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Enzogenol for cognitive functioning in traumatic brain injury: a pilot placebo-controlled RCT

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Background and purpose: Enzogenol, a flavonoid-rich extract from *Pinus radiata* bark with antioxidant and anti-inflammatory properties has been shown to improve working memory in healthy adults. In traumatic brain injury (TBI), oxidation and inflammation have been linked to poorer cognitive outcomes. Hence, this phase II, randomized controlled trial investigated safety, compliance and efficacy of Enzogenol for improving cognitive functioning in people following mild TBI.

Methods: Sixty adults, who sustained a mild TBI, 3–12 months prior to recruitment, and who were experiencing persistent cognitive difficulties [Cognitive Failures Questionnaire (CFQ) score > 38], were randomized to receive Enzogenol (1000 mg/day) or matching placebo for 6 weeks. Subsequently, all participants received Enzogenol for a further 6 weeks, followed by placebo for 4 weeks. Compliance, side-effects, cognitive failures, working and episodic memory, post-concussive symptoms and mood were assessed at baseline, 6, 12 and 16 weeks. Simultaneous estimation of treatment effect and breakpoint was effected, with confidence intervals (CIs) obtained through a treatment–placebo balance-preserving bootstrap procedure.

Results: Enzogenol was found to be safe and well tolerated. Trend and breakpoint analyses showed a significant reduction in cognitive failures after 6 weeks [mean CFQ score, 95% CI, Enzogenol versus placebo −6.9 (−10.8 to −4.1)]. Improvements in the frequency of self-reported cognitive failures were estimated to continue until week 11 before stabilizing. Other outcome measures showed some positive trends but no significant treatment effects.

Conclusions: Enzogenol supplementation is safe and well tolerated in people after mild TBI, and may improve cognitive functioning in this patient population. This study provides Class IIB evidence that Enzogenol is well tolerated and may reduce self-perceived cognitive failures in patients 3–12 months post-mild TBI.

Introduction

Traumatic brain injury (TBI) is one of the most prevalent conditions affecting young adults worldwide, with extensive and disabling consequences [1,2]. Even a mild TBI, accounting for 70–90% of all TBIs [3], can lead to persistent cognitive deficits, including memory difficulties, and post-concussion symptoms that can profoundly impact return to work and social functioning [4–7]. Rehabilitation practice currently focuses on helping people to manage their cognitive difficulties post-injury rather than addressing possible underlying biological factors. Affordable, safe and effective treatments are urgently needed to improve cognitive and social outcomes for patients post-mild TBI [8].

Evidence suggests that there is a close relationship between oxidative stress and excitotoxicity following TBI in humans [9], with significant and sustained changes in cerebral metabolism even after mild TBI

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[10]. There is evidence that neuroinflammation after TBI may continue for months [11] and even years [12]. Cerebrospinal fluid from children after severe TBI has shown increased levels of oxidative stress markers and reduced antioxidant reserves [13]. In animal models of mild TBI, increased oxidative damage and decreased amounts of brain-derived neurotropic factor (BDNF) in the hippocampus, alongside impaired spatial learning capacity could be normalized with antioxidant therapies (curcumin, hydrogen-rich saline) [14,15]. Thus, antioxidant supplementation may be useful to improve cognitive functioning post-TBI by reducing oxidative damage and normalizing expression of BDNF and other factors important in neuroplasticity [13].

Enzogenol is a pine bark extract from New Zealand-grown *Pinus radiata* with antioxidant, anti-inflammatory and potential neuro-protective properties [16,17]. The extract consists of proanthocyanidins (average 84%), taxifolin (1–2%), other flavonoids, phenolic acids and stilbenes (together 8%), including catechin, quercetin, myricetin, astringenin, gallic, ferulic, caffeic and protocatechuic acid, and carbohydrates (5–10%) [18]. Animal toxicity and previous clinical studies with up to a 6-month treatment period support the safe use of Enzogenol in people [18]. Limited pharmacokinetics in dogs has shown absorption of catechin and taxifolin without accumulation in the body [18]. *In vitro* superoxide radical scavenging assays have shown Enzogenol to be a stronger antioxidant than vitamin C, trolox, catechin and grape seed extracts [19].

In a clinical trial, Enzogenol plus vitamin C led to significant reductions in systemic plasma protein oxidation when compared with vitamin C only [20]. In a small randomized controlled trial (RCT) on Enzogenol ($n = 42$), supplementation at 960 mg/day for 5 weeks significantly improved performance on working memory tasks in overweight, generally healthy, males [21]. Another preliminary study has described reduction in the frequency and severity of migraines after taking Enzogenol [22]. Several other studies have also shown that flavonoid-rich plant extracts, particularly those containing high amounts of flavanols, for example pine bark, cocoa and grape seeds, can have beneficial effects on neuro-cognitive functions, likely mediated not through basic antioxidant action, but by influencing signalling pathways involved in neuro-inflammation, neuroplasticity and cerebrovascular blood flow [23].

This is the first clinical study to report on the safety and effects of a flavonoid extract on cognitive functioning after TBI. We hypothesized that Enzogenol 1000 mg/day is safe and well tolerated by people with mild TBI, and may have a positive effect on their cognitive functioning. The aims of the study were: (i) to examine the safety and feasibility of recruitment and administration of the dietary supplement Enzogenol in people 3–12 months post-mild TBI; (ii) to explore trends in efficacy of Enzogenol on memory and post-concussion symptoms in people post-mild TBI; and (iii) to explore the influence of fat-free mass and diet variability on any outcome changes observed following Enzogenol supplement use.

Methods

This was a pilot, double-blind, placebo-controlled, randomized clinical trial consisting of three treatment periods. The trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12610000107022), and received ethical approval from the Northern X Regional Ethics Committee and the AUT University Ethics Committee. Written informed consent was obtained from all participants.

Participants

Traumatic brain injury was defined according to World Health Organization criteria as an acute brain injury resulting from mechanical energy to the head from external physical forces [24]. Operational criteria for clinical identification included the presence of one or more of the following: (i) confusion or disorientation; (ii) loss of consciousness; (iii) post-traumatic amnesia; (iv) other neurological abnormalities (e.g. focal neurological signs, seizure, intracranial lesion) [24,25]. Symptoms needed to be related to the TBI and not due to drugs/alcohol or medications, and not caused by other injuries/treatments (e.g. systemic injuries, facial injuries, intubation) or other problems (e.g. psychological trauma, language barrier, co-existing medical conditions). TBI severity was defined using standard definitions [26–28]. People who had experienced a mild TBI and resided in the Auckland region were approached to participate in the study. Inclusion criteria were: (i) aged 18–64 years; (ii) 3–12 months post-mild TBI as defined by the Glasgow Coma Scale score of 13–15 and post-traumatic amnesia < 24 h [24]; (iii) experiencing persisting cognitive difficulties as indicated by a score of > 38 on the Cognitive Failures Questionnaire (CFQ; 0.5 SD above the mean for healthy controls) [29]; (iv) willing to avoid taking any other anti-oxidant supplements (e.g. Gingko Biloba, Bacopa or vitamins) for the duration of the study. Exclusion criteria were: (i) not fluent in English or had dysphasia, as this would impact on their ability to complete the outcome assessments; (ii) unable to

give informed consent; (iii) known to have another medical condition that could affect the results such as advanced cancer or severe psychiatric disorder (such as significant substance abuse, diagnosed dementia-significant mental illnesses, diabetes requiring insulin injections, severe agitation, advanced cancer or other severe conditions requiring nursing or hospitalization); (iv) dependent on others for everyday activities before the onset of the brain injury; (v) pregnant or breast feeding; (vi) known to have an allergy to pine trees; or (vii) currently taking anticoagulant medication. All potential study participants have been pre-screened by their treating clinicians for inclusion and exclusion criteria before referring them for final eligibility evaluation to the study research staff who confirmed eligibility by reviewing pre-injury health from medical records, interviewing the candidate and assessing for the presence of persistent cognitive failures by CFQ.

Randomization

Participants were randomized using computerized minimization randomization software [30] to receive either the Enzogenol or matching placebo capsules. This approach aimed to ensure balance for possible prognostic factors including age (16–45 and 45–64 years), gender and ethnicity between the two treatment groups. Ethnicity was balanced for Maori (indigenous population of New Zealand) and non-Maori New Zealanders, as the Maori population has been found to be at increased risk of TBI and poorer outcomes [31]. The manufacturer of the supplement and placebo capsules held the group allocation codes until the data analysis had been completed so the research team remained blind to group allocation throughout the study.

Procedure

The study was designed with three treatment periods (Fig. 1). The first period of 6 weeks was the placebo-controlled, parallel design with Group A (n = 30) receiving placebo and Group B (n = 30) receiving Enzogenol. In period two, both groups received Enzogenol for 6 weeks, and in period three both groups received placebo for 4 weeks. This design was chosen to detect the possible time frame for levelling off of treatment effect (within up to 12 weeks), and duration of treatment effect after the end of active treatment (up to 4 weeks), as well as to avoid the need for wash-out periods.

Self-administered questionnaires were posted to all participants for completion prior to, during or after the researcher's visit, and collected or returned by mail. In-person assessments were carried out in the participant's home, at the university or in a private room at their workplace by a researcher (S.M.) at baseline, 6, 12 and 16 weeks. Weekly phone calls between visits were made to monitor any side-effects and their duration/resolution.

At baseline, 6- and 12-week visits, participants were given a white cardboard box (marked group A or group B) containing the allocated supply of capsules for the period packaged in blister cards. Identically looking capsules contained either 500 mg of Enzogenol, or microcrystalline cellulose for the placebo. Participants were advised to take two capsules in the morning, 15 min before breakfast with a large glass of water. Capsules not taken during the allocated period were collected at the next visit. Single-dose administration in the morning was chosen as it had been effective in other trials on Enzogenol. In addition, previous anecdotal observations have suggested a stimulating effect of Enzogenol, therefore the recommendation to take this supplement in the morning was done to avoid the potentially undesirable impact of the supplement on sleep of the study participants.

Outcome measures

Safety and tolerability were assessed by the frequency and nature of self-reported side-effects recorded on a standard study checklist. Compliance was assessed on the percentage of capsules that had not been taken. A set of well-validated tests was used to evaluate cognitive functioning (primarily memory), post-concussion symptoms and mood. Everyday memory was measured by CFQ [32,33], working memory was measured

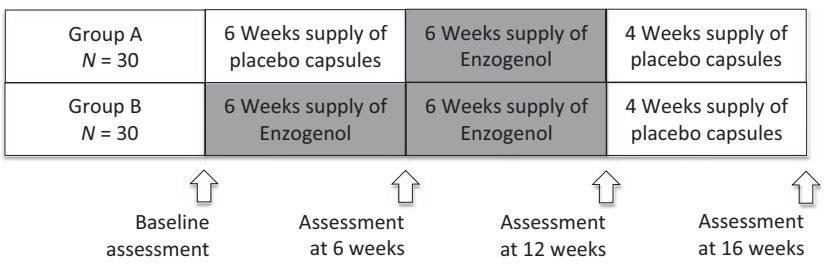

Figure 1 Overview of trial sequence.

by the digit span subtest Wechsler Adult Intelligence Scale (WAIS) Version 3 [34], Arithmetic WAIS Version 4 [35], and Letter Number Sequencing subtests of the WAIS Version 4. All WAIS subtests were administered and responses recorded in a separate test booklet as specified in the instructions [34,35]. The raw scores for each subtest were then transformed to standard scores to account for age effect on cognitive ability, as specified in the respective WAIS-III or WAIS IV Administration and Scoring Manuals [34,35]. Standard scores for all tests were in the range 1–19, with higher scores indicating higher functioning working memory. Episodic memory was measured by the California Verbal Learning Test (CVLT) [36]. Raw scores on each subtest were transformed to standard scores to account for age and gender effects as specified in the manual.

Post-concussion symptoms were measured by the Rivermead Post-Concussion Symptoms Questionnaire [37,38]. Total scores for all 16 items were used to determine the presence or absence of post-concussive syndrome. Mood disorders (anxiety and depression) were measured by the Hospital Anxiety and Depression Scale (HADS) [39,40]. To account for possible confounding effects of diet and body composition we measured these variables by using the Food Variety Questionnaire [41], height and weight of the participants (measured without shoes and in light clothing according to standard methods, duplicate measures were taken to reduce error) to calculate body mass index (kg/m^2) derived from the mean measurements. Direct measurements of resistance R, reactance X, impedance Z and phase θ to a 50-kHz signal were assessed using a bioimpedance analyser (Model Imp 4; Impedimed, Queensland, Australia) with a tetrapolar arrangement of self-adhesive electrodes placed on the hands and feet. Fat-free mass was derived from resistance and height using an equation that has been validated for adults of different ethnicities [42].

Statistical analysis

Descriptive statistics were used to characterize and compare the study participants and frequency of side-effects between the two groups. Initial exploration for trends in treatment effects were observed through calculation of the mean/median scores (dependent on the distribution of the scores). Non-linear modelling was used to estimate the effects on the primary outcome variable (everyday memory as measured by the CFQ) while controlling for baseline covariates and possible confounders. The analysis of the CFQ scores accounted for potential confounders and the study design through a mixed modelling approach that accounted for serial correlation within participants. To account for progressive onset of and eventual levelling off of treatment effects, data were analysed using piecewise linear mixed models with estimated breakpoints. Different linear trends over time were allowed for both the placebo and active treatment observations. These trends were modelled as lasting until some breakpoint (subject to estimation), after which the effect remained constant. These models are similar to the flexible hierarchical linear models of Gallop *et al.* [43] with slope 0 in the second segment; they embody a testable assumption of non-reversible limited healing. The healing was posited as potentially occurring at different rates and over different periods under treatment and under placebo.

The presence of the breakpoint made the models non-linear. Simultaneous estimation of treatment effect and breakpoint was effected with confidence intervals (CIs) obtained by bootstrapping. Breakpoint uncertainty was captured by confidence sets. Further testing as described below was carried out conditionally on the selected breakpoint.

To determine whether the treatment effect differed between the two sequences, reflecting different delays since injury, the treatment–sequence interaction was tested. To explore whether a varied diet (indicative of higher intake of antioxidants from food) or the level of fat-free mass influenced the trends in effect of the supplement, quintiles of these indices were included as main effects and in interaction with treatment effect. Lastly the possibility of a reversible or prolonged treatment effect after weaning from the active treatment was considered. The threshold for statistical significance was established at 5%, based on two-sided alternatives. Statistical analyses were executed using R Version 2.13 [44] and R package nlme [45] v.3.1.

The analysis of the CFQ scores accounted for potential confounders in the study design through a mixed modelling approach that accounted for serial correlation within participants. To determine whether the treatment effect differed between the two sequences, reflecting different duration of the intervention, the treatment–sequence interaction was tested. As this was a pilot study aimed at informing the design and sample size of the phase III trial, no sample size calculation was required and the convenience sample of 60 study participants was driven by financial constraints.

Simultaneous estimation of treatment effect and breakpoint was effected, with CIs obtained through a treatment–placebo balance-preserving bootstrap procedure (participants who withdrew after randomization were included in the resampling). To explore whether a varied diet (indicative of higher intake of

antioxidants from food) or the level of fat-free mass influenced the trends in effect of the supplement, quintiles of these indices were included as main effects and in interaction with treatment effect. Lastly the possibility of a reversible or prolonged treatment effect after weaning from the active treatment was considered. The threshold for statistical significance was established at 5%, based on two-sided alternatives. Statistical analyses were executed using R Version 2.13 [44] and R package nlme [45] v.3.1.

Results

Sixty participants were randomized into the study, with 50 (83.33%) participants completing all outcome measures at the 16-week follow-up (Fig. 2). There were no significant differences between the two groups in regard to demographic characteristics or baseline measurements (subgroup means were not separated by more than one pooled SD) (Table 1). Overall adherence in taking the capsules as instructed was high, with 98% of prepared capsules taken over the course of the study. The recruitment procedure also proved to be feasible, and the main reason for not participating in the trial was due to participants falling outside of the 3–12-month post-TBI timeframe.

The age of participants ranged between 21 and 64 years. Motor vehicle accidents ($N = 20$, 33.3%) and falls ($N = 20$, 33.3%) were the most frequently reported reason for injury, with sports-related injury ($N = 6$, 10.0%), assault ($N = 9$, 15.0%) and being hit by an object ($N = 5$, 8.3%) reported by the remaining participants.

Seven participants across the two groups reported side-effects during the course of the study. Two participants experienced a headache whilst taking Enzogenol and two whilst taking the placebo capsules; two participants reported sleep disturbance (Enzogenol one; placebo one); one participant reported experiencing blurred vision whilst on the placebo capsules. All reported side-effects lasted for < 3 weeks (range 8–20 days).

Analyses of CFQ scores showed a significantly greater reduction in self-reported cognitive failures after 6 weeks on Enzogenol compared with placebo (28% change vs. 22% change, respectively) with a differential change of −6.9 points on the CFQ score (95% CI −10.8 to −4.1; Fig. 3). The treatment effect

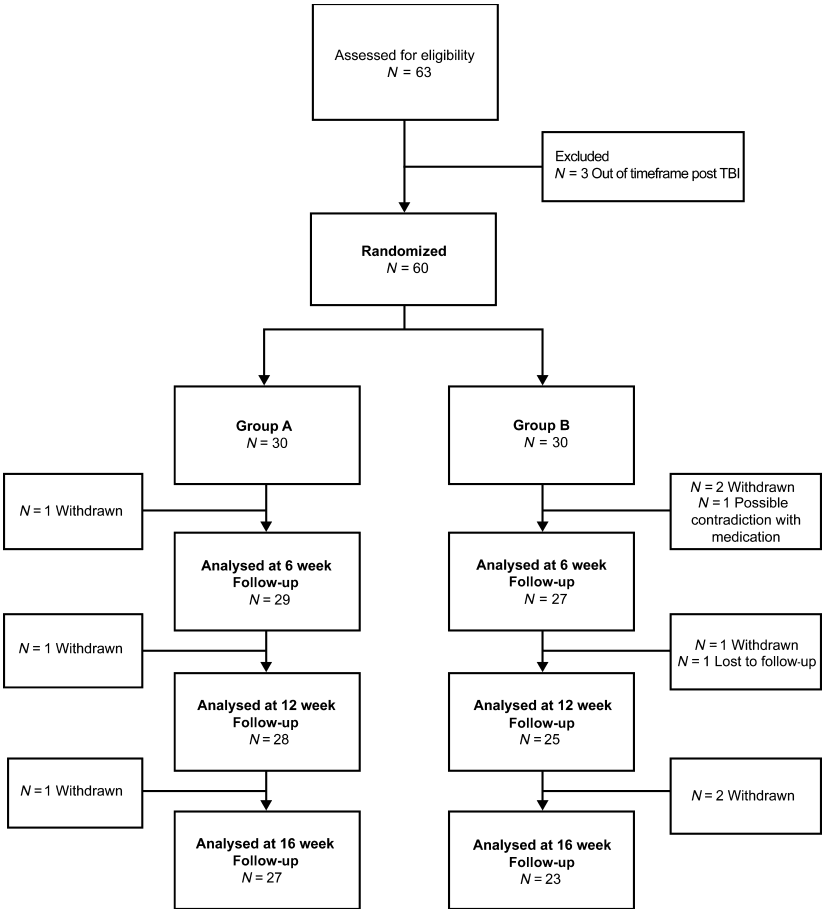

Figure 2 Flowchart of participant recruitment.

breakpoint was estimated to occur at 11 weeks. There was no evidence of treatment and sequence interaction effect ($P = 0.84$). There was also no evidence of departures from constancy after treatment ceased (either wearing off or continued improvement) either by itself ($P = 0.41$) or in interaction with trial sequence ($P = 0.77$), suggesting that observed benefits from Enzogenol were stable in the 4-week period following cessation of the treatment.

The differential change attributable to treatment in 1 week was not significant at the 5% level (−1.2; 95% CI −3.5 to 1.4), while the change after 6 weeks was (−6.9; 95% CI −10.8 to −4.1) equivalent to an improvement of 6.9%. The treatment effect breakpoint was estimated to occur at 11 weeks [92% confidence set (10, 11), 98% confidence set (1, 9, 10, 11)] with an estimated maximal treatment-attributable effect of −12.7 (95% CI −18.4 to −6.6). There was no evidence of an interaction between treatment and trial sequence ($P = 0.84$). There was also no evidence of departures from constancy after treatment ceased (either wearing off or continued improvement) either by itself ($P = 0.41$) or in interaction with the trial sequence ($P = 0.77$), suggesting that observed benefits from Enzogenol were stable in the 4-week period following cessation of the treatment. CFQ scores were estimated to be 7.32 (95% CI: 5.4–9.0) higher when interviews were conducted in person rather than over the phone. The model of linear change needed to be modified to account for a systematic score increase of 7.27 (95% CI 4.0–10.5) at baseline. This increase was in addition to the in-person effect.

Table 1 Demographic and medical characteristics of the study participants

	Group A $N = 30$	Group B $N = 30$
Number of males, *N* (%)	12 (40)	14 (46.67)
Age in years, median (IQR)	44.00 (28.00)	45.00 (27.00)
Ethnicity		
NZ European (non-Maori)	25 (83.33)	21 (70.00)
Highest level of education		
Tertiary education or above, *N* (%)	19 (63.33)	16 (53.33)
Employment status prior to injury		
Full time paid work, *N* (%)	16 (53.33)	18 (60.00)
Marital status		
Married or living with partner, *N* (%)	19 (63.33)	15 (50.00)
Residential status		
Lives with others, *N* (%)	20 (66.67)	18 (60.00)
Time since injury in months, mean (SD)	7.1 (2.66%)	8.04 (2.46%)
Co-morbid conditions		
Yes, *N* (%)	11 (36.67)	9 (30.00)
Supplement use in prior 12 months?		
Yes, *N* (%)	18 (60.00)	18 (60.00)
Perception of supplement benefit		
Positive, *N* (%)	23 (76.67)	20 (66.67)
Number of alcoholic drinks consumed per week, median (IQR)	2.00 (3.00)	1.00 (3.00)
Current smoker, *N* (%)	4 (13.33)	4 (13.33)
Body weight		
Overweight or obese (%)	14 (46.67)	14 (46.67)
Fat-free mass in kg, mean (SD)	38.67 (12.04)	36.63 (13.94)

IQR, interquartile range; NZ, New Zealand.

Influence of diet/physiological factors on supplement effect

People with higher body mass often need higher doses of nutrients or drugs. As flavonoids in Enzogenol are water-soluble nutrients, fat-free mass was chosen as a more precise measure than simple body weight to assess if dose/body weight (fat free) effects need to be considered in future studies. The effect of fat-free mass was found not to be significant by itself ($P = 0.06$) or in interaction with treatment ($P = 0.07$). The

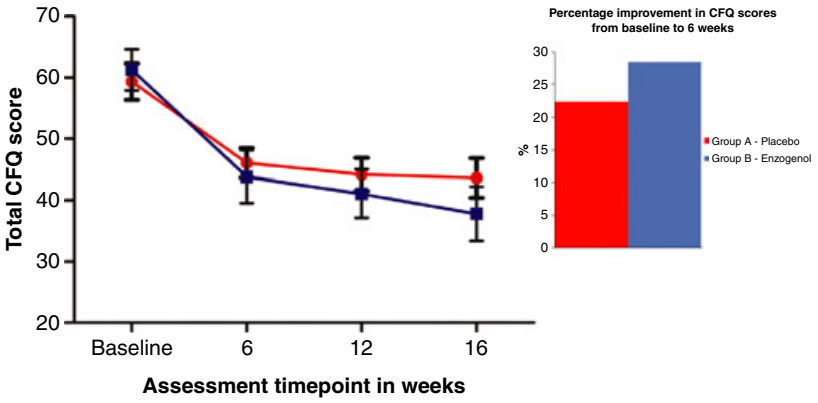

Figure 3 Means and standard deviations of Cognitive Failures Questionnaire (CFQ) total scores between the two groups accounted for potential confounders using a mixed modelling approach.

effect of varied diet was found not to be significant by itself ($P = 0.99$) or in interaction with treatment ($P = 0.65$).

There were no significant treatment effects on working (WAIS scores) and episodic memory (CVLT scores) at 6 weeks. The mean levels for anxiety and depression were within the normal range for both groups at baseline, and had reduced by a similar amount at 6 weeks for both groups. Looking specifically at participants scoring ≥ 11 at baseline, indicative of moderate and severe levels of anxiety and depression, for anxiety 5 out of 16 (31.25%) participants in group A (placebo) and 7 out of 13 (53.84%) participants in group B (Enzogenol) improved to levels within the normal range at 6 weeks. On the depression subscale, 5 out of 7 (71.43%) in group A and 5 out of 6 (83.33%) in group B scored ≥ 11 at baseline and improved at 6 weeks to within the normal range. There was a trend, albeit not statistically significant, towards greater reduction in the frequency of post-concussion symptoms between baseline and 6 weeks in the Enzogenol group compared with the placebo group.

Discussion

The findings suggest that daily ingestion of 1000 mg of Enzogenol pine bark extract is safe for individuals' post-mild TBI. Few side-effects were reported by participants and indeed fewer associated with the active intervention than with placebo. The recruitment rate and adherence were reasonably high, suggesting the feasibility of a larger trial. The treatment effect seen in the frequency of self-reported cognitive failures suggests that there may be a beneficial effect of Enzogenol to aid in the recovery of impaired cognitive function post-TBI. This finding is consistent with previous evidence suggesting that Enzogenol may improve cognitive performance in a group of older individuals [19]. However, this trial was not statistically powered to address the efficacy of the intervention, therefore our findings of the effects of the intervention on self-reported cognitive failures and some other outcomes should be treated with caution. Due to financial constraints, we also did not measure markers of neuroinflammatory or oxidative stress, adding to the limitations of the study. The frequency of cognitive failures was estimated to have decreased for a period of up to 11 weeks and remained stable for 4 weeks afterwards. Consequently, an intervention period of at least 10 weeks would be recommended in order to explore the extent of treatment effects, in comparison to a placebo control group, more comprehensively. There were no trends suggesting a negative effect on any of the outcome measures. As the trial was aimed to assess effects of Enzogenol on patients with mild TBI with persistent cognitive impairment and there is evidence that neuroinflammation after TBI may continue for months [11] and even years [12], we limited the study inclusion criteria to 3–12 months post-TBI (exclusion of patients with TBI at the later stage after the injury was based on the assumption that most of the anti-inflammatory and anti-oxidative stress effects of Enzogenol are happening within the first year after the injury).

Although fat-free mass and dietary variance did not significantly contribute to the explanation of variance in the primary outcome variable (CFQ scores), there was a noticeable association between fat-free mass and treatment effect of the supplement warranting further investigation.

The assessment of mild cognitive impairment is challenging, and it is interesting that trends of memory improvement as measured via neuropsychological assessment did not reach statistical significance and were not observed on all subtests. As neuropsychological testing is always conducted in a controlled environment, where distractions that can exacerbate any impairment are minimized, it may be that the mild deficits were not detected in the neuropsychological tests. In contrast, the CFQ self-report measure asks about situations that occur in everyday life, where people are often required to multi-task or to cope with environmental distractions: these may have been reflected in the results. These findings suggest the inclusion of a neuropsychological assessment requiring participants to multi-task in a future trial, in order to ensure that any treatment-associated change is detected. Because all follow-ups were standardized and used in a consistent manner in both treatment groups, randomization (which is shown to be effective in terms of balancing the groups for major prognostic factors) should have balanced off any differential effect of the follow-ups on any outcomes. However, as any beneficial effects of this contact would have affected both groups, this may have diminished our ability to see clinical effects of the intervention. The marked difference in the results of CFQ assessments obtained over the phone as compared with those obtained in-person suggests a strong interviewer administration effect of the assessment and therefore this was controlled for in the modelling.

There was no observed treatment effect on the frequency of post-concussion symptoms at 6 weeks. Due to the limited sample size, detailed exploration of the frequency of specific post-concussion symptoms was not feasible, but would be worthy of inclusion in a

Table 2 Cognitive function tests, post-concussion symptom, and anxiety and depression scores

Standard scores for subtests, means (SD)	Group A				Group B			
	Baseline	6 weeks	12 weeks	16 weeks	Baseline	6 weeks	12 weeks	16 weeks
CFQ	59.34 (16.03)	46.07 (12.43)	44.19 (13.71)	43.07 (16.72)	61.27 (17.2)	43.83 (20.42)	41.08 (19.19)	40.74 (21.24)
CVLT short-delay free recall	−1.07 (1.01)	−0.53 (1.11)	−1.38 (1.30)	−0.63 (1.14)	−0.95 (1.14)	−0.27 (1.04)	−1.23 (1.15)	−0.42 (1.32)
CVLT long-delay free recall	−0.98 (1.03)	−0.51 (1.09)	−1.20 (1.50)	−0.52 (1.19)	−0.86 (1.08)	−0.23 (0.98)	−1.02 (1.05)	−0.10 (1.25)
CVLT recognition	−1.38 (1.44)	−0.88 (1.26)	−1.21 (1.15)	−0.96 (1.48)	−1.09 (1.31)	−0.64 (1.41)	−1.73 (1.52)	−0.60 (1.38)
CVLT mean total accuracy%	81.18 (15.82)	86.02 (11.74)	83.58 (10.68)	85.04 (15.32)	84.51 (12.58)	88.06 (12.68)	80.79 (14.43)	86.93 (18.98)
WAIS digit span	10.73 (2.35)	11.17 (2.85)	11.32 (2.71)	11.61 (3.20)	9.97 (2.51)	10.15 (2.69)	10.67 (2.24)	10.92 (2.23)
WAIS letter number sequencing	8.70 (1.51)	9.31 (2.09)	9.25 (1.96)	9.14 (2.40)	8.28 (2.07)	8.92 (2.12)	8.58 (2.26)	8.88 (1.54)
WAIS arithmetic	9.13 (3.24)	8.93 (2.58)	9.86 (3.08)	9.54 (3.08)	8.00 (2.14)	8.92 (2.77)	8.71 (2.22)	9.21 (1.91)
RPQ-3 total	5.13 (2.80)	4.25 (2.29)	3.52 (2.18)	3.59 (2.24)	4.36 (3.11)	4.00 (3.03)	3.09 (2.83)	3.48 (2.76)
RPQ-13 total	31.07 (8.08)	24.18 (7.80)	22.71 (8.62)	20.74 (8.79)	27.48 (11.79)	23.42 (9.70)	20.52 (11.55)	20.00 (11.27)
HADS anxiety	10.45 (4.28)	8.46 (4.41)	7.75 (4.33)	7.96 (5.01)	9.29 (4.40)	6.69 (4.37)	6.68 (4.61)	7.17 (4.97)
HADS depression	7.97 (3.56)	5.82 (3.06)	5.54 (3.76)	5.96 (3.49)	6.00 (3.69)	4.65 (3.50)	4.72 (4.12)	5.39 (4.05)

CFQ, Cognitive Failures Questionnaire; CVLT, California Verbal Learning Test; HADS, Hospital Anxiety and Depression Scale; RPQ, Rivermead Post-Concussion Symptoms Questionnaire; WAIS, Wechsler Adult Intelligence Scale.

larger study. Based on previous preliminary research findings linking Enzogenol to reductions in the frequency and severity of headaches in people with migraine, this may be one symptom of particular interest to explore further in people post-TBI.

The study did not find any significant effect on mood, although cognitive performance and anxiety and depression are often closely linked. Mean scores on the HADS (Table 2) were within the normal range, suggesting that participants in this sample did not have elevated levels of anxiety or depression, therefore it was unlikely any treatment effect would be observed. However, it is noteworthy that in participants with high anxiety and depression levels, there was a greater number of participants in the Enzogenol group that showed improvements in their anxiety and depression scores, although the differences did not reach a statistically significant level.

It is acknowledged that the differential rates of withdrawal between the two groups may limit the interpretation of these findings. Another limitation of the study was that we recruited study participants not only from community health services but also via advertisements in local media that may have lead to selection bias. However, this selection bias, if any, should have been balanced by the randomization we used and proven to be effective as judged by the balance of prognostic factors between the treatment groups.

In conclusion, the findings suggest that the Enzogenol pine bark extract is safe and well tolerated post-mild TBI and may have beneficial effects on the frequency of self-reported cognitive failures. A statistically powered RCT is required to assess the efficacy of the supplement.

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Disclosure of conflict of interest

Prof. Valery Feigin developed an educational stroke recovery DVD that was purchased by ENZO Nutraceuticals in a separate agreement. He reports no other disclosures. The remaining authors report no disclosures.

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