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Review Article

Beneficial Effects of Pycnogenol® on Attention Deficit Hyperactivity Disorder (ADHD) : A Review of Clinical Outcomes and Mechanistic Insights

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Abstract

Characterized by developmentally inappropriate levels of inattention, hyperactivity and impulsivity, Attention-Deficit Hyperactivity Disorder (ADHD) is the most prevalent neurodevelopmental disorder, posing a significant public health concern. Currently, methylphenidate (MPH) is the primary pharmacological treatment of choice but associated with notable side effects prompting the search for alternative therapies. Pycnogenol®, an extract rich in polyphenols derived from maritime pine, renowned for its antioxidant, immunomodulatory, and anti-inflammatory properties, emerges as a promising alternative. Limited studies in ADHD consistently reveal that Pycnogenol® treatment for 4 to 10 weeks improves attention span while reducing impulsive and hyperactive behaviors. Its potential to rebalance neurotransmitter levels and positively influence gut microbiota, supposed to be altered in ADHD, coupled with minimal side effects, suggests Pycnogenol® as a viable natural alternative to MPH. This study aims to review existing scientific literature on Pycnogenol® administration in ADHD, addressing etiology, treatment, hypothesized of mechanisms of action and the initial findings on its effects on ADHD symptomatology and cognitive function. While the potential of Pycnogenol® as a therapeutic alternative is encouraging, further investigations are essential to fully elucidate its mechanisms and efficacy. These findings underscore the importance of exploring innovative treatments for ADHD and highlight the challenges in objective assessment and treatment development.

Keywords: ADHD; Pycnogenol®; Methylphenidate (MPH); Oxidative stress; Neuro Inflammation; Dietary supplement

Attention deficit hyperactivity disorder

Prevalence and symptomatology

Attention Deficit Hyperactivity Disorder (ADHD) is the most common neurodevelopmental disorder in child psychiatry [1] with a worldwide prevalence in children and adolescent around 8% [2,3] and an estimated male-to-female ratio of 2-4:1 [4-6]. ADHD is characterized by developmentally inappropriate levels of inattention, hyperactivity and impulsivity [4] which affect daily functioning, social interaction, academic success but also physical and mental health [2,7]. Associated with comorbid disorders, ADHD is actually an undeniable public health priority [8,9]. Its symptoms persist into adulthood in 50% cases and are associated with social and occupational impairment [10,11]. ADHD is also associated with a range of executive and attentional deficits [12-16]. Studies converge to show that the most frequently reported cognitive deficits concern vigilance, working memory, inhibition, delay aversion, selective attention and divided attention [13,16], as well as reaction time variability [17]. These deficits are central to the various explanatory theoretical models of ADHD developed over the past 25 years and converge towards a predominant position of the involvement of executive and attentional functions in the symptomatology of this disorder, associated with structural and functional brain variations [18-26].

Etiology

The etiopathogenesis of ADHD is considered multifactorial, with complex determinism and resulting from an interaction of genetic and environmental factors [27,28]. To date, however, its etiology has not been fully elucidated, since neither genetic nor precise environmental factors have been identified or replicated. This disappointment suggests that the factors are interchangeable and no single factor can be identified as an isolated and direct trigger of ADHD. This lack of evidence, or rather heterogeneity, is consistent with the significant phenotypic variability encountered in ADHD, as well as, most likely, the important role played by environmental factors [29-31]. Also, this lack of understanding of the underlying molecular etiology of ADHD hinders diagnosis and treatment of this disorder [32].

Significant evidence suggests a strong genetic component in ADHD [33-35], with heritability estimated between 60% and 90% based on twin studies [36-37]. Large-scale genomic association research (GWAS) has identified genes linked to ADHD, potentially affecting processes like neuronal plasticity or neurotransmitter function, notably dopamine, noradrenaline, and serotonin [38,36,39,40]. However, no predominant genes have been consistently identified due to insufficient replication, indicating probably minor effects and complex interactions between genes and environment, though their precise mechanisms remain unclear [41]. Environmental factors, including prenatal, perinatal, and postnatal challenges, as well as exposure to pollutants and psychological stressors, are also supposed to play a role [42-44,31]. While their contribution is estimated at 20% to 30% [45], their effect sizes are probably modest, often working alongside genetic factors [41]. The emerging idea from the body of etiological studies conducted to date tends towards the idea that there are genetically susceptible individuals who will be at greater risk of developing ADHD if exposed to certain environmental risk factors [41,39,46,47]. Studies propose that prenatal exposure to such factors could trigger inflammation, impacting neurodevelopment and potentially contributing to ADHD pathophysiology [41-49]. A neuroinflammatory state would negatively influence brain development by acting through glial activation, increased oxidative stress, aberrant neuronal development, reduced neurotropic support and altered neurotransmitter functions, such as dopamine, noradrenaline and serotonin [50,41,51]. Therefore, this neuroinflammatory hypothesis, relatively new and promising, suggests that a neuroinflammatory state, caused by early environmental factors, would be common to neurodevelopmental disorders [52,53], and could have an impact on the pathophysiology of ADHD [41,54].

Moreover, susceptibility genes linked to neuroinflammation have been associated with neurodevelopmental risks in ADHD [55,56]. Genetic polymorphisms in genes related to gene regulation, cell adhesion, and inflammation, such as pro-inflammatory cytokines, antioxidant enzymes, and microglia, have been highlighted [57,58,41,59,60,56]. For instance, a GWAS study found associations between ADHD and the gene encoding IL-1RA [61]. These findings suggest a pro-inflammatory state in ADHD, which could be a cause, effect, or related phenomenon of the condition [59]. Inflammation may mediate ADHD risk factors, which are intricately linked to stress, anxiety, and immune status [41,59]. ADHD is considering as a high inflammation and immune associated disease [62], indeed ADHD patients have higher rates of immune and inflammatory disorders like eczema, asthma, psoriasis, allergic rhinitis and type 1 diabetes [63-65].

This hypothesis of a neuroinflammatory state aligns with a long-standing pathophysiological theory, which suggests that dysfunction in the dopaminergic and noradrenergic systems within certain brain regions are involved to the dysregulation of impulsivity, behavioral control, arousal, and attention in ADHD [66,41,67,68,54]. This is the pathway through which the most widely used ADHD treatments act: they significantly reduce symptoms by modifying the uptake or release of catecholamine's by neurons (agonist of dopaminergic synapses), thus improving neurotransmitter activity [69-70]. At the cerebral level, structural and functional differences have been highlighted, suggesting the existence of a global maturation delay in children with ADHD,

as well as cortical and subcortical activation variations, mainly in prefrontal regions, involved in cognitive control, motor planning and attentional processes [71-76,22,24].

But also, recent studies have suggested an association with immune and oxidant-antioxidant imbalances in ADHD [77,67,78] by demonstrating decreased antioxidant enzyme activity and increased levels of oxidative damage [79,80,70,81] as well as an increase in cellular markers of immunity [37,82]. Oxidative stress-related susceptibility genes have been studied and associated with ADHD [82,83], notably the NOS1 gene (Nitric Oxide Synthase 1) [84], involved in the production of nitric oxide, a molecule that plays a role in oxidative stress and neurotransmission. Variations in the NOS1 gene have been associated by several studies with ADHD [39,85,86]. These findings suggest that the oxidative and immunity imbalances reported in ADHD may contribute to its symptomatology and its severity via neuronal damage and abnormal neurotransmitter regulation [87,79, 88,51,70,89].

Finally, if we return to the emerging idea that genes generate the disorder when they are in the presence of environmental factors unfavorable to the individual, but favorable to the development of ADHD [39,46,47]. Among these, the role of diet, although controversial, constitutes a non-negligible avenue of understanding and prevention of ADHD [90-93]. Let us note that dietary interventions are increasingly studied for their potential to alleviate ADHD symptoms, possibly by reducing subclinical allergic reactions or inflammation, as children with ADHD are more prone to allergies [94,54]. More specifically, the role of the digestive system, described as the “second brain” modulated by the gut microbiota, that could be involved in human health. Recent research on gut microbiota shows a significant influence on our health in virtually every branch of medicine [95]. Gut microbiota plays a significant role, with certain foods causing pro-inflammatory states or oxidative stress by altering gut permeability, microbiome composition and the metabolites production [94,96,59]. Research into the bidirectional “gut-brain axis” is currently booming and represents a revolutionary and compelling new approach to treatment and therapy [97-101]. Only a handful of studies have investigated the gut-brain axis in ADHD, and several of these have demonstrated a significantly different composition of the gut microbiota in ADHD subjects compared to neurotypical subjects [102-107], and the abundance of one genus significantly associated with the severity of inattention symptoms [108]. These findings have important clinical implications as they suggest that modifications of the gut microbiota, via anti-inflammatory and antioxidant dietary interventions, whether through diet or supplements, could have therapeutic potential to reduce inflammation and thus improve clinical symptoms in patients with ADHD [109,110,100,70].

Treatment : Methylphenidate

Methylphenidate (MPH) is the first line pharmacological treatment of choice [111-113] and the most commonly prescribed medication to treat ADHD [114]. According to good clinical practice guidelines, MPH is considered as the best treatment when combined with behavioral and psychoeducational therapies [45,115-119,113]. It has shown very good efficacy in reducing ADHD symptoms in 65 to 80% of cases [120], improving attention and reducing hyperactivity and impulsivity by acting as a dopamine agonist in the striatum [111,116,121,122]. But being a psychostimulant, amphetamine derivative, it belongs to the class of narcotics and presents multiple non-negligible side effects such as loss of appetite, irritability, insomnia, headaches, risk of arrhythmia, behavioral disorders, ... [123,124,40,65,122,125]. Long-terms adverse effects on growth and bone health have also been suggested [111, 126-128].

MPH acts by inhibiting the pre-synaptic reuptake of dopamine and noradrenaline, thus increasing catecholamine transmission, in the striatum and prefrontal cortex (that participates to control hyperactivity and inhibitory behavior) [129,40]. The result is an increase in the concentration of dopamine and noradrenaline in the synaptic cleft, and thus an increase in neurotransmission in the prefrontal cortex, associated with improvement of ADHD symptoms, such as attentional deficit and cognitive functioning [130-131]. To be more precise, when MPH blocks dopamine transporter (DAT), this leads to an increase in dopamine concentration, which disinhibits the presynaptic DRD2 receptor and activates D1 receptors on the postsynaptic neuron. This promotes neuronal transmission, improving attention, concentration and the organization of thoughts and actions in ADHD patients [40,132]. In the long term, MPH use could generate an inflammatory response by promoting the loss of dopaminergic neurons and activating microglia, leading to an increase in pro-inflammatory markers (cytokines TNFa and IL-1b). These mechanisms could trigger a state of neuroinflammation and contribute to a neurodegenerative process [133-134]. As previously mentioned, a neuroinflammation state and defective immunoregulation have been observed in ADHD and other neurodevelopmental disorders, which could partly explain the imbalance in neurotransmitter activity [87,79,41,52,53,51,131]. Consequently, prolonged use of MPH is linked to an increase in the neuroinflammation observed in ADHD, which may lead to a decrease in treatment efficacy by disrupting dopamine transmission. Nevertheless, the molecular mechanisms underlying MPH’s short- and long-term actions are still poorly understood.

In addition, there is parental reluctance to use MPH, as well as therapeutic non-compliance among ADHD patients [135-137] with treatment discontinuation after 12 months in 30-50% of

cases [138,139] and after 3 years in 66-80% of cases [140,141]. On the other hand, we are witnessing a very worrying increase in prescriptions in Europe [142], more specifically, in Belgium, with daily doses for children aged 6 to 12 rising from 1.5 million in 2006 to 2.2 million in 2016 [143,131], which is becoming a real public health concern, especially as the long-term effects of MPH are currently still poorly and insufficiently documented. In this population of children and adolescents, let's not forget that somatically speaking, they are in "the pink of health", and that prescribing MPH, even though it is perfectly indicated, represents a medical risk when we consider the very significant collateral damage to school, family and health. Furthermore, from a clinical perspective, children undergoing MPH treatment do not experience a sense of being their usual selves. Although it improves ADHD symptoms, MPH does not alleviate the increased risk of dropping out of school during childhood and adolescence, nor the rate of unemployment in adulthood [144-146].

Finally, in line with the demonstrated association between oxidative imbalance and ADHD symptoms previously discussed, studies suggest that MPH treatment may be associated with an increase in oxidative stress, which may worsen the pre-existing imbalance [147-150], potentially leading to apoptosis and neurodegeneration. These observations have promising clinical therapeutic implications, including this avenue for future treatment research. However, the exact mechanisms whether MPH use increases or decreases oxidative stress remain unclear and insufficient [40].

Taken together, these data highlight the current priority that must be given to research into alternative natural therapies [70]. As the etiology is not always clear, this can hinder effective treatment research [45], it seems important to be able to identify the short-, medium- and long-term adverse effects of MPH [151]. But also to have recourse to natural treatments that target functional deficits that can improve symptoms in the long term, without side effects and with better treatment compliance. Given previous research highlighting alterations in the immune system and oxidative imbalance [79,77,80,67,78,70,81], as well as a constant neuroinflammatory state in ADHD [41,54] that can affect catecholamine circulatory pathways, these imbalances should be taken into account in both diagnosis and therapeutic pathways [77,152]. This could pave the way for new natural treatments with a mechanism of action based on improving these systems, possibly including a nutritional approach (food supplements or diet) which could have beneficial effects on prevention, treatment and prognosis of ADHD, through a possible rebalancing of the gut microbiota [153]. The latter has been shown to be dysbiotic in ADHD and crucial for physical, mental and cognitive health [99,104,100,105]. To date, several natural treatments considered safer have already demonstrated positive effects on ADHD symptomatology [154,131]. Among these, polyphenols, still under-studied in ADHD, are recognized for their antioxidant, immunomodulatory and anti-inflammatory properties, as well as their probiotic effect on gut microbiota, and constitute an encouraging and convincing new intervention pathway for the treatment and prevention of ADHD [154,54,70].

Pycnogenol®, an alternative to MPH

Composition and toxicology

Pycnogenol®, issued from a maritime pine, Pinus Pinaster, and essentially composed of polyphenols (flavonoids, phenolic acids, catechin, taxifolin and procyanidins) is recognized for its antioxidant, immunomodulatory and anti-inflammatory properties on the human body [155,156]. It is a polyphenol concentrate, composed of procyanidins, catechins, taxifolin and various phenolic acids [157-159], which stimulates antioxidant activities and reduces oxidative DNA damage [160]. The nutritional preparation is extracted from crushed bark, which then undergoes a patented extraction process [161]. Its chemical composition has been shown to be more stable over time than that of other plant extracts, making it more reliable as a therapeutic treatment [162]. The actions carried out in the body after ingestion of Pycnogenol® result from biotransformation and breakdown of its phenolic compounds by microbial enzymes in the colon, yielding smaller molecules that can be absorbed into the bloodstream and transported to organs and tissues [163]. Pycnogenol® components are present in some everyday foods, like some fruits, vegetables, nuts, cereals, grains, and spices, but these can be modified during absorption, under the influence of various factors such as dietary fiber and gut microbiota. Consequently, the biological effects of polyphenols in vivo are variable (enhanced or diminished effects) and to be interpreted cautiously, associated with a limitation of their use as a therapeutic approach [164,165,160]. However, it is important to noticed that Pycnogenol® received the good manufacturing practice (GMP) certification from the French Health Products Safety Agency (ANSM) [131].

The neurocognitive properties of Pycnogenol®

Thanks to its virtues, the beneficial effects of taking Pycnogenol® on health and in the treatment and prevention of diseases have been widely studied and demonstrated for the following diseases [166,159]: asthma [167,168,169] diabetes [170-172], cardiovascular disease [173-175], osteoarthritis [176-177]. These beneficial effects have also been observed in neurodegenerative diseases such as Alzheimer and Parkinson [178,179] and neurodevelopmental disorder such as ADHD [180,125].

Pycnogenol® appears to help maintain good cognitive performance and reduce mild cognitive impairment [181-

183]. Cesarone et al. (2020) [178] showed that after 4 weeks of administering Pycnogenol® to patients with Parkinson's disease, an improvement in physical symptoms and cognitive performance were observed. These beneficial effects have also been observed on memory performance in Alzheimer's disease mice models [179], as well as in human studies, on symptoms of hyperactivity and inattention associated with the diagnosis of ADHD [184,180,153]. Studies have shown that taking Pycnogenol® improves cognitive performance in individuals of all ages and from diverse patient populations. These benefits have been observed in populations of varying ages, notably on the cognitive performance of students, healthy adults and the elderly [185,186,183]. Specifically, taking Pycnogenol® appears to be associated with better performance in working memory, planning, mental flexibility, memory and attention, as well as better scores on the Mini-Mental State Examination (M.M.S.E) [182]. One study evaluated the effect of Pycnogenol® treatment, compared with Placebo, of elderly people with moderate cognitive decline on their cognitive performance, also using blood measures of oxidative stress (clinical liver enzyme levels, serum lipid profile, human growth hormone and lipid peroxidation products). They highlighted an improvement in working memory capacity (spatial and numerical), linked to the level of oxidative stress, reduced by taking Pycnogenol® [183].

Pycnogenol® in ADHD

However, only a few studies have investigated the effects of Pycnogenol® on ADHD [184,187,155,188-190,180,125,81].The studies are methodologically highly variable. To demonstrate the effects of Pycnogenol® treatment, it was either compared with placebo, MPH or both, and participants with ADHD were sometimes compared with a control group. There was also considerable heterogeneity in the variables investigated and the means used (symptoms, diet, questionnaires, catecholamine analyses, oxidation and antioxidant status, etc). The table below (Table 1) lists the studies that have investigated the effects of taking Pycnogenol® on ADHD, their methodological features, objectives and variables studied.

Study	Method	Participants	Age	Treatment	Treatment Duration	Aim	Outcomes
Weyns et al., 2022 (part 1) [125]	Double blinded randomized clinical trial	ADHD (n=88)	6-12 years	Pyc® *vs* MPH vs Pb	10 weeks	**Effects on ADHD symptoms**	ADHD-RS; SEQ; PCQ; FFQ
Trebaticka et al., 2006 [180]	Double blinded randomized placebo-controlled study	ADHD (n=61)	6-14 years	Pyc® *vs* Pb	4 weeks	**Effects on ADHD symptoms**	CAP; CTRS; CPRS; WISC IV
Tenenbaum et al., 2002 [191]	Double blinded randomized control clinical trial	ADHD (n=24)	24-53 years	Pyc® *vs* MPH vs Pb	3 weeks	**Effects on ADHD symptoms**	Self-report rating scales Rating scales completed by individual's significant other; CPT
Hsu et al., 2021 [189]	Double blinded randomized placebo-controlled cross-over study	ADHD (n=20)	7-20 years	Pyc® *vs* Pb	4 weeks	**Effects on ADHD symptoms & Effects in Rebalancing Oxidative Stress Pathways**	Blood sample; SNAP-IV; CPT; Food diaries

Darzi et al., 2022 [187]	Case-control study	ADHD (n=200) *vs* CTRL (n=200)	4-14 years	Diet: Evaluation of the quantity of polyphenols ingested in food	/	**Relationship between dietary polyphenol intake and the risk of ADHD**	FFQ; PhenolExploreData
Weyns et al., 2022 (part 2) [81]	Double blinded randomized clinical trial	ADHD (n=88)	6-12 years	Pyc® *vs* MPH vs Pb	10 weeks	**Effects on immune, oxidative stress and neurochemical biomarkers**	FFQ; Blood sample; Urine sample
Chovanova et al., 2006 [184]	Double blinded randomized placebo-controlled study	ADHD (n=61) *vs* CTRL (n=58)	6-14 years	Pyc® *vs* Pb	4 weeks	**Effects on oxidative DNA damage and total antioxidant status (TAS)**	Blood sample
Dvarkova et al., 2006 [155]	Double blinded randomized placebo-controlled study	ADHD (n=43)	6-14 years	Pyc® *vs* Pb	4 weeks	**Effects in rebalancing Oxidative Stress Pathways**	Blood sample; (+clinical symptoms)
Dvarkova et al., 2007 [188]	Double blinded randomized placebo-controlled study	ADHD (n=57) *vs* CTRL (n=17)	6-14 years	Pyc® *vs* Pb	4 weeks	**Effects in rebalancing Oxidative Stress Pathways**	Urine sample; Blood sample; (+ clinical symptoms)

Table 1: Studies investigating the impact of Pycnogenol® in ADHD, and their methodology; ADHD = Attention Deficit Hyperactivity Disorder ; ADHD-RS = ADHD Rating Scale ; CAP = Child Attention Problems teacher rating scale ; CPRS = Conner's Parent Rating Scale ; CPT= Continuous Performance Test ; CTRL = Controls; CTRS = Conner's Teacher Rating Scale ; FFQ = Food Frequency Questionnaire ; MPH = Methylphenidate; Pb = Placebo ; PCQ = Physical Complaints Questionnaire ; Pyc® = Pycnogenol®; SEQ = Social-Emotional Questionnaire ; SNAP-IV= Sawson, Nolan, and Pelham Version IV ; WISC-IV= Wechsler Intelligence Scale for Children.

Symptoms

To our knowledge, only 3 studies have looked specifically at the effects of Pycnogenol® on ADHD clinical symptoms. In 2006, Trebatická et al. studied the effect of Pycnogenol® on a series of cognitive and clinical variables [180]. Compared with placebo, they found a reduction in hyperactivity and inattention symptoms, and an improvement of cognitive function such as visuomotor coordination and concentration. No significant effects were observed in the placebo group. The authors also measured the effects of treatment on symptoms over time: 1 month after stopping treatment, they observed a relapse of symptoms at the initial level, suggesting that Pycnogenol® has effects on symptoms without fundamentally altering the processes underlying the disorder. Except for the visuo-motor coordination and concentration cognitive tests, which exhibited sustained enhancement in performance even 1 month after stopping treatment. However, the authors attribute this improvement to a learning effect.

Another recent study (2022), controlled not only by placebo but also by MPH, showed a significative improvement on hyperactivity and impulsivity symptoms after 10 weeks of administration, both for MPH and Pycnogenol®, which is an extremely promising result. Regarding attentional aspects, an improvement with both products was shown, but significant only for MPH [125]. It should also be noted that the effects of MPH were already visible after 5 weeks, whereas for Pycnogenol® it took 10 weeks to observe significant effects. This result was expected by the authors, given the slower mechanisms of action known from natural food supplements. What's more, the study revealed a virtual absence of side effects in patients treated with Pycnogenol®, compared with a significant increase in side effects reported in patients treated with MPH, after 5 and 10 weeks. These very promising results concerning side effects will be discussed in greater detail later in this review.

With regard to effects on ADHD symptomatology, we can also cite Hsu et al. (2021) [189], who studied the effects of polyphenolic compounds in pine bark extract (Oligopin®) (same composition as Pycnogenol®: including of 67%–75% oligomeric procyanidins, 4%–10% catechin, 4%–10% ferrulate glucoside, 3%–8% taxifoliol glucoside, 1%–5% ferulic acid) on symptoms of inattention and impulsivity and attentional performance in children with ADHD. The dose administered to patients was similar to studies conducted to date with Pycnogenol®. The polyphenol treatment was compared with placebo. Results revealed a notable decrease in inattention and impulsivity performance assessed through CPT-III, as well as a reduction in hyperactivity/impulsivity and inattention symptoms evaluated by the SNAP-IV, among children with ADHD after four weeks of treatment. Conversely, in line with their expectations, the placebo group did not show any discernible effect. Through the examination of blood samples, the study also revealed a decrease in oxidative stress, but failed to show that this correlated with symptomatic improvement, suggesting the need for future investigations into this link.

Pycnogenol® is characterized by a lack of side effects, compared with MPH. In the study by Weyns et al. (2022) [125], and in line with existing literature [122,180], participants reported up to 5 times more side effects with MPH than with Pycnogenol®. It has been highlighted that in 70 clinical studies conducted on healthy and patient subjects (5723 subjects : children and adults), the overall frequency of adverse reactions to Pycnogenol® is very low (1.8%) and these are mild and unrelated to dose or duration of treatment [122,70]. The gastrointestinal discomfort is the most frequently occurring side effect which can be countered if Pycnogenol® is taken during or after meals [122,180,70]. Dizziness, headaches, and nausea are among the most commonly reported side effects. Moreover, since its introduction on the European market, no severe adverse effects have been reported [161]. Consequently, the administration of Pycnogenol® in children and adolescents could be a very promising alternative to MPH, effective, natural, safe and reassuring for patients and their parents who fear the side effects of existing drugs. Pycnogenol®'s virtual absence of side effects could, in the long term, be accompanied by improved therapeutic compliance.

To date, only one study has shown no significant positive effect of Pycnogenol® on ADHD symptoms [191]. But this study also showed that there was no significant effect of MPH compared with placebo. The three treatments did not differ significantly from each other, which is quite unusual and surprising in the literature, as even MPH showed no effect. They therefore do not fundamentally contradict the 3 studies cited above [54]. The absence of results can probably be explained by the fact that the treatment duration was too short to observe any real effects: 3 weeks. In addition, it would appear that the study lacked power [180]. Today, studies on Pycnogenol® suggest that a treatment duration of at least 10 weeks is considered long enough to observe clear effects while minimizing patient burden and maximizing compliance [180,131,153,125].

In summary, studies investigating the effects of Pycnogenol® on ADHD symptomatology, after a sufficiently long course of treatment, consistently show an improvement in attention and a reduction in impulsive and hyperactive behavior. Combined with a virtual absence of side-effects, these highly promising results suggest that Pycnogenol® could be a fully-fledged, natural therapeutic alternative with no side-effects. However, at this moment, we still lack sufficient evidence since the studies, which are too limited in number, vary in methodology and demand a genuine, rigorous commitment to scientific inquiry.

To date, the effects of Pycnogenol® on ADHD symptoms have been studied exclusively through clinical questionnaires completed by parents and/or teachers, and the 3 studies cited above, while methodologically divergent, each point to differences in results and sensitivity between parent and teacher scales, which has already been discussed and demonstrated in the existing literature [192,193]. Indeed, Weyns et al. (2022) [125] show that the positive effects of ADHD symptoms were found only with teacher ratings and not with parent ratings. Similarly, Trebatická et al. (2006) [180] found a clear improvement with teacher ratings, but a weaker and less obvious improvement with parent ratings. This loss of sensitivity by parent scales was also noted by Hsu et al. (2021) [189] showing improvement with Placebo and this phenomenon could be explained by the fact that children's classroom behaviors are more strictly controlled and visible than behaviors at home [194]. Also that teachers are probably more objective and sensitive to behavioral changes as they compare the child to other children in the class and are less emotionally involved in the task. In contrast, parents may be more stressed and focused on their child, which could affect their sensitivity and reduce the possibility of noticing symptomatic improvements in their child [195,125]. And as Weyns et al. [125] point out, this phenomenon could be all the more important with Pycnogenol® given its slower and more subtle effects, compared with MPH. In addition, it is important to note that MPH acts during school hours and children see their effects fade by the time they go home, while Pycnogenol® seems to offer a prolonged action that should be perceptible both at school and at home, but in a more discreet way.

These results raise question about the use of clinical questionnaires that are highly subjective and sensitive to biases related to the respondent and the conditions of observation. It is highly probable that the evaluation of cognitive and symptomatological repercussions, using behavioral scales alone, is insufficient to specifically and, above all, more objectively identify the impact of the product on cognitive functions. Even more so given the cognitive deficits (executive and attentional) found in ADHD, widely documented in existing scientific literature, and at the heart of its symptomatology [17]. Given also the pro-cognitive effects of Pycnogenol® demonstrated in healthy subjects and in neurodegenerative diseases [185,181,178,182,186,179,183]. At present, therefore, it seems essential to be able to objectivize the response to Pycnogenol® treatment with appropriate and measurable neuropsychological tests, enabling its probable effects on the brain to be explored more directly. Despite these very encouraging initial investigations, this field of research is still in its infancy and requires more in-depth explorations aimed at measuring the impact of taking Pycnogenol® on the cognitive performances shown to be impaired in ADHD and constituting the core of its symptomatology, such as divided attention, selective attention, inhibition, flexibility, working memory, vigilance, delay aversion and reaction time variability [13,14,17,196,16].

As Pycnogenol® is composed exclusively of polyphenols, known for their antioxidant and immunomodulatory properties, Darzi et al. (2022) [187] set out to study the relationship between a polyphenol-rich diet and the risk of developing ADHD in kindergarten and primary school children aged 4 to 12. Impressively, the authors were able to confirm their hypotheses, showing that increased dietary intake of polyphenols, calculated by a questionnaire evaluating the level of polyphenols ingested in their daily diet, is associated with a lower risk of developing ADHD. The authors call for prospective studies to confirm these observations and explore a causal link. Their results are therefore consistent with the idea that polyphenols (contained in a large number of plant foods) could have a protective effect against ADHD, but how exactly do they act in ADHD?

Mechanism of action of Pycnogenol®

The NO pathway and the brain

In its link with the brain, Pycnogenol® is supposed to acts via the nitric oxide (NO) production pathway. The active metabolites of Pycnogenol® (flavonoids, phenolic acids, catechin, taxifolin and procyanidins) that accumulate in endothelial cells have been shown to cross the blood-brain barrier [197]. Indeed, its mechanism of action is based on its ability to enhance endothelial vasodilation by increasing NO production [173,198]. NO influences a range of physiological functions, including neurotransmission, development, plasticity, and neuronal apoptosis [199-200]. Numerous reports have also demonstrated that NO might be involved in memory [160], and learning [201,202], and may be associated with ADHD [75,203]. Since the latter has beneficial effects on cerebral function by vascular smooth muscle relaxation, NO leads to increased blood flow and ensures a sufficient supply of oxygen to neuronal cells, regulating noradrenaline and dopamine release and intake [204-206,197,131]. NO inhibits the activity of monoamine transporters, thus influencing the levels of dopamine and noradrenaline in the extracellular space [206]. This parallels the action of MPH, however, NO, being a gaseous neurotransmitter, operates differently by acting through cell membranes. Furthermore, NOS1 a crucial enzyme responsible for generating the signaling molecule NO in neurons, plays a role in promoting the growth of neurites, indicating a potential impact on early brain development [207]. Simpson et al. (2019) [159] explain the beneficial effects of Pycnogenol® on cognition in their review as follows: "it acts as a regulator and protects cells from oxidative stress 1) by being a powerful free radical scavenger; 2) by protecting DNA from damage; 3) by increasing the synthesis of antioxidant enzymes; and 4) by protecting other endogenous

antioxidants (vitamin C, vitamin E and glutathione) from oxidative damage" [160,161,159].

In animal models, research shows a beneficial effect of Pycnogenol® on the brain. Specifically, studies have shown that Pycnogenol® has neuroprotective properties following traumatic brain injury in rats. This effect appears to be achieved by reducing oxidative brain damage, levels of pro-inflammatory cytokines and loss of synaptic proteins, thereby preserving synaptic function [208,110,209,131]. Moreover, in models of neurodegeneration associated with oxidative stress, Pycnogenol® demonstrates positive effects by enhancing choline acetyltransferase activity (ChAT; an enzyme found in the nervous system that catalyzes the synthesis of the neurotransmitter acetylcholine (ACh), a vital neurotransmitter involved in various physiological functions, including regulation of heart rate and transmission of nerve impulses in the brain) in the hippocampus, increasing Glutathion (GSH) levels (a marker of oxidative stress, considered a relevant clinical marker in disorders in which stress plays a role), and reducing protein carbonyl levels (a marker of oxidative damage to proteins and is commonly used as a measure of oxidative stress in biological systems) [210,131].

In human studies, Pycnogenol® is also believed to exhibit neuroprotective properties through its antioxidant pathway, by preventing B-amyloid-induced neuronal cell death in Alzheimer's disease [211,179]. Belcaro et al. (2014) demonstrated in a study involving healthy adults that Pycnogenol® not only enhanced cognitive function but also reduced anxiety levels by significantly lowering oxidative stress compared to the control group, which maintained elevated levels of oxidative stress [185]. These findings imply that Pycnogenol® could serve as a therapeutic option for individuals experiencing high oxidative stress levels, potentially benefiting cognition and anxiety.

In ADHD

So, as mentioned, Pycnogenol® is supposed to act on the brain via the NO production pathway. Is this the mechanism by which Pycnogenol® could improve symptoms and cognitive function in individuals with ADHD ? Indeed several studies suggest that ADHD may be associated with altered NO signaling pathways [212,203]. NO levels, associated with the oxidant-antioxidant and immune imbalance highlighted in ADHD, modulating stress levels in the brain and affecting neurotransmission, appear to influence behavior and cognitive functioning in several areas: impulsivity, aggression, anxiety, depressive symptoms and cognitive performance [213,214]. More precisely, NOS1 is associated with a range of neurodegenerative and psychiatric disorder, such as ADHD and other impulsivity disorders [213,215-217,84]. This gene variant was one of the prominent discoveries in an ADHD GWAS study as well [39]. Studies have revealed that 28% of adult ADHD patients possess a particular genetic variation in the NOS1 promoter region (termed ex1f-VNTR) leading to reduced NOS1 expression. This variation is closely linked to alterations in the functioning of brain regions such as the prefrontal cortex and ventral striatum, both implicated in the impulsive and aggressive behaviors frequently associated with ADHD [212,218,84]. On the neurobiological level, NO may play a role in the development and brain organization of white matter [85]. Additionally, the NOS1-ex1f gene has been linked to the severity of ADHD symptoms [39, 219, 85]. Depending on the study, this connection was age-dependent (only in adult) [219] and/or gender-dependent (only in girls) [84,86], and was also specifically associated with the impulsive/hyperactive and combined types of ADHD, not inattention type only [84-86]. These findings indicate that the NOS1 gene, which produces the gaseous neurotransmitter NO and is linked to ADHD symptoms, is a potential candidate gene for ADHD [86].

Extended to an animal model, researchers support the hypothesis of the involvement of NO in ADHD, suggesting that NOS dysfunction could lead to ADHD-like symptoms, particularly inattentive phenotype [220,212,214,221,84]. Additionally, authors demonstrated that administering MPH increased NOS expression and that giving mice a NOS inhibitory drug altered their response to MPH [220,222]. Hayman & Fernandez (2018) [223] conducted a human genetic analysis identifying 14 interconnected genes enriched with pathways related to NO and alpha-1 adrenergic synthesis in ADHD. These genes were found in the cerebellum early in life, transitioning to the cortex during childhood and adolescence. To date, the data leads to the hypothesis that a genetic variation and dysregulation in prefrontal NOS1 contribute to cognitive deficits and a downregulation of striatal NOS1 is associated with impulsive phenotypes [213]. These investigations provide understanding into the genetic and neurodevelopmental dimensions of ADHD while also emphasizing the promise of natural therapeutic interventions that target this pathway, such as Pycnogenol®.

At present, the biochemical antioxidant and immunomodulatory effects of Pycnogenol® are not fully elucidated and require further investigation [81]. Nevertheless, several promising results have been demonstrated in ADHD. It has been shown that the concentration of catecholamines (stress hormones) is positively correlated with hyperactivity in children with ADHD [188]. Authors have shown that taking Pycnogenol® for 1 month improves ADHD symptoms, and that this is the result of a reduction in dopamine levels and a tendency to lower adrenaline and noradrenaline levels in the urine. Studies by Chovanová et al. (2006) et Dvořáková et al. (2006) [184,155] concur with these findings, also showing that after 1 month's treatment with Pycnogenol®, there was a

normalization of stress hormone (catecholamine) levels, including adrenaline, noradrenaline and dopamine, in children with ADHD, associated with a reduction in hyperactivity/impulsivity symptoms [184]. In addition, they showed that oxidative stress and incidents of DNA damage were significantly reduced (by 6.3% and 35.4% respectively). In addition, Pycnogenol® increases the reduced glutathione (GSH)/ oxidized glutathione (GSSG) ratio (a marker of oxidative stress, considered a relevant clinical marker in disorders in which stress plays a role), accompanied by an increase in the level of the total antioxidant status (TAS), in favor of an antioxidant effect [188,189]. After treatment with Pycnogenol®, there was a negative correlation between the GSH/GSSG ratio and dopamine concentration, suggesting an improvement in redox homeostasis and dopamine neurotransmission [188,189,54]. These results demonstrate the antioxidant effect of treatment with Pycnogenol® [189], suggesting that the immune and oxidant-antioxidant imbalance track offers potential for dietary supplements composed of polyphenols [54,70].

New perspectives: Gut microbiota

Finally, studies have also shown that polyphenols and their metabolites have a prebiotic effect on the gut microbiota by stimulating its growth [224]. Polyphenols increase the families of good bacteria and reduce the number of pathogenic bacteria in the gut, thereby improving gut permeability [225,226]. This has been studied in human and animal diets, in vitro and in vivo. Studies are converging to show that polyphenols, with their antioxidant and anti-inflammatory properties, can also be used to modulate the gut microbiota [227-234,224,153]. As gut microbiota is thought to be altered in ADHD due to oxidative and immune imbalance [77], Pycnogenol® could act on the latter through its antioxidant and anti-inflammatory effects [102] and would be favorable to the composition of the gut microbiota. Thus, a rebalancing of the gut microbiota could be involved in the effect of Pycnogenol® on ADHD symptomatology and possibly cognitive functioning. Research into the microbiota and ADHD is totally new, and the exploration of this type of data presents a major challenge for the prevention and treatment of this disorder. In view of the existing literature on the gut-brain axis, the study of the association between gut microbiota and cognitive performance remains unexplored in ADHD and nebulous in neurotypical subjects. As gut microbiota and bioinformatics analyses become increasingly advanced, conducting a study in this field would be highly valuable. This research could enhance our understanding of ADHD's etiopathogenesis and aid in developing prevention and treatment strategies that directly target the gut microbiota through diet or dietary supplements, such as, most likely, Pycnogenol®.

Conclusion

In conclusion, ADHD, the most prevalent neurodevelopmental disorder is considered to be multifactorial with complex determinism, but to date, neither genetic nor specific environmental factors have been clearly identified. More recently, studies have suggested the existence of immune, oxidant-antioxidant imbalances and a neuroinflammatory state that may contribute to ADHD symptomatology, in line with the promising new wave of research addressing the potential role of the gut microbiota in the expression of the disorder. This latest research highlights the importance of environmental factors in the etiopathogenesis of ADHD, and more specifically the importance of nutrients ingested through food or dietary supplements.

Pycnogenol®, essentially composed of polyphenols, is recognized for its antioxidant, immunomodulating and anti-inflammatory properties on the human body. Thanks to these virtues, the beneficial effects of taking Pycnogenol® as treatment of prevention of ADHD, seems to be a very promising option. In ADHD, the few studies carried out to date have consistently demonstrated that treatment with Pycnogenol® for a minimum of 4 to 10 weeks leads to an improvement in attention span and a reduction in impulsive and hyperactivity behaviors. Combined with almost no side effects, these highly promising results, suggest that Pycnogenol® could constitute a fully-fledged therapeutic alternative to MPH, natural and without side effects. Polyphenols and their metabolites also have a probiotic effect on the gut microbiota, which is thought to be altered in ADHD. Pycnogenol® offers a new avenue of treatment that could improve ADHD symptoms by reducing neuroinflammation state, oxidative stress, improving neurotransmission and rebalancing the gut microbiota. These lines of research are totally innovative, and the exploration of this type of data presents a major challenge for the prevention and treatment of ADHD, requiring future investigations.

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Conflict of interest

The authors state that their research was carried out without any commercial or financial ties that could be seen as a possible conflict of interest.

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