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Supplementation's effects of polyunsaturated fatty acids omega 3 in Alzheimer's disease animal models: a systematic review

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Abstract

Introduction: There are few randomized clinical trials that studied the effects of omega-3 polyunsaturated fatty acids (ω3 PUFA) on Alzheimer's Disease (AD). Some of these studies showed that patients with mild cognitive impairment have benefits in the treatment, but none of them showed significant improvement in cognitive function in patients with advanced or moderate AD. All these randomized clinical trials had relatively short duration of supplementation, therefore, one of the

reasons that may not have contributed to improvement in patients with moderate and advanced disease would be the short period of study. Animal studies offer better long-term controlled research possibilities, compared to clinical studies. **Methods**: Therefore, a systematic literature review was conducted that focused on the effects of the relevance of long--term ω3 PUFA supplementation on cognitive impairment and neuronal loss in AD animal models. **Results**: This systematic review showed that the long term, the ω3 PUFA supplementation decreased the ratio omega-6 / omega-3 reduced neuronal loss in experimental models of AD, as well as improved cognitive function. This effect was more evident in older mice compared to young mice, and compared with males females. **Conclusions**: These results indicate the importance of new clinical trials be conducted with long-term ω3 PUFA supplementation in patients with AD for possible associations correct dosages in the treatment.

Introduction

The Alzheimer's Disease (AD) is considered to be multifactorial and it has as a characteristic the synaptic loss and as consequence of this the cognitive and memory reduction (Peng *et al*., 2015), is characterized by signs of major oxidative stress and the loss of cholinergic cells (Mani *et al*., 2013; Persson *et al*., 2014). It is the leading cause of dementia and the most common neurodegenerative disease in elderly (Thomas *et al*., 2015).

The nonmodifiable risk factors for AD are well established and include advancing age, genetic factors and family history (Thomas *et al*., 2015; Swaminathan *et al*., 2014). The affected neurons in the brains of people with AD are considered cytologically heterogenic, because the disease is associated with a complex arrangement of neurotransmitters deficits (Peng *et al*., 2015; Anukulthanakorn *et al*., 2016). Adult hippocampal neurogenesis is closely associated with neuronal plasticity, cognitive function and the etiology of neurological dise-

ases such AD (Park *et al*., 2015; Kivipelto *et al*., 2001; Morris *et al*., 2003; Torres *et al*., 2014).

Epidemiological studies have shown that the number of people who have AD has increased substantially (Anukulthanakorn *et al*., 2016; Torres, 2014). As part of the causes remains unknown, the palliative care, as well as details on the treatment, should be carefully reinforced to help these people to have better quality of life (Koivisto, 2014; Chakrabarty, 2011). Some clinical and epidemiological studies have shown that malnutrition may increase the risk of developing AD (Thomas *et al*., 2015; Torres, 2014; Aberg *et al*., 2009; Bryan, 2004).

Studies with herbal medicines show the Efficacy of astragaloside IV was described in experimental models of Parkinson's disease, AD, cerebral ischemia and autoimmune encephalomyelitis, by improving motor deficits and/or neurochemical activity, especially antioxidant systems, reducing inflammation and oxidative stress (Costa *et al*., 2018).

Other cross-sectional and longitudinal studies have shown that increasing the intake of polyunsaturated fatty acids of the omega-3 series (ω3 PUFA) (Bryan, 2004; Fiol-de Roque, 2013; Hibbeln et al., 2007), was important to the brain's health, demonstrated an array of beneficial effects, particularly in improving cognitive function in patients with cognitive impairment (Persson et al., 2014; Thomas et al., 2015).

The ω3 PUFA are essential lipids that play an important role in the nervous system (NS), especially in the hippocampus region (Bryan, 2004). One of the main proposed explanations is based on the composition of cell membranes which possess high lipid concentration, therefore the maintenance of them may vital to the best development and function of the brain and NS (Thomas et al., 2015; Swaminathan et al., 2014; Bryan, 2004).

Among the ω3 PUFA, the docosahexaenoic acid (DHA; 22:6 n-3) is the most abundant in the brain, followed by eicosapentaenoic acid (EPA; 20:5 n-3) and are predominantly sourced from marine fish. The DHA and EPA can also be synthesised from α-Linole-

nic acid (ALA; 18:3 n-3), which is present in a number of green leafy plants, seeds, nuts, herbs, and oils, such as flaxseeds, walnuts, canola oil (Thomas *et al*., 2015; Hibbeln *et al*., 2007; Bourre *et al*., 1991).

The DHA since it is found abundantly in neuronal membranes and myelin sheath and acts by improving the membrane fluidity, as well as acts on nerve neurotransmission and signaling, through higher affinity to the receptors (Thomas *et al*., 2015; Yehuda *et al*., 1992; Tully *et al*., 2003). It is a modulation of the membrane lipid composition and structure, influences cellular homeostasis reversing the neurodegenerative process (Torres, 2014).

In addition, some studies suggest that 2-hydroxy-DHA (2OHDHA), DHA derived from, induced restoration of cell proliferation can be regarded as a major component in memory (Koivisto, 2014).

Therefore, the reduction of levels of DHA is associated to the cognitive impairment and people with AD have a reduction of DHA on the brain tissue, specifically in areas which measure learning and memory (Thomas *et al*., 2015; Anukulthanakorn *et al*., 2016).

Materials and methods

The search strategy and selection of original articles was using search filters in PubMed and Embase (Hooijmans *et al*., 2010; De Vries *et al*., 2011) databases.

Initially it was used the following descriptors to detect all the study with animals, which had been supplemented with ω3 PUFA and they had relation with Alzheimer's disease: used it separately, then searched together. Furthermore, the reference lists of relevant papers were selected, which were manually screened for potential search of articles published recently.

In the search, there was language restriction, since it was used only articles published in English. The studies selection was based on title and abstract and after this, the entire publication was evaluated and compared.

The Inclusion's criteria were for experimental studies, with use of supplementation with ω3 PUFA on Alzheimer's animal models.

And the following exclusion criteria were adopted: 1) If the article was not original; 2) If the omega-3 supplementation was associated to another nutritional component; 3) And in the absence of a control group (the control group had to be comparable to the experimental group, this is group supplemented with polyunsaturated omega 3 fatty acids).

Articles published between 2005 and 2010 and the reading was carried out these full articles that provided the necessary information in relation to all the criteria adopted in this systematic review.

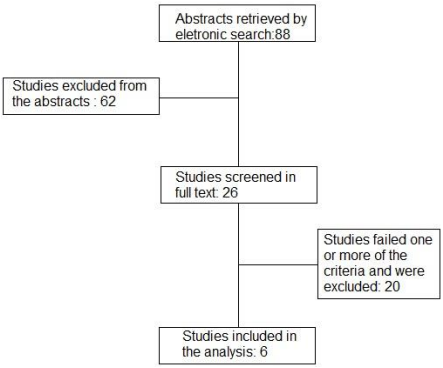
Results

Throughout the initial search criteria, applying descriptors based on the title and abstract, 88 articles, published over the last 10 years, were found. From those ones, 52 were found in the PubMed database and 36 in Embase.

The abstracts and articles were read and evaluated as to the subject matter as to the methodological composition, in order to the accurate extraction of the information.

Based on titles, the 88 articles were separated and shortly after the summaries were read, 62 studies were excluded, and hence 26 articles were fully read. From the collected studies, 20 of them have failed in at least one of the criteria and were excluded, therefore, at the end of all the analysis, 6 articles were selected. All this systematic analysis procedure was demonstrated in Figure 1.

Figure 1: Flow diagram of the data selection process.



There was a variation in most of the studies' aspects. It was emphasized that the animal models used for the studies were different, some studies (2) used only males in the research and others (4) used both males and females.

Regarding the supplementation using ω3 PUFA, 4 of the studies used solely DHA, in 1 study was used the EPA and DHA combination and the other one used the DHA in gum arabic solution.

The approach used to give this supplementation was described as "oral" or through the diet. The age to initiate the supplementation in the studies was between 2 to 19 months and the supplementation's interim varied greatly from study to study, between 3 to 13 months.

These particulars regarding the 6 selected studies were presented in Table 1. Due to the great variation in the studies' designs, the sub-group's analyses were made considering the gender, species used, and the supplementation's duration.

The collected data was concerning 3 aspects only: cognition, neuron loss /neuron degeneration as well the levels of ω3 PUFA in the brain. In 4 of the articles was demonstrated association to cognition (here defined as measure of learning or memory capacity) and in 5 of the articles there solely discussion of the levels of Omega 3 in the brain. Of these 5, it was observed that 4 of them used only the DHA as a manner to supplement the ω3 PUFA, which demonstrates that the DHA has important function in increasing brain levels of the experimental animal's brain tissue. All this systematic analysis procedure was demonstrated in Table 1.

Table 1: Supplementation, analysis and results of selected studies in this review.

Study	Species	Sex	Supplement	Route of administration	Start of Supplementation	Duration of Supplementation
Calon et al, 2005[22]	Mouse	M+F	DHA	Diet	17 months	3-5 months
Green et al, 2007[23]	Mouse	M+F	DHA	Diet	3 months	3, 6 or 9 months
Hashimoto et al, 2008[24]	Rat	M	DHA in gum arabic solution	Oral	20 weeks	12 weeks
Hooijmans et al, 2009[25]	Mouse	M	DHA+EPA	Diet	2 months	6 or 13 months
Lim et al, 2005[26]	Mouse	M+F	DHA	Diet	17-19 months	103 days/3-5 months
Perez et al, 2010[27]	Mouse	M+F	DHA	Diet	3 months	3 months

The neuron loss/ neuron degeneration was argued in 4 of the articles. The general analysis of studies that investigated the Omega-6/Omega-3 relation, demonstrated that this ratio has decreased under the supplementation with Omega-3 influence. In relation to the balance's change between the ω3 PUFA and Omega-6, the relative amount of Omega 6 has decreased whilst the relative amount

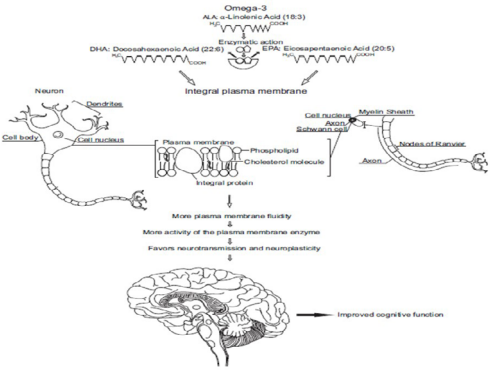
of Omega-3 increases in the experimental animal's models, which were supplemented with Omega-3. This systematic analysis of the entire studies' data demonstrates that the most relevant works were found in this area of research regarding published narrative and comments, which surely illustrates the benefit of conducting searches systematically.

Discussion

The clinical trials randomized using supplementation with ω3 PUFA are more numerous than those long-term studies. This is justified by the greater difficulty to achieve these long-term studies, since it could bring more publication.

Hence the importance of this systematic analysis with studies supplementation of omega 3 fatty acids in the long term. In these studies could be observed clearly from the results that when improved cognitive function mild (AD), and reduced neuronal loss / neurodegeneration in experimental models of (AD) and brain levels of (DHA) increased, especially in the hippocampus, in animal models of (AD). This show that the long-term supplementation with omega-3 suggests beneficial effects on (AD) related parameters in animal models. Action enginery and effects on the nervous tissue was outlined in Figure 2.

Figure 2: Chemical structure, metabolism of omega 3 and actions in nervous tissue.



In addition, analysis of subgroups revealed significant differences between gender and species. For example, the effect of supplementation with omega-3 on cognition appeared to be higher in older mice in compared to young mice, and the reduced amount of neuronal loss due to supplementation was higher in the mixed gen-

der group in compared with males alone.

Conclusion

Finally, it is important to investigate molecular aspects, that imply the (AD) and omega 3 that may influence these aspects, reflecting on cognitive manifestation / behavioral.

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