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Anti-inflammatory Potential of Plants of Genus *Rhus*: Decrease in Inflammatory Mediators *In Vitro* and *In Vivo* – a Systematic Review

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ABSTRACT

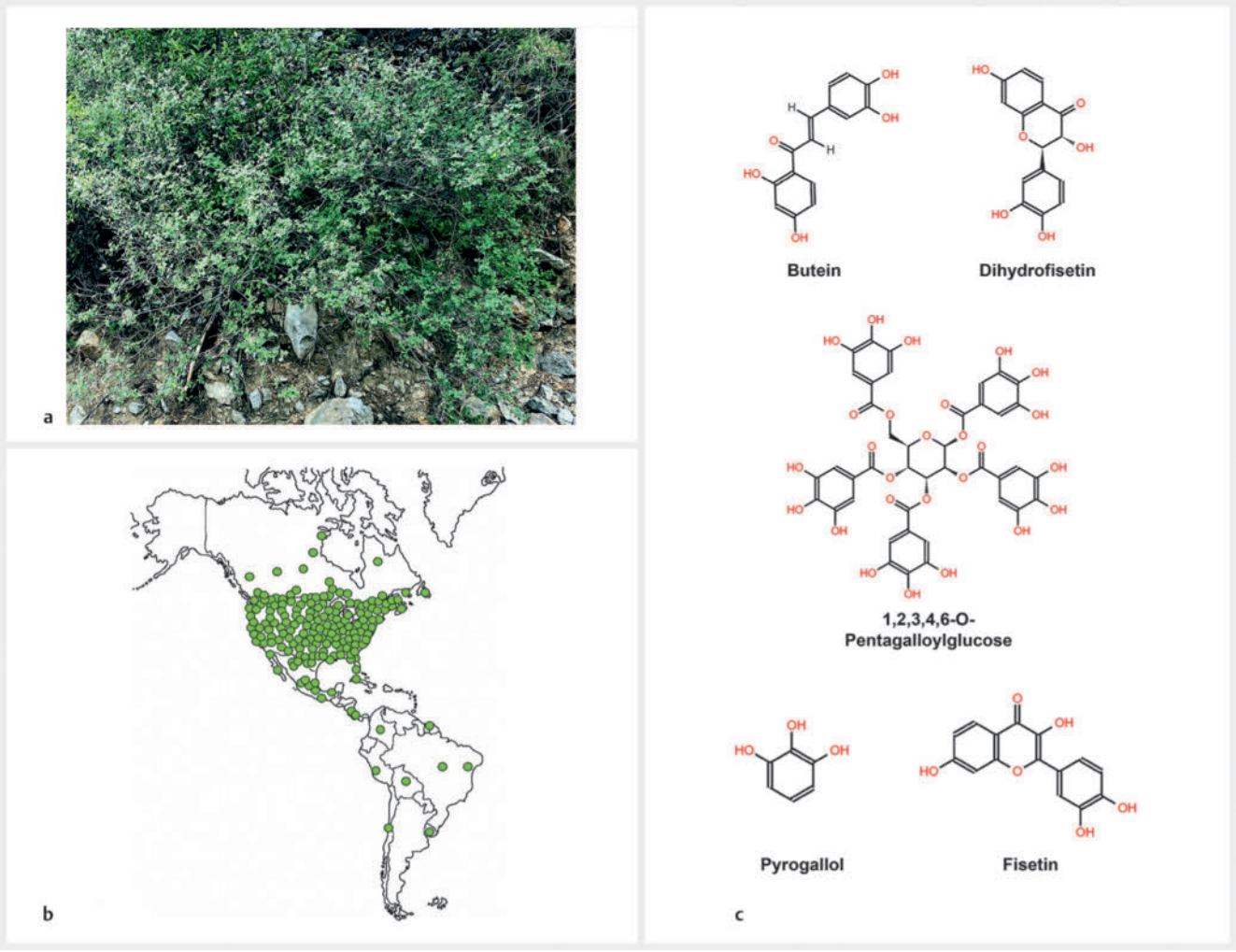
Plants from the *Rhus* genus are renowned for their medicinal properties, including anti-inflammatory effects; however, the mechanisms underlying these effects remain poorly understood. This systematic review, conducted following PRISMA guidelines, evaluated the anti-inflammatory effects of *Rhus* plants and explored their potential pharmacological mechanisms. A total of 35 articles were included, with the majority demonstrating a low-risk bias, as assessed using the SYRCLE tool. *Rhus verniciflua, Rhus chinensis, Rhus coriaria, Rhus succedanea, Rhus tripartite, Rhus crenata*, and *Rhus trilobata* were analyzed in the reviewed articles. *In vitro* studies consistently demonstrated the ability of *Rhus* plants to reduce key inflammatory mediators such as TNF-α, IL-1β, and IL-6. *In vivo* studies confirmed these effects in murine models of inflammation, with doses mostly of 400 and 800 mg/kg body weight, with no reports of toxicity. Fifty-four distinct inflammatory mediators were assessed *in vivo*; no pattern of mediators was identified that could elucidate the anti-inflammatory mechanisms of the action of *Rhus* in acute or chronic inflammation. The clinical trial reported anti-inflammatory effects in humans at 1000 mg/kg for 6 weeks. The review data on the *Rhus*-mediated reduction in inflammatory mediators were integrated and visualized using the Reactome bioinformatics database, which suggested that the mechanism of action of *Rhus* involves the inhibition of inflammasome signaling. These findings support the potential of *Rhus* plants as a basis for developing anti-inflammatory therapies. Further research is needed to optimize dosage regimens and fully explore their pharmacological applications.

Introduction

Chronic inflammatory diseases remain a significant public health challenge [1, 2]. Despite substantial progress in their detection and treatment, these advances come at a considerable cost, significantly contributing to increased health expenditures. The primary goals of treatments for chronic inflammatory diseases are reducing inflammation and pain and preserving functionality. Such treatments are specific to each condition and include pharmacological interventions, lifestyle modifications, and patient education regarding disease management [3, 4].

In vitro and *in vivo* studies provided essential insights into the molecular mechanisms underlying inflammatory processes, enabling the identification of key mediators and the development of targeted therapies [5]. Several inflammatory mediators and signaling molecules are dysregulated in chronic inflammatory diseases, presenting viable targets for current treatments. However, existing therapies often fail to provide consistent efficacy across all patients due to heterogeneity and the dynamic nature of the pathogenic process [6].

Medicinal plants have been traditionally used worldwide as alternative or complementary treatments for inflammatory diseases [7]. Plants and animals share intrinsic intracellular regulatory processes and mediators, and numerous plant-derived compounds exert significant biological effects on animal cells (e.g., digitalis, colchicine, and opioids) [8, 9]. Recently, there has been

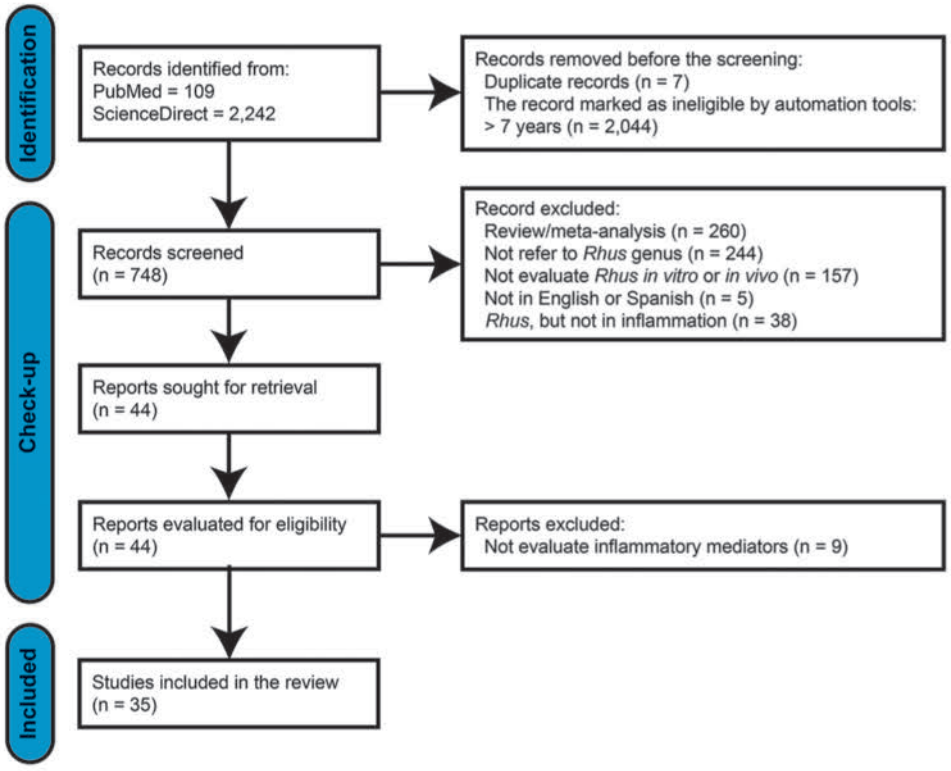


▶ **Fig. 1** Representative images of (**a**) *Rhus trilobata* from the *Anacardiaceae* Family, (**b**) distribution of plants of genus *Rhus* in North America, and (**c**) mainly molecules isolated from *Rhus* plants.

a growing interest in the bioactive compounds in plants, notably polyphenols, for their potential to treat chronic inflammatory conditions [10]. Herbal treatments can be prepared through simple decoctions from plant extracts or by combining multiple plant types. However, the low concentrations of active compounds obtained through basic processing methods may limit their full therapeutic potential [11].

Sumac, a genus (*Rhus*) comprising over 250 species of flowering plants in the family Anacardiaceae, is widely used as a spice and herbal remedy in traditional medicine for its diverse properties [12]. Members of the Anacardiaceae family, including the *Rhus* species, are predominantly trees and shrubs, with occasional subshrubs and lianas found in tropical, subtropical, and limited temperate regions [13] (▶ **Fig. 1 a**). The economic importance of this plant family stems from its ornamental cultivars (e.g., *Schinus spp.*) and fruit- and seed-producing species, such as *Pistacia vera* (pistachio), *Anacardium occidentale* (cashew), *Mangifera indica* (mango), and *Rhus spp.* (sumacs) [14]. In the Americas, *Rhus* species (subgenera: *Lobadium* and *Rhus*) are closely related to other *Rhoeae* species, such as *Actinocheita, Cotinus, Malosma, Schinus, Searsia*, and *Toxicodendron*. In Mexico, representatives of these plants include *Cardenasiodendron, Cotinus, Toxicodendron*, and 35 different species of *Rhus* [15, 16] (▶ **Fig. 1 b**).

Research into the anti-inflammatory mechanisms attributed to plants or their components has expanded remarkably in recent years. These studies aim to support and promote complementary and alternative medicine or identify and characterize specific anti-inflammatory components for therapeutic use in chronic inflammatory diseases [17]. Plants of the genus *Rhus* exhibit antioxidant [18], antimicrobial, anti-aging [19], anticancer [20, 21], and anti-diabetic [22] properties. Additionally, bioactive components of *Rhus spp.* have been investigated, with some molecular mechanisms already described. The anti-inflammatory properties of *Rhus spp.* are of particular interest. While specific mechanisms have been partially reviewed for *Rhus verniciflua Stokes* [23], further experimental strategies, *in vitro, in vivo*, and human trials, are necessary to understand these effects comprehensively.



▶ **Fig. 2** Flow chart of study selection according to the Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Despite the promising therapeutic potential of *Rhus* spp., knowledge gaps remain regarding their mechanisms of action, optimal dosages, and the potential risks associated with their use. Addressing these gaps is crucial for the safe and practical application of *Rhus*-based treatments in managing inflammatory conditions. Therefore, this review aimed to compile studies conducted in *in vitro, in vivo*, and human clinical trials that evaluate the effects of plants of the genus *Rhus* or their isolated components on inflammatory conditions. The goal was to identify and describe the potential anti-inflammatory mechanisms attributed to this plant.

Results

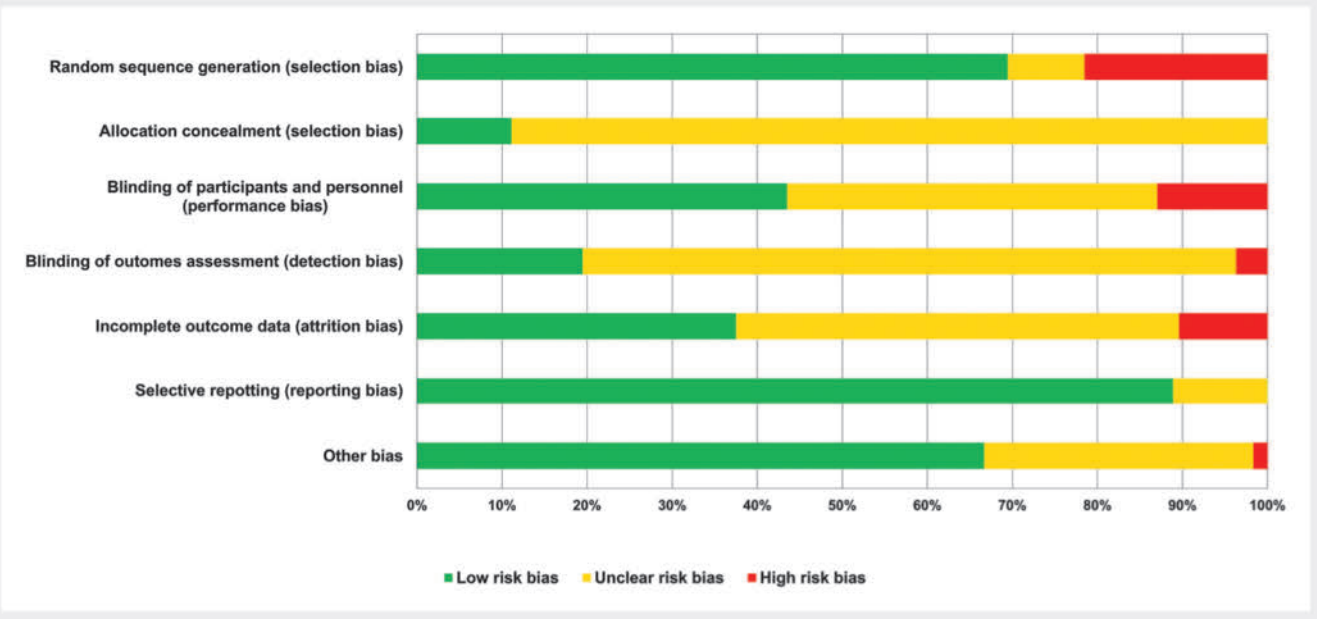
Study selection and risk of bias assessment

The article selection process using the PRISMA guide is shown in ▶ **Fig. 2**, and from the 2351 articles initially identified using the keywords, duplicates and articles older than five years were eliminated. Then, the titles and abstracts of 748 articles were reviewed to meet the inclusion criteria. Of these, 704 articles were excluded because they were review or meta-analysis studies, were not in English or Spanish, did not evaluate *Rhus* plants in any *in vitro* or *in vivo* studies, or did not evaluate anti-inflammatory effects. Of the 44 potentially relevant articles, after a detailed review of the complete text, 9 were excluded because they did not assess inflammatory mediators. Finally, 35 articles that fulfilled the inclusion criteria were included. No published systematic review was found regarding the effect of *Rhus* genus plants on inflammatory mediators *in vitro, in vivo*, or in humans.

The risk of bias assessment in the included studies is shown in ▶ **Fig. 3**. Overall, 57.7% of the articles were classified as low-risk bias for selection. The selection bias was divided into two components: random sequence generation, which showed 21.5% high risk, and allocation concealment, for which no high risk was found (0%). However, most studies (88.9%) were classified as an unclear risk for allocation concealment. Performance biases were classified as low risk (43.5%) or unclear risk (34.5%) because the articles did not specify the information sufficiently. Detection biases were of unclear risk in 76.9%, low risk in 19.4%, and only 3.7% were classified as high risk. Incomplete outcome data (attrition bias) was a low or unclear risk bias in 37.5% and 52.1% of the studies. More than 80% of the articles were classified as low risk for reporting bias biases. Reporting biases were of low risk for all the included articles.

Anti-inflammatory effects of Rhus genus plants *in vitro*

Nineteen articles that evaluated the anti-inflammatory effects of *Rhus* genus plants *in vitro* were included (▶ **Table 1**). The plants studied for their anti-inflammatory effects were *Rhus verniciflua, Rhus chinensis* Mill, *Rhus coriaria* L, *Rhus succedanea, Rhus tripartite, Rhus trilobata* Nutt., and *Rhus crenata*.



▶ **Fig. 3** Risk of bias of the articles included in the review. (n = 35). The potential risk of bias for each article was assessed with the SYRCLE risk of bias tool. Each item was scored using the nominal scale "yes," "no," or "unclear". Subsequently, the risk percentages of each bias of the included articles were graphed.

The preparation methods for *Rhus* treatments varied across studies. Three studies involved testing plant-infused extract [30–32]; one used nearly the entire *Rhus tripartita* plant, including stems, leaves, and roots, preparing an ethanolic extract of its components [40]. Chantarasakha et al. [30] prepared an ethanolic extract (v/v) but combined different plants, including *Rhus chinensis* Mill. Kim et al. [26] used only the bark of *Rhus verniciflua* to prepare a simple aqueous extract tested on the cells' supernatant. Four studies tested *Rhus coriaria* L. fruits using phenolic [35], aqueous [36], and ethanolic [34, 37] fractions extracted from fruits, and one study on *Rhus chinensis* Mill. [43]. Moreover, the aqueous ethanol, ethanol-water (ethanol: water 50 : 50 v/v), ethanol macerate (plant material subjected to maceration with pure ethanol for 48 h), acetone, and ethyl acetate extracts have also been evaluated [34].

Compounds isolated from the plants were evaluated in eight *in vitro* studies. Components such as butein, chemically described as 2′,3,4,4,4′-tetrahydroxichalcone (▶ **Fig. 1 c**) [44], a chalcone derivative produced by species from several diverse botanical families, including the Anacardiaceae to which *Rhus verniciflua* belongs. Liu et al. [25] and Zheng et al. [28] obtained 98 % pure butein from SIGMA and confirmed previous findings about the potential health benefits of compounds of *Rhus verniciflua*. Roh et al. [24] also investigated the chemical synthesis of various butein derivatives to enhance compound 1, a phenolic fraction, as a starting point.

Dihydrofisetin, also named fustin (▶ **Fig. 1 c**) [45], a polyphenol derived from wild and edible herbs and traditional Chinese medicines, including *Rhus verniciflua* Stokes, was another compound analyzed in the included studies. Li et al. [27] used it on macrophages, observing reduced levels of proinflammatory mediators.

Gallic acid (GA), or 3,4,5-trihydroxybenzoic acid, acts as an astringent, antioxidant, plant metabolite, and geroprotector. It inhibits cyclooxygenase-2, and the arachidonate 15-lipoxygenase induces apoptosis and exhibits antitumor activity [46]. A recent study on GA from *Rhus chinensis* showed its concentration-dependent inhibition of GES-1 cell proliferation via G0/G1 cell cycle arrest. RNA sequencing revealed that GA modulates multiple biological pathways, including the Wnt/β-catenin pathway, by suppressing Wnt 10B and β-catenin expression. This regulation likely reverses MNNG-induced epithelial-mesenchymal transition [29].

The compound 1,2,3,4,6 penta-O-galloyl-β-D-glucose (PGG) derived from *Rhus Chinensis* Mill, which has five galloyl groups in the 1-, 2-, 3-, 4- and 6-positions (▶ **Fig. 1 c**) [47], was also tested. Mendonca et al. [33] demonstrated the anti-inflammatory effects of PGG on microglial cells.

Rhoifolin, a 7-O-neohesperidoside derivative of apigenin, features an alpha-(1 → 2)-L-rhamnopyranosyl-beta-D-glucopyranosyl group at the 7-hydroxy position. Classified as a dihydroxyflavone and a glycosyloxyflavone, rhoifolin was first isolated from *Rhus succedanea* in 1952 [48, 49]. Yan et al. [38] demonstrated that rhoifolin reduced inflammatory cytokines (iNOS, COX-2) and cartilage degradation markers (MMP13, ADAMTS5) while enhancing collagen II expression, mitigating IL-1β-induced cartilage damage. It inhibited the phosphorylation of JNK, P38, PI3K, AKT, and mTORkey proteins in inflammation and autophagy regulation and improved histological outcomes [38].

Butin, a trihydroxyflavonone, protects against mitochondrial dysfunction induced by oxidative stress and functions as an antioxidant, protective agent, and metabolite [50]. In the reviewed study, butin treatment significantly reduced lipid peroxidation ($p < 0.001$) compared to the D-GalN group and restored antioxi-

▶ **Table 1** Characteristics of the studies in vitro evaluating the anti-inflammatory effects of plants of genus Rhus.

Plant	Author, year. Country	Cell line	Groups of study and treatment	Techniques to determine inflammatory mediators
Rhus verniciflua Stokes (Isolated butein)	Roh K. et al., 2020. Korea [24]	Peritoneal macrophage from BALB/c mice under inflammatory stimulus (100 ng/mL LPS)	▪ *Rhus* compound 1, 7j, 7 m, 14a (20 µM) ▪ Non-treatment control	▪ ELISA (TNF-α) ▪ RT-qPCR (Pparγ, C/ebpα, Fabp4, CD36) ▪ WB (Pparγ, C/ebpα, Fabp4)
Rhus verniciflua Stokes (Isolated butein)	Liu Y. et al., 2020. China [25]	SH-SY5Y neuroblastoma cells under inflammatory stimulus (BV2 cells + 10 µg/mL LPS culture supernatants)	▪ *Rhus* compound (1, 10, and 30 µg/mL) ▪ Non-treatment control ▪ Non-inflammatory stimulus control	▪ IHC (NF-κB p65) ▪ qPCR (IL-1β, IL-6, TNF-α, ERK, MEK, Raf-1, NF-κB p65) ▪ WB (Erk, MEK, Raf-1, NF-κB p65)
Rhus verniciflua Stokes (NS)	Kim, B. et al., 2018. Korea [26]	Peritoneal macrophage cells under inflammatory stimulus (100 ng/mL LPS)	▪ *Rhus* extract (200 and 1000 µg/mL) TNF 200, IL-6 1000 ▪ Non-treatment control	▪ ELISA (TNF-α, IL-6, IL-12p70, IFN-γ)
		RAW264.7 cells	▪ *Rhus* extract (12.5, 50, and 200 µg/mL) ▪ Non-treatment control	▪ ELISA (TNF-α, IL-6, IL-12p70, IFN-γ)
Rhus verniciflua Stokes (Isolated dihydrofisetin)	Li, K. K. et al., 2018. China [27]	RAW 264.7 cells under inflammatory stimulus (1 mg/mL LPS)	▪ *Rhus* compound (10, 20, and 40 µg/mL) ▪ Non-treatment control ▪ Non-inflammatory stimulus control	▪ ELISA (PGE2, IL-1β, IL-6, MCP-1, TNF-α) ▪ WB (iNOS, COX-2)
Rhus verniciflua Stokes (NS)	Zheng, W. et al., 2017. China [28]	Primary human osteoarthritis chondrocytes under inflammatory stimulus (10 ng/mL IL-1β)	▪ *Rhus* extract (10 and 50 µM) ▪ Non-treatment control	▪ ELISA (NO, PGE2, TNF-α, IL-6) ▪ qRT-PCR (COX-2, iNOS, MMP-1, MMP3, MMP-13, IL-6, TNF-α, ADAMTS-4, ADAMTS-5, SOX-9, COL-2) ▪ WB (COX-2, iNOS, MMP-13, COL-2, SOX-9, P65, IκB-α)
Rhus chinensis Mill. (Isolated Gallic acid)	Liao et al., 2023. China [29]	GES-1 cells under inflammatory stimulus (3 × 105 mol/L of N-methyl-N′-nitro-N-nitrosoguanidine)	▪ *Rhus* compound (60 and 90 µM respectively) ▪ Non-treatment control ▪ Non-inflammatory stimulus control	▪ RNA sequencing
Rhus chinensis Mill (Herbal mix and isolated pyrogallol)	Chantarasakha K. et al., 2022. Thailand [30]	THP-1 and RAW 264.7 macrophages under inflammatory stimulus (10 ng/mL LPS)	▪ Mix with *Rhus* compound (25 to 500 µg/mL) for THP-1 cells ▪ Mix with *Rhus* compound (12.5 to 250 µg/mL) for RAW 264.7 cells ▪ Non-treatment control ▪ Non-inflammatory stimulus control	▪ ELISA (TNF- α) ▪ RT-qPCR (TNF- α, IL- α, IL-6, COX-2)
Rhus chinensis Mill (NS)	Zhou G. et al., 2021. China [31]	HT-29 Human colon cancer cells under inflammatory stimulus (50 ng/mL rhIL17A and 20 ng/mL TNF-α)	▪ Mix with *Rhus* compound (10, 33, 100, and 300 µg/mL) ▪ Non-treatment control ▪ Non-inflammatory stimulus control	▪ ELISA (IL-17A, IL-1β, IFN-γ, TNF-α) ▪ IHC (IL-17A) ▪ qPCR (TNFR, IL-17RA, IL-17A, HSP90) ▪ WB (IL-17A, TRAF3, ERK, P38, JNK)

continued next page

▶ **Table 1** *Continued*

Plant	Author, year. Country	Cell line	Groups of study and treatment	Techniques to determine inflammatory mediators
Rhus chinensis Mill (NS)	Yu, T. et al., 2021. China [32]	Caco-2 cells under inflammatory stimulus (1 mg/mL LPS)	▪ Mix with *Rhus* compound (10, 33, 100, and 300 µM) ▪ Salazosulfapyridine control (20 mg/100 mg) ▪ Indigo control (100 mg/kg) ▪ Gallic acid control (100 mg/kg) ▪ Indirubin and Ginsenoside Rg1 control ▪ Non-treatment control ▪ Non-inflammatory stimulus control	▪ ELISA (IL-6, IL-1β, IL-2, IL-4, IL-5, IL-10, IL-13, IL-18, IFN- γ, TNF-α) ▪ WB (Tyr705, STAT3, JAK, SOCS3)
Rhus chinensis Mill (Isolated 1,2,3,4,6 penta-O-galloyl-β-D-glucose)	Mendonca P. et al., 2017. United States [33]	BV-2 microglia cells under inflammatory stimulus (1 mg/mL LPS and 200 ng/mL IFNγ)	▪ *Rhus* compound at 25 µM ▪ *Rhus* compound at 25 µM and non-inflammatory stimulus ▪ Non-treatment control ▪ Cells + DMSO	▪ ELISA (MCP-5, MMP-9) ▪ Cytokine antibody arrays (MCP-5, MMP-9)
Rhus coriaria L. (Fruits)	Martinelli, G. et al., 2022. Italy [34]	Human GES-1 gastric epithelial cells under inflammatory stimulus (10 ng/mL TNF-α or bacterium: cell ratio of 50 : 1 of H. pylori)	▪ *Rhus* compound (5, 10, 25, and 50 µg/mL) ▪ Non-treatment control ▪ Non-inflammatory stimulus control	▪ ELISA (IL-6, IL-8) ▪ IF (NF-κB) ▪ WB (NF-κB)
Rhus coriaria L. (Fruits)	Khalil M. et al., 2021. Lebanon [35]	BV-2 cells under oxidative stress (50 µM H2O2) BV-2 under inflammatory stimulus (1 µg/mL LPS)	▪ *Rhus* extract (25 and 50 µg/mL) ▪ Non-treatment control	▪ qRT-qPCR (TNF-α, IL-10, iNOS, COX-2) ▪ WB (NF-$\kappa\beta$)
Rhus coriaria L. (Fruits)	Khalilpour S. et al., 2019. Malaysia [36]	HaCaT cells under inflammatory stimulus (10 ng/mL TNF-α)	▪ *Rhus* extract (10, 25, and 50 µg/mL) ▪ 10 µM Quercetin control ▪ 20 µM Curcumin and EGCG control, respectively ▪ 50 µM pf Resveratrol control ▪ Non-treatment control	▪ ELISA (ICAM-1, VEGF) ▪ NF-κB driven transcription (luciferase) ▪ NF-κB nuclear translocation assay
Rhus coriaria L. (Fruits)	Momeni, A. et al 2019. Iran [37]	Synoviocyte cells from horseradish under inflammatory stimulus (20 ng/mL LPS)	▪ *Rhus* compound (0.01, 0.09, 0.1, 0.9, 1, 9, 10, and 90 µg/mL) ▪ Rhus compound (10 µL) and non-inflammatory stimulus ▪ Ibuprofen (50–100 nM) ▪ Non-treatment control	▪ PCR (COX-2, TNF-α, IL-1β) ▪ RT-qPCR (IL-18, IL-1β)
Rhus succedanea L. (Isolated rhoifolin)	Yan, J. et al., 2021. China [38]	Chondrocytes from Sprague–Dawley rats under inflammatory stimulus (125, 26 y 35 270 ng/mL IL-1β)	▪ *Rhus* compound (5, 10, 20 µM) ▪ Non-treatment control ▪ Non-inflammatory stimulus control	▪ WB (COX-2, iNOS, MMP13, ADAMTS5)
Rhus succedanea L. (Isolated fisetin)	Xu M–X. et al., 2020. China [39]	Primary astrocytes from C57BL/6 mice under inflammatory stimulus (contaminated air with PM2.5 particles)	▪ *Rhus* compound (5, 10, and 20 µg/mL) ▪ Non-treatment control ▪ Non-inflammatory stimulus control	▪ qPCR (IL-1β, TNF-α, IL-6, IL-8, Emr-1, MIP-1α, CXCR4, GFAP, CD11b, IKKα, IκBα, Iba-1, MCP-1)
Rhus tripartite (Leaves, roots, and stems)	Ben-Barka Z. et al., 2018. Belgium [40]	Caco-2 cells under inflammatory stimulus (25 ng/mL IL-1β, 50 ng/mL TNF-α, 50 ng/mL IFN-γ, and 1 µg/mL LPS)	▪ *Rhus* extract (0.8, 1.6, 3.2, and 6.5 µg/mL) ▪ EGCG treatment control ▪ Non-treatment control ▪ Non-inflammatory stimulus control	▪ ELISA (IL-8)

continued next page

▶ **Table 1** *Continued*

Plant	Author, year. Country	Cell line	Groups of study and treatment	Techniques to determine inflammatory mediators
Rhus trilobata Nutt. (Stems)	Rodriguez-Castillo et al., 2024. Mexico [41]	Macrophage J774-A under inflammatory stimulus (5 µg/mL LPS)	▪ *Rhus* compound (15 µg/mL) ▪ Non-treatment control ▪ Dexamethasone control (10 µM) ▪ Non-inflammatory stimulus control	▪ RT-qPCR (IL-6, IL-1β, TNF-α) ▪ Metabolites determination in culture supernatant (PGE2)
Rhus crenata (Isolated butein)	Ohmoto et al., 2024 Japan [42]	RAW264 cells co-cultivated with 3 T3-L1 adipocytes under inflammatory stimulus (LPS at 5 µM and 10 ng/mL)	▪ Non-inflammatory stimulus control (3 T3-L1 adipocytes alone negative control) ▪ Non-inflammatory stimulus control (co-cultures of 3 T3-L1 adipocytes and RAW264 cells without LPS and treatment as negative control) ▪ *Rhus* compound group (co-cultures of 3 T3-L1 adipocytes and RAW264 cells with LPS and treatment at 2 and 5 µM, respectively)	▪ RT-qPCR (β-actin, PPA-Rγ, C/EBP α, adiponectin, aP2, TNFα, IL-6, MCP-1, iNOS, GLUT4, IRS-1)

ADAMTS: A disintegrin and metalloproteinase with thrombospondin motifs; C/ebpα: CCAAT enhancer binding protein α Fabp4: Fatty acid-binding protein 4; CD11b: Cluster of differentiation molecule 11B; CD36: platelet glycoprotein 4; COL2: Collagen type II; COX2: Cyclooxygenase type 2; CXCR4: G-protein-coupled chemokine receptor; DMSO: Dimethylsulfoxide; EGCG: Epigallocatechin-3-gallate.; ELISA: Enzyme-Linked ImmunoSorbent Assay; Emr-1: adhesion G protein-coupled receptor E1; ERK: Extracellular-Signal-Regulated Kinase; GFAP: Glial fibrillary acidic protein; HSP90: heat shock protein 90; Iba 1: Allograft inflammatory factor-1; ICAM: intercellular adhesion molecules; IF: Immunofluorescence; IHC: Immunohistochemistry; IKKa: IκB kinase α; IL: Interleukin; INF: Interferon; iNOS: Inducible nitric oxide synthase; IκB: Inhibitor of NF-κB; IκBα: Inhibitor of nuclear factor-κB α; JAK: Janus kinase; JNK: Jun N-terminal kinase; LPS: Lipopolysacharide; MCP: Membrane cofactor protein: MMP: Matrix metalloproteinases; MEK: Mitogen-activated protein kinase kinase; MIP-1α: Macrophage inflammatory protein-1α; MMP: Matrix metalloproteinase; NF-κB: nuclear enhancer factor of kappa light chains of activated B cells; p38: Mitogen-activated protein kinases; PGE2: Prostaglandin E2; Ppary: Peroxisome proliferator-activated receptor gamma; qPCR: quantitative polymerase chain reaction; Raf: Rapidly accelerated fibrosarcoma; RT-qPCR: Quantitative reverse transcription polymerase chain reaction; SOCS: Suppressor of cytokine signaling proteins; SOX: Supercritical Oxygen; STAT3: signal transducer and activator of transcription 3; TNF: Tumor necrosis factor; TNFR: Tumor Necrosis Factor Receptor; TRAF3: TNF receptor-associated factor; Tyr705: Phospho-Stat3; VEGF: Vascular endothelial growth factor; WB: Western blot

dant enzyme activities (GSH, SOD, and CAT). It also prevented the elevation of proinflammatory cytokines (TNF-α, IL-1β, and IL-6) induced by D-GalN ($p < 0.05$). Additionally, butin (25 and 50 mg/kg) markedly reduced MPO activity compared to the D-GalN control group ($p < 0.001$) [51].

Three *in vitro* assays were performed on cell cultures subjected to proinflammatory lipopolysaccharide stimulation. Two of these assays utilized Pyrogallol (▶ **Fig. 1 c**), a benzenetriol with hydroxy groups at positions 1, 2, and 3 [52], derived from *Rhus chinensis* Mill. Chataraska et al. [30] demonstrated its anti-inflammatory effects (▶ **Table 2**). The third assay used an aqueous extract from the infused stems of *Rhus trilobata* Nutt. [41].

Additional plant-derived compounds, including fisetin (▶ **Fig. 1 c**) from *Rhus succedanea* L., were also tested. Fisetin is an orally bioavailable polyphenol found in many fruits and vegetables, with potential antioxidant, neuroprotective, anti-inflammatory, antineoplastic, senolytic, and longevity-promoting activities. Upon administration, fisetin scavenges free radicals, protects cells from oxidative stress, and can upregulate glutathione. It inhibits proinflammatory mediators, such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, and nuclear factor kappa β (NF-$\kappa\beta$) [53]. Xu et al. [39] investigated its effects on primary astrocytes through nanoemulsion formulations employing various solvents, demonstrating its anti-inflammatory effect (▶ **Table 2**).

The included studies reported nine cell types that tested the anti-inflammatory potential of *Rhus*. Macrophage cultures were particularly interesting, comprising three subtypes: RAW macrophages from the peritoneum [26, 30], macrophages J744-A [41], and THP-1 macrophages [30]. BV-2 microglial cells [25, 33, 35], CaCo2 colon cancer cells [32, 40], gastric epithelial cells (GES)-1 [29, 34], and HT-29 colon cancer cells [31] were also frequently reported. Different cell lines, including HaCaT keratinocytes [36], SH-SY5Y cells [25], primary astrocytes [39], primary bovine synoviocytes [37], primary rat chondrocytes [38], and primary human cartilage chondrocytes [28] were used in only one study. These studies showed the reduction in various intra- and extracellular mediators, including proinflammatory cytokines, suggesting the anti-inflammatory effect of *Rhus* in all tested cell lines (▶ **Table 2**).

Regarding the treatment doses, most studies tested different treatment concentrations, with some evaluating eight [37], four [31, 32, 34, 38, 40], three [25–27, 36, 39], or two [26, 28–30, 35, 42] different concentrations. Only three studies evaluated a single concentration [24, 33, 41]. A consistent pattern was observed: the highest concentration consistently showed the most effectiveness in reducing proinflammatory mediators, regardless of the administration route.

The primary outcomes measured were the changes in the concentration of intra- and extracellular inflammatory mediators

▶ **Table 2** Modulation of intra- and extracellular mediators by plants of genus Rhus in vitro.

Plant	TNF-α	IL-1β	IL-6	IL-8	COX-2	iNOS	NF-κβ P65	INF-γ	MIP-1a	Other
Rhus verniciflua stokes [24]	↓									↓ PPAR-γ, CD36. C/ebp-α, Fabp-4
Rhus verniciflua stokes [25]	↓	↓	↓				↓			↓ ERK, MEK, Raf-1
Rhus verniciflua stokes [26]	↓		↓					↑		↑ IL-12 p70
Rhus verniciflua stokes [27]	↓	↓	↓		↓	↓	↓		↓	↓ PGE2
Rhus verniciflua stokes [28]	↓		↓		↓	↓				↓ PGE2, MMP-13, ADAMTS-5, MMP-1, κBα, ADAMTS-4, NO, SOX-9, COL-2, p65
Rhus chinensis Mill. [29]										↓ TGFβ, p53 ↑ VEGF, Wnt, IL-17, MAPK
Rhus chinensis Mill. [30]	↓		↓		↓					↓ IL-1α
Rhus chinensis Mill. [31]	↓	↓						↓		↓ IL-17A, IL17RA, TNFR, ERK, HSP90, TRAF3, p38, JNK
Rhus chinensis Mill. [32]	↓	↓	↓					↓		↓ IL-10, IL-18, IL-2, IL-4, IL-13, IL-5, JAK2, STAT3, Tyr705, SOCS-3
Rhus chinensis Mill. [33]										↓ MMP-9, MCP-5
Rhus coriaria L. [34]			↓	↓			↓		↓	NA
Rhus coriaria L. [35]	↓		↓		↓	↓	↓			↓ IL-10
Rhus coriaria L. [36]										↓ MMP-9, ICAM-1, VEGF1
Rhus coriaria L. [37]	↓	↓			↓					↓ IL-18
Rhus succedanea [38]		↓			↓	↓				↓ MMP-13, ADAMTS-5
Rhus succedanea L. [38]	↓	↓	↓	↓					↓	↓ Emr-1, CXCR-4, GFAP, MCP1, CD11b, Iκκα, κBα, Iba-1
Rhus tripartite [40]				↓						NA
Rhus trilobata Nutt. [41]	↓	↓	↓							↓ PGE2
Rhus crenata [42]	↓		↓			↓				↓ β-actin, PPAR-γ, C/EBP α, adiponectin, aP2, MCP-1, GLUT4, IRS-1

ADAMTS: A disintegrin and metalloproteinase with thrombospondin motifs; CD11b: Cluster of differentiation molecule 11B; CD36: platelet glycoprotein; COL2: Collagen type II; COX2: Cyclooxygenase type 2; CXCR4: G-protein-coupled chemokine receptor; Emr-1: adhesion G protein-coupled receptor E1; ERK: Extracellular-Signal-Regulated Kinase; GFAP: Glial fibrillary acidic protein; HSP90: heat shock protein 90; Iba 1: Allograft inflammatory factor-1; ICAM: intercellular adhesion molecules; IKKa: IκB kinase α; IL: Interleukin; INF: Interferon; iNOS: Inducible nitric oxide synthase; IκBα: Inhibitor of nuclear factor-κB α; JAK: Janus kinase; JNK: Jun N-terminal kinase; MCP: Membrane cofactor protein; MMP: Matrix metalloproteinases; MEK: Mitogen-activated protein kinase kinase; MIP-1α: Macrophage inflammatory protein-1α; MIP-1α: Macrophage inflammatory protein-1α; NF-κB: nuclear enhancer factor of kappa light chains of activated B cells; NO: Nitric oxide; p38: Mitogen-activated protein kinases; p65: ribosome-associated protein; Pparγ: Peroxisome proliferator-activated receptor gamma, C/ebpα: CCAAT enhancer binding protein α; Raf: Rapidly accelerated fibrosarcoma; SOCS: Suppressor of cytokine signaling proteins; SOX: Supercritical Oxygen; STAT3: signal transducer and activator of transcription 3; TNF: Tumor necrosis factor; TNFR: Tumor necrosis factor receptor; TRAF3: TNF receptor-associated factor; Tyr705: Phospho-Stat3; VEGF: Vascular endothelial growth factor

(▶ **Table 1**). The laboratory techniques most frequently used were the enzyme-linked immunosorbent assay (ELISA), followed by Western blot (WB) and reverse transcription (RT)–qualitative polymerase chain reaction (qPCR). Immunohistochemistry (IHC), immunofluorescence (IF), qPCR, and antibody microarray assays were also used. TNF-α was the most commonly measured mediator, with 13 studies demonstrating its reduction following *Rhus* treatments. IL-6, the second most evaluated mediator, decreased in 11 studies, while IL-1β decreased in 8. A decrease in inflammatory mediators was observed in nearly all the studies, except for Kim et al. [26], where INF-γ and IL-12p70 were increased by *Rhus* treatment, and Liao et al., where VEGF, Wnt, IL-17, and MAPK pathways were increased by GA isolated from *Rhus* plants derivates [29] (▶ **Table 2**).

Anti-inflammatory effects of rhus genus plants in in vivo and human studies

Twenty-three articles were conducted *in vivo* using animal models of inflammation, and only one was done in humans (▶ **Table 3**). Eight of these also included *in vitro* assays. The plants used in the *in vivo* studies were *Rhus verniciflua, Rhus chinensis* Mill, *Rhus coriaria* L., *Rhus succedanea*, and *Rhus trilobata* Nutt.

Compounds isolated from the *Rhus* genus were used in six *in vivo* studies [24, 27, 39, 51, 55, 58]; however, most included studies did not fully detail the active compounds tested, including those in which aqueous or methanol extract or a macerate or fermented components were used [26, 41, 43, 54, 57, 59, 61, 64, 66–72]. Two studies tested a mixture of plants that included *Rhus* [31, 32].

Four different rodent strains were reported to be used to evaluate the anti-inflammatory effect of *Rhus in vivo*; additionally, one study was carried out in humans [67] (▶ **Table 2**). Inflammation models in BALB/c [24, 26, 29, 32, 59, 69] and C57BL/6 [39, 54, 55, 61] mice were the most used, followed by the Sprague–Dawley rats used in three studies [32, 43, 54], two studies used Wistar rats [41, 51], one was conducted under Specific Pathogen Free [58], and Kunming mice were used in two studies [70, 71].

The inflammation models and the treatment durations with *Rhus* are shown in ▶ **Table 3**. The most common inflammation models were those of the gastrointestinal tract [29, 31, 32, 54, 57, 58, 62, 68, 71] and liver [51, 61, 62, 64, 66, 69, 70]. However, the effect of Rhus was also evaluated in models of edema [24, 27, 41], neuroinflammation [39, 55], and periodontitis [56]. Treatment durations ranged from hours to weeks, with the shortest being 4 hours in the carrageenan-induced paw edema model and the longest being 20 weeks in the gastric precancerous lesions in BALB/c mice (▶ **Table 3**).

Compounds isolated from the plants were evaluated in seven *in vivo* studies, including butin [51], butein [24, 55], dihydrofisetin [27] isolated or derived from *Rhus verniciflua* Stokes, tannic acid [58] from *Rhus Chinensis* Mill., and fisetin [39] derived from *Rhus succedanea* L. Notably, all of these compounds showed effects in reducing the inflammatory process. Additionally, two studies tested mixed compounds formulated from various plants containing *Rhus Chinensis* [31, 69].

As in *in vitro* studies, most *in vivo* studies tested different treatment doses, with studies evaluating four [54], three [31, 39, 41, 57], or two [26, 27, 29, 32, 43, 51, 59, 61, 65, 66, 69, 71, 73] doses and some using a single concentration [24, 55, 67, 68]. The doses were applied in various ranges, from 5 to 800 mg/kg body weight when injected, as reported by most studies, or from 0.1 to 16 mg/ml when administered in drinking water, as reported by two studies. The most commonly used doses were 400 and 800 mg/kg body weight (▶ **Table 3**). In the reviewed studies, a consistent pattern was observed regardless of dose: the highest concentration consistently proved to be the most effective in reducing proinflammatory mediators, irrespective of the administration route.

The laboratory techniques for assessing the modification of cytokines and other inflammatory mediators used *in vivo* included predominantly protein detection by ELISA followed by WB and, less frequently, IF. As in *in vitro* studies, the inflammatory mediator most commonly measured in the experiments was TNF-α, followed by IL-6 and IL-1β, although 54 different molecules were evaluated. No specific pattern of inflammatory mediators was observed in the models of acute inflammation (hours or days) or chronic inflammation (weeks).

As shown in ▶ **Table 4**, the anti-inflammatory effect of all the *Rhus* species, through any form of administration (components, dosage, and route of administration), was shown to decrease the expression of the classic inflammatory mediators TNF-α, IL-1β, and IL6. Moreover, the potential of *Rhus* to reduce more than 50 extra- and intracellular mediators, including receptors, signal molecules, and transcriptor factors, was demonstrated.

Predicted cellular mechanisms for the anti-inflammatory effect of Rhus plants

We identified 57 different inflammatory mediators in *in vitro* studies (▶ **Table 2**) and 54 in *in vivo* studies to be underexpressed by plants of the genus *Rhus* or its components. Altogether, 84 inflammatory mediators were identified and subsequently analyzed in the Reactome bioinformatic platform to obtain the prediction and overrepresentations of cellular processes and signaling pathways shown in ▶ **Fig. 4**.

Sixty-nine proteins underexpressed by *Rhus* were associated with the immune system signaling pathway (p = 1.11E-16, FDR: 1.32E-14) (▶ **Fig. 4d**). Within this pathway, 23 proteins were related to innate immune system signaling (p = 7.83E-4, FDR: 4.87E-3) and 63 with cytokine signaling in immune system pathways (p = 1.11E-16, FDR: 1.32E-14) as shown in ▶ **Fig. 4b** and **c**, respectively. A more detailed visualization of signaling by interleukins showed that signaling from the families of IL-10 (22 proteins, p = 1.11E-16, FDR: 1.32E-14), IL-4/13 (47 proteins, p = 1.11E-16, FDR: 1.32E-14) and IL-1 (14 proteins, p = 6.3E-10, FDR: 7.67E-8) was the most significantly associated within cytokine-mediated signaling (▶ **Fig. 4a**).

Materials and Methods

Study selection

This review was conducted following the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (http://prisma-statement.org/) [75]. A comprehensive literature search was performed using the databases

▶ **Table 3** Characteristics of the studies in vivo and in humans evaluating the anti-inflammatory effects of plants of genus Rhus.

Plant	Author, year. Country	Animal Model	Groups of study and treatment	Techniques to determine inflammatory mediators
Rhus verniciflua Stokes (Isolated butein)	Althurwi et al., 2023 Saudi Arabia [51]	Hepatic injury in Wistar rats (21 days)	▪ *Rhus* compound (25 and 50 mg/kg i. p.) ▪ Non-treatment control ▪ Non-Inflammation and no-treatment control	▪ Immunoassay (TNF-α, IL-1β and IL-6) in serum
Rhus verniciflua Stokes (Bark)	Kim S. et al., 2021. Korea [54]	Helicobacter pylori-induced gastritis model in C57 BL/6 J mice (49 days)	▪ *Rhus* extract (3, 4, 6, 8, and 16 mg/mL d. w.) ▪ Metronidazole (400 mg/kg) + Omeprazole (20 mg/kg) + Clarithromycin (250 mg/kg) + Rhus extract mixed d. w. control ▪ Non-treatment control	▪ ELISA (TNF-α, IL-1β)
Rhus verniciflua Stokes (Isolated butein)	Roh, K. et al., 2020. Korea [24]	Lymphedema model in BALB/c mice (7 days)	▪ *Rhus* compounds (200 mg/kg b. w.) ▪ Non-treatment control ▪ Non-inflammation and Rhus compounds treatment control	▪ qPCR (Pparγ, C/ebpa, Fabp4, CD36) ▪ WB (Pparϒ, Fabp4)
Rhus verniciflua Stokes (Isolated butein)	Zhu, Y. et al., 2019. China [55]	Sepsis-induced brain injury model in C57BL/6 mice (48 h)	▪ *Rhus* compound (10 mg/kg b. w.) ▪ *Rhus* compound (10 mg/kg b. w.) + EX-527 (5 mg/kg b. w.) ▪ EX-527 (5 mg/kg b. w.) control ▪ Non-treatment control ▪ Non-inflammation and Rhus compound treatment control	▪ ELISA (IL-6, TNF-α, IL-1β) ▪ WB (Bcl2, Bax, SIRT1, Ac-FOXO1, NF-κβ, Ac–p53, SIRT1)
Rhus verniciflua Stokes (NS)	Kim, B. et al., 2018. Korea [56]	Peritonitis-induced model in BALB/c mice model (6 days)	▪ *Rhus* compound (20 and 100 mg/kg b. w.) ▪ Non-treatment control	▪ ELISA (TNF-α, IL-6)
Rhus verniciflua Stokes (Isolated dihydrofisetin)	Li, K. K. et al., 2018. China [27]	Carrageenan-induced paw edema model in mice (4 h)	▪ *Rhus* compound (50 or 100 mg/kg b. w.) ▪ Non-treatment control ▪ Non-inflammation control	▪ ELISA (IL-6, TNF-α) ▪ WB (iNOS, COX-2)
Rhus verniciflua Stokes (NS)	Kim, H. et al., 2017. Korea [57]	Emesis and gastrointestinal inflammation-induced model in Sprague–Dawley rats (5 days)	▪ *Rhus* extract (25, 50, and 100 mg/kg mg/kg b. w.) ▪ Metoclopramide control (25 mg/kg b. w.) ▪ Non-treatment control ▪ Non-inflammation control	▪ ELISA (TNF-α, IL-6) ▪ qPCR (5HT3A, SERT)
Rhus chinensis Mill. (Isolated tannic acid)	Wang et al., 2024. China [58]	DSS-induced colitis model in SPF mice (16 days)	▪ Non-inflammation control ▪ Non-treatment control ▪ *Rhus* compound (0.1, 1, 3 mg/ml d. w.) ▪ Non-inflammation + Rhus compound control	▪ PCR (IL17F, IL-1β, TNF-α) ▪ IHC (IL17F, NFκβ) ▪ RT-qPCR (TNF-α, IL-1β, NFκβ p65, Uhrf1, Mettl17, Asf1b) ▪ WB (Asf1b, Mett17b) ▪ Transcriptome profiles (Chil1, S100A8, S100A9, SphK1, Mmp11, Mmp14, Ccl3, TNF-α, IL1β, IL6, IL17A, IL17F, IL17ra e IL17rb)
Rhus chinensis Mill. (Fruits)	Ma et al., 2023 China [59]	Acetaminophen-induced liver injury in BALB/c, mice BALB/c (7 days)	▪ Rhus extract (400 and 800 mg/kg b. w.) ▪ Non-treatment control ▪ Non-inflammation control	▪ WB (CYP2E1, p-NF-κB/NF-κB, N-NF-κB, COX-2, p- JNK/JNK, p-ERK/ERK, p-P38/P38, p-Akt/Akt, Bax, Bcl-2)

continued next page

▶ **Table 3** *Continued*

Plant	Author, year. Country	Animal Model	Groups of study and treatment	Techniques to determine inflammatory mediators
Rhus chinensis Mill. (Fruits)	Liao et al., 2023. China [29]	Gastric precancerous lesions in BALB/c mice (20 weeks)	▪ *Rhus* compound (5 and 20 mg/kg b.w.) ▪ Non-treatment control ▪ Non-inflammation control	▪ IHC (Wnt 10B, β-catenin) ▪ WB (Wnt 10B, β-catenin, E-cadherin, N-cadherin, and vimentin).
Rhus chinensis Mill. (Fruits)	Zhang et al., 2022. China [43]	Necrotizing enterocolitis model in Sprague–Dawley rat pups (4 days)	▪ *Rhus* extract (200 and 400 mg/kg, respectively) ▪ Non-treatment control ▪ Non-inflammatory stimulus control	▪ IF (Occludin, ZO-1, NrF2) ▪ WB (NQO1, NrF2, NF-κB, pNF-κB, iNOS, Bax, Bcl-2, Caspase-3) ▪ IHC (TLR4, pNF-κB)
Rhus chinensis Mill. (Fruits)	Ma et al., 2022. China [60]	Indomethacin-induced gastric ulcer in Kunming mice (28 days)	▪ Non-treatment control ▪ Non-inflammation control ▪ *Rhus* compound (400 and 800 mg/kg b.w.)	▪ IHC (p-NF-κB) ▪ IF (Nrf2 and p-NF-κB) ▪ WB (IKB-α, p-IKB-α, NF-κB, p-NF-κB and iNOS). ▪ Biochemical indicators in plasma (IL-1β, IL-6, TNF-α, AOPP and PGE2)
Rhus chinensis Mill. (Fruits)	Sun, Y. et al., 2022. China [61]	Cholestasis model in C57 BL/6 J mice (30 days)	▪ *Rhus* extract (400 and 800 mg/kg b.w.) ▪ Non-treatment control ▪ Non-inflammation control	▪ ELISA (IL-6, TNF-α, IL-1β) ▪ IHC (TGF-β y α-SMA) ▪ WB (NF-κB, IκBα, BSEP y MRP2)
Rhus chinensis Mill. (Fruits)	Sun Y. et al., 2023. China [62]	Isoniazid+ rifampicin-induced liver injury in BALB/c, mice (28 days)	▪ *Rhus* extract (400 and 800 mg/kg b.w.) ▪ Non-treatment control ▪ Non-inflammation control	▪ ELISA (IL-6, TNF-α, IL-1β) ▪ WB (Nrf2, HO-1, NQO1, CYP2E1, Bax, Bcl-2)
Rhus chinensis Mill. (NS mix)	Zhou G. et al., 2021. China [31]	Colitis-induced model in BALB/c mice (7 days)	▪ Mix with *Rhus* compound: gallic acid, lutein, and quercetin (50, 100, and 200 mg/kg b.w., respectively) ▪ Gallic acid 50 mg/kg b.w. control ▪ Lutein 100 mg/kg b.w. control ▪ Quercetin 200 mg/kg b.w. control ▪ 5-aminosalicylic acid at 200 mg/kg b.w. control ▪ Non-treatment control ▪ Non-inflammation control ▪ Non-inflammation and Mix with *Rhus* compound treatment control	▪ qPCR (IL-17A, ACT1, Hsp90) ▪ ELISA (IL-10, TNF-α, IL-1β, IFN-ϒ, IL-17A) ▪ IHC (IL-17A) ▪ qPCR (IL-17A, ACT1, Hsp90) ▪ WB (IL-17A, Hsp90, ERK, JNK, P38, IκBα, and iNOS)
Rhus chinensis Mill. (NS mix)	Yu, T. et al., 2021. China [32]	Ulcerative colitis model in Sprague–Dawley rats (24 h)	▪ Mix with *Rhus* compound (140 and 280 mg/kg b.w.) ▪ 2,4,6-Trinitrobenzenesulfonic acid control ▪ Non-treatment control ▪ Non-inflammation control	▪ ELISA (IL-6) ▪ qPCR (TNF-α, IL-6, IL-1β) ▪ WB (Tyr705, STAT3, JAK2, SOCS3, SOCS1, CASP1, IL-1β, ASC)
Rhus chinensis Mill. (Fruits)	Sun Y. et al., 2021. China [63]	Acetaminophen-induced liver injury in BALB/c mice (7 days)	▪ *Rhus* extract (400 and 800 mg/kg b.w.) ▪ Non-treatment control ▪ Non-inflammation and *Rhus* extract treatment control	▪ ELISA (IL-6, IL-1β, TNF-α) ▪ IF (anti-Nrf2) ▪ WB (Nrf2, HO-1, NQO1, CYP2E1, NF-κB, COX-2, JNK, ERK, P38, PI3K, Akt, Bax and Bcl-2)

continued next page

▶ **Table 3** *Continued*

Plant	Author, year. Country	Animal Model	Groups of study and treatment	Techniques to determine inflammatory mediators
Rhus chinensis Mill. (Fruits)	Wu et al., 2020. China [64]	Nonalcoholic fatty liver disease in rats Sprague–Dawley (12 weeks)	▪ *Rhus* extract (200 and 600 mg/kg b. w.) ▪ Non-treatment control ▪ Non-inflammation and treatment control	▪ WB (PPAR-α, CPT1, PPAR-γ, β-Actin, CYP2E1, P38, p-P38, p-NFκβ, iNOS, COX-2, β-Actin) ▪ IF (p-NFκβ)
Rhus chinensis Mill. (Fruits)	Zhou J. et al., 2020. China [65]	Liver fibrosis-induced model in Kunming mice (6 weeks)	▪ *Rhus* extract (400 and 800 mg/kg b. w.) ▪ Non-treatment control ▪ Non-inflammation and *Rhus* extract treatment control	▪ ELISA (IL-1β, IL-6, TNF-α) ▪ IF (anti-MMP9 and anti-TIMP2) ▪ IHC (p-NF-κB, p-P38, PPAR-γ) ▪ qPCR (TNF-α, TGF-β1, Bax, Bcl-2) ▪ WB (TGF-β1, α-SMA, COX-2, iNOS, Bax, Bcl-2)
Rhus coriaria L. (Fruits)	El-Elimat et al., 2023. Jordan [66]	Paracetamol-induced liver toxicity in a male Wistar rat model of hepatotoxicity (29 days)	▪ *Rhus* 25 mg/kg + paracetamol ▪ *Rhus* 50 mg/kg + paracetamol ▪ Negative control ▪ Hepatotoxic control (paracetamol 3 g/kg) ▪ Silymarin positive control (silymarin 100 mg/kg + paracetamol).	▪ qPCR (TNF-α and IL-6) ▪ IHC (TNF-α and IL-6)
Rhus coriaria L. (Fruits)	Hariri, N. et al., 2020. Iran [67]	Women with depression and obesity (6 weeks)	▪ *Rhus* compound (1,000 mg/kg b. w.) ▪ Non-treatment control	▪ ELISA (TNF-α, IL-6)
Rhus coriaria L. (NS)	Isik, S. et al., 2019. Turkey [68]	Necrotizing enterocolitis-induced model in rats (4 days)	▪ *Rhus* extract (2 mL/kg) ▪ Saline solution (2 mL/kg) ▪ Non-treatment control	▪ ELISA (TNF-α, IL-6) ▪ IHC (CASP-3, CASP-8, CASP-9)
Rhus succedanea L. (Isolated fisetin)	Xu M. et al., 2020. China [39]	Neuroinflammation-induced model in C57BL/6 mice (14 weeks)	▪ *Rhus* extract (5, 10, and 20 mg/kg b. w.) ▪ Non-treatment control ▪ Non-Inflammatory stimulus and *Rhus* extract treatment control	▪ qPCR (IL1β, IL-6, TNF-α, IL-8, Emr-1, MIP-1α, CXCR4, GFAP, CD11b, IKKα, IκBα, Iba-1, MCP-1) ▪ WB (IKKβ, IκBα, NF-κβ, GFAP)
Rhus trilobata Nutt. (Stems)	Rodriguez-Castillo et al., 2024. Mexico [41]	LPS-induced paw edema model in Wistar rats (24 h)	▪ *Rhus* compound at 500, 750, or 1000 µg, respectively (50 µL of 10 mg/mL) ▪ Non-treatment control ▪ Dexamethasone control (500 µg) ▪ Non-inflammatory stimulus control	▪ IHC (IL-1β y COX-2)

5HT3A: 5-Hydroxytryptamine Receptor 3A; Ac-FOX01: Acetyl forkhead box protein O; Ac–p53: acetyl-tumor suppressor protein; ACT1: Nuclear factor-kappa-B activator 1; AKT: Protein kinase B; ASC: Apoptosis-associated speck-like protein containing; b.w: body weight; Bax: Bcl-2-associated X protein; Bax: Bcl-2-associated X protein; Bcl-2: B-cell lymphoma 2; Bcl2: inhibitor of the anti-apoptotic protein B-cell lymphoma 2; BSEP: bile salt export pump; C/ebpα: CCAAT enhancer binding protein α CD36: platelet glycoprotein 4; CASP: Caspase; CD11b: Cluster of differentiation molecule 11B; CD36: platelet glycoprotein 4; COX2: Cyclooxigenase type 2; CXCR4: C–X-C chemokine receptor type 4; CYP2E1: Cytochrome P450 family 2 subfamily E; d.w: drinking water; ELISA: Enzyme-Linked ImmunoSorbent Assay; Emr-1: adhesion G protein-coupled receptor E1; ERK: Extracellular-signal-regulated kinase; EX-527: Selisistat, Sirtuin Inhibitor; Fabp4: Fatty acid-binding protein 4; GFAP: Glial fibrillary acidic protein; HO-1: Heme oxygenase 1; Hsp90: heat shock protein 90 kDa; Iba 1: Allograft inflammatory factor; IF: Immunofluorescence; IFN-ϒ: Gamma interferon; IHC: Immunohistochemistry; IKKa: IκB kinase α; IKKβ: Inhibitor kappa-B kinase β; IL: Interleukine; iNOS: Inducible nitric oxide synthase; IκBα: inhibitor of nuclear factor kappa B; IκBα: Inhibitor of nuclear factor-κB; JAK2: Janus kinase; JNK: Jun N-terminal kinase; LPS: Lipopolysacharide; MCP: Membrane cofactor protein; MIP-1α: Macrophage inflammatory protein-1α; MMP9: Matrix Metallopeptidase 9; MRP2: Multidrug resistance-associated protein 2; NF-κB: nuclear enhancer factor of kappa light chains of activated B cells; NQO1: NAD (P)H quinone dehydrogenase 1; Nrf2: Nuclear factor erythroid-derived 2-like 2; NS: Not specified; p38: mitogen-activated protein kinases; PI3K: Phosphatidylinositol-3-kinase; Ppary: Peroxisome proliferator-activated receptor gamma; qPCR: quantitative polymerase chain reaction; SERT: serotonin transporter protein; SIRT1: Sirtuin 1; SOCS: Suppressor of cytokine signaling proteins; STAT3: signal transducer and activator of transcription 3; TGF-β: transforming growth factor; TGF-β: Transforming growth factor beta; TIMP2: Tissue inhibitor of metalloproteinases 2; TNF: Tumor Necrosis Factor; Tyr705: Phospho-STAT3; WB: Western blot.; α-SMA: alpha smooth muscle Actin

▶ **Table 4** Modulation of intra- and extracellular mediators by plants of genus Rhus in vivo and in human studies.

Plant	TNF-α	IL-1β	IL-6	COX-2	iNOS	NF-κβ P65	Bax	Bcl-2	p38	Other
Rhus verniciflua Stokes [51]	↓	↓	↓							NA
Rhus verniciflua Stokes [54]	↓									↓ PparϒC/ebpα, Fabp4, CD36
Rhus verniciflua Stokes [24]		↓								NA
Rhus verniciflua Stokes [55]	↓	↓	↓			↓	↓	↑		↓ SIRT1, p53
Rhus verniciflua Stokes [26]	↓		↓							NA
Rhus verniciflua Stokes [27]	↓		↓	↓	↓					NA
Rhus verniciflua Stokes [57]	↓		↓							↓ 5HT3A, SERT
Rhus chinensis Mill. [58]	↓	↓	↓			↓				↓ IL-17F, Chil1, S100A8, S100A9, SphK1, Mmp11, Mmp14, Ccl3, IL17A, IL17F, IL17ra e IL17rb
Rhus chinensis Mill. [59]										↓ Wnt 10B, β-catenin, E-cadherin, N-cadherin, vimentin
Rhus chinensis Mill. [29]	↓	↓	↓		↓	↓				↓ IKB-α, p-IKB-α, AOP, PGE2 ↑ Nrf2
Rhus chinensis Mill. [43]	↓		↓		↓	↓	↓	↑		↓ TOS, MPO, MDA, TLR4, cleaved CASP-3 ↑ TAS, SOD, GSH-Px, NQO1, Nrf2
Rhus chinensis Mill. [60]	↓	↓	↓		↓	↓	↓	↑		↓ PGE2, AOPP, p-IκBα/IκBα, p-NF-κB/NF-Kb, CASP-3 ↑ Nrf2, HO-1 y NQO1
Rhus chinensis Mill. [61]	↓	↓	↓							NA
Rhus chinensis Mill. [69]	↓	↓	↓	↓		↓	↓	↑		↓ Nrf2, HO-1, NQO1, CYP2E1, p-JNK JNK, p-ERK, ERK, p-P38, P38, PI3K, p-PI3K, Akt, p-Akt
Rhus chinensis Mill. [31]	↓	↓			↓				↓	↓ IL-10, IFN-γ, IL-17A, ERK, JNK, IκBα, ACT1, HSP90
Rhus chinensis Mill. [32]	↓	↓	↓							↓ STAT3, Tyr705, SOCS1, SOCS3, CASP-1, JAK2, ASC
Rhus chinensis Mill. [62]	↓	↓	↓	↓		↓	↓	↑	↓	↓ IL-8, ERK, JNK, Nrf2, NQO1, CYP2E1, Akt, PI3K
Rhus chinensis Mill. [64]				↓	↓	↓			↓	↓ PPAR-α, CPT1, PPAR-γ, β-Actin, CYP2E1, p-P38, β-Actin
Rhus chinensis Mill. [65]	↓	↓	↓	↓	↓	↓	↓	↑	↓	↓ Pparγ, MMP-9, TGFβ, α-SMA, TIMP2
Rhus coriaria L. [66]	↓		↓							NA
Rhus coriaria L. [67]	↓		↓							NA
Rhus coriaria L. [68]	↓		↓							↓ CASP-3, CASP-8, CASP-9

continued next page

▶ **Table 4** *Continued*

Plant	TNF-α	IL-1β	IL-6	COX-2	iNOS	NF-κβ P65	Bax	Bcl-2	p38	Other
Rhus succedanea L. [74]	↓	↓	↓			↓				↓ IκBα, Emr-1, CXCR4, GFAP, CD11b, IKKα, IKKβ, Iba-1, MIP-1α
Rhus trilobata Nutt. [41]		↓		↓						NA

5HT3A: 5-Hydroxytryptamine Receptor 3A; ACT1: Nuclear factor-kappa-B activator 1; AKT: Protein kinase B; ASC: Apoptosis-associated speck-like protein containing; Bax: Bcl-2-associated X protein; C/ebpα: CCAAT enhancer binding protein α; CASP: caspase protein; CD11b: Cluster of differentiation molecule 11B; CD36: platelet glycoprotein 4; COX: Cyclooxygenase type 2; CXCR4: C–X-C chemokine receptor type 4; CYP2E1: Cytochrome P450 family 2 subfamily E; Emr-1: adhesion G protein-coupled receptor E; ERK: Extracellular-signal-regulated kinase; Fabp4: Fatty acid-binding protein 4; GFAP: Glial fibrillary acidic protein; Hsp90: heat shock protein 90 kDa; Iba 1: Allograft inflammatory factor; IFN-Ɣ: Gamma interferon; IKKa: IκB kinase α; IL: Interleukin; IκBα: Inhibitor of nuclear factor-κB; JAK2: Janus kinase; JNK: Jun N-terminal kinase; MIP-1α: Macrophage inflammatory protein-1α; MMP9: Matrix Metallopeptidase 9; NA: Not apply; NF-κB: nuclear enhancer factor of kappa light chains of activated B cells; NQO1: NAD(P)H quinone dehydrogenase 1; Nrf2: Nuclear factor erythroid-derived 2-like 2; p38: mitogen-activated protein kinases; p53: tumor suppressor; PI3K: Phosphatidylinositol-3-kinase; Ppary: Peroxisome proliferator-activated receptor gamma; SERT: serotonin transporter protein; SIRT1: Sirtuin 1; SOCS: Suppressor of cytokine signaling proteins; STAT3: signal transducer and activator of transcription 3; TGF-β: Transforming growth factor beta; TIMP2: Tissue inhibitor of metalloproteinases 2; TIMP2: Tissue inhibitor of metalloproteinases 2; TNF: Tumor necrosis factor; Tyr705: Phospho-STAT3; α-SMA: alpha smooth muscle actin

of PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Elsevier ScienceDirect (https://www.sciencedirect.com/). The search utilized the keyword combination "inflammation" AND "Rhus" and was restricted to articles published between January 1, 2018, and December 27, 2024. Automation tools were used to filter results, and duplicate entries were removed.

Inclusion criteria specified original *in vitro, in vivo*, or human clinical studies that investigated the anti-inflammatory effects of plants from the genus *Rhus* or its components by assessing intra- or extracellular inflammatory mediators. Articles were excluded if they: (1) were reviews or meta-analyses; (2) did not refer to the genus *Rhus*; (3) lacked experimental *in vitro, in vivo*, or human clinical trials; (4) did not assess the anti-inflammatory effect; or (5) were published in languages other than English or Spanish (▶ **Fig. 2**).

Two independent reviewers (AR-C and SAG-Ch) screened the identified studies based on the titles and abstract. Articles deemed relevant were then subjected to full-text examination for eligibility. Discrepancies between reviewers were resolved by a third researcher (RC-M). During the full-text review, studies that did not evaluate the anti-inflammatory effect of *Rhus* through inflammatory mediator measurement were excluded.

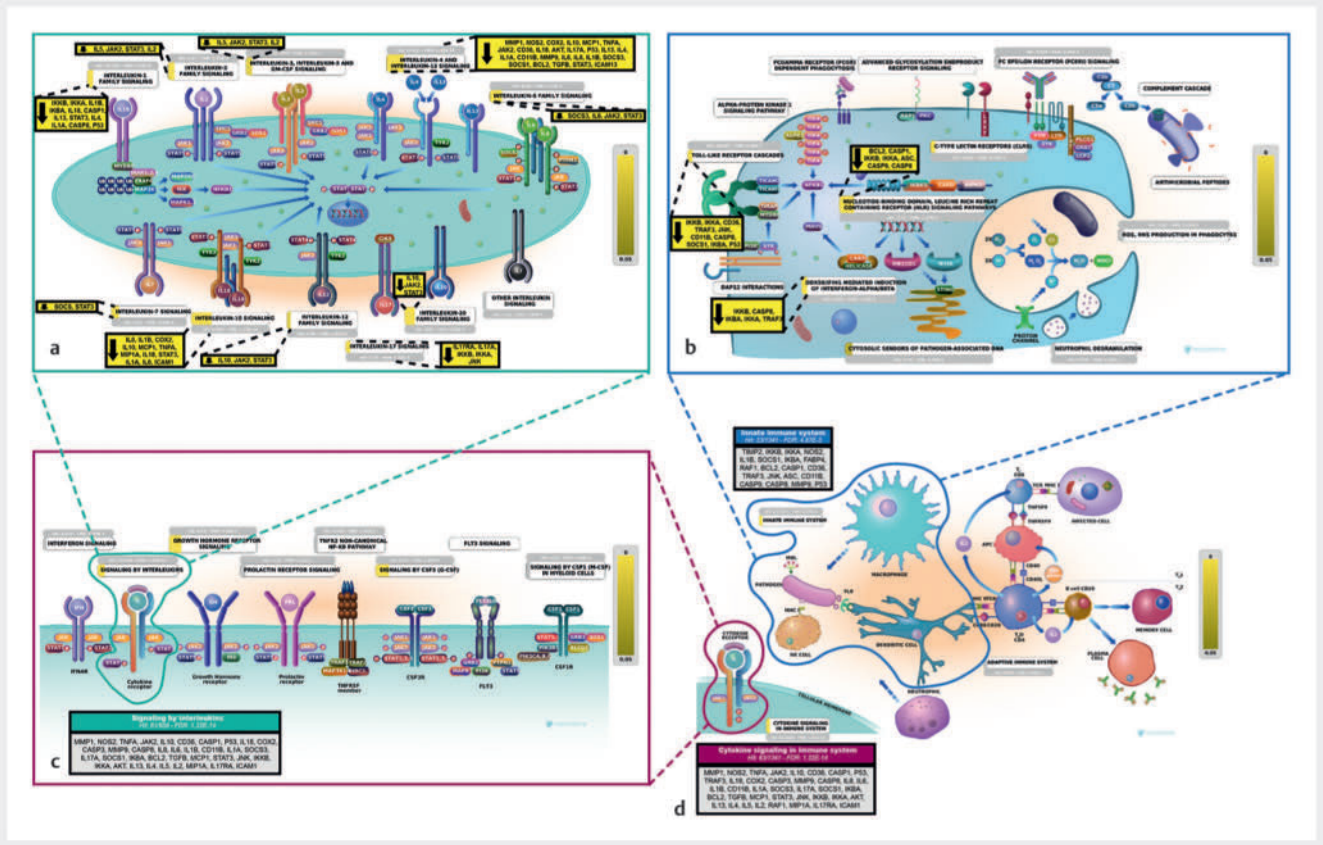
Risk of bias assessment

The potential risk of bias for each selected article was evaluated using the SYRCLE risk of bias tool, adapted from the Cochrane Rob tool for *in vitro* and *in vivo* studies. This tool assesses ten items grouped into six categories of bias: selection, performance, detection, attrition, reporting, and other biases [76]. Two independent reviewers (AR-C and SAG-CH) completed the assessments, and disagreements were resolved by a third reviewer (RC-M). Each item was scored on a nominal scale ("yes", "no", or "unclear"), and the bias risk percentages for the included studies were visualized graphically (▶ **Fig. 3**).

Data extraction

Data extraction focused on two aspects: (1) methodology: information about the plant or its components, the cell line or animal model used to study inflammation, the study and treatment groups, and the techniques employed to measure inflammatory mediators; and (2) results: the effects of treatment on inflammatory mediators. The extracted data were organized into tables for improved interpretation and discussion. To provide a detailed analysis of the anti-inflammatory effects of plants of the genus *Rhus*, the results were organized into the following subtopics: (1) selection of studies and risk of bias analysis; (2) methodological characteristics and results from *in vitro* studies, and 3) methodological characteristics and results from *in vivo* and human studies.

Once data on cytokines and inflammatory mediators affected by *Rhus* treatment were extracted from the studies, they were consolidated into a single list. Subsequently, this list was analyzed using the REACTOME v83 database (https://reactome.org) [77, 78], an open-source, peer-reviewed pathway database designed to visualize, interpret, and analyze biological pathways. The "Analyze Gene List" tool generated visualizations highlighting pathways overrepresented by proteins downregulated after *Rhus* treatment [79].



▶ **Fig. 4** Prediction of anti-inflammatory potential of plants of *Rhus* genus. A list of the mediators modified by *Rhus* treatment was obtained by combining information from all included studies. Subsequently, this was analyzed in the REACTOME v83 database (https://reactome.org) and the overrepresentation visualizations for proteins were obtained. Proteins underexpressed by *Rhus* were associated with the immune system signaling pathway (**d**); including innate immune system signaling (**b**) and cytokine signaling in immune system pathways (**c**). A more detailed visualization of signaling by interleukins shows the association within the cytokine-mediated signaling (**a**). [rerif]

Discussion

Research into traditional treatments for inflammatory diseases, mainly herbal medicine, has garnered increasing attention as a promising strategy for developing more effective therapies. As a result, scientific evidence regarding the benefits and risks of various alternative and complementary therapies is now more readily available [80–84].

This systematic review of research on plants in the *Rhus* genus reveals that numerous species exhibit significant anti-inflammatory potential, both *in vitro* and *in vivo*, despite variations in purity, dosage, administration routes, and inflammation models. We confirmed that *Rhus* extracts can effectively reduce classic inflammatory cytokines, including TNF-α, IL1β, IL6, IFNγ, and others. *Rhus* plants can modulate intracellular mediators and transcription factors, including ERK, MEK, p38, JAK, STAT, JNK, Raf, NFκB, IκB, COX-2, iNOS, PPAR, C/EBP, and SOX-9. Extracellular mediators such as MMPs, VEGF, PGE, and ADAMTS, as well as receptors like TNFR, IL17RA, and ICAM, are also targeted. Furthermore, the bioinformatics analysis of these inflammatory mediators suggests that *Rhus* compounds regulate immune system signaling, diminishing the innate immune response, and inhibiting critical proinflammatory interleukins and inflammasome signaling.

While several reviews have examined the anti-inflammatory properties of plants, most are region-specific, and, to date, none have been focused on *Rhus* species [17, 85, 86]. Thus, this study represents the first comprehensive peer-reviewed examination of the anti-inflammatory effects of *Rhus* fruits, extracts, and compounds. It provides new insights into their potential therapeutic applications in managing inflammation-related conditions.

Previous research on *Rhus* plants has explored their chemical composition, ethnobotanical uses, and therapeutic benefits, with findings suggesting effects beyond placebo [18, 87, 88]. *Rhus* species have shown antioxidant, antineoplastic, and antimicrobial properties. For example, *Rhus longipes* increased antioxidant enzyme activity and hepatic glutathione levels while reducing malondialdehyde *in vivo* [89]. *Rhus trilobata* extracts reduced tumor growth in ovarian cancer models [90], and *Rhus vulgaris* inhibited MRSA and *Streptococcus mutans* growth [91]. Given the role of inflammation and oxidative stress in cancer and infections [92–94], *Rhus*'s ability to decrease these processes may help alleviate inflammation.

The pharmacological effects of herbal drugs vary significantly depending on their geographic origin, harvesting conditions, and preparation methods [95]. Our results indicate that seven *Rhus* species have been studied, with *Rhus verniciflua* and *Rhus chinensis* being the most extensively researched. These species are primarily distributed in Asia [96], a region known for their deep-rooted traditions, complementary medicine, and scientific advancements in this field [97]. However, species such as *Rhus trilobata*, collected in Mexico [41], have also been investigated, which indicates that the study of *Rhus*-based medicine is expanding to other parts of the world.

Medicinal plant extracts differ from chemically defined pharmaceuticals due to their complex composition, where the identities and quantities of active ingredients or marker compounds are often not fully characterized [98]. Our review highlights the diverse preparations of *Rhus* used in research, including aqueous and organic extracts and isolated bioactive compounds such as butein [99], fisetin [100], GA [101], and PGG [102]. Regardless of their origin or the extraction method, *Rhus* plants consistently exhibited anti-inflammatory activity in both *in vitro* and *in vivo* studies. This suggests that the anti-inflammatory properties of *Rhus* are robust across species and preparation methods, indicating a versatile therapeutic potential. However, these findings also emphasize the need for further studies focused on standardization and addressing potential variability in efficacy and safety.

In vitro studies in our review showed that *Rhus* exhibits a consistent anti-inflammatory effect across different plant species and extract types compared to untreated controls, with some effects comparable to those of conventional pharmaceuticals. This effect spans a wide dosage range, from less than 1 to 500 µg/mL, and in various cell types, suggesting a stable mechanism of action that is not dependent on specific conditions. These findings indicate that *Rhus* may address a variety of inflammatory diseases with a broad therapeutic margin, allowing for dose adjustments. Our review further validates these *in vitro* results by establishing non-toxic doses subsequently used in murine inflammation models.

Animal models play an essential role in drug development by evaluating candidate compounds' safety, efficacy, pharmacokinetics, and pharmacodynamics before human testing [103, 104]. In the reviewed studies, inflammation models cover a range of types of acute and chronic inflammation affecting the gastrointestinal tract, liver and bile ducts, periodontal tissues, and conditions like edema and neuroinflammation. This could suggest the widespread efficacy, stability of the mechanism of action, broad therapeutic potential, and foundation for clinical research of plants from the *Rhus* genus.

Different doses ranging from 5 to 800 mg/kg body weight were tested in the *in vivo* models, demonstrating an effect on the reduction in inflammatory mediators, which increased as the dose was increased. The duration of models and treatment varied significantly across the studies, depending on the design used to investigate acute or chronic effects [105]. Most studies lasted around 7 days, although some involved treatment periods as short as a few hours. The most prolonged analysis periods extended up to 20 weeks. All studies demonstrated measurable anti-inflammatory effects, regardless of treatment duration, suggesting immediate and sustained impacts.

In both acute and chronic inflammation models, TNFα, IL-1β, and IL-6 were the most measured inflammatory mediators, recognized for their predominant role in inflammation [106]. However, 54 different inflammatory mediators were evaluated, including those of the NF-κB, MAPK, and JAK-STAT pathways, which play a key role in the pathological progression of organ inflammatory disease [107]. The heterogeneity between studies prevented the establishment of a differential or explanatory pattern of the anti-inflammatory effect of *Rhus* or even the differentiation of mechanisms in acute or chronic inflammation. For this reason, bioinformatics was employed to establish the potential mechanisms of *Rhus* more comprehensively.

The *in vivo* studies also evaluated the toxic effects of the treatments using different strategies, including liver function tests, organ measurements, and morphological assessments through histopathology. It is worth noting that the doses tested in the *in vivo* models were derived from previous *in vitro* studies that confirmed non-cytotoxic doses through strategies such as the TUNEL assay and MTT. However, the assessment of adverse effects was limited to a maximum analysis period of 20 weeks in one murine model study and 6 weeks in the human clinical trial, underscoring the need for long-term studies to ensure the safe use of the *Rhus* treatment. Despite these challenges, animal models remain indispensable for understanding drug effects and optimizing therapeutic interventions [104, 108].

The only clinical study in humans was conducted in women with obesity and depression [67], showing that a 6-week treatment with *Rhus coriaria* L. (fruits) at a dose of 1000 mg/kg body weight significantly reduced TNF-α and IL-6 levels compared to the untreated group. No significant adverse events were reported during this evaluation period. This trial provides a more consistent approach to using *Rhus* for human inflammatory conditions.

We conducted a bioinformatics analysis to better understand *Rhus*'s mechanism using data from studies. The Reactome database was employed to identify significant associations between inflammatory mediators reduced by *Rhus* and various signaling pathways. Proteins downregulated by *Rhus*, both *in vitro* and *in vivo*, were linked to immune response signaling, particularly cytokine and interleukin pathways. The involvement of these molecules in numerous diseases, including rheumatoid arthritis [109], systemic lupus erythematosus [110], inflammatory bowel disease [111], osteoarthritis [112], obesity [113], diabetes [114], atherosclerosis [115], cancer [92], dermatological immune-mediated diseases [116], neuroinflammation [117], epilepsy [118], and periodontitis [119], is well documented. Many current therapies target the inhibition of specific cytokines, suggesting that *Rhus* compounds may offer a potentially adjunctive role in reducing inflammation.

The genes downregulated by *Rhus* compounds indicate a potential regulatory effect on NLR (nucleotide-binding domain leucine-rich repeat-containing receptor) signaling pathways involved in inflammasome activation. Inflammasomes are protein complexes within the innate immune system that initiate inflammation in response to exogenous or endogenous danger signals. Inflammasome activation leads to pyroptosis, triggering the release of proinflammatory cytokines such as IL-1β and IL-18. Dysregulated inflammasome signaling has been implicated in cardiovas-

cular and metabolic diseases, cancer, and neurodegenerative disorders, making inflammasomes a promising therapeutic target [120]. Our results demonstrate that *Rhus* compounds decrease IL-1β, and studies by Yu T. et al. [32] and Momeni A. [37] have shown that *Rhus chinensis* Mill and *Rhus coriaria* L. reduce IL-18 *in vitro*. Additionally, two *in vivo* studies in rat models of inflammation reported a reduction in IL-1β and caspase-1 by *Rhus chinensis* Mill [32], and caspases 3, 8, and 9 by *Rhus coriaria* L. decrease [68]. These findings suggest that *Rhus* compounds may target the inflammasome, as evidenced by the association of proteins such as CASP1, CASP8, CASP9, IKKB, IKKA, ASC, and BCL2 with NLR signaling pathways.

Our review followed PRISMA guidelines [75] to ensure transparency and rigor in the study selection process. We also utilized the SYRCLE risk of bias tool for animal studies [76] to assess the quality of the included research. While the methodological quality of the included studies was thoroughly evaluated and multiple anti-inflammatory mechanisms of *Rhus* were identified, there are still several limitations to consider. Our SYRCLE analysis revealed some studies with a risk of performance and detection biases, mainly due to the lack of details of active compounds tested or the incomplete description of blinded experimental methodologies, leading to the potential selection, performance, or detection biases. Therefore, a more thorough chemical characterization of the compounds is needed to draw more definitive conclusions. Additionally, although we used the Reactome database to map the mediators modulated by *Rhus*, the data were not derived from a single controlled experiment, and the analysis should be interpreted cautiously. Nevertheless, this bioinformatics approach provides a broader perspective on *Rhus*'s effects. Finally, our review primarily focused on anti-inflammatory effects, leaving room for future research into other potential therapeutic properties of *Rhus* plants.

Conclusion

Rhus species and their active compounds, such as butein, dihydrofisetin, and GA, have demonstrated significant anti-inflammatory effects in both *in vivo* and *in vitro* studies. *In vivo, Rhus* extracts from *Rhus verniciflua* and *Rhus chinensis* effectively reduced inflammation in models of both chronic and acute inflammation, modulating cytokines like TNF-α, IL-6, and IL-1β, and regulating key signaling pathways such as NF-κB and MAPK and the inflammasome. The extracts showed notable anti-inflammatory activity across various doses, with higher concentrations proving more effective in reducing proinflammatory mediators. Furthermore, the human clinical trial further supports its potential in addressing obesity-related inflammation. No significant adverse effects were reported at the doses used *in vivo*; however, the analysis periods were limited to 6 weeks in humans and 20 weeks in murine models, so long-term trials are still needed to assess the safety of *Rhus* treatment. These findings highlight the potential of *Rhus* species as therapeutic agents for inflammatory diseases, although further research is required to clarify their mechanisms of action and optimize their clinical application.

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Compliance with ethical standards

This article does not contain any studies involving animals performed by any of the authors. This article contains no studies involving human participants performed by any of the authors.

Data availability statement

The authors declare that the data supporting the findings of this study are available within the paper. We do not analyze or generate datasets because our work proceeds within a theoretical framework.

Contributors' Statement

SAGC prepared the manuscript, collected the information, prepared the figures, and provided overall supervision. AJRC prepared the manuscript and collected the information. CPT prepared the figures and provided overall supervision. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare that they have no conflict of interest.

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