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Clinical Investigation of French Maritime Pine Bark Extract on Attention-Deficit Hyperactivity Disorder as compared to Methylphenidate and Placebo: Part 1: Efficacy in a Randomised Trial

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ABSTRACT

Objectives: Determine the effect of French Maritime Pine Bark Extract (PBE; Pycnogenol®) on Attention-Deficit Hyperactivity Disorder (ADHD) behaviour and co-morbid physical/psychiatric symptoms, compared to placebo and the medicine MPH, and to assess its tolerability. Behaviour (measured by the ADHD-Rating Scale (ADHD-RS) and Social-Emotional Questionnaire (SEQ)) and physical complaints were evaluated in weeks 5 and 10.

Results: Eighty-eight paediatric ADHD patients (70 % male, mean age 10.1 years) were randomised to placebo (n = 30), PBE (n = 32) or MPH (n = 26). Teachers reported significant improvement of total and hyperactivity/impulsivity ADHD-RS scores by PBE and MPH after 10 weeks compared to placebo. MPH also improved inattention. SEQ ratings support ADHD-RS results. Adverse effects were reported five times more frequently for MPH than for PBE.

Conclusions: PBE appears a good alternative for MPH in paediatric ADHD and especially in the primary school environment, a fortiori when considering its almost complete lack of adverse effects.

Abbreviations: ADHD, Attention-Deficit Hyperactivity Disorder; ANOVA, Analysis of Variance; CNS, central nervous system; FFQ, Food Frequency Questionnaire; GI, gastrointestinal; HI, hyperactivity/impulsivity; HPLC, High Pressure Liquid Chromatography; IA, inattention; IQ, Intelligence coefficient; LMM, Linear Mixed Model; MPH, Methylphenidate; PBE, French Maritime Pine Bark Extract; PCQ, Physical Complaints Questionnaire; RS, Rating-Scale; SEQ, Social-Emotional Questionnaire; USP, United States Pharmacopeia; UZA, University Hospital Antwerp; UZ Ghent, University Hospital Ghent; ZNA, Hospital Network Antwerp.

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1. Introduction

Attention-Deficit Hyperactivity Disorder (ADHD) is the most common paediatric neurocognitive behavioural disorder with a prevalence of 2–7 %. ADHD is characterised by developmentally inappropriate levels of hyperactivity, impulsivity and inattention, and is often associated with other psychiatric disorders (Sayal et al., 2018). Methylphenidate hydrochloride (MPH) is the first-choice medication for ADHD and therefore used as a reference treatment during this trial (Hoge Gezondheidsraad, 2021). Non-stimulant drugs such as atomoxetine and guanfacine were shown to be efficacious in ADHD treatment, however, due to their smaller effect sizes they are generally recommended as second-line treatment (Mechler et al., 2022). Nevertheless, MPH frequently causes adverse effects and potential publication bias in reported efficacy exists (Antshel et al., 2011; Storebø et al., 2015). Other therapeutic options are therefore sought after.

ADHD is a prevalent neurodevelopmental disorder that has been associated with numerous structural and functional central nervous system (CNS) abnormalities but also findings on neurobiological mechanisms linking genes to brain phenotypes begin to emerge (Purper-Ouakil et al., 2011). Although its exact pathophysiology remains unclear, besides dopaminergic dysfunction, also immune and oxidant-antioxidant imbalances appear to be involved (Ceylan et al., 2010, 2012; Kawatani et al., 2011). These imbalances offer potential for new therapeutic approaches in ADHD therapy (Verlaet et al., 2014).

French Maritime Pine Bark Extract (PBE; *Pinus Pinaster,* Pycnogenol®, Horphag Research), a patented, proprietary commercially available extract from French maritime pine (*Pinus pinaster*) bark, was selected for the present study (D'Andrea, 2010; Trebatická et al., 2006). This polyphenol-rich extract, standardised to contain 70 ± 5 % procyanidins, is known for its antioxidant and anti-inflammatory properties, among other biological effects (Rohdewald, 2002). Therapeutic benefit in paediatric ADHD was suggested by a small randomised trial and observational studies (Dvoráková et al., 2006; Trebatická et al., 2006). However, its efficacy and value as compared to standard treatment with MPH were to be confirmed.

The full objective of this randomised trial was to evaluate the effect of PBE on ADHD behaviour, co-morbid physical/psychiatric symptoms, immunological markers, oxidative damage and antioxidant and neurochemical status, compared to placebo and MPH (Verlaet et al., 2017). This publication focusses on behaviour and co-morbid physical/psychiatric symptoms. Based on the available data, it was hypothesised that:

1 In ADHD therapy, PBE is more effective than placebo and not less effective than MPH;
2 Compared to placebo and MPH, PBE reduces co-morbid physical and psychiatric complaints;
3 The tolerability of PBE is higher than that of MPH.

2. Material and methods

2.1. Ethics and registration

Ethical approval was obtained in the Belgian University Hospitals of Antwerp (UZA) (EC 15/35/365) and Ghent (UZ Ghent) (2016/0969) and Hospital Network Antwerp (ZNA) (EC approval 4656). The trial was registered at Clinicaltrials.gov (NCT02700685, registered 18 January 2016) and EudraCT (2016–000215-32, registered 4 October 2016) (Verlaet et al., 2017).

2.2. Quality control

PBE quality control was performed according to the United States Pharmacopeia (USP) spectrophotometric method (United States Pharmacopeial Convention, 2014). Specific phenolic constituents were also determined by HPLC (see Methods in the Supplementary Material). PBE complied with USP requirements, with an average procyanidin content of 78.3 % ± 3.0 %, including 1.276 % ± 0.031 % catechin, 1.375 % ± 0.012 % taxifolin, 0.287 % ± 0.005 % caffeic acid and 0.274 % ± 0.003 % ferulic acid (Supplementary Tables S4 and S5).

2.3. Inclusion and randomisation

Participants from 6 to 12 years, diagnosed with ADHD, were included between September 2017 and November 2020 at the UZA, UZ Ghent and the ZNA, with recruitment also via conventional and social media, schools, pharmacies, paediatricians, speech therapists and physiotherapists. Written consent of the patients' legal representative and written assent by the patient were obtained prior to inclusion. Excluded were patients with autism spectrum disorder, psychosis, depression, inflammatory disorders, and/or use of some drugs and nutritional supplements 3 months before inclusion (detailed eligibility criteria in Supplementary Table S1).

Following screening (see protocol in Supplementary Material), enrolment by a child neurologist/psychiatrist and baseline assessments, patients were randomised, stratified by trial centre and body weight (randomisation list created by pharmacists via randomization.com with 1:1:1 allocation ratio). Patients, their parents and teachers, physicians and investigators were blind to treatment allocation. Treatments included 1 or 2 oral capsules at breakfast:

- MPH (Medikinet® Retard, Medice GmbH, MPH modified release): 20 or 30 mg/day if $<$ or $\geq$ 30 kg, resp. Treatment started with 10 mg/day, increasing 10 mg per week.
- PBE (Pycnogenol®, Horphag): 20 or 40 mg/day if $<$ or $\geq$ 30 kg, resp. (20 mg/day during the first two weeks).
- Placebo: excipients (microcrystalline cellulose and magnesium stearate) only.

Forty-eight patients per group were necessary based on following assumptions:

- PBE reduces teacher ADHD-RS total score by 0.75 SD after 10 weeks (Pelsser et al., 2011; Trebatická et al., 2006);
- Power of 80 %, dropout of 20 %;
- Two-sided testing, 0.05 significance level with Bonferroni post-hoc testing correction.

2.4. Outcomes

Teachers and parents filled out various questionnaires at baseline and after 5 and 10 weeks (Supplementary Table S2) (D'Andrea, 2010; de Vriese et al., 2005; Pelsser et al., 2010; Verlaet et al., 2017). The ADHD-Rating Scale (ADHD-RS) includes 9 inattention (IA) and 9 hyperactivity/impulsivity (HI) items (Döpfner et al., 2006; Trebatická et al., 2006). The Social-Emotional Questionnaire (SEQ) assesses, besides ADHD, core symptoms of social behaviour problems, anxiety and autism. Its ADHD score can be subdivided into a hyperactivity (H), impulsivity (I) and inattention (IA) score. The Physical Complaints Questionnaire (PCQ) enquires physical and sleep complaints (Supplementary Table S3). Various questions can be combined. Open questions on adverse events were included. The Food Frequency Questionnaire (FFQ) includes 50 questions on different food groups to assess global dietary habits (de Vriese et al., 2005).

The primary outcome was the summed ADHD score of the teacher-rated ADHD-RS. Behavioural assessment by teachers is preferred as primary objective due to its higher sensivity (Power et al., 1998; Tripp et al., 2006).

Secondary outcomes were:

- Summed ADHD score of the parent-rated ADHD-RS.

- Summed ADHD score of the teacher- and parent-rated SEQ.
- Sub scores of the teacher- and parent-rated ADHD-RS and SEQ.
- Percentage of treatment responders (≥20 % reduction of total ADHD-RS score) (Buitelaar et al., 2003).
- Teacher- and parent-rated SEQ social behaviour problems, anxiety and autism scores.
- Parent-rated PCQ scores.

A final objective was to investigate the acceptability of PBE compared to MPH and placebo, based on adverse effects (open questions), treatment compliance (greater than 90 % ingestion as scheduled) and dropouts.

2.5. Statistics

SPSS 27.0 (IBM) was used for statistical analyses. Data were checked for outliers and normality (Shapiro-Wilk test and QQ-plot). In case of more than 2 missing answers regarding a (sub)score within a patient, this (sub)score was set to missing. Participants were excluded from analyses only for those outcomes without any data available. For ADHD-RS, SEQ and combined PCQ scores, blood pressure and heart rate, the effect of treatment was modelled using linear mixed models (LMMs). Scores were entered as dependent variable. Time point (categorical), treatment and their interaction were included as fixed effects and sex as covariate. Participant ID was entered as random intercept. Individual PCQ scores were compared between start and end of the trial within each treatment group by Cochran-Armitage trend tests. Due to lack of power, no subgroup analyses were performed. Non-inferiority of PBE compared to MPH is demonstrated when the difference in effect on ADHD-RS score was no more than 5 points (Berek et al., 2011; Christensen, 2007). All analyses were by original assigned groups. A 2-sided p-value < 0.05 was considered significant. For secondary outcomes, a stricter 2-sided p-value < 0.01 was applied to account for increased type 1 error. Bonferroni correction accounting for all secondary analyses would be overly conservative, since these do not represent independent tests. Post-hoc analysis with pairwise testing of the difference in effect between treatments was performed using Bonferroni correction for multiple testing with $p < 0.05$ considered significant.

A detailed study protocol was published before in Verlaet *et al.* (Verlaet et al., 2017).

3. Results

3.1. Participants and baseline characteristics

Eighty-eight paediatric ADHD patients (89 % Caucasian), both diagnosed *de novo* and formerly treated, were randomised (Fig. 1). 12 participants (14 %) dropped out (i.e., discontinued intervention and lacking further questionnaires). Adverse events reported for dropping out were anger management problems and palpitations (placebo), hospitalisation due to headache (PBE; unrelated to PBE intake since caused by a neck blockage), and sadness (MPH). Serious adverse events related to the intervention have not been observed. Several teacher questionnaires were missing due to teachers never responding/not responding anymore, starting/ending the study during the summer holiday, covid-19 (home-schooling), or a combination of these.

Treatment groups were comparable regarding baseline characteristics (Table 1) as well as regarding general dietary habits and parents' highest educational achievement as proxy for socioeconomic status (data not shown). The proportion of dropouts was not significantly different between groups (Chi-Square test, data not shown) (Cabrera et al., 2018). Moreover, dietary habits did not change significantly within treatment groups during the 10-week study period (Cochran-Armitage trend test, data not shown).

3.2. ADHD-Rating Scale

3.2.1. Teacher ratings

Mean teacher and parent ADHD-RS scores per treatment group at baseline and follow-up are listed in Supplementary Table S6 and graphically depicted by Fig. 2. P-values, testing for a different effect between treatments over time, were generated by testing for interaction between time and treatment. Regarding the teacher-rated summed ADHD-RS score (primary outcome), and inattention and hyperactivity/

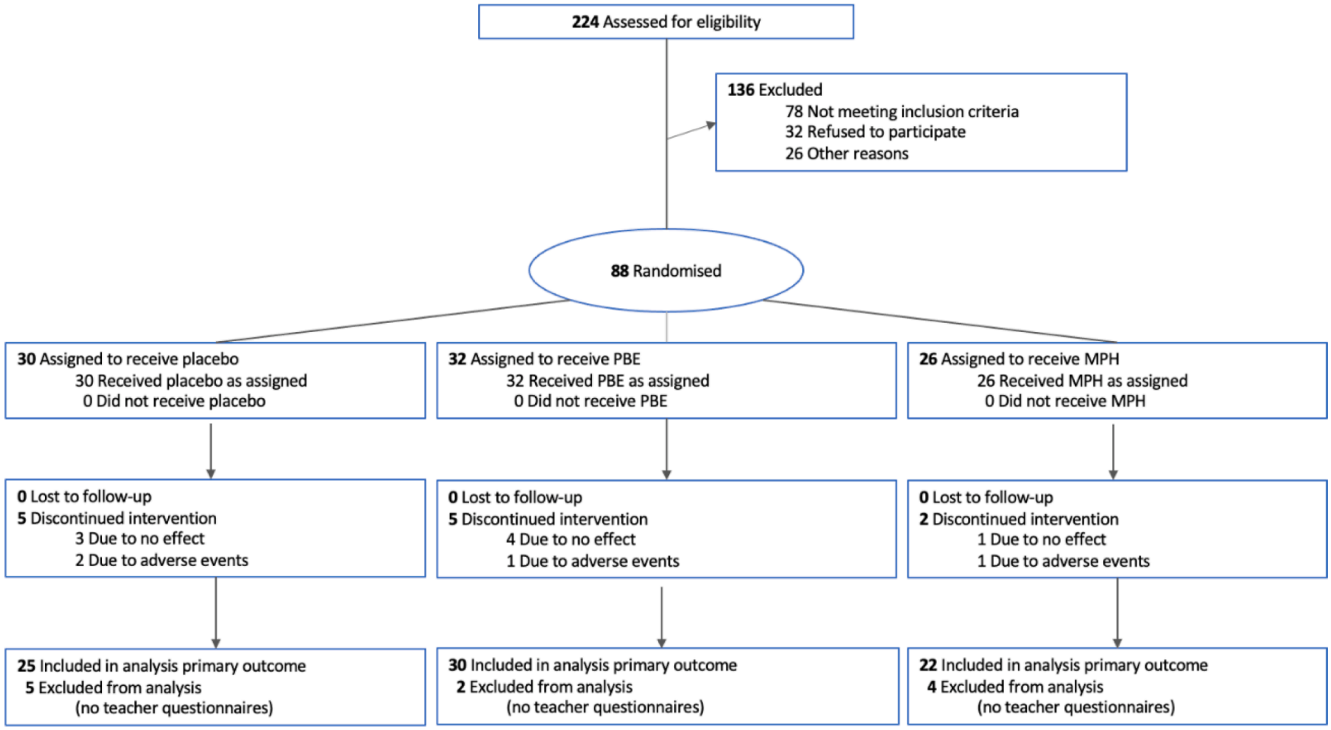

Fig. 1. Flow chart of included patients and dropouts. PBE: French Maritime Pine Bark Extract; MPH: methylphenidate hydrochloride.

Table 1
Baseline characteristics per treatment group.

	Placebo	PBE	MPH
No. male/female (% male)	24/6 (80)	21/11 (66)	17/9 (65)
Age, mean (SD), years	9.96 (1.90)	10.31 (1.37)	10.0 (1.73)
Weight, mean (SD), kg	36.21 (11.68)	35.47 (9.82)	34.32 (8.79)
Height, mean (SD), m	1.42 (0.14)	1.42 (0.11)	1.39 (0.10)
No. months since diagnosis, median (IQR)	13.00 (30.50)	18.00 (18.00)	16.50 (24.50)
No. eating fruits and vegetables daily, yes/no (% yes)	13/16 (45)	21/11 (66)	15/9 (63)
Dose, mean (SD), mg/kg	–	0.88 (0.03)	0.78 (0.02)
Compliance, mean (SD), %	0.94 (0.24)	0.99 (0.38)	0.89 (0.15)
Compliance ≥ 90 %, yes/no (%)	12/9 (57 %)	19/5 (79 %)	15/6 (71 %)
ADHD-RS total ADHD score teachers, mean (SD)	30.06 (13.54)	26.07 (9.62)	24.77 (12.68)
ADHD-RS IA score teachers, mean (SD)	17.13 (6.74)	14.40 (5.32)	14.75 (6.59)
ADHD-RS HI score teachers, mean (SD)	12.94 (7.86)	11.67 (6.22)	10.11 (7.87)
ADHD-RS total ADHD score parents, mean (SD)	31.29 (10.27)	32.19 (9.67)	30.46 (8.28)
ADHD-RS IA score parents, mean (SD)	17.55 (5.32)	17.81 (4.88)	16.78 (4.94)
ADHD-RS HI score parents, mean (SD)	13.74 (6.07)	14.38 (5.97)	13.72 (5.76)

ADHD-RS:ADHD-Rating Scale; HI: hyperactivity/impulsivity; IA: inattention; IQR: interquartile range; MPH: methylphenidate hydrochloride; PBE: French Maritime Pine Bark Extract.

impulsivity sub scores, significant differences in effects between treatments after 10 weeks were found (Supplementary Table S6), with mean (SD) total scores at baseline and after 10 weeks being 26.07 (9.62) and 18.43 (12.57) for PBE, 24.77 (12.68) and 13.50 (11.94) for MPH, and 30.06 (13.53) and 28.60 (13.95) for placebo ($p = 0.008$). Post-hoc analyses (Supplementary Table S7 and Fig. 2) show that effects do not differ between the two active treatments (MPH and PBE), whereas effects of both active treatments differ from placebo for the total and hyperactivity/impulsivity score. For the inattention score, only MPH shows an effect that is significantly different from placebo.

Already after 5 weeks, significant differences in effects between treatments were observed. Post-hoc analyses show that the effect on inattention score differs between the two active treatments, while MPH significantly differs from placebo (total and inattention score).

Although after 10 weeks, the difference in effect on total ADHD-RS score between MPH and PBE is 3.23 (no more than 5 points, based on LMM), non-inferiority cannot be demonstrated because 5 is included in the 95 % confidence interval of this difference (-3.40 to 9.86).

3.2.2. Parent ratings

Regarding the parent-rated summed ADHD-RS score and inattention sub score, significant differences between treatments after 10 weeks, but not after 5 weeks, were found (Supplementary Table S6). Post-hoc analyses (Supplementary Table S7 and Fig. 2) show that effects do not differ between the two active treatments. MPH's effects are significantly different from placebo (total score, hyperactivity/impulsivity and inattention sub scores).

3.3. Social-Emotional Questionnaire: ADHD scores

3.3.1. Teacher ratings

Based on teacher SEQ ratings, a significant difference in effect between the three treatments was only found for the hyperactivity sub score (Supplementary Table S8). Post-hoc pairwise comparisons show that the effect on the hyperactivity score does not differ between the two active treatments, whereas the effect of both active treatments differs from the effect of placebo (Supplementary Table S9, Fig. 3).

3.3.2. Parent ratings

Based on parent SEQ ratings, a significant difference in effect between the three treatments was found for the total, hyperactivity and inattention scores (Supplementary Table S8). Post-hoc analyses show that the two active treatments differ significantly regarding these (sub) scores, whereas MPH differs significantly from placebo for the total and hyperactivity score (Supplementary Table S9, Fig. 3).

3.4. Social-Emotional Questionnaire: autism, social problem behaviour and anxiety scores

For teacher and parent ratings, no significant difference in effects between the three treatments was found regarding SEQ autism, social problem behaviour and anxiety (sub)scores (Supplementary Table S10).

3.5. Percentage of treatment responders

Based on teacher (but not parent) ratings, the percentage of treatment responders was significantly different between treatment groups (Supplementary Table S11). Post-hoc analyses on teacher ratings revealed that the percentage of treatment responders differs significantly between MPH and placebo (data not shown, $p = 0.007$ after Bonferroni correction).

3.6. Physical complaints and adverse effects

No significant differences in effects between the three treatments were found for combined (Supplementary Table S12) and individual PCQ scores. Moreover, no significant changes regarding individual PCQ scores were found within treatment groups during the study period (Cochran-Armitage trend test, data not shown).

Regarding blood pressure and heart rate, no significant differences in effects between treatments were found (Supplementary Table S13), despite a slightly increased average heart rate in the MPH group ($p = 0.1414$ after Bonferroni correction for the difference in effect between PBE and MPH).

No serious adverse events related to the intervention were reported. The frequency of nonserious adverse events reported by parents after 5 and 10 weeks (open question) was significantly different between treatment groups (Supplementary Table S14). Post-hoc analyses revealed that both after 5 and 10 weeks, significantly more adverse events were reported for participants receiving MPH than for those receiving PBE ($p = 0.004$ and $p = 0.0255$ after Bonferroni correction). Adverse effects reported for PBE were headache, dizziness, nausea and diarrhoea. Adverse effects reported for MPH were GI symptoms, reduced appetite, insomnia, headache, a feeling of tachycardia, sneezing and being emotional.

4. Discussion

This double-blind trial addresses the potential of a procyanidin-rich extract in ADHD as compared to standard therapy and placebo. Although 144 patients were to be included based on power calculation, the trial was ended with 88 participants due to expiry of study capsules in combination with poor inclusion during the covid-19 pandemic.

Based upon teacher-rated ADHD-RS, the primary outcome, MPH treatment caused, as expected, significant improvement (total and inattention score, not hyperactivity/impulsivity) as compared to placebo after 5 weeks (Schachter et al., 2001). After 10 weeks, both PBE and MPH significantly improved the total and hyperactivity/impulsivity score, while MPH also improved inattention. PBE thus had a slower

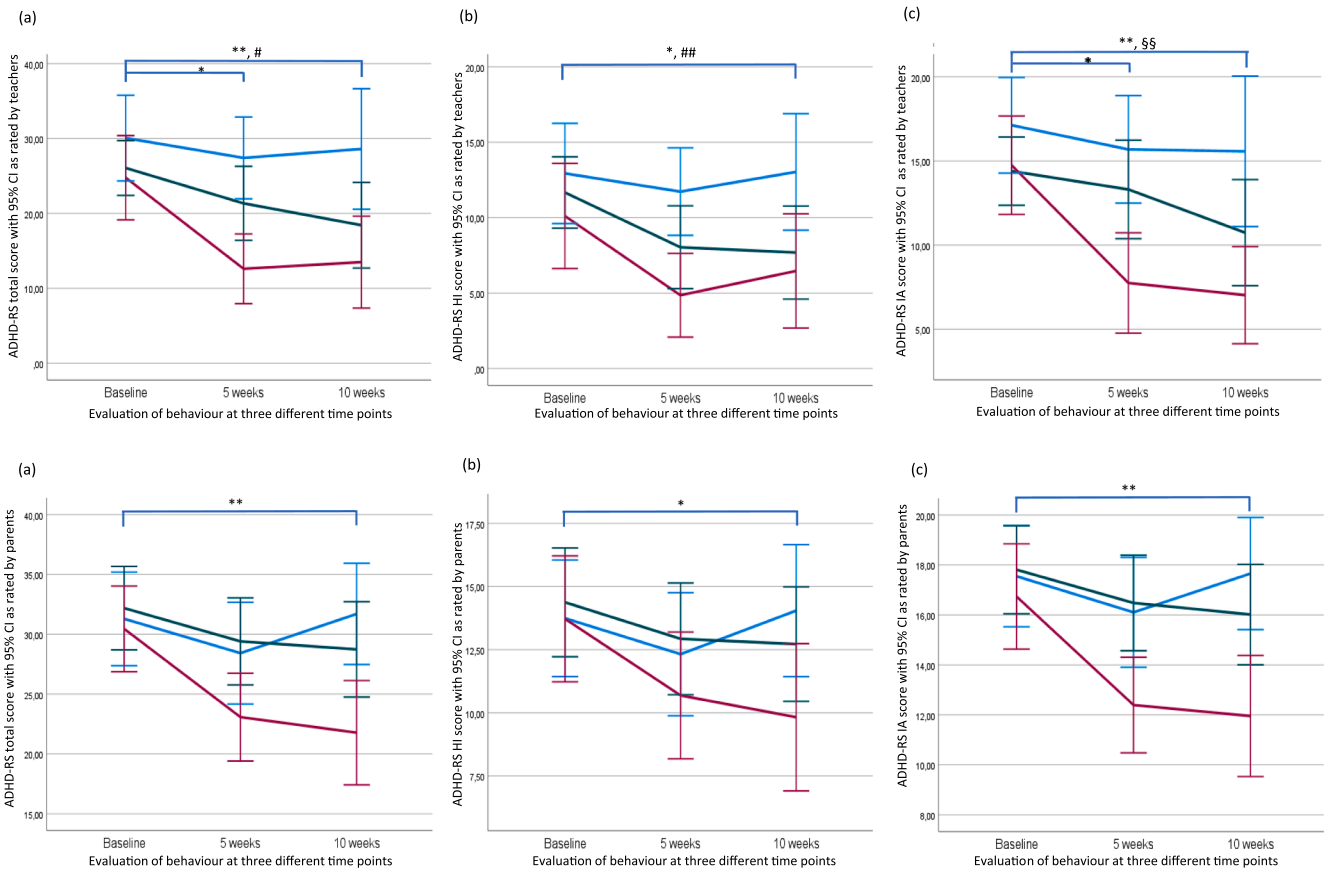

Fig. 2. ADHD-RS total score (a) and HI (b) and IA (c) sub scores rated by teachers (upper part) and parents (lower part of the figure). Blue: placebo; green: PBE; red: MPH. *: p-value < 0.05 for the difference between placebo and MPH; **: p-value < 0.01 for the difference between placebo and MPH; #: p-value < 0.05 for the difference between placebo and PBE; ##: p-value < 0.01 for the difference between placebo and PBE; §§: p-value < 0.01 for the difference between PBE and MPH. ADHD-RS: ADHD-Rating Scale; CI: confidence interval; HI: hyperactivity/impulsivity; IA: inattention; MPH: methylphenidate hydrochloride; PBE: French Maritime Pine Bark Extract. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

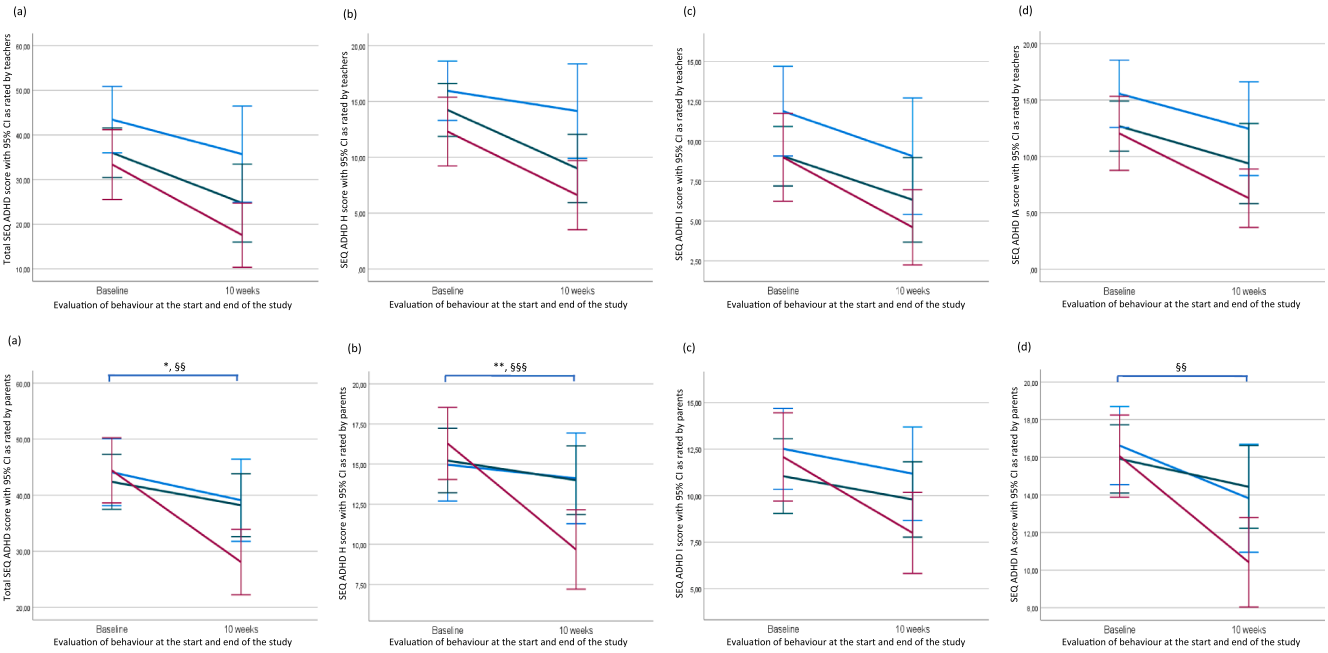

Fig. 3. SEQ total score (a) and H (b), I (c) and IA (d) sub scores rated by teachers (upper part) and parents (lower part of the figure). Blue: placebo; green: PBE; red: MPH. *: p-value < 0.05 for the difference between placebo and MPH; **: p-value < 0.01 for the difference between placebo and MPH; §§: p-value < 0.01 for the difference between PBE and MPH; §§§: p-value < 0.001 for the difference between PBE and MPH. CI: confidence interval; H: hyperactivity; I: impulsivity; IA: inattention; MPH: methylphenidate hydrochloride; PBE: French Maritime Pine Bark Extract; SEQ: Social-Emotional Questionnaire. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

effect than MPH. This was also expected, since nutritional supplements often require weeks to months to exert an effect due to their mechanism of action, while MPH's effects can be expected promptly (Kimko et al., 1999). Earlier research for instance demonstrated that taking PBE at least 5 weeks before the start of the allergy season reduced allergic symptoms. It is likely that the immune modulating effects of PBE may require sufficient time to manifest noticeable symptom reduction (Wilson et al., 2010).

Nevertheless, though statistical non-inferiority analysis was inconclusive, both treatments were evenly matched after 10 weeks except for their effect on inattention. Improvement of ADHD behaviour at school is a desirable treatment outcome with impact on school performance, relationships and self-esteem. Since the FFQ indicates comparable baseline dietary habits (and thus polyphenol intake) between treatment groups, effects in the PBE group can be ascribed to PBE's polyphenol content.

Based on parent ratings, significant improvement on all ADHD-RS (sub)scores was found only for MPH after 10 weeks. The difference in effects between teacher and parent ratings is striking and appears to emphasize the higher sensitivity of teacher ratings (Verlaet et al., 2017). Possibly, parenting stress and exceptional focus on one child (evidenced by slightly higher baseline scores), especially during a trial focused on ADHD behaviour, affect parents' perceptions and reduce their ability to notice improvements. This might specifically be true for PBE, as its effects are expected to appear very subtle after several weeks, gradually increasing over the course of another number of weeks – as opposed to MPH's effects. This underlines the importance of parental/family psychological support and education for ADHD therapy to reach its full potential (Heath et al., 2015). Teachers might be more objective and sensitive to behavioural improvements since they are less emotionally involved, less focused on one child and can compare between children in the classroom. Nevertheless, MPH extended-release formulation is effective for about 8 h, while PBE's effect is not expected to wear off suddenly. Since study treatments were taken at breakfast, teachers, as opposed to parents, might not have noticed potential 'rebound' effects of MPH.

SEQ ratings largely confirm ADHD-RS results, thus consolidating our findings. Differences between ADHD-RS and SEQ results could be attributable to different phrasing, divergent differentiation into sub scores and the 4- vs 5-point rating scales. Moreover, our results confirm successful treatment of paediatric ADHD with PBE in an earlier controlled trial, in which improvement was also evidenced by teacher but not parent ratings (Trebatická et al., 2006).

Both PBE and MPH did not significantly affect co-occurring psychiatric and physical complaints. However, as the study population was not specifically chosen based on these conditions, potential for improvement by PBE might have been limited.

MPH frequently causes adverse effects. It is therefore important to consider both behavioural improvement and adverse effects when assessing PBE's value in ADHD therapy. Up to five times more adverse effects were reported for MPH than for PBE. Reported side effects were generally comparable to those in literature (Storebø et al., 2015; Trebatická et al., 2006). Moreover, though not statistically (but possibly clinically) significant, a slightly increased average heart rate (but not blood pressure) was observed for those treated with MPH at the end of the trial.

Treatment adherence and proportion of dropouts can be considered indicators of treatment effectiveness, based on achievement of positive effects and absence of adverse effects. Both were not significantly different between treatments. The overall acceptability of PBE, based on adverse effects, compliance and dropouts, therefore seems at least not inferior to MPH.

A strength of the current trial is the active control arm MPH. In one previous trial in adult ADHD, neither MPH nor PBE outperformed placebo, possibly due to the 3-week treatment period (Tenenbaum et al., 2002). Moreover, our trial takes into account co-morbid symptoms and adverse effects, which influence the choice of therapy as well. Another strength are stricter significance limits for secondary outcomes and Bonferroni correction for post-hoc testing, which control type 1 error. Finally, LMM is an added value in case of incomplete observations (e.g., dropouts, missing questionnaires) compared to ANOVA, which is a complete case analysis. Also, validity of the proportion of responders can be questioned as this is also a complete case analysis.

A limitation of the current trial is inclusion of only 88 patients as opposed to 144 based on power calculation. Though the dropout ratio was lower than predicted (14 % vs 20 %), power was too low to perform subgroup analyses. Moreover, specific differences between treatments might remain undetected (e.g., PBE versus MPH). Nevertheless, several striking significant differences were found despite this reduced power. As observed in many trials, selection bias should also be considered. It is for instance unlikely that those experiencing a high symptom burden would 'risk' a 10-week placebo treatment. Moreover, despite a solid ADHD diagnosis, very low ADHD-RS scores were reported for several participants. This underscores the subjectivity of questionnaires and leaves little opportunity for improvement. The 10-week study duration is another limitation but was chosen to limit patient burden. Moreover, compliance analysis was based on medication counts, the validity of which could be questioned, especially as this was possible for only ± 75 % of the participants. Nevertheless, compliance control by blood analyses would increase participants' burden and is expensive.

Further research on long-term effects, effects on specific subgroups (e.g., dietary habits, ADHD subtype/severity) and dose ranging is indispensable to fully understand PBE's therapeutic potential.

5. Conclusions

In conclusion, in paediatric ADHD and especially in the primary school environment, PBE was proven to be a good alternative for MPH for those willing to wait a few weeks for effects, a fortiori when considering its almost complete lack of adverse effects as opposed to MPH. Its absence of significant behavioural effects reported by parents might be attributed to parenting stress and lower sensitivity of parents' ratings. Results of this study strengthen the evidence underlying 'natural' treatment options, which is highly desired by medical staff, patients and parents. These results should be confirmed by future trials involving a greater number of patients, providing more information on specific subgroups, dosing and mechanisms of action of therapeutic modalities for ADHD. An additional publication focusses on effects on immunological markers, oxidative damage and antioxidant and neurochemical status.

Statement of human rights

The clinical trial was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Statement of informed consents

All participants and their legally accepted representatives agreed with and signed the written informed consent.

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CRediT authorship contribution statement

Anne-Sophie Weyns: Investigation, Formal analysis, Writing – original draft, Writing – review & editing. **Annelies A.J. Verlaet:** Conceptualization, Methodology, Investigation, Funding acquisition,

Data curation, Formal analysis, Writing – original draft. **Annelies Breynaert:** Investigation. **Tania Naessens:** Investigation. **Erik Fransen:** Methodology, Formal analysis. **Helene Verhelst:** Conceptualization, Methodology, Investigation, Data curation. **Dirk Van West:** Investigation, Supervision. **Ingrid Van Ingelghem:** Investigation. **An I. Jonckheere:** Investigation, Data curation. **Diane Beysen:** Investigation. **Sandra Kenis:** Investigation. **Els Moens:** Investigation. **Aalt P.J. van Roest:** Resources. **Huub F.J. Savelkoul:** Conceptualization, Methodology. **Tess De Bruyne:** Writing – review & editing. **Luc Pieters:** Funding acquisition, Resources. **Berten Ceulemans:** Conceptualization, Supervision. **Nina Hermans:** Conceptualization, Methodology, Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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