



# Resveratrol adjunct to methylphenidate improves symptoms of attention-deficit/hyperactivity disorder: a randomized, double-blinded, placebo-controlled clinical trial

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## Abstract

Current pharmacological approaches have failed to provide complete remission for patients with Attention-Deficit/Hyperactivity Disorder (ADHD). This study aimed to evaluate the efficacy and tolerability of resveratrol (that have been shown to have antioxidative, anti-inflammatory, and anti-apoptotic effects) as an adjunct to methylphenidate in pharmacologic treatment of ADHD. This 8-week, double-blinded, placebo-controlled trial randomized 66 participants to receive either 500 mg/day resveratrol or matched placebo in addition to methylphenidate. ADHD symptoms were evaluated in the patients using the Parent and Teacher versions of ADHD-Rating Scale (ADHD-RS) at three measurement points with time intervals of 4 weeks. Furthermore, the tolerability of the treatment strategies was systematically compared. Repeated measures analysis demonstrated a significant effect for time–treatment interaction on all three subscales of the Parent ADHD-RS during the trial period (total:  $p = 0.015$ ; inattention:  $p = 0.032$ ; hyperactivity/impulsivity:  $p = 0.036$ ). Nevertheless, the effect for time–treatment interaction was not significant for the Teacher version of ADHD-RS (total:  $F = 0.81$ ,  $df = 1.33$ ,  $p = 0.401$ ; inattention:  $F = 0.57$ ,  $df = 1.37$ ,  $p = 0.507$ ; hyperactivity/impulsivity:  $F = 0.65$ ,  $df = 1.34$ ,  $p = 0.466$ ). The frequencies of complications in the treatment groups were similar. Resveratrol administration for a duration of 8 weeks improved characteristic symptoms in patients with ADHD according to their parents. Further investigations containing larger sample sizes, longer supplementation periods, and dose–response evaluations are required to replicate these findings in ADHD children more confidently.

**Keywords** ADHD · Antioxidant · Clinical trial · Resveratrol

## Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a heterogeneous neurodevelopmental condition characterized by age-inappropriate behaviors including inattention, hyperactivity, and impulsivity maintained for at least 6 months [1]. ADHD is one of the most prevalent psychiatric disorders affecting 3–7% of children and adolescents worldwide [2]. ADHD accounts for a remarkable proportion of familial,

psychosocial, and academic problems if untreated. Moreover, it has been realized that 60–80% of childhood onset ADHD persist into adulthood [3].

Currently, pharmacotherapy is considered as the most effective approach for alleviating ADHD symptoms [4]. Pharmacotherapy in ADHD patients comprises administration of stimulant and non-stimulant medications. Particularly, methylphenidate is the most extensively prescribed medication for ADHD patients with generally safe and highly effective properties [5]. Nevertheless, these agents are not always promising as 10–30% of the patients exhibit intolerable adverse events or resistant symptoms [6, 7]. Hence, investigations on novel or complementary treatment strategies seem to be mandatory.

The exact etiology of ADHD is still unclear. However, the primary deficits in either specific regions (the prefrontal cortex, caudate, and cerebellum) or their linking networks in the brain (dopaminergic and noradrenergic systems) have

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been extensively addressed in ADHD [5]. Moreover, patients with ADHD have been shown to have lower concentrations of brain-derived neurotrophic factor (BDNF) [8]. Recently, there has been a growing concept that oxidative and inflammatory pathways contribute to the mediation of aforementioned pathologies in brain of patients with ADHD [9]. Oxidative mechanisms can easily affect the brain due to its high oxygen consumption and high lipid but relatively low antioxidant concentrations [10].

Resveratrol (3,5,4'-trihydroxystilbene) is a natural stilbenoid polyphenol that can be found in dietary resources such as peanuts, the skin of red grapes, red wine, and berries [11]. Numerous studies have investigated the beneficial effects of resveratrol showing antioxidative, anti-inflammatory, and anti-apoptotic characteristics [12, 13]. Furthermore, resveratrol can easily access the brain through the blood–brain barrier due to its lipophilic structure and exert aforementioned beneficial effects [14]. There is increasing interest regarding the use of nutritional components in treatment of neuropsychiatric disorders due to their multiple neuroprotective effects. The neuroprotective effects of resveratrol in Alzheimer's, Huntington's, and Parkinson's disease have been confirmed [15–17]. More recently, the beneficial effects of resveratrol in a variety of neuropsychiatric disorders and their related conditions have also been addressed such as anxiety, depression, sleep disturbance, and fatigue [18–20].

We designed this randomized, double-blinded, placebo-controlled trial using the Parent and Teacher versions of ADHD-Rating Scale for eight weeks since no study has evaluated the efficacy and tolerability of resveratrol add-on to methylphenidate in drug-naïve patients with ADHD. The objective of the current study stems from our hypothesis that resveratrol adjunct to methylphenidate improves the ADHD symptoms without exerting significant side effects.

## Methods

### Trial design and oversight

This study was an 8-week, single-center, randomized, parallel group, double-blind placebo-controlled trial conducted from January 2019 to January 2020 with outpatients of the child and adolescent clinics at the Roozbeh Psychiatric Hospital affiliated with Tehran University of Medical Sciences (TUMS). The trial was in consistence with the Declaration of Helsinki and its consecutive revisions and the protocol was approved by the Institutional Review Board (IRB) of TUMS (IR.TUMS.VCR.REC.1397.502). After a complete explanation of the procedures and purpose of the study, written informed consent was acquired from either patients' parents or their legal guardian. Patients and their guardian were aware of their freedom to withdraw from the

trial without any negative effect on their treatment plan. The trial was registered in the Iranian registry of clinical trials ([www.irct.ir](http://www.irct.ir); trial identifier with the IRCT database: IRCT20090117001556N115).

### Participants

Patients were recruited from drug naïve outpatients aged 6–12 years who met the criteria for the diagnosis of ADHD according to the Diagnostic and Statistical Manual of Mental Disorders, 5<sup>th</sup> edition (DSM-5) supported by the Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS) and clinical evidence [21]. Children were excluded from the trial if they had any psychiatric comorbidity except for Oppositional Defiant Disorder (ODD). Other exclusion criteria were history or current diagnosis of pervasive developmental disorder; presence of any medical condition such as uncontrolled seizures, cardiac and/or brain abnormalities, and impaired liver function; weight less than 13.5 kg; mental retardation (defined as intelligence quotation below 70); history of allergy to either resveratrol or methylphenidate; use of any medication that might affect the psychiatric condition of the patients in the last 2 weeks; history of drug abuse or dependency in the past 6 months. In particular, resting pulse rate, systolic blood pressure, and liver function test of the eligible participants were defined to be in the normal range.

### Intervention

Eligible subjects were randomly assigned to two separate groups receiving 0.3–1.5 mg/kg/day methylphenidate hydrochloride (MPH; Ritalin; Novartis, Switzerland) in two equal doses at 30 min before breakfast and lunch. Methylphenidate was titrated up during the trial according to the following protocol: for the first and second weeks of the trial, 10 mg/day and 20 mg/day of methylphenidate were administered, respectively, followed by a maintenance dose of 20 mg/day from week 3 until the end of the trial. Patients who weighed more than 30 kg received a maintenance dose of 30 mg/day. Resveratrol (ACER, Tehran, Iran; 500 mg/day) was started as an add-on to MPH for one of the groups while the other group received 500 mg/day of starch as placebo. From the first day of trial, both resveratrol and placebo were administered in two separate doses of 250 mg before breakfast and bedtime. Medication adherence was tightly controlled by weekly comparison of tablet counts with parent reports of medication intake.

### Outcome

Main ADHD symptoms of the patients were evaluated using the Teacher and Parent versions of ADHD-RS-IV, which have been extensively utilized in school-age children and are

considered valid measurement tools for detecting behavioral abnormalities [1, 7, 22]. Guardians and teachers of the patients were interviewed at baseline and weeks 4 and 8 of the trial. Additionally, they were asked to complete the relevant ADHD-RS-IV questionnaire during the interviews. Primary outcome measure was alteration in total scores of the parent and the teacher ADHD-RS-IV from baseline to week 8, while the secondary outcome was defined as the change in subscores of the questionnaires.

### Tolerability

All participants underwent complete physical examination, Electrocardiogram (ECG), liver function tests, and complete blood count (CBC) evaluations at the screening session prior to the beginning of the trial. Body weight and vital signs of the subjects were monitored at each visit. Moreover, adverse events were systematically detected throughout the trial using a 25-item checklist of probable side effects by a child psychiatrist at each visit [23–25]. Furthermore, participants and their parents were asked to inform the research team in case of any unexpected complication during the trial period.

### Randomization, allocation concealment, and blinding

Patients were randomly allocated to treatment groups by a computer-generated random queue (blocks of 4 and an allocation ratio of 1:1). The allocation was carried out using sealed opaque envelopes with an aluminum foil inside to ensure that the contents are not detectable even in intense light. Resveratrol and placebo tablets were completely identical in all their properties including size, shape, color, and smell. The medication distributors, participants and their guardians, research coordinators, and the outcome assessors were all blinded to allocation.

### Sample size

A minimal sample size of 56 (28 in each group) was calculated based on the assumption of a clinically significant difference of 4 and a standard deviation of 5 on the Teacher and Parent ADHD-RS according to our previous trials, an attrition rate of 10%, a power of 90%, and a two-tailed significance level of 0.05. In the current trial, we provided a larger sample size (33 patients for each group) to increase the statistical power.

### Statistical analysis

All analyses were performed using the Statistical Package of Social Science Software (SPSS version 24; IBM Company), considering a  $p$  value level of 0.05 or below as

significant. The Shapiro–Wilk test and probability graphs tested normality of the baseline data. Categorical variables were reported in percentage (%), while continuous data were represented as mean  $\pm$  SD. Baseline data were compared between groups using the independent samples  $t$  test with Levene’s test for equality of variance for normally distributed variables and the Mann–Whitney  $U$  test for non-parametric conditions. For the general linear model (GLM) repeated measures analysis of ANOVA, the groups and the measurement points were defined as between-subject and within-subject factors, respectively. GLM analysis was used to compare scores of the Parent and Teacher ADHD-RS-IV subscales between the trial groups during the study course. The GLM-related degrees of freedom were corrected by the Greenhouse–Geisser test when the Mauchy’s test of sphericity was significant. Finally, the Fisher’s exact test was conducted to compare frequency of adverse events between groups.

## Results

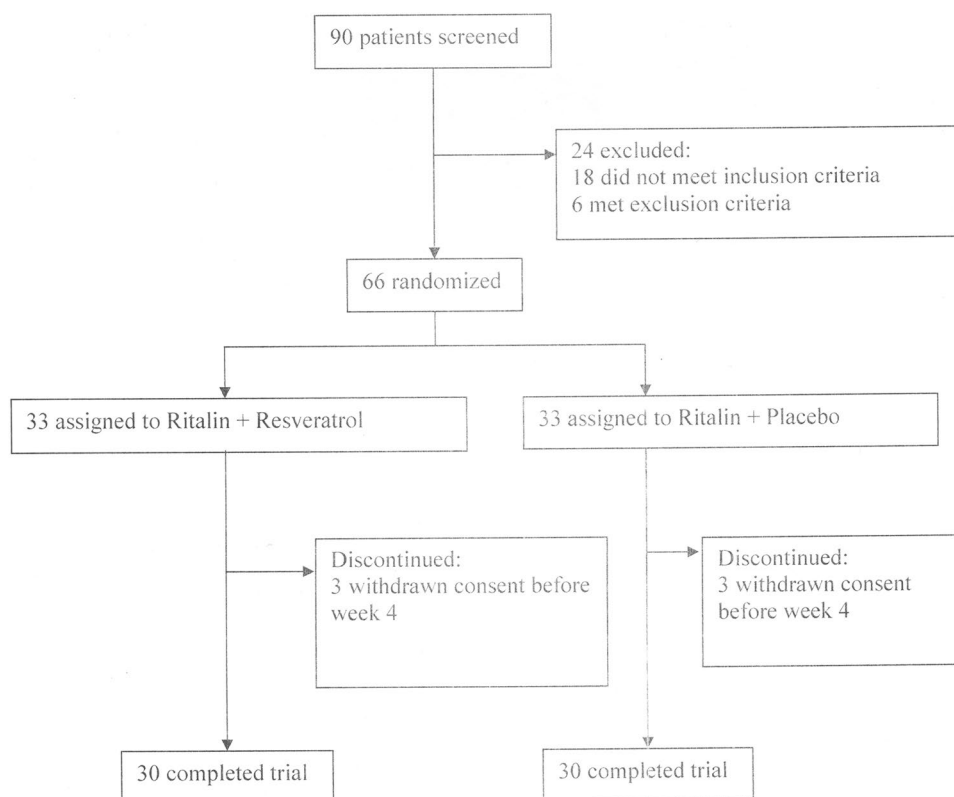
### Baseline characteristics of the participants

Out of 90 children screened for the trial, 66 patients met the inclusion criteria and were randomized into two arms to receive either methylphenidate + Placebo ( $n=33$ ) or methylphenidate + resveratrol ( $n=33$ ). 60 participants completed the trial as 3 patients from each group withdrew from the trial before week 4 (Fig. 1). As described in Table 1, all of the baseline characteristics of the subjects were similar between treatment groups ( $p$  values  $> 0.05$ ) (Table 1).

### The parent ADHD-RS

The parent ADHD-RS Fig. 2 represents changes in the Parent ADHD-RS subscales during 8 weeks of study. GLM analysis of repeated measures demonstrated that effects of time (Greenhouse–Geisser corrected:  $F=550.02$ ,  $df=1.50$ ,  $p<0.001$ , partial  $\eta^2=0.91$ ) and time–treatment interaction ( $F=5.08$ ,  $df=1.50$ ,  $p=0.015$ , partial  $\eta^2=0.08$ ) for the total score were significant showing that the treatment groups differed significantly from each other across the trial period on the total Parent ADHD-RS-IV scores. Similarly, the two-way ANOVA indicated significant effects of time–treatment interaction (hyperactivity/impulsivity:  $F=3.99$ ,  $df=1.38$ ,  $p=0.036$ , partial  $\eta^2=0.06$ ; inattention:  $F=3.88$ ,  $df=1.61$ ,  $p=0.032$ , partial  $\eta^2=0.06$ ) for scores of hyperactivity/impulsivity and inattention subscales, proposing that the groups had different behavior in both ADHD symptoms during the study course (Fig. 3) (Table 2).

**Fig. 1** Flowchart on number of patients participating in the trial



**Table 1** Baseline characteristics of the patients

Variables	Resveratrol ( <i>n</i> = 30)	Placebo ( <i>n</i> = 30)	<i>p</i>
Age in years, mean (SD)	9 (1.98)	8.53 (1.41)	0.30
Gender, F/M (F%)	8/22 (26.67%)	9/21 (30%)	1.00
Positive family history (%)	13 (43.3%)	8 (27%)	0.28
Parent ADHD-RS			
Total score	33.93 (6.99)	34.10 (4.54)	0.91
Inattention score	16.33 (4.11)	16.20 (3.85)	0.90
Hyperactivity score	17.60 (3.85)	17.90 (3.21)	0.74
Teacher ADHD-RS			
Total score	20.70 (10.16)	20.87 (6.54)	0.94
Inattention score	11.33 (5.42)	11.87 (3.94)	0.66
Hyperactivity score	9.37 (5.57)	9.00 (5.42)	0.80

ADHD-RS ADHD-Rating Scale, *F* female, *M* male, *SD* standard deviation

All the variables were compared between the groups using the independent samples *t* test except for gender and family history that were compared using the Fisher exact test

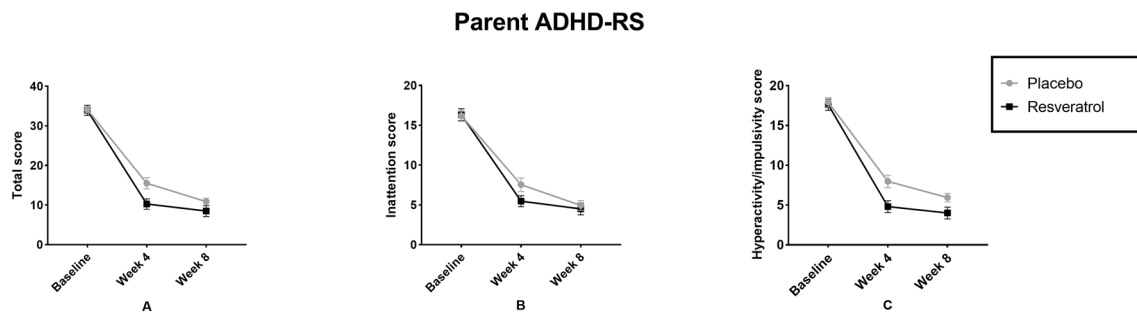
### The teacher ADHD-RS

Repeated measures analysis of ANOVA on total subscale of the Teacher ADHD-RS revealed significant effect for time (Greenhouse–Geisser corrected:  $F = 29.29$ ,  $df = 1.33$ ,  $p < 0.001$ , partial  $\eta^2 = 0.34$ ), whereas the effect

for time–treatment interaction was not significant (Greenhouse–Geisser corrected:  $F = 0.81$ ,  $df = 1.33$ ,  $p = 0.401$ , partial  $\eta^2 = 0.01$ ), indicating that the alterations in the Teacher ADHD-RS total score were similar for both treatment groups. Moreover, the effect of time–treatment interaction for the inattention and hyperactivity/impulsivity subscales represented similar behaviors (inattention:  $F = 0.57$ ,  $df = 1.37$ ,  $p = 0.507$ , partial  $\eta^2 = 0.01$ ; hyperactivity/impulsivity:  $F = 0.65$ ,  $df = 1.34$ ,  $p = 0.466$ , partial  $\eta^2 = 0.01$ ).

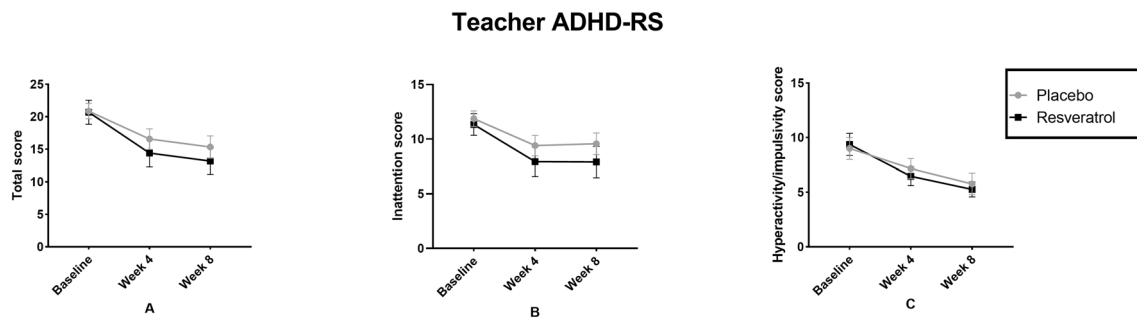
### Adverse events

According to the independent samples *t* test, subjects of the resveratrol group had a statistically similar body weight as the placebo group [mean difference (confidence interval) = 1.63 (− 1.56 to 4.83),  $F = 2.54$ ,  $t(58) = 1.02$ ,  $p = 0.311$ ]. As listed in Table 3, different types of side effects with mild to moderate severity were identified during the trial. The most common complications in both groups were decreased appetite (Resveratrol: 20%; Placebo: 26.7%) and headache (Resveratrol: 16.6%; Placebo: 23.3%). The Fisher exact test analysis demonstrated no significant difference between frequencies of detected side effects in the groups ( $p$  values > 0.05) (Table 3).



**Fig. 2** Repeated measure for comparison of the effects of the two treatment groups on subscales of the Parent version of ADHD-Rating Scale (ADHD-RS) questionnaire: **a** total score subscale. **b** Inatten-

tion subscale. **c** Hyperactivity/impulsivity subscale. Values represent mean  $\pm$  standard error mean (SEM)



**Fig. 3** Repeated measure for comparison of the effects of two treatment groups on subscales of the Teacher version of ADHD-Rating Scale (ADHD-RS) questionnaire: **a** total score subscale. **b** Inatten-

tion subscale. **c** Hyperactivity/impulsivity subscale. Values represent mean  $\pm$  standard error mean (SEM)

## Discussion

In the current study, we have demonstrated that adding resveratrol to methylphenidate as an adjuvant medication is beneficial and well tolerated in patients with ADHD. Patients treated with resveratrol had significantly improved symptoms according to the parent ADHD-RS total score, inattention and hyperactivity/impulsivity subscores ( $p = 0.015$ ,  $0.032$  and  $0.036$ , respectively). However, observed improvements in the Teacher ADHD-RS were not significantly different between the two groups probably due to overcrowded classrooms (with up to 35 students in a class), and therefore lack of enough time for teachers to detect changes in each student's behavior. Moreover, both treatment options were well tolerated, safe, and similar regarding the observed side effects. Since patients were assigned to the treatment arms randomly and baseline characteristics were not significantly different, the improved ADHD symptoms can be attributed to the beneficial effects of resveratrol.

It has been shown that in patients with ADHD, the cerebellum, caudate, and prefrontal cortex are the most

affected areas [26]. These regions are believed to be associated with controlling behavior, attention, and thought processes [26]. Dopamine and noradrenaline are the two main neurotransmitters involved in these networks [5]. The most common treatments for ADHD are stimulants such as amphetamines and methylphenidates besides non-stimulant agents such as clonidine and atomoxetine [5, 27]. These drugs increase the extracellular level of dopamine and noradrenaline via several mechanisms such as acting on the transporters and inhibiting the reuptake of the mentioned neurotransmitters, acting on presynaptic and postsynaptic receptors, provoking direct release of presynaptic neurotransmitters, and inhibiting monoamine oxidase (MAO). Although these medications are widely used, they can be accompanied with various side effects. Besides, long-term effects of these drugs on patients' social and occupational functioning can be debated [28, 29]. Therefore, there has been tremendous effort to find adjuvant therapies affecting other pathways in order to add to the effectiveness of conventional treatments.

There has been a trend in psychiatry to evaluate the immune-mediated pathways such as oxidative stress (OS) in the pathophysiology of diseases. For instance, analyzing

**Table 2** A summary of changes in the scores of the Parent and Teacher ADHD-RS subscales during trial period

Variables	Measurement points	Resveratrol (n = 30)	Placebo (n = 30)	Time–treatment interaction <sup>a</sup>
<b>Parent ADHD-RS</b>				
Total score	Baseline	33.93 (6.99)	34.10 (4.54)	<b>0.015</b>
	Week 4	10.27 (7.24)	15.50 (7.71)	
	Week 8	8.50 (7.49)	10.87 (4.64)	
Inattention score	Baseline	16.33 (4.11)	16.20 (3.85)	<b>0.032</b>
	Week 4	5.47 (3.78)	7.53 (4.68)	
	Week 8	4.50 (4.05)	4.93 (3.36)	
Hyperactivity score	Baseline	17.60 (3.85)	17.90 (3.21)	<b>0.036</b>
	Week 4	4.80 (4.07)	7.97 (4.37)	
	Week 8	4.00 (4.07)	5.93 (2.96)	
<b>Teacher ADHD-RS</b>				
Total score	Baseline	20.70 (10.16)	20.87 (6.54)	0.403
	Week 4	14.40 (11.57)	16.57 (8.60)	
	Week 8	13.17 (10.97)	15.33 (9.40)	
Inattention score	Baseline	11.33 (5.42)	11.87 (3.94)	0.507
	Week 4	7.93 (7.43)	9.40 (5.08)	
	Week 8	7.90 (7.87)	9.57 (5.40)	
Hyperactivity score	Baseline	9.37 (5.57)	9.00 (5.42)	0.466
	Week 4	6.47 (4.62)	7.17 (5.00)	
	Week 8	5.27 (3.76)	5.77 (5.42)	

Bold indicates  $P < 0.05$

ADHD-RS ADHD-rating scale, SD standard deviation

<sup>a</sup> $p$  value for time–treatment interaction is reported using repeated measures ANOVA analysis

**Table 3** Frequency of side effects in the trial groups

Side effect	Ritalin + Resveratrol (n = 30)	Ritalin + Placebo (n = 30)	$p$ values <sup>a</sup>
Headache	5 (16.7%)	7 (23.3%)	0.75
Insomnia	4 (13.3%)	6 (20%)	0.73
Drowsiness	3 (10%)	4 (13.3%)	1.00
Fatigue	3 (10%)	3 (10%)	1.00
Dry mouth	4 (13.3%)	3 (10%)	1.00
Decreased appetite	6 (20%)	8 (26.7%)	0.76
Nausea	4 (13.3%)	6 (20%)	0.73
Vomiting	3 (10%)	4 (13.3%)	1.00
Diarrhea	2 (6.7%)	3 (10%)	1.00
Abdominal pain	4 (13.3%)	3 (10%)	1.00

<sup>a</sup> $p$  values for comparison of side effects between trial arms are reported using the Fisher's exact test

data from 23 studies has revealed that depression has a well-established association with elevated oxidative stress and lower antioxidant levels [30]. This association was also observed in bipolar patients, in which a higher level of nitric oxide, DNA/RNA damage and lipid peroxidation

were reported compared to healthy individuals [31]. In this regard, studies have proposed a role of OS in the etiology of ADHD. A meta-analysis by Joseph and colleagues has suggested that patients with ADHD have normal levels of antioxidants; however, they are faced with oxidative damage due to their insufficient response to OS [32]. On this subject, it has been shown that omega-3 levels are lower in ADHD patients compared to healthy controls and its dietary supplements can result in modest improvements in these patients [33]. Zinc was also proposed as supplementary medication in patients with ADHD [22]. Although the evidence on the efficacy of the two aforementioned supplementation is not convincing and needs further attention, other anti-inflammatory and antioxidant dietary supplementations should also be evaluated for their beneficial effects on ADHD symptoms.

Resveratrol (3,4',5-trihydroxystilbene) is a phytoalexin that is found in various plants including grapes, berries, and peanuts [34]. It is known to act as an antioxidant agent giving rise to neuroprotective and anti-inflammatory effects [35]. Therefore, it has attracted a lot of research attention especially in diseases concerning the nervous system and inflammation. It has been shown that resveratrol modulates the activity of SIRT1, PCG-1 $\alpha$ , and AMPK, which are involved in the initiation of neurologic disorders [34]. In this

regard, caloric restriction could postpone the onset of these diseases and resveratrol can mimic the effects of caloric restriction by increasing the activity of deacetylases sirtuins, mostly SIRT1 [36, 37]. Moreover, AD patients treated with resveratrol have been shown to have decreased activity of matrix metalloproteinase-9 (MMP-9), which is associated with pathologic extracellular matrix degeneration observed in AD [38]. Besides, it has been indicated that resveratrol is able to regulate the impaired autophagy that is present in AD [39]. Although we have not evaluated the molecular pathways of resveratrol in the current study, some of the shared mechanisms could justify the effectiveness of resveratrol as an adjuvant therapy in ADHD patients.

Other than the mentioned deficits observed in patients with ADHD, it has been shown that brain-derived neurotrophic factor (BDNF) is lower in these patients [8]. BDNF has been identified to be critical for synaptic plasticity, neuroprotection, and important tasks such as memory and learning [40]. It has been shown that OS might significantly alter the level of BDNF and subsequently cause brain damage [41]. In this regard, animal studies have suggested that treatment with resveratrol could up-regulate BDNF levels [42], which might be one of the mechanisms responsible for the observed results of our study. On another note, dopamine is the key affected neurotransmitter in ADHD patients [43]. Avshalumov and colleagues indicated that increased hydrogen peroxide level is associated with suppressed dopamine release in the striatum [44]. Furthermore, excess OS is involved in dopaminergic neuron degeneration [45] and modulates dopamine receptor function [46]. Although the exact link between OS and pathologic changes in ADHD patients is not fully understood yet, restricting these changes by administering antioxidant agents such as resveratrol might be beneficial in patients.

Although this study has several advantages such as having a double-blinded and placebo-controlled design, rigorous adjustment for baseline variables and novelty, some limitations should be considered to prevent overgeneralization of the findings. First, molecular biomarkers and neurotransmitters were not investigated in our study. Second, our follow-up period was not extensive. Third, larger sample size seems necessary to provide a better insight into the extent of improvement in ADHD symptoms following resveratrol adjuvant therapy. Moreover, evaluating Teacher ADHD-RS in classrooms with fewer students would probably yield more reliable results in this regard. Fourth, a diverse nutritional status of the patients might have affected the findings of this study. Finally, cognitive assessment of attention in ADHD children and adolescents could provide better insight into this condition. Hence, results of this trial must be considered as preliminary.

In conclusion, the current study provides evidence supporting a beneficial and safe role for the administration of

resveratrol as an adjuvant therapy in management of patients with ADHD. Future studies with larger sample sizes and longer follow-up periods could confirm these observations and possibly shed light on the underlying pathways.

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## Compliance with ethical standards

**Conflict of interest** The authors have no conflict of interest to disclose.

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