The effect of *Rosa canina* L. and a polyherbal formulation syrups in patients with attention deficit/hyperactivity disorder: A study protocol for a multicenter randomized controlled trial

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Research Article

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Abstract

Background: Attention deficit/hyperactivity disorder (ADHD) is the most common behavioral disorder in childhood and adolescence. A number of these patients do not respond to the current pharmacological treatments and there may also be drug side effects. This study aims to determine the efficacy and safety of two herbal medicine products, including *Rosa canina* L. (RC) and a polyherbal formulation (PHF) syrups on the clinical manifestations of ADHD in children and adolescents.

Methods: Ninety ADHD patients based on DSM-5 diagnostic criteria will be randomly assigned equally to three groups: (1) RC syrup + methylphenidate (MP); (2) PHF syrup + MP; (3) placebo + MP according to the inclusion criteria (30 subjects in each group). The syrups dosage is 5 cc every 8 hours and MP has a stabilized dose for 8 weeks during the study. Moreover, Conner's questionnaires will be completed by the teacher and parents before the intervention and then every 4 weeks. Also, the child symptom inventory-fourth edition (CSI-4) and temperament questionnaires will be completed before the intervention and every four weeks until two months.

Discussion: This trial is the first experiment to determine the effects of RC and PHF syrups on the clinical manifestations of ADHD in children and adolescents. Our findings provide new insight into the effect of these herbal products on the clinical manifestations of ADHD.

Trial registration: The trial was registered at https://en.irct.ir/ (Registration number: IRCT20190923044855N1). Registration date: 2020-01-14.

Background

Attention deficit/hyperactivity disorder (ADHD) belongs to subset of neuropsychiatric disorder in children and adolescents, which is described by persistent impairing symptoms of inattention, hyperactivity, and impulsivity [1]. More than half of these patients, exhibit these symptoms during adulthood [2–4]. This disorder is frequently combined with learning problems, inability the psychosocial functioning also family, and public health problems [1–3, 5, 6]. ADHD carries a high risk of comorbidities such as anxiety, affective disorders, substance abuse, and personality disorders, also poor education consequences, a great chance for inoccupation, divorcement or imprisonment are more diagnosed among them compared to the general population [3, 5]. Moreover, mood disorder is reported in 15–75% of them and 25% have anxiety [7]. The prevalence rate of ADHD in children is approximately 8–12% all over the world [3]. Treatment strategies for ADHD mainly include drug therapy, psychological and behavioral therapy. Psychostimulant drugs, especially methylphenidate (MP) are highly efficacious and the primary choice of pharmaceutical medications for ADHD treatment [3, 6, 7]. Stimulant medication effectively improves ADHD symptoms in most of these patients; however, about 30% of them do not respond to its pharmacological treatments, and there may also be drug side effects such as loss of appetite, sleep disturbances and anxiety; therefore, many parents seek complementary and alternative medicines (CAMs) such as food recommendations, herbal medicine, homeopathy, and exercise for controlling

overactivity and inattention of ADHD [7]. Herbal medicine is the most commonly administered CAMs method for ADHD due to its well-tolerance and also parent's acceptance [8, 9]. There are several mechanisms of action for these medicinal plants associated with the pathogenesis of ADHD, including anxiolytic and antidepressant effects, improvement of cognitive function that help to increase serotonin levels and central stimulating [7]. Although limited information has been reported on the beneficial effects of these plants, clinical studies are needed to support their efficacy and safety.

Rosa canina L. (RC) belongs to Rosacea family, which its different parts such as roots, leaves, and fruits have been used to treat several diseases for centuries in traditional medicine [10]. Studies have shown that RC has neuroprotective effects when used in combination with other herbs [11, 12]. Moreover, it has demonstrated that RC extract has anxiolytic properties and can improve recognition memory and depressive-like behavior [13, 14]. In an experimental animal model, it is shown that chronic administration of *Malus domestica* Borkh. fruit juice has valuable antidepressant activity [15]. *Ocimum basilicum* L. is an edible herb, which has anxiolytic, sedative, and antidepressant-like effects [16, 17]. Also, its neuroprotective properties, especially the improvement of memory and neurological deficit have been documented previously [18]. Pharmacological studies displayed that *Vitis vinifera* L. has beneficial effects on cognitive function and neuropsychological status; additionally, indicates anxiolytic-like activity [19, 20]. Therefore, we hypothesized that a polyherbal formulation (PHF) syrup contains *Malus domestica* Borkh., *Ocimum basilicum* L. and *Vitis vinifera* L. extract may have beneficial effects on ameliorating memory and cognitive function, and anxiety in children with ADHD.

This randomized clinical trial aim to determine the efficacy and safety of RC and PHF syrups on the clinical manifestations of ADHD in children and adolescents.

Methods

Study design

This study is a double-blind randomized clinical trial (two arms factorial design) to determine the efficacy of two herbal products in children with ADHD. The study protocol was reviewed and approved by the Medical Ethics Committee of Iran University of Medical Sciences [session no: IRIUMS.REC. 1398.561], and registered in the Iranian Registry of Clinical Trials [registration code: IRCT20190923044855N1]. Figure 1 provides details of the study schedule.

Study population

The patients will be mainly recruited from the children and adolescents aged 5 to 14 years who refer to the outpatient clinics of neurology and psychiatry of the study centers (at the Rasoul Akram academic hospital, the Firooz Abadi academic hospital and community clinics, Tehran, Iran) for diagnosis and treatment of ADHD. Those who meet the inclusion criteria will enroll in the trial.

Eligibility criteria

Patients will enroll in this trial if they have these criteria:

1) Male and female children aged 5 to 14 years; 2) Parents and children willing and able to follow all study visits; 3) Diagnosis of ADHD, according to DSM-5 diagnostic criteria; 4) Treatment with a stabilized dose of oral stimulant medications (e.g., MP) through the study period; 5) Non-use of other alternative and complementary medications that may interact with the herbal product.

Exclusion criteria

Children with any of the following criteria will be excluded from the trial:

1) History of mental retardation; 2) History of bipolar disorder, psychosis, severe conduct disorder, autism; 3) History of neurological diseases, seizures or other serious medical conditions.

Withdrawal criteria

The study withdrawal criteria are listed as follows:

1) Parents' or children's unwillingness to continue treatment or move to another location; 2) Possible side effects of treatment; 3) Adding another illness or not taking or misusing the drug.

Sample size calculation According to the previous studies, the mean ± SD of ADHD questionnaires and methods mean deviation in three groups were 6.5 and 6, respectively. The sample size was 18 patients per group with a CI of 95%, power of 80%, and loss of 15%. A total of 90 patients will be invited and divided into three equal groups by using the block randomization method.

Randomization

The subjects who meet the eligibility criteria will be randomly divided into the intervention and placebo groups using permuted block randomization method. Moreover, stratified randomization will be used to match the subjects based on the age distributions (5-10 and 10-14 years old). Participants will be randomly assigned to three treatment groups of (1) RC syrup + MP; (2) PHF syrup + MP; (3) placebo + MP. Then they will be followed up for 8 weeks. Both investigators and participants will be blinded to the study design.

Intervention

RC, PHF and placebo are in the form of syrup and will be provided by the Sanabel Darou Co., Tehran, Iran. RC contains *Rosa canina* L. extract ((Vardibel ™); PHF contains *Malus domestica* Borkh., *Ocimum basilicum* L. and *Vitis vinifera* L. extract (Pardihan ™); and placebo is considered sucrose.

Ninety children and adolescents with ADHD will be invited to the study and randomly assigned to three groups. Subjects will be required to consume 5 cc/day every eight hours according to the recommended dosage for children in the syrup brochure.

The syrups will be prepared in 250 cc glassware and will suffice for about a month. The syrups are identical in size, color, and shape. Any possible complications regarding the numbers of syrups and package will be recorded. Also, the study progress will be pursued by recruiting the subjects every four weeks. Details of the study protocol (SPIRIT flowchart) are provided in Figure 2.

Adherence

To evaluate the compliance of the patients, they will be called every 4 weeks. At the first visit, the participants will receive interventions and will be asked to bring all eaten ones every month. Returned supplements will be observed to evaluate the level of compliance and adherence to the intervention.

Patient safety

All participants will be monitored and any probable adverse events will be reported during the study period.

Study outcomes

Primary outcomes

The primary objective of this research is to determine the efficacy and safety of these herbal medicine products on clinical manifestation of ADHD in children and adolescents.

Secondary outcomes

The secondary outcome of this study includes the changes in attention and activity function levels, socio-educational function levels, sleep, appetite and comorbidity (e.g. anxiety, depression, and obsessive-compulsive disorders) at the end of the study in comparison with the baseline values.

Procedure

At the beginning of the study, goals, methods, and benefits of the trail will be clarified to the parents and participants and an informed consent form will be provided to them. Conners Comprehensive Behavior Rating Scales (Conners CBRS) will be used for obtaining information about several important domains of participant's behavior, including behavioral, communal, educational topics, and their symptoms. In this study, two of Conner's CBRS questionnaires will be completed (both parent and teacher rating scales):

1- Conners' Parent Rating Scale (CPRS); a tool for effectively collecting parental reports of child behavior problems

2- Conners' Teacher Rating Scale (CTRS); a tool for obtaining teacher reports of children's behavior in the classroom [21-24].

Also, Child Symptom Inventory-4 (CSI-4) questionnaire will be used to evaluate attention problems in children. It is a behavior rating scale that is used for diagnosis and also severity assessment of ADHD in

children between 5 and 12 years old [25, 26]. Moreover, another questionnaire is temperament determinant questionnaire [27].

These questionnaires will be completed before the intervention and then only Conner's questionnaires will be used every 4 weeks by teacher and parents during the study. The interviewer will evaluate children signs and symptoms every 4 weeks for two months. There is no specific intervention to change the participants' lifestyle (diet, sleep, activity and etc.).

Lifestyle changes

No intervention is made in the patient's living conditions to evaluate the drug's efficacy.

Data analysis

The symptoms of hyperactivity/inattention are the most important indicator to investigate. Other indicators rank secondary importance. Descriptive statistics for qualitative variables include frequency tables, appropriate graphs. In addition, Chi-square or Fisher's exact tests will be used to investigate the relationship between the two qualitative variables. Regression imputation method will be used where the value of that variable is missing. The mean and standard deviation (SD) will be reported for quantitative variables and percentages for qualitative variables. ANOVA and Chi-square tests will be used in the three groups to compare quantitative and qualitative variables. A CI of 95% will be applied to all the tests. The significance level will be considered less than 0.05. Finally, SPSS 21 statistical software will be used to analyze the data.

Data accessibility

The final trial dataset will be only available to the principal investigator, and others investigators will have limited access. Finally, the study results will be presented only in the publication.

Discussion

To the best of our knowledge, this is a novel multicenter study designed for the first time to evaluate the therapeutic effects of two herbal formulations on the treatment of children and adolescents with ADHD and also their comorbidity, appetite and sleep.

The long-term use and side effects of conventional medications are a concern for parents, so they are increasingly looking for treatment options of CAMs [7]. A number of patients with ADHD diagnosis are frequently used CAMs, including dietary modifications, nutritional supplementation, and herbal medicine alone or along with current pharmacological treatments in order to manage of hyperkinetic and concentration disorders [2]. Diet, exercise and nutritional supplements all have some potential benefits for a child with ADHD. Herbal remedies, which have been shown to have good effects on restlessness, anxiety, and depression can also be proper options; however, more research is needed [7]. Moreover, the

role of chronic inflammation and oxidative stress has been noted in ADHD. Dietary polyphenols have antioxidant and immunomodulatory properties; so, they may be useful in the management of ADHD [28].

Different herbal preparations have been evaluated in clinical trials as a treatment for children and adolescents with ADHD. The findings propose that some of them may be as effective as MP [6]. RC has some beneficial effects on anxiety, recognition, memory and, depressive-like behaviors [13, 14]. Numerous studies have shown that the ingredients in PHF syrup have considerable ameliorating effects on anxiety, depression and memory [15–20]. So, the authors hypothesized that RC and PHF syrups will be valuable for the management of ADHD.

The Strengths And Limitations

Our study has several strengths such as providing a randomized double-blinded design and protocol publication. Currently, no side effects and drug interactions are reported on selected herbs in the related review articles. The limitations of this study include lack of cooperation of some participants to complete the intervention (child or parents unintentional for continuing intervention).

Abbreviations

ADHD: Attention deficit/hyperactivity disorder; DSM–5: Diagnostic and statistical manual of mental disorders; CSI-4: Child symptom inventory-fourth edition; CAMs: Complementary and alternative medicines; SD: Standard deviation; CI: Confidence interval; Conners CBRS: Conners Comprehensive Behavior Rating Scales; CTRS: Conners' Teacher Rating Scale; CPRS: Conners' Parent Rating Scale

Declarations

Ethics approval and consent to participate

The Ethics Committee of Iran University of Medical Sciences has approved study protocol [session no: IRIUMS.REC. 1398.561]. At the beginning of the study, a written informed consent form will be obtained from a parent or guardian for participants under 16 years old.

Consent for publication

Not applicable.

Availability of data and material

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

MB and MK designed the idea of this work. HG, MD and MVS coordinated the study. MQ advised on statistical analysis. HG, HM, MVS and EA organized participant management and data collection. HG, MD and SS drafted the manuscript. The manuscript has been read and approved by all authors.

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Not Applicable

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Figures

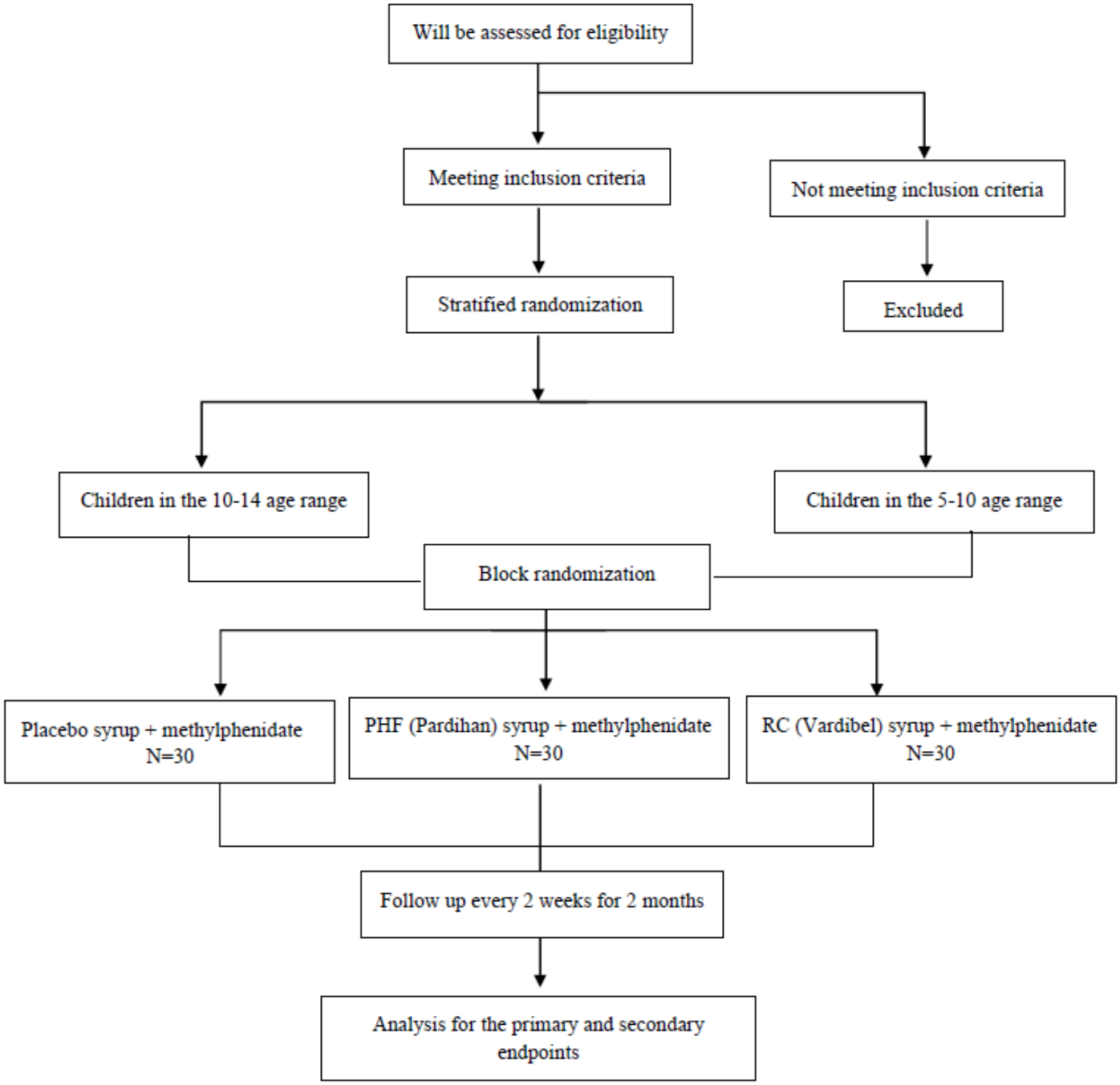

Figure 1

CONSORT Flow Diagram of the study

Assessments	Baseline (1st Week)	4th Week	End of the study (8th Week)
Enrollment (inclusion/exclusion criteria)	*		
Written informed consent (signed and dated)	*		
Randomization	*		
General demography and relevant medical history	*		
Physical examination	*	*	*
Current medication use	*	*	*
Conners' Parent Rating Scale	*	*	*
Conners' Teacher Rating Scale	*	*	*
Child Symptom Inventory-4 (CSI-4) questionnaire	*	*	*
Temperament determinant questionnaire	*		
Compliance of intervention	*	*	*

Figure 2

Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) flowchart of the study.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SPIRITChecklist17.3.2021.doc