Anti-inflammatory Effect of Alcoholic Extract of *Nigella sativa* L on Bovine Fibroblast-like synoviocyte and THP-1

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Abstract:

Due to the side effects of current therapies for osteoarthritis one of the alternative medicine is using herbal medicine such as *Nigella sativa* L which in Iranian traditional medicine has been used as a treatment option. The purpose of this study is evaluating the effect of alcoholic extract of *Nigella sativa* (AENS) on pro-inflammatory cytokines in Bovine Fibroblast-like BFLs (BFLS) and THP-1. BFLS cells were isolated from Radiocarpal joint. After evaluating of LC50 (27 µg/mL), both cells (5x10⁵ (cells/well)) were incubated at 37 °C and 5% CO2 and 90% humidity for 72 hours with AENS (6.13 µg/ml as a media LC50). One set of cells was activated for 1h with LPS for RT-PCR analysis of COX-2, INOS, IL-1β, TNF-α expression and another set of cells was activated for 24h, cells supernatant were analyzed for PGE2 and nitrite content. The present study demonstrates that AENS reduced expression levels of COX2 and INOS was significantly along with the reducing production of NO and PGE2. Also, AENS decreased the expression of TNF-α and iL-1β in control group. Our results showed that the anti-inflammatory effect of AENS not only has anti-inflammatory effect on the BFLS cells but also related to the THP-1 that are active in the synovial membrane.

Keywords: *Nigella sativa* L, bovine fibroblast-like, THP-1, osteoarthritis, proinflammatory cytokine

corresponding author

1. Introduction:

It's a well-known fact that Osteoarthritis (OA) is slowly degenerative joint disease which is one of the most common chronic disease in aged people. Most of the joint have capability to infect by OA for instance hands, feet and knees. Articular cartilage degeneration is main reasons of osteoarthritis (OA). Low-grade chronic inflammation in the joint can promote OA progression [1]. Inflammatory mediators such as cytokines, lipid derivatives, reactive oxygen species or advanced-glycation end
products can be produced and activate cells from joint tissues (mainly synovium, cartilage and subchondral bone), thus leading to the release of matrix metalloproteinases (MMPs) into the joint cavity and eventually cartilage degradation[2] which cause pain in daily activities. Therefore, our primary aim in this study is finding a way to decrease the inflammatory effect of OA in joint, consequently, it reduces swelling and pain in joints, and it prevent the demoliotion of articular cartilage. Series of biochemical events such as overproduction of pro-inflammatory cytokine IL1β , tumor necrosis alpha TNFα cause inflammation in the joint [3]. Many studies have been illustrating that some Interleukin play important role in OA, for example, Over-expression of IL-1β In cartilage cells of the proximal cause OA [4-7]. Overexpression of TNF-α, such as IL-1β, also have been found in OA [8]. In addition, TNF-α has been found as obstacle of the synthesis of proteoglycan [9]. IL-6 is an interleukin that acts as both a pro-inflammatory cytokine and an anti-inflammatory myokine. IL-6 activity also found in synovial of OA patients [10]. TNF-α is considered as the main inflammation mediators and it’s because of involving in pro-inflammatory cytokines during the development of OA. TNF-α also stimulates the production of some of inflammatory mediators in the osteoarthritis disease. For instance, it causes increasing in genes expression of iNOS and COX-2, and consequently, increase of amount of NO and PGE2. Currently, Steroidal and nonsteroidal anti-inflammatory drugs (NSAIDs) suggested to patient for treatment, but these drugs have wide range of side effects. NSAIDs may cause a nonspecific colitis, liver damage [11], kidney damage [12] and Non-infectious meningitis [13], interfere with bone healing [14] and Gastric and intestinal disorders [15]. In this study for comparing the effect of Nigella Sativa with NSAIDs Ibuprofen has been used.

Herbal medicine has no side effects, therefore medical communities tend to use herbal medicine instead of chemical which has many side effects. Nigella sativa, often called black cumin, is an annual flowering plant in the family Ranunculaceae, native to south and southwest Asia. Many active compounds have been isolated, identified and reported so far in different varieties of black seeds. The most important active compounds are thymoquinone (30%-48%), thymohydroquinone, dithymoquinone, p-cymene (7%-15%), carvacrol (6%-12%), 4-terpineol (2%-7%), t-anethol (1%-4%), sesquiterpene longifolene (1%-8%) α-pinene and thymol etc. Black seeds also contain some other compounds in trace amounts. Seeds contain two different types of alkaloids; i.e. isoquinoline alkaloids e.g. nigellicicine and nigellicimine-N-oxide, and pyrazol alkaloids or indazole ring bearing alkaloids which include nigellidine and nigellicine. Moreover, N. sativa seeds also contain alpha-hederin, a water soluble pentacyclic triterpene and saponin, a potential anticancer agent [16]. The extensive researches using modern scientific techniques were carried out by various researchers on N. sativa. A number of pharmacological actions of N. sativa have been investigated in the past few decades, for instance, Antibacterial activity[17], Antifungal activity[18], Anti-schistosomiasis activity[19], Antioxidant activity[20], Antidiabetic activity[21], Anticancer activity[22], Immunomodulatory activity[23], Cardiovascular activity[24], Gastro-protective activity[25], Hepato-protective activity[26], Nephroprotective activity[27], Pulmonary-protective activity and anti-asthmatic effects[28], Testicular-protective activity[29], Neuro-pharmacological activities[30], Anticonvulsant activity[31], Contraceptive and anti-fertility activity[32], Antioxytocic activity[33] and Anti-inflammatory and analgesic activity[34-37]. Besides, as it known inflammation paly important role in OA, therefore its good choice to use black seed for inflammation. The aim of this experiment is survey effect of ethanol extract of black seed in decreased expression Citrullus colocynthis inflammatory cytokine TNF-α and iNOS and IL1β and COX-2 and PGE2 , NO at the molecular level on chondrocytes and monocytes / macrophages.

2. Material and Methods:
All steps of research have been proceeding in Reys Payam Noor University biotechnology laboratory in Tehran.

2.1. Nigella sativa L extract preparation:
*Nigella sativa* L was initially obtained from Iran’s center of genetic resources, and then its alcoholic extraction (AENS) was prepared.

2.2. BFL and THP-1 cell culture:
Synovial fluid was punctured from the radiocarpal joint cartilage of an 8-month-old Holstein cow and washed out three times by 1 Molar PBS buffer (PH = 7.2). Then, it was incubated in collagenase type II

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at 37°C for 16 h. After incubation, it was filtered through 1 mm Wire Strainer Screen, which was sterilized, and the wastes resulted from the effect of the collagenase type II were isolated from BFL cells. The tube was centrifuged for 3 min, the supernatant was discarded and the pellet cells were washed four times with HBSS. The supernatant was removed with a pipette and finally deposited cells were incubated in the medium containing DMEM-F12 supplemented with FBS, 50 μg/ml ascorbic acid, 100 μ/ml penicillin and 0.25 μg/ml streptomycin, with a density of 5 × 10^5 cells in the 22.2 cm plates at a temperature of 37°C, the humidity of 90% and 5% CO₂ to reach cell density of 80-85%.[38] THP-1 cells were obtained from the Pasteur Institute of Iran, and were amplified in a sterile medium to the extent necessary. The next steps were accomplished completely identical and separately in the two groups of BFL cells and THP-1 cells. Following pretreatment, cells were activated with LPS (20 ng/ml) for (1) 1 h for gene expression analysis using reverse-transcriptase PCR (RT-PCR) and (2) 24 h to measure secreted PGE₂ and nitrite levels using immunoassay.[38]

2.3. Determination the toxicity effect on synoviocyte with MTT:

Toxicity of AENS excelsior assessed by MTT Assay, Trypan blue Assay and LC50 were determined.

MTT assay:

MTT assay was conducted to determine the cytotoxicity of the test compounds. Briefly, BFLs and THP-1 cells (3 × 10^4 cells/well) were seeded on a 96-well plate and pretreated with AENS and the component extracts (0.001–100 μg/mL) for 24 h; after that, 200 μL of MTT (200 μg/mL) was added to each well and incubated for 1 h. To dissolve formazan, 100 μL of DMSO solution was added to each well and measured using a spectrophotometer (SpectraMAX M5, Molecular Devices, CA) at an absorbance of 595 nm.[39]

2.4. LC50 determination for AENS:

LC50 is defined as amount of compound to induce death in 50% of cell population. 5 × 10^5 cells incubated in 12 wells with 1 ml of DMEMF-12 media enriched 10% FBS, 50 μg/ml ascorbic acid, 100 units 50 μg/ml, 100 μg streptomycin and 0.25 μg/ml amphotericin. Plates rotated 2-3 minutes then kept in incubator 37°C, 5% CO₂, 90% humidity about 20-30 minutes. AENS in 0.01, 0.09, 0.1, 0.3, 0.5, 1, 9, 18, 27, 36, 45, 54, 63, 72, 81, 90 and 100 μg/ml added to 12 wells plates, followed by keeping in incubator 37°C, 5% CO₂, 90% humidity. After 24 hours, plates check out for LC50 determination. Accumulation of cell mass is sign of Cell lysis. by AENS injection to media nearly 50% of cell population died. In order to avoid error, median LC50 estimated 5.62 mcg/ml.

2.5. Cell stimulation and treatment:

2.5.1. Expression analysis:

RNA was isolated and RNA concentration was determined. In the following, isolated RNA was employed to produce cDNA using RT-PCR method, PCR was used to amplify cDNA and finally Real Time PCR was used to determine the expression levels of IL-1B, TNF-α, PGE₂ and NO genes by specific primers.

2.5.2. PGE₂ high sensitivity immunoassay:

A commercial PGE₂ immunoassay (R&D Systems, Minneapolis, MN, USA) was used to quantify secreted PGE₂ levels in the cellular supernatant, according to the manufacturer's instructions (Invitrogen, Eliza kit, Catalog # KHL1701, Carlsbad, California, United States). A PGE₂ standard was run in parallel to the supernatant samples. Briefly, 100 μl of each supernatant sample was assayed in triplicates on a 96-well microplate coated with a goat anti-mouse polyclonal antibody. Fifty microliters of PGE₂ high sensitivity conjugate was added to each sample well. Next, 50 μl of PGE₂ antibody solution was added to each sample well. Microplate wells were aspirated and washed with PGE₂ wash buffer for a total of three washes. After the last wash, 200 μl of pNPP substrate was added to the microplate wells. After incubation for 1 h at 37°C, 50 μl of Stop Solution was added to the sample wells. Optical density was measured immediately using the SpectraMAX 340 microplate reader (Molecular Devices) at 405 nm with wavelength correction set between 570 nm and 590 nm.[38]

2.5.3. Nitrite determination assay:

Production of NO was assayed by measuring the levels of the stable NO metabolite, nitrite, using sodium nitrite resuspended in distilled H₂O as the standard. The culture supernatant (100 μl) was allowed to react with an equal volume of Griess
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reagent (one part 0.1% naphthylethylenediamine and one part 1% sulfanilamide in 5% H3PO4) in a flat bottom 96-well microplate for 10 min at room temperature in the dark. Nitrite levels were determined by measuring absorbance at 540 nm using a spectrophotometer (SpectraMAX 340; Molecular Devices; Sunnyvale, CA, USA). Levels of nitrite were normalized to standard values [38].

2.5.4. Grouping of cell cultures:
Cultured BFL and THP-1 cells were divided into 5 groups and treated according to the table 1.

<table>
<thead>
<tr>
<th>Group</th>
<th>Bovine BFL</th>
<th>Extract</th>
<th>LPS</th>
<th>Placebo (PBS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>+</td>
<td>-</td>
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<td>3</td>
<td>+</td>
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<td>4</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
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<tr>
<td>5</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

2.6. Statistical analysis:
Data were presented as mean ± standard error of the mean (SEM). All experiments were performed in triplicate, and their results were analyzed by one-way analysis of variance (ANOVA), REST software version.20 followed by Dunnett’s post hoc test using GraphPad Prism version 5 for Windows (GraphPad Software Inc., San Diego, CA, USA). The statistically significantly value was set at p < 0.05.

3. Results & Discussion:

3.1. The effect of ASU on cytokine gene expression in bovine Sinoviocytes:
Bovine sinoviocytes cultured for 72 h with control media alone and AENS alone expressed low levels of TNF-α and IL-1β relative to LPS-activated chondrocytes (Table 1, Fig.1).

Sinoviocytes activated for 1 h with 20 ng/ml LPS expressed increased levels of TNF-α and IL-1β. AENS suppressed TNF-α expression by approximately 60% in activated chondrocytes when compared to the activated control. IL-1β expression was reduced by approximately 40% when compared to activated control. AENS profoundly suppressed TNF-α expression in activated chondrocytes to levels similar to baseline nonactivated levels (Table 1, Fig.1).

3.2. The effect of AENS on COX-2 gene expression and PGE2 production in bovine Sinoviocytes:
Bovine sinoviocytes incubated with control media alone and AENS alone expressed low levels of COX-2 relative to activated sinoviocytes (Table 1, Fig.1). Sinoviocytes also secreted low levels of PGE2 in the cellular supernatant (Fig.2). Sinoviocytes activated with 20 ng/ml LPS expressed high levels of COX-2 and secreted a significant increase in PGE2 in the cellular supernatant. AENS downregulated COX-2 expression by greater than 35% when compared to activated control levels (Table 1, Fig.1). Pretreatment with AENS in activated sinoviocytes reduced PGE2 levels by 40% when compared to activated control (Fig.2). COX-2 expression and PGE2 production in AENS-treated activated sinoviocytes was reduced to levels similar to nonactivated control levels (Table 1, Fig1.1).

3.3. The effect of AENS on iNOS gene expression and nitrite production in bovine Sinoviocytes:
Bovine chondrocytes incubated with control media alone and AENS alone displayed low levels of iNOS expression (Table1, Fig.1), and nitrite production (Fig.3), compared to activated chondrocytes. Activated chondrocytes expressed high levels of iNOS expression. Nitrite levels increased three-fold in activated chondrocytes compared to nonactivated cells. Activated chondrocytes pretreated with ASU showed significant downregulation of iNOS expression by greater than 40% (Table1, Fig.1). Pretreatment with AENS in activated sinoviocytes suppressed nitrite secretion by 30% in activated chondrocytes relative to activated control levels (Fig.3).

3.4. The effect of AENS on cytokine gene expression in human THP-1 cells:
Human THP-1 cells incubated for 72 h with control media alone and AENS alone displayed low levels of TNF-α and IL-1β relative to LPS-activated cells (TABLE2, Fig.4). Cells activated with 20 ng/ml LPS showed a significant upregulation of TNF-α and IL-1β expression. In activated THP-1 cells pretreated with AENS, TNF-α was reduced by 35%
when compared to activated control cells. Pretreatment with ASU suppressed IL-1β expression by approximately 35%. AENS suppressed TNF-α and IL-1β expression to levels similar to nonactivated control levels (Table 2, Fig 4).

3.5. Tables and figures

<table>
<thead>
<tr>
<th>Table 1. The effect of ASU on proinflammatory gene expression in chondrocytes using semiquantitative RT-PCR analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gene</strong></td>
</tr>
<tr>
<td>-----------</td>
</tr>
<tr>
<td>Bovine TNF-α</td>
</tr>
<tr>
<td>Bovine IL-1β</td>
</tr>
<tr>
<td>Bovine INOS</td>
</tr>
<tr>
<td>BovineCOX-2</td>
</tr>
</tbody>
</table>

Bovine chondrocytes were incubated with ASU for 72 h and activated with LPS for 1 h. Normalized gene expression is shown as percent of activated control (C+LPS). *P<0.05; **P<0.001.

![Graph showing gene expression analysis](https://example.com/graph.png)

Relative gene expression analysis of proinflammatory cytokine with Pfaffi method. The data represented as the mean±S.E.M of three different experiment run in duplicate, P<0.05, One-way repeated ANOVA, *=p<0.05 and **=p<0.001.

Fig. 1. The effect of AENS on proinflammatory gene expression in bovine synoviocytes using real-time PCR. Bovine synoviocytes were incubated with AENS for 72 h and activated with LPS for 24 h. Quantification of normalized TNF-α, IL-1β, COX-2 and iNOS expression are shown. Statistical significances between activated control and other groups were analyzed using the Student–Newman–Keuls test (mean ± 1 SD, n = 3).

**Fig. 2. The effect of AENS on PGF\(_2\alpha\) levels in synoviocytes.** Bovine synoviocytes were incubated with AENS for 72 h and activated with LPS for 24 h. Mean PGF\(_2\alpha\) levels released into the cellular supernatant are shown as percent of activated control. Statistical significances between activated control and other groups were analyzed using the Student– Newman–Keuls test (mean ± 1 SD, \(n = 3\)).

**Fig. 3. The effect of AENS on nitrite levels in synoviocytes.** Bovine synoviocytes were incubated with AENS for 72 h and activated with LPS for 24 h. Mean nitrite levels released into the cellular supernatant are shown as percent of activated control. Statistical significances between activated control and other groups were analyzed using the Student–Newman–Keuls test (mean ± 1 SD, \(n = 3\)).

**Table II. The effect of AENS on proinflammatory gene expression in THP-1 cells using semiquantitative RT-PCR analysis.**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Cell</th>
<th>Cell+</th>
<th>Cell+LPS</th>
<th>Cell+LPS</th>
<th>Cell+LPS</th>
<th>Cell+LPS</th>
<th>Cell+LPS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vehicle</td>
<td>Dexamethasone</td>
<td>NSAID</td>
<td>AENS</td>
<td>Vehicle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>THP-1</td>
<td>31.29±3.5</td>
<td>100</td>
<td>32.56±3.1</td>
<td>34.56±4.9</td>
<td>65.98±5.9</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>INF-(\alpha)</td>
<td>32.45±2.9</td>
<td>100</td>
<td>33.12±2.8</td>
<td>35.28±3.9</td>
<td>69±4.9</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

THP-1 cells were incubated with ASU for 72 h and activated with LPS for 1 h. Normalized gene expression is shown as percent of activated control (C + LPS). *\(P < 0.05\); **\(P < 0.001\).
3.6. Discussion:

Osteoarthritis (OA) is a degenerative joint disease which mostly happen for old age people. Mechanical factor plays important role in these disease, it is changing both structure and function of joint [40]. OA affected on all of the section in joints, for instance, Meniscus, bone, Cartilage, Muscle, Rabat, Capsule, synonym. In addition, it is intensified by age, genetics, trauma, obesity, biomechanical stress on the joints. During the growth of cartilage in the presence of osteoarthritis chondrocytes is very complex mechanism. However, researcher believe that the unbalancing between anabolic and metabolic mechanisms (which is hold Homeostasis extracellular matrix (ECM)) cause destruction of joint cartilage and its source of creation of osteoarthritis. For treatment, because of the analgesic and anti-inflammatory effects of nonsteroidal anti-inflammatory drug (NSAIDs), NSAIDs suggest to patient [39]. However, it has been approved that the treatment methods are often ineffective in some patients [40], and there is no cure for OA [41]. In addition, the mechanism of the disease and its progression is unknown [42], consequently the main goal of our study is to reduce symptoms of the disease.

OA treatment options are fall into 4 major categories: nonpharmacological, pharmacologic, complementary and alternative, and surgical. Generally, treatment should start with non-invasive and safest one before proceeding to more invasive and expensive one [43]. Nonpharmacological therapy often starts with physical exercise. The exercise program consisted of muscle strengthening and range of motion exercises. Pharmacologic treatment start with is acetaminophen. It is inexpensive, safe, and effective [44]. Towheed suggest that acetaminophen is better than placebo for treating mild osteoarthritis, and equal to nonsteroidal anti-inflammatory drugs (NSAIDs), but with fewer gastrointestinal adverse effects. Acupuncture is a good example of complementary and alternative treatment [45], however the effect of it stable only for short time. Our treatment classified in this group of treatment. Surgery should be reserved for patients whose symptoms have not responded to other treatments. The well-accepted indication for surgery is continued pain and disability despite conservative treatment [43].

In the next, Nigella sativa feature will be considering and the reason for selecting this plant. Nigella sativa (N. sativa) is an herbaceous plant which is known as the black seed. It has been used as a natural food additive. Traditionally these seeds are also used for the prevention and cure of many ailments in the Middle East and South East Asia [46]. Nigella sativa seeds contain 36%–38% fixed oils, proteins, alkaloids, saponin and 0.4%–2.5%
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essential oil. Many component has been found in the black seed, but major one is thymoquinone (27.8%–57.0%), ρ -cymene (7.1%–15.5%), carvacrol(5.8%–11.6%), t-anethole (0.25%–2.3%), 4-terpineol(2.0%–6.6%) and longifoline (1.0%–8.0%)\(^\text{47}\). Many studies has been prove that black seed has anti-inflammatory effect [34, 35, 37, 48-50]. In addition to all of benefit of Black seeds, this plant is native of Iran and it’s very in-expensive. Therefore, it’s an intelligent choice to test the effect of black seed on inflammation caused by OA. Evidence from in-vivo and in-vitro studies indicates that BFLs, chondrocytes, and cells from other joint tissues can produce and respond to a number of cytokines and chemokines that may also be detected in osteoarthritis synovial fluid, for instance, iNOS, COX, TNFα, iL1β, iL18 [58].

TNF-α are responsible for synthesis of IL-1β in the joint secreted and increased expression of IL-1β in the same tissues such as synovial fluid, synovial membrane, cartilage and subchondral bone layer has been found, TNF-α in the process pathogenesis of OA is important [51-53].

IL-1β and TNF-α secretion are usually at the same time and increased secretion of cell signaling pathway in addition to impact on the joints tissue and increased catabolism of inflammation, in reducing efficiency and reducing respiratory chain ATP in the mitochondria of cartilage cell sand thus decreased mitochondrial membrane potential, as well as synthesis of PGE2 iNOS; NO; COX-2 is induced [54-56].

4. Conclusion:

During the study was conducted on the pathophysiology of OA that increased expression of inflammatory cytokines in this disease, including IL-1β and TNF-α PGE2, NO, iNOS, COX-2, catabolic pathways that degradation joint cartilage and thus inducing apoptosis and activate the immune system. The best way to prevent symptoms is to reduce the synthesis of the cytokine. Nowadays, there are synthetic drugs with adverse side effects for reducing inflammation and arthritis pain for arthritis patients. For reducing side effects of chemical drugs can be as effective drugs with little side effects from medicinal seeds for the treatment this disease. One of those alternative solution is Black seed. Studies were conducted in the past black seeds was observed the effect anti-inflammation and reduction of apoptosis and necrosis. Our research examined on the effect of ethanol extract of black seed on inflammatory cytokine expression in inflamed cells and monocytes with LPS20 both cartilage cells /macrophage. Our tests showed that ethanol extract of this seed reduce the amount of IL-1β and it can affect very high levels of expression TNF-α, PGE2, NO, iNOS , COX-2 and it can reduce the expression of cartilage cells and monocytes /macrophage. We suggest that the future of this seed as a medicine for reducing the expression of inflammatory cytokines and reduce inflammation and joint pain and swelling caused by the expression of these cytokines used in people with osteoarthritis.

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