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ORIGINAL RESEARCH ARTICLE

Cardioprotective Effect of *Nigella sativa* in Pediatric Patients with Type 1 Diabetes Mellitus: A Randomized Controlled Study

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Abstract

Background and Objective *Nigella sativa* is a widely used medicinal plant with several potential therapeutic uses. This study aimed to investigate the possible beneficial cardioprotective effect of *Nigella sativa* in pediatric patients with type 1 diabetes mellitus.

Methods Sixty children and adolescents with type 1 diabetes were randomized into two groups: group I ($n = 30$) who received *Nigella sativa* seed oil 450 mg twice daily after meals for 3 months in addition to insulin, and group II ($n = 30$) who received insulin alone. Echocardiographic examinations were performed before and after the treatment. The lipid profile, malondialdehyde, nitric oxide, tumor necrosis factor-α, transforming growth factor-β, and troponin I were also measured before and after *Nigella sativa* treatment.

Results After 3 months of *Nigella sativa* administration, group I had significantly lower cholesterol and low-density lipoprotein-cholesterol, malondialdehyde, nitric oxide, tumor necrosis factor-α, transforming growth factor-β, and troponin I levels compared with their pretreatment levels and compared with group II. In addition, group I had a significantly higher left ventricular E'/A' ratio and two-dimensional left ventricular global longitudinal strain (2D-LV GLS) compared with baseline values and compared with group II after treatment.

Conclusions *Nigella sativa* can improve subclinical left ventricular dysfunction in pediatric patients with type 1 diabetes mellitus.

Clinical Trial Registration: this clinical trial was registered at www.pactr.org with ID: PACTR202302478939306.

Key Points

Nigella sativa is a widely used medicinal plant with several potential therapeutic uses. This study aimed to investigate the possible beneficial cardioprotective effect of *Nigella sativa* in pediatric patients with type 1 diabetes mellitus.

After 3 months of *Nigella sativa* administration, pediatric patients with type 1 diabetes had significantly lower cholesterol and low-density lipoprotein-cholesterol, malondialdehyde, nitric oxide, tumor necrosis factor-α, transforming growth factor-β, and troponin I levels than the control group. Similarly, echocardiographic data improved significantly in the treatment group.

We concluded that *Nigella sativa* may improve subclinical left ventricular dysfunction in pediatric patients with type 1 diabetes.

1 Introduction

Diabetic cardiomyopathy (DCM) is a diabetes mellitus (DM)-induced cardiac dysfunction associated with myocardial structural and functional changes. This occurs in the absence of hypertension, coronary artery disease, and valvular abnormalities [1]. Subclinical myocardial dysfunction due to DCM has been reported in type 1 diabetic children and adolescents [2–5]. The pathophysiology of DCM is complex. It involves several factors: chronic hyperglycemia,

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oxidative stress, increased fatty acid oxidation, inflammation, impaired calcium homeostasis, activation of the renin-angiotensin system, autonomic cardiac dysfunction, cardiac cell apoptosis, and cardiac fibrosis [6–8].

Oxidative stress plays a central role in the development and progression of several DM-associated complications. Reactive oxygen species (ROS) can damage DNA, proteins, and lipids. They can also produce reactive nitrogen species from nitric oxide. Increased ROS, hyperglycemia, and the production of inflammatory cytokines lead to myocardial inflammation. Oxidative stress can also activate cardiac cell death through apoptosis and necrosis [8–10].

Myocardial fibrosis is the main structural feature in DCM that occurs because of the activation of several fibrogenic pathways due to hyperglycemia, overproduction of advanced glycation end products, oxidative stress, inflammatory cytokines, and the activation of growth factor cascades. Increased cardiac fibrosis in DCM is associated with cardiac stiffness, hypertrophy, and dysfunction [11].

Nigella sativa (NS), also known as the black seed, is a medicinal plant widely used throughout the world. Its main active constituent, thymoquinone, has shown several potential therapeutic effects in type 2 DM, hypertension, obesity, renal disorders, asthma, and several chronic diseases [12–14].

Previous studies found that NS can reduce cardiovascular risk factors and decrease cardiac dysfunction in patients with type 2 DM [15–17]. The effect of NS on cardiac function in pediatric patients with type 1 DM has not been previously studied. This study aimed to investigate the possible beneficial cardioprotective effect of NS in children with type 1 DM.

2 Methods

2.1 Patient Selection

This randomized clinical trial included 60 patients with type 1 DM aged between 10 and 18 years recruited from the pediatric endocrinology outpatient clinic of Tanta University hospitals. The local ethics committee of the Faculty of Medicine, Tanta University approved the study. The researchers registered the clinical trial at www.pactr.org with ID: PACTR202302478939306 before the recruitment of the patients, and the parents of all included children provided a written consent.

Inclusion criteria were pediatric patients with type 1 DM who can swallow capsules, with a DM duration of more than 1 year. Exclusion criteria were clinical evidence of rheumatic fever, heart failure, hypertension, coronary artery disease, the presence of any chronic systemic disease, other endocrine diseases, and the administration of drugs that may affect cardiac function or drugs that may have antioxidant or anti-inflammatory effects.

2.2 Randomization, Blinding, and Concealment

Included diabetic patients were randomized to:

Group I (NS treatment): 30 pediatric patients with type 1 DM who received NS seed oil 450 mg (Baraka; Pharco Pharmaceuticals, Cairo, Egypt) twice daily after meals for 3 months in addition to insulin.

Group II (control group): 30 pediatric patients with type 1 DM who received insulin alone.

Randomization of patients was carried out by an independent statistician who used simple randomization through a randomization table created by a computer software program, "Research Randomizer." For allocation concealment, we used sealed opaque envelopes with sequential numbers. After a written consent was obtained, the sealed opaque envelope was opened, and the patient was included in the respective group. The investigators and outcome assessors were blinded to the study groups. All patients underwent a complete physical examination, and a full medical history including age, sex, duration of DM, insulin regimen, and a history of other medications was obtained from all included patients.

2.3 Laboratory Investigations

Venous blood samples after at least 8 hours of fasting were obtained at baseline and after a 3-month treatment period from all patients to measure the following biochemical markers.

1. Fasting blood glucose (FBG) and hemoglobin A1c (HbA_{1c}) were determined using commercially available reagent kits (Spinreact and Biosystems Reagents, Gerona, Spain).
2. A lipid profile, including total cholesterol, triglycerides (TG), and high-density lipoprotein-cholesterol (HDL-C), was measured using commercial kits (Biodiagnostic, Giza, Egypt). Low-density lipoprotein-cholesterol (LDL-C) was estimated using the Friedewald formula [18].
3. Serum malondialdehyde (MDA) was measured using thiobarbituric acid according to the Draper and Hadly method [19].
4. Serum nitric oxide was measured according to the method of Miranda et al. as total nitric oxide metabolites (nitrate plus nitrite) [20].
5. Serum tumor necrosis factor alpha (TNF-α), transforming growth factor beta-1 (TGF-β1), and troponin-I were

measured using ELISA kits (DRG International Inc., Springfield, NJ, USA).

2.4 Echocardiography

Echocardiography was carried out for all patients at baseline and after 3 months of drug treatment using a Vivid 7 ultrasound machine (GE Healthcare, Oslo, Norway) with a 3.5-MHz transducer. Left ventricular ejection fraction (LV EF) was obtained using conventional two-dimensional (2D) echocardiography to assess the systolic function, while the ratio of mitral early-to-late annular diastolic velocity (mitral *E*/*A* ratio) was measured to assess left ventricular (LV) diastolic function. Tissue Doppler imaging was performed to assess the peak mitral annular systolic velocity (*S*) and to assess the LV diastolic function parameter (LV *E′*/*A′* ratio); the ratio of mitral early-to-late annular diastolic velocity was measured. Two-dimensional speckle tracking echocardiography was performed to assess LV systolic function parameters, specifically the 2D LV global longitudinal strain (2D-LVGS). All echocardiographic examinations were carried out by an experienced echocardiographer who was blinded to the study groups.

2.5 Assessment of Participants' Adherence and Safety

The patients were followed up through face-to-face meetings every 2 weeks to provide the study materials, to ensure compliance with treatment by counting the capsules, taking packages of the used drugs, and recording any side effects during the study period. Patients who consumed less than 90% of the study drug were considered non-adherent and were excluded from the study.

2.6 Primary and Secondary Outcomes

The primary outcome was to assess the effect of NS on the echocardiographic parameters of the heart. The secondary outcomes were to assess the effect of NS on the lipid profile, troponin I, MDA, nitric oxide, TNF-α, and TGF-β, and to assess the safety of NS.

2.7 Statistical Analysis

Based on a previous study, a sample size of 28 patients with type 1 DM in each group was required to achieve a power of 90% with alpha = 0.05 to detect a mean difference of more than four 2D-LVGSs between the two groups after treatment [21]. A statistical analysis was carried out using SPSS software version 23, and quantitative data were presented as mean ± standard deviation, while qualitative data were presented as numbers and percentages. The Student's *t*-test was used to compare the means of the two studied groups, while the paired *t*-test was used to compare the mean within the same group before and after the treatment. A chi-square test was used to compare categorical data between the two groups. The Pearson correlation coefficient was used to measure the correlation between biochemical and echocardiographic parameters. A P-value < 0.05 was considered statistically significant.

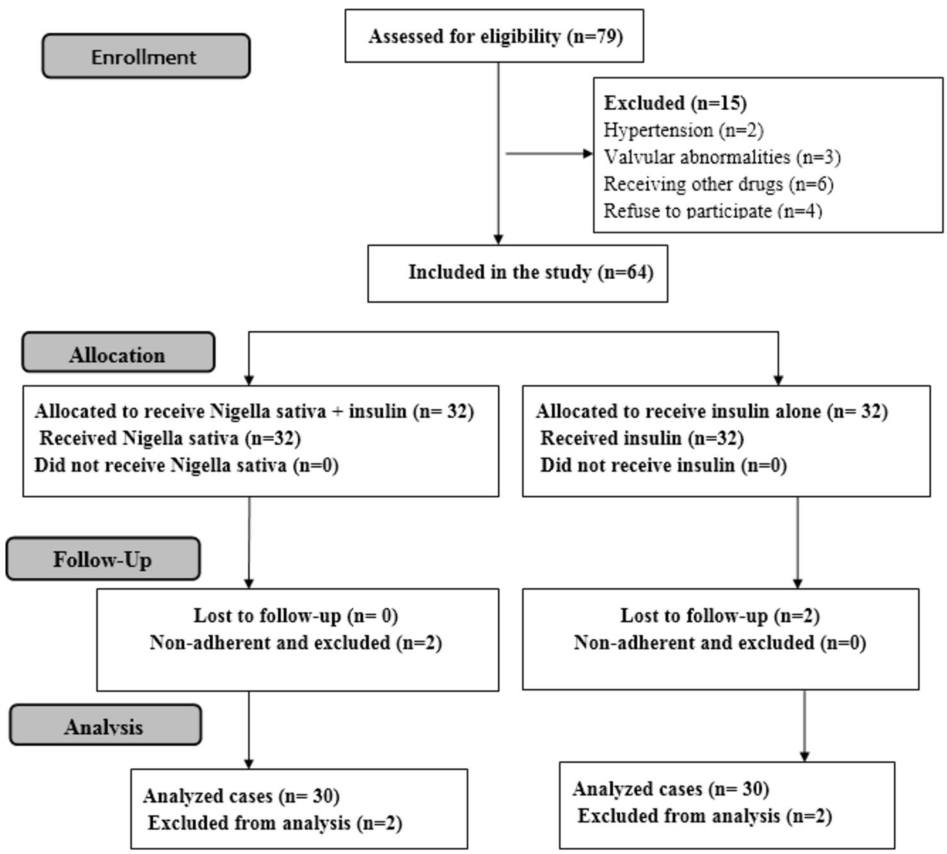
3 Results

We screened 79 children with type 1 DM for eligibility; 15 children were excluded, and 64 patients were enrolled in the study and were randomly assigned into two groups, each including 32 patients. Two patients in the treatment group were non-adherent to NS treatment and were excluded from the study, and another two patients were lost to follow-up from the control group and were also excluded from the study. Finally, 60 pediatric patients with type 1 DM completed the study (27 were male and 33 were female) with a mean age of 12.4 ± 2.3 years and a mean DM duration of 3.1 ± 1.8 years (the flow chart is shown in Fig. 1).

Table 1 presents the baseline clinical, anthropometric, and laboratory data of the two studied groups. There was no significant difference with regard to age, sex, weight, height, body mass index, or the duration of DM between the two studied groups. In addition, there was no significant difference in the pre-treatment mean levels of FBG, HbA_{1C}, total cholesterol, TG, LDL-C, and HDL-C between both groups. Similarly, the mean levels of MDA, nitric oxide, TNF-α, TGF-β, and troponin I were comparable between both groups before treatment. There was a non-significant difference in echocardiographic data, including the mean values of LV EF, mitral *E*/*A* ratio, LV *S*, LV *E′*/*A′* ratio, and two-dimensional left ventricular global longitudinal strain (2D-LVGLS) between the two groups at baseline before treatment (Table 2).

After 3 months of treatment, there was a non-significant change in FBG, HbA_{1C}, TG, and HDL-C levels in group I, while the levels of cholesterol and LDL-C were significantly decreased in group I compared with pre-treatment levels. The mean level of cholesterol and LDL-C was significantly lower in group I than in group II after treatment. In contrast, there was a non-significant change in FBG, HbA1C, TG, cholesterol, LDL-C, and HDL-C levels in group II after drug treatment. However, the levels of MDA, nitric oxide, TNF-α, TGF-β, and troponin I were significantly decreased compared with their corresponding levels before treatment. In addition, the mean levels of MDA, nitric oxide, TNF-α, TGF-β, and troponin I were significantly lower in group I than in group II. In contrast, there was a non-significant

Fig. 1 Flow chart of the study



change in the levels of MDA, nitric oxide, TNF-α, TGF-β, and troponin I in group II after 3 months (Table 3).

Regarding echocardiography, after 3 months of administration of NS, 2D-LVGLS, which represents the systolic function, and the LV *E′*/*A′* ratio, which represents the diastolic function, were significantly increased in group I compared with their pre-treatment levels and to group II. However, group II showed a non-significant change in the 2D-LVGLS and LV *E′*/*A′* ratio after 3 months. In addition, LV EF, LV *S*, and mitral *E*/*A* ratio showed a non-significant change in both groups either before or after treatment (Table 4).

A correlation between biochemical and echocardiographic data showed that the LV *E′*/*A′* ratio had significant negative correlations with each of MDA, nitric oxide, TNF-α, and TGF-β, while 2D-LVGLS showed that there were significant positive correlations with each of MDA, nitric oxide, TNF-α, and TGF-β. In addition, there were significant positive correlations of troponin I with each of MDA, nitric oxide, TNF-α, and TGF-β (Table 5). No side effects were recorded for NS during treatment in group I.

4 Discussion

Diabetes is a major risk factor for cardiovascular diseases, and patients with type 1 DM show a significantly increased risk of heart failure. Diabetic cardiomyopathy progresses from an asymptomatic period associated with cellular and structural abnormalities leading to functional changes, degenerative pathological remodeling, and progressive LV dysfunction that finally may lead to symptomatic heart failure [22, 23].

Therefore, early detection and prevention of myocardial dysfunction in diabetic patients may prevent the development of heart failure. Tissue Doppler and 2D longitudinal strain are used for the assessment of LV diastolic and systolic function and can help in the early diagnosis of DCM [2–5]. Previous clinical studies have also reported increased levels of troponin I in diabetic children as a marker of myocardial injury [3, 24, 25], which may be related to increased oxidative stress and lipid peroxidation that can trigger necrotic cardiomyocyte death [26].

Previous studies investigating the effect of NS in adult patients with type 2 DM have shown that NS can reduce cardiovascular risk factors; Hadi et al. [15] reported that

Table 1 Baseline clinical, anthropometric, and laboratory data of the two groups before treatment

Parameter	Group I ($N = 30$)	Group II ($N = 30$)	*P*-value
Age (years)	12.3 ± 2.3	12.5 ± 2.3	0.782
Sex (male:female)	16:14	17:13	0.795
Weight (kg)	44.6 ± 10	46 ± 9.9	0.633
Height (cm)	148.7 ± 12	150 ± 10	0.561
BMI (kg/m^2)	19.9 ± 1.6	20.1 ± 2.1	0.617
Duration of diabetes mellitus (years)	3.2 ± 2	3.1 ± 1.7	0.782
FBG (mg/dL)	155 ± 11.3	153 ± 9.5	0.373
HbA_{1C} (%)	8.1 ± 1.3	8.2 ± 1.6	0.765
Cholesterol (mg/dL)	163 ± 17.4	161 ± 14.5	0.719
Triglycerides (mg/dL)	87 ± 10.3	89 ± 13	0.916
LDL-C (mg/dL)	89.4 ± 11.5	87.6 ± 10.4	0.992
HDL-C (mg/dL)	46 ± 3.3	45.3 ± 2.9	0.54
MDA (nmol/mL)	4.74 ± 1.16	4.76 ± 0.99	0.943
Nitric oxide (nmol/mL)	49 ± 4	48 ± 4.3	0.351
TNF-α (pg/mL)	10.3 ± 2.9	10.18 ± 2.7	0.854
TGF-β (pg/mL)	8.9 ± 2.94	9 ± 2.9	0.964
Troponin I (ng/mL)	0.061 ± 0.02	0.063 ± 0.02	0.81

BMI body mass index; *FBG* fasting blood glucose; *HbA_{1C}* glycated hemoglobin; *LDL-C* low-density lipoprotein-cholesterol; *HDL-C* high-density lipoprotein-cholesterol; *MDA* malondialdehyde; *TNF-α* tumor necrosis factor-α; *TGF-β* transforming factor-β

Table 2 Baseline echocardiographic data of the two groups before treatment

Parameter	Group I ($N = 30$)	Group II ($N = 30$)	*P*-value
Conventional echocardiography			
LV EF (%)	66.3 ± 2	65.7 ± 2	0.222
Mitral *E*/*A* ratio	1.3 ± 0.2	1.4 ± 0.3	0.87
Tissue Doppler echocardiography			
LV *S* (m/s)	0.069 ± 0.006	0.069 ± 0.005	0.829
LV *E′*/*A′* ratio	1.2 ± 0.17	1.23 ± 0.17	0.597
Speckle tracking echocardiography			
2D-LVGLS	−17.6 ± 1.56	−17.7 ± 2.1	0.71

2D-LVGLS two-dimensional left ventricular global longitudinal strain, *A'* peak atrial phase filling velocity, *E'* mitral flow early-phase filling velocity, *LV EF* left ventricular ejection fraction, *LV S* left ventricular peak mitral annulus systolic velocity

the use of NS for 8 weeks significantly improved glycemic control, lipid profile, and body weight, and decreased systolic and diastolic blood pressure in adult patients with type 2 DM. Similarly, Badar et al. [17] investigated the effect of NS over a 1-year period in adult patients with type 2 DM on oral hypoglycemic agents and found that NS significantly improved the lipid profile and decreased heart rate and blood pressure. Moreover, Bamosa et al. [16] reported that NS decreased cardiac dysfunction in adult patients with type 2 DM. To the best of our knowledge, there are no previous studies investigating the effect of NS in children with type 1 DM.

The present study showed that the administration of NS in children with type 1 DM significantly increased the LV *E′*/*A′* ratio and 2D-LVGLS but decreased troponin I levels, which reveals that NS may improve LV diastolic and systolic dysfunction and decrease myocardial damage in children with type 1 DM. Conventional echocardiography using LV EF and the LV *E*/*A* ratio failed to reveal any systolic or diastolic LV dysfunction in our patients. This can be explained by the low sensitivity of conventional echocardiography to detect minor ultra-structural changes that occur in the diabetic heart, as the early stage of DCM occurs at the myocytic level and can be detected only with recent echocardiographic techniques such as 2D speckle tracking echocardiography and pulsed tissue Doppler, which is the case in our patients. Interestingly, Bamosa et al. [16] reported that NS increased LV EF in adult patients with type 2 DM, unlike our results, which may be because of the longer duration of DM in their patients (7.2 ± 4.19 years), compared with the shorter duration of DM in our patients (3.2 ± 2 years), which means that their patients may experience more advanced stages of DCM. In addition, they reported that NS increased LV EF after 6 months with a non-significant change after 12 months of treatment, while our study period was shorter (3 months only). Moreover, the age and type of diabetic patients are different in the two studies.

Lipid profile abnormalities in children with type 1 DM have been reported in previous studies [27, 28]. Hyperglycemia in type 1 DM is associated with increased fatty acid uptake by cardiomyocytes, and the accumulation of fatty acids leads to increased production of ROS, mitochondrial dysfunction, and apoptosis contributing to DCM development [29, 30].

In our study, NS significantly decreased cholesterol and LDL-C levels in children with type 1 DM while FBS and HbA_{1c} have not changed significantly. Several previous studies reported that NS promotes glucose homeostasis and improves the lipid profile in adult patients with type 2 DM through several proposed mechanisms, including enhancing insulin secretion, inducing β-cell proliferation and regeneration, and enhancing tissue sensitization to insulin, especially the liver and muscle [15, 17, 31]. Nevertheless, to the best of our knowledge, the effect of NS has not been previously studied in children with type 1 DM; hence, the mechanism of lipid lowering could be different.

In our study, NS had a non-significant effect on FBS and HbA_{1c}, but it decreased cholesterol and LDL-C levels, which is in line with the results of Pelegrin et al. [32] who reported

Table 3 Changes in laboratory data before and after treatment in both groups

Parameter	Group I ($N = 30$)		Group II ($N = 30$)		P-value
	Before	After	Before	After	
FBG (mg/dL)	155 ± 11.3	154.5 ± 8.4	153 ± 9.5	151.3 ± 9.2	0.165
HbA_{1C} (%)	8.1 ± 1.3	7.9 ± 1.2	8.2 ± 1.6	8.1 ± 1.4	0.459
Cholesterol (mg/dL)	163 ± 17.4	153 ± 13.5*	161 ± 14.5	160.5 ± 13.2	0.024
Triglycerides (mg/dL)	87 ± 10.3	85.7 ± 10.7	89 ± 13	87.5 ± 15.9	0.589
LDL-C (mg/dL)	89.4 ± 11.5	78.9 ± 9.8*	87.6 ± 10.4	88.3 ± 9.9	<0.001
HDL-C (mg/dL)	46 ± 3.3	46.4 ± 2.5	45.3 ± 2.9	45.1 ± 3.1	0.383
MDA (nmol/mL)	4.7 ± 1.2	3.8 ± 0.9*	4.8 ± 0.9	4.9 ± 1.2	<0.001
Nitric oxide (nmol/mL)	49 ± 4	40.5 ± 3.7*	48 ± 4.3	48.6 ± 4.8	<0.001
TNF-α (pg/mL)	10.3 ± 2.9	8.5 ± 2.4*	10.2 ± 2.7	10.3 ± 2.8	0.009
TGF-β (pg/mL)	8.9 ± 2.94	7.4 ± 2.5*	9 ± 2.9	9.1 ± 2.8	0.02
Troponin I (ng/mL)	0.06 ± 0.02	0.04 ± 0.02*	0.06 ± 0.02	0.06 ± 0.02	0.002

FBG fasting blood glucose, *HDL-C* high-density lipoprotein-cholesterol, *LDL-C* low-density lipoprotein-cholesterol, *MDA* malondialdehyde, *P* difference between group I and group II after treatment, *TGF-β* transforming factor-β, *TNF-α* tumor necrosis factor-α, *significantly different compared with its respective value before treatment ($P < 0.05$)

Table 4 Changes in echocardiographic data before and after treatment in both groups

Parameter	Group I ($N = 30$)		Group II ($N = 30$)		P-value
	Before	After	Before	After	
LV EF (%)	66.3 ± 2	66 ± 2.2	65.7 ± 2	66 ± 1.5	0.73
Mitral *E*/*A* ratio	1.3 ± 0.2	1.4 ± 0.3	1.4 ± 0.3	1.4 ± 0.2	0.751
LV *S* (m/s)	0.069 ± 0.006	0.068 ± 0.006	0.069 ± 0.005	0.07 ± 0.005	0.127
LV *E′*/*A′* ratio	1.2 ± 0.17	1.33 ± 0.16*	1.23 ± 0.17	1.21 ± 0.16	0.008
2D-LVGLS	−17.6 ± 1.56	−20.1 ± 1.5*	−17.7 ± 2.1	−17.7 ± 2	<0.001

2D-LVGLS two-dimensional left ventricular global longitudinal strain, *A′* peak atrial phase filling velocity, *E′* mitral flow early-phase filling velocity, *LV EF* left ventricular ejection fraction, *LV S* left ventricular peak mitral annulus systolic velocity, *P* difference between group I and group II after treatment, * significantly different compared with its respective value before treatment ($P < 0.05$)

Table 5 Correlation between biochemical and echocardiographic data

Parameter	MDA		Nitric oxide		TNF-α		TGF-β	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Troponin I	0.863	<0.001	0.848	<0.001	0.865	<0.001	0.96	<0.001
LV *E′*/*A′* ratio	−0.815	<0.001	−0.84	<0.001	−0.735	<0.001	−0.768	<0.001
2D-LVGLS	0.856	<0.001	0.8	<0.001	0.74	<0.001	0.81	<0.001

2D-LVGLS two-dimensional left ventricular global longitudinal strain, *A′* peak atrial phase filling velocity, *E′* mitral flow early-phase filling velocity, *EF* ejection fraction, *LV S* left ventricular peak mitral annulus systolic velocity, *MDA* malondialdehyde, *TGF-β* transforming factor-β, *TNF-α* tumor necrosis factor-α

that the administration of NS did not modify fasting plasma glucose and serum insulin levels in healthy volunteers, but it had a beneficial effect on lipid profiles in hyperlipidemic subjects. Moreover, Sabzghabaee et al. [33] reported that NS lowered total cholesterol, TG, and LDL with no significant change in FBG in hyperlipidemic patients. In addition, Farzaneh et al. [34] reported that NS lowered total cholesterol, TG, and LDL in overweight female individuals. This reveals that the effect of NS on the lipid profile was independent of its effect on glucose hemostasis. The effect of NS on the lipid profile may be explained by its ability to regulate genes modulating cholesterol metabolism, decreasing the expression of the HMG-CoA reductase enzyme, and upregulating the LDL receptor [35].

Chronic hyperglycemia induces oxidative stress and increases the production of ROS that causes damage to cellular DNA and protein, stimulating inflammatory processes through transcription factor nuclear factor-kappa B activation and stimulation of apoptosis leading to myocardial dysfunction [36]. Hyperglycemia and oxidative stress also enhance inducible nitric oxide synthase enzyme expression through nuclear factor-kappa B activation [37], leading to increased nitric oxide levels that can induce apoptosis, decrease cardiomyocyte contraction, and lead to the formation of the powerful oxidant peroxynitrite [38].

Elevated levels of MDA, nitric oxide, and increased oxidative stress in children with type 1 DM were reported in previous studies [39, 40]. The observed significant correlations of MDA and nitric oxide with the LV *E′/A′* ratio, 2D-LV GLS, and troponin I level in our study may reflect the role of oxidative stress in DCM. In the present study, NS significantly decreased MDA and nitric oxide levels, which is in line with others who reported NS decreased oxidative stress in patients with type 2 DM [41, 42]. The antioxidant effect of NS may be due to upregulation of antioxidant gene expression through activation of transcription factor nuclear factor erythroid 2-related factor 2, downregulation of inducible nitric oxide synthase gene expression, and the ability of NS to scavenge free radicals [12, 43, 44].

Hyperglycemia and increased ROS induce inflammatory responses and increased levels of inflammatory cytokines, including TNF-α, interleukins (e.g., interleukin-6, interleukin1-β), and TGF-β [45]. Tumor necrosis factor-α can induce cardiomyocyte hypertrophy, promote cardiac fibrosis, and activate apoptosis [46], while TGF-β is a profibrotic cytokine that activates cardiac fibroblast differentiation, increases the production of the extracellular matrix collagen, and promotes cardiac fibrosis, stiffness, myocardial hypertrophy, and dysfunction [10, 47].

In previous studies, high levels of TNF-α and TGF-β were observed in patients with type 1 DM [48–50]. Our results showed significant correlations between TNF-α and TGF-β with the LV *E′/A′* ratio, 2D-LVGLS, and troponin I levels, which may be a mirror image of the role of inflammation in DCM.

In our study, NS significantly reduced TNF-α and TGF-β levels, which is in line with other studies reporting that NS has anti-inflammatory effects in patients with type 2 DM [31, 51]. The anti-inflammatory effect of NS may be explained by its inhibitory effects on lipoxygenase and cyclooxygenase pathways and its ability to suppress the activation of the nuclear factor-kappa B transcription factor that regulates the expression of proinflammatory cytokines, including TNF-α and fibrosis-related genes, including TGF-β [52, 53].

Our results suggest that NS can decrease cholesterol and LDL-C levels, reduce oxidative stress, proinflammatory cytokine TNF-α, and profibrotic cytokine TGF-β levels; therefore, it can decrease LV systolic and diastolic dysfunction in pediatric patients with type 1 DM. Regarding the safety of NS, no adverse effects were observed in our patients who received NS, and this is consistent with previous studies that reported no adverse effects for NS in adults [54, 55] and also in children infected with cestodes and in children with intractable pediatric seizures except for mild gastrointestinal symptoms if administered on an empty stomach [56, 57].

The results of the present study reveal that NS may provide therapeutic potential in DCM in pediatric patients with type 1 DM. The potential mechanisms of NS in DCM in type 1 DM may include its ability to improve the lipid profile and decrease oxidative stress, anti-inflammatory markers, and anti-fibrotic effects, which are all integrated in the pathophysiology of diabetic cardiomyopathy.

The present study showed that NS is safe and beneficial in children and adolescents with type 1 DM, as it can decrease LV systolic and diastolic dysfunction, improve cholesterol and LDL-C levels, and reduce oxidative stress, proinflammatory cytokine TNF-α, and the pro-fibrotic cytokine TGF-β level; therefore, it may provide a cardioprotective effect in these patients. Our results suggested that NS could be useful as a complementary treatment in pediatric patients with type 1 DM. However, multicenter studies on larger sample sizes with different races and for longer periods of treatment to validate our results are recommended.

Limitations of the study included a lack of placebo, the relatively small sample size, and the short duration of treatment and follow-up. Being a single-center study is another limitation of the study.

5 Conclusions

Nigella sativa is safe and may have beneficial effects in pediatric patients with type 1 DM, as it may improve subclinical LV dysfunction, decrease cholesterol and LDL-C levels, and reduce oxidative stress, proinflammatory cytokine TNF-α, and pro-fibrotic cytokine TGF-β levels; therefore, it may provide a cardioprotective effect in these patients.

Declarations

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Conflicts of Interest Dalia El-Afify and Doaa El Amrousy have no conflicts of interest that are directly relevant to the content of this article.

Ethics Approval The study obtained ethical approval from the Faculty of Medicine's local ethical committee at Tanta University. The human subjects were enrolled following the principles of the Declaration of Helsinki.

Consent to Participate Participants and their parents signed a consent form.

Consent for Publication Not applicable.

Availability of Data and Material All the data from the study are available from the corresponding author upon reasonable request.

Code Availability Not applicable.

Authors' Contributions DE and DE: conceptualization and methodology. DE: methodology, writing (reviewing and editing of the manuscript). DE: data curation and methodology. The manuscript was reviewed and the final version agreed by all authors.

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