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Preparing of Probiotic Tahini as A Novel Functional Food and Investigate its Effect along with Fish Oil against Alzheimer's Disease in Rats

Fatma Elzamzamy
Nutrition & food science, Faculty of specific Education, Mansoura University

ABSTRACT

Aluminum is a neurotoxic element naturally and abundantly occurs in the environment in drinking water, foodstuffs, Drugs, cosmetics. Evidence indicates that Probiotics can improve cognitive impairment through Gut-Brain Axis communication. Fish oil, sesame, wheat germ and olive oil were previously used in reducing the risk of Alzheimer disease. Objective of thhis study was to produce probiotic nutraceutical product by using *Bifidibacterium longum* in fermentation of Tahina made from Sesame seeds, wheat germ and olive oil and investigate its effect on rat experimental model of Alzheimer's disease induced by Alcl3. Methods: Product was chemically and sensory evaluated and biological evaluation was carried out as follows: Group 1: Normal control group, administered drinking water only; Group 2: (Neurogenerative) rats was orally administered by aluminum chloride (20 mg/kg b.w) daily for one month; Group 3: Rats given aluminum chloride and treated with Omega 3 fatty acids (FA) for six weeks; Group 4: Rats given aluminum chloride and treated with Omega 3 FA (7.0 g/ kg bw) + sesame Tahini; Group 5: Rats given aluminum chloride and treated with Omega 3 FA + fermented sesame Tahini. Memory and oxidative stress biomarkers were assessed represented as acetylcholin (Ach), (acetylcholinesterase) AchE, brain derived neurotrophic factor (BDNF). Amyloid β, GSH, GSSG, total protein (TPL) and Cholesterol. Results showed that AchE, Amyloid β peptide, GSSG and cholesterol levels were significantly elevated in AlCl3 treated group, however Ach, BDNF, GSH, TPL levels were declined. All previous markers were ameliorated by fish oil treatment. Addition of Tahina with fish oil was more effective than only fish oil treated group, however the most effective treatment was that included the malty therapeutic factors; Fish oil, and Sesame Tahina fermented by B.longum. In conclusion; Tahina composed of Sesame seeds, wheat germ and olive oil and fermented by B.longum might have anti neurodegeneration properties against AlCl3 induced Alzheimer's disease.

Keywords: *Bifidibacterium longum*, AlCl3, Alzheimer's disease, Omega-3 fatty acids, Sesame, Wheat germ, olive oil.

INTRODUCTION

Alzheimer' disease (AD) is a progressive neurodegenerative disorder that represents the major cause of dementia in the world today (Jicha and Carr 2010). The main risk factors for Alzheimer' disease represent age, age-related diseases such as diabetes, head trauma, cardiovascular disease, and obesity, and exposure to heavy metals such as iron, aluminum, zinc and copper (Ahmed *et al.*, 2014). Recent studies indicated that the pathogenesis of various neurodegenerative diseases, including Alzheimer's disease, Parkinson disease, amyotrophic lateral sclerosis and multiple sclerosis may involve the generation of reactive oxygen species (ROS), resulted in oxidative stress (Sun *et al.*, 2008). Aluminum chloride (AlCl3) is neurotoxic factor and has been referred to be one of the environmental agent causes neurodegenerative disease like Parkinson's disorders and Alzheimer's disease (Miguel *et al.*, 2015) by impairing cholinergic functions and inducing oxidative stresses. Aluminum leads to cognitive dysfunction as it can easily cross blood brain barrier through specific high affinity receptors (Anand *et al.*, 2017). Aluminum is the third most abundant element in the earth's crust and occurs naturally in the environment and drinking water, drugs, cosmetics, foodstuffs and processed foods and other utilized materials (Klotz *et al.*, 2017).

Probiotics are known as live microorganisms which have beneficial effects on the host's body if administrated in adequate amount (Bercik *et al.*, 2010 and Ohland *et al.*, 2013). Many recently investigations have pointed out that the gut microbiota seriously has a role to modulate the gut-brain axis, probably through neural system pathways immune and endocrine (Cryan and Dinan 2012). Probiotics may represent an effective and safe way of targeting central nervous system function (CNS). Number of preclinical studies has recorded that probiotics acting on gut-brain axis can affect brain behavior, development and function (Wang *et al.*, 2016). These direct relationships between Alzheimer's disease development and gut microbiota composition have been pointed at attractive opportunity for products development for gut microbiota modifying for prevention and/or treatment of Alzheimer's disease (Westfall *et al.*, 2019). From probiotic strains, *Bifidobacteriumlongum*1714™ (Zenflore), has been shown to affect in modulating central nervous system functions in both animals and humans. However preclinical studies proved that B. longum 1714™ has the ability to reduce stress-related behaviors (Savignac *et al.*, 2014 and Savignac *et al.*, 2015) and ameliorate cognitive functions and stress responses in healthy volunteers (Allen *et al.*, 2016).

Fatty acids are referred to be energy substrates and integral membrane components substantial for appropriate brain and neuronal function (Cole and Ma 2009).

Triglycerides are the source of energy metabolism in low glucose conditions, while polyunsaturated fatty acids are integral membrane lipids which maintain membrane associated proteins, protein complexes and neuronal membranes function and structure (Jicha and Markesbery 2010). PUFA incorporation increased membrane fluidity can increase the affinity and number of receptors in the synapse and ameliorate neurotransmission. This fluidity is essential in promoting synaptic plasticity that is important for memory, learning and other cognitive functions (Jicha and Markesbery 2010). PUFAs also are powerful antioxidants that are also easily oxidized in a nonenzymatic pattern under the excessive neuronal oxidative stresses (Montine and Morrow 2005). Sesame is known to have superior oxidative stability due to its content of good amounts of phytochemicals (Jeng *et al.*, 2005). Natural antioxidants have been reported as free radical scavengers, which can act against the risk of oxidative damage and can protect from apoptosis and cell death in different human diseases like neurodegneration cancer and hypertension (Zhao 2009). Wheat germ which is the byproducts of wheat milling have been reported to have antioxidant, lipid-lowering and anti-inflammatory activity attributed to its abundance content of different

phytonutrients and phytochemicals like Omega-3 fatty acids, phenolic compounds, tocopherols, dietary fibers and phytosterols (Kumar and Krishna, 2015). Olive oil may be safe for using for reductions of risk of Parkinson's and Alzheimer's diseases and improved the central nervous system as a sedative drug (Bawazir 2011). The present study aimed to develop probiotic nutraceutical product against Alcl3 brain toxicity by modification on Sesame Tihini (one of the most Egyptian common dishes). The modification included substitution of wheat flour and sun flour oil by wheat germ and olive oil and fermentation of the modified product using *bifidobacterium longum*.

MATERIALS AND METHODS

Materials:

Sesame (Sesamum indicum L), wheat germ, olive oil, Corn starch and corn oil were purchased from local market Cairo, Egypt. Fish oil (Omega-3 fatty acids capsules containing 120 mg of DHA and 180 mg of EPA plus vitamin E were obtained from pharmacy, Cairo, Egypt.

Strains: *Bifidibacterium longum* Reuter 1963 AL (ATCC 15707) was obtained from Microbioligical Resources Center (Mircen), Cairo, Egypt; Egypt Miccrobial Culture Collection (EMCC); (UNESCO/UNEP/WFCC). B. longum was activated on milk before utilization.

Chemicals: Aluminum Chloride (AlCl 3), Plate Count Agar media (REF 247940; Difico; Dickinson and Company sparks, France) was obtained from new technology Co, Cairo, Egypt. Vitamins, minerals, casein, choline chloride and cellulose were obtained from El-Nasr Pharm. and chem. Ind. Comp. Cairo, Egypt. All chemicals in this study were of analytical grade.

Preparing and fermentation: Dry Sesame seeds were cleaned from any residues, heated (in oven at 177°C for 7 min), cooled to 25°C and grinded by blender to get smooth butter and wheat germ was ground into powder. Ground sesame (58%) and wheat germ powder (21) were remixed with olive oil (21%) to produce Tahina mix. Half of Tahini mix amount was used to produce fermented Tahini by inoculation of 5% (v/v) single culture of *Bifidibacterium longum* Reuter 1963 activated in milk, and then incubated for 18 h at 37 ◦ C. The population of lactic acid bacteria was enumerated and pH was assessed at initial and during three days in refrigerator. Samples were stored at refrigerator for the first two days, and then stored at -20 ◦ C for further analysis and biological experiment. n3/n6 ratio in treatment diet was adjusted to be 1:4 in treated groups.

Chemical and microbial assessments: determination of the content of moisture, crude fat, crude protein and ash was carried out following the methods of AOAC (2000). Total carbohydrates content was obtained by difference as follows: Carbohydrates = 100 – (g/100g moisture + g/100g protein + g/100g fat + g/100g ash) (Gul and Safdar, 2009). Method of Sink *et al.* (1964) was followed Omega3 and Omega6 determination by methylation of fatty acids for GLC (gas liquid chromatography analysis). Viable cell count was enumerated on total plate count (TPC) according to standard procedures (APHA, 1992).

Experimental animals: forty nine adult male Albino rats (body weight of 250±10 g were obtained from the Animal House Agriculture Research Centre, Egypt. The animals were kept at a diffused light room with an ambient temperature (25±3.2°C) and a light cycle of 12 hrs.. Animals received standard laboratory diet and water adlibitum. Neurodegenerative impairment was induced by aluminum chloride administration of 20 mg/kg b.w daily for one month (Balawi *et al.,* 2018). Fish oil (Omega -3 fatty acids) was given orally by stomach tube as 0.4 g/kg bw (Songur *et al*., 2004). Two experiments were carried out. Rats were randomly divided into two main groups: Normal (n=14) received standard diet and drinking water and AlCl3 group (n=35): received standard diet and given aluminum chloride daily for one month. At the end of the first month, seven rats from normal group and seven rats from AlCl3 induced group were randomized selected and sacrificed. Brain was isolated for biochemistry assessment of neurotoxicity and oxidative stress markers (Experiment 1). For the experiment 2: the remaining seven normal rats and thirty AlCl3 induced rats were divided and administered as following: Group 1: control group, administered drinking water only for six weeks; Group 2: (Neurogenerative) rats were orally administered by aluminum chloride (20 mg/kg b.w) daily for six weeks; Group 3: Rats given aluminum chloride and treated with Omega 3 for six weeks for six weeks; Group 4: Rats given aluminum chloride and treated with Omega 3 (0.4 g/kg bw) + sesame Tahini (15% of the diet) for six weeks for six weeks; Group 5: Rats given aluminum chloride and treated with f (0.4 g/kg bw) + fermented sesame Tahini (15% of the diet) for six weeks.

Estimation of Biochemical parameters:

Brain tissue homogenate preparation: According to Tsakiris *et al.* (2004), Brain was dissected out after rats sacrificing and washed thoroughly with saline solution. Brain of each rat was instantaneously homogenized in solution containing Tris-Hcl at 50 mM, pH 7.4 and sucrose (300 mM). Tissue homogenates were centrifuged at 10000 rpm for 10 min at 4°C and the supernatant was separated for the following biochemical estimations out according to the methods of Lowry *et al.* (1951).

Brain derived neurotrophic factor (BDNF) was detected by ELSA technique according to the method of Barakat-Walter (1996). The assays based on monoclonal antibody specific for BDNF precoated onto a microplate. When the standard and samples are pipetted into the wells, any BDNF present is bound by the immobilized antibody. Then, the enzyme-linked monoclonal antibody specific for BDNF is added to the wells and, then washed to remove any unbound antibody enzyme and substrate solution was added to the wells. The color develops in proportion to the amount of BDNF bound in the initial step. The color development is stopped and the intensityof the color can be measured at 450 nm.

Brain Ach level :was measured calorimetrically according to the method of Oswald *et al.* (2008). The assay method is based on oxidation of choline to betaine via the intermediate betaine aldehyde. The reaction generates products which can be measured at 570 nm. Total Protein: Quantitative estimation of brain homogenate total protein was carried. Amyloid-β according was assessed by the method described with Wang *et al.* (1996). Acetycholinesterase activity was measured according to Magnottl *et al.* (1987). GSH was determined according to

Baker *et al.* (1990). The experimental protocol of the study was approved by the ethical committee of Faculty of Specific Education, Mansoura University.

Statistical analysis: Values were presented as means ± SD. the obtained data was statistically analyzed by SPSS program version 20.0. Tests used are the independent sample T test for two sample comparisons, one way analysis of variance test ($p<0.05$) was used for over two samples comparison and Duncans multiple range test.

Sensory evaluation: Organoleptic evaluation was carried out by fifteen randomized volunteers to score Tahini samples. Sensory aspects were expressed as taste, color, aroma, appearance and overall acceptability as reported by Zhang and Zhang (2007).

RESULTS AND DISCUSSION

Tahini is a popular ingredient in Mediterranean meal which widely used in Egypt. It is a condiment made mostly from toasted ground hulled sesame and served by itself (as a dip) or as a major ingredient in condiment or sauce. Sesame was used as the major component. The modification in this study included substitution of wheat flour and sun flower oil by wheat germ and olive oil then using *bifidobacterium longum* for fermentation to produce probiotic nutraceutical product.

Macronutrients composition and viable cells count of Tahini:

Table 1 shows the proximate macronutrient compositions of modified Tahini components. Results show that sesame seeds are rich source of protein (19.50±0.03g/100g), minerals expressed as ash content (4.50±0.02 g/100g), and good fats defined as polyunsaturated (25.49±0.04 g/100), monounsaturated (23.90±0.02 g/100g), where Omega 3 FA represents 263.00±10.00 mg/100g and Omega 6 FA recorded (25226.00±10.00 mg/100g). Wheat germ had an abundant content of protein (23.05±0.11 g/100g), minerals (4.80±0.02 g/100g), notable content of Omega 3 fatty acids (830.00±8.50 mg/100g) and Omega 6 fatty acids (6080.67±8.50 mg/100g). On the other hand olive oil has remarkable concentration of monounsaturated fatty acids (73.01±0.06 g/100g), Omega3 (761.00±4.62 mg/100g) and Omega6 (69760.33±4.62 mg/100g). These results are in agreement with Makinde *et al.* (2013) who reported high crude fat content for the raw sesame seeds (51.02±0.08 %) which is comparable to other oil seeds such as groundnut 46%, cotton seed 24% and linseed 40%, (Odunfa and Oyeyiola 1985). Ground sesame seeds are used to produce a smooth paste namely *tahini*, which common in Middle Eastern cuisine (Amoo *et al.*, 2004). Sesame oil concentration of monounsaturated fatty acids (MUFA) is higher than its content of saturated fatty acids (SFA), and the predominant fatty acid compositions are archidic, palmetic stearic, oleic and linoleic (Ahmad *et al.*, 2005). Olive oil (*Olea europaea L.*) a fundamental component of the Mediterranean diet is an essential source of mono-unsaturated fat. The beneficial effects of olive oil are attributed to both its high content of anti-oxidative substances and its high content of mono-unsaturated fatty acids (Serra-Majem *et al*., 2003).

Table 1. Macronutrients composition of Thini ingredientst

Composition	Sesame	Wheat germ	Olive oil
Moisture (g/100)	3.70±0.02	11.27±0.15	0.00±0.00
Ash (g/100)	4.50±0.02	4.80±0.02	0.00±0.00
Protein (g/100)	19.50±0.03	23.05±0.11	0.00±0.00
Total fat (g/100)	52.20±0.04	9.70±0.03	100.00±0.00
Saturated Fat (g/100)	9.08±0.07	2.00±0.11	13.82±0.13
Monounsaturated fats	23.90±0.02	1.60±0.02	73.01±0.06
Polyunsaturated fats	25.49±0.04	6.90±0.03	13.50±5.17
Omega3 FA mg	263.00±22.00	830.00±63.50	761.00±45.62
Omega6 FA mg	25226.00±800	6080.67±300.5	9760.33±49.62
Total carbohydrates (g/100)	20.10±1.00	51.23±0.18	0.00±0.00
Fiber (g/100)	11.63±0.25	15.20±0.20	0.00±0.00

Values in table represents means ± standard deviation

The changes pattern in the proximate macronutrint composition of Modified Tahini and Tihini fermented by *bifido bacterium longum* is presented in Table 2. Data shows slight decrease by fermentation in both of protein content from 16.16±0.02 to 16.11 ±0.19 and in total fats (from 53.21 ±0.20 to 53.31 ±0.53 in unfermented and fermented Tahini, respectively. However a significant decrease was observed in carbohydrates content from 22.43 ±0.04 to 18.20 ±0.44 and increase was found in moisture, ash and fat content. These changes due to the hydrolysis process of lipids, proteins and carbohydrates by both indigenous sesame enzymes and micro-organisms enzymes. Results showed that pH value deceased from 6.30 into 5.3. Viable count was 2.41± 0.001 in unfermented sample however it reached 5.055±0.012 after 18 hours fermentation with B.longum. A decrease in protein content was observed parallel to fermentation progresses indicated high nitrogen loss during the process (Makinde *et al*., 2013). Similar result was reported by Eze and Ibe (2005) who found that fermentation decrease the protein content from 3.35% to 2.29% of *B. Eurycoma* "Achi" (leguminous plant). High crude fat concentration was stated for sesame seeds and it was comparable to other oil seeds like groundnut, cotton seed and linseed (Odunfa and Oyeyiola 1985). High fat content of sesame seeds indicated it is a good source of oil for industrial nutritional purposes. The increase in fat concentration by fermentation is also in agreement with the findings on fermented products (Achinewhu (1986). The lower carbohydrate content in fermented sample was because of using carbohydrates as the main energy source during fermentation process. Ash content significantly increased ($p<0.05$) by fermentation of bean seeds oil which indicated the increase in some major minerals concentrations like calcium and phosphorus (El Faki *et al*., 1991). The same effect of fermentation was observed on locust bean component where ash content increased after fermentation by about 30% (Eka 1980). Changes observed in acidity may resulted from leaching out of the acidic constituents by hydrolysis of carbohydrates, proteins and lipids by both activated indigenous enzymes in the seeds as well as the fermentative micro-organisms enzymes. Acidity has been recorded to be responsible for flavor development and product stability (Okigbo 1890). Results showed that *Bifidibacterium longum* Reuter 1963 grew well in sesame/wheat germ/olive oil mix. This means that carbon

was in adequate amount which had been interpreted by Wankhede and Tharanathan (1976) who found that sesame seed contains glucose, galactose, fructose, raffinose, sucrose and stachyose.

Table 2. Macronutrients composition and viable cells count of fermented Tahini compared to unfermented:

Composition	Tahini	Fermented Tihini
	g/100	g/100
Moisture (g/100)	4.48 ±0.01	6.70** ±0.02
Ash (g/100)	3.60 ±0.02	4.50** ±0.04
Protein (g/100)	16.16±0.02	16.11 ±0.19
T. fat (g/100)	53.21 ±0.20	53.31 ±0.53
Saturated Fat (g/100)	8.58 ±0.01	9.47 ±0.59
Monounsaturated fats	29.37 ±0.32	30.07 ±0.24
Polyunsaturated fats	18.47 ±0.03	19.16** ±0.05
Omega3 mg	486.86 2.00	326.28 ±282.57
Omega6 mg	17958.32 ±1.00	17998.67** ±1.15
T. carbohydrates	22.43 ±0.04	18.20** ±0.44
Fiber (g/100)	9.59 ±0.63	8.07* ±0.35
pH	6.5	5.3
Viable cells (log CFU/mL)	2.41± 0.021	5.055±0.012

USFA: Unsaturated fatty acids; Values in table represents means ± standard deviation

Sensory aspects of unfermented and fermented sesame Tahini:

As shown in Table 3 no significant differences were found between Sesame Tahini and Tahini fermented by *bifidobacterium longum* concerning sensory aspects. Meanwhile data indicated slight differences were found between the two samples in sensory parameters expressed as taste (9.53 ±0.15 and 9.20 ± 0.20), color (9.90 ±0.17 and 9.43 ±0.12), aroma (9.90 ±0.17 and 9.23 ±0.25), consistency (9.67 ±0.29 and 9.33 ±0.29) and overall acceptability (9.61 ±0.09 and 9.22 ±0.05) for fermented and unfermented Tahini respectively. On the other hand a decrease was observed in appearance in fermented sample comparing to the unfermented one (9.07 ±0.12 and 8.90 ±0.17, respectively) which attributed to the quantity of mucus produced during fermentation.

El-Adawy and Mansour (2000) reported that a good-quality of Tahina could be obtained by roasting using hot air at 130˚C for 1h for dehulled sesame seeds. Sesame seed is also used for sesame oil production and as ingredient for many various food products, i.e. snacks such as fermented food (called *cabuk* in Indonesia), an *onde-onde*, and cookies. Like peanut and soybean, sesame seed can be processed to produce sesame milk (Shahidi 2006). However, Afaneh *et al.* (2011) reported that flavor produced during fermentation by lactic acid can cover the unfavored flavor of sesame milk. This phenomenon may be associated with the glucosidase activity produced by lactic acid bacteria. The lactic acid bacteria growth and activity depend on its ability to use nutrients in the fermentation media especially carbon source (Fitroti *et al*., 2015). This result was in agreement with those indicated that the higher antioxidant activity of sesame seeds is exhibited by the free sesaminol aglycon which exhibit a higher ability in radicals scavenging (Fitrotin *et al*., 2015). Also other researches pointed that a remarkable increase of total phenolic content leading to an increase of antioxidant activity (Banu e al., 2010) such as in fermentation of, , wheat dan rye, buckwheat, barley mixture by *Lactobacillus rhamnosus* and *Saccharomyces cerevisiae* separately (Coda *et al*., 2012).

Table 3. Effect of fermentation on sensory aspects of Sesame Tahini

Parameters	Tihini	Fermented Tihini
	g/100	g/100
Taste	9.53 ±0.15	9.20 ± 0.20
color	9.90 ±0.17	9.43 ±0.12
Aroma	9.90 ±0.17	9.23 ±0.25
Appearance	9.07 ±0.12	8.90 ±0.17
Consistency	9.67 ±0.29	9.33 ±0.29
OA	9.61 ±0.09	9.22 ±0.05

Values in table represents means ± standard deviation

Effect of aluminum chloride (AlCl3) treatment on neurotoxicity and oxidative stress markers:

As indicated in Table 4 Aluminum chloride (AlCl3) group showed significant (P>0.01) changes in levels of all neurotoxicity and oxidative stress markers. There was a marked decline in Ach (from 91.25 ±1.17 to 66.87 ±1.19µmol/mg protein), BDNF (from 107.61±2.87 to 77.26 ±1.71 pg/mg protein), GSH, GSH/GSSG Ratio (from 78.66±2.85 to 30.39±1.99) and TPL in AlCl3 group comparing to normal group. On the other hand, a significant increase (P>0.01) was observed for AlCl3 group in AchE (from 602.58 ±6.70 to 879.35 ±15.18 U/mg protein), Amyloid β peptide (from 12.26 ±0.36 to 32.83 ±2.05 pg/mg protein), GSSG (from 0.52 ±0.02 to 0.85 ±0.04 µ M/mg protein) and Chol (from 607.67 ±5.71 to 1054.10 ±39.88 µg/mg).

Studies have demonstrated that long-term exposure to Aluminum chloride (AlCl3) affects axonal transport causing structural abnormalities in synaptic cleft leading to memory impairment (Kawahara *et al*., 1994). Aluminum also induces inflammatory responses (Campbell *et al*., 2004), protein like neurofilaments, microtubules associated protein and Aβ of highly phosphorylated cytoskeletal implicated in Alzheimer's disease (Kawahara *et al*., 1994). AlCl3 exposure leads to lipid peroxidation referred to as MDA levels in rat cortex and hippocampus. The cellular antioxidant enzymes CAT, GPx, GR, SOD and GST levels were markedly declined in AlCl3 administered group ($p < 0.05$) comparing to that of normal group (Anand *et al*., 2017). Investigations Studies have recorded that AlCl3-induced memory impairment is correlated with oxidative stress elevation within the brain in mice and rats model (Prakash *et al*., 2013). This is because of reactive oxygen species continuous generation in brain during neuronal activity normal and metabolism. Moreover, many studies have shown that increased in the oxidative stress of amnesic rats resembled the clinical status of membrane lipid peroxidation and oxidative stress in demented patients (Lovell *et al*., 1995 and Marcus *et al*., 1998). AlCl3 treatment has significantly increased the generation reactive oxygen species, which resulted formation of lipid peroxidation as in the present study. Also reduced levels are found of the enzymes involved in antioxidant defense, viz. CAT, GPx, SOD, GR and GST in cortex and hippocampus of AlCl3 treated rats (Anand *et al*., 2017).

Our findings are also in concordance with those of Ali *et al.* (2014) which also documented a significant decrease in the activities of SOD and CAT in brain after Al treatment.

Table 4. Effect of aluminum chloride (AlCl3) administration on neurotoxicity and oxidative stress markers in rats (experiment 1)

Groups Exp. 1	Ach (µmol/mg protein)	AchE (U/mg protein	BDNF (pg/mg protein)	Amyloid β peptide (pg/mg protein)	GSH (µg /mg protein)	GSSG (µ M/mg protein)	GSH/ GSSG Ratio	TPL (µg/mg peotein	Chol (µg/mg)
Ng. cont.	91.25	602.58	107.61	12.26 ±0.36	41.14	0.52	78.66	1183.47	607.67
1cont.	±1.17	±6.70	±2.87		±0.70	±0.02	±2.85	±23.66	±5.71
AlZ . 1	66.87***	879.35***	77.26***	32.83**	25.78***	0.85***	30.39***	749.83***	1054.10***
	±1.19	±15.18	±1.71	±2.05	±0.58	±0.04	±1.99	±14.95	±39.88

***: Significant (P<0.05); **: high significant (P<0.01); ***: highly significant (P<0.001)**

Ach, AchE, BDNF and Amyloid β are markers of cognitive function and neurodegenerative disorder. As shown in Table 5; AlCl3 led to a significant decrease (p< 0.01) in both of Ach and BDNF level and a significant increase in both AchE activity and Amyloid β peptide accumulation. In present study three therapeutic treatments are administered to improve cognitive functions: fish oil, fish oil plus Sesame Tihini and fish oil plus Sesame Tahihni fermented by *bifidobacterium Longum.*

Effect of Sesame Tahina fermented by B.longum with fish oil treatment on Ach, AchE, BDNF and Amyloid β peptide in AlCl3 induced rats (experiment 2):

Results in Table 5 indicated that all neurodegenerative disorder markers improved in all treated groups as compared to AlCl3 group. Overall, fish oil improved cognitive impairment markers and fish oil with Sesame Tahini were more effective when administered together, however administration of fish oil with Sesame Tahini fermented by *bifidobacterium Longum* recorded the most ameliorative effect. Ach and BDNF levels significantly increased (p< 0.01) from 57.77±2.59 and 71.90±1.61 in positive control group into 71.07d±0.44 µmol/mg protein and 79.69b ±1.90 pg/mg protein in fish oil group. More increase was found in Ach and BDNF levels by administration of fish oil together with Sesame Tahini. Fish oil with sesame Tahini fermented by *bifidobacterium longum* recorded the highest Ach and BDNF levels (78.77 ±1.53 U/mg and 86.00 ±6.78 pg/mg, respectively). Concerning AchE and BDNP concentration, significant increases were observed in AlCl3 group compared to negative control. On the other hand a reduction was shown in both of AchE and Amyloid β peptide levels in all treated groups comparing to AlCl3 group (positive control) (947.80 ±16.24 U/mg protein and 37.06 ±1.05 pg/mg protein). Among all treatments, the most effective one which neutralize AchE and Amyloid β peptide levels was that combined Fish oil with Sesame Tahini and its fermentation by *bifidobacterium longum* (698.89 ±15.78 U/mg protein and 23.00 ±1.83 pg/mg protein respectively). PUFAs are converted into essential membrane phospholipids and second messengers that modulate neuronal health, inflammation, and oxidative stress (Russo 2009). The probiotic administration either during fetal life or postnatal period ameliorated the impaired behavioral functions. Probiotic supplementation has favorable effects on the brain functions correlated to the gut-brainmicrobiota axes and hypothalamicpituitary-adrenal (HPA) (Hadizadeh *et al*., 2019). Pervious study reinforced the significance of low n-3/n-6 ratios in dementia development in Japan (Jicha and Markesbery 2010). Beside that sesame seed oil has been considered a potent antioxidant source (Shad *et al*., 2007), wheat germ is abundant source of vitamin B. Low intake of vitamin B12, B6, folic acid and Omega-3 fatty acids is associated with the Alzheimer's disease and dementia incidence (Dangour *et al*., 2010). On the other hand, results showed that diet contains olive oil can induce new cells generation in the adult brain, and of strengthening the neural functions which become affected with age and in neurogenerative processes like Alzheimer's disease, as well as protect neurons from neural and oxidative damage (Tony *et al*., 2009). Treatment with probiotic and synbiotic formulations exhibits beneficial effects for promoting longevity through coordination activity on risk factors (Westfall *et al*., 2017).

For example, *Lactobacillus fermentum* NCIMB 5221 potently produces ferulic acid (FA), a phytochemical that reduces amyloid β fibril formulation, neuroinflammation and restores memory and learning deficits in AD animal models (Mori *et al*., 2013). There have also been indirect studies implicating the gut microbiota in managing risk factors to the neurological diseases development including inflammation, insulin resistance, oxidative stress, metabolic stress, and age-related cognitive decline (Burokas 2015). Previous findings from human studies indicate that the probiotic supplementation positively affect some of metabolic statuses and behavioral functions of Alzheimer's diseases patients (Akbari *et al*., 2016) and multiple sclerosis (Kouchaki *et al*., 2017). Current evidence suggests several mechanisms by which probiotics may affect brain functions. Probiotics underlie brain biochemistry, by affecting neuromodolators levels or neurotransmitters like BDNF, dopamine, serotonin and γ-aminobutyric acid (GABA), and acetylcholine. (Cryan and Dinan 2012), norepinephrine, the vagus and enteric nerves (Liu *et al*., 2016), the immune and endocrine systems and HPA axis (Desbonnet *et al*., 2010). The gut microbiota communicates with the brain via several neurological, endocrine and biochemical pathways through the gut-brain-axis a bidirectional communication system (GBA) (O'Mahony *e al.,* 2014). B. longum 1714™ in preclinical studies has been shown to reduce stress-related behaviors (Savignac *et al*., 2015) and improve cognitive function and stress responses in healthy volunteers (Allen *et al*., 2016).

Effect of Sesame Tahina fermented by B.longum with fish oil treatment on antioxidant status, TPL and cholesterol levels in AlCl3 induced rats (experiment 2)

Table 6 shows brain total protein, total cholesterol and antioxidant status represented as GSH, GSSG, GSH/ GSSG Ratio. As the results show, a significant elevation was occurred in brain total cholesterol for AlCl3 group as compared to the normal control. However significant

decrease was observed in all treated groups especially in group administered with fish oil with fermented Sesame Tahini (832.43 ±37.34 µg/mg). On the other hand AlCl3 group showed a significant decrease (P<0.05) in brain total protein (TPL) (703.67 6.97) as compared to negative control (1184.10 ±13.03 µg/mg). Antioxidant status significantly improved (P<0.05) as expressed by GSH/ GSSG Ratio which elevated from 25.22e ±0.98 in positive control to be 36.91d ±0.65 in group received fish oil, 46.93c ±2.80 in fish oil with Sesam Tahini and 58.52b ±4.06 by fish oil with fermented Tahini.

Table 5. Effect of Sesame Tahina fermented by B.longum with fish oil treatment on Ach, AchE, BDNF and Amyloid β peptide in AlCl3 induced rats (experiment 2)

Groups Exp: 2	Ach (µmol/mg protein)	AchE (U/mg protein	BDNF (pg/mg protein)	Amyloid β peptide (pg/mg protein)
Neg contro	91.81a ±0.86	603.30d ±3.49	105.05a ±1.90	12.08e ±0.25
AlCl3 group	57.77e ±2.59	947.80a ±16.24	71.90c ±1.61	37.06a ±1.05
Fish oil	71.07d ±0.44	761.80b ±9.83	79.69b ±1.90	29.21b ±1.12
Fish oil + Tihini	75.30c ±1.56	714.59c ±21.50	85.13b ±0.56	25.66c ±0.76
Fish oil + Fermented Tihini	78.77b ±1.53	698.89c ±15.78	86.00b ±6.78	23.00d ±1.83

The significance differences (p≤0.05) are indicated by different superscripts in each column.

Long chain PUFAs in the brain include Omega-6 PUFAs (eg, arachidonic acid [AA, 20:4n6]) and Omega-3 PUFAs, (eg, docosahexanoic acid [DHA, 22:6n3]). High cholesterol, total fats and saturated fats were linked to the increased risk of dementia, consumption of herring fish was inversely related to both all-cause dementia and more effectivly with incident AD (Jicha and Markesbery 2010). Sesame oil contains good amounts of sesamin,phenol, sesamolin and sesamol and relatively small amounts of tocopherol, which contribute to its superior oxidative stability (Jeng *et al*., 2005). Wheat milling and wheat germ is reported as lipid-lowering, anti-inflammatory and antioxidant activity which was attributed to its content of different phytonutrients and

phytochemicals such as Omega-3 fatty acids, phenolic compounds, tocopherols, dietary fibers and phytosterols (Kumar and Krishna, 2015 and Al-Okbi *et al*., 2014). Fermentation of sesame milk decreased the concentration of sesaminol triglucoside, which increased total phenolic content and scavenging activity of DPPH radical (Fitrotin *et al*., 2015). For the carbon source requirements, the bacteria obtain the glucose moietiex from synthesizing more β-glucosidase for obtaining sesaminol glucoside complex. The free sesaminol aglycon exhibit a higher scavenging radical's reactivity producing a higher antioxidant activity. This result was in agreement with other researches who pointed a significant increase of antioxidant activity by fermentation of cereal mixture (Coda *et al*., 2012 and Ulyatu Fitrotin *et al*., 2015).

Table 6. Effect of Sesame Tahina fermented by B.longum with fish oil treatment on antioxidant status, TPL and cholesterol levels in AlCl3 induced rats (experiment 2)

Groups Exp. 2	Chol (µg/mg)	TPL (µg/mg peotein	GSH (µg /mg protein)	GSSG (µ M/mg protein)	GSH/ GSSG Ratio
Neg contro	605.93e ±5.38	1184.10a ±13.03	41.56a ±0.34	0.55e ±0.02	75.15a ±2.51
AlCl3 group	1379.33a ±11.88	703.67e ±6.97	24.03e ±0.44	0.95a ±0.02	25.22e ±0.98
Fish oil	1008.23b ±33.32	817.83d ±14.66	27.94d ±1.24	0.76b ±0.03	36.91d ±0.65
Fish oil + Tihini	922.67c ±18.59	881.93c ±12.78	31.86c ±0.66	0.68c ±0.03	46.93c ±2.80
Fish oil + fermented Tihini	832.43d ±37.34	928.93b ±15.05	36.38b ±0.74	0.62d ±0.04	58.52b ±4.06

The significance differences (p≤0.05) are indicated by different superscripts in each column.

CONCLUSION

Probiotic action includes changes in metabolites as a microorganism activity and increase the count and survival of beneficial microorganisms in the gut. This study indicated that using *Bifidibacterium longum* in fermentation of Tahini infusion which composed of sesame, wheat germ, and olive oil may exhibit anti-neurotoxicity properties against AlCl3 induced Alzheimer's disease. Results suggest the mechanism of action of treatment with these food components almost was by their ability in oxidative stress reduction which decreases the concentration of βA peptide in the AD rat. This decrease of βA peptide concentration rat attenuates the acetylcholinesterase level which increases the acetylcholine concentration in the brain tissue. This study suggests that nutritional formula composed of sesame, wheat germ and olive oil and fermented by L. longum may exhibit anti-neurodegenerative properties through gut brain axes when received along with fish oil.

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إعداد طحينة متخمرة بالبكتيريا الحيوية كغذاء وظيفي جديد و دراسة تأثيرها على مرض الزهايمر مع المعاملة بزيت السمك في الفئران

فاطمة محمد الزمزمي

التغذية و علوم الأطعمة ، قسم الاقتصاد المنزلي، بكلية التربية النوعية جامعة المنصورة

الألومنيوم من المعادن السامة الموجودة طبيعيا و بوفرة في البيئة. أشارت الدلائل إلى قدرة المتخمرات بالبكتيريا الحيوية على تحسين القصور الإدراكي من خلال محور الاتصال بين الأمعاء و المخ. ثبتت فاعلية كل من زيت السمك و السمسم و جنين القمح و زيت الزيتون في خفض خطر الإصابة بالزاهايمر. هدفت الدراسة إلى إعداد مغذي علاجي باستخدام سلالة (*Bifido longum*) في تخمير الطحينة من السمسم و جنين القمح و زيت الزيتون و دراسة تأثيره ضد الزاهايمر المسبب بكلوريد الألومنيوم في الفئران. تم تقييم التركيبة حسيا و كيمائيا. وقيمت بيولوجيا كالتالي: المجموعة الأولى: الكنترول السالبة عوملت بماء الشرب؛ المجموعة الثانية: الكنترول المصابة المعاملة بكلوريد الألومنيوم (٢٠ملجم/يوم لمدة شهر. المجموعة الثالثة: المصابة و المعاملة بزيت السمك؛ المجموعة الرابعة: المصابة و المعاملة بزيت السمك مع الطحينة؛ المجموعة الخامسة: المصابة و المعاملة بزيت السمك مع الطحينة المتخمرة ب (*B. longum*). تم تقدير المؤشرات الحيوية للذاكرة و الحالة التأكسدية. أظهرت النتائج أن كلوريد الألومنيوم أدى إلى ارتفاع مستويات الأستيل كولين استريز و البيتا أميلويد بتيد و GSSG و الكوليسترول و انخفضت في المخ بشكل معنوي مستويات الأستيل كولين و BDNF و GSH و TPL. بينما تحسنت كل المؤشرات السابق ذكرها في المجموعة المعاملة بزيت السمك و تحست بدرجة أكبر في المجموعة المعاملة بزيت السمك مع الطحينة و سجلت أفضل النتائج من المجموعة المعاملة بزيت السمك مع الطحينة المتخمرة.

الخلاصة: أوحت الدراسة إلى أن التركيبة الغذائية المكونة ممن السمسم و جنين القمح و زيت الزيتون، و المتخمرة ببكتيريا البيفيدو *B.longum* قد يكون لها خصائص مضادة للقصور الإدراكي من خلال محور الاتصال بين الأمعاء و المخ عند تناولها مع زيت السمك.