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Pycnogenol® improves cognitive function, attention, mental performance and specific professional skills in healthy professionals aged 35-55

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Aim. **This 12-week, product-evaluation registry study aimed to compare the effects of supplementation with French Pine Bark Extract (Pycnogenol®) on cognitive function, attention, and mental performance in healthy professionals with increased oxidative stress in a professional context.**
Methods. **Professionals were screened for increased oxidative stress: 60 subjects (range 35-55 years, no risk conditions, no addictions) voluntarily decided to be followed-up. Diet, alcohol and lifestyle patterns, including exercise, were controlled. Pycnogenol® (150 mg/day) was used in combination with a health plan to enhance mental performance and control oxidative stress.**
Results. **A group of 30 professionals used Pycnogenol®, and 29 acted as comparable controls for a period of 12 weeks. The two registry groups were comparable. Cognitive function, attention, mental performance, sustained attention, memory, executive functions, mood and oxidative stress values were comparable at inclusion. At 12 weeks the improvement in Pycnogenol® subjects was more significant than in controls. Plasma-free radicals (oxidative stress) were significantly decreased (median -30.4%) at 12 weeks in Pycnogenol® subjects in comparison with a non-significant variation observed in controls (+0.9%; difference between groups). Considering the cognitive test battery (PASAT, pattern recognition memory, spatial recognition memory, spatial working memory), Pycnogenol® subjects showed a small but significant improvement with spatial recognition memory unchanged. Mood parameters (alertness, anxiety, contentedness) also improved in professionals using the supplement. In the evaluation of 12 professional daily tasks all items were improved with Pycnogenol® supplementation. The score relative to semi-professional minitasks was improved more in Pycnogenol® subjects. Tolerability and compliance were optimal with >94% of the doses of supplement correctly used.**
Conclusion. **Pycnogenol® supplementation for 12 weeks appears to improve cognitive function and oxidative stress in healthy professionals.**

KEY WORDS: Cognitive therapy - Oxidative stress - Pycnogenols - Dietary supplements.

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Impairment in cognitive function is associated with aging, hormonal alterations and several clinical or subclinical conditions.[1-5] Thyroid function alteration, particularly hypothyroidism, is possibly the most common, treatable cause of clinical and subclinical impairment of cognitive function.[6-11]

Mild cognitive impairment, even borderline dementia, may be evident only in mentally stressful situations and does not appear to be an evident impairment in "normal" standard conditions or in simpler aspects of life characterized by repeated, automatized behavioral patterns, i.e., in retired people not living in a demanding work environment.[10-13] The evaluation of some modifiable risk factors in decreasing attention and cognitive function is important to exclude common clinical problems such as hypothyroidism.[12]

An increase in plasma-free radicals and oxidative stress may be associated with important alterations in cognitive functions, *i.e.*, in subjects with hypothyroidism treated with thyroid hormonal replacement.[13, 14] Modifiable risk factors for an impairment in cognitive function include hypertension, diabetes, hyperlipidemia, renal failure, vitamin B12 deficiency, hyper-homocysteinemia, testosterone deficiency, thyroid hormonal alterations, estrogens, and hepatic failure. Lifestyle factors may also be involved in cognitive function alterations (diet, physical activity, alcohol, smoking, drugs).[12] There are also a number of situations when normal cognitive function may be altered or improved even in normal subjects, for example, in an academic context such as student examinations.[15]

An interesting, acute model of cognitive function impairment is observed with jet-lag syndrome.[16] Most subjects affected by jet-lag show a decreased level of attention and perception, desynchronization of sleep, mood alterations and daily rhythm changes that require some days to disappear. Jet-lag symptoms are more significant in subjects using anti-hypertensive treatment with a subclinical edema that is evident at the distal part of the limbs after a long flight but may also be present at cerebral and retinal levels (as seen by CT scans or MRI after long flights).[16]

Pycnogenol® French maritime pine bark extract (Horphag Research, Ltd.) has been used as a supplement in several clinical and non-clinical conditions and has demontrated a high level of safety, very good tolerability and a strong activity in controlling free radicals, oxidative stress, microcirculatory alterations, edema and different levels and causes of inflammation.[30-50] The explanation of the positive effects of Pycnogenol® on cognitive function and attention in other studies [17, 18] has indicated that a combined anti-inflammatory action, anti-oxidative and possibly the anti-edema action may be the basis of cognitive enhancement.

Previous studies with Pycnogenol® [40-50] have shown that in long-term studies this compound reduces C-reactive protein levels and strongly controls plasma-free radicals (PFR).[43] The same studies indicated that patients treated for at least 4-6 weeks with Pycnogenol® improve both their physical performance and their mental attitude and mood.[43, 44]

The strong, anti-edema action of Pycnogenol® may also be involved in improving mental functions as observed in flight studies during/after which subjects with peripheral and subclinical cerebral edema had shown decreased attention, signs of jet-lag, desynchronization and generally altered cerebral functions. The alterations in cerebral functions – possibly associated with edema - had been almost completely prevented by Pycnogenol® use.[16]

A different study [17] has indicated that supplementation with ginkgo biloba may acutely improve attention and memory in young, healthy students in tests of attention, memory and executive function. Sustained attention, episodic and working memory, mental flexibility and planning were evaluated in association with mood rating scales. Acute oral treatment with ginkgo improved sustained-attention and pattern-recognition memory tasks. There were no effects on working memory, planning, mental flexibility and mood. Chronic treatment (6 weeks) did not show significant effects. This model study was repeated with Pycnogenol® [18] to evaluate cognitive function, attention and mental performance in normal students treated for 8 weeks. The supplement was used with the aim of enhancing "normal" mental performance. Attention, memory, and evaluation of executive functions were included. Students were also evaluated according to results of actual university tests. Oral Pycnogenol® improved sustained attention, memory, executive function and mood ratings. Actual performance on university tests indicated significantly better results in the Pycnogenol® group. This study therefore indicated a potential role for Pycnogenol® in improving cognitive function in normal students.

On the basis of the model study [17] and on our previous study,[18] the present 12-week, product-evaluation registry study aimed to evaluated the effects of supplementation with Pycnogenol® in healthy professionals with high oxidative stress [13, 14] to measure improvement in:

— cognitive function;
— attention;
— mental performance in a professional context; and
— oxidative stress (by measuring plasma free radicals).

Materials and methods

Healthy professionals were screened for an elevated oxidative stress. Out of 224 subjects screened within the framework of a cardiovascular, epidemiological screening study, 188 subjects were found

TABLE I.—*Details of the two resulting registry groups.*

Total	30	29
Females	12	13
Age	44.5; 4.3	45.6; 6.3
BMI	24.6; 0.7	24.8; 0.5
Mean		
Follow-up	88.5; 2.6 days	89.5; 4.2

to have elevated oxidative stress in the absence of any other clinical problems. After presentation of the project and open discussion, 60 of the subjects (range 35-55 years; no risk conditions, no addictions) voluntarily decided to be followed up in a registry evaluating cognitive function and oxidative stress. Details of the volunteers are given in Table I.

Registry subjects agreed not to use drugs or stimulants during the registry study. Diet, alcohol and lifestyle patterns including exercise were controlled. A course of 150 mg/day of Pycnogenol® was suggested and used in healthy individuals, without any disease or risk factors. In our working hypothesis Pycnogenol® – in combination with a health plan - had the function of enhancing "normal" mental performance and controlling higher oxidative stress.

Thyroid function and functional blood tests (hematocrit, kidney and liver function, coagulation, urines) and oxidative stress [13-16] were assessed in all subjects at inclusion and at 12 weeks. Carotid duplex scanning and a vascular evaluation were normal at inclusion**.** Also a cerebral MRI (without contrast) was normal at inclusion. Attention, memory, and executive functions were evaluated in defined, tested scales (Table II).[18] Professionals were also subjectively and objectively evaluated according to professional perfomance results relative to their specific professional tasks.

Health plan

A personal improvement plan was suggested to all registry subjects with the aim of improving cognitive function and attention including:

TABLE II.—*Cognitive function evaluated by VAS in Pycnogenol and controls at inclusion and after 12 weeks.*

PYCNOGENOL SUBJECTS (PY), COMPARISON WITH CONTROLS (CO): * = P<0.05; ANOVA; ** = P<0.01
S =SUBJECTIVE SCORE; O= OBJECTIVE SCORE;
COLUMNS: PY= PYCNOGENOL; CON= CONTROLS

		INCL		12 WEEKS		DIFF PY (CON)
		PY	(CON)	PY	(CON)	
A- cognitive function	S	6.7;1.1	(6.6;1.2)	7.4;1.3	(7.1;1)	0.7 (0.5)
	O	7.4;1.2	(7.3;1)	8.1;0.9	(7.4;1.3)	0.7 (0.1)
Total difference						1.4 (0.6)*
B- attention	S	6.2;1.3	(6.3;0.8)	7.1;1.2	(6.9;0.8)	0.9 (0.6)
	O	7.3;1.1	(6.9;1.2)	8.2;0.8	(6.7;0.3)	0.9 (-0.2)
						1.8 (0.4)*
C- mental performance	S	6.6;1.3	(6.5;1)	7.3;0.9	(6.6;0.8)	0.7 (0.1)
	O	6.9;0.3	(6.4;0.9)	7.4;0.8	(6.7;1.2)	0.5 (0.3)
						1.2 (0.4)*
D- sustained attention	S	7.1;1.1	(7;0.9)	8.2;0.7	(7.1;0.8)	1.1 (0.1)
	O	8.1;0.9	(7.8;0.7)	8.4;1	(7.5;0.9)	0.3 (-0.3)
						1.4 (-0.2)*
E- memory	S	7.1;1.2	(6.9;1)	7.7;0.8	(7.3;0.7)	0.6 (0.4)
	O	7.8;1.1	(7.7;0.8)	7.7;0.6	(7.2;0.9)	0.1 (-0.5)
						0.7 (-0.1)*
F- executive functions	S	7;1.1	(6.8;0.4)	7.6;1.1	(7;1.1)	0.6 (0.2)
	O	7.5;0.9	(7.3;0.8)	7.9;1.2	(6.9;0.8)	0.4 (-0.4)
						1.0 (-0.2)*
G- mood	S	6.3;1.2	(6.7;0.8)	7.6;0.9	(6.6;0.5)	1.3 (-0.1)
	O	7.1;0.8	(7.4;0.7)	7.9;0.7	(7.2;0.7)	0.8 (-0.2)
						2.1 (-0.3)**
Oxidative stress CARR UNITS		448;32	(442;28)	312;19	(446;16)	
				-30.35%**	(+0.9%)	

RANK TESTS (WILCOXON) OR SEMI-QUANTITATIVE (ANOVA); RANK ADAPTATION TO SEMI-QUANTITATIVE VALUE (RANGE 0-10)

— at least 8 hours sleep per night;
— early night rest (not later than 10.30 pm);
— regular meals (defined hours and a balanced diet adapted to the weight and age of the registry subjects including an ideal quantity of fruits/vegetables and vitamins);
— reducing salt and controlling excess sugar;
— caffeine was reduced to one cup of coffee per day and not more than one caffeine drink/day;
— not more than one glass of an alcoholic beverage per day;
— at least 20 minutes of excercise/day;
— not more than 1 hr of video or TV/day;
— defined – within a 20% range - hours for working time, transfers and rest.

The plan was suggested rather than imposed, and the registry subjects were briefed about the association between a better lifestyle and better performance at the professional level. It was completely suitable for the professional activities of these subjects as all of them were able to follow it with only minor variations.

Pycnogenol® supplementation

Pycnogenol® was supplied as tablets with the suggestion to use 3 tablets, 50 mg each, total 150 mg/day.

At the final test, subjects were evaluated at least 24 hours after their last dose of Pycnogenol®.

Subjects were instructed to avoid coffee or caffeine-drinks for at least 4 hours before the tests and to avoid alcohol for 2 days before the tests.

Simple cognitive functions

Simple cognitive functions were evaluated on a subjective, self-administered, visual analogue scale line (VASL ranging from 0 to 10) by the registry subjects and then re-evaluated by the observing investigators using the same VASL. The differences in subjective and objective measurements were compared at 12 weeks. This evaluation included simple cognitive parameters (cognitive function, attention, mental performance, sustained attention, memory, executive functions and mood). Professionals were tested before inclusion (baseline) and after at least 12 weeks of supplementation.

Cognitive tests battery

According to the "model study" [17] an evaluation of verbal IQ was measured with the NART-R (National Adult Reading Test – Revised).[19]

Subjects with signs of anxiety and depression – before inclusion – were excluded as measured with the HAD scales.[20] The test list for cognitive function is given in Table II.

Sustained attention

The Paced Auditory Serial Addition Task (PASAT) measures sustained attention.[21] Participants had to add together successive pairs of single digits read from a list. There were four digit-presentation speeds: digits were shown every 2.4, 2.0, 1.6 and 1.2 seconds. The first two trials consisted of 31 digits and were used as practice; the two fastest trials included 61 digits and were used to assess performance. The number of correct responses were recorded from a score out of 60 for the two fastest presentation speeds.

Episodic memory - pattern recognition memory

The pattern recognition memory (PRM) task is derived from the Cambridge Neuropsychological Test Automated Battery (CANTAB).[22] A series of patterns were memorised. In the recognition phase the subjects had to choose between the right pattern they recognised and a distracting pattern. Two test blocks (each with 12 patterns) were used. The percentage of correct responses and the latency to correctly respond were recorded.

Spatial recognition memory

The spatial recognition memory (SRM) test is derived from the CANTAB.[22] After the presentation of five white boxes (at different positions on a monitor, one after the other), the subjects had to choose between the box they had recognised (in the same earlier position) and a distracting box. Four test blocks were used with five trials each. The percentage of correct responses and the latency to respond were observed.

Delayed recall of words and pictures

A list of 36 words (from two different logic/meaning categories) [23] was shown on a monitor (3 seconds) with an interstimulus interval of 200 ms. Subjects had to remember as many words as possible and recall them later on. A series of 20 pictures of

objects [24] were shown on the screen (5 s; interstimulus interval of 200 ms). Subjects had to name each picture remembering as many pictures as possible to recall them later. After 25 min (during which the CANTAB tests were completed), subjects were required to write down as many words and pictures as they could remember. The number of correctly recalled items was scored.

Spatial working memory

In the spatial working memory (SWM) test (CANTAB), subjects were required to search through a system of boxes for 'blue tokens' to fill up the column at the side of the screen. The aim was not to return to a box where a blue token had already been hidden. This test has strategic and mnemonic elements and is sensitive to frontal lobe damage.[25] Three stages were included, involving four, six or eight boxes. During this test two types of errors are possible: returning to a box where a token has already been found ("between errors"), and returning to a box that was previously visited and found empty ("within errors"). The sum of between errors and within errors was recorded. The use of strategy was also recorded (a lower strategy score indicates a better strategy).

Mental flexibility

The Intra Dimensional/Extra Dimensional set shifting task (IDED: from CANTAB) evaluates mental flexibility. This capacity is impaired by frontal lobe lesions [26] and is related to the prefrontal cortex.[27] In this test there are 9 stages. Subjects have to learn rules, reverse rules and shift rules. The number of stages completed were recorded for the whole group. The number of errors before the extradimensional shift (Pre-EDS errors) and errors at the extradimensional shift (EDS errors) were recorded for subjects able to complete the whole test.

Planning

The Stockings of Cambridge (SoC) task (CANTAB) is used to quantify planning ability. The test is sensitive to frontal lobe lesions. The dorsolateral and prefrontal cortex [28] are activated during this task. Subjects see an arrangement of three coloured balls housed in "stockings". They must be rearranged with the fewest possible moves to match a goal defined on the screen. Subjects must plan their moves before the beginning of the test. Difficulty was variable between two and six moves. Two initial stages were used for practice. The initial and subsequent thinking times and the number of moves made to complete the task were registered (for the two most difficult stages).

Visual analogue mood scales

Mood was scored with a VASL using 16 opposed adjectives linked by a 10-cm line. Subjects placed a mark indicating individual elements ("anxiety", "alertness", "contentedness" derived from the mood rating scale).[18, 29]

Real daily life and professional tasks

The actual, practical efficacy of Pycnogenol® supplementation was obtained by evaluating 12 test-items based on VASL (0-10) at inclusion and after 12 weeks. Table III shows how these parameters appeared to the registry subjects and investigators. The test includes a comparative evaluation after 12 weeks using both a subjective evaluation by the subjects and an objective re-evaluation by the investigators. Results of the first test were not visible during the second test.

Exclusion criteria

Exclusion criteria included the use of any medication, any form of dependency, sleep deprivation, pregnancy or lactation, BMI >26, use of any other food supplement or vitamins and any unusual, unbalanced diet in the two weeks before inclusion (and during the observation period). Smokers were excluded. Also, professionals who worked night shifts were excluded.

Semi-professional minitasks (0-100 SCALE)

This test measured 12 minitasks related to professional activity (Table VI). Units for each minitask (0-10) were extrapolated from primary results based on 3 parameters scored by the observing investigator: time (in seconds), accuracy (0-10), and efficiency (0-10). Only 10 out of 12 items were scored (2 were not done, on the basis of personal preference). The resulting added score varied fom 0 to 100.

TABLE III.—*Daily tasks, global cognitive functions and physical evolution scale.*

1. GETTING UP		
0----------5----------10		
Impossible	Normal	With great pleasure
	Uneventful	Very easy
2. SHOPPING		
0----------5----------10		
Impossible	Normal	With great pleasure
	Uneventful	Very easy
3. DEALING WITH MONEY		
0----------5----------10		
Impossible	Normal	Very easy
	Uneventful	
4. DEALING WITH PEOPLE		
0----------5----------10		
Impossible	Normal	With great pleasure
	Uneventful	Very easy
5. SIMPLE DECISION-MAKING		
0----------5----------10		
Impossible	Normal	Very easy
	Uneventful	
6. COPING WITH PROBLEMS		
0----------5----------10		
Impossible	Normal	Very easy
Needs help	Uneventful	
7. MOVING AROUND		
0----------5----------10		
Impossible	Normal	With great pleasure
Needs help	Uneventful	Very easy
8. PHYSICAL STATUS (for normal tasks)		
0----------5----------10		
Confined	Normal	Great form
Impossible Needs help		No limit
9. VISION & HEARING		
0----------5----------10		
Handicaps	Normal	Very good
Needs aid		
10. EATING/TASTE		
0----------5----------10		
Impossible	Normal	With great pleasure
Special needs		
11. EXERCISE		
0----------5----------10		
Impossible	Normal	With great pleasure
Confined Needs aid		Very easy
12. SLEEPING		
0----------5----------10		
Impossible	Normal	Very regular/relaxing
(<2 hrs/day) Very irregular	Uneventful	or >8 hrs

Plasma free radicals

The evaluation of plasma free radicals (PFR) was made with FRAS equipment (Diacron, Parma, Italy). FRAS 4 is a photometric analytical system for the global assessment of oxidative stress by measuring reactive oxygen metabolites (using the d-ROMS test) and biological antioxidant potential (using the PAT test) in whole plasma samples. FRAS measures plasma free radicals with a drop of blood by the absorbance measurement of a sample solution through a monochromatic light beam. The centrifuge and the aluminum case with the photometric unit are temperature-controlled (37 °C). This method has been validated and used [13, 14, 51-55] in several preventive, epidemiological and clinical studies that showed good reproducibility and low intra-individual and inter-individual variability even in tests repeated on different days. Plasma free radicals and oxidative stress tend to be increased in several clinical conditions and in risk conditions (*i.e.* hypertension, diabetes, hyperlipidemia).[51]

Statistical analysis

A Sigma-Plot software was used. All data and measurements were analyzed and compared by the Tuckey test. Psychometric test measurements cannot be considered parametric or normally distributed. The analysis of variance (ANOVA) was also used to analyze before-after and different variations in data within groups. Considering variations in measurements a number of at least 25 subjects in each group was considered needed to overcome unwanted intraindividual and inter-individual variability. The visual analogue scale lines used and their statistical evaluation were performed acording to Maxwell.[52]

Results

At the end of the registry period a group of 30 professionals (12 females) used Pycnogenol® and an equivalent group of 29 professionals (13 females) acted as controls. There was one drop-out for a non-medical reason (logistic problems) in the control group. The two resulting registry groups were comparable (Table I) for their main parameters including the average length of the observation period. The cognitive function, attention, mental performance, sustained attention, memory, executive functions, mood and oxidative stress values were also comparable at inclusion.

Table II shows changes in these cognitive function items. They were all improved in both groups, but

TABLE IV.—*Evaluation of daily tasks (visual analogue scale 0-10).*

		Controls	Pycnogenol®	P
1. Getting up	Inclusion	6.2; 1.1	6.1; 2.1	NS
	12 Weeks	6.1; 1.8	7.3; 1.1	*
2. Shopping	Inclusion	6.5; 1	6.7; 1.1	NS
	12 Weeks	5.9; 1.4	7.2; 1.4	*
3. Dealing with money	Inclusion	5.7; 1.4	5.5; 1.8	NS
	12 Weeks	6.3; 1.1	7.4; 1.1	*
4. Dealing with people	Inclusion	5.5; 2.1	5.6; 2.4	NS
	12 Weeks	4.9; 2.6	7.3; 1.8	*
5. Simple decision-making	Inclusion	5.7; 1.5	4.9; 3.2	NS
	12 Weeks	5.5; 1.1	6.9; 1.4	*
6. Coping with problems	Inclusion	5.1; 2.8	5.2; 1	NS
	12 Weeks	5.3; 1.3	6.9; 1.8	*
7. Moving around	Inclusion	4.8; 2.2	4.9; 1.3	NS
	12 Weeks	5.1; 1.1	7.2; 1.8	*
8. Psychophysical status	Inclusion	4.9; 2.1	5.2; 1.7	NS
	12 Weeks	5; 1.8	6.8; 1.2	*
9. Vision&hearing	Inclusion	5.2; 2.1	5.1; 2.2	NS
	12 Weeks	5.1; 1.1	7.2; 1.4	*
10. Eating & taste	Inclusion	5.4; 2.1	5.4; 1.8	NS
	12 Weeks	5.2; 1.6	6.9; 2.2	*
11. Exercise	Inclusion	5.3; 2.1	5.1; 1.4	NS
	12 Weeks	5.1; 2	6.9; 1.1	*
12. Sleeping	Inclusion	5.3; 1.1	5.2; 1.6	NS
	12 Weeks	5.1; 1.2	6.9; 2.1	*

NS: not significant; *P<0.05.

in Pycnogenol® subjects the improvement was more significant than in controls (P<0.05). With Pycnogenol® both subjective and objective measurements were improved. Table II also shows the variations in plasma free radicals. The test was made just after completing the cognitive function questionnaire. Oxidative stress was significantly decreased (-30.4%) at 12 weeks in Pycnogenol® subjects in comparison with a non-significant variation observed in controls (+0.9%; difference between groups: P<0.05).

Considering the cognitive test battery (Table V) (PASAT, pattern recognition memory, spatial recognition memory, spatial working memory, IDED, Stockings of Cambridge), Pycnogenol® subjects showed a small but significant (P<0.05) improvement (excluding spatial recognition memory, which was unchanged).

Mood parameters (VASL) including alertness, anxiety and contentedness significantly improved on average in professionals using the supplement (P<0.05) in comparison with controls (no significant change).

In the evaluation (Table IV) of the 12 daily tasks (VASL 0-10), all items in the questionnaire were improved (P<0.05) with Pycnogenol® supplementation at the end of the study in comparison with controls. While the variations observed with the cognitive test battery are related to daily activity, the evaluation of cognitive functions and the evaluation of professional daily tasks could offer a better evaluation of professional performance.

Considering the semi-professional minitasks (Table VI) control subjects at inclusion scored 86.8 (SD 4.2; range 78-94); the score was comparable (87.4; SD 5.7; range 77-96) in the Pycnogenol® group. At 12 weeks the score was unchanged in controls (87.1; SD 4.4; 74-96) but it was improved in Pycnogenol® subjects (89.8; SD 3.1; 77-97) (P<0.05).

Tolerability and compliance were optimal with >94% of the doses of supplement correctly used. At the end of the observation period there was a request to continue Pycnogenol® in 75% of the subjects that had used it.

Conclusions

This pilot study on cognitive function indicates a possibly important role for Pycnogenol® in improving cognitive functions and attention in healthy professionals with elevated oxidative stress but otherwise

TABLE V.—*Treatment with Pycnogenol® in comparison with controls cognitive tests and mood rating scales.*

1: before-after difference (*=Difference: P<0.05). 2: difference between groups (#=Difference: P<0.05) at 12 weeks.

		Controls	Pycnogenol	P (1)	Between groups end-difference (2)
PASAT (1.6 s)					
Number correct	Inclusion	28.2; 1.2	28.7; 1.3	NS	NS
	12 Weeks	28.4; 1.3	30; 1.1	*	#
Picture recall	Inclusion	6; 0.8	6.3; 1.1	NS	NS
Number correct	12 Weeks	6.1; 1.1	6.5; 1.2	*	#
PRM (Pattern recogn. memory)	Inclusion	2.1; 0.3	2.01; 0.4	NS	NS
Latency (s)	12 Weeks	2.2; 0.2	1.8; 0.4	*	#
SRM (Spatial recognition memory)	Inclusion	1.9; 0.5	2.02; 0.8	NS	NS
Latency (s)	12 Weeks	1.8; 0.6	1.9; 0.7	*	NS
Correct responses (%)	Inclusion	74; 4.4	76.2; 2.9	NS	NS
	12 Weeks	75.2; 4.2	86.9; 4.9	*	#
Spatial Working Memory					
Between errors	Inclusion	16.4; 1	16.3; 3.2	NS	NS
	12 Weeks	16.5; 2.1	18.5; 2.2	*	#
IDED (intra dimensional/extra dimensional)					
Stages completed	Inclusion	8.3; 0.9	8.19; 0 .6	NS	NS
	12 Weeks	8.2; 0.6	9; 0.4	*	#
Stockings of Cambridge					
Initial thinking time (s)					
(4 moves)	Inclusion	8.3; 0.23	8.4; 0.4	NS	NS
	12 Weeks	8.2; 0.3	7.1; 0.32	*	#
Subsequent thinking time (s)					
(4 Moves)	Inclusion	8.85; 0.7	8.6; 0.6	NS	NS
	12 Weeks	8.3; 0.4	7.1; 0.4	*	#
Mood (0-100)					
Visual analogue scale					
Alertness	Inclusion	48.4; 6.4	49.3; 4.2	NS	NS
	12 Weeks	46.8; 4.3	58.6; 2.9	*	#
Anxiety	Inclusion	61.1; 2.6	60.8; 4.1	NS	NS
	12 Weeks	62.3; 3.1	52.1; 3.7	*	#
Contentedness	Inclusion	45.6; 3.8	44.7; 3.4	NS	NS
	12 Weeks	51.5; 3.9	66.9±3.1	*	#

TABLE VI.—*Semi-professional minitasks.*

Units (0-10) were extrapolated from primary results based on 3 parameters: time (in seconds), accuracy (0-10), efficiency (0-10).
Only 10 out of 12 items were scored by the observing investigators (2 were not done, on the basis of personal preference). The resulting score varied from 0-100.

1. Find five international addresses on Google maps
2. Find 5 local addresses on Google maps
4. Driving and parking time/efficiency
5. Time to write a new unknown, correct message on smartphone
6. Same message sent as e-mail
7. Remembering five known phone numbers
8. Rembembering three unknown phone numbers
9. Dial 10 phone numbers on a smartphone
10. Redraw on board four shapes seen for ten seconds
11. Find the equivalent value of 3 currencies
12. Find the first name of 10 well known persons (only surname given)

normal blood tests and metabolic functions. Also in normal subjects and in athletes "underperformance syndrome" [56] is known and not easy to associate with any blood test or metabolic value alteration.

It is possible that in very active, stressed professionals the increase in oxidative stress could be both the result and the cause (in some subjects) of temporary, subclinical, often even subliminal cognitive function alterations that significantly affect lifestyle, performance and possibly even personal life. Changes in lifestyle, exercise and in daily habits may, over the long run (*i.e.* possibly, more than 6 months), improve both cognitive function, quality of life and professional performances considering that it is very difficult to improve already "normal" subjects. However, the observation of an increased oxidative stress

associated with minimal cognitive function and attention alterations that can be improved is an interesting factor to consider.[51, 53]

This study indicates that the same professionals with normalized oxidative stress tend to perform better on professional tasks. Several studies have indicated the important role of oxidative stress both in risk conditions and in preclinical diseases.[43, 51, 53-55] This is the first observation evaluating the effects of increased oxidative stress in otherwise healthy professionals.

The rating scales used to assess cognitive function and attention or professional performance cannot work or express meaningful values in all professional contexts (*i.e.* they work better in an academic environment) and are, in general, affected by repetitions and external, environmental factors.

While "positive" pressure stress (*i.e.* from a coach or professional supervisor) tends to improve performances, it has been shown that some people under increased levels of professional or 'personal' stress tend to underperform.[56] Professional stress (as also seen in athletes and professional sportsmen/women) tends to improve performance but only up to a point, and thereafter performance begins to decline.[57] Professional and working conditions, environmental factors, competitive values, health factors and nutrition and possibly balanced supplementation may help to peak performances without crossing into an excess creating "stress underperformance".

The development of new methods of evaluation that are less artificial and more connected with the professional world [59] may offer a better opportunity to study this condition of minor, temporary underperformance.

This preliminary registry study in a completely non-clinical situation indicates that Pycnogenol® supplementation seems to improve cognitive function, attention and performance in professional activities without causing any problems of compliance or tolerability.

Clinical subjects or preclinical subjects at risk for different conditions (*i.e.* diabetes, hypertension) could also benefit from this type of supplementation, but specific studies are needed.

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