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Effects of Polyphenolic Extract from Pine Bark on the Improvement of Attention Deficit/Hyperactivity Disorder in Children and Adolescent

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Abstract

Purpose: To examine the hypothesis that intervention with the polyphenolic complex (PE) from pine bark improves the symptoms of ADHD and reduces oxidative stress in children and adolescent.

Methods: It was a randomized, double-blind, crossover and placebo-controlled 10-weeks period study, including two interventional periods (4weeks/period) and one washout period (2 weeks). Data were from 8 participants with attention deficit hyperactivity disorder (ADHD) at ages 7~16 years (seven boys and one girl). During the first interventional period, participants were received a capsule of PE from pine bark, which contain 25mg Oligopin® per capsule, or a capsule of placebo, which contains 25mg cellulose. Then, participants entered the washout period for 2 weeks. After 2 weeks of washout, the participants entered the second interventional period and crossed over to receive an Oligopin® or placebo capsule. Neuropsychological assessment, routine blood biochemical parameter and antioxidative status were carried out in this study.

Results: All blood biochemical parameters were normal in the interventional periods. However, the lipid peroxidation was significantly decreased when participants received the PE capsules. Moreover, the participants had a significant higher hit accuracy, inhibition, sustainability in CPT-II performanceduring the PE interventional period.

Conclusions: The administration of the polyphenolic extract from pine bark (25 mg/day) for one month might improve the inattention and impulsivity and reduce plasma lipid peroxidation levels in children and adolescent with ADHD.

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Introduction

Attention deficit hypertension disorder (ADHD) is one of the common neurodevelopment psychiatric disorders in children and adolescent, even in adults who are characterized by inattention, impulsivity and hyperactivity [1]. In Taiwan, an early community study in 1993 reported that the prevalence rates of ADHD was 19.8% for boys and 12.3% for girls among elementary students with a boy and girl ratio of 3:1[2]. However, comprehensive(nutritional) researches of ADHD in Taiwan is still rare.

At present, the real causes of ADHD are unknown, but it is thought to be biological and multifactorial, including genetic factors, the damage in catecholamine metabolism, lead toxicity, food sensitivities, or nutritional problems etc [3]. Recently, it is assumed that oxidative stress caused by the abnormal metabolism of adrenaline, noradrenaline and dopamine may play an important role in pathology of ADHD. Therefore, antioxidant supplements have been reported to replace the classical treatment of ADHD by psychostimulants and antidepressants because of the side effects of these psychomedicaments [4].

The bark extract of French maritime pine (Pinuspinaster) contains abundant polyphenolic compounds that are considered as the potent antioxidants. Heimann collected case reports about beneficial effects following treatment of polyphenolic extract (PE) from pine bark in French children with ADHD [5]. In our country, the active drugs use to ADHD patients is still controversial and the replacement therapy becomes the focal point, especially nutritional supplements. The purpose of this study was to investigate the improvement effects of PE from pine bark on the symptoms of ADHD and oxidative stress in children or adolescents. This is the first pilot study to discuss the effects of nutritional supplements on ADHD symptoms in Taiwan.

Methods

Subjects

The Clinical trials registry site of this study is TMU-JIRB (Taipei Medical University-Joint Institutional Review Board) and the TMU-JIRB number is 201404107. Participants were recruited from Psychiatric Clinic of the Shuang Ho hospital, Wanfang hospital, Taipei city hospital Songde branch and Grace counseling center, Taiwan. The inclusion criteria included participants who were 7~16 years old and met the definition of with attention deficit hyperactivity disorder (ADHD) as defined by SNAP-IV (Swanson, Nolan, and Pleham Version-IV). Then, in order to exclude the intelligence and other behavior problems, CPM (Clolured Progressive Matrices), SPM (Standard Progressive Matrices) and CBCL (Child Behavior Checklist) were used.

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Study design

It was a randomized, double-blind, crossover and placebo-controlled 10-weeks period study, including two interventional periods (4 weeks/period) and one washout period (2 weeks). During the first interventional period, participants were received a capsule of PE from pine bark, which contain 25mg Oligopin® (Les Derives Resiniques Et Terpeniques, French) per capsule (Y), or a capsule of placebo (R), which contains 25mg cellulose. Then, participants entered the washout period for 2 weeks. After 2 weeks of washout, the participants entered the second interventional period and crossed over to receive an Oligopin® or placebo capsule. Neuropsychological assessment, blood biochemical parameter and antioxidative status were determined at baseline and the end of every period.

Blood biochemical parameters

An autoanalyzer (SYNCHRON CX System, Hitachi 7170, Tokyo, Japan) was used to analyze blood biochemical parameters including liver function, kidney function, nutritional status, lipid profile, hematology and iron status.

	Baseline	R	Y
Physical measurement			
Height (cm)	130.6±13.3	131.6±13.1*	131.4±13.3*
Body weight (kg)	29.9±7.5	30.9±8.2*	31.4±7.1*
Body mass index(kg/m^2)	17.4±2.1	17.6±2.2	18.0±1.8*
Liver function			
AST (U/L)	28.14±3.18	26.29±1.89	28.57±3.87
ALT (U/L)	15.71±3.25	15.14±2.48	18.71±3.35
Bilirubin-Total (mg/dL)	0.59±0.11	0.49±0.18	0.37±0.14
Kidney function			
BUN (mg/dL)	12.69±3.26	12.69±2.98	13.37±3.23
Creatinine (mg/dL)	0.48±0.06	0.49±0.09	0.46±0.07
Uric acid (mg/dL)	4.54±1.12	4.63±1.12	4.06±0.95
Sodium (meq/L)	140.71±1.25	140.29±1.11	139.86±1.35
Potassium (meq/L)	4.53±0.37	4.44±0.26	4.71±0.25
Nutritional status			
Albumin (g/dL)	4.76±0.17	4.89±0.25	4.71±0.23
Lipid profile			
Triglyceride (mg/dL)	57.86±26.43	59.00±19.74	66.43±36.29
Cholesterol (mg/dL)	171.14±16.43	168.57±29.44	165.00±22.23
HDL-Cholesterol (mg/dL)	59.14±9.48	59.71±14.42	60.14±12.25
LDL- Cholesterol (mg/dL)	100.43±14.74	100.00±23.9	93.57±13.04
Hematology			
WBC (10e3/μL)	6.90±2.56	7.20±1.83	7.17±1.44
RBC (10e6/μL)	5.09±0.74	5.01±0.64	5.03±0.76
Hemoglobin (g/dL)	13.50±1.23	13.31±0.95	13.26±1.27
Platelet (10e3/μL)	343.86±44.7	378.14±35.18	367.00±72.94
Iron status			
Iron (μg/dL)	118.29±40.49	94.86±16.64	72.00±23.01
TIBC (μg/dL)	374.29±35.95	375.14±37.94	376.14±29.23
Ferritin (ng/mL)	63.33±34.49	48.89±23.77	44.94±23.36
Oxidative stress			
TBARS (μM)	2.12±0.54	2.11±0.48	1.80±0.42*†

Table 1: Characteristics and clinical data of the placebo (R) and intervention (Y) groupsin participants with ADHD[1].

[1]Values are expressed as the mean ± SD.Data from 7 participants with attention deficit hyperactivity disorder (ADHD). *p < 0.05 compared to baseline by pair t-test.† p < 0.05 compared to R by pair t-test.AST, aspartate aminotransferase; ALT, alanine aminotransferase; BUN, blood urea nitrogen; HDL, high density lipoprotein; LDL, low density lipoprotein; WBC, white blood cell; RBC, red blood cell; TIBC, total iron binding capacity; TBARS, thiobarbituric acid reactive substances

	Concepts	Baseline	R	Y
Inattention		%	%	%
Omissions	Accuracy/hit	58.84±17.12	57.68±16.56	53.24±20.65
Commissions	Accuracy/inhibition	54.1±11.58	50.72±10.17	44.29±9.44*†
Hit RT	Reaction time	49.64±17.11	52.08±16.10	53.21±18.78
Hit RT SE	Consistency/ sustainability	51.7±12.36	54.63±12.52	50.55±12.72
Variability	Consistency/ sustainability	51.24±11.13	52.37±11.69	48.16±8.88
Detectability	Accuracy/hit	52.53±9.36	52.21±9.00	45.18±8.08†
Hit RT ISI Change	Consistency/ sustainability	52.97±6.26	60.04±12.46	55.59±4.97
Hit SE ISI Change	Consistency/ sustainability	48.67±13.65	55.11±8.03	49.44±5.18†
Impulsivity				
Commissions	Accuracy/inhibition	54.1±11.58	50.72±10.17	44.29±9.44*†
Hit RT	Reaction time	49.64±17.11	52.08±16.1	53.21±18.78
Perseverations	Accuracy/inhibition	48.09±6.74	51.94±8.82	52.02±21.6
Vigilance				
Hit RT Block Change	Consistency/ sustainability	52.28±10.92	51.55±13.38	49.35±10.59
Hit SE Block Change	Consistency/ sustainability	48.05±13.68	46.14±10.08	48.48±7.45

Table 2 The Conners' ContinuousPerformance Test (CPT-II) of the placebo (R) and intervention (Y) groupsin participants with ADHD1

1 Values are expressed as the mean ± SD.Data from 7 participants with attention deficit hyperactivity disorder (ADHD). *$p < 0.05$ compared to baseline by pair t-test. †$p < 0.05$ compared to R by pair t-test. RT, reaction time; ISI, inter-stimulus interval; SE, standard error

Antioxidative status

Plasma thiobarbituric acid-reactive substance (TBARS) concentration was used as the lipid peroxidation indicator, which was quantitatively measured the TBARS concentration in plasma by the method of Ohkawa et al. [6].

Neuropsychological assessment

Neuropsychological test was assessed by psychologists. Conners' Continuous Performance Test (CPT-II) was used to evaluate the inattention, impulsivity and vigilance for children with ADHD.

Statistical analysis

All data are expressed as the mean ± standard deviation (SD). Pair t-test was used to compare the baseline values of the groups (PE versus placebo) and also changes in each evaluated parameter during the course of the study between the groups using EXCEL software (Redmond, WA, USA). Statistical significance was assigned at the $p< 0.05$ level.

Results

Sixteen participants were recruited at first and 7 of them passed the screening test of SNAP-IV, CPM, SPM and CBCL. The characteristic of 7 participants (6 boys and 1 girl) was shown as Table 1. The average age was 8.4±2.1. The heights and body weights of participants were significantly increased after 10 weeks. However, all blood biochemical parameters didn't change during the experimental period and maintained in the normal range (Table 1). In addition, the lipid peroxidation was significantly decreased when participants received PE capsules (Y group) (Table 1). On the other hand, the result of neuropsychological test was shown in Table 2. The variables may represent one or more clinical concepts at the same time, such as the data of commissions represents the concept of inattention and impulsivity. Compared with R group, participants had a significant lower commissions (accuracy/inhibition), detectability (accuracy/hit) and Hit SE ISI change (consistency/sustainability) during the PE interventional period (Y group). That is, the inattention and impulsivity were significantly improved when participants received PE capsules.

Discussion

This study demonstrated that polyphenolic extract from pine bark extract may have the potential to ameliorate the symptoms of ADHD in children. Simultaneously, the lipid peroxidation was also diminished when ADHD participants were supplemented by polyphenolic extract (PE) capsules.

The results reported by Tenenbaum et al. showed no treatment effect of PE extract on the ADHD symptoms of adults [7]. However, Trebatická et al. pointed to an option to use PE as a natural supplement (1mg/kg BW/day) to relive ADHD symptoms of children [8]. The reasons for the inconsistent research findings are complicated, such as methodological factors of psychologicalmeasurements, age, ethnicity, and dosage of supplement etc. In this study, CPT-II which is the authorized assessment method for ADHD symptoms was used. Additionally, compared with the previous studies, the moderate dosage of PE (25 mg/day) was used in this study.

The mechanisms of intervention success remains to be elucidated. In this study, although PE reduced the oxidative stress by decreasing the plasma lipid peroxidation products in children with ADHD, more evidences supporting the link between oxidative stress and ADHD are necessary.

Conclusion

In conclusion, the administration of the polyphenolic extract from pine bark (25 mg/day) for one month might improve the inattention and impulsivity and reduce plasma lipid peroxidation levels in children and adolescent with ADHD.

Conflict of Interest

The authors declared no potential conflict of interest with respect to the research, authorships and publication of this study.

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Author Contributions

Suh-Ching Yang designed the study. Yu-Ju Su and Ya-Ling Chen did the data analysis. The psychiatric evaluation was provided by Ying-Ru Chen, Wan-Lin Hsieh and I-Cheng Lin. Yannick Piriou provided the professional information and analyzed the composition of the pine bark extract.

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