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ORIGINAL ARTICLE

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Reduction of expression of IL-18, IL-1β genes in the articular joint by sumac fruit extract (*Rhus coriaria* L.)

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Abstract

Background: Osteoarthritis is the most common malignant disease in the world. The disease is caused by changes in the metabolism, the structure and function of multiple joints, and joint tissues. Sumac is one of the indigenous plants of Iran and has traditionally been used as a spice in Iran. The aim of this study was to investigate the reduction of expression of IL-18, IL-1β genes in the articular joint by sumac fruit extract (*Rhus coriaria* L.).

Methods: The alcoholic extract of sumac fruit (E.E.R.C.L) was prepared from the Genetic Reserve Center. Bleeding was used to provide synoviocyte cells from the joint and fluid of the anatomical metacarpal limb of the 8-month-old Holstein healthy calf without any signs of inflammation. Using cell-hemocytometer count, their viability was evaluated by trypan blue and after lipopolysaccharide (LPS) proliferation and injection to enhance the level of cytokines. After isolating the RNA and preparing the cDNA, RT-PCR and PCR were performed and then, using the real-time PCR method, the expression of the desired genes was investigated.

Results: In this study, after the expression of IL-18 cytokines, IL-1β increased to 100%, and following the treatment with alcoholic extract, the reduction of expression of these cytokines was 33.61% and 29.01%, respectively. The results of anti-inflammatory effects showed that the alcoholic extract of sumac reduced the IL-1β, IL-18 expression in LPS-stimulated cells.

Conclusion: Sumac fruit extract can be an effective medication for reducing pain.

KEYWORDS
cytokines, osteoarthritis, sumac alcoholic extract (E.E.R.C.L), synoviocytes

1 | INTRODUCTION

Osteoarthritis (OA) is the most common arthritis disease and one of the most important causes of disability in the elderly. This condition is associated with pain and motor limitation. The involvement of knee joints is one of the most common forms of disease and the most important cause of referral of patients (Glyn-Jones et al., 2015; Litwic, Edwards, Dennison, & Cooper, 2013). An important part of the patients needs surgery. In OA, erosion of the articular cartilage and bone scoliosis underlying cartilage and soft tissue lesions around the joint, resulting in joint failure (Berenbaum, Eymard, &

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Houard, 2013; Glyn-Jones et al., 2015). Currently, existing treatments are mostly symptomatic that affects joint pain, but they do not prevent the progression of the disease, and so far there are no effective drugs that can affect the course of the disease (Glyn-Jones et al., 2015; Hochberg et al., 2012), and treatment with acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) used alone or in combination. In addition, topical ointments can be used with them (Hochberg et al., 2012).

If conventional treatments are not effective for pain, especially in cases of joint swelling associated with fluid accumulation in the joint, internal corticosteroids are also recommended (Hochberg et al., 2012), and in severe cases resistant to surgical treatment (Richmond, 2013), the goals of inflammation of the Synovial membrane (ventricular membrane inflammation) are in the recent and subsequent stages of OA. In the later stage, its distribution is limited to adjacent spaces for cartilage diseases and depends on the acceleration of cartilage degradation (Ayral, Pickering, Woodworth, Mackillop, & Dougados, 2005). This finding suggests that inflammation begins with cartilage deficiency (Tables 1 and 2).

In advanced bone arthritis, synovial membrane inflammation extends along the membrane and progresses to the formation of fibrous and hypertrophic tissue of the intestinal parenchyma (Shibakawa et al., 2003). During the process of chondrocyte disease, it has been shown that synoviocytes are activated, and mononuclear cells (monocytes and macrophages) also accumulate in the joint (Kapoor et al., 2015). These activated cells produce inflammatory cytokines including: iL-1β, TNFα, and increase the production of Prostaglandin E2 (PGE2), NO. These proinflammatory materials are characterized by known mechanisms such as: stimulating the synthesis of metalloproteinases and inhibiting the production of metalloproteinase inhibitors, stimulating the apoptosis of chondrocytes, inhibiting the synthesis of proteoglycans, and play a role in increasing cartilage degradation (Goldring, 2000; Melchiorri et al., 1998).

In this study, the role of anti-inflammatory fruits of *Rhus coriaria* L. was investigated by effecting the expression of IL-18, IL-1β in isolated synoviocyte cells isolated from carpometacarpal (CMC) horseradish 8-month-old calf and production of PGE2, NO in synoviocyte cells was considered as a model similar to cellular monocyte and macrophage infiltration in arthritic joint. The use of medicinal herbs for the treatment of diseases has been recognized for centuries. Today, there is a significant portion of chemical drugs, but it is estimated that about one third of all drug products or herbal origin have undergone transformation after extraction. *Rhus coriaria* L. is a pistachio plant peanut. Its main compounds are tannic acid, which has been used as astringent for the treatment of diarrhea and the remission of oral bleeding in the past, especially after the tooth was pulled, it was used as antiperspirant (Shabbir, 2012). In Iran, *Rhus coriaria* L. is used as a special spice along with rich foods. It is recommended in diabetic patients to regulate blood lipids. Previous studies have shown that sapwood has antioxidant properties (Shen, 2007).

We showed for the first time that the anti-inflammatory effects of the alcoholic extract of the sapwood on the synoviocytes and fibroblasts cells are not limited and extend to monocyte/macrophage replacement cells. We prove that cavity suppresses the expression of the genetically effective anti-inflammatory cytokines suppressed by lipopolysaccharides (LPS).

2 | MATERIALS AND METHODS

The dried fruit of *Rhus coriaria* L. obtained from Lorestan province located at latitude 32°, 37 min to 34° and 22 min north, and longitude: 46°, 51 min to 50°, and 30 min east. The plant was authenticated by the experts of Iran's Genetic Reserves Center and used for the preparation of the alcoholic extract.

2.1 | Synoviocytes cell culture

For isolation of synoviocyte cells, an 8-month-old healthy CMC was used. First, the external condyle of the joint was removed by a curette in sizes less than millimeters and after two washings with 1 M PBS buffer, pH 7.2, using collagenase Type II enzyme for 16 hr, in Bain Marie 37°C and then cells were separated by sterilization filter, and transferred to a special flask for subculture. Until 85 volumes of

TABLE 2 F-static results from synoviocytes

	Vehicle	*Rhus coriaria*	Critical Value	Result
Bovine IL-1β	32.48	1.3	3.89	Acceptable
Bovine IL18	32.48	1.45	3.89	Acceptable

TABLE 1 CT Results in cytokines

	Cell	Cell + LPS	Cell + LPS + Steroid	Cell + LPS + NSAID	Cell + LPS + Extract	Cell + PBS
Bovine IL-1β	15.57 ± 0.1137	100 ± 0.017	16 ± 0.7147	18.58 ± 0.4948	29.01 ± 0.4948	16 ± 0.1137
Bovine IL18	15.57 ± 0.1137	100 ± 0.017	16 ± 0.7147	18.58 ± 0.4948	33.61 ± 0.2308	16 ± 0.1137

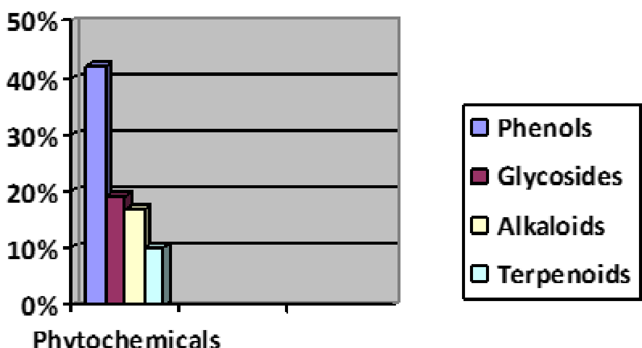

FIGURE 1 The phytochemicals present in sumac fruit extract (*Rhus coriaria* L.)

the flask are covered by a single cell layer, the incubator was maintained at 5°C with temperature of 37°C and humidity. Then, 0.25% trypsin solution was used for counting the cells and 0.3% trypan blue for cell count (Figure 2).

2.2 | Determination of extract cytotoxicity on synoviocytes by LDH, SDH, and MTT assay

The level of toxicity of the alcoholic extract was determined using trypan blue assay, lactate dehydrogenase (LDH) assay, succinate dehydrogenase (SDH) assay, and LC 50 values (Figure 2).

2.3 | MTT assay

In this method, the enzymatic method is used as a substrate for the reaction of tetrazolium solution salts, the most important of which is MTT. The tetrazolium salt is soluble in water, and when the compound is prepared in a phenol-free or PBS medium, it creates a yellow color, and when this MTT coloring solution is added to the culture medium, the MTT loop is broken down only in the mitochondria of the healthy cells in the presence of the dehydrogenase enzyme and converted to the formazan insoluble crystals. The insoluble crystals in formazan are dissolved by organic solvents such as DMSO or isopropyl acid, and then the optical absorption of purple color produced by spectrophotometry at 570 nm was read.

By this simple and accurate test, the response of different cells to external factors such as growth factors, cytotoxic drugs, and other chemical agents can be evaluated. All stages of the test are carried out in 96-well plates. To prepare the standard curve, a cell suspension with a well-defined concentration of at least one million cells per milliliter was prepared from the cells in question. After reviewing their viability, an increasing concentration of it was quadruplicate on a 96-well culturing plate of cell culture. Then the plate was transferred to the CO2 incubator and 24 hr later, MTT test was done and standard curve was drawn by obtaining the optical absorption values against the corresponding cell number. The reading of the amount of purple color absorbed by the fracture of the MTT ring is determined by the enzyme in the dehydrogenase and the percentage of live cells, and the MMT is calculated through extrapolation on the standard curve.

2.4 | SDH assay

Succinate dehydrogenase is an important mitochondrial enzyme. It is found only in the mitochondria of the eukaryote cells is highly stable and high concentration. SDH is useful as a marker enzyme for mitochondria, and it is the only enzyme that participates in the electron transfer chains, and Krebs cycle, via the oxidation of succinate into fumarate. Mutations in SDH cause disturbances such as paraganglioma/pheochromocytoma syndrome and Leigh's neurodegenerative syndrome. The SDH activity is also determined by generating a product with absorption at 600 nm relative to the present enzymatic activity. One unit of SDH is the amount of enzyme that produces 1.0 μmole of DCIP in 1 minute at 25°C at pH 7.2.

2.5 | LDH assay

The lactate dehydrogenase enzyme is an oxidoreductase that catalyzes and metabolizes pyruvate to lactate and liberates cells to LDH into the bloodstream after tissue damage or homeostasis of blood cells. Because lactate is a highly stable balanced enzyme, LDH is thus a potentiator of some pathophysiological conditions, such as cancer and the

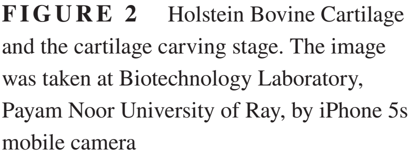
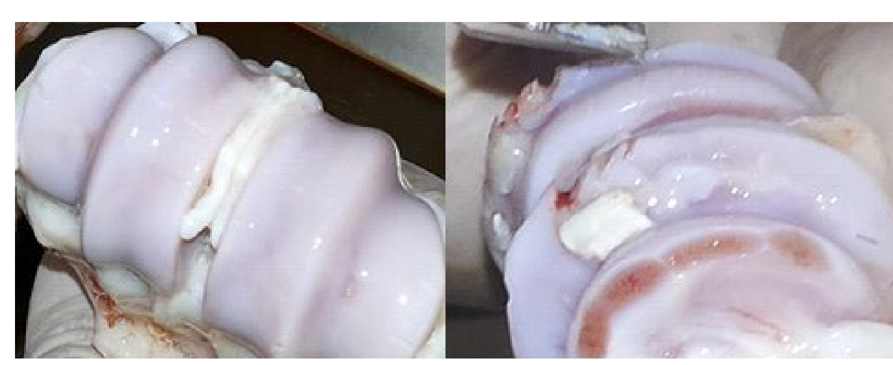

FIGURE 2 Holstein Bovine Cartilage and the cartilage carving stage. The image was taken at Biotechnology Laboratory, Payam Noor University of Ray, by iPhone 5s mobile camera

determination of LDH has a wide range of functions. LDH reduces NAD to NADH, which is specifically identified with color activity at wavelength 450 nm.

2.6 | Determination of LC 50

This is the average effective concentration (EC50), the statistical concentration obtained from a substance to produce a specific effect in 50% of test subjects in a specific population of LC50. The aim of this analysis was to determine the mortality rate and target 5 × 105 cells in 12-well plates with 1 ml of DMEM F-12 enriched with 10% FBS, 50 μg/ml ascorbic acid, 50 μg/ml penicillin 100 units, streptomycin 100 μg, amphotericin 0.25 μg/ml were added. The plates were rotated slowly for 2–3 min, and then kept for 20–30 min in a temperature-controlled incubator at 37°C and a 5% CO2 with 90% moisture content, and then the alcoholic extract of sumac at concentrations of 0.01, 0.09, 0.1, 0.9, 1, 9, 10, and 90 μg/ml were prepared using DMEMF-12 culture medium and added to the 12-well plates, incubated for 24 hr at 37°C, 5% CO2 and 90% humidity (Cole 2010). After 24 hr, the plates were monitored for LC50 determination. Signs of cell lysis is a formation of accumulated cell mass caused by the cells, in other words, the accumulated old cells are accumulated. Following the injection of this amount into the culture medium, 50% of the cells will be destroyed, which, as a result of the final result, has a significant effect and, therefore, to prevent this error, the median LC 50 is calculated to be equal to 0.42 μg/ml (Cole 2010).

2.7 | Stimulation and treatment of synoviocyte cells

2.7.1 | Treatment by LPS

PS 20 ng/mL was used to provide conditions similar to the disease and to increase the expression of preinflammatory cytokines. First, we cultivate 6×10^6 cells in the medium. After 72 hr, the LPS was added to the medium at 100 ng. The first series of plates was stored for 24 hr in order to express the anti-inflammatory cytokines such as COX-2, iNOS, and TNF-α in the CO2 incubator.

2.7.2 | Cell treatment by dexamethasone

Glucocorticoids have many disadvantages such as: Immunosuppressive and anti-inflammatory immunosuppressive agents, but are increasingly being used to treat a wide range of diseases and syndromes such as, in cases of susceptibility, suppressing the increased expression of cytokines in the course of various diseases, especially in the case of immune system deficiencies (Lang, Dale, & Vincent, 2003). In this analysis, dexamethasone was used as a positive control, which was able to reduce the expression of inflammatory cytokine, at a dose of 1–100 nmol (Lewis & Crawford, 1999).

2.7.3 | Treatment of cells with NSAIDs

Nonsteroidal anti-inflammatory drugs are very effective in reducing pain, reducing fever, and preventing swelling. In this analysis, to compare the anti-inflammatory effect of asparagus with NSAIDs, ibuprofen at a dose of 50–100 nM, as a representative of NSAIDs, the ability to reduce the expression of preinflammatory cytokines in the cells stimulated by LPS was used.

2.7.4 | Treatment by DMSO or PBS

In order to investigate whether the solvent (extract, effective substance, or essential oil) has no effect on the reduction of the expression of the cytokine gene produced in the cells stimulated by LPS, this treatment was used.

2.8 | RNA isolation and PCR

2.8.1 | RNA separation steps

Using the Trizol Reagent (Invitrogen) (Gregory T.Lucier Carlsbad, California, United States), Synagen Co. was used and finally, a spectrophotometer (UV-2100 Spectrophotometer) was used to determine the concentration of RNA. In the presence of DNA contamination, the DNase enzyme is used to eliminate additional DNA. The Vivantis (Malaysia-Selangor) kit was used to convert the RNA to cDNA using two-step RT-PCR kit based on the protocol. Finally, on the cDNA, by performing PCR, the concentration of the sample produced was increased.

2.8.2 | The production of cDNA from RNA extracted from synoviocyte cells

For each 1 μg sample, RNA (by two-step RT-PCR kit) from Vivantis (Malaysia-Selangor) is converted to cDNA.

RT-PCR was performed at 42°C for 60 min and at a temperature of 94°C for 5 min (to discontinue cDNA synthesis). To convert the RNA to the cDNA, the two-step RT-PCR kit from Vivantis was used based on the protocol. Finally on the cDNA, by performing PCR, the concentration of the sample produced was increased.

2.8.3 | Semiquantitative PCR

The list of specific primers for the studied cytokines is as follows:

1. Specific primers for Bovine—COX2:

   Forward: 3′-CTC TTC CTC CTG TGC CTG AT-5′.
   Reverse: 3′-TG AGT ATC TTT GAC TGT GGG A-5′.
   Tm forward: 52.9°C, Tm reverse: 52°C, PCR product size: 100 bp.

2. Specific primers for bovine TNF-α:

   Forward: 3′-TAA CAA GCC GGT AGC CCA CG-5′.
   Reverse: 3′-GCA AGG GCT CTT GAT GGC AGA-5′.
   Tm forward: 61°C, Tm reverse: 59.4°C, PCR product size: 100 bp.

3. Specific primers for bovine IL-1β:

   Forward: 3′-TTC TCT CCA GCC AAC CTT CTA T-5′.
   Reverse: 3′-ATC TGC AGC TGG ATG TTT CCA T-5′.
   Tm forward: 56.5°C, Tm reverse: 57.2°C, PCR product size: 100 bp.

4. Specific primers for bovine glyceraldehyde 3-phosphate (GAPDH):

   Forward: 3′-ATT CCA CCC ACG GCA AGT T-5′.
   Reverse: 3′-CGC TCC TGG AAG ATG GTG AT-5′.
   Tm forward: 56.3°C, Tm reverse: 56, PCR product size: 100 bp.

2.8.4 | Quantitative real-time PCR

RT-PCR was performed using the same primers used for qualitative PCR, and evergreen was used as the masterpiece of Sina Clone. The results obtained from cycle threshold (CT) were evaluated by two methods: (1) standard curve and (2) Pfaffl method.

3 | RESULTS

3.1 | Phytochemical analysis

Following the phytochemical analysis of sumac fruit extract (*Rhus coriaria* L.), it was found that most part of the extract is made up of phenols, whereas terpenoids account for the lowest of the phytochemicals present in it (Figure 1).

3.2 | Antioxidant activity

Following the MTT, LDH, and SDH assays, the progeny was described in Figure 3. As shown in the diagram, at a concentration of 1 μg/ml, the population of dead and alive cells are equally 50% following 24 hr confirmation to determine the percentage of cell viability and the count of live and dead cells from the trypan blue staining. Following the MTT, LDH, and SDH assays, the progeny was described in Figure 3.

3.3 | LDH assay

Figure 3 shows the effect of asparagus extract at a concentration of 1 μg/ml, the amount of healthy and defective cells is 50%, which is equivalent to LD50%. But, since this concentration causes half of the cells to be destroyed, it is necessary to use a concentration that does not have a toxic effect on the cell, which is possible with Median LD50% and is equivalent to 0.42 μg/ml.

3.4 | SDH assay

Figure 3 shows the effect of asparagus extract at a concentration of 1 μg/ml, the amount of healthy and defective cells is 50%, which is equivalent to LD50%. But, since this concentration causes half of the cells to be destroyed, it is necessary

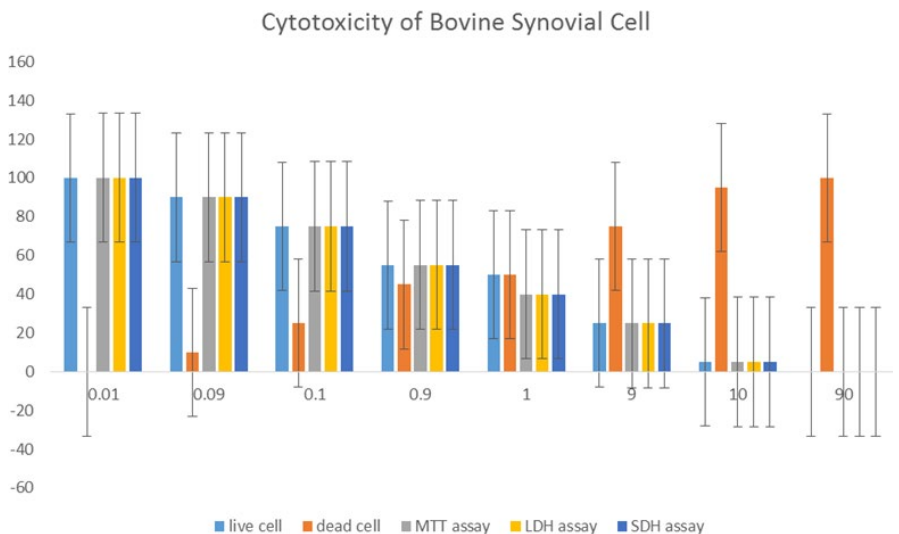

FIGURE 3 The progeny MTT, lactate dehydrogenase (LDH), and succinate dehydrogenase (SDH) assays

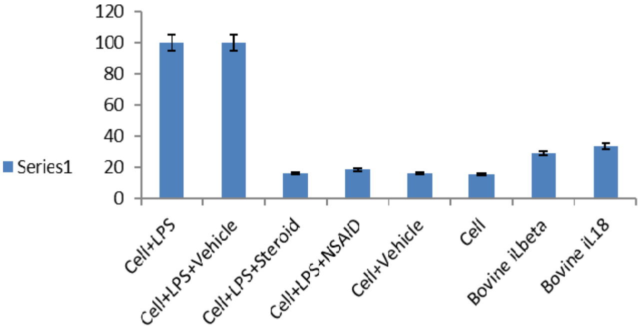

FIGURE 4 Evaluation of IL18, IL-1β gene expression in synoviocytes. Significant difference was observed between the control and treatment group by SPSS version (ANOVA) (mean ± *SD* 1, $n = 3$)

to use a concentration that does not have a toxic effect on the cell, which is possible with Median LD50% and is equivalent to 0.42 μg/ml (Figure 4).

3.5 | Statistical analysis

All data are expressed as mean ± *SD*. Statistical analysis was performed using one-way ANOVA, student *t* test and SPSS version 21 software were used. For CT analysis, $p < 0.05$ was considered statistically significant.

3.6 | Analysis of results and data analysis

An analysis of the effect of sumac on the expression of cytokines gene in synoviocytes:

Group I: synoviocyte cells without treatment.
Group II: synoviocyte cells with alcoholic extract of sumac (E.E.R.C.L).
Group III: synoviocyte cells with 20 ng/ml LPS plus 10μl alcoholic extract of sumac (E.E.R.C.L).
Group IV: synoviocyte cells with 20 ng/ml LPS (Table1).

The quantitative analysis of the effect of alcoholic extract of crushed sumac fruit (E.E.R.C.L) on Bovine IL-1β:

Analysis of IL-1β gene expression was performed by ANOVA and increased by 100% by stimulation with LPS, resulting in 29.01% reduction in treatment with alcoholic extract of sumac.

The quantitative analysis of the effect of alcoholic extract of crushed sumac fruit (E.E.R.C.L) on Bovine IL18:

The analysis of IL18 gene expression was performed by ANOVA and increased by 100% by stimulation with LPS, which resulted in a reduction of 33.61% as a result of treatment with alcoholic extract of sumac.

Investigating the results of proliferation cytokines gene using ANOVA and F-static, the formula ΔΔCT 2-:

To compare the expression of the genes used, the expression of the housekeeping gene (GAPDH) will not affect it, and as a result, all conditions for the expression of the desired genes and housekeeping genes are completely identical. Whether the treatment of cells with extracts, essential oil, or active ingredient can affect the expression of the desired genes and house genes, it will be our hypothesis. In this case, the null hypothesis (H0) represents this point. The experiment's endurance has no effect on the expression of the genes and housekeeping genes, and the changes caused by the treatment of the cells with the extract, essential oil, or active ingredient are measured by a different CT value (Table 2).

In CT analysis by ANOVA, the final statistical result is F, which examines the changes between groups, difference between groups numerator, and differences between groups denominator, in this study, the two groups were analyzed (Cell + LPS and Cell + LPS + Extract), which eventually led to the production of F. The dispersion of F is expressed by two degrees of freedom, one called the difference between the numerator groups and the other as the difference in the denominator group that combined the two-dimensional distribution or dispersion of the F. If the F spreadsheet number is less than the amount taken from the dispersion table, the proposed hypothesis is acceptable, and the obtained level is acceptable at 5% level and there is no difference between samples. However, if F-static is more than the amount taken from the dispersion table, the proposed hypothesis is unacceptable, and the amount obtained at the level of 5% is acceptable and there is a significant difference between the samples.

Therefore, if the F-static FOA value is less than 3.89, our hypothesis is acceptable, which means that the extract, essential oil, and the active ingredient have reduced the expression of the cytokine gene in the cells treated with LPS. Our hypothesis is unacceptable if the F-static exceeds 3.89.

3.7 | Analysis of Bovine IL-1β gene expression results using ANOVA and F-static

The final F-static IL-1β cytokine rate is lower than the p-value inserted in the frequency distribution table and is 1.3, as well as the results obtained by the ANOVA are equal to $\alpha = 0.05 > \sigma = 0.028$. So, we can conclude that the hypothesis is acceptable, which means that sumac can reduce the expression in IL-1β, which is consistent with the results of ANOVA, spectrum, and real-time PCR techniques (Figure 4).

3.8 | Analysis of Bovine IL18 Gene expression results using ANOVA and F-static

The final F-static cytokine IL18 value is lower than the p-value inserted in the distribution table and is 1.45, as well as the results obtained from the ANOVA are equal to $\alpha = 0.05 > \sigma = 0.0001$. Therefore, we can conclude that the hypothesis is acceptable, meaning that the sumac could reduce the expression in IL18, which is consistent with the

results of ANOVA, spectrum, and real-time PCR techniques (Figure 4).

4 | DISCUSSION AND CONCLUSION

Soluble inflammatory mediators, including cytokines and chemokines increase in synovial fluid OA and in tissues after injury. The activity of the signaling pathways of the inherent PRRS and complement system of the immune system can produce these inflammatory mediators of the solution produced by a variety of cells in the joints, including synovial fibroblasts, macrophage, and chondrocyte. Among these inflammatory intermediates, IL-1β and TNF-α have been widely studied, which are the most involved in the pathogenesis of OA (Kapoor, Martel-Pelletier, Lajeunesse, Pelletier, & Fahmi, 2011).

Synovial inflammation plays a vital role in the symptoms and structural progress of OA. However, the mechanism that causes synovial tissue inflammation is still unclear. Studies have shown that interactions between the joint tissues, such as synovium and cartilage, can lead to inflammation and cartilage destruction at the cellular level within an inflammatory immune system. Intrinsic immunity can also trigger a chronic, harmful acquiring immune response, which can report the presence of Th1 cells and suggest synthetic OA synovial markers (Ishii et al., 2002).

There was no study on the effect of sumac fruit extract and its anti-inflammatory effect. In this study, for the first time, the effect of sumac fruit extract on inflammatory activity of synoviocyte cells was investigated. Our findings suggest the anti-inflammatory effect of sumac fruit extract on synoviocyte cells in inflammation. And so, the likelihood of having an effect on the various regions of the joints with arthritis is high.

In this study, after stimulation of cells, the expression of IL-18, IL-1β cytokines increased by 100%. Following the treatment with alcoholic extract, the reduction of expression of these cytokines was 29.01% and 33.61%, respectively. A group (negative control) of PBS was used for treatment. There was no change in the level of cytokine expression, and if in a group, positive control was used to treat steroid, a significant change in expression was predicted. These results reflect the fact that the alcoholic extract of sumac fruit extract significantly reduced the expression of IL-1β and IL-18 cytokines, it has an anti-inflammatory effect.

With regard to these results, it has been shown that the alcoholic extract of sumac decreases the expression of inflammatory genes, and for the first time this study documented that the sumac fruit extract is a suppressor of cytokine gene, it suppresses the expression of the cytokine gene in synoviocyte cells, and since synoviocytes are the only articular cartilage compounds that can change phenotype, the production of these cells plays a major role in the development of joint disease. Given that the ability of sumac to reduce proinflammation in several types of multi-cellular tissue has been studied, its potential role as a complementary or alternative therapy to traditional steroids in the treatment of OA can be confirmed. Finally, sumac fruit extract can be an effective medication for reducing pain, but the effects of it still need to be studied more accurately.

CONFLICT OF INTEREST

The authors deny any conflict of interest in any terms or by any means during the study. All the fees are provided by research center fund and disbursed accordingly.

AUTHOR CONTRIBUTIONS

SR and MM: Planned the study, wrote the protocol, collected the data and drafted the manuscript, and accepted the final draft; AM and HM: Planned and designed the study, collected the data, analyzed the data and critically revised the draft, and finally approved the manuscript.

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