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Topical *Nigella Sativa* in the treatment of oro-genital ulceration in Behcet's disease.

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Abstract

To assess the effect of *Nigella sativa* oil as a topical preparation for treatment of oro- genital ulceration of Behcet's disease. This is a double blinded therapeutic trial in which 40 patients with Behcet's disease manifested as recurrent episodes of oral and genital ulceration were enrolled into 2 groups; *Nigella sativa* oil was applied as 10% in glycerin topically 3 times / daily to the first 20 patients. The other 20 were given glycerin only. Assessment was done 4 days then 8 days after treatment.

Results were recorded as they appeared in clinical examination and those records were arranged in tables for both groups concerning oral and genital ulceration cases.

Nigella sativa oil is a new topical agent for promotion of healing of oro- genital ulceration of Behcet's disease which may act through Pits anti-inflammatory effect.

Keywords: *Nigella sativa*, Behçet's disease, oral ulcers, genital ulcers, oro- genital ulceration.

Introduction

Behcet's disease (BD) is a chronic relapsing disease characterized by multiple signs and symptoms. The etiology of the disease is not well understood although viral and immunological factors are implicated ⁽¹⁾. It is a chronic multisystemic inflammatory disorder with oral ulcers, genital ulcers, uveitis and vasculitis along with mucocutaneous manifestations ^{(2), (3)}. The concept of the disease has changed from a triad of signs and symptoms to a multisystemic disorder including articular, vascular, gastrointestinal, cardiopulmonary and neurological involvement ⁽⁴⁾.

The diagnostic criteria (ISG) (International Study Group for Behçet's Disease) are summarized in 1990 ⁽⁵⁾. These are based on a cohort of 914 patients from several centers around the world. Clinical features

were compared with those of 308 patients with connective tissue diseases who had also had recurrent oral ulceration. The use of the new criteria offered an increase in diagnostic sensitivity and specificity compared with previously published diagnostic criteria. Although it was specified that recurrent oral ulceration was a prerequisite, it was acknowledged that cases existed in which there was pathologically proven Behçet's syndrome without oral ulceration; it was stated that the criteria would exclude only 3% of patients in whom recurrent oral ulceration was not a feature. At least 3 episodes of oral ulceration must occur in a 12-month period. They must be observed by a physician or the patient and may be Herpiform or aphthous in nature. At least 2 of the following must occur: (1)

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recurrent, painful genital ulcers that heal with scarring; (2) ophthalmic lesions, including anterior or posterior uveitis, or retinal vasculitis; (3) skin lesions, including erythema nodosum, pseudofolliculitis, or papulopustular lesions (may also include atypical acne); and (4) pathergy, which is defined as a sterile erythematous papule larger than 2 mm in size appearing 48 hours after skin pricks with a sharp, sterile needle (a dull needle may be used as a control) ^(6,7). Concerning genital ulcers, in females, these lesions may appear on the vulva and vagina; in males, they appear at the perianal region, penis, and scrotum.

The lesions are deeper and more likely to scar than the oral ulcerations, and they last longer. Ulcerations in women may be related to menstruation ⁽⁷⁾.

Nigella sativa, one of the Ranunculaceae, commonly grows in the Middle East, Eastern Europe and Middle Asia. In Arab countries it is commonly known as 'Habba Al-Sauda' or 'Habba Al-Baraka'⁽⁸⁾. The *Nigella sativa* seeds have a great medicinal importance and known to include many medicinal and recently reported pharmacological effects including anti-parasitic, anti-helminthes⁽⁹⁾, anti-cestodal⁽¹⁰⁾ and anti-schistosomal⁽¹¹⁾, anti-bacterial⁽¹²⁾, anti-fungal⁽¹³⁾, anti-viral⁽¹⁴⁾, anti-oxidant⁽¹⁵⁾, anti-inflammatory⁽¹⁶⁾ activities and have been shown to enhance the T cell mediated immune response⁽¹⁷⁾. Large number of studies worldwide carried out the pharmacological effect of *Nigella sativa* seeds and its fixed oil topically and systemically with no reports on its toxic effect.

Recently Zaoui et al suggests a wide margin of safety for therapeutic doses of *Nigella sativa* fixed oil ⁽¹⁸⁾. This study aims to reveal the role of anti-inflammatory effect of *Nigella*

sativa fixed oil on curing rate of recurrent oro- genital ulceration of Behçet's disease.

Material and methods

Fourty Iraqi patients who fulfilled the International Study Group (ISG) criteria for diagnosis of Behçet's disease were included in this study. Those 40 patients were 27 male and 13 female. They were divided randomly into 2 groups, 20 patients for each. Full history was taken concerning age, family history of Behçet's disease, history of present illness, chief complaint, what treatments given to him either systemically or topically and the response to these treatments. Clinical examination was performed. Those 40 patients were reported clinically to have recurrent oral and genital ulceration; assessment was done by clinical examination only.

Seeds of *Nigella sativa* were purchased from a herbal shop in Baghdad. After a good cleaning of the seeds they were kept in a clean container away from sunlight, heat and humidity until they were used. The fixed oil was prepared by using the mechanical pressure device ⁽¹⁹⁾. In this method after weighing 500 g of seeds, they were compressed mechanically using a pressure of 400 Bar by hydraulic compressor, the oil was expressed by a Millipore filter paper of gage 0.4 micrometers; the expressed oil was then weighed and kept in a clean and tight container till usage. A reversed thin layer chromatography (TLC) was carried out for identification of the fixed oil.

Nigella sativa oil preparation is then done by diluting the previously prepared fixed oil in glycerin in a ratio 1:10. First 20 patients were instructed to use *Nigella Sativa* oil preparation topically 3 times /day, other 20 patients were asked to use glycerin topically 3

times/ day. Applications include both oral and genital ulcers. Re-assessment was conducted 4 days later, and then another assessment was done after 8 days of treatment, by using the same procedure.

Results

Concerning sex distribution, the males were 67.5 % of total study sample while females were 32.5 % of it.

Regarding age distribution, 30-39 years have the highest ratio among the patients while ages below 20 years have the least.

1- Treatment of oral ulcers

By analyzing table (1), observations were recorded in the table in comparison with the observations of the patients' first visits. From these observations we conclude that *Nigella sativa* oil affects healing rate that the oral ulcers cured within 8 days of treatments unless few scars were still noticed which may totally disappear after further application of the fixed oil while pain disappeared from the first application. Glycerin affects only pain sensation but for a short time at every application and no effect at all on cure rate.

2- Treatment of genital ulcers

Genital ulcers were qualified and reported clinically; notes were recorded about their appearance and location for all involved patients, after assessments results were recorded as in table (2). It was necessary to separate the records of oral ulcers from genital ulcers due to differences in location from that of oral ulcers and differences between both sexes. According to this we expected that the healing rate will be slower in genital ulcers.

Discussion

The results of this study proved that *Nigella sativa* oil preparation has a tremendous therapeutic effect on the healing rate of oral and genital ulcers of Behçet's disease, and this was confirmed by the control group who show no effect for glycerin which acts only as a diluting agent for the *Nigella sativa* oil and a little soothing agent. This may be due to its anti-inflammatory effect which is mainly contributed to its sole active ingredient (thymoquinone) content which had been proved to possess anti inflammatory action⁽¹⁹⁾. Many active principles have been isolated from *N. sativa* fixed oil, including thymoquinone, thymohydroquinone, dithymoquinone, thymol, carvacrol, nigellicine, nigellimine-N- oxide, nigellidine and alpha-hedrin^(20, 21, 22, 23, 24 & 25). Over the last few decades, a number of pharmaco-therapeutic effects of various extracts of *Nigella sativa* and some of its active principles have been investigated, using modern scientific techniques⁽²⁶⁾.

To the best of our knowledge which concerns our subject this was the first study that employed *Nigella sativa* oil topically in the treatment of recurrent oro-genital ulceration in Behçet's patients.

From this study it can be concluded that *Nigella sativa* fixed oil is a promising local therapeutic agent beyond the extent of our simple study, since it is safe and non toxic for either systemic and topical applications.

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Table No. (1) The effect of therapeutic trial using *Nigella sativa* fixed oil compared with glycerin for the treatment of oral ulcers in Behçet's disease as indicated by clinical examination.

Type of treatment	<i>Nigella sativa</i> fixed oil 10% in glycerin	Glycerin
Number of patients	20 patients	20 patients
4 days after treatment	Healing noticed in all patients but not totally cured, pain was recorded to disappear from the first application.	No healing noticed only comfortable feeling because of absence of pain for short period after each application.
8 days after treatment	Healing process was greater in all patients compared with the 1 st assessment with few scars left, in 17 of them, which may disappear with further applications.	No healing noticed.

Table No. (2) The effect of therapeutic trial using *Nigella sativa* fixed oil compared with glycerin for the treatment of genital ulcers.

Type of treatment	<i>Nigella sativa</i> fixed oil 10% in glycerin		Glycerin	
Number of patients	13 male	7 female	14 male	6 female
4 days after treatment	Healing noticed in all patients but not totally cured specially the ulcers that are observed in penis and peri-anal area.	Healing noticed in all patients but not totally cured. Healing process were better in ulcers in vulva area.	No healing noticed only comfortable feeling because of absence of pain for short period after each application.	No healing noticed only comfortable feeling because of absence of pain for short period after each application.
8 days after treatment	Healing process was better in 11 patients and only scars were left	Healing process was better in 4 patients and only scars were left	No healing noticed.	No healing noticed.
Total	15 from 20 patients were responded to treatment		None of the 20 patients were responded to treatment	