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SHORT COMMUNICATION

Effectiveness of *Nigella sativa* Oil in the Management of Rheumatoid Arthritis Patients: A Placebo Controlled Study

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The constituents of *Nigella sativa* modulate the immune system. The aim of the present work was to study the effectiveness of *Nigella sativa* oil in RA patients. Data from 40 female RA patients diagnosed according to the 2010 ACR/EULAR were analysed and discussed. The patients took two placebo (starch filled) capsules daily for 1 month. This was followed by a month of *Nigella sativa* oil capsules 500 mg twice/day. The disease activity score (DAS-28) significantly decreased after receiving the *Nigella sativa* capsules (4.55 ± 0.82) compared with before and after placebo (4.98 ± 0.79 and 4.99 ± 0.72, respectively) ($p = 0.017$). Similarly, the number of swollen joints and the duration of morning stiffness improved. A marked improvement in the disease activity was shown by both the ACR20 and EULAR response criteria in 42.5% and 30% of the patients, respectively, after intake of Nigella. Supplementation with *Nigella sativa* during DMARD therapy in RA may be considered an affordable potential adjuvant biological therapy. Copyright © 2011 John Wiley & Sons, Ltd.

Keywords: rheumatoid arthritis; *Nigella sativa* capsules; disease activity.

INTRODUCTION

Thymoquinone (TQ), the major constituent of *Nigella sativa*, is a novel inhibitor of proinflammatory pathways that provides a promising therapeutic strategy (Chehl *et al*., 2009). The oil and seed constituents have shown different immunomodulatory and immunotherapeutic potentials and possess reproducible antioxidant effects through enhancing the oxidant scavenger system (Salem, 2005). The seeds/oil have antiinflammatory, analgesic, antipyretic, antimicrobial and antineoplastic activity (Ali and Blunden, 2003).

Thymoquinone inhibits proinflammatory cytokine production, demonstrating its antiinflammatory effect. Thymoquinone in a concentration dependent manner showed a blunted effect on the stimulated release of inflammatory mediators (Ali and Blunden, 2003).

The extracts of *Nigella sativa* exhibit an inhibitory effect on nitric oxide production, which further validates its traditional use for the treatment of rheumatism (Mahmood *et al*., 2003).

The aim of the present work was to study the therapeutic effectiveness of *Nigella sativa* on the parameters of disease activity, functional capacity and radiological changes in RA patients.

PATIENTS AND METHODS

Forty female patients with definite RA, diagnosed according to the 2010 ACR/EULAR classification criteria for RA (Aletaha *et al*., 2010), were recruited from the Rheumatology outpatient clinic, Faculty of Medicine, Cairo University. Two placebo (starch filled) capsules were used daily by the patients for 1 month followed by a month of *Nigella sativa* oil capsules (cold pressed, 100% purity, Nigellar 'Kahira Pharmaceutical and Chemical Industries Company, Cairo, Egypt' 500 mg twice/day).

All patients were on the combined therapy of methotrexate (MTX), hydroxychloroquine, folic acid and diclophenac sodium. None of the patients had received any form of corticosteroid for at least 6 months before the start of the study.

Full history taking, clinical examination and laboratory investigations were performed before starting the study, after the placebo and after the intake of the Nigella capsules. The modified Larsen score of hands and feet was calculated as well as the percentage of damage. Posteroanterior radiographs of hands, wrists and feet were obtained from all patients at enrolment and after 2 months. The DAS28, EULAR response criteria and ACR20 were determined.

The study has been approved by the local ethics committee.

RESULTS

The study included 40 female RA patients with the demographic features presented in Table 1. Their mean functional class before the study was 2.63 ± 0.95 and after the end of the *Nigella sativa* intake it became 2.2 ± 0.82 and the difference was significant ($r = 0.85$, $p = 0.000$).

Rheumatoid nodules were present in 14 patients (35%) and rheumatoid factor was positive in 31

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Table 1. Demographic features of the rheumatoid arthritis patients

Feature	Mean ± SD
Age	42.83 ± 12.45
Age at disease onset	36.45 ± 10.28
Disease duration	6.43 ± 5.22
Body mass index (BMI)	27.92 ± 7.27

(77.5%), while anti-CCP was present in 27 (67.5%). They were all receiving MTX with a mean dose of 16.81 ± 3.62 mg/week, hydroxychloroquine (200 mg/day), folic acid 5 mg (taken on the day following the MTX injection) and diclophenac sodium 50 mg once or twice daily as needed. The worst joint involved at the time of the study was as follows: knee (25%), MCPS and PIPs (22.5%), wrist (7.5%), ankle (5%), while the rest of the patients had polyarthritis.

Clinical and laboratory parameters of disease activity in the rheumatoid arthritis patients before and after use of placebo and after *Nigella sativa* intake are shown in Table 2. Further laboratory investigations initially performed for the patients showed normal levels of the red blood cell count, hematocrit value, liver enzymes and kidney function tests.

The mean modified Larsen's score was (24.85 ± 21.96) and the mean % damage was 12.42 ± 10.98% and these results remained the same after Nigella intake. Seventeen patients (42.5%) showed an ACR20 improvement after the intake of *Nigella sativa*, while the improvement according to the EULAR response criteria was shown in 12 patients (30%); the improvement being good in five patients and moderate in seven.

The DAS28, after intake of Nigella, significantly correlated with the age at disease onset ($r = 0.66$, $p < 0.001$), platelet level ($r = 0.7$, $p < 0.001$) and negatively correlated with the hemoglobin level ($r = -0.48$, $p = 0.002$) and the WBC count ($r = -0.36$, $p = 0.023$). The modified Larsen score significantly correlated with the DAS28 and functional class at the start of the study ($r = 0.54$, $p = 0.005$ and $r = 0.48$, $p = 0.012$ respectively) while it became insignificant after Nigella ($r = 0.35$, $p = 0.084$ and $r = 0.19$, $p = 0.36$). The modified Larsen score significantly correlated with the presence of anti-CCP ($r = 0.56$, $p = 0.003$). At the start of the study, the methotrexate dose significantly correlated with DAS28 ($r = 0.34$, $p = 0.03$).

DISCUSSION

In the present study, the mean DAS-28, the number of swollen joints and morning stiffness were significantly decreased after receiving *Nigella sativa* capsules. A significant improvement in the disease activity was shown by both the ACR20 and EULAR response criteria. Previous studies on the pharmacological effects of NS seeds and TQ confirmed clinically and radiologically the suppression of adjuvant-induced RA with a significant improvement in the signs of inflammation in a dose-dependent manner (Ghannadi *et al*., 2005). Antioxidants may protect against the development of RA by combatting oxidative stress. Another element in the evolving optimism about treatment of RA has been the use of multiple agents in combination therapy (Costenbader *et al*., 2010).

In the present study, there was a tendency for an increase in the hemoglobin (Hb) level and a significant decrease within normal values of the WBC count. The seeds/oil induce changes in the hemogram, including an increase in the packed cell volume (PCV) and Hb, and are characterized by a very low degree of toxicity (Ali and Blunden, 2003).

The patients included in the present study were receiving MTX and diclophenac sodium. Thymoquinone can be used similar to MTX as a safe, effective and useful therapy for RA (Budancamanak *et al*., 2006). Thymoquinone showed multiple benefits including both antioxidant and antiinflammatory properties. Increased levels of glutathione were seen with increasing TQ (Ali and Blunden, 2003).

The constituents of NS are inhibitors of eicosanoid generation and membrane lipid peroxidation. Thymoquinone is a very potent inhibitor of 5-lipoxygenase and cyclooxygenase. These pharmacological properties of the oil support the traditional use of NS and its derived products as a treatment for rheumatism and related inflammatory diseases (Houghton *et al*., 1995).

There was a significant decrease in the VAS for pain in RA patients. *N. sativa* oil and thymoquinone produce antinociceptive effects through indirect activation of the supraspinal mu(1)- and kappa-opioid receptor subtypes (Abdel-Fattah *et al*., 2000). Supplementation with NS during DMARD therapy in RA may be considered a potential adjuvant therapy that is affordable.

Conflict of Interest

The authors have declared that there is no conflict of interest.

Table 2. Clinical and laboratory parameters of disease activity in rheumatoid arthritis patients before and after use of placebo and after *Nigella sativa* intake

Parameter (mean ± SD)	Before placebo	After placebo	After Nigella	*p*
MS	30.63 ± 28.04	30.63 ± 28.04	17.13 ± 11.6[a]	0.016
RAI	6.58 ± 4.17	6.43 ± 3.88	4.68 ± 2.66	0.075
Swollen joints	2.4 ± 1.17	2.3 ± 1.14	1.35 ± 0.92[a]	0.000
VAS pain	60.25 ± 12.71	60.25 ± 12.71	52.75 ± 18.81[a]	0.039
Hb	12.19 ± 1.28	12.18 ± 1.27	12.21 ± 0.95	0.98
ESR	36.25 ± 18.43	36.48 ± 18.6	32.75 ± 13.38	0.28
WBC	8.85 ± 2.67	8.82 ± 2.63	7.49 ± 1.33[a]	0.012
Platelets	316.18 ± 59.06	315.45 ± 59.43	334.35 ± 81.6	0.37
DAS-28	4.98 ± 0.79	4.99 ± 0.72	4.55 ± 0.82[a]	0.017

[a]Significantly different from the corresponding parameter before starting the study.

DAS, disease activity score; ESR, erythrocyte sedimentation rate; VAS, visual analogue scale of pain; RAI, Ritchie articular index; MS, morning stiffness; Hb, hemoglobin; WBC, white blood cell count.

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