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Review

Immunomodulatory and anti-inflammatory action of *Nigella sativa* and thymoquinone: A comprehensive review

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ABSTRACT

Many herbal products are now used as remedies to treat various infectious and non-infectious conditions. Even though the use of herbs and natural products is much more evident in the Eastern world, their use in Western cultures is continuously increasing. Although the immunomodulatory effects of some herbs have been extensively studied, research related to possible immunomodulatory effects of many herbs and various spices is relatively scarce. Here, we provide a comprehensive review of the immunomodulatory and anti-inflammatory properties of *Nigella sativa*, also known as black seed or black cumin, and its major active ingredient, thymoquinone (TQ). This review article focuses on analyzing *in vitro* and *in vivo* experimental findings that were reported with regard to the ability of *N. sativa* and TQ to modulate inflammation, cellular and humoral adaptive immune responses, and Th1/Th2 paradigm. The reported capability of *N. sativa* to augment the cytotoxic activity of natural killer (NK) cells against cancer cells is also emphasized. The molecular and cellular mechanisms underlying such immunomodulatory and anti-inflammatory effects of *N. sativa* and TQ are highlighted. Moreover, the signal transduction pathways implicated in the immunoregulatory functions of *N. sativa* and TQ are underscored. Experimental evidence suggests that *N. sativa* extracts and TQ can potentially be employed in the development of effective therapeutic agents towards the regulation of immune reactions implicated in various infectious and non-infectious conditions including different types of allergy, autoimmunity, and cancer.

Contents

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1. Introduction

The medicinal use of natural herbs and spices is deeply rooted in the history and folklore of human beings, and many herbs and spices have been incorporated into the traditional medicine of virtually all human cultures. Throughout history, people have used a variety of herbs and plants to prevent or treat diseases. In a study done by Barrett and colleagues, it was found that as many as 50% of Americans use herbal remedies in a given year [1], indicating that the use of herbal medicine is both widespread and growing dramatically. It is the gentle, nourishing, and synergistic actions of herbal remedies that make them an excellent treatment choice [2]. Whether a treatment is approached using natural herbs or chemical drugs, whose synthesis is based on properties and actions of those herbs, medicinal herbs have played a major role in the development of modern, conventional medicine, and they will remain, like a historical treasure, as a source of therapy. Immunomodulation involves immunostimulation or immunoinhibition of certain cellular and/or humoral immune responses. This suggests that the immune system functions as an open integrated system, rather than functioning in a strictly autarchic manner. Many herbs and food additives have been shown to exert immunomodulatory effects by stimulating various branches and components of the immune system. For example, black pepper (*Piper nigrum*) and cardamom (*Elettaria cardamomum*) have been shown to possess potent immunomodulatory effects [3]. Some food products have been shown to trigger certain molecular and cellular mechanisms that lead to food allergies and oral tolerance including immunomodulation [4]. "Immunonutrition" is a term that has emerged during the last decade, which has been adopted to describe diets that have certain chemicals in the form of arginine, glutamine, fish oil, and nucleotides alone or in combination [5,6]. Although the link between many herbal products and various aspects of immunity is well-established and although the immune-related therapeutic potential of such herbal products cannot be underestimated, the exact molecular pathways and cellular mechanisms by which these products manifest their immunomodulatory effects are not fully understood.

Nigella sativa, commonly known as black seed or black cumin, is a dicotyledonous flowering plant that belongs to the botanical family *Ranunculaceae* [7,8]. Although it originated in South and Southwest Asia, it is widely grown in the Middle East, Northern Africa, and Southern Europe [9,10]. Morphologically, the plant is 20–90 cm tall and produces 5–10 petal-bearing flowers that are typically white, pale blue, pale purple, or in some cases, dark blue [11]. *N. sativa* plant and its seeds are shown in Fig. 1. The black seed reproduces asexually, whereby the fruit forms with its encapsulated white seeds. Once ripen, the encapsulated white seeds break open, become exposed to the air, and turn black in color, and hence their name [11]. *N. sativa* seeds are traditionally used as a food preservative, additive, or a spice in various cultures. However, many cultures use the seeds or their oil for their various medical benefits. Several therapeutic effects have been attributed to *N. sativa* seeds in their purified as well as crude components. Thymoquinone (TQ) (2-isopropyl-5-methyl-1,4-benzoquinone), which has the chemical formula $C_{10}H_{12}O_2$ and a molecular weight of 164.2 g/mol, is a major phytochemical bioactive ingredient in *N. sativa* oil and extracts [12–14]. The chemical structure of TQ is shown in Fig. 2. TQ makes about 30–48% of *N. sativa* seeds [11], and since its isolation and characterization in 1963 [15], it has been extensively studied by many researchers worldwide. Some of the medical benefits of *N. sativa* and TQ are due to their anti-histaminic, anti-inflammatory, anti-hypertensive, hypoglycemic, anti-cancer, and immunity-boosting effects [7–14, 16–19]. There is a growing research interest in evaluating TQ as a therapeutic agent against various *in vitro* and *in vivo* disease models.

Fig. 1. *N. sativa* plant and its seeds.

In this review, the molecular and cellular mechanisms utilized by *N. sativa* and TQ to modulate inflammation, cellular and humoral adaptive immune responses, and Th1/Th2 differentiation are summarized. The signal transduction pathways involved in mediating the immunomodulatory and anti-inflammatory effects of *N. sativa* and TQ are also reviewed. Very recent *in vitro* and *in vivo* experimental findings related to the immunoregulatory roles of *N. sativa* and TQ and their pathophysiological significance are discussed.

2. Effects on inflammation

2.1. Effects of N. sativa on inflammation

Inflammatory reactions are protective biological processes carried out by endogenous mediators to eliminate harmful stimuli. The most common inflammatory mediators include eicosanoids, oxidants, cytokines, chemokines, and lytic enzymes. These are often secreted by macrophages and neutrophils, but could also be produced by the injured tissue itself [20,21]. Moreover, cyclooxygenase (COX) and lipoxygenase (LO) enzymes are key factors in the biosynthesis of prostaglandins (PGs) and leukotrienes (LTs), which are critically involved in inflammatory responses [22,23]. Despite being a protective biological process, inflammation can have detrimental outcomes in the affected tissue leading to its damage, especially if the inflammatory reaction is accompanied by the production of reactive oxygen species (ROS). Nitric oxide (NO) is a highly reactive free radical that could trigger toxic oxidative reactions leading to inflammation and tissue damage.

Houghton and colleagues have shown that *N. sativa* fixed oil significantly inhibited cyclooxygenase (COX) and 5-lipoxygenase (5-LO) pathways of arachidonate metabolism in rat peritoneal leukocytes due to inhibited formation of thromboxane B2 (TXB2) and leukotriene B4 (LTB4) metabolites [24]. Similarly, *N. sativa* oil treatment was accompanied by inhibited production of 5-LO products and 5-hydroxyl-eicosa-tetra-enoic acid (5-HETE) in rat polymorphonuclear leukocytes at half maximal inhibitory concentration (IC_{50}) of 25 ± 1 μg/ml and 24 ± 1 μg/ml, respectively [25]. Mutabagani and El-Mahdy evaluated the anti-inflammatory effects of *N. sativa* seeds oil by assessing carrageenan-induced hind paw edema and cotton seed pellet granuloma formation in rats [26]. Intraperitoneal injection of *N. sativa* oil (0.66 ml and 1.55 ml/kg) led to a significant dose-dependent suppression of hind paw edema by 64.1% and 96.3%, respectively [26]. Moreover, intraperitoneal injection of *N. sativa* oil (0.33 ml and 0.66 ml/kg) significantly reduced granuloma weight by 17.6% and 46.9%, respectively [26]. These effects were comparable to those caused by indomethacin (3 mg/kg), which inhibited edema by 46.9% and granuloma formation by 34.4% [26]. The researchers suggested that such potent anti-inflammatory effects of *N. sativa* oil could be attributed to the inhibited generation of eicosanoids and lipid peroxidation [26]. Very similar findings using *N. sativa* seeds oil were reported in mice [27]. Moreover, Al-Ghamdi demonstrated that an aqueous extract of *N. sativa* (500 mg/kg) significantly reduced carrageenan-induced inflammation (paw edema) in Albino Wistar rats and Albino Swiss mice [28]. The anti-inflammatory effects of *N. sativa* were comparable to 100 mg/kg aspirin [28]. Similar anti-inflammatory and analgesic effects of *N. sativa* seeds