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# A Prophetic Medicine: Potential Therapeutic Effect of *Nigella sativa* for Osteoarthritis

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**ABSTRACT**

Osteoarthritis (OA) is the most common type of arthritis (inflammation of the joints). OA can affect all cartilage throughout the body, including the spine, but mainly attacks the legs from the pelvis, especially the knee to the ankle which affects about 10% of men and 18% of women over 60 years old. Pharmacotherapy, surgery, and complementary therapy are the currently managements of OA. Nigella sativa (NS) is one of the herbal plants which is part of the prophet's medicines in the Islamic world which still used. Thymoquinone (TQ) is one of NS compound, has an anti-inflammatory effect by inhibit the formation of eicosanoids in leukocytes and lipid peroxidation, or inhibit the expression of PF NF-κB subunits and p50 subunits with TNF-a promoters, and reduce levels of C-reactive protein (CRP). TQ also has a chondroprotective effects mechanism by decreases prostaglandin E2 (PGE) mediated by IL-1β and inhibits MMP synthesis in chondrocytes. Through its anti-inflammatory and chondroprotective effect, NS is a potential therapeutic agent which beneficial use for OA management without toxicological effects when given.

## Introduction

Osteoarthritis (OA) is a joint disease with the highest prevalence wide world, affecting about 10% of men and 18% of women over 60 years (Glyn-Jones, 2015). Based on study, radiographic results of knee OA are found in 14% to 37% of US adults and are more common in women (Nelson, 2017). According to Basic Health Research (Riskesdas) on 2013 the prevalence of joint disease based on diagnosis in Indonesia was 11.9% and decrease to 7.3% on 2018 (Health Ministry Republic of Indonesia, 2018).

Management of OA includes pharmacotherapy, surgery and complementary therapy. However, some therapies are not completely effective. Even from the literature it has been mentioned the use of nonsteroidal anti-inflammatory drugs (NSAIDs) which increase cardiovascular disease or gastrointestinal disorders as side effects (Kooshki, 2016).

*Nigella sativa* (NS) is one of the herbal agents that is part of islamic prophet's medicines which still used. Also known as *al-habbah as-sauda* or often also known as black cumin (Mushodiq, 2017). Bioactive

compounds from NS seeds based on the results of previous studies concluded that the most important bioactive substance was Thymoquinone (TQ). In several studies showing that TQ has anti-inflammatory and chondroprotective effects which are potential effects for OA management (Yimer, 2019).

### *Nigella sativa* as Prophetic Medicine

Prophetic medicine also known as *Tibb e-Nabwi* is a Prophet's (PBUH) special statement (*hadits*) that use 61 types of plants and shrubs as a preventive medicine and treatment for many types of diseases (Musharraf, 2018). NS or black cumin is part of Prophetic medicine, derived from the *al-habbah as-sauda* plant often found in Mediterranean countries, Central Europe and West Asia. The types that are very diverse, are *Nigella sativa* (*al-Habbahas-Sauda*), *Nigella damascena (Habbah Sauda Damascus*), and *Nigella orientalis* (*Eastern Habbah Sauda*) (Mushodiq, 2017).

According to Pise *et al* study, NS is believed to be an herbal medicine and can be used as a food product, has been used for centuries widely throughout the world (Pise, 2017). NS compound has been studied since long times by the most famous doctors and philosophers in the Islamic world namely Ibn Sina, commonly known as Avicenna, mentioning that there are many benefits on it. In fact, NS oil has been applied with oral medication as much as one tablespoon three times a week to relieve knee pain in geriatric patients with a diagnosis of knee OA (Tuna, 2018).

## Osteoarthritis

### Diagnosis of Osteoarthritis

OA can be diagnosed by clinically, pathologically, or radiographically. Based on American College of Rheumatology (ACR) criteria, OA classified by hands, hips, and knees. The clinical symptom are usually defined as pain, tenderness, or stiffness in joints which can be supported by radiographic OA (Nelson, 2017).

### Pathophysiology of Osteoarthritis

The pathology of OA provides evidence of the involvement of many joint structures in this disease. Initially the cartilage shows surface fibrillation and irregularities. When the disease develops, there is an erosion process in the cartilage, and over time it will aggravate physiological function. Cartilage erosion occurs in the bones so that it involves most of the joint surface (Felson, 2018).

The inability of chondrocyte homeostasis is the cause of OA to maintain the extracellular matrix component. The mechanism is not well known. This imbalance of homeostasis increases levels and decreases the proteoglycan content of the extracellular matrix, weakens the collagen tissue due to decreased synthesis of type II collagen and increases the breakdown of pre-existing collagen. In addition, an increase in chondrocyte apoptosis, release of proinflammatory cytokines, such as TNFα, IL-1 and IL-6. Which binds to chondrocyte receptors, causing further release of metalloproteinases and inhibits the production of type II collagen and ultimately increases cartilage degradation (Man, 2014).

### Management of Osteoarthritis

Comprehensive OA therapy planning is needed to increase the success of the treatment program. Planning includes education, lifestyle interventions, physical therapy, and medical therapy in the form

of oral, topical, and intra-articular injection (Kolasinski, 2020). In mild to moderate OA, NSAIDs such as Acetaminophen and topical NSAIDs can be given, but patients at risk of the digestive system can be given selective NSAIDs, namely Cyclooxy genase-2 (COX-2) inhibitors, such as meloxicam and piroxicam, with administration. gastric protective agents. In moderate to severe OA which is contraindicated against specific COX-2 inhibitors and NSAIDs, Tramadol can be used. However, it is important to watch out for side effects, such as nausea, vomiting, constipation, dizziness, and drowsiness (Indonesian Rheumatology Association, 2014).

Intra-articular injection can also be given. Analgesics, NSAIDs, steroids, and hyaluronic acid are most commonly used. Glucocorticoid injections are highly recommended for knee or hip OA, and conditionally can be given for hand OA (Kolasinski, 2020) (Indonesian Rheumatology Association, 2014).

**Anti-inflammatory effect of *Nigella sativa***

Pise and Padwal (2017) found that NS inhibited the formation of eicosanoids in leukocytes and lipid peroxidation. And it is reported to inhibit cyclooxygenase (COX) and 5-lipoxygenase (5-LOX) pathways from arachidonic acid metabolism (Pise, 2017). Other studies have shown satisfying results, significantly increasing anti-inflammatory cytokines (IL-10) and suppressing insignificant proinflammatory cytokines. This study uses an experimental animal model in the form of mice that has been taught inflammation factors. Other studies also shown that TQ able to suppress inflammatory factors form of TNF-α in experimental animals that have been induced with arthritis experimentally (Hadi, 2016).

TQ inhibit the expression of nucleus NF-κB P65 subunits and inhibit the binding of p50 subunits in-vivo with the TNF-α promoter. TNF-α, IL-6, and other proinflammatory cytokines are not only regulated by NF-κB, but also act as NF-κB activators that lead to maintaining proinflammatory conditions (Hadi, 2016). Several studies have also reported that NS decreases the synthesis of monocyte chemoattractant-1 proteins (MCP-1), Tumor Necrosis Factor alpha (TNF-a), and Interleukin beta 1 (IL-β1) and inhibits histone COX-2 deacetylases and shows anti-agent anti-COX-2 inflammation with hyper histone acetylation stimulation. As a result, the expression of COX-1 and PGE-2 is found in mild effects in animal models of respiratory tract allergies applied by NS oils (Kooshki, 2016). Arjumand *et al* study showed that TQ reduced the level of C-reactive protein (CRP) on the treated group study (Arjumand, 2019).

The results of a statistically experimental study by Pise and Schedule showed that NS has a therapeutic effect of legs swelling in the mice model groups that significantly reduce with a variety of different treatments ($P < 0.001$). However, it was statistically lower compared to the control group using NSAID type aspirin. Table 1 shows that the anti-inflammatory effect of NS is 69.60% and its closes to anti-inflammatory effect of NSAIDs such as aspirin (79.90%) (Pise, 2017).

In addition, another bioactive agent that has similar anti-inflammatory and analgesic effect of TQ is polyphenols. Based on Kooshki *et al* the analgesic effect works on the central nervous system. Several studies also revealed that NS

inhibits inflammation by reducing the production of nitric oxide (Kooshki, 2016).

Those study shows that it is more effective in reducing knee pain in elderly patients with topical use of NS oil compared to paracetamol agents, which are usually used as a safe supplement for the elderly. NS oil can even be applied for long-term use (Kooshki, 2016).

and reduces MMP synthesis in chondrocytes. From both studies, show the promising effect of TQ by reducing inflammation and cartilage degradation in the development of OA (Chen, 2010) (Wang, 2015).

**Table 1.** Comparison of *Nigella sativa* Anti-inflammation effect with Aspirin

| Group (n=6 in each group) | Mean day 1 LCS (mm) | Mean day 10 MCS (mm) | Mean difference in LCS (mm) | % anti-inflammatory effect |
|---|---|---|---|---|
| Control (normal saline 2 ml/kg p.o) | 4.117±0.09458 | 7.517±0.1108 | 3.400±0.05774 | |
| Aspirin (300 mg/kg p.o) | 3.983±0.06009 | 4.667±0.1667*** | 0.6833±0.212*** | 79.90 |
| *NS* (10 ml/kg p.o) | 4.017±0.07032 | 4.717±0.008724*** | 1.0333±0.049441*** | 69.60 |

*NS: Nigella sativa*, LCS: Linear cross section, values aren mean±SEM, n=6 in each group, *** $P<0.001$ as compared to control, SEM: Standard error of the mean

## Chondroprotective effect of *Nigella sativa*

In addition to oral and topical medications, OA can be given by intra articular injection. Analgesics, NSAIDs, steroids, and hyaluronic acid are the most commonly used agents. An experimental study by Turhan *et al* investigated the chondroprotective effect of NS oil by intra-articular injection in a rabbit model of knee OA. Using NS oil as a whole, showed significant effect on articular cartilage (Turhan, 2019).

Inflammation is a major factor on the development of OA. Chen *et al* conclude that the TQ effect decreases regulation of some MMPs and upregulated TIMP-1 expression in both chondrocytes and rabbit cartilage, which are associated with inhibiting the risk of NF-κB. According to Wang *et al* showed that TQ suppresses prostaglandin E2 (PGE) induced by IL-1β

## Safety and toxicity of *Nigella sativa*

The toxicological evaluation of NS seeds has been carried out in several studies. It has been agreed that NS has no toxic effects when given. These studies proven the toxicity effect on rats given NS treatment orally or intraperitoneally with varying drug administration times, then evaluate liver function tests and histopathologically evaluate for cardiac, hepar, and kidney organs, both of them did not show organ damage (Ahmad, 2013) (Şeyda, 2017). Another study, Arjumand *et al* showed that TQ has no hepatotoxic or nephrotoxic effects according to levels of ALT, AST, creatinine and urea in serum (Arjumand, 2019).

## Conclusion

Based on existing studies, NS has a potential therapeutic effect for OA management as an anti-inflammatory and

chondroprotective effect. In terms of toxicological evaluation, NS has no toxicity effects. NS is betterly when compared with another agent, such as NSAIDs that able to trigger gastrointestinal disorders and steroid agent which can trigger metabolic diseases and may be contraindicated for some patients. Can be conclude that NS is a herbal agent which part of prophetic medicine that benefice for OA management. The limitation may about the standard of therapy, according to various studies there are many variations of doses and routes of administrations drug.

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