Journal of Functional Foods 143 (2026) 107403

Contents lists available at ScienceDirect

Journal of Functional Foods

journal homepage: www.elsevier.com/locate/jff

Leaf extracts from Sicilian sumac (*Rhus coriaria* L.) show promising antioxidant and anti-inflammatory activities in gastrointestinal epithelial cells: A comparison with fruit extracts activity and role of digestion

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ARTICLE INFO

Keywords:
Sumac
Polyphenols
Inflammation
Oxidative stress
Gastric
Intestinal

ABSTRACT

Sumac (*Rhus coriaria* L.) is reaching high attention as source of polyphenols and healthy properties. Most of the available studies were conducted on plant materials (fruit) from Middle East, in line with the geographical area of traditional use. Despite the wide consumption as spice or traditional medicine, the biological activity at gastrointestinal level is still poorly investigated. We previously suggested that fruit extracts from Iranian sumac may counteract *H. pylori*-related gastritis through anti-inflammatory mechanisms. Here, we investigated the antioxidant and anti-inflammatory effect of fruit and leaf from Sicilian sumac (Sicily, Italy) in gastric (GES-1) and intestinal (CaCo-2) cells, together with a chemical characterization of the phenolic profile. Extracts obtained by traditional methods, such as hot water infusion and hydroalcoholic maceration, were selected for polyphenolic content and stability evaluations after simulated gastrointestinal digestion. Fruit and leaf extracts both inhibited IL-8 and MCP-1 release in both models and reduced the level of ROS in CaCo-2 cells, but not in GES-1 cells. Since the hydroalcoholic leaf extract showed the most pronounced effects at the lowest concentrations among the extract, it was qualitatively characterized by its polyphenolic profile and quantified for its most abundant flavonoid, myricetin 3-rhamnoside, which accounts for approximately 13.66 mg/g of the extract, thus suggesting a potential role of this compound for the observed biological activities.

The overall data suggest that traditional extracts from fruit and leaf of Sicilian sumac may counteract inflammation and oxidative stress related to gastrointestinal disorders, highlighting the interesting properties of leaf extracts, poorly investigated till now.

1. Introduction

Rhus coriaria L. (sumac) is a Mediterranean plant belonging to the Anacardiaceae family, widely used as spice or botanical medicinal product in the Middle East. The main forms of use reported by the folk medicine are powders and polar extracts (such as water and ethanol) from fruit and leaf, applied topically or orally to control a wide variety of diseases (Alsamri et al., 2021). The traditional use is also documented in the European Mediterranean coast, including Sicily, where the plant is called "Sicilian sumac" and is topically applied for wound healing (Guarrera, 2009).

Leaves from *Rhus coriaria* L. are included in Annex 1 to the Italian Ministerial Decree of 10 August 2018 among the botanical ingredients allowed for food supplements, with related health claims concerning lymphatic drainage and improvement of intestinal transit.

Sumac is a rich source of polyphenols with potential antioxidant and

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https://doi.org/10.1016/j.jff.2026.107403
Received 11 May 2026; Received in revised form 12 June 2026; Accepted 19 June 2026
Available online 27 June 2026

anti-inflammatory properties, including flavonoids, and hydrolysable tannins (Beretta et al., 2009; Lo Vecchio et al., 2022; Regazzoni et al., 2013). Most of the available in vitro and in vivo studies, including ours (Khalilpour et al., 2019; Nozza et al., 2020), concerned the nutritional and pharmacological properties of polar extracts from sumac collected in the Middle East area (see (Alsamri et al., 2021; Elagbar et al., 2020; Sakhr & Khatib, 2020) for reviews on the topic). The overall evidence suggests a potential role in a variety of diseases, such as metabolic and urinary tract disorders, infections, enteritis, and skin lesions.

Despite the wide use as spice, the biological activity of sumac fruits at gastrointestinal level is still poorly investigated. We recently suggested that polar extracts from sumac fruits, rich in gallotannins and flavonoids, may exert anti-inflammatory and antibacterial properties in a model of gastric epithelium infected by *Helicobacter pylori* (Martinelli et al., 2022). The mechanism of action involved the impairment of the NF-κB pathway and the inhibition of pro-inflammatory interleukins (IL-6, IL-8). Moreover, other authors reported the inhibition of the urease activity (Mahernia et al., 2015). Only one published paper reported that an aqueous extract from fruit (2 mL/Kg, orally) may reduce the intestinal damage in a model of necrotizing enterocolitis (Isik et al., 2019).

Regarding Sicilian sumac, we found no studies currently available, highlighting the need to investigate this plant material from different Mediterranean regions, to consider the potential geographic variability. Moreover, to the best of our knowledge, sumac leaves have never been evaluated in vitro models of gastric and intestinal inflammation until now.

The aim of the present study was to evaluate the antioxidant and anti-inflammatory activity of polar extracts from fruits and leaves of Sicilian sumac in models of human gastric (GES-1) and intestinal (CaCo-2) epithelial cells, providing preliminary evidence for their potential gastrointestinal relevance.

2. Materials and methods

Dulbecco's Modified Eagle's Medium/F12 (DMEM)/F12 (1:1), penicillin, streptomycin, L-glutamine, sodium pyruvate and trypsin-EDTA were from Gibco (Life Technologies Italia, Monza, Italy). DMEM, MEM non-essential amino acid solution, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), Natural Product (NP), and polyethylene glycol (PEG 4000), were from Sigma Aldrich (Milan, Italy). All reagents used for analytical determinations and for the biological assays were HPLC grade. Human IL-8 and MCP-1 ELISA Development Kit were from Peprotech Inc. (London, UK). Fetal bovine serum (FBS), and disposable materials for cell culture were purchased by Euroclone (Euroclone S.p.A., Pero-Milan, Italy). Cyanidin 3-O-glucoside chloride, hyperoside, rutin, apigenin, gallic acid, luteolin-7-glucoside,myricetin-3-O-rhamnoside, quercetin-3-O-glucoside, kaempferol-3-rutinoside, kaempferol-3-glucoside, ellagic acid, quercetin, luteolin, kaempferol, apigenin and epigallocatechin-3-O-gallate (EGCG) were purchased from Phytolab (Dutendorfer Straße 5–791,487 Vestenbergsgreuth, Germany). Dichlorofluorescein probe (CM-H2DCFDA) was purchased from Invitrogen (Thermo Fisher Scientific, Waltham, MA, USA) The plasmid NF-κB-LUC containing the luciferase gene under the control of three κB sites was a gift of Dr. N. Marx (Department of Internal Medicine-Cardiology, University of Ulm, Germany). Britelite™ plus was from Perkin-Elmer (Monza, Italy).

2.1. Plant material and extraction

Plant materials from Sicilian sumac (*Rhus coriaria* L.) were kindly provided by Redess s.r.l. (TI, Sicily, Italy); supply chain is certified as organic spontaneous sumac harvesting. Plant samples were collected around the area of Monterosso (RG, Sicily) and San Biagio Platani (AG, Sicily). Samples from the two locations were pooled by plant organ before extraction. The plant material was identified as *Rhus coriaria* L. by our laboratory, which has expertise in botanical recognition and characterization of plant materials. Voucher specimens representative of the same plant material have been registered and retained at the internal collection of the Laboratory of Pharmacognosy, Department of Pharmacological and Biomolecular Sciences "Rodolfo Paoletti", University of Milan, Italy, under the internal accession codes FARMACOGNOSIA-RC-2025-0001 for leaves and FARMACOGNOSIA-RC-2025-0002 for fruits. In addition, photographic documentation of the Sicilian *Rhus coriaria* L. botanical samples has been deposited in our university repository and is available through the following DOI: https://doi.org/10.13130/RD_UNIMI/XJWR0L. A representative specimen of fruit and leaf is shown in the Supplementary Materials (Fig. S1).

The plant extracts (see Supplementary Table, Table S1 for a summary) were prepared according to our previous works, with minor changes (Khalilpour et al., 2019; Martinelli et al., 2022). In brief, water, or ethanol/water mixture 50:50 (100 mL) was added to 10 g of dried and powdered plant material in a glass flask. The extraction procedure was conducted for 24 h, under temperature control (25 °C, 40 °C, 100 °C) and constant agitation, using a magnetic stirrer. To limit the evaporation and allow the constant recovery of water, the extraction at 100 °C was conducted by covering the flask with a watch glass. To compensate for evaporation, the extraction volume was checked at predefined time points and adjusted to 100 mL with water at the corresponding extraction temperature. The infusion procedure was carried out by pouring boiling water on plant material, steeped for 5 mins under constant agitation. Then, the fluid extracts were filtered by filter paper, the ethanol residue, where present, was removed by rotavapor (Heidolph Instruments GmbH & CO, Schwabach, Germany), and the final extracts were freeze-dried (Edwards, 5Pascal, Trezzano, Italia).

Dry extracts were dissolved in water/DMSO (50:50) at the stock concentration of 50 mg/mL, then aliquoted and stored at −20 °C.

2.2. Total polyphenols content

Phenolic compounds were measured using Folin–Ciocâlteu reagent, according to Singleton and Rossi, and our previous works (Martinelli et al., 2022). In brief, an aliquot from 1 mg/mL of stock extract (20 μL) was diluted in water (780 μL), then 50 μL of Folin–Ciocâlteu reagent and 150 μL of Na_2CO_3 were added to perform the colorimetric reaction at 40 °C for 20 min. A standard calibration curve ranging from 0 to 30 μg/mL was prepared by serial dilution of gallic acid (GA). The absorbance at 600 nm was measured by UV-VIS spectrophotometer (JASCO International Co. Ltd., Tokyo, Japan). The total amount of phenols was expressed as mg/g GA equivalents of dry extract. The potential interference of gastric and intestinal fluids was excluded by comparing the absorbance of blanks (freeze-dried digestion fluids alone) with respective plant samples (freeze-dried plant extracts added with digestion fluids). Reported data were obtained by subtracting blank values from each corresponding sample.

2.3. TLC analysis of polyphenols

Thin-layer chromatography (TLC) was performed using silica plates as stationary phase and ethyl acetate: acetic acid: formic acid: water (100:11:11:22 *v*/v) as mobile phase, according to Wagner and Bladt manual (Wagner, 1960). In brief, 20 μL of the methanol solution of each dry extract (10 mg/mL) were seeded and run for 15 cm; then, the derivatization was performed using natural product-polyethylene glycol 4000 (NP/PEG) to detect generic phenolic compounds. The polyphenolic profile was observed in the visible spectrum or under a UVA lamp, emitting far wavelength (366 nm). The identification of phenolic classes was gathered by color comparison (UV-VIS) with reference standards: gallic acid for galloyl-derivatives (free gallic acid and gallotannins); cyanidin-3-O-glucoside for anthocyanins, and hyperoside and rutin (quercetin-glycosides) for flavonols.

2.4. Polyphenolic fingerprint and Myricetin-3-rhamnoside quantification

The polyphenolic profile of leaf hydroalcoholic sumac extract was performed through an Exion LCTM AC System (AB Sciex, Milano, Italia) and a Triple QuadTM 3500 system (AB Sciex, Milano, Italia) in ESI negative ionization, separated on a Phenomenex Synergi Hydro-RP (80 Å, 4 μm, 150 × 4.6 mm) column. The mobile phase was composed of 0.1% formic acid in water (A) and methanol (B), with a rate flow set at 0.600 mL/min. The following elution gradient was applied: minute 0 95% A–5% B, minute 1 95% A–5% B, minute 10,100% A–0% B, minute 13,100% A–0% B, minute 13.10 95% A–5% B, minute 15 95% A–5% B. The extract was injected at an amount of 10 ng/mL, and the peaks obtained were analyzed by selecting only peaks with an intensity greater than 10^2. The compounds were putatively identified either by injection of the corresponding analytical standards, when available, or by comparison of the mass spectra with the *m/z* ratios and related fragmentations to the ones found in literature (Elagbar et al., 2020; Lo Vecchio et al., 2022; Regazzoni et al., 2013).

Myricetin-3-rhamnoside was quantified without any modification to the LC-MS/MS method described above. Calibration curves were made by serial dilutions of Myricetin 3-rhamnoside in MeOH, ranging from 0 to 0.4 ng/μL.

2.5. Cell culture and treatment

Human gastric non tumoral epithelial cells (GES-1) were a kind gift of Dr. Dawit Kidane-Mulat (University of Texas, Austin, TX, USA). Cells were cultivated in RPMI 1640 medium, added with penicillin 100 units/mL, streptomycin 100 mg/mL, L-glutamine 2 mM and 10% FBS. Cells were incubated at 37 °C, 5% CO_2, in humidified atmosphere, upon reaching confluency. Then, cells were detached from the flask every 48–72 h by EDTA 0.25% solution (Gibco, Thermo Fisher Scientific, Waltham, MA, USA), then counted, and seeded in a new flask (1×10^6 cells) for the following sub-culture.

CaCo-2 (clone HB237) from American tissue collection (ATCC, Manassas, VA, USA). Cells were cultured in DMEM containing 10% FBS, 4 mM L-glutamine, 1 mM sodium pyruvate, 1% non-essential amino acids, 100 units penicillin per mL, and 100 mg streptomycin per mL, under previously described environmental conditions. The sub-culture was always conducted before reaching confluency.

Cells treatments were always performed using FBS-free media. The pro-inflammatory challenge was conducted for 6 h with human cytokines, based on our previous experience and the available literature. Namely, TNF-α (10 ng/mL) was used to stimulate GES-1 cells, for a better comparison with our previous work regarding Iranian sumac (Martinelli et al., 2022). IL-1β (10 ng/mL) was used as widely characterized inducer of CaCo-2 cells inflammation (Muto et al., 2015; Schuerer-Maly et al., 1994).

The pro-oxidant challenge (1 h) was conducted with H_2O_2, at the concentration of 500 μM for GES-1 cells and 1 mM for CaCo-2 cells, respectively, according to widely applied protocols (e.g. (Bollati et al., 2023)). EGCG and apigenin (10 μM) were used as reference anti-inflammatory polyphenols, while apigenin was used as a reference flavonoid in cell-based ROS assays.(Di Lorenzo et al., 2013; Gutierrez-Orozco et al., 2010; Thiruvengadam et al., 2021).

2.6. Cell viability

The integrity of cell morphology was verified at the beginning and the end of each treatment by optical microscope. Cell viability was measured by MTT test (Denizot & Lang, 1986) after 6 or 24 h of treatment with fruit (60 μg/mL) or leaves extracts (20 μg/mL) (Fig. S3). Viability over 80% in respect to the untreated control was considered acceptable. A significant reduction of GES-1 cell viability (−45%) was observed after the treatment for 24 h with hydroalcoholic extract from leaf (LHM), only. The viability was not statistically different from untreated control regarding the other experimental conditions.

2.7. Release of chemokines: IL-8 and MCP-1

GES-1 and CaCo-2 cells were seeded in 24 wells plates (3×10^4 cells/well) for 48 h, then treated simultaneously with plant extracts and pro-inflammatory cytokines (TNF-α or IL-1β, 10 ng/mL) for 6 h. EGCG (10 μM) was used as reference anti-inflammatory polyphenol. The release of human chemokines IL-8 and MCP-1 was detected in cell culture media by Human ELISA ABTS Development Kit, according to manufacturer instructions (Peprotech Inc., UK), as previously described (Sangiovanni et al., 2015). For the quantification, the absorbance (405 nm) of sample media (100 μL/well) was compared with the calibration curves of human recombinant IL-8 and MCP-1 (0–1000 pg/mL), respectively.

2.8. NF-κB-driven transcription

The measurement of NF-κB-driven transcription was carried out after transient plasmid transfection (NF-κB LUC), followed by luciferase assay, as previously described (Sangiovanni et al., 2015). In brief, GES-1 and CaCo-2 cells were seeded in 24 wells plates (3×10^4 cells/well) for 48 h. Then, the day before treatment, the medium was replaced with FBS-free medium containing NF-κB LUC plasmid (50 ng and 100 ng for GES-1 and CaCo-2, respectively), according to Lipofectamine® 2000 transfection kit (Life Technologies, Monza, Italy). The day after, GES-1 and CaCo-2 cells were treated simultaneously with pro-inflammatory cytokines (TNF-α or IL-1β) and plant extracts for 6 h. Apigenin (10 μM) was used as reference anti-inflammatory polyphenol. Then, luciferase assay was performed by cell lysis with Britelite™ plus and luminescence measurement (VictorTM X3, Perkin Elmer, Walthman, MA, USA).

2.9. Radical scavenging (ORAC assay)

The evaluation of radical scavenging property was conducted by oxygen radical absorbance capacity (ORAC) assay, according to Dávalos and colleagues (Dávalos et al., 2004). Briefly, 20 μL of stock solution of each extract (1 μg/mL) was distributed into a black 96-well plate. Then, 120 μL of fluorescein solution (70 nM final concentration), previously prepared with a phosphate buffer (pH 7.4, 75 mM), was added to each well. Peroxyl radicals were generated by adding 60 μL of AAPH 40 mM (Sigma-Aldrich, St. Louis, MO, USA). The final concentration of each extract in the assay well was 0.1 μg/mL. The fluorescence was read by setting the detector at excitation and emission wavelengths of 484 and 528 nm, respectively (Victor X3, PerkinElmer, USA), every 2 min for 60 min at 37 °C. Trolox (0–50 μM) was used as reference antioxidant compound. The area under the curve (AUC) was calculated and the results were expressed as μM Trolox equivalent.

2.10. Intracellular ROS production

GES-1 and CaCo-2 cells were seeded in black 96 wells plates (2×10^4 cells/well) for 48 h. Intracellular ROS production was measured as previously described (Nwakiban et al., 2020). In brief, cells were pre-treated with plant extracts for 24 h, washed with PBS 1×, and added with H2- CM-H2DCFDA intracellular probe (10 μM) for 1 h. Apigenin (10 μM) was selected as reference antioxidant polyphenol. Then, the pro-oxidant stimulation (H_2O_2) was conducted for another 1 h, and the fluorescence emission (ex./em. 488/525 nm) was measured by photometer (Victor™ X3, Perkin Elmer, Walthman, MA, USA).

2.11. In vitro gastrointestinal digestion

The simulated gastrointestinal digestion was conducted as previously reported (Sangiovanni et al., 2015) and adapted with minor modifications (Oomen et al., 2003; Versantvoort et al., 2005). In brief,

the extract (200 mg) was sequentially added with 6 mL of reconstituted saliva (5 min), 12 mL of reconstituted gastric juice (2 h), 12 mL of reconstituted duodenal juice, and 6 mL of reconstituted bile (2 h) kept under shaking at 37 °C. The incubation times were selected according to the previously reported in vitro digestion protocol adopted in this study. Then, samples were freeze-dried and stored at −80 °C, as previously described. Samples from gastric digestion were used for GES-1 cells treatment, while samples from intestinal digestion were used for CaCo-2 cells treatment, in comparison with the respective controls treated with vehicles.

2.12. Statistical analysis

All data were expressed as mean ± standard error (SEM) of at least three independent experiments; the confidence interval (C.I. 95%) related to the half maximal inhibitory concentrations (IC_{50}s) calculation was reported in the Results session. Data were elaborated by unpaired ANOVA test and Bonferroni post-hoc analysis. Statistical measures were conducted by GraphPad Prism 8.0 software (GraphPad Software Inc., San Diego, CA, USA). Values of $p < 0.05$ were considered statistically significant. The IC_{50}s were calculated by GraphPad Prism 8.0 software.

3. Results

The first step of this work was the selection of extracts from Sicilian sumac fruit and leaf, as suitable candidates for biological screening at gastrointestinal level. The extraction methods were defined according to the traditional uses, the available literature, and the potential consumption of Sicilian sumac as tea, spice, or food supplement. Accordingly, only food grade solvents, namely water and ethanol, were chosen. Three aqueous extracts, obtained at different temperature conditions (25, 40, 100 °C) for 24 h, in comparison with typical hot infusion (100 °C for 5 min), and hydroalcoholic maceration (water:ethanol 50:50), were prepared. The hydroalcoholic extract was selected as the reference method for polyphenols extraction and, consequently, biologically interesting at gastrointestinal level, according to our previous publication (Martinelli et al., 2022). As expected, the hydroalcoholic maceration was confirmed as suitable method to obtain considerable yields, with specific reference to leaf extraction (LHM, 37.84% w. dry extract/w. dry plant material). Remarkably, hot, and short-time infusion (FIN, LIN) was sufficient to obtain yields comparable to long-time aqueous maceration (F25, L25) (Table S1, Supplementary Material).

3.1. Characterization of Sicilian sumac extracts

The qualitative polyphenolic profile of each extract from fruit and leaf was preliminarily compared by TLC analysis (Fig. S2), which suggested a similar composition, except for decoction of fruit (F100), showing remarkable degradation. In line with previous articles (Beretta et al., 2009; Lo Vecchio et al., 2022; Regazzoni et al., 2013), the main polyphenol classes identified were galloyl-derivatives and flavonoids, with relatively higher abundance in leaf. As expected, the fruit differed from leaf with respect to the presence of anthocyanins.

Consequently, the extracts were further analyzed for total phenolic content (Folin–Ciocâlteu assay) to obtain a quantitative measure, reported in Fig. 1. Generally, both fruit and leaf were confirmed as relevant sources of phenolic compounds. The comparison between extracts from fruit (Fig. 1A) and extracts from leaf (Fig. 1B) denoted a generally higher level of polyphenols in the latter, thus suggesting that leaf is a concentrated source of polyphenols. The comparison among methods of extraction showed that hydroalcoholic extracts (FHM, LHM) were richer in polyphenols (namely 258.5 and 732.3 mg/g GA eq. d.e., respectively) than aqueous extracts. Moreover, similarly to what observed by comparing the yields of extraction, hot infusion process guaranteed a comparable or higher phenolic presence with respect to the other water extracts.

The overall preliminary data suggested the selection of the hydroalcoholic extracts (FHM, LHM) and the hot infusions (FIN, LIN) for further investigations. Then, biological experiments were carried out in gastric and intestinal epithelial cells.

3.2. Impact of the simulated gastrointestinal digestion on the stability of Sicilian sumac extracts

The selection of extracts from Sicilian sumac, characterized by high levels of polyphenols, induced the investigation of the anti-inflammatory and antioxidant properties at gastrointestinal level. We previously proposed that hydroalcoholic extract from Iranian sumac fruit, showing comparable chemical properties to that evaluated in the present work (FHM), may counteract gastritis through the impairment of NF-κB pathway and IL-8 release (Martinelli et al., 2022). The antioxidant activity at this level was not investigated. Thus, in this study, we supposed a similar bioactivity for Sicilian sumac, including leaves, against either gastric or intestinal inflammation and oxidative stress.

We first assessed whether exposure to simulated gastrointestinal conditions could affect the chemical and biological stability of the selected extracts. Thus, we performed a simulated digestion and collected the resulting samples after gastric and intestinal phases, separately. To verify the chemical stability of polyphenols, the total content of phenols was measured again and compared with previous results. In addition, it was also correlated with the antioxidant capacity, measured by ORAC test. The ORAC test was selected as well-established method to measure the scavenging activity in comparison to the reference antioxidant compound Trolox .

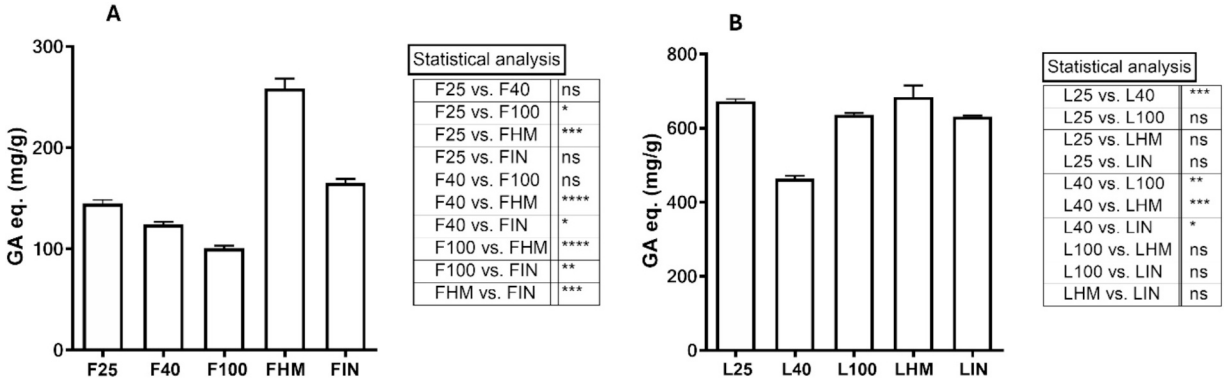

Fig. 1. Total phenolic content of fruit (A) and leaf (B) extracts from Sicilian sumac (*Rhus coriaria* L.), measured by Folin–Ciocâlteu assay. Data are expressed as GA eq. mean (mg/g) ± SEM. The statistical comparison among extracts was reported (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$). GA eq., gallic acid equivalents; d.e., dry extract. F, fruit; L, leaf; IN, hot infusion (100 °C); 25, aqueous maceration (25 °C); 40, aqueous maceration (40 °C); HM, hydroalcoholic maceration (25 °C).

The digestion process showed a slight impact on the phenolic content of fruit extracts (FHM, FIN), although a significant reduction was observed at gastric level for the hydroalcoholic extract FHM (Fig. 2A). Regarding the leaf, the phenolic content of the hydroalcoholic extract (LHM) was only significantly reduced at intestinal level, while that of the corresponding hot infusion (LIN) was reduced at both gastric and intestinal levels (Fig. 2B).

The value of the antioxidant capacity (ORAC test) was close to 5.5 mM of Trolox equivalents per gram (Fig. 2C, Fig. 2D) for fruit and leaf extracts, although different content in total phenolics was observed.

Moreover, the antioxidant capacity was not modified by the gastric digestion processes, whereas slightly increased after intestinal digestion.

The overall data suggested that the substantial conservation of relevant levels of total phenols after simulated digestion may theoretically account for biological effects along the gastrointestinal tract.

Then, to address the biological stability, the effect on IL-8 released by human gastric (GES-1) or intestinal (CaCo-2) epithelial cells was investigated by preliminary experiments. The release of IL-8 was selected as well-known biomarker of acute gut inflammation, leading to neutrophils recruitment (Kaulmann & Bohn, 2016; Smith et al., 2011). TNF-α (10 ng/mL) was selected to stimulate IL-8 release by GES-1 cells, with the aim to compare the results with our previous work concerning Iranian sumac (Martinelli et al., 2022). IL-1β (10 ng/mL) was selected as well-known inducer of IL-8 in CaCo-2 cells, which, are less responsive to TNF-α (Muto et al., 2015; Schuerer-Maly et al., 1994).

Firstly, the viability of GES-1 (Fig. S3 A) and CaCo-2 cells (Fig. S3B) was measured after 6 h of treatment with fruit and leaf extracts, namely the time of inflammatory stimulation. The viability was not statistically different if compared to the untreated control.

Regarding GES-1 cells, fruit extracts (FHM, FIN) significantly impaired the release of IL-8 at 20 μg/mL, either before or after the application of the gastric digestion protocol (Fig. 3A). The digestion showed only a slight impact on the inhibitory effect of FHM, in line with the previous data regarding the chemical stability (Fig. 2A) and our previous work (Martinelli et al., 2022). On the contrary, the inhibitory effect of FIN was unchanged, again reflecting the previous data regarding the complete conservation of polyphenols at gastric level for the hot infusion.

At the same concentration (20 μg/mL), leaf extracts completely suppressed IL-8 release (Fig. 3B), thus showing stronger inhibitory effect than fruit extracts. Again, the result was consistent with the evidence that leaf extracts showed generally higher amount of polyphenols before and after simulated gastric digestion. Notably, the partial degradation of LIN (Fig. 2B) was not enough to counteract the inhibitory effect, thus supporting the stability of the bioactive compounds.

The same experiments were conducted in CaCo-2 cells, to address the bioactivity before or after simulated intestinal digestion. In this context, FHM, but not FIN, both at 20 μg/mL, significantly inhibited IL-8 release after intestinal digestion (Fig. 3C). Since the qualitative composition of FHM and FIN was comparable, a possible explanation could be the higher content of polyphenols measured in the first extract. For this reason, FHM was selected for further investigations aimed at evaluating the impairment of inflammatory markers at intestinal level.

The extracts from leaf (LHM, LIN, at 20 μg/mL) entirely suppressed the release of IL-8 in CaCo-2 cells (Fig. 3D); thus, both the extracts were included in the following bioassays.

Based on the first data, we proceeded with further experiments to characterize the biological properties of the hydroalcoholic extracts (FHM, LHM) and hot infusions (FIN, LIN), underwent to simulated gastrointestinal digestion.

3.3. *Effect of Sicilian sumac extracts on inflammatory markers*

During mucosal inflammation, IL-8 is often associated with MCP-1 expression as key factor for monocyte recruitment (Smith et al., 2011). According to our previous experience, these chemokines are

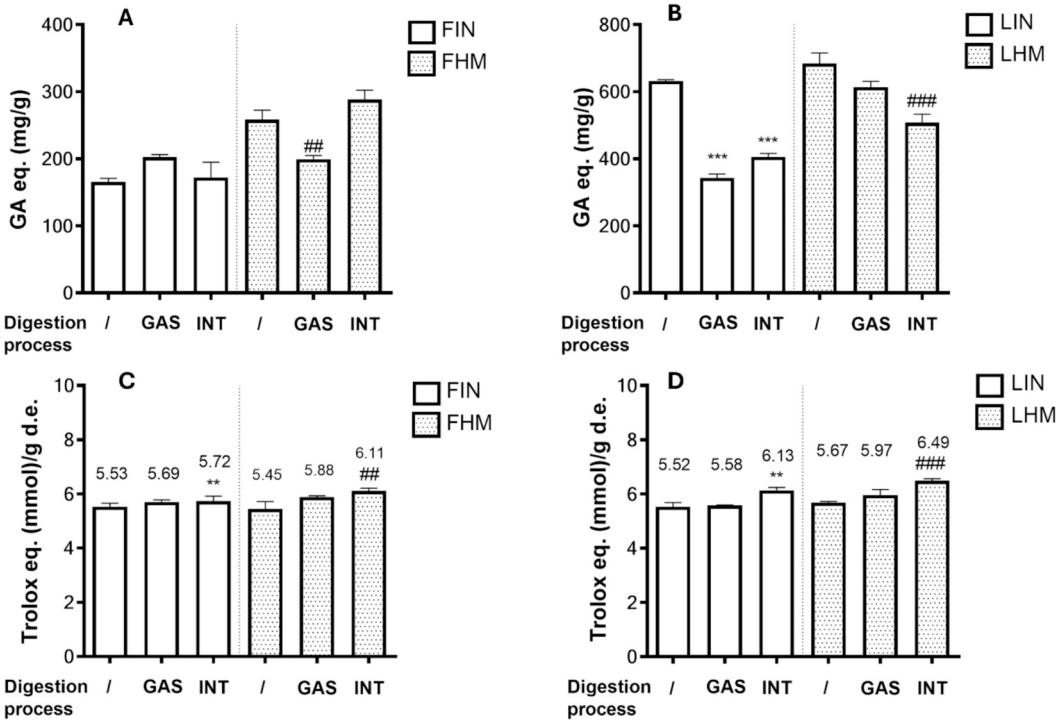

Fig. 2. Total phenolic content (A, B) was compared with scavenging activity (C, D) of fruit and leaf extracts from Sicilian sumac (*Rhus coriaria* L.), measured by Folin–Ciocâlteu assay, and ORAC test, respectively. The assays were performed before and after gastric (GAS) and intestinal (INT) simulated digestion. Data are expressed as mean (mg/g) ± SEM. The statistical comparison among extracts was reported as follows: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ vs non-digested infusion extracts (FIN, LIN); #p < 0.05, ##p < 0.01, ###p < 0.001 vs non-digested hydroalcoholic extracts (FHM, LHM). GAS, simulated gastric digestion; INT, simulated intestinal digestion; F, fruit; L, leaf; GA eq., gallic acid equivalents; d.e., dry extract; Trolox eq./g, Trolox equivalents on gram.

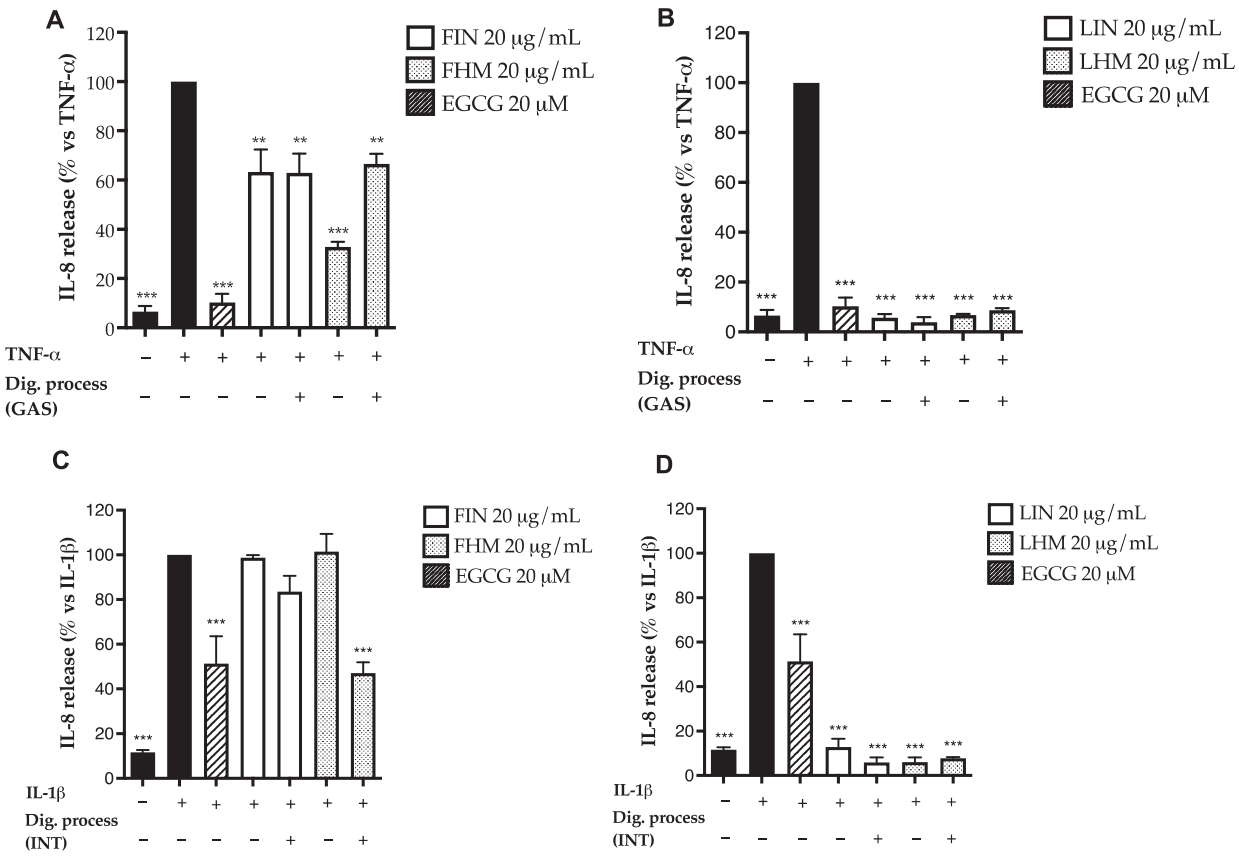

Fig. 3. Effect of fruit and leaf extracts from Sicilian sumac (*Rhus coriaria* L.) on IL-8 release, measured by ELISA assay. IL-8 release was measured in GES-1 (A,B) or CaCo-2 (C—D) cell media after treatment for 6 h with TNF-α (10 ng/mL) or IL-1β (10 ng/mL) and fruit (A,C) or leaf extracts (B,D) at the same concentrations (20 μg/mL). The inhibitory effect before and after gastric simulated digestion (GAS) or after intestinal simulated digestion (INT) was compared. Results were expressed as relative % in comparison to stimuli (TNF-α) (A,B), or (IL-1β) (C,D), to which was arbitrarily assigned the value of 100%. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ vs. stimulus. GAS, gastric simulated digestion; FIN, fruit hot infuse; FHM, fruit hydroalcoholic extract; LIN, leaf hot infuse; LHM, leaf hydroalcoholic extract; EGCG, epigallocatechin-3-O-gallate.

highly expressed in GES-1 and CaCo-2 cells after the induction with pro-inflammatory cytokines (unpublished data). For a better comprehension of the mechanisms involved, we carried out concentration-response experiments by treating cells with in vitro digested extracts, also including the evaluation of MCP-1 release. Moreover, we included the evaluation of NF-κB as well-known transcription factor involved in the regulation of both chemokines (Smith et al., 2011). EGCG and apigenin were used as reference anti-inflammatory polyphenols for comparison (Di Lorenzo et al., 2013; Gutierrez-Orozco et al., 2010; Thiruvengadam et al., 2021).

All the selected extracts showed a concentration-dependent inhibition of IL-8 release in GES-1 cells (Fig. 4A and Fig. 4B). The extracts from fruit (FHM, FIN) exhibited comparable IC_{50}, below 30 μg/mL, while extracts from leaf (LHM, LIN) exhibited identical and notable IC_{50}, equal to 0.2 μg/mL.

The inhibitory activity on MCP-1 release by GES-1 cells was less pronounced, but still relevant for all the extracts (Fig. 4C and Fig. 4D), since the IC_{50} were close to 55 μg/mL and 10 μg/mL, referring to fruit and leaf extracts, respectively (Supplementary material, Table S2).

Accordingly, all the extracts showed a concentration-dependent inhibition of IL-8 release in CaCo-2 cells (Fig. 5A and Fig. 5B). The selected hydroalcoholic extract from fruit (FHM) exhibited an IC_{50} of 51.63 μg/mL, while the extracts from leaf (LHM, LIN) exhibited again similar IC_{50} (< 11 μg/mL).

As observed before in GES-1 cells, the inhibitory activity on MCP-1 released by CaCo-2 cells was less pronounced for leaf extracts (LIN, LHM), showing only moderate inhibition at 20 μg/mL, whereas the extract from fruit (FHM) showed again a concentration-dependent inhibition (Fig. 5C and Fig. 5D), with IC_{50} of 42.18 μg/mL (Supplementary material, Table S3).

The transcription factor NF-κB is known to regulate the expression of chemokines, including IL-8 and MCP-1, acting as a downstream of typical pro-inflammatory challenges, such as TNF-α and IL-1β. Moreover, NF-κB is a well-known sensor of oxidative stress supporting the inflammatory response (Dijkstra et al., 2002). Polyphenols may act on inflammation through NF-κB impairment and antioxidant activity (Kaulmann & Bohn, 2016).

Fruit extracts from Sicilian sumac (FIN, FHM) significantly inhibited the NF-κB-driven transcription in GES-1 cells, at the same concentration evaluated before (20 μg/mL) (Fig. 6A). The activity was in line with our previous work regarding an hydroalcoholic extract from Iranian sumac fruit (Martinelli et al., 2022). Here, for the first time, this anti-inflammatory mechanism was also clearly attributed to extracts from sumac leaf (Fig. 6B).

Surprisingly, we observed that NF-κB was not responsible for the inhibitory activity on chemokines released from CaCo-2 cells, even at the highest concentration of the extracts tested (Fig. 6C and Fig. 6D).

This data suggested that NF-κB may explain the anti-inflammatory effect observed in GES-1 cells while further studies in CaCo-2 cells are required to clarify the mechanism of action.

3.4. Inhibitory effect of Sicilian sumac extracts on intracellular ROS production

Our data regarding the phenolic content and the antioxidant capacity suggested that the selected extracts from Sicilian sumac may counteract

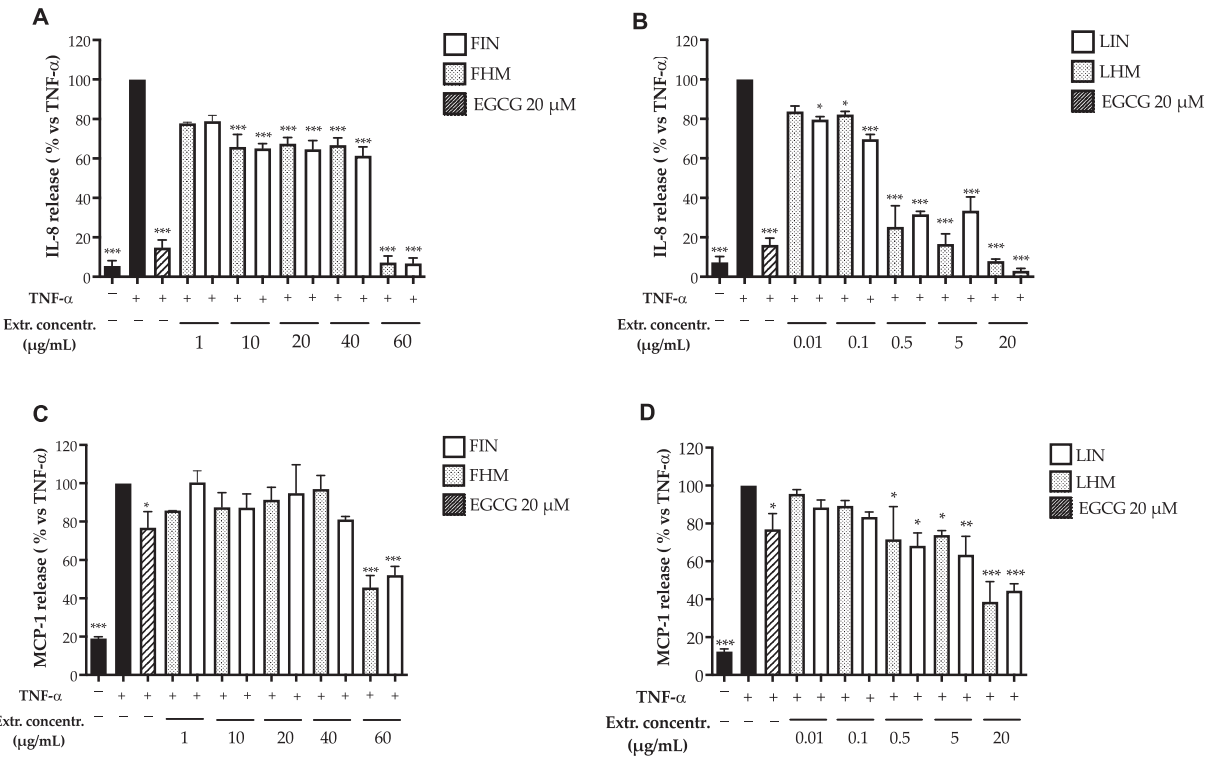

Fig. 4. Concentration-dependent inhibition of IL-8 and MCP-1 release by fruit and leaf extracts from Sicilian sumac (*Rhus coriaria* L.), measured by ELISA assay. Chemokine release was measured in GES-1 cell media after treatment for 6 h with TNF-α (10 ng/mL) and fruit (A, C) or leaf extracts (B, D) at increasing concentrations (0–60 μg/mL, or 0–20 μg/mL, respectively). The inhibitory effect was measured after gastric simulated digestion. Results were expressed as relative % in comparison to stimulus (TNF-α), to which was arbitrarily assigned the value of 100%. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$ vs. stimulus. FIN, fruit hot infusion; FHM, fruit hydroalcoholic extract; LIN, leaf hot infusion; LHM, leaf hydroalcoholic extract; EGCG, epigallocatechin-3-O-gallate.

the production of ROS in cell systems. To address the antioxidant activity, GES-1 and CaCo-2 were exposed to the extracts for 24 h, followed by H_2O_2 challenge, according to well-established protocols (Nwakiban et al., 2020). For comparison, apigenin (10 μM) was used as reference antioxidant flavonoid (Gutierrez-Orozco et al., 2010; Thiruvengadam et al., 2021).

Firstly, the viability of cells after 24 h exposure was measured (Fig. S3C, Fig. S3D). A significant reduction of GES-1 cell viability (−45%), but not CaCo-2, was observed after the treatment with hydroalcoholic extract from leaf (LHM, 20 μg/mL). For this reason, LHM was excluded by the antioxidant assay. The viability was not significantly altered by the other extracts.

At the highest concentrations tested in the previous experiments (60 μg/mL for fruit, and 20 μg/mL for leaf, respectively), all the extracts showed a slight (−20%), but not significant, prevention of ROS production in GES-1 (Fig. 7A and Fig. 7B). These data did not show any correlation with the antioxidant capacity (see Fig. 2), thus suggesting that the scavenging mechanism did not apply to gastric cells.

On the contrary, ROS levels were abrogated in CaCo-2 cells (Fig. 7C and Fig. 7D), in analogy with the reference antioxidant compound. In this case, both scavenging and biological mechanisms may have contributed; thus, the data represent a base for further investigation on the potential antioxidant properties of Sicilian sumac at intestinal level.

3.5. 3.5. Characterization of sumac leaf hydroalcoholic extract by LC-MS/MS

Given the higher anti-inflammatory inhibition and antioxidant capacity exhibited by leaf hydroalcoholic extract among all tested extracts from Sicilian sumac, a qualitative LC-MS/MS analysis on leaf hydroalcoholic extract was carried out to elucidate its polyphenolic composition. The chromatographic and mass spectrometric data allowed the putative identification of 20 compounds, mainly belonging to the classes of flavonols, flavanols and phenolic acids (Table 1). Among them, myricetin-3-O-rhamnoside appeared to be the most abundant glycosylated flavonol. Thus, it was selected for targeted quantification to estimate its content. The targeted LC-MS analysis allowed the quantification of myricetin-3-rhamnoside, which was present at 13.65 ± 0.84 (mean ± SEM) mg/g in the extract.

4. Discussion

Despite the wide use in traditional medicine as a spice or ingredient in food supplements, sumac (*Rhus coriaria* L.) is still poorly investigated for biological activity at gastrointestinal level. Most of the available studies regards plant samples from the Middle East market, where sumac has a long history of traditional use (Elagbar et al., 2020), whereas little is known about sumac grown in the Mediterranean area, including Sicily. Most studies to date have focused on the bioactive properties of sumac fruits, while biological activities of leaves, which are used as ingredients of food supplements in several countries, are less documented.

This paper represents the first investigation concerning the role of fruit and leaf extracts from Sicilian sumac (*Rhus coriaria* L.), harvested, and marketed in Italy (Sicily), with the aim to fill several gaps including geographical diversity, the potential activity of leaves at gastrointestinal activity, which may account for plant use in functional foods or nutraceuticals.

Our data demonstrated that extracts obtained by hydroalcoholic maceration and hot infusion of Sicilian sumac, namely ecological and traditional methods of extraction, are botanical ingredients providing high levels of polyphenols (Fig. 1). Leaf extracts were particularly rich, with a phenolic content higher than 600 mg GA eq/g for hydroalcoholic extract.

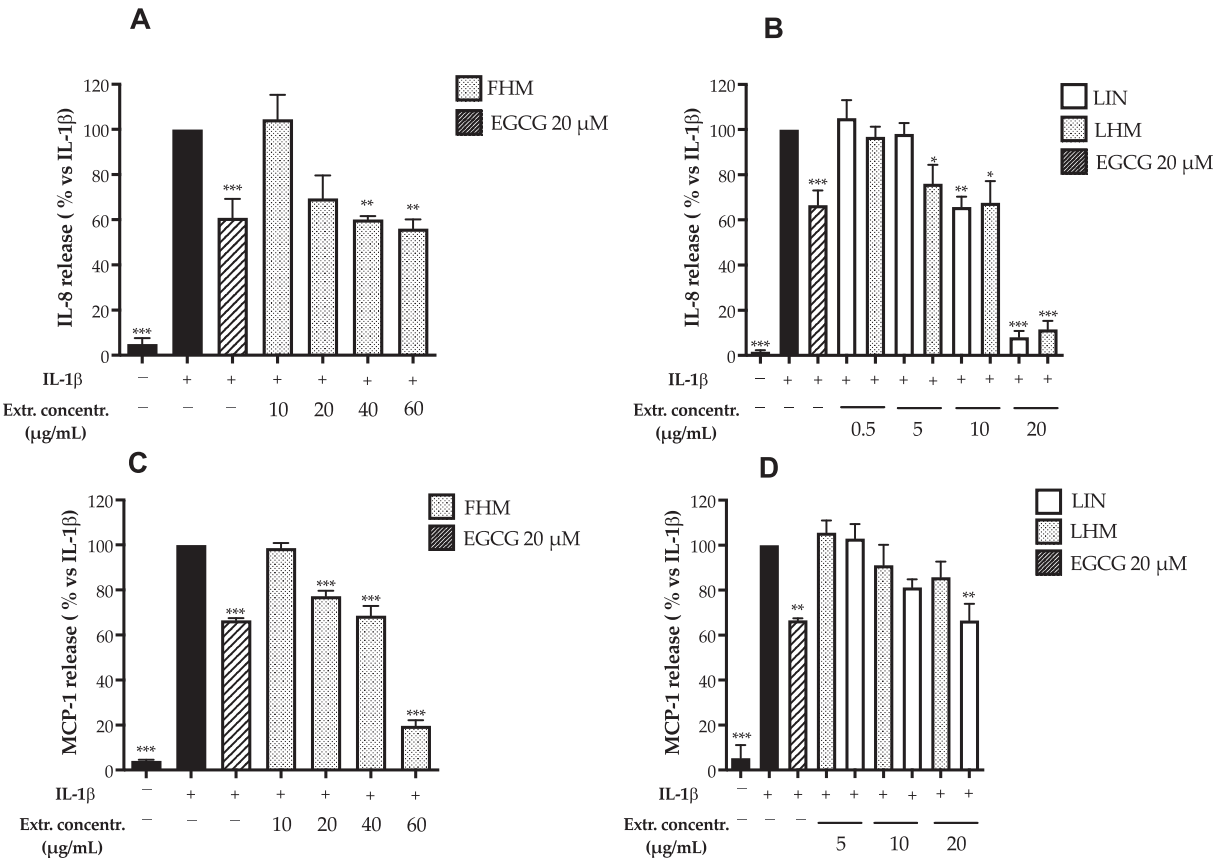

Fig. 5. Concentration-dependent inhibition of IL-8 and MCP-1 release by fruit and leaf extracts from Sicilian sumac (*Rhus coriaria* L.), measured by ELISA assay. Chemokine release was measured in CaCo-2 cell media after treatment for 6 h with IL-1β (10 ng/mL) and fruit (A, C) or leaf extracts (B, D) at increasing concentrations (0–60 μg/mL, or 0–20 μg/mL, respectively). The inhibitory effect was measured after intestinal simulated digestion. Results were expressed as relative % in comparison to stimulus (IL-1β), to which was arbitrarily assigned the value of 100%. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ vs. stimulus. FHM, fruit hydroalcoholic extract; LIN, leaf hot infusion; LHM, leaf hydroalcoholic extract; EGCG, epigallocatechin-3-O-gallate.

The chemical analysis revealed similar qualitative composition, reflecting the previous literature (Beretta et al., 2009; Khalilpour et al., 2019; Regazzoni et al., 2013): free gallic acid, gallotannins and flavonoids were the main identified polyphenol classes.

The polyphenolic level and the antioxidant capacity (ORAC) remained relevant after simulated gastrointestinal digestion (Fig. 2), thus suggesting the chemical stability of the extracts. The maintenance of the inhibitory activity on the release of IL-8 in GES-1 cells after digestion (Fig. 3) also supported the biological stability at gastric level. Similarly, the bioactivity was maintained in CaCo-2 intestinal cells, except for fruit hot infusion (FIN) (Fig. 4). The potential inhibitory activity on chemokines was also confirmed by the experiments on MCP-1 release, showing a concentration-dependent fashion (Fig. 5 and Fig. 6), starting by the concentration of 60 μg/mL and 20 μg/mL, respectively for fruit and leaf extracts (the summary of the IC_{50} is reported in Table 2 and Table 3). Although biological activity and relevant polyphenol content were retained after simulated digestion, these results should be interpreted considering that the static in vitro model does not fully reproduce the dynamic conditions and physiological residence times occurring in vivo. Nevertheless, it provides standardized and reproducible conditions to compare the behaviour of the different extracts during simulated digestion. The anti-inflammatory mechanism observed in GES-1 cells was ascribed, at least in part, to the NF-κB impairment (Fig. 7). This data paralleled our previous experiments regarding Iranian sumac (Martinelli et al., 2022). On the contrary, the chemokines inhibition observed in CaCo-2 cells was NF-κB-independent, thus suggesting the involvement of other inflammatory targets, demanding for specific investigation.

Consequently, the presence of polyphenols in Sicilian sumac, with potential stability along the gastrointestinal tract, was clearly associated with anti-inflammatory properties in gut epithelium.

Sumac was also reported for strong antioxidant properties (Batiha et al., 2022), but their relevance in biological systems, including gastrointestinal tract, has been poorly documented. We previously reported that sumac fruit may prevent UVA-induced oxidative stress at endothelial level (Nozza et al., 2020). Here, we suggest that the antioxidant capacity of Sicilian sumac may be preserved after gastrointestinal digestion, thus leading to the control of ROS development in intestinal epithelial cells (Fig. 7). On the contrary, ROS production was not inhibited in GES-1 cells. Our observation is in line with other authors, suggesting that food preparations fortified with sumac extracts may retain the antioxidant properties in the gastrointestinal environment(Simonetti et al., 2021).

It is worth highlighting that the antioxidant effect was observed at the same concentrations able to exert the anti-inflammatory activity (20–60 μg/mL). The molecular mechanism behind the antioxidant activity, according to the anti-inflammatory activity, still demands further studies. Notably, inhibitory concentrations are potentially achievable after the consumption of dry plant material as an infusion, as a spice or as a food supplement. Indeed, the biological effect was generally observed at concentrations lower or close to 50 μg/mL.

Moreover, a LC-MS qualitative phenolic profile on the most promising extract, i.e. leaf hydroalcoholic extract, allowed the putative identification of various compounds belonging to several phenolic classes, including phenolic acids, flavones, flavonols, and flavonol glycosides (Table 4). Among these, myricetin-3-O-rhamnoside was one of

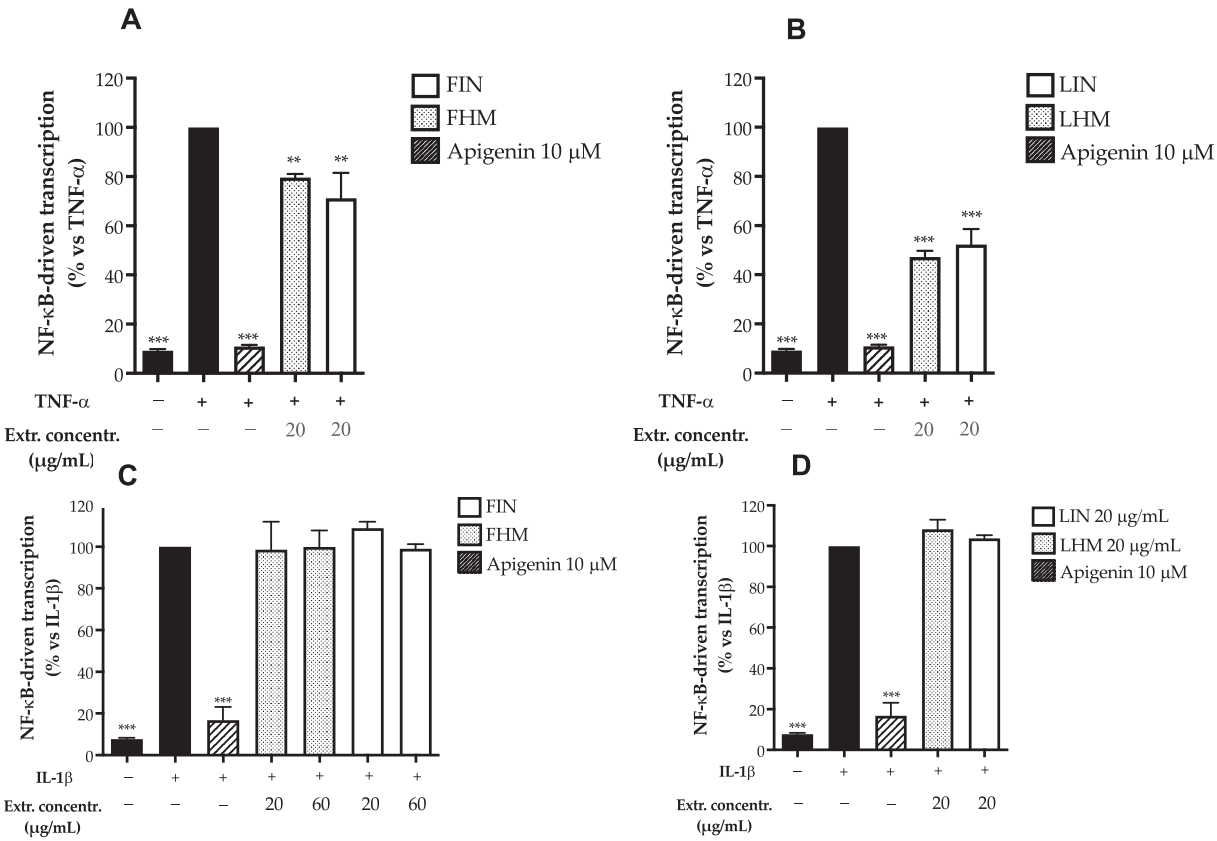

Fig. 6. Effect of fruit and leaf extracts from Sicilian sumac (*Rhus coriaria* L.) on NF-κB driven-transcription. NF-κB driven-transcription was measured in GES-1 (A, B) and CaCo-2 cells (C, D) after treatment for 6 h with TNF-α or IL-1β (10 ng/mL) and fruit (A, C) or leaf extracts (B, D). The inhibitory effect was measured after gastric (A, B) or intestinal (C, D) simulated digestion. Results were expressed as relative % in comparison to stimulus (TNF-α, IL-1β), to which was arbitrarily assigned the value of 100%. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$ vs. stimulus. FIN, fruit hot infusion; FHM, fruit hydroalcoholic extract; LIN, leaf hot infusion; LHM, leaf hydroalcoholic extract.

the most abundant compounds. Its abundance is consistent with that reported by other authors for *Rhus coriaria*, in which glycosylated derivatives of myricetin are characteristic components of the phenolic fraction (Beretta et al., 2009; Lo Vecchio et al., 2022; Regazzoni et al., 2013). This compound was therefore selected for targeted quantification, with the aim of estimating its contribution to the overall chemical profile of the extract.

The detected amount of this flavonol in hydroalcoholic leaf extract (13.66 ± 0.84 mg/g), suggests that myricetin-3-O-rhamnoside may be proposed as potential marker for extract standardization. Since the isolated compound was not tested in the biological assays, no direct causal relationship between myricetin-3-O-rhamnoside and the observed bioactivity can be inferred. Nevertheless, its abundance, together with previous literature on myricetin glycosides, supports its usefulness as a phytochemical marker of the extract. The compound may contribute to the antioxidant and anti-inflammatory activities observed in our work, consistent with the properties already attributed to myricetin and its glycosides (Schwanke et al., 2013; Hiermann et al., 1998; Rha 2019). Overall, the combination of relative abundance and biological relevance supports the hypothesis that this glycosylated flavonol plays a significant role in the functional potential of sumac leaves, contributing to their traditional utilization and interest as a natural source of bioactive compounds.

The potential role of polyphenols like flavonoids, anthocyanins, gallotannins, and their metabolites, against gut inflammation and oxidative stress was not surprising, since it was already suggested by several groups, including ours (Piazza et al., 2022; Santino et al., 2017; Yang et al., 2020). Importantly, the bioactivity of polyphenols may also involve gut microbiota, thus, specific investigations are needed to clarify the interest of Sicilian sumac extracts in this regard.

5. Conclusion

This work addresses for the first time the bioactivity of polar extracts from Sicilian sumac, and sumac leaf in general, at gastrointestinal level, including a chemical characterization of the phenolic profile. The overall evidence suggests that traditional extracts from fruit and leaf of Sicilian sumac may counteract inflammation and oxidative stress related to gut disorders.

A limitation of the present study is that a detailed chromatographic characterization of the digested fractions was not performed. Future studies should investigate the changes in the phenolic profile after simulated gastrointestinal digestion in order to better correlate specific compounds or metabolites with the observed biological activities. Moreover, the present in vitro digestion model does not account for the role of the gut microbiota, which may extensively metabolize dietary polyphenols and generate metabolites with different bioavailability and biological activity.

Further studies in models of gut inflammation are therefore required to confirm the plausibility of these biological properties and promote the commercial use of sumac extracts as products for human health.

CRediT authorship contribution statement

Nicole Maranta: Writing – review & editing, Writing – original draft, Investigation, Formal analysis. **Giulia Martinelli:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis. **Marco Fumagalli:** Investigation, Formal analysis. **Elisabetta Grillo:**

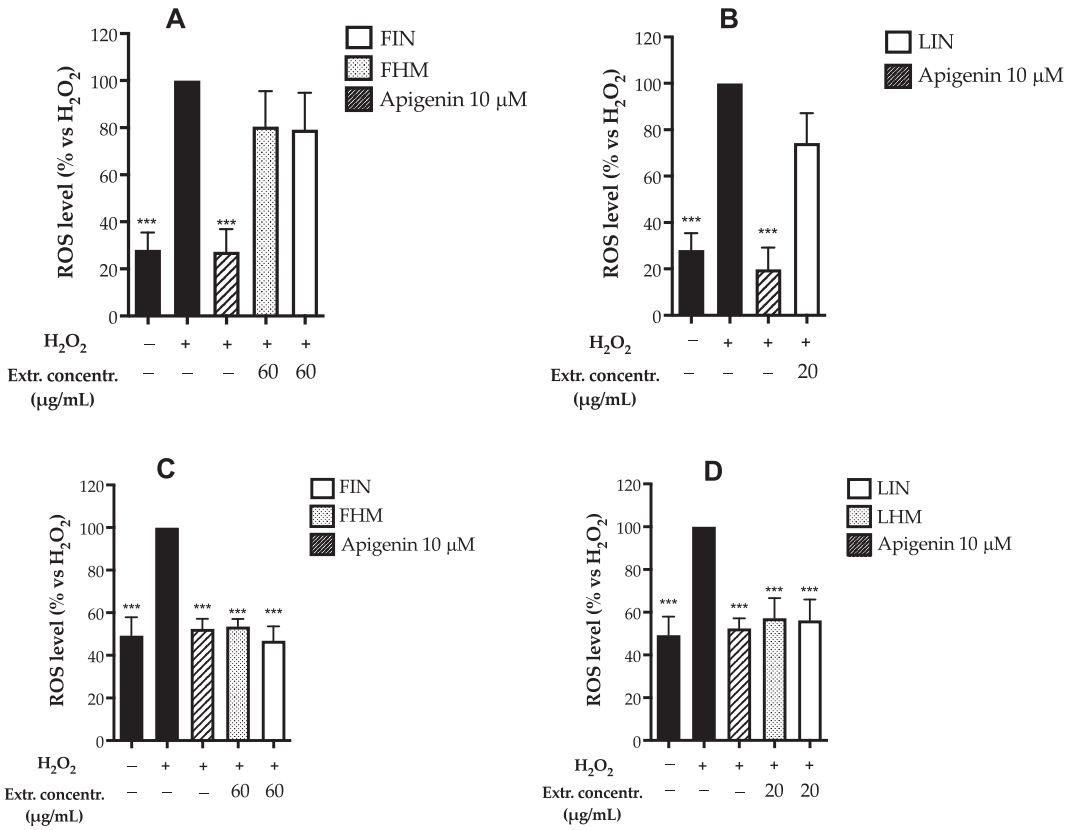

Fig. 7. Effect of fruit and leaf extracts from Sicilian sumac (*Rhus coriaria* L.) on intracellular ROS level, measured by CM-H2DCFDA probe uptake. ROS production was measured in GES-1 (A, B) and CaCo-2 cells (C, D) after pro-oxidant stimulation for 1 h with H_2O_2 (500 μM or 1 mM, respectively), following the treatment (24 h) with fruit (A, C) or leaf extracts (B, D). The inhibitory effect was measured after gastric (A, B) or intestinal (C, D) simulated digestion. Results were expressed as relative % in comparison to stimulus (H_2O_2), to which was arbitrarily assigned the value of 100%. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ vs. stimulus. FIN, fruit hot infusion; FHM, fruit hydroalcoholic extract; LIN, leaf hot infusion; LHM, leaf hydroalcoholic extract.

Table 1
Polyphenols putatively identified in the leaf hydroalcoholic extract of Sicilian sumac.

N	RT (min)	(M-H)	Product Ion (*m/z*)	Putative Identified Molecule
1	5.71 / 6.91	331	169	Monogalloyl glucoside
2	6.44	169	124	Gallic acid*
3	7.98	317	124	Myricetin
4	8.05 / 8.44	787	169	Tetragalloyl glucoside
5	9.07	493	193	Myricetin-3-glucuronide
6	9.15	625	316	Myricetin-3-rhamnoglucoside
7	9.19	479	316	Myricetin-3-O-glucoside
8	9.52	315	300	Isorhamnetin
9	9.52	447	285	Luteolin-7-glucoside*
10	9.52	463	316	Myricetin-3-O-rhamnoside*
11	9.78	463	300	Quercetin-3-O-glucoside*
12	9.78	463	300	Hyperoside (quercetin-3-galactoside)*
13	9.81	609	301	Rutin (quercetin-3-rutinoside)*
14	10.05	593	284	Kaempferol-3-rutinoside
15	10.15	447	284	Kaempferol-3-glucoside*
16	10.17	301	145	Ellagic acid*
17	10.74	301	151	Quercetin*
18	11.05	285	132	Luteolin*
19	11.05	285	151	Kaempferol*
20	11.53	269	151	Apigenin*

Compounds marked with an asterisk (*) were confirmed by comparison with analytical standards.

Conceptualization. **Rita Nasti:** Investigation. **Giangiacomo Beretta:** Writing – review & editing, Supervision. **Enrico Sangiovanni:** Writing – review & editing, Supervision. **Carola Pozzoli:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation. **Mario Dell'Agli:** Writing – review & editing, Supervision, Conceptualization. **Stefano Piazza:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization.

Funding

The present work was partially funded by Redess s.r.l., Contrada Monte snc – 90018 Termini Imerese, (PA) Italy. This research was supported by grants from MIUR "Progetto Eccellenza" 2023–2027.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Stefano Piazza reports financial support was provided by Redess srl. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors thank Dr. Dawit Kidane-Mulat (University of Texas, Austin, TX, USA) for providing GES-1 cells.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.

org/10.1016/j.jff.2026.107403.

Data availability

Data will be made available on request.

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