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Review Article

Repercussions of Linseed Oil in Morphofunctional Mechanisms of the Nervous System: A Systematic Review

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ABSTRACT
Flaxseed oil has been widely introduced in the diet as a rich source of omega-3 polyunsaturated fatty acids important for brain health. In light of this, the present study aims to discuss the main morphofunctional changes promoted by linseed oil in the nervous system. The research was developed through a systematic review of the literature, without meta-analysis, based on the following electronic data base: PubMed and Science Direct, based on the following descriptors: "linseed oil" and "nervous system". The inclusion criteria were: full text, search time (without delimitation), in vivo and in vitro studies, interventions (effects and benefits on the nervous system) published between 2007 and 2017 and language (English). It was verified from the articles included on the research, that the oil of flaxseed exerts diverse beneficial effects to the nervous system. Among them, it acts against oxidative stress and neurotoxicity, increases levels of neurotransmitters and DHA, acts on the development of astrocytes and has implications for growth, memory and locomotion in the hippocampus region. Linseed oil has numerous beneficial effects on the nervous system. Nevertherless, further studies are necessary on the theme, for example in the experimentals models of neurodegenative desorders.

KEYWORDS: Linseed oil; nervous system; morphofunctional changes.

INTRODUCTION

Among the essential polyunsaturated fatty acids there are the omega 3 fatty acids and omega 6 fatty acids, which participate in the synthesis of eicosanoids, a biological substance that takes part several physiological processes. Alpha-linoleic (omega-6) and alpha-linolenic (omega-3) acids are obtained through dietary supplementation, since the human body does not synthesize them [1].

An important long chain omega 3 fatty acid is docosahexaenoic acid, which is hardly found in the diet. This acid is extremely important because it is a lipid component in structures such as heart and brain. When the levels of decosahexaenoic acid are reduced in the central nervous system, some functions such as photoreception and cognition are deficient. Vegetable oils such as flaxseed oil present in their composition alpha-linolenic acid (ALA), which needs to be converted to eicosapentaenoic acid (EPA) and decosahexaenoic acid (DHA), to ensure to the organism obtain the benefits allied to the omega 3 long chain. However, the studies show that this conversion is very slow for DHA, which allows a deficiency of long chain omega 3 polyunsaturated fatty acids in vegetarian groups. In some neurodegenerative pathologies the levels of this acid are diminished, as in Parkinson's and Alzheimer's diseases, schizophrenia, among others [2].

One of the main nutrients that participate in neurological development is polyunsaturated long chain fatty acids, because the nervous system has a large amount of lipids, with omega 3 and omega 6 corresponding to the highest percentage of acids and DHA containing the richest amount in omega 3 in the brain region. DHA is very important for some brain functions, having influence on cognition, mental health, synapses and cell membrane, by increasing its fluidity [3].

Flaxseed is one of the richest vegetable substances in polyunsaturated fatty acids, the omega-3 fatty acid, contained in the seed oil. Supplementation with flax, whether in the form of an oil or an enriched source, can prevent some diseases, with this preventive benefit being attributed mainly to the omega 3 contained in the seed [1]. It is also identified as a source rich in industrial vegetable oil being the basis for the production of oil paints. It has become industrial oil due to its composition, rich in linolenic acid, which has high oxidation power, allowing a quick drying to the oil. Oxidation of the acid produces rancidity, which renders the oil inedible. It becomes edible, from the process of converting linolenic acid to linoleic acid. The percentage of supply of linseed oil in the world is a byproduct of flax fiber seeds [4].

Flaxseed oil, as mentioned above, has in its composition essential fatty acids of the omega-3 group after conversion of ALA. Studies have shown that animals supplemented with diets based on omega-3 essential fatty acids had beneficial and important brain effects, such as increased neurotransmitter concentrations, increased control of neuronal excitability, increased membrane fluidity and nerve growth in the brain. hippocampus, as well as increased cerebral flow, among other benefits. Flaxseed oil has been a focus of study in the nutritional field, due to its innumerable health benefits, its biological components and antioxidant effects [5]. The aim of this study was evaluate and discuss the main benefits of flaxseed oil in the nervous system, since it is still scarcely studied, through a systematic review of the literature.

MATERIALS AND METHODS

This study consisted of a systematic review of the literature, without meta-analysis, on the main benefits of linseed oil in the nervous system.

The research was developed through the following electronic databases: PubMed and Science direct. It was done through the following descriptors: "linseed oil" and "nervous system", from July to September 2017. The articles found by the defined search strategy were evaluated by more than an author. The inclusion criteria were strictly adhered to: full text, search time (without delimitation), in vitro and in vivo studies being rats as experimental models, interventions (effects and benefits on the nervous system), articles published between 2007 and 2017 and language (English). These strategies were designed with the aim of maximizing the results of the research, since a shortage of scientific base on the subject was identified. We excluded from this research, review articles, incomplete texts, and studies that had as basis other animals and humans, such as those that were not related to the effect of linseed oil on the nervous system, ie, those that did not meet the criteria inclusion criteria.

RESULTS

Through the selected descriptors "linssed oil" and "nervous system", in the chosen databases, PubMed and Science Direct, 22 and 55 articles were found, respectively, totaling 77 articles. A careful selection of articles was carried out through the analysis of the title and abstract, following the inclusion and exclusion criteria proposed for the study, of which articles were included and/or excluded in the research. After the evaluation, seven articles were selected from the PubMed database and none from the Science Direct database, according to the flowchart (Figure 1) described below and in Table 1, which describes the studies performed with linseed oil in the nervous system, as well as the methodologies used and main findings.

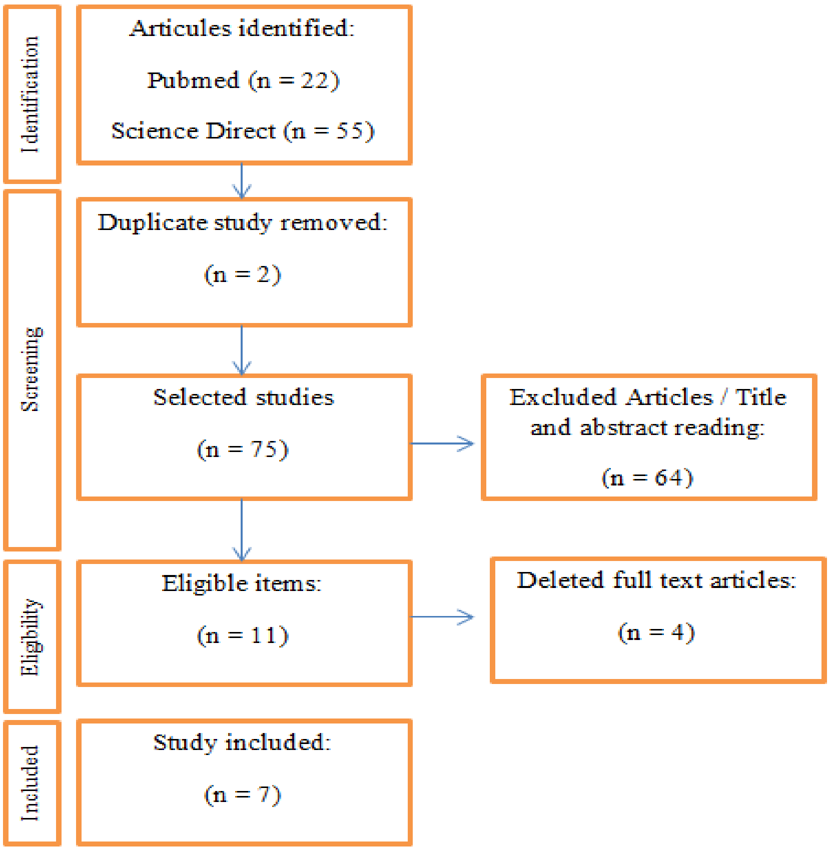

Fig. 1: Process of Identification and selection of articles. Source. Moher et. Al., 2009 [6]

Table 1: Studies investigating the effect of linseed oil on the nervous system in in vivo and in vitro models

Reference	Experimental model and purpose of the study	Experiment	Main findings
[7]	In vitro study - Glial cells - Development of astrocytes.	Separation of fatty acids by shaking some oils, such as mustard, sunflower, linseed, among others, with 2N NaOH. Acidified with HCL and isolated with chloroform. Glial cell culture of neonates for 5 days. They are then supplemented with the acids isolated from the cited oils. Flax, mustard and coconut have been supplemented in the culture of astrocytes. Immunocytochemistry was performed against GFAP.	It was concluded through these studies that the contribution of linseed oil fatty acids to maturation in astrocyte culture results in an important contribution of alpha linolenic acid in the morphogenesis and development of astrocytes.
[10]	Albino wistar rats exposed to lead - assessing toxicity and oxidative stress - levels of oxidative stress biomarkers and oxidizing agents were determined.	Total of 48 rats. 4 groups of 12 animals. Group I (control): 0.3 ml saline, Oral use. 100 micro liters of the same solution, intraperitoneal, 1h after. Group II: (lead) 20mg / kg, intraperitoneally, daily.	It was observed that with the increase of lead in some brain regions, there was an improvement of the lipid peroxidation with production of nitric oxide, increasing the cerebral toxicity, leading to a reduction in the activity of some of the aforementioned compounds.

		Group III: (linseed oil), 1000mg / kg, gavage. Group IV: (line oil + lead), 1000mg / kg, gavage. 100 micro liters of 20mg / kg bp + 1h after flaxseed. Duration: 5 days Lead: 20 mg / kg Linseed oil: 100mg / kg	Biomarkers of oxidative stress, and oxidizing agents such as GSH, GR, SOD, GST and GPx, released during the oxidation process, were decreased in the lead group and remained in the group treated with linseed oil.
[5]	Rats exposed to lead. To evaluate oxidative stress and neurotoxicity levels of neurotransmitters, antioxidants, sodium and potassium ions, ATPase and acetylcholinesterase, were determined	Total of 48 rats. 4 groups of 12 animals. Group I (control): 0.3 ml saline, Oral use. 100 micro liters of the same solution, intraperitoneal, 1h after. Group II: (lead) 20mg / kg, intraperitoneally, daily. Group III: (linseed oil), 1000mg / kg, gavage. Group IV: (line oil + lead), 1000mg / kg, gavage. 100 micro liters of 20mg / kg bp + 1h after flaxseed. Duration: 5 days Lead: 20 mg / kg Linseed oil: 100mg / kg	A protective effect on the activity of ions and enzymes (ATPase) was observed, bringing them to levels close to normal. Flaxseed also decreased the decline in Dopamine caused by exposure to lead in the brain regions evaluated (cortex, striatum, cerebellum and midbrain). The level of Norepinephrine was elevated after supplementation. Serotonin was increased in the cerebellum, region by which there was decrease of this neurotransmitter after induction the exposure to the lead. The AChE activity decreased in the presence of lead and was protected after treatment with flaxseed oil. Indicating neuroprotection against oxidative stress and neurotoxicity.
[12]	Male Albumin Rats - Investigate the supplementation of linseed oil in rats with streptozotocin-induced diabetes, assessing its effect on brain oxidative stress caused by diabates.	60 rats - 4 groups of 15. Group I - control - healthy rats - 1.2 ml corn oil / kg, orally. Group II - with flaxseed oil - healthy rats - 1.2ml of flaxseed oil / kg, orally. Group III - diabetic - diabetic rats - 1.2 ml of corn oil / kg, orally. Group IV - diabetic treated with linseed oil - 1.2 ml of linseed oil / kg oral. Experiment lasted 8 weeks. After that period were kept without diet and collected blood sample for analysis.	After estimating glucose, pentosidine and insulin levels, as well as some products of the oxidation process of proteins that are undesirable, such as advanced protein oxidation products (AOPPs), and delimited the total support of plasma antioxidant. It also estimated serotonin, dopamine and norepinephrine, and markers of oxidative stress such as nitric oxide (NO) and malondialdehyde (MDA), prior to the start of the experiments. A comparison was made between the groups and parameters studied, and it was evaluated that all of them, with the exception of serotonin that did not suffer any type of alteration in the groups mentioned, increased levels in the diabetic group and decreased those levels in the group treated with linseed oil . This suggests, like the study (5,9), that flaxseed has a protective effect against oxidative stress in the brain, in this case caused by streptozotocin-induced diabetes. (11)
[13]	Wistar rats - Females in pre-conception period, during pregnancy, breastfeeding and weaning.	18 rats - 3 groups. (after weaning) Control group: casein diet Group with linseed oil: casein supplemented with linseed	. It was observed at the end of the study that the group supplemented with linseed oil in the behavioral tests, took a shorter time to find the platform, since for locomotion there were no differences. The flax group

	Male rats for behavioral testing. They evaluated flaxseed oil as an exclusive source of lipids in the nervous system, analyzing the fatty acids composed in this oil, in the hippocampus region, and the functions of congnition and locomotion	Modified control group: casein with soybean oil. After 90 days, 3 females were submitted to 1 male coupling, and after pregnancy was detected, the diet was maintained until the end of breastfeeding. After weaning the pups received their mothers' diets. After 30 days, 8 males from each group underwent behavioral testing.	also had lower body mass and higher level of alpha linolenic acid. Decosehexaenoic acid was present in a greater amount in the hippocampal region, in perinatal and post-cleaning periods, resulting in an increased spatial memory performance of this group, due to the supplementation with linseed oil. (12)
[14]	Rats in the pre-conception and lactation period. The study evaluated the different proportions of fatty acids from the studied oils (flaxseed and flaxseed/fish) in brain development.	Diet with linseed oil. Diet with linseed oil / fish oil. Diet deficient in omega - 3 fatty acids. Diet period: 2 months pre-conception and during lactation. The groups supplemented with a diet rich in fatty acids were compared with the deficient diet.	Diet may be beneficial to promote early brain development when ingested during pregnancy and breastfeeding, where this effect seems to be linked to peroxisome proliferator expression activated gamma receptor, acting on the pathways of omega - 3 polyunsaturated fatty acids. It also increases the expression of some proteins such as glial fibrillary acidic protein, expressed in astrocytes which was discussed by (6), its maturation linked to flaxseed oil, and enzymes found in the neuron cytoplasm as the specific enolase in the neuron. (13)
[18]	Wistar rats - To evaluate the enrichment of the synaptic membranes with DHA, through linseed oil in the form of microemulsion.	2 groups - 6 rats in each group (random distribution) Group with diet based on linseed oil in the form of emulsion. Group with diet based on linseed oil in the form of microemulsion. Fed for 60 days through gavage, every day at 10:00 a.m. After the experiment period, the fasted rats were sacrificed for brain removal and subsequent analysis of the synaptic membrane.	Supplementation was done for 60 days and the two forms were compared, demonstrating that in the form of microemulsion, the conversion of ALA to DHA is increased in the cerebral synaptic membrane, also increasing sodium, potassium, ATPase and acetylcholine ions in the synaptic membrane, and some neurotransmitters such as Dopamine and Serotonin in the brain, as had already been observed in a previous study (reference 8), all these factors with brain health infuenciators. (17)

The articles excluded after refinement, as detailed above, were not related to the proposed study, which evaluated flaxseed oil from another perspective, with no relation to the nervous system. And there were still some where flaxseed oil was not the focus of the study, and only appeared at punctual moments in the discourse. Therefore, they were not included in this systematic review.

These studies were carried out in different countries, following the sequence: two in India and two Egypt, and one study in China, Spain and Brazil. All using as rats as a animal model.

DISCUSSION

Effect of linseed oil on the development of astrocytes

Studies have evaluated the effect of fatty acids of some dietary oils, including linseed oil, on the development of astrocytes, evaluating the effects of these oils on cell morphology [5]. Some dietary oils are consumed as major sources of fatty acids, and possess alpha linolenic acid (ALA) in its composition. It participates in the synthesis of docosahexaenoic acid (DHA), an acid that has been shown to be important in the vitality of astrocytes [7]. In addition, DHA also exerts an influence on normal and visual cognitive development [8].

It was concluded through these studies that the contribution of flaxseed oil fatty acids to maturation in astrocyte culture results in an important contribution of alpha linolenic acid in the morphogenesis this cell groups (Figure 2). Alpha-linolenic acid, which is the precursor of the synthesis of omega-3 fatty acids, and based on the benefits of docosahexaenoic acid, which can be formed from this type of acid, under the maturation of astrocytes [8], it is assumed that oils such as flaxseed, which are rich in ALA, are strongly linked to the development of astrocytes [7].

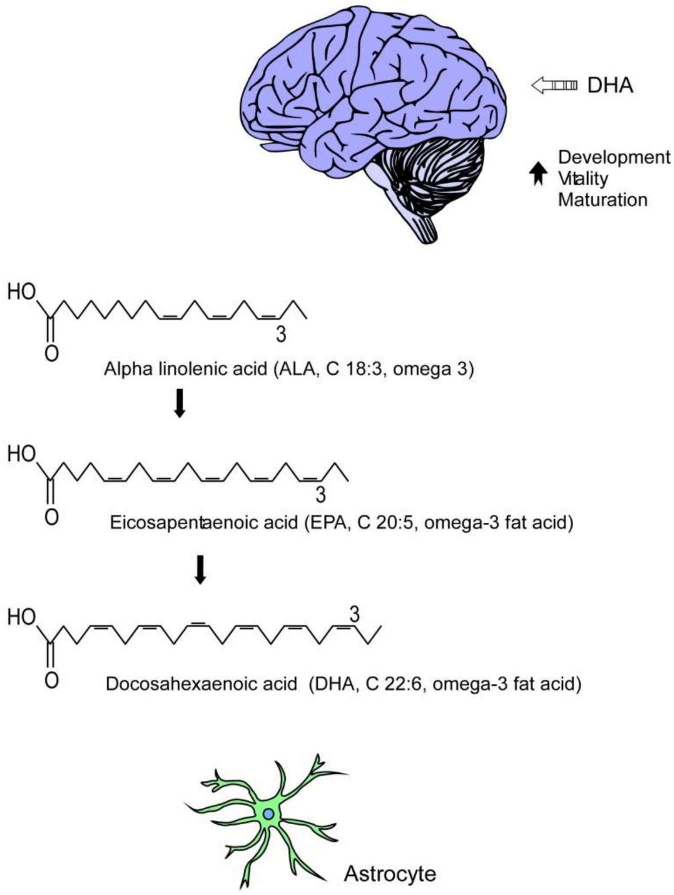

Fig. 2. Linseed oil enhances astrocytic response
Authoral figure, based in references [7] and [9]

Linseed oil against oxidative stress and neurotoxic effects induced by lead

Flax has been shown to be important for brain health, and some studies have pointed to its neuroprotective effect and the neurotoxicity caused by lead acetate [5]. The effect of prolonged exposure to lead modifies several tasks related to behavior in rats [10], but it is also extremely neurotoxic to the Central Nervous System, affecting strikingly regions such as cortex, hippocampus and cerebellum [5]. Studies confirmed that supplementation of flaxseed oil in rats acts as a neuroprotective agent against oxidative stress and neurotoxicity [5,10]. When it comes to oxidative stress in the nervous system, it generates harmful chemical side products, with the possibility of highlighting the reactive aldehydes, which invade healthy neighboring cells through their intact membranes [11].

In the first study in 2011, levels of lead, nitric oxide, lipid peroxidation, catalase activity (CAT), reduced glutathione (GSH), glutathione reductase (GR), superoxide dismutase (SOD), glutathione-s-transferase (GST)) and glutathione peroxidase (GPx). It was observed that with the increase of lead in some brain regions, there was an improvement of the lipid peroxidation with production of nitric oxide, increasing the cerebral toxicity, leading to a reduction in the activity of some of the aforementioned compounds [10].

In a subsequent study in the following year, levels of some similar compounds in the brain, such as lipid peroxidation, nitrite/nitrate (NO), and glutathione (GSH), and new ones such as norepinephrine (NE), dopamine and serotonin (5-HT), as well as sodium (Na^+), potassium (K^+),-ATPase and acetylcholinesterase (AChE) activity. Corroborating with a previous study in the sense that when there was cerebral increase of lead, nitric oxide and lipid peroxidation were also increased, decreasing levels of neurotransmitters, enzyme, protein and ions estimated at the beginning of the study [5].

With the supplementation of the rats with linseed oil, it was observed that the substances evaluated in the first study as GSH, GR, SOD, GST and GPx, which are biomarkers of oxidative stress, and oxidant agents released during the oxidation process, were decreased in the lead group and remained in the group treated with linseed oil [10]. In the later research wich evaluated Na^+, K^+, enzyme ATPase, GSH and AChE, and neurotransmitters such as DA, NE and 5-HT, a protective effect on the activity of ions and enzymes (ATPase) was observed, bringing them to levels close to normal. Flaxseed also reverted the decline in Dopamine levels caused by exposure to lead in the brain regions evaluated (cortex, striatum, cerebellum and midbrain). The level of Norepinephrine was elevated after supplementation. Serotonin was increased in the cerebellum, region in which there was decrease of this neurotransmitter after induction the exposure to the lead. The AChE activity decreased in the presence of lead and was protected after treatment with flaxseed oil [5].

Both studies found that five days' supplementation with flaxseed oil in rats exposed to lead had beneficial effects, such as reduction of oxidative and neurotoxic damage caused by lead and a decrease in the level of lead in the brain [5,10].

Flaxseed oil against oxidative stress caused by diabetes in the brain.

Flaxseed oil has also been shown to be useful in diseases such as diabetes for its usefulness in treating brain dysfunction caused by this disease. In order to evaluate this utility, the supplementation of this oil in rats with diabetes induced by streptozotocin, commonly used for this purpose, was investigated, evaluating its effect on the oxidative stress caused by this pathology. A comparative study was carried out between the groups; control, supplemented with linseed oil, with diabetes and those with diabetes and supplementation. And they did an estimate of glucose, pentosidine and insulin levels, as well as some products of the oxidation process of proteins that are undesirable, such as advanced protein oxidation products (AOPPs), and delimited the total support of plasma antioxidant. Serotonin, dopamine and norepinephrine, and markers of oxidative stress such as nitric oxide (NO) and malondialdehyde (MDA) were also estimated [12].

All parameters evaluated with the exception of serotonin, which did not suffer any type of alteration in the groups mentioned, increased levels in the diabetic group and decreased those levels in the group treated with flaxseed oil. This suggests that flaxseed has a protective effect against oxidative stress in the brain, in this case caused by streptozotocin-induced diabetes [12].

Linseed oil in the hippocampus: implications for growth, locomotor activity and spatial memory

The numerous effects of linseed oil on the central nervous system have been discussed. In this perspective, studies with rats evaluated this oil as an exclusive source of lipids in this system, analyzing the compound fatty acids in flaxseed oil, the hippocampus region and the functions of cognition and locomotion.

After selecting the groups based on diets, control group, flaxseed and modified control, rats were supplemented at different periods, before pregnancy, during pregnancy, during lactation and after. Following they went through maze behavioral tests to analyze the functions mentioned above. It was observed that the group supplemented with linseed oil in the behavioral tests, took a shorter time to find the platform, since for locomotion there were no differences. The flax group also had lower body mass and higher level of alpha linolenic acid. Decosehexaenoic acid was present in a greater amount in the hippocampal region, in perinatal and post-cleaning periods, resulting in an increased spatial memory performance of this group, due to the supplementation with linseed oil [13].

In a similar study, supplementation with flaxseed oil in pregnancy and lactation was also observed, corroborating the results for the benefits of this intake in these periods, for brain health, indicating that the diet may be beneficial to promote early brain development when ingested during pregnancy and breastfeeding, where this effect seems to be linked to peroxisome proliferator expression activated gamma receptor, acting on the pathways of omega-3 polyunsaturated fatty acids. It also increases the expression of some proteins such as glial fibrillary acidic protein, expressed in astrocytes, which was discussed by [7], its maturation linked to flaxseed oil, and enzymes found in the neuron cytoplasm as the specific enolase in the neuron [14].

Flaxseed oil enriches the brain's synaptic membrane with DHA and increases levels of neurotransmitters.

As previously discussed, flaxseed oil contains alpha-linolenic acid (ALA), which is a precursor to DHA, which is important for brain health. The ALA present in flaxseed oil showed an effect on neuroplasticity, as well as a neuroprotective effect. Its lack in the diet, can alter structures and functions of the membranes of the cells, as well as, cause dysfunctions in the brain [15, 16].

Studies have shown that this conversion can be increased when flaxseed is given in the form of a microemulsion rather than an emulsion. Supplementation was done for 60 days and the two forms were compared, demonstrating that in the form of microemulsion, the conversion of ALA to DHA is increased in the cerebral synaptic membrane (Figure 3), also increasing sodium, potassium, ATPase and acetylcholine levels in the synaptic membrane, and some neurotransmitters such as Dopamine and Serotonin in the brain, as had been observed in a previous study [9]. The neurotransmitter dopamine plays an important role in the synaptic connections in the brain, where a neural network forms through these connections. Dopamine transmits excitation and inhibition to other neurons through these synapses [17]. Becoming essential for the central nervous system. All of these factors have brain health influencers [18].

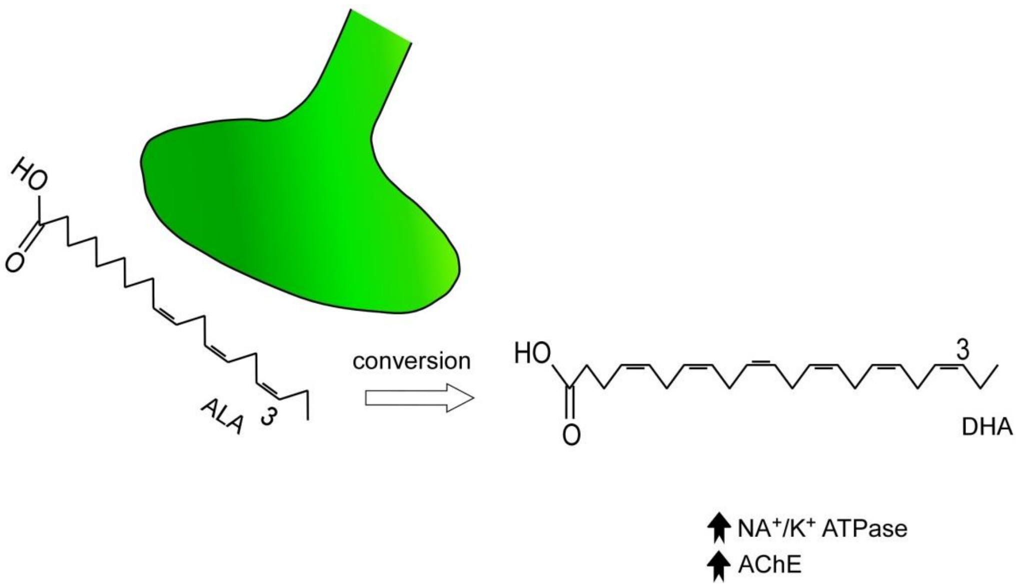

Fig. 3: Linseed oil enhances synaptic membrane with DHA and improves levels of neurotransmitters in the brain.
Authoral figure, based in the reference [9]

CONCLUSION

Linseed oil has numerous beneficial effects on the nervous system, such as the development of astrocytes, acts against oxidative stress, as well as acts positively on specific regions of the brain, such as the hippocampus, which it is linked to growth, memory and emotion. In addition, it acts on the neurotransmitters, increasing his brain levels. In fact, the linseed oil is gaining attention in research related to the nervous system around the world. In light of this, further studies are needed to characterize all the possible benefit action of this substance in the nervous system, for instance in the experimentals models of neurodegenerative desorders.

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CONFLICT OF INTEREST STATEMENT
The authors declare no conflict of interest in this review article.

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