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EFFECTS OF HONEY SUPPLEMENTATION ON CHILDREN WITH IDIOPATHIC DILATED CARDIOMYOPATHY: A RANDOMIZED SINGLE BLINDED CONTROLLED STUDY

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ABSTRACT

Objectives: Evaluation of the effects of 12-weeks honey consumption on the echocardiographic parameters of children with idiopathic dilated cardiomyopathy (IDCM). **Design:** This study was a randomized controlled study, which was carried out on 54 children, aged 2 to 12 years, suffering from IDCM. They were randomly assigned to two groups: the honey group and the control group. **Setting:** The study was conducted at the Children's Hospital of Ain Shams University, Egypt during the period from November, 2015 to May 2016. Intervention: In the honey group, honey was provided in a dose of 1.2g/kg/day for three months in addition to the standard heart failure medical therapy. The patients in the control group received only their standard medical treatment, without honey. The main outcome measure was the percent change in the ejection fraction (EF) and the fraction shortening (FS) shown in echocardiography after 12 weeks. Results: In both groups, the FS and the EF increased after 12 weeks, but the rate of increase of either parameter was significantly higher in the honey group ($p = 0.00$). The other echocardiographic parameters, on the other hand, did not show significant change between the two groups. The honey ingestion was well tolerated and did not produce side effects in the patients of the honey group. Conclusion: Twelve weeks- honey

consumption resulted in significant improvement in the EF and FS in a group of children suffering from IDCM.

KEYWORDS: Honey; antioxidants; dilated cardiomyopathy; children.

1. INTRODUCTION

Honey is a natural substance produced by the honey bees, which feed on the nectar and sweet deposits from plants. The history of honey as a medicine is as rich as the history of man. The ancient Egyptians, as listed in the Ebers and Edwin Smith Papyri, used honey frequently for both internal and external therapeutic purposes. Also, honey has a religious significance as a medicine; it was mentioned in several religious books, including Quran and Bible.

Some studies showed that honey consumption resulted in positive effects on cardiovascular diseases as systemic hypertension[1,2] and myocardial ischemia.[2,3] For this, the present study was constructed to see whether honey could have an effect on dilated cardiomyopathy in children. The American Heart Association recommended not more than 5% of calories should come from sugar[4] because added sugars might be implicated in the development of cardiovascular diseases, including cardiomyopathy, through reactive oxygen species (ROS) generated by sugars.[5] Although honey is composed mainly of sugars, it differs from other added sugars in the fact that it contains, in addition to sugars, many beneficial substances, which have anti-oxidant,[6–12] anti-microbial,[13–17] anti-inflammatory,[18–21] anti-tumor,[22–24] prebiotic, probiotic[25,26] and immune-modulator effects.[27,28] Moreover, if honey is used as a sweetening agent, people may consume less honey than table sugar because honey is sweeter and denser.[29]

2. MATERIALS AND METHODS

This study is a randomized, controlled interventional clinical trial, which was conducted at the Children's Hospital of Ain Shams University, Egypt during the period from November, 2015 to May 2016. Fifty four children already diagnosed as having IDCM were consecutively recruited from the pediatric cardiology unit of Ain Shams University hospitals. Their age ranged from 2 to 12 years, and they were of both sexes. The criteria of diagnosis of IDCM included absence of any congenital, valvular, coronary artery disease or any systemic disease known to cause myocardial dysfunction and the presence of the echocardiographic findings of dilated cardiomyopathy (DCM), which included left ventricular dilatation and systolic dysfunction with an ejection fraction <45%, with or without mitral regurgitation.[30] All the

patients diagnosed as having IDCM were subjected to history taking, clinical examination and investigations to exclude children with history of drug-induced cardiac toxicity, and children with pulmonary or vascular disease, immunological disease, mitochondrial disease (evaluated by complete neurological examination, plasma lactate and amino acids, urine amino and organic acids), and neuromuscular disease (studied by neurological examination, blood creatine kinase, electromyography, and skeletal muscle biopsy if indicated). However, genetic testing and endomyocardial biopsy with polymerase chain reaction (PCR) analysis were not performed.

Echocardiography was performed mainly with Vivid 7, and in a few instances E9, ultrasound scanners (GE Vingmed Ultrasound, Horten, Norway). The patients were examined in the lateral recumbent position after > 5 minutes of rest. Three heartbeats were recorded with each registration. Cine loops comprising ultrasound raw data were digitally stored and later analyzed off line using Echo-Pac (GE Vingmed). 2D parameters and conventional Doppler parameters were measured. Valvular regurgitations were graded as mild, moderate or severe by visual assessment. Left ventricular ejection fraction (EF) and fraction shortening (FS) were assessed by M mode technique. The echocardiography was done two times, at baseline and at 12th week (endpoint of the study). Each time, the echocardiography was done twice by two investigators from the research team (Mamdouh N and El Guindy W), who were blinded to the study groups of the patients, and the results were averaged. The echo readers were also blinded to the time point of the study.

The exclusion criteria included children with systemic or chronic illness, including cancer, endocrine disorders and sepsis, children with diabetes mellitus, children with ischemic heart disease diagnosed by coronary angiography or a history of myocardial infarction and children with systemic hypertension with a blood pressure above 95th centile for age.

Eligible patients were randomly assigned following a simple randomization procedure (computerized random numbers) to either the honey (group 1) or the control group 2 with a 1:1 allocation ratio. The main outcome measure of this study was the percent change in the ejection fraction (EF) and the fraction shortening (FS). Based on the study of Saad,[31] which showed a mean (SD) increase of 4.4 (1.8) % in the EF of 55 children with IDCM after a 3 month follow-up, then a minimum total sample size of 52 children (26 patients in each group) is required to have an 80% chance of detecting, as significant at the 5% level, a mean increase or decrease in the EF by 3% at the end of the 12th week.

Patients of both groups continued their medical treatment during the study period. They received furosemide, spironolactone and captopril; each in a dose of 2 mg/kg/24 hours. They also received digitalis 0.01mg/kg/24 hours and aspirin 5mg/kg/24 hours.

In the honey group, the patients received oral honey in addition to their conventional treatment. Each patient in this group received Ziziphus honey (sider honey) orally in a dose of 1ml (1.2g)/kg/day for 3 months. The dose of honey was empirical as there was no identification of a particular dose of honey in earlier clinical trials using honey in different diseases. The oral dose of honey used for infants and children in previous clinical trials ranged from 0.5 to 2 ml/kg/day.[32–34] Moreover, dose-related toxicity to honey has not been previously reported.

The honey used was a pure unprocessed Ziziphus honey from Yemen. It was supplied directly from a beekeeper without heating or irradiation. Physicochemical analysis of the honey was done in the Chemical Analysis Laboratory of Honey Bee Products, Beekeeping Research Center, Plant Protection Research Institute, Agriculture Research Center, Giza, Egypt. The honey used was dark in color having a pH of 4.1; moisture content of 16.3%; electrical conductivity of 4.2 mS/cm; and a fructose to glucose ratio of 1.5:1, respectively, and a sucrose content of 3.4 g/100 g. The Hydroxymethylfurfuraldehyde (HMF) content was 1.8 mg/kg. Values of HMF less than 15 mg/kg indicate fresh honey not exposed to heat.[35] The total phenolic content as determined by the Folin-Ciocalteu procedure[36] and expressed in mg/100g of honey as catechin equivalent (CE) was 186.5 mg CE/100g honey. Microscopic examination of samples from honey confirmed the presence of pollen grains, which were mainly of *Rhamnus* and *Nigella sativa sp*. The physicochemical characteristics of this honey are shown in table 1.

Table 1: Physicochemical characters of the honey used in the study.

Studied parameter	Value
Specific gravity	1.412
Fermentation	Safe
Pollen grain	Found
Moisture (g/100 g)	16.3
pH	4.1
Electric conductivity (mS/cm)	4.2
Ash (g/100 g)	2.3
Sugar Glucose g/100 g Fructose g/100 g	 25.5 38.8

Reducing sugars g/100 g Fructose/glucose ratio Sucrose g/100 g	64.3 1.5 3.4
Hydroxymethylfurfuraldehyde (mg/kg)	1.8
Total phenolic content (mg CE/100g honey)	186.5 mg

Each participant was provided by 7 glass containers each week. Each container contained the calculated daily dose of honey. The parent or care-giver was instructed to keep the containers well closed and away from light until the time of administration before breakfast every day. They were also instructed not to give any additional doses of bee honey to their children during the study. Just before ingestion, the honey was dissolved in water in a ratio of 1 to 3. Dissolving honey in water enhances its anti-microbial properties,[14,15] facilitates swallowing and helps taking the honey dose completely. In the control group, the patients received only their conventional treatment, without honey for 3 months. The parents or the caregivers of the patients of both groups were instructed not to give bee honey to their children during the study period.

Evaluation of patients of both groups was done at baseline and at the end of the 12th week. The main outcome measure was the average change in the ejection fraction (EF) and the fraction shortening (EF) after a 3-month study period.

All study procedures were in accordance with the ethical standards of the responsible institutional committee on human experimentation and with the Helsinki Declaration of 1975 (as revised in 1983). Assent consent was obtained from all participants before the study, and the study was approved by the local Ethics Committee of the Pediatric Department of Ain Shams University Hospitals.

Statistical analysis

Standard computer program SPSS for Windows, release 24.0 (SPSS Inc, USA) was used for data entry and analysis. All numeric variables were expressed as mean ± standard deviation (SD) or median and interquartile range (IQR). Comparison of different variables in various groups was done using student *t* test and Mann Whitney test for normal and non-normally distributed variables, respectively. Wilcoxon signed rank test was used to compare multiple readings of the same variables. Chi-square (X^2) test was used to measure the association between two qualitative variables. Percent change between first and second readings of various variables was calculated using the formula: Rate of change = (2nd reading – 1st

reading / 1st reading) x 100. Analysis of Covariance (ANCOVA) was done to increase the precision of comparisons between the two groups.

For all tests a probability (p) less than 0.05 was considered significant.[37]

3. RESULTS

No one of the enrolled patients met any of the exclusion criteria. However, 7 (13%) of the 54 enrolled patients were excluded from the final analysis; one refused to continue the study after one week, 3 lost to follow up during the first 2 weeks of the study, and 3 patients died after 6 weeks (figure 1). The total number of patients, who completed the study and included in the final analysis was thus 47 patients (24 in the honey group and 23 in the control group). During the study, there was no a change in the drug treatment of the patients of both groups. All patients in the honey group tolerated well the honey intake; no patient developed any adverse effect.

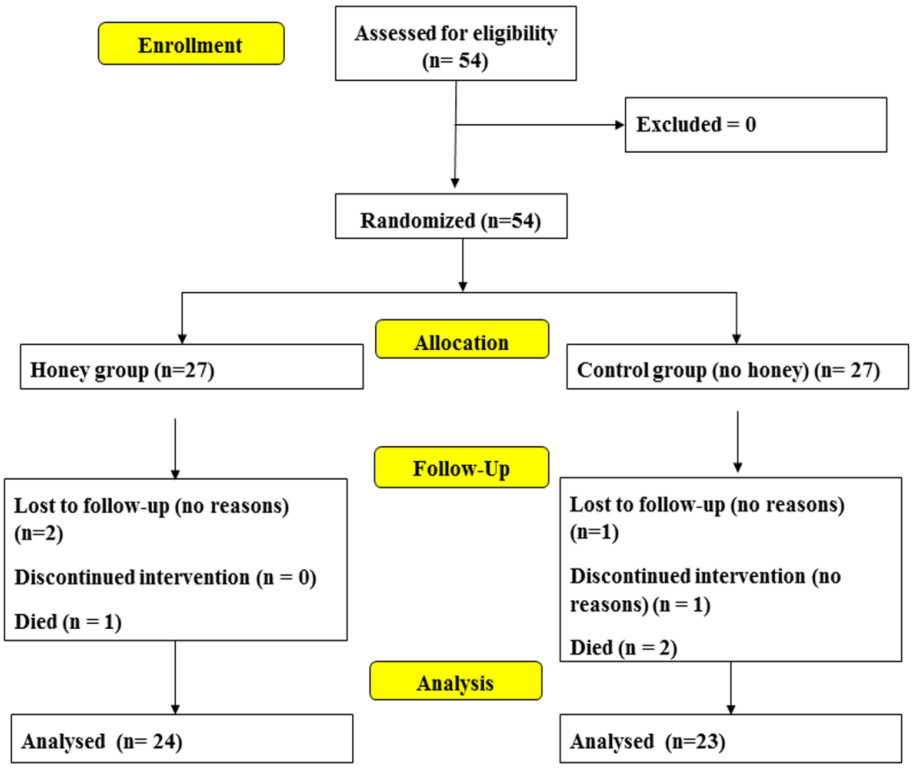

Figure 1: Flow chart.

The baseline characteristics of the patients are shown in table 2. Patients of both groups were comparable as regards the age, length of time from diagnosis to the study entry, presence of family history of dilated cardiomyopathy, sex ratio, body weight, height, heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), cardiothoracic ratio (CTR), and

echocardiographic parameters; aortic root diameter (AORD), fraction shortening (FS), ejection fraction (EF), septal wall thickness (SWT), left ventricular end diastolic diameter (LVED), and left ventricular end systolic diameter (LVESD). However, the two groups were not matched as regards the age of the patients at onset of cardiomyopathy, as the patients in the honey group were significantly older (p = 0.02).

Table 2: Baseline characteristics of patients.

Characteristic	Group 1 (honey) 24 patients	Group 2 (no honey) 23 patients	P
Age (yr.)	5.8±3.8	5,5±3.7	0.66*
Age at onset of disease (yr.)	2.7±2.8	1.9±2.7	0.02*
Length of time from diagnosis to the study entry (months)	41.16±29.49	44.04±30.72	0.64*
Positive family history of dilated cardiomyopathy	3	2	0.64†
Males Females	15 10	14 11	1.00†
Body weight (kg)	18.6±10.8	17.8±8.7	0.82*
Height (cm)	112±28.7	112.2±25.8	0.93*
Heart rate (b/min)	94.76±8.8	100.2±13.9	0.06*
Symptoms of CHF	Absent	Absent	
SBP (mmHg)	94.5±5.7	92.1±8.6	0.5*
DBP (mmHg)	64.3±7.1	62.1±9.9	0.07*
CTR (%)	57.6±6.2	58.03±3.1	0.77*
AORD (cm)	1.86±0.47	1.91±0.41	0.6*
LAD (cm)	2.37±1.01	2.32±1.12	0. 98*
FS (%)	15.17±4.56	17.35±4.73	0. 12*
EF (%)	31.38±9.09	34.39±9.02	0.28*
SWT (cm)	0.69±0. 22	0.77±0.26	0.4*
LVED (cm)	5.19±1.1	5.05±1.3	0.43*
LVESD (cm)	4.25±1.2	4.30±1.2	0.88*

yr.: year; b/min: beats/min; CHF: congestive heart failure; SBP: systolic blood pressure; DBP: diastolic blood pressure; CTR: cardiothoracic ratio; AORD: aortic root diameter; LAD: left atrial diameter; FS: fraction shortening; EF: ejection fraction; SWT: septal wall thickness; LVED: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter.

**Mann-Whitney Test.*

†Chi square test

At the end of 12th week (end point of the study), the echocardiographic findings did not also show significant changes between the two groups, as shown in table 3. However, when the

echocardiographic parameters were analyzed in each group separately, as shown in tables 4 and 5, we found in the honey group a highly significant increase in the fraction shortening (FS) and the ejection fraction (EF) (p = 0.000), and a significant decrease in the left ventricular end systolic diameter (LVESD) (p = 0.02), whereas the other echocardiographic parameters did not show significant difference. In the control group 2, on the other hand, there was a significant increase in the FS and EF (p = 0.02), whereas the other echocardiographic parameters did not show significant difference between baseline and the end of the study.

Table 3: The echocardiographic findings at the end of the 12th week (end point of the study).

Parameter	Group 1 (honey) 24 patients	Group 2 (no honey) 23 patients	P
AORD (cm)	2 (0.5)	1.9 (0.2)	0.53
LAD (cm)	2.8 (1.3)	2.5 (1.36)	0.54
FS (%)	22.25±6.71	19.65±6.29	0.2
EF (%)	45.21±12.64	39.61±12.62	0.14
SWT (cm)	0.6 (0.26)	0.8 (0.3)	0.05
LVED (cm)	4.42 (1.63)	4.6 (2)	0.89
LVESD (cm)	3.5 (1.25)	3.7 (2.31)	0.97

AORD: aortic root diameter; LAD: left atrial diameter; FS: fraction shortening; EF: ejection fraction; SWT: septal wall thickness; LVED: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter. Values are expressed as median and interquartile range (IQR), and mean±SD. Mann-Whitney Test was used for statistical analysis.

Table 4: The echocardiographic findings between the baseline and the end point of the study (12th week) in the honey group.

Parameter	Group 1 (honey) 24 patients		P
	Baseline	12th week	
AORD (cm)	1.9 (0.55)	2 (0.5)	0.05
LAD (cm)	2.6 (1.62)	2.8 (1.3)	0.09
FS (%)	15.17±4.56	22.25±6.71	0.000
EF (%)	31.38±9.09	45.21±12.64	0.000
SWT (cm)	0.61 (0.16)	0.6 (0.26)	0.69
LVED (cm)	4.9 (1.8)	4.42 (1.63)	0.09
LVESD (cm)	3.84 (1.6)	3.5 (1.25)	0.02

AORD: aortic root diameter; LAD: left atrial diameter; FS: fraction shortening; EF: ejection fraction; SWT: septal wall thickness; LVED: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter. Values are expressed as median and interquartile range (IQR), and mean±SD. Wilcoxon Signed Rank Test was used for statistical analysis.

Table 5: The echocardiographic findings between the baseline and the end point of the study (12th week) in the control group 2.

Parameter	Group 2 (no honey) 23 patients		P
	Baseline	12th week	
AORD (cm)	1.8 (0.56)	1.9 (0.2)	0.2
LAD (cm)	2.1 (1.7)	2.5 (1.36)	0.36
FS (%)	17.78±4.94	19.65±6.29	0.02
EF (%)	35.70±9.05	39.61±12.62	0.02
SWT (cm)	0.7 (0.4)	0.8 (0.3)	0.2
LVED (cm)	4.64 (1.8)	4.6 (2)	0.45
LVESD (cm)	3.84 (1.4)	3.7 (2.31)	0.18

AORD: aortic root diameter; LAD: left atrial diameter; FS: fraction shortening; EF: ejection fraction; SWT: septal wall thickness; LVED: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter. Values are expressed as median and interquartile range (IQR), and mean±SD. Wilcoxon Signed Rank Test was used for statistical analysis.

Comparing the rate of changes of the echocardiographic parameters between the honey and the control group between the baseline and the end point of the study, as shown in table 6, found the fraction shortening (FS) and the ejection fraction (EF) increased significantly in the honey group as compared with the control group (p = 0.00). When ANCOVA was done, it showed that honey has a significant but small effect size on both EF (F= (1, 37) =14.19; P <0.5; Partial Eta Squared 0.277) and FS differences (F= (1, 37) =27.12; P <0.5; Partial Eta Squared 0.423). On the other hand, the rate of change of the other echocardiographic parameters; AORD, LAD, SWT, LVED and LVESD did not show significant difference between both groups.

Table 6: Rate of change (%) of echocardiographic findings between the baseline and the end point of the study (12th week) in the honey and control groups.

Parameter	Group 1 (honey) 24 patients	Group 2 (no honey) 23 patients	P
AORD	11.11 (37.26)	0.00 (53.97)	0.86†
LAD	6.25 (55.13)	0.00 (67.14)	0.64†
FS	49.93±28.75	11.16±19.98	0.000*
EF	46.78±24.47	10.66±19.27	0.000*
SWT	0.00 (41)	0.00 (85.58)	0.3†
LVED	-4.93±-15.42	-0.90±-19.14	0.25*
LVESD	-4.17 (18.22)	-8.93 (22.98)	0.96*

AORD: aortic root diameter; LAD: left atrial diameter; FS: fraction shortening; EF: ejection fraction; SWT: septal wall thickness; LVED: left ventricular end diastolic diameter; LVESD:

left ventricular end systolic diameter. Values are expressed as mean ± SD, or median and interquartile range (IQR).

** Independent t-test*

†Mann-Whitney U Test

DISCUSSION

In this study, the EF and the FS increased after 12 weeks in both the honey and the control groups, but the rate of increase in either parameter was significantly higher in the honey group. It was unexpected to find this quite difference between the two groups (in the honey group, the EF increased from 31% to 45% and the FS increased from 15% to 22% after 3 months, whereas in the control group the EF increased from 35% to 39% and the FS increased from 17% to 19%). There are two possibilities for this finding: First, the two groups might be heterogeneous at baseline in terms of predictors of outcome of cardiomyopathy. Second, honey might have the potential to improve the cardiac status in cardiomyopathy.

Regarding the first possibility; the two groups, at baseline, were not matched as regards the age at onset of cardiomyopathy, which was older in the honey group ($p = 0.02$). Given that the duration of survival before the study (length of time between diagnosis and the study entry) did not differ significantly between the two groups, the prognosis, in relation to the age at diagnosis, is supposed to be less favorable in the honey group, where the patients were older,[31,38–40] but, on the contrary, the response was better in these patients. However, we did not investigate for an underlying viral[41] or genetic etiology,[42] which may influence the outcome of dilated cardiomyopathy.

The second possibility that honey might have the potential to improve the cardiac status in cardiomyopathy is supported by some studies,[1,2,43,44] which demonstrated the positive effects of honey on cardiovascular diseases. However, we did not find in the literature studies evaluating the effects of honey as a complementary agent in children or adults with IDCM. Alagwu et al[43] reported the beneficial effects of Nigeria honey on the lipid profile and the computed cardiovascular disease predictive index in male albino rats. Erejuwa et al[1] found that honey supplementation reduced significantly elevated systolic blood pressure in spontaneously hypertensive rats through amelioration of oxidative stress in the kidney. Khalil et al[44] found that Malaysian Tualang honey had cardio-protective effects against isoproterenol- (ISO-) induced myocardial infarction in rats by improving the antioxidant

enzyme levels in heart tissue and lowering lipid peroxidation levels following exposure to high dose ISO. Abdulrhman[2] demonstrated the positive effects of long-term honey consumption, as a sole treatment for almost 4 years, on blood pressure and cardiovascular status of six adult patient volunteers suffering from type 2 diabetes mellitus, hypertension and coronary heart disease.

The underlying cause of IDCM is not known. However, oxidative stress due to excess production of reactive oxygen species (ROS), along with free radicals may play a major role in oxidative stress- related disorders, including cardiovascular diseases (CVD).[45,46] The prevention of cardiovascular diseases has been linked to the intake of fresh food and plants rich in natural antioxidants because of their superior efficacy and safety compared to synthetic products.[47] Honey, a natural substance produced by honey bees, contains at least 181 different substances[48] that might have a therapeutic role in CVD. Its therapeutic value has been partly attributed to its antioxidant properties.[49] The antioxidant constituents of honey include phenolics, flavonoids, ascorbic acid, proteins and certain enzymes (glucose oxidase, catalase).[7,14,15,50] The antioxidant activity of honey is mainly attributed to its phenolic content. There is a significant correlation between the antioxidant activity and the phenolic content of honey. Generally, the darker the honey, the higher the phenolic content and the antioxidant power.[51,52] In the present study, Ziziphus (Sidr) honey from Yemen was used. This honey had a phenolic content of 186.5 mg CE/100g honey. All Yemeni types of honey are known by their higher phenolic contents, which range from 75.13 to 246.21 mg CE/100g honey, compared to many other types of honeys.[36]

Our study has some limitations. First, the rarity of this disease among children influenced the size of the sample studied. Second, the duration of follow-up was short. Third, the study had a high drop-out rate; 7 (13%) of the 54 patients recruited did not complete the study (3 deaths; 3 lost to follow up and 1 refused after one week), but this may be related to the small sample size. Fourth, genetic testing and viral studies were not done.

4. CONCLUSION

A 3 month-honey intervention in a group of children with idiopathic dilated cardiomyopathy improved both the ejection fraction and the fraction shortening. However, multi-center studies using honey for longer duration in larger groups of patients may be needed to confirm our findings.

AUTHORSHIP

All authors have made substantial contributions to the conception and design of the study, acquisition, analysis and interpretation of data. All authors revised the manuscript and approved the final version.

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