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File: ■ Black Cumin (*Nigella sativa*, Ranunculaceae)
■ Thymoquinone
■ Neuropharmacology Effects

HC 031756-578

Date: October 13, 2017

RE: Neuropharmacological Activity of Black Cumin and Its Constituents Reviewed

Javidi S, Razavi BM, Hosseinzadeh H. A review of neuropharmacology effects of *Nigella sativa* and its main component, thymoquinone. *Phytother Res*. 2016;30(8):1219-1229.

Black cumin (*Nigella sativa*, Ranunculaceae) seeds' essential oil contains approximately 32 active ingredients, with the main component being thymoquinone (TQ), which is thought to contribute to anticonvulsant, antioxidant, anti-inflammatory, antibacterial, and antifungal activity. However, other components in the seeds act synergistically with TQ to produce the benefits. Black cumin oil also contains vitamins, carbohydrates, minerals, fats, and proteins that contain up to nine essential amino acids. The purpose of this study was to review the neuropharmacological effects of black cumin and TQ. The review is a topline summary rather than detailed analysis evaluating the effects of black cumin in various forms, including oil, hydroalcoholic, ethanolic, and methanolic extracts.

Antioxidant and anti-inflammatory effects
In vitro studies demonstrate that black cumin and TQ modulate inflammation via inhibition of cyclooxygenase and 5-lipoxygenase pathways. Black cumin and TQ also have radical scavenging activity and decrease hepatic lipid peroxidation. In vivo, black cumin and TQ "elevated the antioxidant defense system," reduced lipid oxidation, and increased glutathione and catalase activities.

Anticonvulsant effects
TQ and p-cymene are the primary constituents in black cumin that have demonstrated antiepileptic activity. The authors briefly describe six studies in rats and mice that evaluated the effect of black cumin and TQ on seizure. The mechanisms of anticonvulsant effects were inhibition of calcium channels, antioxidation, opioid receptor-mediated increase in GABAergic tone (activation of gamma-aminobutyric acid [GABA] receptors and associated processes), inhibition of reactive oxygen species (ROS) formation, decrease in malondialdehyde (MDA) levels, decrease in erythrocyte glutathione peroxidase, and mediation of an increase in GABAergic response. Two studies in humans hypothesized that black cumin and TQ indirectly activated supraspinal mu1 and kappa opioid receptor subtypes. One study found that coadministration of black cumin with the antiepileptic drug valproate potentiated valproate's antiepileptic effects

while simultaneously attenuating some of the medication's hepatotoxic and teratogenic side effects.

Antinociceptive and analgesic effects
In vivo studies show that black cumin and TQ have analgesic effects in several rodent models. The mechanism of action is through the opioid mu and kappa subtypes or suppression of inflammatory mediators. According to the authors, there are no studies evaluating antipyretic effects.

Antianxiety and antidepressant properties
Black cumin and TQ represented antianxiety and antidepressant effects in several rodent models. The antidepressant activity may be mediated through serotonin, tryptophan, and cytokine production. Two human studies showed improved mood state. In one study in which subjects received 50-mg capsules of black cumin, researchers noted mood improvement after four weeks. In the second study referenced, researchers observed improvements in mood stabilization, cognition, and anxiety in subjects who took black cumin as a food-based supplement.

Effects on memory and learning
In several rodent models, it was shown that black cumin and TQ have memory and learning effects. The memory and learning effects may be mediated through serotonin levels in the brain, increases in aspartate and glutamate, inhibition of neuron degeneration, and increases in acetylcholine.

Effects on withdrawal syndromes
In vivo studies show that black cumin and TQ can decrease the effects of withdrawal through blockade of nitric oxide overproduction and oxidative stress. It may lessen symptoms of opioid dependence, as noted by marked decreases in jumps observed in morphine-dependent animals.

Effects on neurodegenerative diseases in vivo and in vitro
TQ has been shown to inhibit formation and aggregation of amyloid beta and slow degeneration of cognition in models of Alzheimer's disease. In Parkinson's disease models, the anti-inflammatory and antioxidant properties protected dopaminergic neurons. TQ may have antipsychotic effects by decreasing acetylcholinesterase activity and increasing glutathione levels. Black cumin may protect against cerebral ischemia by inhibiting lipid peroxidation, reducing MDA levels, decreasing oxidative stress, protecting against hippocampal glutathione depletion, and reducing catalase activity. In a rat model of spinal cord injury, black cumin decreased MDA, superoxide dismutase, and glutathione levels to protect the neurons. In a rat model of autoimmune encephalomyelitis, black cumin and TQ decreased levels of nitric oxide, MDA, and protected neurons. Animal studies show that TQ can decrease behavioral signs of neuropathic pain.

The authors conclude that the mechanisms of neuropharmacological activities of black cumin and TQ can be considered to be acetylcholinesterase inhibition, β-amyloid reduction, increased cerebral blood flow, neurotransmitter modulation (acetylcholine, serotonin, and dopamine), and interaction with $GABA_A$ and opioid receptors. Clinical trials are needed to evaluate the efficacy and safety of black cumin and TQ in humans. The authors did not explain how they chose the studies to include in the review. The authors state that while their review reveals the promise of black cumin for a variety of

neurological indications, more studies need to be conducted in humans for confirmation regarding its therapeutic uses. The authors declare no conflict of interest.

—Heather S. Oliff, PhD

The American Botanical Council has chosen not to reprint the original article.