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Cerebronal® food supplement improve status of markers of dementia and regeneration

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ABSTRACT

Background: Brain diseases, including neurodegenerative disorders such as Alzheimer's disease, represent a significant global health burden with rising prevalence due to aging populations. Cerebronal® (Medicinalis) is a dietary supplement formulated with a proprietary blend of plant extracts, acetyl L-carnitine, nucleotides, vitamins, and antioxidants designed to support brain health and cognitive function.

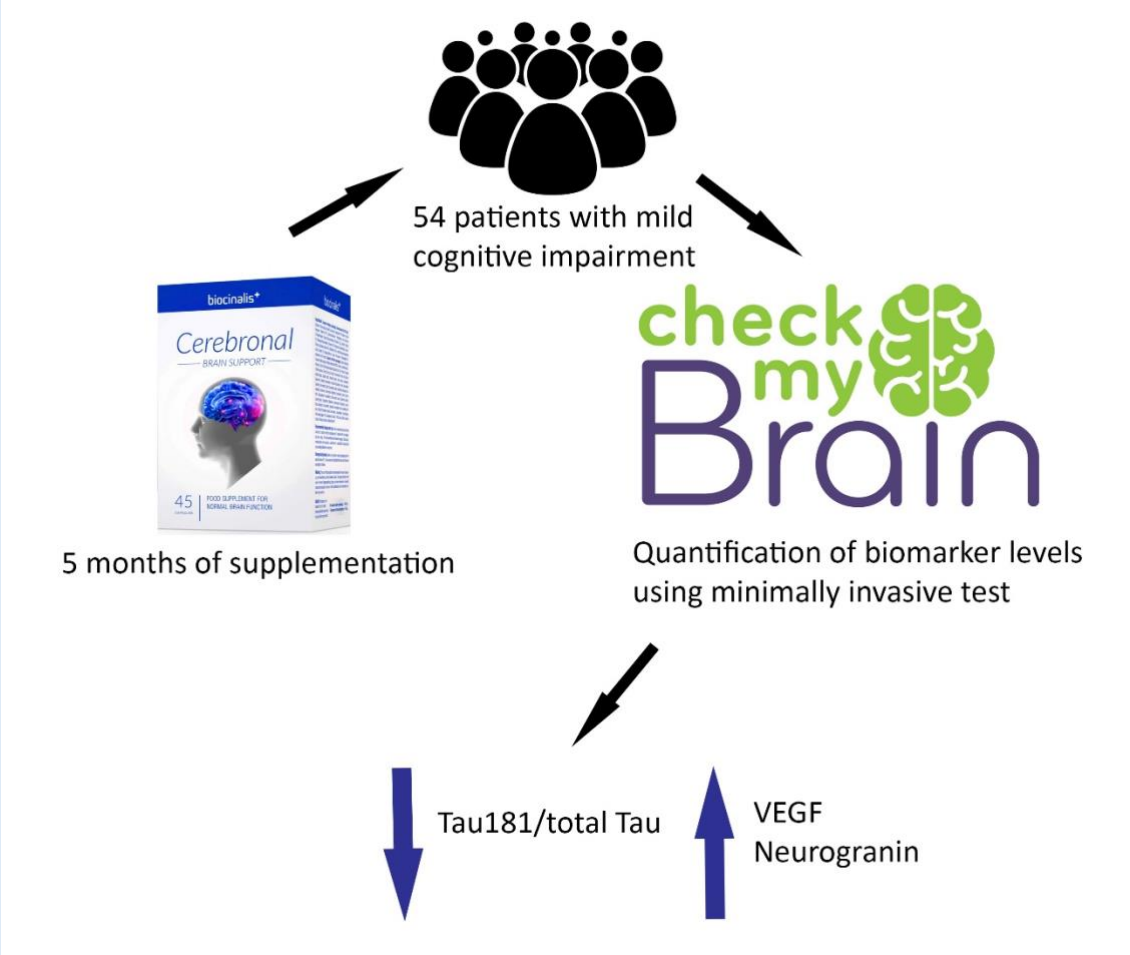
Objective: This study evaluated the effects of Cerebronal® supplementation during three to six months implementation on biomarkers associated with neurodegeneration and brain regeneration in 54 outpatients experiencing memory problems. Hair follicle cells were collected and directly reprogrammed into neurons for analysis of key proteins including total Tau, phosphorylated Tau181, beta-amyloid 42, neurogranin, and VEGF using ELISA assays (Check My Brain®, Omnion Research International).

Results: While total Tau and beta-amyloid levels showed no significant changes, a subgroup of patients with elevated Tau181/total Tau ratios exhibited a significant reduction after supplementation. Additionally, patients with initially low levels of neurogranin and VEGF demonstrated significant increases, indicating potential improvements in synaptic function and neurovascular support.

Novelty: These novel findings suggest that Cerebronal® may beneficially modulate specific molecular markers linked to neurodegeneration and brain repair in vulnerable individuals. In addition, the study highlights the utility of hair follicle-derived neuronal cultures as a minimally invasive tool for monitoring biomarker changes.

Conclusion: Although more research with higher number of participants will be needed, overall, Cerebronal® shows promise as an adjunctive intervention for cognitive health, with quantitatively proven benefits.

Keywords: neurodegenerative disorders, biomarkers, food supplements, Tau, Tau181, beta amyloid, neurogranin, VEGF



Graphical Abstract: Cerebronal® food supplement improve status of markers of dementia and regeneration.

BACKGROUND

Brain diseases pose a significant global burden, accounting for over 10% of the global disability-adjusted life years (DALYs) and contributing to over 6 million deaths annually [1]. With the aging population, the prevalence of neurodegenerative disorders like Alzheimer's and Parkinson's disease is rising sharply, particularly in high- and middle-income countries [2, 3]. The economic cost of brain disorders in Europe alone was estimated at over €800 billion per year, indicating a massive financial impact worldwide [4]. As life expectancy increases globally, the urgency to invest in prevention, early detection, and treatment of brain diseases becomes ever more critical [5].

Dementia is a complex and multifaceted disorder that poses a significant challenge to modern society, affecting millions of people worldwide. It is characterized by cognitive decline, memory loss, and changes in behavior, significantly impacting the quality of life for both patients and their caregivers. The major pathogenic mechanisms underlying dementia, particularly Alzheimer's disease (AD), involve the accumulation of amyloid-beta (Aβ) plaques and tau protein neurofibrillary tangles, leading to neuronal damage and loss. These pathological features are accompanied by oxidative stress, inflammation, and synaptic dysfunction, contributing to the disease's progression. Thus, it is not surprising that the global market offers numerous types of food supplements, some of which are without any proven efficacy and some of which have demonstrated positive effects [6, 7, 8, 9, 10, 11].

Cerebronal® is a dietary supplement thoughtfully developed by Medicinalis GmbH Austria, and distributed by Nemec Pharmacia D.O.O, Zagreb, Croatia, featuring the exclusive NTBX3® complex—a scientifically backed blend of nootropic ingredients designed to support and revitalize brain function and formulated to support brain health and cognitive function. It contains a proprietary blend of ingredients, including the NTBX3® complex, which comprises 29 concentrated extracts from vegetables, herbs, and fruits. The supplement also includes acetyl L-carnitine, an amino acid involved in energy metabolism.

For this research, we utilized a method which measures the status of markers linked to dementia and brain regeneration (Check My Brain, Omnion Research International) to analyze the potential positive effects of the Cerebronal® supplement. Since Cerebronal® has been prescribed to a rather large number of outpatients reporting problems with memory, for these analyses we selected a group of patients who were taking Cerebronal® and measured the levels of specific markers in two intervals: at the very beginning of Cerebronal® supplementation and six months later. Interestingly, we have found that taking the Cerebronal® supplement significantly improves status of some markers, which brings quantitative confirmation of prior subjectively reported improvements.

METHODS

Participants: This study aimed to compare possible effects of taking Cerebronal® in people with symptoms of mild cognitive impairment (MCI). Volunteers were selected in the outpatient private facility “Poliklinika Aviva”, Zagreb, Croatia, by their neurologist. All participants signed informed consent forms and the research has been approved by the Ethical body of the aforementioned institution.

Inclusive criteria were mild symptoms of forgetfulness and diagnosis of early-stage mild cognitive impairment (MCI). Participants with any other diagnosed neurological or psychiatric disorders, and MMSE higher or lower of the above defined range were excluded. MCI was defined as a subjective concern in cognitive features declared by a person or a family and a score achieved on Mini Mental Score Examination (MMSE) between 23 and 27.

Control group of participants had the same inclusion and exclusion criteria and were selected by randomization among eligible candidates. Randomization and all other procedures in this study were performed by blinded researchers. The controls were age and sex matched with the treatment group and were not exposed to any supplements during the 6-month period of the study duration.

Average age of the tested group was 52±4 yrs and the control group 51±3 yrs. We selected 60 outpatients/participants whose hair samples were analyzed prior to the study intervention. Six participants were lost during the study since they were non-compliant with the study protocol. Majority of participants (54) completed the study by performing planned check-ups after 3 to 6 months (on average 5 months), when a second hair sample was obtained and analyzed.

Table 1. List of inclusion and exclusion criteria.

Inclusion Criteria	1. Mild symptoms of forgetfulness and diagnosis of early-stage mild cognitive impairment (MCI).
	2. Mini Mental Score Examination (MMSE) score between 23 and 27.
	3. Subjective concern in cognitive features declared by the person or family.
	4. Ability and willingness to give informed consent.
	5. Age between 45 and 75.
Exclusion Criteria	1. Diagnosed neurological disorders other than MCI.
	2. Diagnosed psychiatric disorders.
	3. MMSE score outside the range 23 - 27.
	4. Non-compliance with study protocol (e.g., lost during study).
	5. Use of other brain health supplements or treatments during study period.

Cerebronal® supplement: Cerebronal® is a dietary supplement which contains: nucleotides, low molecular compounds found in brain and body cells (e.g. cytidine monophosphate, uridine monophosphate), ingredients which help in the synthesis and metabolism of nerve impulses (e.g. choline, vitamins B6, B9, B12), a mix of 29 plant extracts and ingredients which protect brain cells from oxidative stress, B-vitamin complex, omega-3, acetyl L-carnitine, astaxanthin and vitamin D. The standard recommended dosage for adults, which was used for this study, is three capsules per day, consisting of one capsule from the pink packaging and two capsules from the blue packaging, taken together. They are to be swallowed with a small amount of liquid, such as water, and taken with a meal.

Hair Sample Collection: Hair strands were plucked from the scalp using sterile forceps, ensuring the retention of the follicular bulb. The samples were immediately placed into Dulbecco's Modified Eagle Medium (DMEM, Gibco) supplemented with 1% penicillin-streptomycin (Sigma-Aldrich) and maintained at 4°C until further processing.

Isolation and Culturing of Hair Follicle Cells: The plucked hair follicles were washed twice with phosphate-buffered saline (PBS) to remove the debris. The follicular bulbs were enzymatically digested with 0.25% trypsin-EDTA (Gibco) at 37°C for 10 minutes. The enzymatic reaction was neutralized using DMEM containing 10% fetal bovine serum (FBS, Gibco). The dissociated cells were centrifuged at 300g for 5 minutes and resuspended in a fibroblast growth medium consisting of DMEM supplemented with 10% FBS and 1% penicillin-streptomycin. The cells were seeded onto 6-well plates pre-coated with poly-D-lysine (Sigma-Aldrich) and maintained in a humidified incubator at 37°C with 5% CO_2. Medium was changed every two days until cells reached 80% confluency [12].

Direct Reprogramming of Hair Follicle Cells into Neurons: Cells at passage 2 were transduced with lentiviral vectors carrying the neuronal transcription factors Ascl1, Brn2, and Myt1l, under the control of the EF1α promoter. The viral particles were added to the culture medium containing 8 µg/mL polybrene (Sigma-Aldrich) to enhance transduction efficiency. After 24 hours, the medium was replaced with neuronal induction medium consisting of Neurobasal Medium (Gibco) supplemented with B27 (Thermo Fisher), N2 (Gibco), 20 ng/mL brain-derived neurotrophic factor (BDNF, PeproTech), 20 ng/mL glial cell line-derived neurotrophic factor (GDNF, PeproTech), and 1 mM cyclic AMP (Sigma-Aldrich). Cells were maintained in neuronal induction conditions for three weeks, with medium changes every 48 hours [13, 14].

Protein Isolation for ELISA: After three weeks of differentiation, neuronal cultures were washed twice with cold PBS and lysed using RIPA buffer (Thermo Fisher) containing a protease inhibitor cocktail (Roche). The

lysates were incubated on ice for 20 minutes and then centrifuged at 14,000g for 15 minutes at 4°C. The supernatant was collected, and protein concentration was determined using the bicinchoninic acid (BCA) assay (Thermo Fisher). The extracted protein samples were stored at -80°C until further analysis.

Enzyme-Linked Immunosorbent Assay (ELISA): To quantify target protein levels, ELISA was performed using a commercially available kit (Thermo Fisher Scientific) following the manufacturer's protocol (total Tau KHB0041, Tau181 KHO0631, amyloid beta 42 KHB3441, VEGF KHG0111). For neurogranin, an Abcam Elisa kit (ab277083) was used. Briefly, 96-well plates pre-coated with capture antibodies were washed three times with PBS-Tween (0.05% Tween-20) before blocking with 5% bovine serum albumin (BSA) for 1 hour at room temperature. Cell lysate samples (diluted 1:2 in assay buffer) and standard protein solutions were added to the wells and incubated for 2 hours at 37°C. After washing, biotinylated detection antibodies were added and incubated for 1 hour, followed by streptavidin-HRP incubation for 30 minutes. Color development was achieved using tetramethylbenzidine substrate solution, and the reaction was stopped using 1M sulfuric acid. Absorbance was measured at 450 nm using a microplate reader (BioTek). Sample concentrations were determined by interpolating the absorbance values against the standard curve.

Statistical Analysis: This study employed a per-protocol (PP) analysis, including only data from the 54 participants who fully adhered to the protocol, completed the intervention, and provided both pre- and post-treatment hair samples. Since the dropout rate was very low (10%), this minimized concerns over selection bias.

All experiments involved paired samples, comparing protein expression levels in induced neurons derived from pre- and post-treatment hair follicles of the same participant. Protein concentrations were normalized as percentages of standard reference values, derived from averages of over 400 prior measurements: 900 pg/mL for total tau (set as 100%), 500 pg/mL for amyloid beta 42, 700 pg/mL for vascular endothelial growth factor (VEGF), and 200 pg/mL for neurogranin. Phospho-tau 181 was expressed as a ratio to total tau.

Statistical analyses were conducted using R (version 4.4.1). Differences in normalized protein levels pre- and post-treatment were assessed using paired Student's t-tests. To account for multiple comparisons across the five biomarkers, the Bonferroni correction was applied, adjusting the significance threshold to $p < 0.01$ (0.05/5). Data are presented as mean ± standard deviation (SD), with p-values < 0.05 considered statistically significant prior to correction; adjusted p-values are reported for interpretation.

An a priori power analysis was performed using G*Power version 3.1 to determine the minimum sample size required to detect a medium effect size (Cohen's d=0.5) in a paired-samples t-test with an alpha level of 0.05 and statistical power of 0.80. The calculation indicated a minimum of 44 participants. With 54 participants included in the analysis, the study was adequately powered to detect medium or larger within-subject effects.

RESULTS

Food supplementation with Cerebronal® does not influence total levels of tau and beta amyloid: To estimate if the food supplement Cerebronal® has a positive effect on some markers of neurodegeneration and regeneration, we engaged 60 persons, who, as a part of their regular check-ups, underwent initial hair sampling for biomarker detection and were later taking Cerebronal® supplementation. The average period of supplementation—the period between two biomarker measurements—was 5 months, and the final sample count after supplementation was 54 participants. For this study, levels of the following proteins were quantified: total Tau, beta amyloid, tau 181, neurogranin and VEGF.

When total tau levels were measured, no statistically significant difference was observed after 6

months of Cerebronal® supplementation (121±11% vs 123±13%; p-value equals 0.27381). Likewise, no difference was observed in the control group after 6 months (119±21% vs 121±22%; p-value equals 0.09076).

The same was observed when levels of beta amyloid were compared before and after 6 months of Cerebronal® supplementation (105±19% vs 106±17%; p-value equals 0.06107). Likewise, no difference was observed in beta-amyloid levels in the control group after 6 months (105±25% vs 106±25%; p-value equals 0.09063).

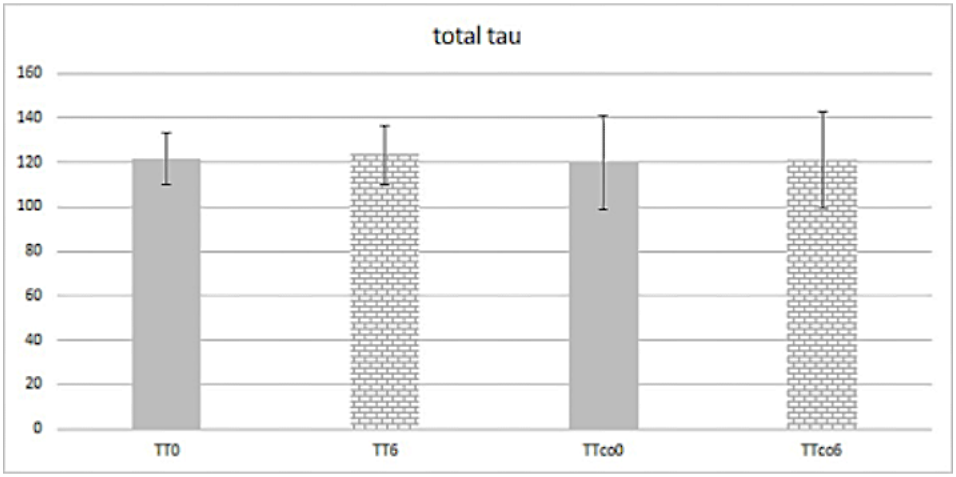


Figure 1. No statistical difference was observed in the total level of Tau between treated (TT0 - baseline, TT6 – 6 months after supplementation) and untreated (TTco0 - baseline, TT6 - after 6 months) groups.

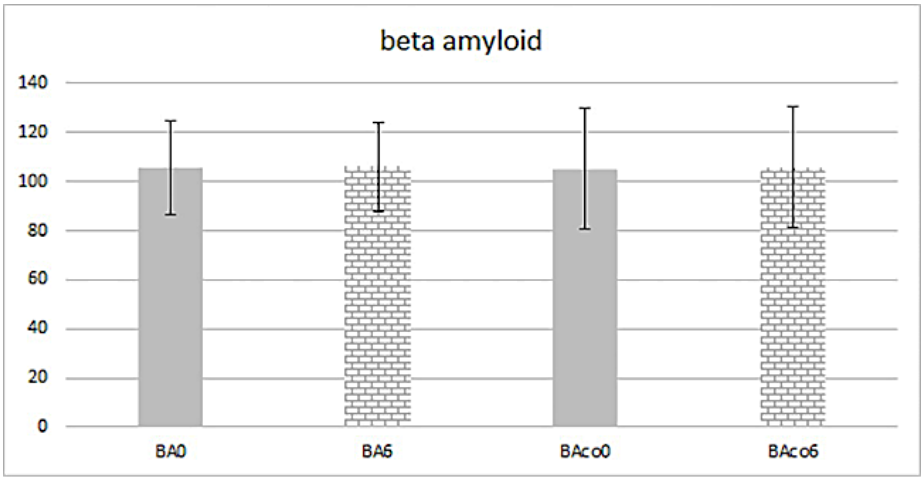


Figure 2. No statistical difference was observed in the total level of beta amyloid between treated (BA0 - baseline, BA6 – 6 months after supplementation) and untreated (BAco0 - baseline, BAco6 - after 6 months) groups.

Upon measurement of tau181 and total tau protein, no statistical significance was found when all the samples were included in statistical analysis (121±13% vs 120±11%; p-value equals 0.10134). However, when subgroup samples of participant whose total tau levels exceeded 130% and normalized after the intervention (19 samples in total), a statistically significant decline in tau181 values was observed (139±5% vs 135±5%. p-value equals 0.0001). No statistically significant difference was found in participants whose tau181 exceeded 130% and were not taking Cerebronal supplementation (137±4% vs 138±5%. p-value equals 0.05189).

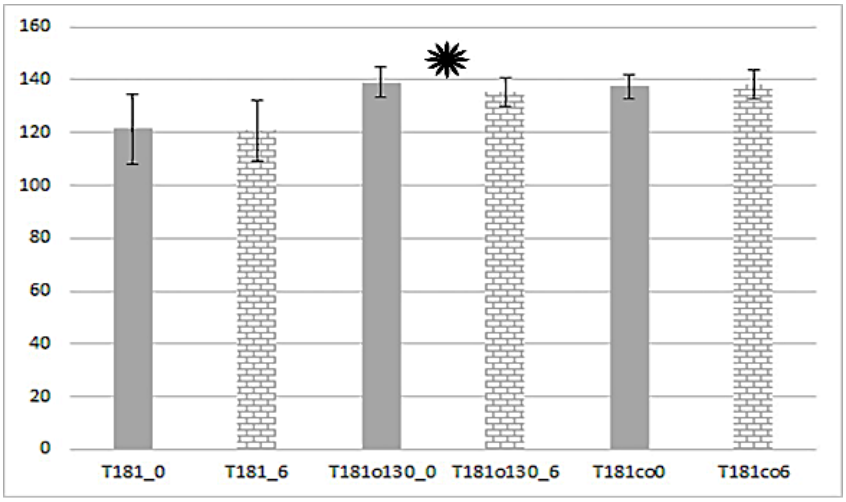


Figure 3. No statistical difference was observed in the level of Tau181 between treated (T181_0 - baseline, T181_6 - 6 months after supplementation) and untreated (T181co_0 - baseline, T181co_6 - after 6 months) groups after taking Cerebronal®. However, when samples in which initial tau 181 levels exceeded 130% and normalized after Cerebronal supplementation were taken in account, significant difference after taking Cerebronal® was found (T181o130_0 – baseline, T181o130_6 – 6 months after supplementation).

Similar positive effects were found with measurement of levels of neurogranin. While no statistically significant change between two measurements of neurogranin in all 54 samples was found (85±9% vs 85±8%; p-value equals 0.66731), when samples with levels of neurogranin below 80% of the average value were subanalysed, statistically significant increases in levels of neurogranin were observed (73±3% vs 77±4%. p-value equals 0.0002). No statistically significant difference was found in participants whose value of neurogranin was below 80% of the average value and in which no Cerebronal supplementation was administered (77±2% vs 76±2%. p-value equals 0.33887).

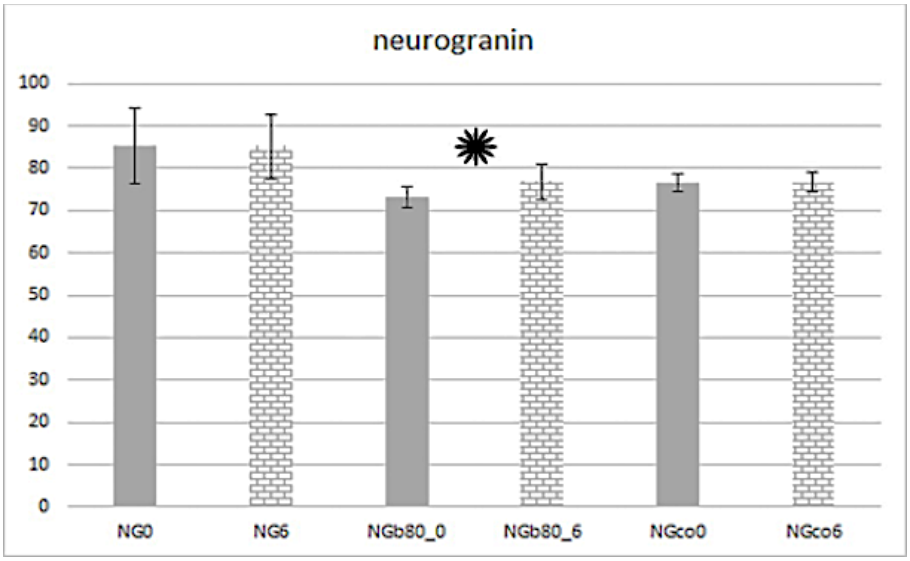


Figure 4. No statistical difference was observed in the level of neurogranin between treated (0 NG0 – baseline, NG6 – 6 months after supplementation) and untreated (NGco0 – baseline, NGco6_6 – after 6 months) groups after taking Cerebronal®. However, when only samples in which neurogranin levels below 80% of the normal value were taken in account, a significant difference after taking Cerebronal® was found (NGb80_0 – baseline, NGb80_6 – 6 months after supplementation).

The last measured marker was VEGF. While no statistically significant change between two measurements of VEGF in all 54 samples was found (91±15% vs 92±13%; p-value equals 0.52689), when only those with levels of VEGF below 80% were considered (15 samples), statistically significant increases in levels of VEGF were found (72±4% vs 78±2%. p-value equals 0.001). No statistically significant difference was found in samples in which the value of VEGF was below 80% of average value and in which no Cerebronal® was taken in the measured period (76±8% vs 75±6%. p-value equals 0.07551).

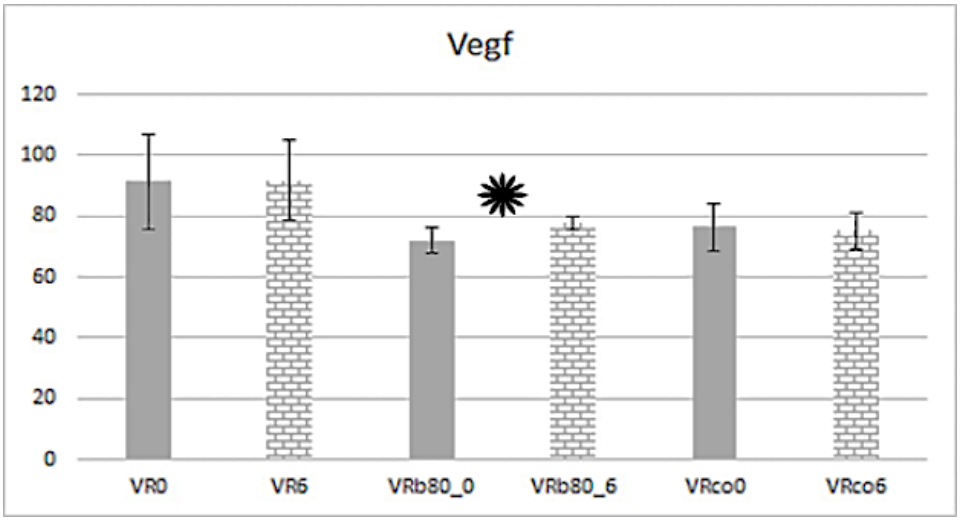


Figure 5. No statistical difference was observed in the level of VEGF between treated (VR0 – baseline, VR6 – 6 months after supplementation) and untreated (VRco – baseline, Vrco6 – after 6 months) groups after taking Cerebronal. However, when only samples in which VEGF levels below 80% of normal value were taken in account, significant difference after taking Cerebronal was found (VRb80_0 – baseline, VRb80_6 – 6 months after supplementation).

DISCUSSION

This study explored how the supplement Cerebronal® affects neurodegenerative biomarkers linked to Alzheimer's disease (AD). We measured levels of total tau, tau181, beta amyloid, neurogranin, and VEGF in neurons obtained from hair samples (54 participants) before and after taking Cerebronal® for 6 months. The focus was on understanding if Cerebronal® could positively influence these markers, given its potential role in supporting brain health, as discussed in relation to dementia and AD in the introduction.

Overall, there were no significant changes in total tau, beta amyloid, or the tau181/total tau ratio across all participants. However, in a subgroup with elevated tau181/total tau (above 130% of the average), we observed a significant decrease, suggesting a reduction in pathological tau, which is beneficial for AD. Additionally, in this subgroup, neurogranin and VEGF levels were significantly increased. These increases might indicate improved synaptic function and neuroprotection.

Cerebronal's ingredients, including omega-3 fatty acids, astaxanthin, and B vitamins, may contribute to these effects by reducing inflammation, protecting against oxidative stress, and supporting neuronal function. The benefits were seen mainly in those with higher initial pathology, suggesting a targeted approach for at-risk individuals.

To understand these findings, we must consider the roles of these biomarkers in AD. Tau protein, particularly its phosphorylated form (tau181), is crucial for microtubule stability in neurons. In AD, hyperphosphorylated tau forms neurofibrillary tangles, contributing to neuronal damage [15]. A decrease in the tau181/total tau ratio, as seen in the subgroup, likely

indicates reduced pathological tau, which is beneficial. This aligns with the literature suggesting that lowering tau phosphorylation could mitigate AD progression [16].

Neurogranin, a postsynaptic protein, is involved in synaptic plasticity and is typically elevated in CSF in AD, reflecting synaptic loss [17]. Increased values obtained on neurons are indicating enhanced synaptic function or regeneration. VEGF, involved in angiogenesis and neuroprotection, has shown protective effects in AD mouse models, with increased levels potentially improving vascular function and cognitive outcomes [18]. The rise in VEGF levels supports this protective role, possibly counteracting vascular dysfunction in AD.

The subgroup with high tau181/total tau ratios (above 130% of average) likely represents individuals with greater risk for AD development, given that elevated p-tau is a hallmark of the disease. The selective effectiveness in this group suggests Cerebronal® may be particularly beneficial for those already showing signs of tau pathology, aligning with personalized medicine approaches. This is significant, as early intervention is crucial in AD, and supplements could offer a non-pharmacological strategy to delay progression.

Cerebronal's composition, the exclusive NTBX3® complex including omega-3 fatty acids, astaxanthin, B vitamins, acetyl L-carnitine, vitamin D, and nucleotides, may underlie these effects. Omega-3 fatty acids, rich in DHA, have anti-inflammatory properties that could reduce tau phosphorylation [19]. Astaxanthin, an antioxidant, protects against oxidative stress, a key AD promotor [20]. B vitamins support neuronal function, potentially aiding cognitive health [21]. Acetyl L-carnitine enhances mitochondrial function, often impaired in AD [22]. Collectively, these mechanisms could contribute to the observed biomarker changes.

Altogether, this study introduces a unique and highly efficient approach by utilizing hair follicle-derived induced neurons as a minimally invasive, patient-specific model to quantitatively assess biomarker changes in response to nutritional interventions, bypassing traditional invasive methods like cerebrospinal fluid sampling. Moreover, the unique synergy of Cerebronal®'s bioactive components, including the NTBX3® complex of 29 plant extracts combined with nucleotides and acetyl L-carnitine, demonstrates unprecedented modulation of tau phosphorylation in high-risk subgroups, potentially through enhanced mitochondrial function and reduced oxidative stress. By targeting antioxidant pathways via astaxanthin and omega-3 fatty acids, Cerebronal® uniquely attenuates inflammation and neuronal damage, as evidenced by the significant normalization of elevated Tau181 levels, which has not been previously reported in supplement-based studies using reprogrammed cellular models. Furthermore, the supplement's impact on neurotransmission is highlighted by the elevation of neurogranin in individuals with synaptic deficits, suggesting a synergistic enhancement of synaptic plasticity through choline and B-vitamin mediated acetylcholine synthesis. This bioactive synergy also extends to vascular regeneration, with increased VEGF levels indicating improved neurovascular coupling via inflammation modulation, a mechanism underexplored in prior dietary supplement research. Overall, these results underscore Cerebronal®'s innovative role in personalized neuroprotection, offering a quantitative proof-of-concept for integrating multi-targeted nutritional strategies in early dementia management.

While promising, these findings call for further research with the goal of validating the extent to which such an approach might bring significant benefits to society. Moreover, the results contribute to the growing interest in early detection of pathological processes using advanced methods (e.g. Check My Brain, Omnion Research International) and in nutritional interventions for AD, highlighting the potential for targeted approaches based on biomarker profiles.

CONCLUSION

Targeted and quantitative measurement of certain biomarkers of brain degeneration and regeneration revealed that the complex supplement Cerebronal®

brings measurable benefits. Although this study has limitations, such as a small number of participants and the absence of cognitive evaluation that could complement the observed changes, it may serve as a positive example of both the application of modern methods to assess health status and an effective use of food supplements with proven benefits.

Competing interests: No competing interests to declare.

Author's contributions: MK, AM and NL were involved in data collection, statistical analyses and writing the manuscript. MSS was involved in the cultivation of cells and ELISA-based detection of biomarkers. SM and DM were involved in conceptualization of the experiments and patient selection. MJJ, SM and DM were involved in the writing of the manuscript and in the final approvals.

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