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Title: Beneficial effects of a nano formulation of pomegranate seed oil, GranaGard®, on the cognitive function of Multiple sclerosis patients

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Introduction: Cognitive impairment is a common feature of MS patients and as for today no MS treatments, were shown to restore or prevent cognitive damage. GranaGard, a nano formulation of Pomegranate seed oil (PSO) comprising 80-90% of Punicic Acid (PA), was shown to prevent neuronal death in several mice models, such as EAE for MS, TgMHu2ME199K for genetic CJD and 5XFAD for AD.

Study aim: To examine the effects of GranaGard on the cognitive function of MS patients.

Study design: The study included 30 MS patients, of which 15 were given GranaGard for the first three months, then placebo for additional three months and 15 received placebo for the first three months, and GranaGard for the second period. All patients received GranaGard for additional six months. GranaGard was administrated in addition to the designated MS treatment. Patients follow up included: Short quality of life and fatigue questionnaires (SF-12, MFIS-5), Expanded Disability Status Scale (EDSS), Multiple Sclerosis Functional Composite (MSFC) and cognitive examinations: Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS), Symbol Digit Modalities Test (SDMT), California Verbal Learning Test (CVLT-II), Brief Visuospatial Memory Test (BVMT-R).

Results: There was a significant beneficial effect of GranaGard on the verbal testing in the relevant periods of treatment. This was reflected by an increase in z score from 0.891 to 1.415 in CVLT-II ($p=0.00825$, paired T test) in the period that patients received GranaGard, while there was no significant change in the placebo group. For the patients receiving GranaGard in the initial 3 months, the value of z score remained high ($z=1.415$) at the following three months, when these patients received placebo, suggesting a long-term effect.

Conclusion: This is the first study in which GranaGard, a brain targeted nano-formulation of PSO, was tested in humans. Our preliminary results suggest that while no side effects were observed, GranaGard administration to MS patients under diverse treatments may improve/maintain the cognitive status of these patients.