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# Effect of thymoquinone on the lung pathology and cytokine levels of ovalbumin-sensitized guinea pigs

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**Abstract:**
Different pharmacological effects from *Nigella sativa* have been demonstrated in guinea pig tracheal chains in previous studies. In the present study, the prophylactic effects of thymoquinone on lung pathology as well as blood IL-4 and IFN-γ levels in sensitized guinea pigs were examined. Three groups of guinea pigs sensitized to ovalbumin were given drinking water alone (group S) or drinking water containing low (LTQ) or high (HTQ) concentrations of thymoquinone (groups S + LTQ and S + HTQ). The lung pathology as well as blood IL-4 and IFN-γ levels of the sensitized and the control guinea pigs were evaluated in three sensitized and one control group (n = 8, for all groups). The lungs of the S group showed significant pathological changes ($p < 0.001$). Blood IL-4 and IFN-γ levels were increased in the sensitized animals compared to those of controls ($p < 0.01$ and $p < 0.001$, respectively). Treatment of the S animals with thymoquinone significantly improved their pathological changes to the lung and decreased their IL-4 levels ($p < 0.05$ to $p < 0.001$) but increased their IFN-γ levels ($p < 0.001$). These results showed a preventive effect of thymoquinone on lung inflammation in sensitized guinea pigs.

**Key words:**
thymoquinone, asthma, sensitization, inflammation, cytokines, pathological changes

## Introduction

Asthma is an inflammatory disorder of the airway [13]. Many inflammatory cells, including eosinophils, mast cells, macrophages and neutrophils, are involved in the pathogenesis of airway inflammation in asthma [27]. These inflammatory cells produce more reactive oxygen species than cells obtained from normal subjects [14]. Reactive oxygen species contract airway smooth muscles and simulate both histamine release from mast cells and mucus secretion from airway epithelial cells [1].

Thymoquinone (TQ), the main constituent of *Nigella sativa* seeds [6, 7, 17, 29], has been shown to exhibit antioxidant properties. It inhibits the production

of 5-hydroxyeicosatetraenoic acid and 5-lipoxygenase products [18]. Both *Nigella sativa* oil and TQ can partially protect the gastric mucosa from acute alcohol-induced mucosal injury, which is ascribed to their radical scavenging activity [25]. The neuroprotective effects of TQ against transient forebrain ischemia-induced neuronal damage in the rat hippocampus has also been reported [3] in addition to the protective effects of TQ against doxorubicin-induced cardiotoxicity [4].

The anti-proliferative effects of TQ have been demonstrated in cancer and normal cell lines, including canine osteocarcinoma (COS31) and its cisplatin-resistant variant (COS31/rCDDP), human breast adenocarcinoma (MCF-7), human ovarian adenocarcinoma (BG-1) and Mandin-Darby canine (MDCK) cells [37]. The preventive effects of TQ on the proliferation of a PANC-1 cell line in culture were also demonstrated [39].

It has also been shown that TQ triggers apoptosis in HCT-116 cells in a dose- and time-dependent manner [40]. TQ has been shown to initiate apoptosis, even *via* p53-independent pathways, through the activation of caspase-3, 8 and 9 in p53-null myeloblastic leukemia HL-60 cells [19]. These results are also supported by reports using prostate and other cancer cells [26, 35]. These effects are believed to be caused by the up-regulation of the pro-apoptotic Bax protein along with the down-regulation of anti-apoptotic effects.

The immunomodulatory and immunotherapeutic potentials of black seed oil and its active ingredients have been discussed by Salem [29]. El-Mahmoudy and co-workers [20, 21] found that TQ normalized the elevated nitrite and cytokine profiles both *in vitro* and *in vivo* but had no significant effect on the already decreased parameters in chronically affected Otsuka Long-Evans Tokushima Fatty (OLETF) rats.

The therapeutic effects of *N. sativa* oil, which includes TQ as its principal active agent, on patients with allergic diseases (including allergic rhinitis, bronchial asthma, and atopic eczema) were also demonstrated [24]. Furthermore, Ali and Blunden [2] showed that most of the biological activity of *N. sativa* is due to TQ, the major component of the essential oil. The anti-inflammatory activity of TQ in experimental asthma has been showed previously [16].

Although our previous study showed that *N. sativa* had a relaxant effect on guinea pig tracheal chains, in another study, we showed that this relaxant effect is not due to its constituent, TQ [8]. A possible prophylactic effect of this plant was also shown in asthmatic patients [9].

Therefore, the effect of TQ on lung inflammation (lung pathology and cytokines) of sensitized guinea pigs was examined in the present study.

## Materials and Methods

### Animal sensitization and animal groups

Sensitization of the animals to ovalbumin (OA) was performed using the method described by McCaig [30, 31]. Briefly, adult Dunkin-Hartley guinea pigs (400–700 g, both sexes) were sensitized to OA (Sigma Chemical Ltd., UK) by injecting 100 mg, *ip* and 100 mg, *sc* on day one and a further 10 mg, *ip* on day eight. From day 14, sensitized animals were exposed to an aerosol of 4% OA for 18 ± 1 days for 4 min daily. The aerosol was administered in a closed chamber of dimensions 30 × 20 × 20 cm using a nebulizer (CX3, Omron Healthcare Europe B.V., Netherlands). Control animals were treated similarly, but saline was used instead of the OA solution. The study was approved by the ethical committee of the Tabriz University of Medical Sciences. Animals were housed in individual cages with access to food and water *ad libitum* and were maintained at 22 ± 2°C on a 12 h light/dark cycle (light period between 07:00 and 19:00 h).

The study was performed in control animals (group C, which was treated the same as the sensitized group but with normal saline used instead of OA, and the animals were given drinking water alone) and three different groups of sensitized animals that were given various types of drinking water during the sensitization period as follows (n = 8 for each group):
1) Drinking water alone (group S, sensitized group).
2) Drinking water containing 20 μM (0.0033 w/v) TQ (Aldrich Chemical Co., Germany) (group S + LTQ).
3) Drinking water containing 40 μM (0.0066 g %) TQ (group S + HTQ).