX           | 10 + 50      | 37.7 ± 5.3        |
| L-NAME + CEX        | 70 + 50      | 18.0 ± 3.1*       |
| Carbexonolone       | 100          | 14.6 ± 4.2*       |

Results are expressed as mean ± SD, n = 7. Analysis of variance followed by Dunnett’s test. *P < 0.01 compared with the respective control.

IND, Indomethacin; NEM, N-ethylmaleimide; L-NAME, N-nitro-L-arginine methyl ester.
Regarding prostaglandins, they seem to have participation in the gastroprotective action of CEX since the inhibition was reduced by pretreatment with IND (Table 4).

**DISCUSSION**

Today, it is well known that gastric diseases are a problem around the world and are commonly associated with the consumption of non-steroidal anti-inflammatory drugs (Wallace, 2019a). Despite the wide use of therapies toward gastric ulcers, the recurrence index is high. In this sense, gastroprotective natural drugs could be a cheap and affordable alternative to prevent gastric ulcers and improve the way of life of humans living with this gastrointestinal condition. The disability of the balance between aggressive and defensive factors in the gastric mucosa could lead to gastric ulcers (Lewis and Hanson, 1991). Several medicinal plants and fruits showed ability to protect the gastric mucosa in different animal models (Lewis and Hanson, 1991; Tundis et al., 2008; De Lira Mota et al., 2009; Khan et al., 2018). Plants have produced interesting gastroprotective drugs such as carbexolone from Glycyrrhiza glabra L., gefarnate from cabbage, solon from sopheradin, to mention a few (Lewis and Hanson, 1991). Furthermore, Cactaceae plants have demonstrated gastroprotective activity. As an example, the medicinal plant O. ficus-indica (Cactaceae) has showed gastroprotective, hepatoprotective, neuroprotective, and antioxidant effects, it has also showed antimicrobial and nutraceutical properties, the extract could serve as diuretic, anti-cancer, anti-stress, anti-diabetic and anti-inflammatory and is good for the healing of skin lesions (El-Mostafa et al., 2014; Aragona et al., 2018; Arowa et al., 2019; Smeriglio et al., 2019).

**Mode of Gastroprotective Action**

Peptic ulcer disease (PUD) is formed when the protective mechanisms of the gastrointestinal mucosa, such as bicarbonate secretion and mucus, are surpassed by the damaging effects of pepsin and gastric acid (Sung et al., 2009). The main factors involved in the development of ulcers include an increase in gastric acid secretion and a decrease in mucosal protection due to the reduction of mucus secretion, mucosal blood flow, and prostaglandin biosynthesis (Konturek et al., 1990, Brzozowski et al., 2005). Constant renewal of epithelial cells is fundamental in the protection of the mucosa of the gastrointestinal tract. The most important targets to study the mechanism of action of this pathology are NO, endogenous sulfhydryls, and prostaglandin biosynthesis. Nitric oxide in the gastrointestinal tract play a fundamental role in the correct repairing of the gastric mucosa (Wallace and Ma, 2001, Wallace, 2019b). Indeed, it has been demonstrated that endogenous NO regulates the gastric mucosal blood flow, angiogenesis, and gastric mucus secretion. In this study, pretreatment with L-NAME have not attenuated the gastroprotection of CEX extract (Table 4). This finding suggests that endogenous NO have no participation in the gastroprotective activity of this extract. Endogenous PGs are involved in the mechanism of gastroprotective action elicited by mild irritants and necrotizing agents. PGs stimulate release of mucus and bicarbonate, inhibit the gastric acid secretion, and increase blood flow on gastric mucosal (Wallace, 2019a). In our case, PGs seem to have participation in the gastroprotective action of CEX since the inhibition was reduced by pretreatment with IND.

Endogenous sulfhydryls such as glutathione are well-known agents whose main function is the protection of the gastric mucosa. Glutathione protects the integrity and permeability of the cell membrane and may act as antioxidant as a scavenger of free radicals; it works in the maintenance of immune function, regulation of protein synthesis and degradation, and the maintenance of global protein structure (Lewis and Hanson, 1991). In this study, pretreatment with NEM (an SH blocker) reduced the gastroprotective effect of CEX, suggesting that the protective effect of this extract is can be explained thorough the participation of endogenous SHs.

**Infections**

The mortality of PUD decreased in the last few decades, due to treatment of infections with the bacteria H. pylori (Lau et al., 2011). The significance of several bioactive compounds against this bacteria such as polysaccharides obtained from fruits (acidic heteroxylans, from Olea fruits, and Maytenus ilicifolia Mart. ex Reissek leaves), arabinogalactanes (mango, jambo, and lyceum fruits), rhamnogalacturonan (grapes and ginseng), terpenoids (such as limonene, pinene, citral, lupeol, ursolic acid, and nomilne), and flavonoids such as quereticin (Bonifacio et al., 2014) have been discussed (Khan et al., 2018). These compounds can difficult the adherence, colonization, and invasion of H. pylori into the gastric cell wall and prevent gastric cancer formation, suppressing cancer growth, which is prevalent in H. pylori infected patients.

**Fruit Extracts and Gastroprotection.**

A comparative analysis with gastroprotective extracts from fruits are explained below. The berries from Morus nigra L. and Rubus niveus Thunb showed antioxidant and gastroprotective activities due to the presence of flavonoids. The extracts from these species inhibited gastric lesions at 300 mg/kg by 64.06% and 81.86% respectively. The authors indicated that the studied berries are a source of antiulcer compounds and this may be related to their high polyphenol contents (Nesello et al., 2017). In our case, the inhibition displayed by CEX at 100 mg/kg, p.o. was 73% considering a lower dose. Previous study reported that the ethanolic extracts from seeds of Pouteria campechiana (Kunth) Baehni at 100 mg/kg (80% inhibition) and 200 mg/kg (90% inhibition) showed gastroprotective effect in the ethanol-induced ulcer model in rats (ElSayed et al., 2016). In the same study the authors published the isolation of the phenolic compounds: protocatechuic acid, gallic acid, quercetin, myricetin, myricetin-3-O-L-rhamnoside, and myricetin-3-O-D-galactoside, which were linked to the antiulcerogenic effects (ElSayed et al., 2016). In our case, the inhibition displayed by CEX at 100 mg/kg was close to that observed with Pouteria extracts. Schlickmann et al., 2015 showed that the methanolic
extract from seeds of *Mimusops balata* fruits had more gastroprotective activity than peel or pulp at 300 mg/kg. This activity was associated to the maintenance of Glutathione (GSH) levels, reduction of Lipid Peroxidation (LPO) content, inhibition of neutrophil migration, and potent free radical scavenger activity (Schlickmann et al., 2015). Then, seed extract was subjected to chromatographic analyses and the flavonoid taxifolin was isolated, that also displayed gastroprotective effect on HCl/EtOH at 1.14 mg/kg (Schlickmann et al., 2015). Interestingly, *C. brevistylus* pear fruits have the presence of several dietary phenolic compounds and other important dietary compounds such as antioxidant fatty acids, that could prove its ethnobotanical and medicinal use in Perú. As an example, we demonstrated that Sanky fruits belonging to the Cactaceae family has important flavonoids such as rutin, isorhamnetin-3-O-rutinoside, taxifolin, quercetin, and methyl queretin in a similar way to the *O. ficus-indica* (L.) Mill. (Cactaceae). These compounds have been reported to reduce gastric ulcer formation (Suzuki et al., 1998; De Lira Mota et al., 2009). Therefore, the presence of those dietary flavonoids could explain in part the antioxidant and gastroprotective activities.

**CONCLUSIONS**

From the edible endemic *Corryocactus brevistylus* (Sanky) pears, 38 compounds were detected by UHPLC-ESI-HR-MS including twelve organic acids (peaks 1–8, 10–11, and 20, 21), nine hydroxyacinnamic acids (peaks 9, 12–14, 16, 19, and 22–24), three isoamericanol derivatives (25–27), six flavonoids (peaks 15, 17, 18, 28–30), five fatty acids (peaks 31–33 and 35–36), and two sterols (peak 34 and 38) for the first time. The CEX from *C. brevistylus* fruits had antioxidant (DPPH, ABTS, and FRAP) and gastroprotective activities on the model of HCl/EtOH-induced gastric lesions in mice. Our results suggest that sulfhydryl groups, taxifolin, queretin, and methyl queretin in a similar way to the *O. ficus-indica* (L.) Mill. (Cactaceae) family has important flavonoids such as rutin, isorhamnetin-3-O-rutinoside, taxifolin, quercetin, and methyl queretin in a similar way to the *O. ficus-indica* (L.) Mill. (Cactaceae). These compounds have been reported to reduce gastric ulcer formation (Suzuki et al., 1998; De Lira Mota et al., 2009). Therefore, the presence of those dietary flavonoids could explain in part the antioxidant and gastroprotective activities.

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**DATA AVAILABILITY STATEMENT**

The datasets generated for this study are available on request to the corresponding authors.

**ETHICS STATEMENT**

The animal study was reviewed and approved by The Animal Use and Care Committee of the Universidad de Chile.

**AUTHOR CONTRIBUTIONS**

BS, TC, and CA designed this study. FC and JT collected the edible fruit. CC and TC performed the experiments. MH and TC performed extraction process and biological activities, while JB and BS analyzed the LC/MS data. Draft preparation: JE, MS, CA, and BS. Funding acquisition: BS. All authors read and approved the final manuscript.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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