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Sumac Extract Mitigates Rheumatoid Arthritis in Rats via Redox Modulation, Hematological Rebalancing, and T-cell Transcriptional Control

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Abstract

Objective: Brown sumac extract may reduce rheumatoid arthritis (RA) inflammation due to its anti-inflammatory and antioxidant properties. This study tested freeze-dried sumac extract in a RA model.

Methods: Sumac extract's effects were evaluated in healthy and RA induced Wistar rats. Healthy rats received 0, 100, 200, or 400 mg/kg of the extract orally for one month. RA was induced by injecting Freund's adjuvant, followed by the same extract doses from day 7 to 25 post-induction, after the arthritis index exceeded one.

Results: The extract contained 179.45 mg/g total phenolics and FRAP antioxidant activity of 101.9 mmol Trolox equivalents/100 g. Gallic acid content was 58.38 mg/ml. In healthy rats, the extract increased serum TAC dose-dependently, without affecting blood levels. In RA rats, treatment reduced disease progression, especially at 200/400 mg/kg, with 400 mg/kg showing the best results. Extract at 200/400 mg/kg improved anemia, normalizing WBC and elevating RBC, Hb, and Hct. TAC levels were restored dose-dependently. C-reactive protein, nitric oxide, and myeloperoxidase decreased with increasing extract dosage, particularly at 200/400 mg/kg. Sumac extract reduced mRNA ratios of RORγt/T-bet, RORγt/GATA-3, RORγt/FoxP3, T-bet/GATA-3, and T-bet/FoxP3, while increasing GATA-3/FoxP3 in RA rat joints.

Conclusion: Sumac extract reduced RA symptoms, especially at higher doses (200 mg/kg), by lowering CRP, MPO, and nitric oxide. It shifts the immune system away from inflammation, mainly reducing Type 3 immunity. This shift, along with fewer arthritis symptoms, suggests sumac promotes immune balance and reduces inflammation.

Keywords: Sumac extract , Rheumatoid arthritis, Complete Freund's adjuvant, Immunomodulation, Anti-inflammatory, T-cell transcription factors.

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Introduction

Rheumatoid arthritis (RA) is a prevalent autoimmune disease affecting 0.5%–1.0% of white Westerners.[1] It leads to inflammation and damage to cartilage and bone, influenced by genetic and environmental factors.[1,2] Treatment focuses on alleviating symptoms through physical therapy, surgery, NSAIDs, corticosteroids, and DMARDs such as methotrexate and TNF inhibitors.[3] Many medications have side effects, and some patients may not respond effectively.[1,3] Natural alternatives like phytomedicines are being investigated for their potential to reduce side effects, but they should be used cautiously under professional supervision.[4]

Rat models, including adjuvant-induced arthritis, play a crucial role in RA research.[5,6] This model mimics human arthritis with swelling and joint damage, making them valuable for testing treatments for RA and other inflammatory disorders.[6]

Sumac is a spice derived from the fruit of Rhus coriaria, which is native to temperate and warm climates, particularly in countries bordering the Mediterranean, Southern Europe, North Africa, Iran, and Afghanistan. It

has also been recognized as a medicinal plant since ancient times.[7-9] It contains phenolic compounds and flavonoids that possess antioxidant properties.[9] Gallic acid is one of the primary pharmacologically active compounds found in sumac. Numerous benefits such as digestive aid, antimicrobial effects, skin care benefits, anti-tussive properties, and, more importantly, antioxidant and anti-inflammatory effects have been suggested for sumac.[7,10,11] These last two effects may be beneficial in RA. The anti-inflammatory mechanism of sumac extract primarily involves inhibiting the NF-κB signaling pathway and modulating the MAPK pathway. This action, driven by sumac's rich polyphenol content, results in a decrease in the production of key pro-inflammatory molecules such as IL-8 and IL-6. [10,11] Given the limited research on brown sumac for RA, this study evaluates its impact in a rat model of Freund's Complete Adjuvant (CFA)-induced rheumatoid arthritis.

Materials and methods

Reagents and Kits:

SibZist Fan Co (Iran) provided myeloperoxidase and nitric oxide assay kits. PeproTech EC, Ltd. (UK) supplied ELISA kits. DENAZIST (Iran) provided RNX-Plus. TAKARA (China) provided SYBR Premix Ex TaqII and cDNA kits. Sigma-Aldrich (USA) provided other reagents.

Extract preparation and evaluation

Shade-dried Sumac fruits were ground and extracted using 70% ethanol (1:10 w/v) for 48 hours. The extract was filtered, concentrated via rotary evaporation at 40°C, and then lyophilized to yield a powder.

The total phenolic content of Sumac extract was measured using the Folin-Ciocalteu method, with slight modifications.[12] Results are expressed as milligrams of Gallic Acid equivalents per 100 grams of dry weight. All tests were done three times.

The antioxidant property was also evaluated using the FRAP method. The FRAP reagent (acetate buffer, TPTZ, and FeCl3) was freshly prepared daily. A mixture of FRAP reagent, water and sample was incubated for 30 minutes, and absorbance was read at 595 nm. Trolox was used for calibration. Ferric reducing power was reported as µmol TE/100 g .[13] Gallic acid content was determined by HPLC method as described previously.[7]

Animals:

Forty-five male Wistar rats (8 weeks old, 150 ± 10 g), obtained from the faculty's animal facility, were housed at 23 ± 1 °C under a 12-hour light/dark cycle, with ad libitum access to food and water. All protocols adhered to National Institutes of Health guidelines and received approval from the Faculty Ethics Committee. Proper housing is essential for animal welfare and the integrity of research.

Extract safety assessment for animal studies

In the first experiment, 20 rats were divided into four groups (n=5): a control group (PBS) and three groups administered Sumac extract at doses of 100, 200, and 400mg/kg orally for 30 days. Blood samples were collected to count RBCs and WBCs and to isolate serum. RBC and WBC counts were determined using a Neubauer chamber. Hemoglobin and hematocrit levels were measured using Shali's and Micro-Hematocrit methods, respectively. Serum total antioxidant capacity (TAC) was assessed using the Benzie and Strain method.[14] Serum was mixed with a working solution, incubated, and read at 532 nm. TAC was reported as mmol/L.

RA induction and Evaluation

In the second experiment, 25 rats were divided into five groups. Group 1 (control) was healthy. Group 2 had induced RA but received no treatment. Groups 3, 4, and 5 had induced RA and were given daily Sumac extract at doses of 100, 200, and 400 mg/kg, respectively.RA was induced in the rats by administering an intradermal injection of 0.1 mL of Complete Freund's adjuvant (CFA) into the hind paw, containing 10 mg/mL of killed Mycobacterium. Therapies were initiated between days 7 and 25 post-induction, once the arthritis index exceeded one in all induced rats. A scoring system was used: a score of 4 indicated total swelling of the entire leg, resulting in an inability to flex it; a score of 3 indicated swelling of the ankle; a score of 2 represented erythema and swelling of the paws; a score of 1 denoted erythema of the toe; and a score of 0. The severity of the condition was assessed by measuring the volume of the non-injected hind paw at two-day intervals. Thus, the maximum attainable clinical score for a rat is 12.

Serum sample evaluations

Blood samples from anesthetized rats were used to measure WBC, RBC, hemoglobin, hematocrit, and total antioxidant capacity (TAC), as previously described.

Serum myeloperoxidase (MPO) activity was measured using a method similar to a published protocol, comparing absorbance changes to a horseradish peroxidase standard curve.[15,16]

Serum nitric oxide was measured using the Griess method, following instructions and comparing to a standard curve.[17] C-reactive protein (CRP) was measured via sandwich ELISA.[18]

Quantitative real-time RT-PCR (qRT-PCR)

Total RNA was extracted from rat joints using animal tissue RNA isolation kit(Denazist,Iran), adhering to the provided protocol. The extracted RNA was then reverse-transcribed into complementary DNA (cDNA) using a kit

from Denazist (Iran). The mRNA expression levels of key transcription factors involved in lymphocyte polarization (T-bet, RORγt, Foxp3, and GATA-3) were determined via qRT-PCR. GAPDH served as the internal control for normalization. 2X qPCRBIO SyGreen Mix Hi-ROX kit (PCRBIOSYSTEMS, The UK) was employed to quantify the mRNA levels of the target genes. The data are presented as fold change ($2^{-\Delta\Delta Ct}$) and reflect a minimum of three independent experiments. The primer sequences utilized for mRNA amplification are detailed in the table1.

Statistical evaluations

Data are expressed as Mean ± SD and were subjected to one-way ANOVA followed by Tukey's post-hoc test. Statistical significance was defined as $P<0.05$.

Results

The extract exhibited a total phenolic content of 179.45 ± 3.12 mg/g, expressed as gallic acid equivalents (GAE), alongside a FRAP antioxidant capacity of 101.9 ± 0.98 mmol Trolox equivalents per 100 g. HPLC analysis further quantified the gallic acid concentration at 58.38 mg/mL, underscoring its significant contribution to the extract's bioactive profile (Supplementary File 1).

Statistical analysis indicated that the one-month sumac extract treatment did not significantly alter red blood cell (RBC) count, white blood cell (WBC) count, or Hb and Hct levels in rats (Tabel 1) . However, rats treated with Sumac extract showed a dose-dependent increase in serum total antioxidant capacity (TAC) levels compared to the control group (Tabel 1).

RA and its animal models exhibit joint inflammation. Treatments were initiated post-immunization when rats displayed an arthritis index of ≥1.As shown in Figure 1A, the disease progressed less severely in the treatment groups, particularly those given extract at 200 and 400 mg/kg. The group treated with 400 mg/kg of freeze-dried sumac fruit extract showed the lowest average arthritis index and the lowest arthritis index on the final day, as depicted in Figure 1B. The RA group receiving 100 mg/kg of extract did not display a statistically significant change in average arthritis index (Figures 1B). Significant weight loss is observed in arthritic rats. Treatment with lyophilized sumac extract effectively improved weight gain in a dose-dependent manner(Figures 1B).

Arthritic rats exhibited elevated WBC levels but decreased RBC, Hb, and Hct (Table 2). These parameters collectively suggest anemia, a common feature of arthritis. Treatment with sumac fruit extract at doses of 200 and 400 mg/kg improved the anemic condition, evidenced by a reversal in WBC count and increases in RBC count, Hb concentration, and Hct value relative to the AIA group (Tabel 2). CFA exposure reduced blood TAC by approximately threefold, signifying oxidative stress. Sumac reinstated TAC in a dose-dependent manner (Table 2).

Table 1. Effect of one month administration of freeze-dried sumac extract (LSE, 100, 200, and 400 mg/kg; p.o.) on hematological and antioxidant capacity of healthy Wistar rats.

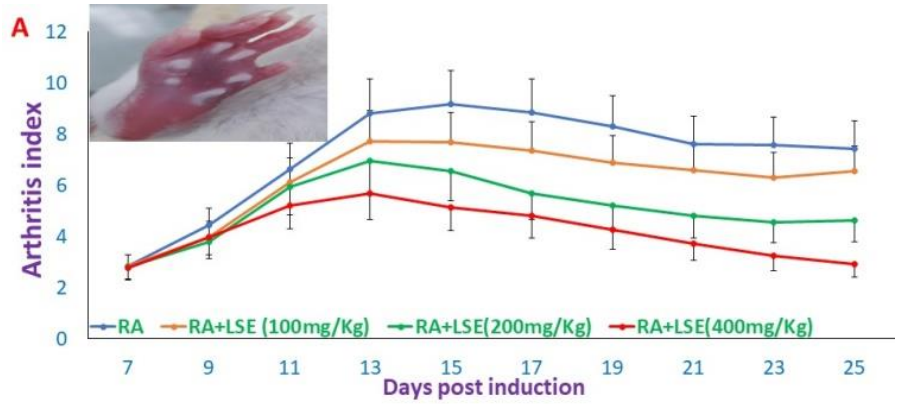
Experimental groups	RBC (10^6/µl)	WBC (10^3/µL)	Hb (g/dL)	Hct%	TAC(mmol/L)
Vehicle control	5.25±0.68^{A}	9.12±2.01^{A}	12.85±0.48^{A}	52.35±2.86^{A}	735.16±80.9^{A}
LSE (100 mg/kg)	4.85±0.83^{A}	10.35±3. 26^{A}	11.65±0.46A	52.99±5.37^{A}	878±74.72^{B}
LSE (200 mg/kg)	4.29±0.57^{A}	10.57±2.35^{A}	12.09±0.62A	51.73±4.38^{A}	1034±97.01^{C}
LSE (400 mg/kg)	4.31±0.76^{A}	11.01±1.92^{A}	12.68±0.7A	51.14±3.72^{A}	1237±111.25^{D}

WBCs: White blood cells, **RBCs:** Red blood cells, **Hb:** Hemoglobin, **Hct:** Hematocrit, **TAC:** Total antioxidant capacity.
Values are presented as mean ± SD. Statistical significance was analysed by one-way ANOVA with Tukey post-hoc test. Different letters placed next to the table indicate statistically significant differences between groups.

Table 2. Effect of three weeks administration of freeze-dried sumac extract (LSE, 100, 200, and 400 mg/kg; p.o.) on hematological and antioxidant capacity in a rat model of adjuvant-induced arthritis (RA).

Experimental groups	RBC (10^6/µl)	WBC (10^3/µL)	Hb (g/dL)	Hct%	TAC(mmol/L)
Vehicle control	5.34±0.75^{A}	9.41±2.25^{A}	12.85±0.48^{A}	52.35±2.86^{A}	725.11±81.02^{A}
RA	2.19±0.21^{B}	29.35±3.67^{B}	7.38±0.58^{B}	36.57±4.06^{B}	367±36.42^{B}
RA+LSE (100 mg/kg)	3.01±0.32^{B}	21.35±4.59^{B}	8.98±0.61^{B}	38.16±3.51^{BC}	498±28.91^{c}
RA+LSE (200 mg/kg)	4.09±0.12^{C}	18.28±1.44^{C}	10.18±0.38^{C}	42.61±4.71^{BC}	544±41.53^{d}
RA+LSE (400 mg/kg)	4.51±0.42^{D}	13.01±2.11^{D}	11.13±0.49^{D}	48.27±3.31^{D}	639±45.05^{e}

RA was induced by injecting Freund's adjuvant. Treatment was begun from day 7 to 28 post-induction.
WBCs: White blood cells, **RBCs:** Red blood cells, **Hb:** Hemoglobin, **Hct:** Hematocrit, **TAC:** Total antioxidant capacity.
Results are reported as mean ± SD. Statistical significance was analyzed by one-way ANOVA with Tukey post-hoc test. Different letters placed next to the table indicate statistically significant differences between groups.



B

Group	average arthritis index	Arthritis index on the last day	The weight difference on the last and first day(g)
RA	7.15±1.63^{A}	7.43±1.07^{A}	-9.41±1.07^{A}
RA+LSE(100mg/Kg)	6.19±1.17^{A}	6.53±1.05^{A}	-7.53±0.96^{B}
RA+LSE(200mg/Kg)	5.08 ±0.99^{B}	4.61±0.82^{B}	-4.7±0.82^{C}
RA+LSE(400mg/Kg)	4.16±0.82^{C}	2.82±0.51^{C}	-3.23±0.53^{D}

Figure 1. Clinical features of rheumatoid arthritis in rats after freeze-dried sumac extract treatments. RA was induced in rats, and freeze-dried sumac extract was given from day 7 to 25. (A) Shows the arthritis index over time. (C) Summarizes the data. The 400 mg/kg group had the lowest average and final arthritis index. Lyophilized sumac extract improved weight gain in a dose-dependent manner. Data are mean ± SD (ANOVA, Tukey's test, $P < 0.05$). Different letters indicate significant differences. LSE, Lyophilized sumac extract.

As illustrated in Figure 2, the levels of CRP, MPO, and NO in the blood of rats with rheumatoid arthritis were approximately 5.3, 2.24, and 8.5 times higher than those in the control group, respectively. A significant dose-dependent reduction in blood CRP levels was noted after three weeks of administering sumac extract compared to the RA group (Figure 2A). The administration of lyophilized hydroalcoholic extract of sumac fruit led to a decrease in MPO levels in rats with rheumatoid arthritis. Notably, the group receiving 400 mg/kg of sumac fruit extract exhibited a significant decrease compared to the other treatment groups. The reduction in MPO levels in arthritic rats treated with doses of 100 and 200 mg/kg of sumac fruit extract was not significantly different (Figure 2B). There was no significant effect on NO levels at a dose of 100 mg/kg of sumac fruit extract. However, a significant reduction in NO levels was observed following doses of 200 and 400 mg/kg of sumac fruit extract in arthritic rats compared to the control group. Once again, the most pronounced effect in reducing this factor was seen in the group receiving sumac fruit extract at a dose of 400 mg/kg (Figure 2C).

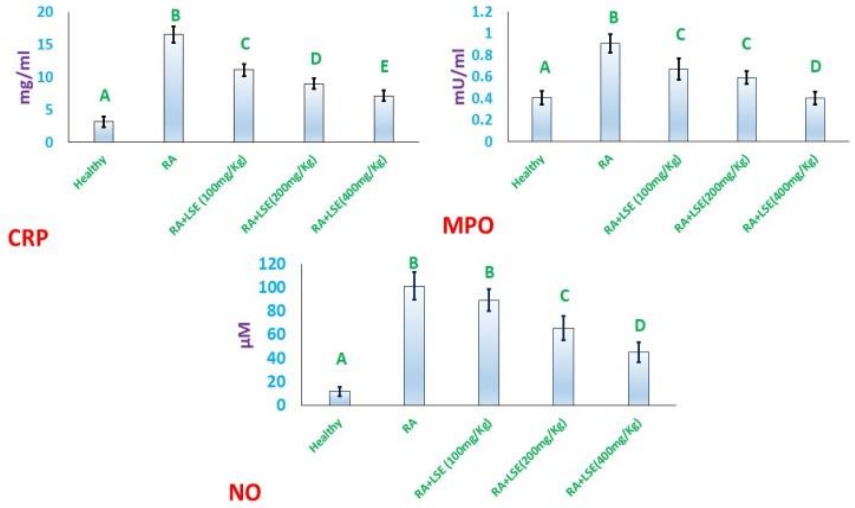


Figure 2. Serum biochemical factors in RA rats. Bar graphs show serum C-reactive protein (CRP), Myeloperoxidase (MPO), and Nitric Oxide (NO). RA rats had higher levels than controls. Extract dosages, especially 200/400 mg/kg, lowered CRP, nitric oxide, and myeloperoxidase. Data are mean ± SD (ANOVA, Tukey's test, $P < 0.05$). Different letters indicate significant differences. LSE, Lyophilized sumac extract.

The mRNA expression of these factors and their ratios were measured for each rat in a group to monitor the expression of master regulators that influence how lymphocytes become polarized. As shown in Figure 3, Sumac extract resulted in a decrease in the mRNA ratios of RORγt/T-bet, RORγt/GATA-3, RORγt/FoxP3, T-bet/GATA-3, and T-bet/FoxP3, while simultaneously increasing the ratio of GATA-3/FoxP3. The results of the statistical analysis indicated that for the RORγt/T-bet ratio, a dose of 100 mg/kg of the extract was ineffective, whereas doses of 200 and 400 mg/kg of lyophilized sumac extract reduced this level in a dose-dependent manner (Figure 3). Based on statistical analysis of the ratios of RORγt/GATA-3 and RORγt/FoxP3, the reduction in these ratios occurred in a dose-dependent manner(Figure 3). Furthermore, the analysis indicated no significant difference in the reduction of the T-bet/GATA-3 ratio following treatment with the extract in arthritic rats between doses of 100 and 200 mg/kg, as well as between doses of 200 and 400 mg/kg of sumac extract (Figure 3). Regarding the reduction in the ratios of T-bet/FoxP3 in arthritic rats, statistical analyses indicated that the most significant effect was associated with the dose of 400 mg/kg of sumac extract. No statistically significant difference was observed between the doses of 100 and 200 mg/kg of the extract (Figure 3). Finally, concerning the increase in the A to B ratio, the results of the statistical analysis indicated that a dose of 100 mg/kg of the extract was ineffective, whereas doses of 200 and 400 mg/kg of lyophilized sumac extract elevated this level in a dose-dependent manner (Figure 3).

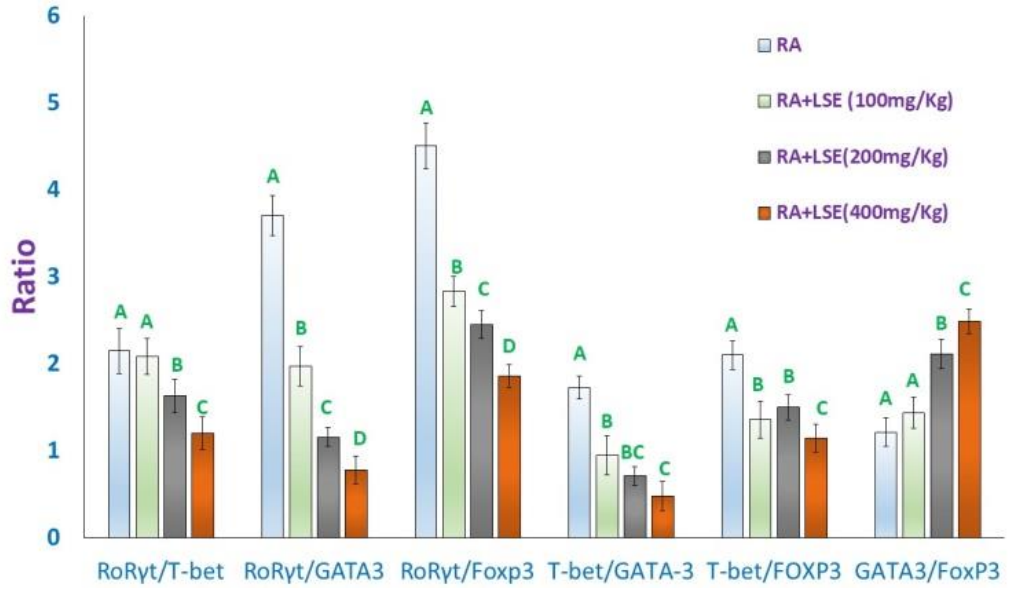


Figure 3. Sumac extract's effect on lymphocyte ratios in RA rat . Sumac reduced RORγt/T-bet, RORγt/GATA-3, RORγt/FoxP3, T-bet/GATA-3, and T-bet/FoxP3 mRNA ratios, while increasing GATA-3/FoxP3 in RA rat joints. Data are mean ± SD (ANOVA, Tukey's test, $P < 0.05$). Different letters indicate significant differences. LSE, Lyophilized sumac extract.

Discussion

Historically, plants, particularly spices, have been utilized as remedies, forming the foundation of herbal medicine.[19,20] Sumac fruit was selected for this RA study after a thorough review of the evidence. In vitro, sumac extract decreases cytokines such as IL-18 and IL-1β from stimulated cells involved in RA inflammation.[21] Chinese sumac fruit extract effectively inhibits gouty arthritis induced by monosodium urate in rats by modulating inflammatory pathways, specifically the NLRP3, NF-κB, and MAPK pathways.[10] Our results showed that hydroalcoholic extract of sumac fruit especially at 200-400 mg/kg, effectively reduced RA symptoms and related features in the experimental model.

Herbal medicines are valued for their effectiveness, safety, and low toxicity; however, recent studies indicate potential side effects.[20,22] Therefore, it is crucial to test medicinal plant extracts for toxicity. Rhus coriaria is regarded as safe for both humans and animals. It protected diabetic rats without toxicity, even at high doses (1000 mg/kg) over 3 days.[23] Another study demonstrated that 300 mg/kg of Rhus coriaria seed extract improved blood parameters in diabetic mice without side effects.[24] Our data indicated that Sumac at doses of 100-400 mg/kg did not alter RBC, WBC, Hb, or Hct levels in healthy rats but did enhance serum antioxidant capacity, with higher doses resulting in greater increases.

RA affects joints, but immune issues can cause other problems like anemia and hyperlipidemia. Traditional drugs have side effects ,[2,25] creating a need for new treatments. This study explores Sumac's effects on arthritis in rats, including its potential to combat arthritis, reduce oxidation, improve anemia, and lower lipid levels. Arthritic rats showed high white blood cell counts and low red blood cell counts, hemoglobin, and hematocrit, indicating anemia. Sumac (200-400 mg/kg) improved anemia by normalizing white blood cell counts and increasing red blood cell counts, hemoglobin, and hematocrit compared to untreated rats with experimental arthritis.

Sumac's main antioxidants are gallic acid, methyl gallate, and gallotannins.[7] The FRAP assay tests antioxidant capacity by measuring the reduction of ferric ions (Fe^{3+}) to ferrous ions (Fe^{2+})(Benzie and Strain 1996). Sumac extract has 2.5 times more antioxidant activity than saffron, as measured by FRAP values.[26]

CRP, an acute-phase protein indicative of inflammation, is a crucial marker for RA; its reduction is a favorable sign.[25,27,28] Sumac extract lowered CRP levels in RA rats in a dose-dependent manner, significantly at 200 and 400 mg/kg.

Oxidative and nitrative stress are key in rheumatoid and adjuvant-induced arthritis via interconnected mechanisms.[5,29,30] In RA, immune cells' reactive oxygen species (ROS)overproduction, via enzymes like NADPH oxidase,[31] and reduced antioxidants worsen oxidative damage due to consumption/production imbalances.[32] Our in vivo study showed that sumac fruit extract dose-dependently increased TAC levels in rats with rheumatoid arthritis.

Myeloperoxidase (MPO) activity in serum samples is a key indicator of inflammation and oxidative stress in autoimmune conditions, including adjuvant-induced arthritis.[5,29,33] Elevated MPO links to RA severity and correlates with CRP.[34] Sumac extract reduces oxidative stress in gouty arthritis by lowering malondialdehyde and MPO, increasing superoxide dismutase and glutathione.[35] It accelerates wound healing by promoting collagen and reducing MMP-8 and MPO.[7] Sumac extract decreased MPO levels in RA rats, especially at 400 mg/kg.

Inflammation boosts NO production, forming peroxynitrite, which damages proteins in RA joints.[27,28] Peroxynitrite damages DNA, lipids, and enzymes .[36] Nitric oxide levels are higher in arthritis patients.[37] Sumac extract decreased NO levels in RA rats, significantly at 200 and 400 mg/kg.

Balancing immune cells is crucial for immunity and self-tolerance. Type 1 immunity (T-bet$^+$ lymphocytes) produces IFN-γ, which may lead to autoimmune issues. Type 2 immunity (GATA-3$^+$ lymphocytes) generates IL-4, IL-13, and IL-15, combating parasites or triggering allergies.[27,38] Type 3 immunity (RORγt$^+$ lymphocytes) produces IL-17A and IL-17F, protecting against pathogens but also contributing to inflammation .[27,39] FoxP3$^+$ Treg lymphocytes uphold self-tolerance. Th1 and Th17 lymphocytes play significant roles in RA and CFA-induced arthritis.[27,40] Therefore, shifting the immune response towards Th2/Treg pathways appears to be a highly effective strategy for managing this condition. Our findings showed that administering Sumac significantly lowered the mRNA ratios of T-bet/GATA-3, T-bet/Foxp3, RORγt/Foxp3, and RORγt/GATA-3 in the paws of rats with RA compared to untreated rats with RA rats. Consequently, the RORγt/T-bet ratio decreased following Sumac treatment in the RA rats, indicating a reduction in the proportion of Type 3 immunity relative to type one immune responses. Th17 cells are more detrimental than Th1 cells in arthritis models and rheumatoid arthritis because they release inflammatory signals,[27,41] damage tissues, and adapt readily. They exacerbate joint inflammation by attracting neutrophils and activating osteoclasts via IL-17. Reducing Th17-related signals (IL-17A, IL-23) alleviates the disease. Th1 cells require Th17 signals to maintain inflammation.[42,43] Similar findings are observed in models for multiple sclerosis and uveitis.[19,44] The mRNA ratios of RORγt/Foxp3, RORγt/T-bet , and T-bet/FoxP3 expression showed a further decrease in RA rats treated with 400 mg/kg Sumac extrac compared to the other groups. Thus, this Sumac extract dosage was more effective at redirecting immune responses away from Type 3 and type 1 immunity and towards regulatory lymphocytes. Crucially, our findings indicate that there was an increase in the GATA-3/FoxP3 ratio (Th2 vs Treg) after sunac extract treatment in arthritic rats. This means the expression of the Th2 master regulator GATA-3 increased relative to the Treg master regulator FoxP3. This suggests that while Tregs increased relative to Th1/Th17, they decreased relative to Th2. The decrease in the ratios T-bet/GATA-3 (Th1 vs Th2) and RORγt/GATA-3 (Th17 vs Th2) indicates that the expression of the Th2 master regulator GATA-3 has increased relative to the pro-inflammatory Th1 (T-bet) and Th17 (RORγt) master regulators. This suggests enhanced Th2 activity or presence compared to Th1/Th17. As mentioned earlier, the increase in the GATA-3/FoxP3 ratio (Th2 vs Treg) directly demonstrates that Th2 activity/presence has risen relative to Treg activity/presence. As a summary, sumac extract suppressed pro-inflammatory pathways (type 1 and type 3 immunity responses), particularly type 3 immunity response in relation to both regulatory (Treg)

and anti-inflammatory type 2 pathways. It favored type 2 immunity response over Treg, resulting in a net increase in the type 2 immunity/Treg balance (GATA-3/FoxP3 ratio). This indicates a stronger relative enhancement of the Th2 pathway compared to the Treg pathway. The effects were generally dose-dependent, with higher doses (200 mg/kg and 400 mg/kg) proving more effective than 100 mg/kg.

Conclusion

Sumac extract alleviated rheumatoid arthritis symptoms, particularly at doses of 200 mg/kg and above, by decreasing CRP, MPO, and nitric oxide levels. It redirects the immune system away from inflammation, primarily suppressing Type 3 immunity. This alteration, coupled with diminished arthritis symptoms, indicates that sumac fosters immune regulation and anti-inflammatory pathways. Sumac may benefit autoimmune diseases such as RA, but additional research on dosage and protein levels is necessary.

Highlights

What Is Already Known?

Sumac is a rich source of antioxidants and exhibits notable anti-inflammatory properties, which may contribute to alleviating symptoms associated with rheumatoid arthritis.

What Does This Study Add?

Sumac extract significantly attenuated rheumatoid arthritis symptoms, particularly at higher doses (200 mg/kg), by reducing key inflammatory markers such as C-reactive protein , myeloperoxidase , and nitric oxide. Mechanistically, it modulates the immune response by downregulating Type 3 immunity, thereby shifting the immunological milieu away from pro-inflammatory pathways. This immunoregulatory shift, coupled with clinical improvement, suggests that sumac fosters immune homeostasis and exerts potent anti-inflammatory effects.

Authors' Contributions

SMAF , ND and RH conceived and designed the study, and conducted research. AEN collected and organized data. wrote the initial and final draft of the article and provided logistical support. All authors have critically reviewed and approved the final draft.

Consent For Publication

Not applicable.

Ethics approval

This research project, with the code IR.UU.AEC-3/5, has been approved by the Ethics Committee of Veterinary Faculty of Urmia.University,Urmia,Iran.

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The extent of AI use

The authors made limited use of ChatGPT (OpenAI) to assist in editing language and improving clarity during preparation of the article. All content was reviewed and approved by the authors.

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Conflicts of interest:

None declared.

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