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ORIGINAL PAPER

Anti-Inflammatory Activity of Copao (*Eulychnia Acida* Phil., Cactaceae) Fruits

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Abstract Copao (*Eulychnia acida* Phil., Cactaceae) is an endemic species occurring in northern Chile. The edible fruits of this plant are valued for its acidic and refreshing taste. Phenolic-enriched extracts from copao fruit pulp and epicarp, collected in the Elqui and Limari river valleys, were assessed by its *in vitro* ability to inhibit the pro-inflammatory enzymes lipoxygenase (LOX) and cyclooxygenases (COX-1 and COX-2). At 100 μg/mL, pulp extracts showed better effect towards LOX than epicarp extract, while COX-2 inhibition was observed for both epicarp and pulp samples. In general, the extracts were inactive towards COX-1. A positive correlation was observed between the anti-inflammatory activity and the main phenolic compounds found in this fruit. Copao fruits from the Limari valley, a main place of collection and commercialization, showed major activity, adding evidence on the possible health-beneficial effects of this native Chilean fruit.

Keywords *Eulychnia acida* · Cactaceae · Copao · Anti-inflammatory capacity

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Abbreviations

COX	Cyclooxygenase
DMSO	Dimethyl sulfoxide
IRH	Isorhamnetin-3-O-[α-rhamnopyranosyl-(1→6)-β-glucopyranoside]
LOX	Lipoxygenase
RE	Rutin equivalents
TEAC	Trolox-equivalent antioxidant capacity

Introduction

Plants from the Cactaceae family have shown relevant biological activities [1] including antioxidant [2], antiproliferative [2–4] and anti-inflammatory effects [5–7]. Little is known on the bioactivity of the edible fruits from Chilean native Cactaceae. Copao (*Eulychnia acida* Phil.) fruits (Fig. 1) are collected and commercialized in northern Chile, mainly in the longitudinal valleys from the Elqui and Limari rivers, Region de Coquimbo. The fruits are valued for its acidic and refreshing taste. The antioxidants from copao fruits have been recently described and the main compounds were identified [8], but there is no information on the anti-inflammatory effect of this fruit. Inflammation plays a relevant role in several diseases of high global prevalence. Acute inflammatory reactions are characterized by changes in vascular permeability and local hemodynamics resulting in edema and cellular influx [9]. Inflammatory models of several types allow evaluation of test compounds, and provide a better understanding of the inflammatory process. *In vitro* assays for anti-inflammatory effect that can be applied to food and medicinal plants, include the inhibition of pro-inflammatory enzymes [10, 11]. Cyclooxygenases (COXs) and lipoxygenases (LOXs) are key enzymes in arachidonate metabolism, since they are

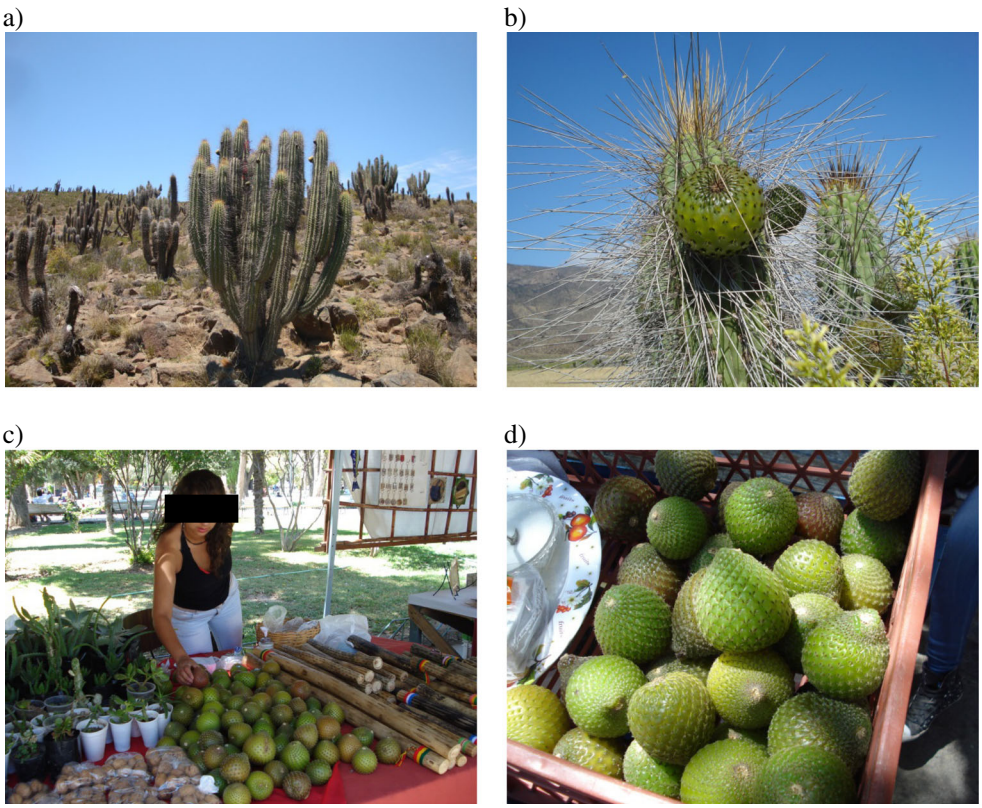

Fig. 1 **a** Copao (*Eulychnia acida* Phil.) growing in the Region de Coquimbo, Chile. **b** Detail of the plant and fruits. **c** Fruit commercialization in a local handcraft market. **d** Fruits on sale, the fruits are consumed with sugar

involved in the biosynthesis of inflammatory lipid mediators, such as prostaglandins (PG), thromboxanes (TX), leukotrienes (LT) and hydroxyeicosatetraenoic acids (HETE). These enzymes play an important role in inflammation and their inhibition is important in the prevention of diseases linked to oxidative stress and inflammation [12]. The isoenzymes COX-1 and COX-2 catalyze the first two steps of the arachidonic acid (AA) cascade, leading to the production of PG and TX which play a major role in inflammatory reactions. COX-1 is constitutively expressed and plays an important role in the protection of gastric mucosa. COX-2 expression is mainly induced by external stimuli. The inhibition of COX-1 by non-steroidal anti-inflammatory drugs (NSAIDs) may induce gastrointestinal bleeding and ulcers. The anti-inflammatory, analgesic, and antipyretic effects of NSAIDs are accomplished by the inhibition of COX-2 [13–15]. LOX catalyzes the oxidation of AA to HETE and LT. Leukotrienes are potent mediators of inflammatory and allergic reactions [16]. The simultaneous inhibition of COX and LOX has been proposed as a new strategy in the anti-inflammatory therapy. The development of dual inhibitors may improve the anti-inflammatory effects and reduce the side effects, especially those associated with the gastrointestinal tract [17]. The aim of this work was to assess the anti-inflammatory potential of copao fruits extracts by *in vitro* assay of pro-inflammatory enzymes LOX and COX-1 and COX-2 inhibition.

Materials and Methods

Chemicals

The following reagents were purchased from Sigma-Aldrich (St. Louis, MO, USA), the catalogue numbers are given in parentheses: caffeic acid (C0625), indomethacin (I7378), nimesulide (N1016), naproxen (N8280), soy lipooxygenase-1 (L7395). Linoleic acid (L-5900) was from Fluka (Germany). COX-1 and COX-2 kit assay (560131) was from Cayman Chemical (MI, USA). All solvents used were of analytical grade.

Sample Preparation

Ripe fruits were hand collected from the main production and harvesting areas of copao during the summer season (December 2013 and January 2014), Coquimbo Region, Chile. The samples collected in the Elqui valley were from: El Manzano (n=76), Juan Soldado (n=12) and La Campana (n=7). The samples collected in the Limari valley samples were from: Ovalle (n=12) and Salala (n=17). The samples from Salala included green colored epicarp (Salala 1, n=7) and red colored epicarp (Salala 2, n=10) fruits. Briefly, the epicarp and pulp from fresh fruits were separated, homogenized in a waring blender and extracted three times with MeOH at room temperature under sonication (10 min each) in a 1:3 *v*/*v*

homogenate:solvent ratio. The MeOH extract was taken to dryness under reduced pressure, resuspended in distilled water and adsorbed in Amberlite XAD-7 resin. Phenolic compounds were desorbed using MeOH to obtain the phenolic-enriched extract.

Inhibition of Pro-Inflammatory Enzymes

For the assay, the extracts were dissolved in dimethyl sulfoxide (DMSO). The assay to obtain the 100 % of LOX and COX activity was performed with DMSO as solvent control. The inhibitory assays were performed in presence of 100 μg/mL of the phenolic-enriched extracts or commercial anti-inflammatory compounds: indomethacin (equipotent inhibitory effect on COX-1 and COX-2 [18], nimesulide (specific inhibitor for COX-2) [10, 19], caffeic acid (specific inhibitor for LOX) [20] and naproxen (the best NSAIDs on LOX) [21].

Lipoxygenase Enzyme Assay

LOX activity was determined spectrophotometrically based on the enzymatic oxidation of linoleic acid to the corresponding hydroperoxide [10, 11, 22]. The assay mixture containing soybean lipoxygenase (948 U), sodium borate buffer (200 mM, pH 9.0) and 100 μg/mL of fruit extracts was pre-incubated at 25 °C during 5 min. Then, linoleic acid (50 mM) was added and absorbance at 234 nm was recorded every 30 s during 4 min using a Unicam Spectronic (Genesys) spectrophotometer. The activity was graphically determined from the slope of the linear portion of the curve. Positive and negative controls were also included. Caffeic acid and naproxen were used as reference compounds. LOX-1 from soybean is routinely used since it resembles human LOXs in its substrate specificity and inhibition characteristics [23]. Results are expressed as percentage of inhibition of hydroperoxide production.

Cyclooxygenase Enzyme Assay

The capacity of the extracts to inhibit the conversion of AA to prostaglandin H_2 (PGH_2) by ovine COX-1 and human recombinant COX-2 was determined using a COX inhibitor screening assay kit (No. 560131; Cayman Chemical, Ann Arbor, MI, USA) by enzyme immunoassay as described by some authors [10, 11, 22], following the manufacturer instructions. The inhibitory assays were performed in presence of extracts or commercial anti-inflammatory drugs. Enzyme and samples were pre-incubated during 10 min and then AA was added. The reaction was conducted for exactly 2 min at 37 °C and halted by boiling for 5 min. The PGH_2 produced in the above mentioned reaction was reduced to the more stable $PGF_{2\alpha}$ with stannous chloride and determined by enzyme immune assay (EIA) at 412 nm. Results were expressed as percentage of inhibition of $PGF_{2\alpha}$ production.

Statistical Analysis

The enzyme inhibition assays were carried out in triplicate and data are presented as mean values±SD. The correlation between the main flavonoid contents of the extracts, as described by Jiménez-Aspee et al [8], and the anti-inflammatory effect was analyzed by the Pearson test correlation coefficients with 95 % confidence. Statistical analysis was performed by one-way ANOVA followed by Tukey's multiple comparison test ($p<0.05$). All statistical analyses were carried out using the SPSS 14.0 software for Windows (IBM North America, NY, USA).

Results and Discussion

Six copao samples from the Elqui and Limari valleys, including fruit epicarp and pulp, were assessed for anti-inflammatory activity by the inhibition of the LOX, COX-1 and COX-2 enzymes at 100 μg/mL (Table 1). The inhibitory capacity of LOX by the phenolic-enriched extracts of Limari valley fruits were 1.5–64.3 % for pulp and 23.0–35.6 % for epicarp. The LOX inhibitory capacity of extracts was≥50 % for two out of three fruit pulp samples from the Limari valley. All Elqui valley pulp and epicarp samples inhibited LOX by 34.5–38.4 % and 3.3–33.8 %, respectively. Under our

Table 1 Anti-inflammatory activity of Amberlite-retained phenolic from the methanol extracts of copao fruits (100 μg/mL)

Collection place	Fruit part	Inhibition (%)		
		LOX	COX-2	COX-1
Elqui valley				
Cerro La Campana	Pulp	35.2±5.5^{c}	27.0±1.6^{c,d}	0
	Epicarp	3.3±2.7^{a}	39.6±2.7^{e}	15.1±0.7^{b}
El Manzano	Pulp	38.4±5.6^{c}	0	43.0±2.1^{c}
	Epicarp	33.8±4.0^{b,c}	1.1±0.1^{a}	0
Juan Soldado	Pulp	34.5±5.2^{b,c}	16.1±1.2^{b}	6.8±0.34^{a}
	Epicarp	30.3±3.3^{b,c}	13.9±0.8^{b}	0
Limari valley				
Ovalle	Pulp	51.7±2.5^{d}	57.6±3.0^{f}	0
	Epicarp	31.9±5.0^{b,c}	12.8±0.7 ^{b}	0
Salala (1)	Pulp	1.46±3.2^{a}	20.2±0.1^{b,c}	0
	Epicarp	35.6±1.1^{c}	44.0±3.0^{e}	0
Salala (2)	Pulp	64.3±2.2^{e}	35.8±2.5^{c,d}	0
	Epicarp	23.0±4.6^{b}	0	0

Different letters (a, b, c, etc.) in the same column show significant differences among each treated group, according to Tukey's test ($p\leq0.05$)

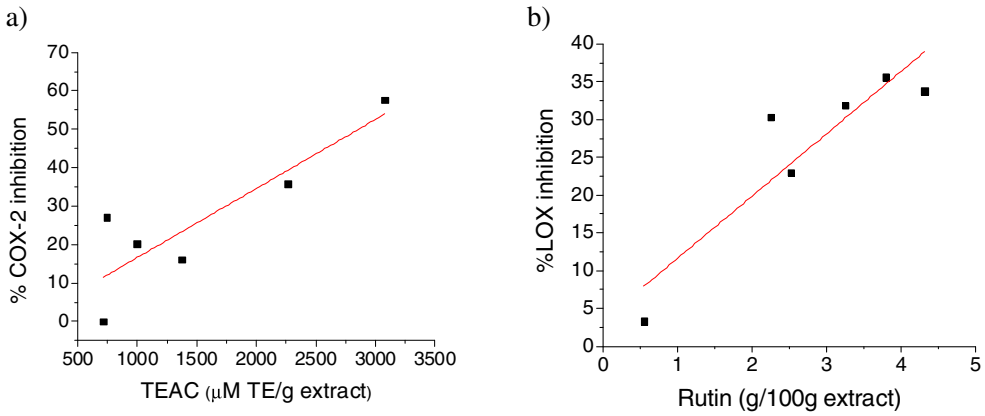

Fig. 2 Correlation found in pulps of copao fruits extracts from Elqui and Limari valleys between **a** TEAC activity (μM TE/g) and the inhibition of COX-2 (%); **b** Content of rutin (g/100 g extract) and the inhibition of LOX (%)

	COX-2		LOX
TEAC	r=0.8751 *p*=0.0224	Rutin	r=0.9120 *p*=0.0113

experimental conditions naproxen and caffeic acid inhibited the LOX activity with IC_{50} values of 14.0±0.7 and 57.0±4.0 μg/mL, respectively. Inhibition of the inflammatory mediators biosynthesis by blocking LOX activity would be an alternative to treat inflammatory and allergic diseases [24, 25]. Food polyphenols are natural antioxidants with LOX inhibition activity lacking the undesirable side effects of anti-LOX drugs [26].

PGE_2 level increases markedly and provokes inflammation and pain in pathological events due to the activation of COX enzymes. Hence, the extracts were tested for their ability to inhibit COX enzymes. The extracts presented different results against the COX-1 and COX-2 enzymes. At 100 μg extract/mL, three out of 12 extracts inhibited COX-2 by≥40 %. The COX-2 inhibition of the Limari valley fruits ranged from 20.2 to 57.6 % for pulp and 0–44 % for epicarp. The COX-2 inhibition values for the copao fruit from Elqui valley ranged between 0 and 27 % for pulp and 1.1–39.6 % for epicarp. Only one out of 12 samples (Elqui valley, El Manzano, pulp) showed relevant effect on COX-1, with 43 % inhibition. In general, the COX-1 enzyme was not inhibited by the copao fruits phenolic-enriched extracts. This result is important considering the side effects derived from COX-1 inhibition, such as gastric ulcer [17]. The IC_{50} value of nimesulide, the standard inhibitor for COX-2 was 0.39±0.02 μg/mL, while the IC_{50} value of indomethacin, the reference inhibitor of COX-1, was 0.04±0.01 μg/mL.

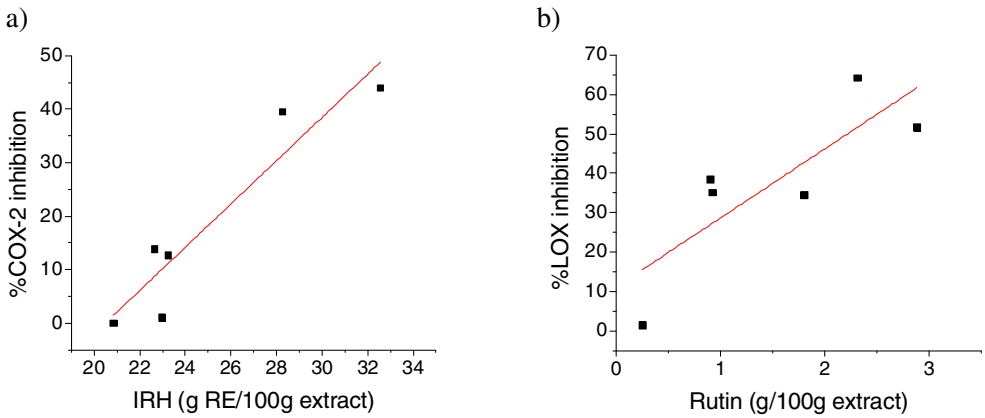

Fig. 3 Correlation found in epicarps of copao fruits from Elqui and Limari valleys between **a** Content of IRH (g RE/100 g extract) and the inhibition of COX-2 (%); **b** Content of rutin (g/100 g extract) and the inhibition of LOX (%)

	COX-2		LOX
IRH	r=0.9422 *p*=0.0049	Rutin	r=0.8236 *p*=0.0439

We have previously reported the antioxidant activity and phenolic composition of copao fruits [8]. In the pulp, the concentration of the main glycoside isorhamnetin-3-O-[α-rhamnopyranosyl-(1→6)-β-glucopyranoside] (IRH) ranged between 1.47 and 10.93 g rutin equivalent/100 g phenolic-enriched extract for the Elqui valley samples and 0.45 to 4.20 g rutin equivalent/100 g phenolic-enriched extract for the Limari valley samples, respectively.

The rutin content in the pulp was between 0.90 and 1.80 g rutin equivalent/100 g phenolic-enriched extract for the Elqui valley and from 0.25 to 2.88 g rutin equivalent/100 g phenolic-enriched extract for the Limari valley, respectively. The fruit pulp from the Limari valley with higher anti-inflammatory activity also showed higher antioxidant effect and flavonoid content. The differences in extraction yield, phenolic content and composition of the different samples might explain the differences in COX and LOX inhibitory activities. In order to confirm this observation, a correlation analysis was carried out between the anti-inflammatory effect, antioxidant activity, IRH and rutin content. Copao fruit pulp from the Limari and Elqui valleys showed a positive correlation between the anti-COX-2 activity and the Trolox-equivalent antioxidant capacity (TEAC) (r=0.8751; p<0.05) (Fig. 2a). Copao fruit epicarp from the Limari and Elqui valleys also showed positive correlations between the COX-2 inhibitory activity and the IRH content (r=0.9108, p<0.05) (Fig. 3a). Kim et al. [27] reported that some flavonoids are preferential COX inhibitors. The LOX inhibitory activity of epicarp and pulp extract showed a positive correlation against the total content of rutin with r=0.9120 (p<0.05) and r=0.8236 (p<0.05), respectively (Figs. 2b and 3b).

Pathological events such as inflammation, aging and degenerative dysfunction are associated with the generation of reactive oxygen species. Thus, the effectiveness of copao to ameliorate inflammatory responses may be due to its capacity to reduce oxidative stress and the inhibitory activity on pro-inflammatory enzymes. Based on the inhibitory activity towards both COX and LOX products, Copao fruits could be considered as dual inhibitors.

Rutin and its hydrolysis product quercetin have demonstrated to inhibit soybean LOX activity in a dose-dependent manner, with IC_{50} values of 14 and 11 μM [28]. Isorhamnetin, the hydrolysis product of IRH, has been shown to prevent acute inflammation through blocking NF-κB activation [29] and shows antioxidant activity [30]. Isorhamnetin glycosides have been isolated as the active anti-inflammatory constituents from *Opuntia dillenii* flowers [7]. Extracts of the cactaceae *Opuntia humifusa* from Korea presented free radical scavenger and anti-inflammatory effect [5]. The antioxidant and antimutagenic properties from Argentinian cactaceae fruits belonging to genus *Rhipsalis*, *Lepismium* and *Pfeiffera* have been reported, indicating the nutraceutical properties of South American cactaceae [31].

Conclusions

This is the first report on the *in vitro* anti-inflammatory effect of copao fruit extracts, adding evidence on the possible health-beneficial effects of this native Chilean fruit. The effect was associated with the main phenolics from the Amberlite-retained extract, namely isorhamnetin and quercetin glycosides. The COX-2 inhibitory activity was correlated with the content of isorhamnetin rutinoside, while the LOX inhibitory activity was correlated with the content of rutin. Our results on the anti-inflammatory activity of copao, along with the lack of toxicity and antioxidant properties, encourages further studies and applications of this natural resource from the semiarid northern of Chile.

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Conflicts of Interest The authors declare that they have no conflict of interest.

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