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Effects of Standardized Black Seed Oil Cold Press Supplement Over A Six Week Period on Blood Pressure and Heart Rate in Healthy Patients: A Nonrandomized Clinical Trial

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ABSTRACT

Background: *High blood pressure is considered to be one of the leading causes of death in the western world. Nigella sativa, part of the Ranunculaceae family, was shown to have many therapeutic properties including hypertension diminution.*

Objective: *To determine if adding 3% thymoquinone supplement to the normal routine diet improves vascular function in healthy adults.*

Design: *Twenty healthy adults (average age 55 ± 13 years BMI avg 29.6 ± 14.2) with normal blood pressure were all treated with a daily dose of 3% thymoquinone black seed oil as small capsules for six weeks. Following a three-week washout period, patients were given placebo treatment for a period of six weeks. Blood pressure was measured daily throughout the study.*

Results: *Twenty patients received 500mg daily of ThymoQuin™ (3% thymoquinone) for six weeks. A significant decrease in blood pressure and an increase in heart rate could be observed. Following the washout period and placebo treatment, blood pressure was slightly increased and the treatment effects started diminishing.*

Conclusion: *Daily dosing with 3% thymoquinone was successful in reducing blood pressure in healthy adults.*

Keywords

Black seed oil, Nigella sativa, Black cumin.

Abbreviations

BP: Blood pressure; DBP: Diastolic blood pressure; FDA: Federal drug administration; IUD: Intrauterine device; MSQ: Medical symptom/toxicity questionnaire; NO: Nitric oxide; N. sativa: Nigella sativa; NS: Not statistically significant; NSO: N. sativa oil; NSP: N. sativa powder; SBP: Systolic blood pressure; SD: Standard deviation; SEM: Standard error of the mean; TQ: ThymoQuin; TQN: Thymoquinone.

Introduction

Elevated blood pressure (BP) or, hypertension, is a global public health concern and affects billions of people worldwide. In the United States alone, the prevalence of hypertension in the adult population is more than 29% and is estimated to affect 71 million individuals [1]. Hypertension can increase the risk of cardiovascular diseases including coronary artery disease, stroke, heart failure and others [2,3].

Plant based remedies have long been used by humans throughout history and are used today in modern medicine. Nigella sativa (N. sativa) or black seed has been known for its therapeutic properties [4] for many years and is used especially in Asian countries [5] for its health benefits and diseases management. Several key components in N. sativa are the source of its medicinal properties including proteins, amino acids, fibers, oils (especially polyunsaturated fatty

acids), volatile oil (including thymoquinone), mineral, alkaloid and more [6].

Thymoquinone (TQN) is one of the main components of the essential oil extracted from black cumin seeds of N. sativa making up to 48% [7]. This component was found to be beneficial in a myriad of pathologies including cancer [8], inflammatory disorders [9], pain [10], diabetes [11], hypertension [12] and more. The protective effect of TQN can be attributed to its ability to mitigate oxidative stress and inflammation through various mechanisms [13,14].

Previous nonrandomized controlled clinical trials have shown that supplement of 2 g daily of black cumin for one year displayed a noticeable reduction in systolic, diastolic, and mean arterial BP, heart rate, as well as other parameters [15]. In another randomized controlled clinical trial, a trend towards reduction in BP was observed after N. sativa administration, but failed to show a significant reduction of BP in elderly patients with hypertension [16]. Additional clinical studies conducted on mild hypertensive patients with the dosage of 200 mg N. sativa oil (NSO) for 8 weeks reduction SBP 2.26 ± 1.86 , reduction of DBP -1.82 ± 2.5 [17] and 2,000 mg N. sativa powder (NSP) for 6 weeks [18] showed a significant reduction of systolic blood pressure (SBP) 13.5 ± 16.28 and reduction of DBP 0.95 ± 11.32.

Products for black seed oil in the market today have low concentrations of TQN and have high free fatty acid. The product tested in this study, ThymoQuin™, was shown to have high bioavailability in pre-clinical studies [Unpublished data] and is the highest commercial N. sativa oil cold press available at 3% TQN concentration and a free fatty acid level of 1.8%. The effect of low level of FFA (below 2.5%) have been shown to reduce nitric oxide (NO) production in an in vitro model of LPS induced inflammation, and promoted the anti-inflammatory capacity of the black cumin seed oil [Unpublished]. An additional study showed that 3% TQN with low FFA (<2.5%) treatment attenuated obesity-mediated decrease of oxygen consumption, fasting glucose and improved mitochondrial biogenesis [19].

The aim of the current study was to evaluate the effects of 3% TQN and low FFA <2.5% on physiological parameters of blood circulation in healthy subjects. To this end, a non-randomized clinical trial was conducted in 20 subjects. Our findings revealed a significant decrease in BP following a six-week daily treatment. This study further validates the beneficial effects of black seed oil for the treatment of hypertension.

Methods

The study was approved by the Institutional Review Board at the testing site, and each participant provided a written informed consent (see supplementary materials). The study was conducted as a single center open label clinical trial, evaluating the effects of ThymoQuin 3% (TQ) oral dose for managing blood pressure in healthy adults.

Subjects

Subjects were recruited from the database of individuals interested in volunteering for clinical research studies. Individuals were asked to come for a screening exam at which they were asked to sign an informed consent form. Subjects were required to arrive at Natural Medicine of Stillwater three times throughout the study for baseline, mid-treatment and end of the study evaluation. Each visit, Medical Symptom/ toxicity questionnaire (MSQ) and BP measurements were performed and treatment or placebo was administered. One patient withdrawn voluntarily from the study.

Eligibility to participate was determined by the inclusion/exclusion criteria:

Inclusion criteria

- Subjects were male or female, between 18 and 65 years of age.
- If female subjects were of childbearing age, they were included only if they were using reliable contraceptive measures.
- Written informed consent was read and signed.
- Resting blood pressure was between SBP 135-159/ DBP 85-99.

Exclusion criteria

- Women who were pregnant or nursing.
- Non-pregnant women of child bearing potential who were not using reliable contraceptive measures (diaphragm, pill or IUD) on a regular basis.
- Subjects with congestive heart failure, resting bradycardia of 60 beats per minute or less (unless related to exercise, e.g., jogging).
- Subjects with severe neurological or cerebral dysfunction.
- Subjects who participated in another clinical study of an investigative drug or who have participated in a clinical trial within the past 30 days.
- Any subject considered not to be reliable based on the investigator's interview in terms of taking medication as instructed, adherence to keeping scheduled appointments and other aspects of the protocol.

Experimental design

All subjects were given ThymoQuin 3% containing 15 mg TQN from black seed oil daily for the first 42 days. Following a wash-out period of three weeks, a placebo was administered instead for six weeks until study day 108.

Subgroups

All subjects received the same dosage daily. Several subjects received additional medication and were therefore separated for analysis purposes as described in Table 1. Results are displayed as all patients or only patients without additional medications.

Intervention

Subjects were given a daily dose of 500 mg ThymoQuin containing 15 mg (Thymoquinone) in the form of capsules for 42 days. Following this treatment was a three-week wash-out period. From Day 66, subjects started taking placebo capsules every morning for

six weeks on an empty stomach until Day 108.

Blood pressure measurement

Blood pressure was measured while sitting with the arm supported at the level of the heart under physician supervision and recorded using FDA Approved blood pressure cuff- BPM-337 by iProvèn. Following baseline measurements, subjects were required to take one resting blood pressure measurement daily, but were encouraged to take twice a day (day/ night).

Medical Symptom/toxicity Questionnaire score

Subjects were interviewed for any adverse events such as reaction to the medication using the Medical Symptom/ Toxicity Questionnaire (MSQ). A score of 1-100 was given according to the patient's answers, 0 being the favorable score translating to no adverse events. A sample of the questionnaire can be found in the supplementary materials.

Black Seed Oil

ThymoQuin contains 15 mg Thymoquinone extracted from black seed oil. Administration was in the form of liquid capsules (BCC002) manufactured by Nature's Value Inc. The placebo was placebo Vege liquid capsules manufactured by Nature's Value Inc. that closely matched the color and size of the ThymoQuin capsules.

Statistical analysis

The results are expressed as means ± standard error of the mean (SEM). Statistical analysis was performed using unpaired Student's t-test for the direct comparison between two groups. Statistical analysis of data sets was carried out with the aid of GraphPad Prism 6.01 for Windows (Graphpad Software, CA, USA). A p value of < 0.05 was considered significant.

Results

Study Participants

A total of twenty participants were appointed for the study. Overall, the mean age was … years (SD, … years), with …% of participants aged … years or older (Supplementary Table). Participants were male and female (add percentage).

Blood pressure

At baseline, the mean SBP was 143.5 mm Hg (SD, 12.6 mm Hg) and the mean DBP was 90.7 mm Hg (SD, 8.5 mm Hg). Following the six week treatment with TQ 3%, SBP was 127.3 mm Hg (SD, 12.8 mm Hg) and the mean DBP was 79.6 mm Hg (SD, 11.6 mm Hg). During this six week treatment period (day 1 to 42), a marked decrease of 11.2% in SBP and 12.2% in DBP was observed. This was followed by a washout period from day 43 to day 66. At the conclusion of the trial, following a six week treatment with the placebo, the mean SBP was slightly elevated back to baseline levels with mean SBP at 131.0 mm Hg (SD, 13.3 mm Hg) and the mean DBP was 77.9 mm Hg (SD, 12.1 mm Hg). Results are summarized in Figure 1A.

When taking into account the medication prescribed to subjects, and quantifying only the non-treated patients, a more pronounced reduction can be seen in BP after initial treatment with TQ 3% (Figure 1B). However, when looking only at patients with prescription drugs, only a slight reduction in BP can be observed (Figure 1C).

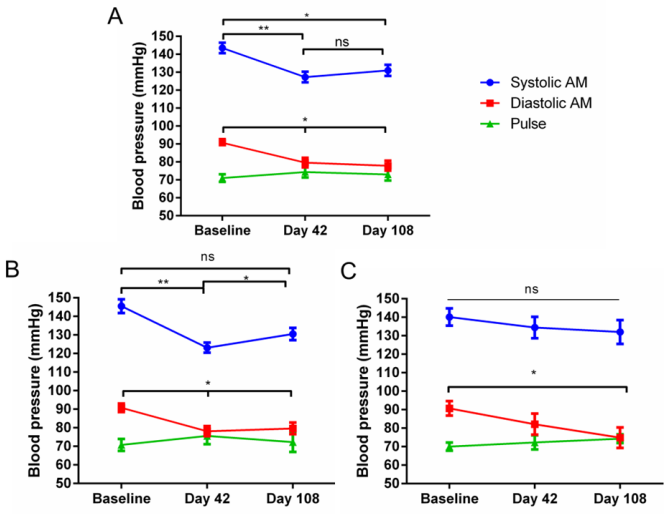

Figure 1: Blood pressure and heart rate measurements throughout the study.

Resting BP and pulse were measured once daily in the morning hours. Treatment with ThymoQuin was given to all subjects from Day 1 to 42. Wash-out between Days 43-66 followed by placebo administration until day 108. Average (± SEM) of A) all subjects, B) subjects that did not take additional drugs or C) subjects that did take additional drugs during the study. **P ≤ 0.01,*P ≤ 0.05, paired two-tailed t-test between marked data points. Ns-not significant.

When evaluating the initial effect of ThymoQuin, 48 hours after initial treatment, a significant decrease in BP was observed in all patients (Figure 2) with no increase in pulse rate.

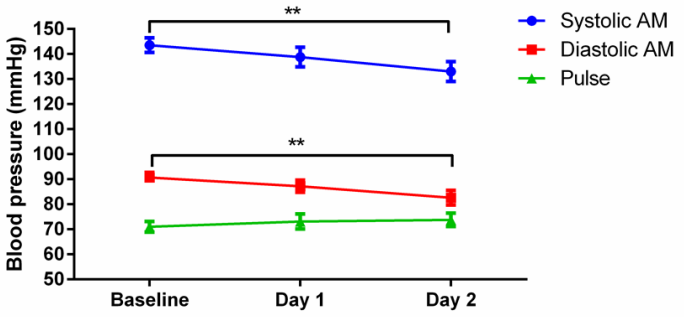

Figure 2: Blood pressure and pulse measurements from all subjects 48 hours after initial treatment.

Resting BP and pulse were measured once daily and, in this figure, the initial 48 hours measurements are shown. Treatment with ThymoQuin 3% was given to all subjects. Average (± SEM) of all subjects. **P ≤ 0.01, according to paired two-tailed t-test between the marked data points.

Medical Symptom/toxicity Questionnaire score

Subjects were evaluated at three time points throughout the study. Scoring consists of a score from 0-100. Score evaluation is summarized in Figure 2. A clear reduction is observed throughout

the study compared to baseline. Complete individual data can be found in the supplementary materials.

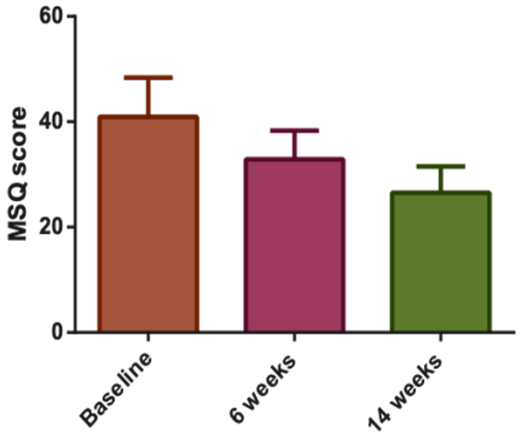

Figure 3: MSQ score throughout the study.
Questionnaire for toxicity and adverse event was given three times during the study. A reduction in overall score can be observed although with no statistical significance. Lower score means less toxicity related events.

Discussion

As humans, we have been using plants and natural ingredients for millennia in our everyday life. From the abundance of plants, black cumin has been used by different human cultures around the world for centuries to treat numerous ailments. To date, various studies have shown that black seed and its components including TQN show a remarkable natural therapy for treatment of a wide range of illnesses including neurologic disorders, hypertension, inflammatory disorders, cancer, as well as infectious diseases.

In this clinical trial, 20 healthy patients were enrolled and 19 were treated with a daily dose of ThymoQuin 3% containing 15 mg TQN from black seed oil for 42 days. This resulted in a significant decrease in blood pressure and an increase in heart rate. Following a washout period, placebo was administered for an additional 42 days which resulted in a regression towards baseline blood pressure measurements.

Several participants in this study were taking additional drugs in addition to ThymoQuin 3%. Drug interaction may have resulted in a slightly less reduced blood pressure as compared to non-drug taking participants. Drug interactions should be monitored closely while administering ThymoQuin 3% treatment in future studies.

In line with our findings, two previous clinical studies, N. sativa oil [17] or powder [18] demonstrated a significant reduction in blood pressure. This provides further evidence of the potential therapeutical effects of N. sativa.

In conclusion, the use of the bioactive components from black cumin and its oil are known to be safe at the selected doses and are recommended for the treatment of hypertension. Additional studies of their therapeutic effects using specific clinical models are further recommended.

Limitations

This study has several limitations. First, the treatment was given to all patients at the beginning of the trial instead of splitting the treatment to two separate tiers. Second, the trial did not enroll many patients and should be further expanded upon in a multiple research centers. Third, the wash out period was considerably short and should be longer to return patients to their baseline levels.

Conclusion

Healthy subjects treated with ThymoQuin for the 42-day period showed a significant reduction in overall BP and an increase in heart rate. This effect was enhanced in subjects that did not take additional drugs during the trial period and resulted in a reduction from 140/90 to 120/80 on the average. Taking all subjects into account, an initial significant decline in BP was also measured after two days of treatment and exhibited the rapid effect of ThymoQuin. A return to relative baseline levels of BP was observed once treatment with ThymoQuin was halted and a placebo was administered instead. Recent publications have noted the beneficial effects of Nigella Sativa on blood pressure in clinical trials. This study supplied an additional proof that black seed oil, ThymoQuin, is an effective treatment for lowering blood pressure. For future experiments, it should be recommended to prolong the washout period further in order to obtain a more accurate differentiation between the treatment and placebo groups.

Supplementary material

Subject	Additional drug prescribed
1	Ran out of HTN 7/12/19 - no HTN
2	-
3	Amlodipine Besylate 5mg 1x day; Hydrochlorothiazide 25 mg 1x day; Klor Con 10 meq. 1 tab 2x day
4	Spironolactone 25 mg 1.5 tab/day; 1 tab 10 AM - 1/2 tab 2 PM - HTN 6 PM
5	Lisinopril 10 mg @HS - 5/30; Lisinopril 5 mg - at baseline;Quit Lisinopril on Day 28
6	-
7	Added Fish Oil on day 5
8	-
9	Lisinopril 30 mg Metoprolol
10	-
11	-
12	-
13	-
14	-
15	25 mg Losartan
16	-
17	-
18	Dropped out of study
19	Lisinopril 10 mg
20	-

Table S1: Patient summary and prescribed drug depiction.

References

1. Nwankwo T, Yoon S.S, Burt V, et al. "Hypertension among adults in the United States: National Health and Nutrition Examination Survey, 2011-2012," NCHS Data Brief. 2013; 133: 1-8.
2. Rapsomaniki E, Timmis A, George J, et al. "Blood pressure and incidence of twelve cardiovascular diseases: lifetime risks, healthy life-years lost, and age-specific associations in 1·25 million people," Lancet Lond. Engl. 2014; 384: 1899-1911.
3. Flint AC, Conell C, Ren X, et al. "Effect of Systolic and Diastolic Blood Pressure on Cardiovascular Outcomes," N. Engl. J. Med. 2019; 381: 243-251.
4. Ahmad A, Husain A, Mujeeb M, et al. "A review on therapeutic potential of Nigella sativa: A miracle herb," Asian Pac. J. Trop. Biomed. 2013; 3: 337-352.
5. Fokunang CN, Ndikum V, Tabi OY, et al. "Traditional Medicine: Past, Present and Future Research and Development Prospects and Integration in the National Health System of Cameroon," Afr. J. Tradit. Complement. Altern. Med. 2011; 8: 284-295.
6. Mohammed N K, Abd Manap M Y, Tan C P, et al. "The Effects of Different Extraction Methods on Antioxidant Properties, Chemical Composition, and Thermal Behavior of Black Seed (Nigella sativa L.) Oil," Evidence-Based Complementary and Alternative Medicine. 2016.
7. Al-Jassir M S. "Chemical composition and microflora of black cumin (Nigella sativa L.) seeds growing in Saudi Arabia," Food Chem. 1992; 45: 239-242.
8. Gali-Muhtasib H, Roessner A, Schneider-Stock R. "Thymoquinone: A promising anti-cancer drug from natural sources," Int J Biochem Cell Biol. 2006; 38: 1249-1253.
9. Woo C C, Kumar A.P, Sethi G, et al. "Thymoquinone: Potential cure for inflammatory disorders and cancer," Biochem. Pharmacol. 2012; 83: 443-451.
10. Abdel-Fattah A F M, K. Matsumoto, H. Watanabe. "Antinociceptive effects of Nigella sativa oil and its major component, thymoquinone, in mice," Eur. J. Pharmacol. 2000; 400: 89-97.
11. Pari L, Sankaranarayanan C. "Beneficial effects of thymoquinone on hepatic key enzymes in streptozotocin–nicotinamide induced diabetic rats," Life Sci. 2009; 85: 830-834.
12. Khattab M M, Nagi MN. "Thymoquinone supplementation attenuates hypertension and renal damage in nitric oxide deficient hypertensive rats," Phytother. Res. 2007; 21: 410-414.
13. Nagi M N, Alam K, Badary O A, et al. "Thymoquinone protects against carbon tetrachloride hetatotoxicity in mice via an antioxidant mechanism," IUBMB Life.1999; 47: 153-159.
14. El Gazzar M, El Mezayen R, Marecki J C, et al. "Anti-inflammatory effect of thymoquinone in a mouse model of allergic lung inflammation," Int. Immunopharmacol. 2006; 6: 1135-1142.
15. Badar A, Kaatabi H, Bamosa A, et al. "Effect of Nigella sativa supplementation over a one-year period on lipid levels, blood pressure and heart rate in type-2 diabetic patients receiving oral hypoglycemic agents: nonrandomized clinical trial," Ann. Saudi Med. 2017; 37: 56-63.
16. Rizka A, Setiati S, Lydia A, et al. "Effect of Nigella sativa Seed Extract for Hypertension in Elderly: a Double-blind, Randomized Controlled Trial," Acta Medica Indones. 2017; 49: 307-313.
17. Dehkordi F R, Kamkhah A F. "Antihypertensive effect of Nigella sativa seed extract in patients with mild hypertension," Fundam. Clin. Pharmacol. 2008; 22: 447-452.
18. Qidwai W, Hamza H B, Qureshi R, et al. "Effectiveness, Safety, and Tolerability of Powdered Nigella sativa (Kalonji) Seed in Capsules on Serum Lipid Levels, Blood Sugar, Blood Pressure, and Body Weight in Adults: Results of a Randomized, Double-Blind Controlled Trial," J. Altern. Complement. Med. 2009; 15: 639-644.
19. Maria Licari, Marco Raffaele, Zachary F. Rosman, et al. "Beneficial Effects of Thymoquinone on Metabolic Function and Fatty Liver in a Murine Model of Obesity. 2019; 9: 9.