Integrative Medicine Research 10 (2021) 100714

Contents lists available at ScienceDirect

Integrative Medicine Research

journal homepage: www.elsevier.com/locate/imr

Original Article

A mixed herbal extract as an adjunctive therapy for attention deficit hyperactivity disorder: A randomized placebo-controlled trial

Sujin Bae[a], Sunhye Park[b], Doug Hyun Han[c,*]

[a] Office of Research, Chung Ang University, 221 Heukseok-ro, Dongjak-gu, Seoul, South Korea
[b] Industry Academic Cooperation Foundation, Chung Ang University, 221Heukseok-ro, Dongjak-gu, Seoul, South Korea
[c] Department of Psychiatry, Chung Ang University Hospital, Seoul, South Korea

ARTICLE INFO

Article history:
Received 17 August 2020
Revised 26 December 2020
Accepted 28 December 2020
Available online 16 January 2021

Keywords:
Attention deficit hyperactivity disorder
Dimocarpus longan Lour
Gastrodia elata Blume
Liriope platyphylla Wang et Tang
Salvia miltiorrhiza Bunge

ABSTRACT

Background: Methylphenidate improves clinical symptoms and brain activity in attention deficit hyperactivity disorder (ADHD) patients through the attention-regulation network's dopamine system. Additionally, water-soluble extracts (HX106) of four plants (*Gastrodia elata* Blume, *Liriope platyphylla* Wang et Tang, *Salvia miltiorrhiza* Bunge, and *Dimocarpus longan* Lour) improve cognitive function. We hypothesized that the combination of HX106 and methylphenidate would improve ADHD symptoms and brain activity of the attention network more effectively than the combination of placebo and methylphenidate.

Methods: Twenty-seven patients with ADHD were administered a herbal mixture and methylphenidate (n=13), or placebo and methylphenidate (n=14) during a 4-week, randomized, double-blind, placebo-controlled clinical trial. Changes in ADHD symptoms (K-ARS scores), as well as brain activity and functional connectivity, were assessed at baseline and 4 weeks later.

Results: The HX106 group showed a greater improvement in total attention (16.8%) and inattention (17.2%) scores than the placebo group. The HX106 group showed increased brain activity within the left precuneus compared to the placebo group. The HX106 group also showed increased functional connectivity from the precuneus seed to the left middle temporal gyrus compared with the placebo group. In all participants, the changes in K-ARS scores were negatively correlated with changes in brain activity in the left middle temporal gyrus.

Conclusions: HX106 enhanced the effect of methylphenidate on ADHD symptoms and increased brain activity in the attention-regulation network. Therefore, HX106 may be an effective adjunctive therapy for patients with ADHD.

1. Introduction

Attention deficit disorder (ADHD) is a well-known childhood and adolescent neurodevelopmental disorder with a global prevalence ranging from 2–10%.[1] The main symptoms of ADHD include persistent patterns of inattention, hyperactivity, and impulsivity.[2] Studies have suggested that the dopamine neurotransmitter system plays a central role in the pathophysiology of ADHD.[3] ADHD treatments generally target the dopamine pathway, and methylphenidate is among the first lines of medication.[4–6] These medications' pharmacodynamics are associated with increased dopamine levels at the neuronal synapse.[7,8] Several brain function studies have suggested that methylphenidate increases the functional connectivity (FC) of the attention network, including the anterior cingulate, ventrolateral prefrontal cortex, and precuneus while counteracting the underactivation of the frontoparietal network.[9–11]

The water-soluble herbal extract HX106 is derived from four plants: *Gastrodia elata* Blume (*G.elata*), *Liriope platyphylla* Wang et Tang (L.*platyphylla*), *Salvia miltiorrhiza* Bunge (*S.miltiorrhiza*), and *Dimocarpus longan* Lour (*D.longon*). In an 8-week clinical trial, Kwon et al. found that HX106 increased working memory performance and brain white matter connectivity within the temporoparietal regions.[12] Further, it has been established that *G.elata* and *S.miltiorrhiza* affect the cardiovascular system.[13,14] Although

* Corresponding author at: Department of Psychiatry, Chung Ang University Hospital, 102 Heukseok-ro, Dongjak-gu, Seoul, South Korea.
E-mail address: hduk70@gmail.com (D.H. Han).

https://doi.org/10.1016/j.imr.2021.100714

dopamine and its receptors have been studied concerning the central nervous system, they also play a crucial role in the cardiovascular system,[15] where dopamine is associated with blood pressure and heart activity via dopamine D1 and D2 receptors.[15]

This study aimed to investigate whether the combination of HX106 and methylphenidate would be more effective in improving ADHD symptoms and brain activity in the attention-regulation network than the combination of a placebo and methylphenidate.

2. Methods

2.1. Study design

This was a randomized, double-blind, placebo-controlled study conducted in the Department of Psychiatry at the Chung Ang University Hospital, Seoul, Korea. We studied participants with ADHD who were randomly assigned to receive either methylphenidate + HX106 or methylphenidate + placebo. This study was registered in the Clinical Research Information Service of the Korea Disease Control and Prevention Agency (KCT0005285).

2.2. Participants

Patients with ADHD were recruited from the outpatient department of psychiatry at Chung Ang University Hospital, Seoul, Korea, between June 2018 and November 2019. The inclusion criteria were as follows: age 6–23 years, diagnosis of ADHD, continuous consumption of methylphenidate for at least one month, body weight over 25 kg, and intelligence quotient (IQ) > 70. The exclusion criteria were a history of trauma or seizures and contraindications for magnetic resonance imaging (MRI), including claustrophobia and metal implants.

This study was approved by the Institutional Review Board of Chung Ang University Hospital (IRB number: 1861–007–330). All participants provided written informed consent—this study adhered to the principles of the Declaration of Helsinki.

2.3. Interventions

2.3.1. Herbal formulation HX106

The HX106 granules comprised *G. elata* rhizomes (2 g), L. *platyphylla* radices (10 g), *S. miltiorrhiza* (6 g), *D. longan* fruit (6 g). The preparation, filtration, and validation procedures have been described in detail in previous reports.[12,16] Granules weighing 2000 mg included 300 mg of the HX106 extract and were packaged in a stick form with a non-moisture-permeable aluminum laminating film. Complete toxicology tests were performed in humans, and safety was confirmed.[16]

2.3.2. Control

The placebo granules consisting of 97% dextrin, 2% SiO2, and 1% lemon balm powder, had the same taste, flavor, shape, and color as the HX106 granules.

During the baseline evaluation, all participants taking methylphenidate were reevaluated and diagnosed by a child adolescent psychiatrist (DHH). All participants underwent a computerized comprehensive attention test (CAT; Happymind, Seoul, Korea) and brain scanning and were clinically assessed using the Korean version of Dupaul's ADHD rating scale (K-ARS), Beck Depressive Inventory (BDI), and Behavioral Inhibitory System/Behavioral Activation System (BIS/BAS) scale. After four weeks, all participants underwent CAT and brain scanning and were clinically assessed using the ADHD, BDI, and BIS/BAS scales.

2.4. Randomization

All participants were randomly assigned to receive either methylphenidate + HX106 or methylphenidate + placebo daily for four weeks, according to a randomization sequence generated using SPSS ver. 24.0 (IBM Corp., Armonk, NY, USA) with a 1:1 allocation (placebo : HX106).

2.5. Outcome measures

2.5.1. Primary outcome: clinical scales and comprehensive attention test

The severity of ADHD symptoms was assessed using the K-ARS[17,18] composed of 18 items with nine attention evaluation and nine inattention evaluation items.[17] The ARS has been reported to have good internal consistency, ranging from 0.77–0.89.[18] Depressive symptoms were assessed using the Beck Depression Inventory, which consists of 21 questions and has internal consistency ranging from 0.75–0.85.[19] Impulsivity was assessed using the BIS/BAS scale,[20,21] a 24 item self-report questionnaire with good internal consistency ranging from 0.78–0.79.

The participants' attention was evaluated using CAT, a tool consisting of selective attention (visual and auditory), sustained attention to response, flanker, divided attention, and spatial working memory tests. CAT is a standardized test, and its reliability and validity have been confirmed.[22]

2.5.2. Secondary outcome: resting-state functional brain activity

Functional magnetic resonance images (Rs-fMRI) were acquired using a 3.0 T Achieva scanner (Philips, Amsterdam, Netherlands). During scanning, all participants used a cushion for head immobilization and were asked to lie down with their eyes closed but stay awake. Rs-fMRI images were acquired axially with an echo-planar imaging (EPI) sequence using the following parameters: TR/TE = 3000/40 ms, 40 slices, 64 × 64 matrix, 90° flip angle, 230 mm FOV, and 3 mm section thickness without a gap. For each participant, the scan lasted 720 s, and 230 volumes were obtained.

For data preprocessing and processing, Data Processing Assistant for Resting-State fMRI (DPARSFA; http://www.restfmri.net) was used. This is a plug-in software that works with the Statistical Parametric Mapping software (SPM12; http://www.fil.ion.ucl.ac.uk/spm/software/spm12/) and the Resting-State fMRI Data Analysis Toolkit (REST; http://resting-fmri.sourceforge.net). All images were corrected for slice acquisition time differences, realigned, normalized, spatially smoothed with a 6 mm full-width half-maximum (FWHM) kernel, de-trended, and temporally band-pass filtered to 0.01-0.08. DPARSF provides nuisance covariate regression functions. These incorporated signals from the white matter and cerebrospinal fluid were obtained from T1 segmentation on each subject's images. The normalization step employs two sequences: template generation and application. The EPI of healthy adolescents was co-registered with the MNI template to acquire a customized template. Spatial normalization was performed by mapping the images to the MNI space using a customized template. Fisher-transformed correlation coefficients were measured for each pair of regions of interest (ROIs) for each participant. The FC between ROIs was calculated using the CONN-fMRI functional connectivity toolbox (version 15; https://www.nitrc.org/projects/conn). After preprocessing, the size of each voxel was 3 mm × 3 mm × 3 mm. Based on the realignment processing outcome by SPM, a participant with a translation or rotation motion greater than 3 mm or 2°, respectively, in any direction was excluded from the study. However, no participants from either patient group were excluded because of excessive head motion. There was no difference in head movement between the two groups (HX106 group: 0.089 ± 0.034, placebo group: 0.083 ± 0.041, $t = 0.086$, $p = 0.42$).

To assess the differences in brain activity and FC between the two groups during treatment, regional homogeneity (ReHo) and seed-based FC analysis were performed using the REST software. First, the ReHo method was used to find regions where local connectivity changes were different between the two groups during treatment. As an indicator of the ReHo value, Kendall's coefficient of concordance (KCC) of a given voxel was calculated with the surrounding 20 voxels to evaluate the time series's similarity and then standardized using z-scores to perform the group analyses. The correlation between the ReHo map and clinical measures from the K-ARS, BDI, and BIS/BAS was calculated using SPM12. The ROIs were drawn based on the cluster of the t-map with a given threshold (FDRq <0.05, k > 20).

Second, seed-based correlation analyses were used to assess resting-state functional brain connectivity in a predefined ROI. Our seed was defined using the ReHo analysis results. The FC between ROIs was calculated using the CONN-fMRI functional connectivity toolbox (version 15; https://www.nitrc.org/projects/conn). Pearson's correlation coefficients were calculated for the averaged blood-oxygenation level-dependent (BOLD) time course from the seed to voxel analysis throughout the whole brain. Correlation coefficients were converted to normally distributed z-scores using Fisher's z-transformation.

2.6. Statistical analysis

Differences in demographic data and clinical scales, including age, education year, IQ, methylphenidate dose, K-ARS, BDI scores, BIS/BAS scores, and CAT scores, were analyzed using the Mann–Whitney U test. Statistical significance was set at $p < 0.05$.

To investigate the differences in local connectivity between the two groups, an independent *t*-test was performed on the ReHo and seed-based correlation maps using SPM12 software. In addition, differences in local connectivity changes according to treatment response between the two groups were examined using repeated-measure ANOVA and were marked on the ReHo and seed-based correlation maps using the SPM12 software. The resulting maps were set to a threshold using $p < 0.05$, as the false discovery rate (FDR) correction for multiple comparisons, with an extent of more than 20 contiguous voxels and subjected to cluster analysis (derived from an uncorrected $p < 0.001$ and 20 extended voxels).

Correlations between changes in clinical scales and changes in brain activity were assessed using Pearson's correlation analysis.

3. Results

3.1. Demographic data

Of the 31 patients with ADHD who were treated at the outpatient department and were taking methylphenidate, one patient was excluded because of low IQ, and one patient was excluded because of low body weight. The remaining 29 patients were randomly assigned to one of the two groups. Furthermore, one patient could not complete the study because of palpitations during the treatment period, and one patient absconded follow-up without any reason. Finally, the data of 27 patients with ADHD were analyzed (Fig. 1).

At baseline, there were no significant differences in age, IQ, K-ARS scores, BDI scores, and BIS/BAS scores between the HX106 and placebo groups (Table 1). Furthermore, there was no significant difference in the CAT scores between the two groups.

3.2. Changes in clinical scales during the treatment period

During the 4-week treatment period, the HX106 group showed greater improvement in K-ARS total scores than the placebo group

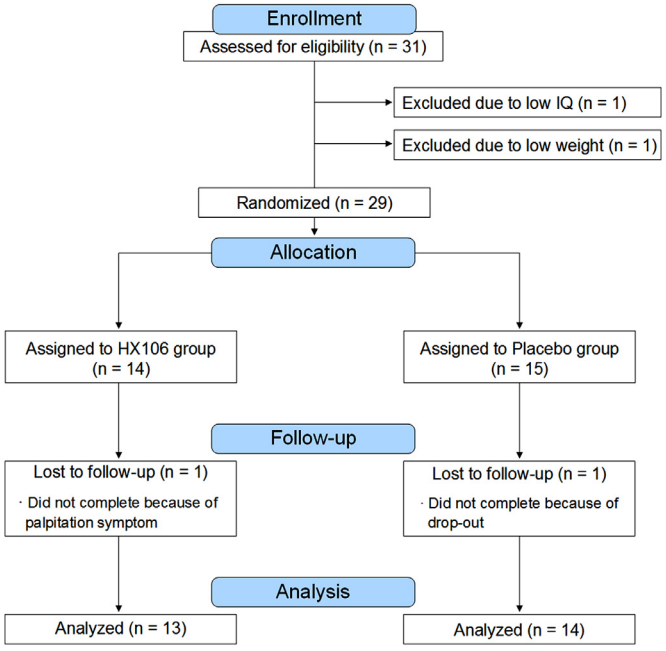

Fig. 1. CONSORT flow chart for the study.
IQ: intelligence quotient.

($F = 5.3$, $p = 0.03$) (Table 2). ADHD symptoms assessed using the K-ARS in the HX106 group improved by 26.8%, while those in the placebo group improved by 10.0%. In the post hoc test, the HX106 group showed greater improvement in K-ARS inattention scores than the placebo group ($F = 5.8$, $p = 0.02$). Inattentive ADHD symptoms assessed using the K-ARS in the HX106 group improved by 22.8%, while those in the placebo group improved by 5.6%. However, there were no significant differences in the hyperactivity scores between the two groups ($F = 2.8$, $p = 0.11$) (Table 2).

During the four weeks, the HX106 group showed greater improvement in BDI scores than the placebo group. However, this difference was not statistically significant ($F = 3.8$, $p = 0.06$). There were no significant differences in the BIS/BAS and CAT scores between the two groups (Table 2).

3.3. Adverse events of HX106

One participant who stopped taking the medication due to palpitations was identified as being in the HX106 + methylphenidate group.

3.4. Changes in brain functions in response to HX106 adjunctive treatment

At baseline, there were no significant differences in ReHo between the two groups. There were no significant differences in the left precuneus seed analysis between the two groups. During the four weeks, the HX106 group showed increased ReHo within the left parietal lobe precuneus (MNI, *x, y, z*: −18, −52, 56, FDRq < 0.05, $T = 4.92$, voxel $= 48$) compared with the placebo group (Fig. 2).

There were no significant differences in the left precuneus seed analysis at baseline between the two groups. During the four weeks, the HX106 group showed increased FC from the precuneus seed to the left middle temporal gyrus (MNI, *x, y, z*: −47, 13, −36, $P_{uncorrected} = 0.001$, $T = 5.63$, voxel $= 29$) compared with the placebo group (Fig. 3).

Table 1
Comparison of demographic data for the HX106 and placebo groups.

	HX106 (n = 13) (mean± standard deviation)	Placebo (n = 14) (mean± standard deviation)	z	P
Age (years)	13.0±4.4	14.5±5.9	−0.75	0.46
Education (years)	6.2±4.2	7.2±5.4	−0.81	0.42
Intelligent Quotient (IQ)	94.8±12.3	101.5±15.1	−1.26	0.22
Methylphenidate dose (mg/d)	25.6±8.1	25.7±6.9	−0.03	0.97

Mann–Whitney U test.

Table 2
Comparisons of scores of clinical scales for the HX106 and placebo groups.

	HX106 (n = 13) (mean± standard deviation)		Placebo (n = 14) (mean± standard deviation)		F*	P
	Before	4 weeks after	Before	4 weeks after		
K-ARS						
Total*	20.5±8.9	15.0±8.3	17.9±1.4	16.1±10.4	5.31	0.03
Inattention*	11.4±4.1	8.8±4.7	10.7±5.8	10.1±6.1	5.82	0.02
Hyperactivity	9.1±5.9	6.3±5.3	7.2±1.1	6.0±5.2	2.54	0.07
BDI	7.5±8.7	5.8±6.9	9.0±9.5	10.7±11.3	1.58	0.21
BIS/BAS	65.2±7.5	66.5±8.1	72.9±12.4	70.3±14.3	1.12	0.36
CAT						
Selective Visual OE	105.2±6.6	106.3±5.0	102.3±10.5	107.6±2.4	2.06	0.17
Selective Visual CE	110.1±13.3	114.1±9.8	108.5±12.5	115.7±8.2	0.35	0.56
Selective Auditory OE	105.9±3.1	104.5±5.3	101.0±11.5	101.2±14.3	0.07	0.78
Selective Auditory CE	104.3±10.9	106.5±10.5	101.3±14.6	106.5±6.1	0.86	0.36
Sustained OE	96.5±11.5	100.6±8.4	101.1±11.3	102.3±6.3	0.02	0.89
Sustained CE	101.4±24.2	103.9±21.9	97.5±20.1	105.9±21.0	0.14	0.71
Flanker OE	92.5±16.4	100.8±12.9	97.2±12.9	97.1±12.2	0.02	0.88
Flanker CE	104.5±21.2	105.3±17.0	95.1±20.4	109.7±19.2	0.70	0.42
Divide OE	94.7±15.3	103.1±11.0	103.9±17.4	103.1±9.8	1.72	0.21
Divide CE	95.4±13.9	99.9±9.4	94.6±15.0	95.3±18.3	0.04	0.84
WM_forward	93.8±20.9	99.1±18.4	92.0±17.4	101.6±15.6	0.80	0.38
WM_backward	95.6±22.4	102.7±12.9	89.6±17.3	99.6±14.6	0.06	0.82

* Repeated-measures ANOVA, statistically significant (p<0.05); BDI, Beck Depression Inventory; BIS/BAS, Behavioral Inhibitory System/Behavioral Activation System; CAT, comprehensive attention test; CE, commission error; K-ARS, Korean Attention Deficit Hyperactivity Disorder rating scale; OE, omission error; WM, working memory.

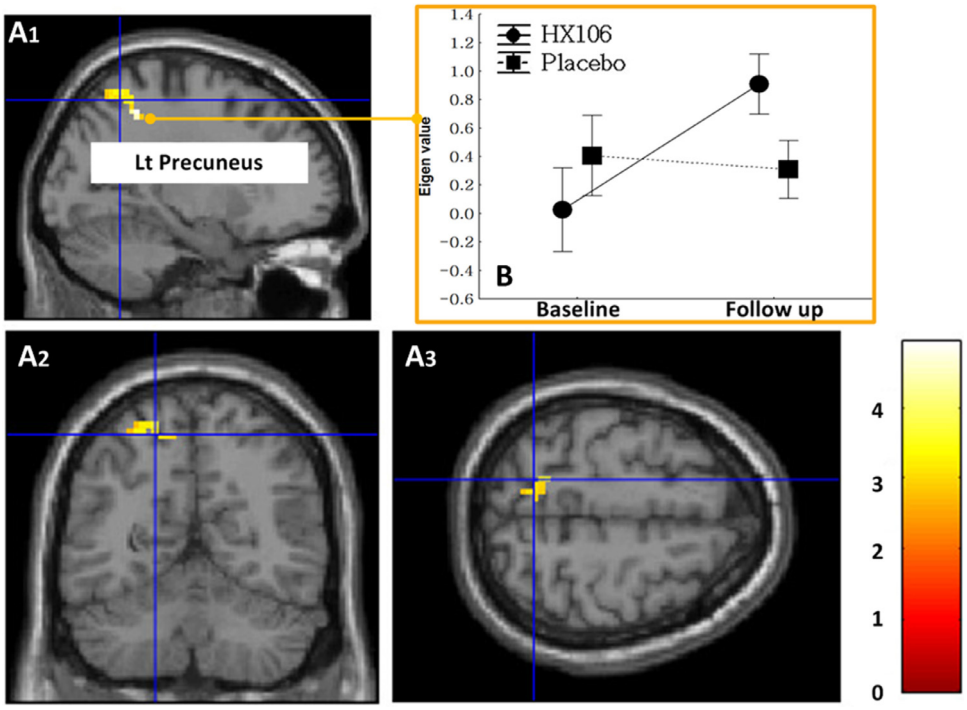

Fig. 2. Comparison of regional homogeneity (ReHO) in the HX106 and placebo groups during the treatment period
A. (1–3) Region of increased regional homogeneity (ReHo) in the HX106 group compared with the placebo group during treatment (MNI, *x, y, z*: −18, -52, 56, FDRq < 0.05, T = 4.92, voxel = 48), Lt Precuneus, left parietal lobe, precuneus
B. Repeated-measures ANOVA, the ReHo for the left parietal lobe precuneus increased compared with that in the placebo group (F = 23.6, p < 0.01).

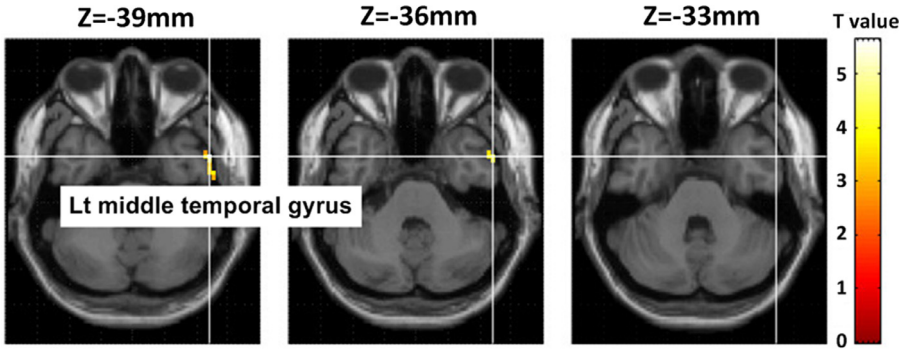

Fig. 3. Comparison of the changes in functional connectivity from the left precuneus seed to the voxel through the whole brain in the HX106 and placebo groups
Region of increased functional connectivity from the left precuneus to the middle temporal gyrus in the MNI coordinates, *x, y, z*: −47, 13, −36, $P_{uncorrected} = 0.001$, $T = 5.63$, voxel = 29)
Lt middle temporal gyrus, left middle temporal gyrus.

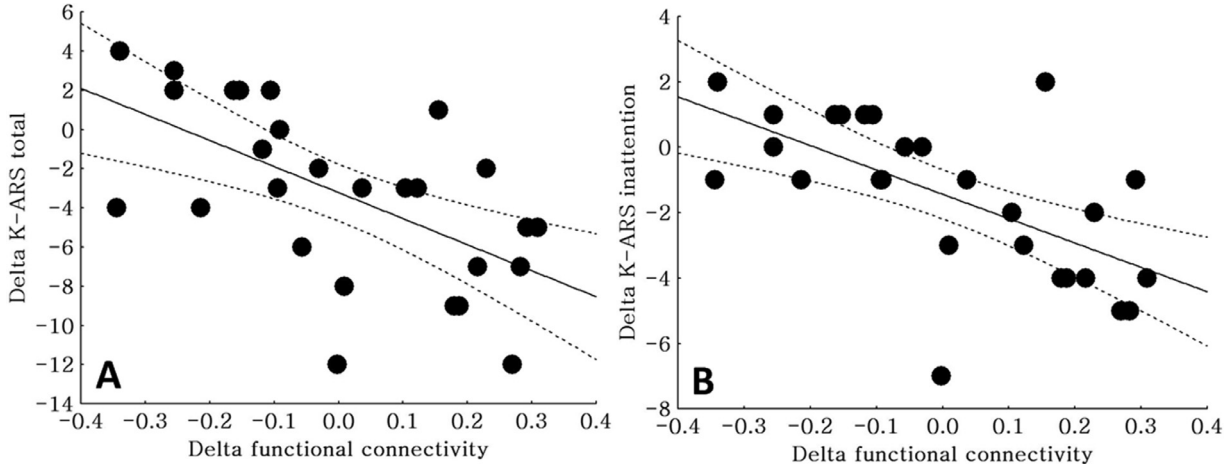

Fig. 4. Correlation between attention scale and brain activity
A. In all participants (HX106 group + placebo group), changes in the total scores of the Korean version of Dupaul's ADHD rating scale (K-ARS total) negatively correlated with the changes in functional connectivity from the precuneus seed to the left middle temporal gyrus, Pearson's correlation, $r = -0.59$, $p < 0.01$.
B. In all participants (HX106 group + placebo group), changes in the K-ARS inattention scores were negatively correlated with the changes in functional connectivity from the precuneus seed to the left middle temporal gyrus, Pearson's correlation, $r = -0.62$, $p < 0.01$.
ADHD, attention-deficit hyperactivity disorder.

3.5. Correlation between clinical scales and brain activity

In all participants (HX106 group + placebo group), changes in the K-ARS total scores were negatively correlated with changes in FC from the precuneus seed to the left middle temporal gyrus ($r = -0.59$, $p < 0.01$) (Fig. 4). Moreover, in all participants (HX106 group + placebo group), changes in the K-ARS inattention scores were negatively correlated with changes in FC from the precuneus seed to the left middle temporal gyrus ($r = -0.62$, $p < 0.01$) (Fig. 4). However, there was no significant correlation between changes in the K-ARS total scores (and inattention) and changes in the FC from the precuneus seed to the left middle temporal gyrus in either the HX106 or the placebo groups.

There was no significant correlation between changes in other clinical scales, including BDI and BIS/BAS, and FC changes from the precuneus seed to the left middle temporal gyrus in all participants.

4. Discussion

During the four weeks, the HX106 group showed greater (16.8% in total and 17.2% in inattention) improvement in ADHD symptoms as assessed by the K-ARS total scores, compared with the placebo group. In a post hoc analysis, the inattention scores' subscale improved in the HX106 group compared with the placebo group. In a study of zinc augmentation of methylphenidate, inattention scores changed in response to augmentation therapy.[23] These results suggest that HX106 might enhance the effects of methylphenidate on ADHD symptoms. It is well known that the pharmacodynamics of methylphenidate are crucially associated with dopamine functions.[5] In previous neurocognitive function studies, HX106 improved working memory performance compared with a placebo.[12] The functioning of working memory is heavily influenced by dopamine function.[24]

Although the results were not statistically significant, HX106 improved depressive moods in patients compared with the placebo. Plant compounds of *G. elata* are known to be antidepressants.[25,14] Furthermore, there was no difference in the outcome of the comprehensive attention tests between the two groups.

Traditionally, two plant compounds in HX106 derived from *G. elata* and *S. miltiorrhiza*, have been used to manage cardiovascular diseases in oriental Korean medicine.[13,14] Dopamine is also an essential neurotransmitter in the cardiovascular system.[15] Interestingly, the participants who experienced palpitations belonged to the HX106 group, which may have been caused by dopamine, known to increase heart rate.[15] Additionally, the adverse effects of methylphenidate include increased blood pressure and palpitations.[26]

During the 4-week study period, the HX106 group showed increased brain activity in the left precuneus and increased brain FC from the left precuneus to the left middle temporal gyrus compared with the placebo group. The parietal lobe and middle temporal gyrus form the attention regulation network, which includes the default mode network.[27] Methylphenidate is thought to improve default mode network dysfunction in ADHD patients[28] and increase FC in the fronto-cingulo-parietal cognitive control network.[29]

However, there were no significant correlations between the middle temporal gyrus' K-ARS scores and brain activity in either the HX106 or placebo group. These effects may be noticeable after prolonged treatment with methylphenidate. Therefore, no premature conclusions could be drawn based on these results.

Since the current study did not directly measure dopamine levels or evaluate heart rate change, we cannot comment on the effect of HX106 on the dopamine system. However, it can be speculated that the brain functional changes and the patient's palpitations may have been due to the adverse effects of methylphenidate enhanced by HX106.

This is the first trial to examine the improvement in ADHD symptoms and brain changes in response to HX106 administration to the best of our knowledge. Current research has shown the possibility of herbal formulations as an adjuvant of medications that could affect the clinical symptoms and brain functional changes.

There are several limitations to the current study. First, the number of participants was inadequate to prove differences in psychological testing and generalizing the findings. Second, the current study was designed concerning combination therapy for ADHD. HX106 is a mixed compound derived from four plants. Therefore, the mechanism of each plant compound and the synergistic effect of these compounds are not clear. Future studies should be designed to assess each plant compound's effect in the HX106 extract using a large number of participants.

Our findings suggest that HX106 enhances the effect of methylphenidate on ADHD symptoms and increases brain activity in the attention-regulation network. Therefore, HX106 may be a promising adjunctive therapy option for patients with ADHD.

Author contribution

Conceptualization: SB, DHH, Methodology: SB, SP, Formal analysis: SB, DHH, Writing-original draft: SB, writing review & editing: DHH, Supervision: DHH

Conflict of interest

The authors declare that they have no conflicts of interest.

Funding

This research was supported by the Korea Institute of Planning and Evaluation for Technology in Food, Agriculture, Forestry (IPET) through the High Value-added Food Technology Development Program, funded by the Ministry of Agriculture, Food and Rural Affairs (MAFRA; 318027-4).

Ethical statement

This study was approved by the Institutional Review Board of Chung Ang University Hospital (IRB number: 1861–007–330). All participants provided written informed consent—this study adhered to the principles of the Declaration of Helsinki.

Data availability

The data for this article will be available upon request.

References

1. Polanczyk GV, Willcutt EG, Salum GA, Kieling C, Rohde LA. ADHD prevalence estimates across three decades: an updated systematic review and meta-regression analysis. *Int J Epidemiol*. 2014;43(2):434–442.
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*. Washington DC: American Psychiatric Association; 2013.
3. Chandler DJ, Waterhouse BD, Gao WJ. New perspectives on catecholaminergic regulation of executive circuits: evidence for independent modulation of prefrontal functions by midbrain dopaminergic and noradrenergic neurons. *Front Neural Circuits*. 2014;8:53.
4. Klein MO, Battagello DS, Cardoso AR, Hauser DN, Bittencourt JC, Correa RG. Dopamine: functions, signaling, and association with neurological diseases. *Cell Mol Neurobiol*. 2019;39(1):31–59.
5. Childress AC, Komolova M, Sallee FR. An update on the pharmacokinetic considerations in the treatment of ADHD with long-acting methylphenidate and amphetamine formulations. *Expert Opin Drug Metab Toxicol*. 2019;15(11):937–974.
6. Sharma A, Couture J. A Review of the pathophysiology, etiology, and treatment of Attention-Deficit Hyperactivity Disorder (ADHD). *Ann Pharmacother*. 2014;48(2):209–225.
7. Hammerness P, McCarthy K, Mancuso E, Gendron C, Geller D. Atomoxetine for the treatment of attention-deficit/hyperactivity disorder in children and adolescents: a review. *Neuropsychiatr Dis Treat*. 2009;5:215–226.
8. Costa R, Oliveira NG, Dinis-Oliveira RJ. Pharmacokinetic and pharmacodynamic of bupropion: integrative overview of relevant clinical and forensic aspects. *Drug Metab Rev*. 2019;51(3):293–313.
9. Wong CG, Stevens MC. The effects of stimulant medication on working memory functional connectivity in attention-deficit/hyperactivity disorder. *Biol Psychiatry*. 2012;71(5):458–466.
10. Kowalczyk OS, Cubillo AI, Smith A, Barretta N, Giampietroc V, Brammer M, et al. Methylphenidate and atomoxetine normalise fronto-parietal underactivation during sustained attention in ADHD adolescents. *Eur Neuropsychopharmacol*. 2019;29(10):1102–1116.
11. Zhu Y, Gao B, Hua J, Liu W, Deng Y, Zhang L, et al. Effects of methylphenidate on resting-state brain activity in normal adults: an fMRI study. *Neurosci Bull*. 2013;29(1):16–27.
12. Kwon O, Lee S, Ban S, Im JJ, Lee DS, Lee EH, et al. Effects of the combination herbal extract on working memory and white matter integrity in healthy individuals with subjective memory complaints: A randomized, double-blind, placebo-controlled clinical trial. *Korean J Biol Psychiatry*. 2015;22(2):63–77.
13. Chen C, Guo C, Gao J, Shi K, Cheng J, Zhang J, et al. Vasorelaxant and antihypertensive effects of Tianshu Capsule on rats: An in vitro and in vivo approach. *Biomed Pharmacother*. 2019;111:188–197.
14. Lu CY, Lu PC, Chen PC. Utilization trends in traditional Chinese medicine for acute myocardial infarction. *J Ethnopharmacol*. 2019;241.
15. Bucolo C, Leggio GM, Drago F, Salomone S. Dopamine outside the brain: The eye, cardiovascular system and endocrine pancreas. *Pharmacol Ther*. 2019;203.
16. Lee DS, Choi J, Kim S-H, Kim S. Ameliorating effects of HX106N, a water-soluble botanical formulation, on Aβ25–35-induced memory impairment and oxidative stress in mice. *Biol Pharma Bull*. 2014;37(6):b13–00906.
17. DuPaul GJ, Power TJ, Anastopoulos AD, Reid R. *ADHD Rating Scale—IV: Checklists, norms, and Clinical Interpretation*. Guilford Press; 1998.
18. So YK, Noh JS, Kim YS, Choi NK, Kim SJ, Ko YJ. The reliability and validity of Korean parent and teacher ADHD rating scale. *J Korean Neuropsychiatr Assoc*. 2002;41:283–289.
19. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry*. 1961;4(6):561–571.
20. Carver CS, White TL. Behavioral-inhibition, behavioral activation, and affective responses to impending reward and punishment - The BIS/BAS scales. *J Pers Soc Psychol*. 1994;67(2):319–333.
21. Kim K, Kim WS. Korean-BAS/BIS scale. *Korean J Health Psychol*. 2001;6:19–37.
22. Seo J-M, Lee J-S, Kim S-Y, Kim H-W. Diagnostic significance of comprehensive attention test in children and adolescents with attention-deficit hyperactivity disorder. *J Korean Acad Child Adolesc Psychiatry*. 2011;22(4):246–252.
23. Noorazar SG, Malek A, Aghaei SM, Yasamineh N, Kalejahi P. The efficacy of zinc augmentation in children with attention deficit hyperactivity disorder under treatment with methylphenidate: A randomized controlled trial. *Asian J Psychiatr*. 2019;48.
24. Ott T, Nieder A. Dopamine and cognitive control in prefrontal cortex. *Trends Cogn Sci*. 2019;23(3):213–234.
25. Zhan HD, Zhou HY, Sui YP, Du XL, Wang WH, Dai L, et al. The rhizome of Gastrodia elata Blume - An ethnopharmacological review. *J Ethnopharmacol*. 2016;189:361–385.
26. Liang EF, Lim SZ, Tam WW, Ho CS, Zhang MW, McIntyre RS, et al. The effect of Methylphenidate and Atomoxetine on heart rate and systolic blood pressure in young people and adults with Attention-Deficit Hyperactivity Disorder (ADHD): Systematic review, meta-analysis, and meta-regression. *Int J Environ Res Public Health*. 2018;15(8):1789.
27. Aboitiz F, Ossandon T, Zamorano F, Palma B, Carrasco X. Irrelevant stimulus processing in ADHD: catecholamine dynamics and attentional networks. *Front Psychol*. 2014;5:183.
28. Santos PH, Goncalves R, Pedroso S. How does methylphenidate affect default mode network? A systematic review. *Rev Neurologia*. 2019;68:417–425.
29. van Amelsvoort T, Hernaus D. Effect of pharmacological interventions on the fronto-cingulo-parietal cognitive control network in psychiatric disorders: A transdiagnostic systematic review of fMRI studies. *Front Psychiatry*. 2016;7:82.