Study Of The Benefits Of Omega-3 Oil From Fish

10th July 2018

More Reasons to Take Fish Oil



Clinical trials have focused on the cardiovascular benefits of omega-3 fatty acids derived from fish oil.

More recent data show the biological effects that **omega-3s** confer extend beyond cardiovascular issues and impact virtually every aspect of our health.

A meta-analysis published last year found that the *highest* consumption of **omega-3s** from fish oil was associated with a **14% reduction** in the risk of dying from *any* cause, compared to the lowest category of consumption.¹

Fish-oil benefits range from improved cognition to reduction of metabolic disorders. In this article, we describe recent studies that evaluate the effects of **fish oil** on **human** health and longevity.

Fish Oil Reduces Death Rates

In **2017**, a study was published that looked at the effects of **fish-oil** ingestion on human **mortality** rates. The implications from this report pertain to us all.

This analysis revealed a significant **14%** reduction in the risk of dying from *any* cause in the group consuming the highest, versus the lowest amount of omega-3 fish oil.

Epidemiologists call this "all-cause mortality," and it serves as an important metric in evaluating the overall effect of any intervention on lifespan.¹

To study the longer-term effects of omega-3 consumption, the researchers combined data from more than **one million subjects** whose fish and fish-oil consumption had been evaluated in 23

separate studies. A separate sub-analysis of six studies involving over **400,000** participants yielded information on **omega-3** fats from **fish**, specifically.¹

The researchers undertook this study to resolve lingering questions. Regular consumption of the major omega-3s in fish oil (EPA + DHA) has been found to reduce specific health threats like heart arrhythmias, and risk factors for disease and death, like endothelial dysfunction, lipid disturbances, and inflammation.²

Data on **all-cause mortality**, however, had been clouded by differences in study design and populations.¹

In this **2017** published analysis, researchers found a modest but significant **6%** reduction in all-cause mortality risk among those eating the most fish compared with those having the lowest fish consumption.

That's encouraging, but not everyone can manage the US government recommendations of two fish servings per week.³

For this reason, the researchers also evaluated the pooled data from six of the 23 studies relating to intake of the most relevant components of fish, the omega-3s **EPA** and **DHA**.¹

They found a greater impact against the risk of dying from *any* cause among those subjects consuming the most omega-3s. They showed that all-cause mortality risk was **14%** lower in those consuming the most EPA/DHA. This is more than double the figure calculated for fish consumption alone.¹

Further analysis revealed a **7%** reduction in overall risk of dying for each additional **200 mg** of **fish oil** consumed per day. ¹

From this enormous study, it is clear that people who consume more fish oil are at substantially lower risk of dying from any cause—a worthwhile finding in its own right.

But people die from specific causes that include cardiovascular disorders, obesity, diabetes, fatty liver, cancer, neurodegenerative diseases, and even major depression.

Underlying these degenerative conditions are pathological processes like **inflammation**, which we know is strongly associated with most age-related illnesses.

Here, we examine specific ailments that rob us of life quality, and, when severe enough, of life quantity as well.

The Many Benefits of Fish Oil

- Fish oils, rich in anti-inflammatory omega-3 fats, are wellestablished as cardioprotective nutrients.
- New evidence supports the benefits of omega-3 supplementation in a wide range of metabolic disorders, including obesity, diabetes, metabolic syndrome, and fatty liver disease.
- Omega-3s have been shown to help with depression and some types of dementia, perhaps largely through their powerful antiinflammatory effects.



- Even cancer, autoimmune disease, and kidney disorders are showing signs of responding favorably to omega-3 supplements.
- Like many inflammation-fighting strategies, fish oil may work best before major clinical disease is evident, highlighting the importance of prevention.

Anti-Inflammatory Fats

Studies have shown that omega-3 fatty acids like EPA and DHA have benefits in metabolic disorders such as obesity and diabetes, in neurological disorders like depression and Alzheimer's, as well as in cancer and autoimmune disease.

Omega-3s favorably affect this wide variety of conditions because they reduce the body's overall burden of **inflammation**.⁴

Chronic inflammation plays a key role in the diseases associated with aging.⁵ By combatting inflammation, omega-3s help us combat numerous age-related issues.

This is especially evident in metabolic disorders.

Metabolic Disorders

Metabolic syndrome is a cluster of conditions that includes some combination of high blood pressure, belly fat, high blood sugar, and abnormal lipid profiles. Metabolic syndrome is associated with a sharp increase of risk for heart disease, stroke, and diabetes.⁶

Omega-3 supplements show remarkable effects on the causes⁷—and the consequences— of **metabolic syndrome**. And one of the main driving forces behind metabolic syndrome is **obesity**. Obesity is a major risk factor for chronic illnesses, in large part because in obese individuals, fat cells churn out massive amounts of inflammation-inducing proteins (called cytokines).⁸ These cytokines play a role in promoting insulin resistance as well as two related diseases: non-alcoholic fatty **liver disease** and type II **diabetes**.⁹⁻¹²

Omega-3 oils from fish exert beneficial effects against obesity. A study published in **2016** concluded that fish-oil supplementation reduced waist circumference and blood pressure. ^{13,14} Human studies confirm that supplementing with omega-3s each day may reduce weight, body mass index (BMI), waist/hip ratio, and total fat mass—when combined with sensible diet and exercise. ^{15,16} Omega-3s achieve these effects through mechanisms that include enhancing oxygen consumption (indicating increased fuel-burning), boosting levels of the protective signaling molecule *adiponectin* (which mitigates insulin resistance and inflammation), and favorably modulating the gut microbiome. ¹⁶⁻¹⁸

Type II diabetes is a common consequence of obesity, because the inflammation it causes leads to insulin resistance, high blood sugar, and worsening obesity—creating a vicious cycle. ¹⁹ Fish-oil supplementation has been shown to have remarkable benefits in people with type II diabetes. These include decreasing fasting blood sugar, markers of sustained high blood sugar (e.g., hemoglobin A1c), and insulin requirements, as well as reducing episodes of dangerously low blood sugar. ^{14,20}

Fatty Liver Disease

Non-alcoholic fatty liver disease (NAFLD) is a major consequence of obesity and diabetes that occurs when fat cells build up in the liver causing massive amounts of inflammation.²¹ When not properly controlled, NAFLD can progress to **non-alcoholic steatohepatitis** (NASH), a more serious condition in which the liver becomes damaged or scarred.²²

Human studies show that supplementing with omega-3s has substantial benefits in patients with the condition.

For example, omega-3s have been found to significantly improve liver blood flow, decrease deposits of liver fat, reduce liver enzyme levels in the blood (a marker of liver-cell injury), and lead to significant increases in insulin sensitivity. ²³⁻²⁷

Studies also show an over **98% reduction** in the risk of having more severe liver disease after treatment with **DHA**, compared with a placebo group. ^{27,28}

One study also showed that omega-3 supplementation not only slowed the progression of NAFLD to NASH, but *reversed* some of the structural damage that had already occurred in the liver.²⁹ This is a landmark finding, considering this type of liver damage is considered *irreversible*.

Finally, in a **2017** review of clinical trials in which NAFLD was treated with fish-oil supplementation, 12 separate trials reported decreased **liver fat** or other markers of NAFLD. The authors suggested that longer treatment duration and improved patient compliance may be important factors for success.³⁰

NOT ALL FISH-OIL PREPARATIONS ARE THE SAME

Quality counts with all supplements, but it is especially critical when considering fish-oil.

The sources, processing, shipping, and final concentration of fish-oil products are critical indicators of their quality—and many fall short.

Before choosing a fish-oil supplement, you should consider two important categories:

- 1. Concentration and value
- 2. Freshness and sustainability

As an example, a readily-available commercial "natural fish oil" supplement sold at a major US pharmacy chain offers an enormous jar of softgels at an apparently reasonable price. But if you take a closer look, you'll see that the recommended dose contains **3,600 mg** of "total fish oil," but *only* **1,080 mg** of "total omega-3" fats—and there are no details about exactly how much EPA and DHA is present.

That means that just **30**% of the **daily dose** may be composed of beneficial EPA/DHA. To achieve desired intake, you would need to take six large softgels of the commercial product, risking fishy burps and other unpleasant side effects.

In addition, few major fish-oil distributors reveal their geographical location, the amount of processing, or the environmental impact of their operations. Many processing plants are located far from the harbors where fresh fish are brought. And few fish-oil operations are owned or operated by the fishermen who bring home the harvest, limiting their personal and ethical investments in the product.

A High-Quality Fish Oil

A partnership between a "lipid technology" expert and the two largest fishing companies in Chile (a major source of ocean fish worldwide) began active production in 2012. 56

This partnership has a pilot processing plant on-site, where fishing boats arrive daily to unload the freshest possible catch. The operation has a tiny ecological footprint and is in compliance with the very latest sustainable fisheries recommendations and certifications.



Achieving a high concentration of the active EPA and DHA forms of omega-3 is a *priority*. At their new seaside plant, fish are harvested, and oil is extracted with a process called *selective crystallization*, which achieves final concentrations of EPA and DHA in the range of 60% to 85% of the product (compared with 30% in most commercial products). This high concentration means smaller softgels are packed with more essential omega-3 fatty acids.

A daily dose of the new fish-oil composition (two softgels, taken twice daily with meals), provides a total **3,580 mg** of fish oil that supplies **1,500 mg** EPA and **1,000 mg** DHA. That means **70% of the daily dose is composed of the beneficial omega-3 fats**.

Omega-3s are a virtual necessity for sustaining heart, brain, and overall body health. Choose fish oil as selectively as you would choose fish for the table—wholesome, sustainably harvested, and fresh.

Powerful Brain Protection

Omega-3s play vital roles in the brain's very structure and function. ³¹⁻³⁴
The amount of omega-3 fats in the brain dwindles as we age. ³⁵ This leads to losses of brain *plasticity*, which is the ability to rapidly form new connections and retain new impressions and memories. ³³ It is also correlated with the diminished ability to use glucose as fuel—an energy deficit that has been linked to mental slowing and neurological impairment. ³⁴

The good news is that supplementing with omega-3s can favorably alter brain structure and function. And what's more, supplementing with omega-3s improves age-related conditions associated with inflammatory changes, such as memory impairments and Alzheimer's. 36-38

Combat Cognitive Impairment

Cognitive impairment, **dementia**, and **neurodegenerative diseases** are now recognized as inflammatory conditions.

The inflammatory changes may begin years—perhaps *decades*—before symptoms occur, ³⁶⁻³⁸ which reinforces the importance of supplementing with **fish oil** *before* major symptoms arise. For example, in a study of adults with mild cognitive impairment (which often precedes dementia), a daily supplement of **720 mg EPA/480 mg DHA** improved basic cognitive aptitude, speed of perception, and working memory compared with people receiving a **placebo**. ³⁹

In a study of healthy adults between 50 and 75 years old, supplementation with **1,320 mg EPA/880** mg DHAdaily for 26 weeks improved memory performance and ability to recall object locations.³⁸

Defeat Depression

Depression comes in many different forms and can arise for any number of reasons. Studies consistently show that omega-3s have benefits against depression, regardless of the cause.

For example, one study evaluated the impact of omega-3s on women with major depression associated with menopause. After eight weeks of taking **930 mg EPA/750 mg DHA** daily, the average standardized depression score fell by **56%**.

Even more compelling data from this same study showed that **45**% of participants reported feeling normal and experiencing no depression by the end of the trial.⁴⁰ As an added benefit, the women experienced a reduction in the frequency of hot flashes with supplementation.

In a more recent study, young adults with symptoms of depression were randomly assigned to take either a placebo or **1,000 mg EPA/400 mg DHA** daily. ⁴¹ After just 21 days, scores on the depression

inventory (a self-reported test that measures the *severity* of depression) fell significantly in supplemented subjects, but not in the placebo group. This study found that **67**% of the patients taking omega-3s "no longer met the criteria for being depressed."

A human and an animal study both suggest that the antidepressant effects of fish oil/omega-3s may be a result of **anti-inflammatory** activity. 42,43

Additional Omega-3 Benefits

The ability of omega-3 fats/fish oil to fight inflammation and induce favorable gene expressions in various tissues is now attracting the attention of researchers in virtually all fields of medicine.

Here are just a few highlights of some recent studies:

- **Cancer** is highly dependent on inflammatory changes for its promotion once a malignant cell has developed. Animal and human studies are revealing multiple ways in which omega-3 fats may quell cancer-associated inflammation, with far-reaching effects, in colorectal, breast, pancreatic, and blood system cancers. Ar-50
- Autoimmune diseases are a group of destructive disorders characterized by out-of-control inflammation and the immune system attacking one's own tissues. These conditions are relatively common in the elderly. Current treatments are less than adequate, often requiring high doses of immunosuppressive drugs. A pair of studies has shown impressive results of fish oil/omega-3 supplementation in patients with rheumatoid arthritis, a notoriously painful autoimmune disease for which conventional treatments can be highly problematic. 51-53
- Chronic kidney disease and its progression are closely linked with high levels of inflammation, making it an ideal target for omega-3 intervention. Two recent papers examined the role of omega-3 supplementation in chronic kidney disease. One showed that omega-3 fats were an effective solution for one of the most frustrating and even disabling symptoms of this disease, chronic itching, also known as pruritus. In another study, omega-3 supplementation resulted in longer *telomeres*, which are the longevity-associated chromosomal "clocks" that shorten as we age. 54,55

 These findings are almost certainly the tip of a very large iceberg, as researchers pursue potential benefits of omega-3s in a host of inflammation-related disorders.

Late-Breaking Findings On Omega-3 Fat

New studies on omega-3 fats suggest still more mechanisms of action—and ultimately more roles for these versatile nutrients in preventing disease and promoting good health. Here is a summary of their findings:

- The long-chain omega-6 and omega-3 fatty acids are molecular precursors of the endocannabinoid signaling compounds. ⁵⁷ The brain-signaling *endocannabinoid system* is involved in regulation of appetite, pain sensation, mood, and memory. ⁵⁸
- Blood levels of total omega-3 and DHA fats are strongly correlated
 with diversity in the *gut microbiome*, the intestinal community of microbes that is intimately
 related to our health.⁵⁹ Greater diversity is nearly always associated with greater disease
 resistance and better health.
- In a further exploration of relationships between omega-3 fats and the microbiome, researchers leveraged omega-3's anti-inflammatory powers, coupling them with a probiotic formulation to reduce the inflammation-induced side effects of chemotherapy.⁶⁰ In a group of patients with colorectal cancer, this approach improved quality of life, relieved some chemotherapy side effects, and reduced key markers of inflammation.

Summary

Peer-reviewed published studies continue to document the anti-inflammatory value of omega-3 supplements in some of the most troubling symptoms and chronic diseases of aging.

Metabolic disorders such as obesity, diabetes, and fatty liver are yielding to treatment with omega-3s, as are numerous brain-related conditions including major depression and dementia.

Evidence is also accumulating about roles of omega-3s in inflammation-dependent conditions such as cancer, autoimmune disease, and chronic kidney disease.

Supplementing with fish oil ensures you remain on the higher end of the omega-3 scale that has been shown to reduce human mortality rates, along with many chronic conditions of older age.

References

- Wan Y, Zheng J, Wang F, et al. Fish, long chain omega-3 polyunsaturated fatty acids consumption, and risk of all-cause mortality: a systematic review and dose-response meta-analysis from 23 independent prospective cohort studies. Asia Pac J Clin Nutr. 2017;26(5):939-56
- 2. Mozaffarian D, Wu JH. Omega-3 fatty acids and cardiovascular disease: effects on risk factors, molecular pathways, and clinical events. *J Am Coll Cardiol*. 2011;58(20):2047-67
- 3. Available at: https://health.gov/dietaryguidelines/2015/guidelines/. Accessed November 14, 2017
- Calder PC. Omega-3 fatty acids and inflammatory processes: from molecules to man. Biochem Soc Trans. 2017;45(5):1105-15
- 5. Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. *J Gerontol A Biol Sci Med Sci.* 2014;69 Suppl 1:S4-9
- 6. Available at: https://www.nhlbi.nih.gov/health/health-topics/topics/ms. Accessed November 6, 2017
- 7. Gao H, Geng T, Huang T, et al. Fish oil supplementation and insulin sensitivity: a systematic review and metaanalysis. *Lipids Health Dis.* 2017;16(1):131
- 8. Greenberg AS, Obin MS. Obesity and the role of adipose tissue in inflammation and metabolism. *Am J Clin Nutr.* 2006;83(2):461s-5s
- 9. Pi-Sunyer X. The medical risks of obesity. Postgrad Med. 2009;121(6):21-33
- 10. Must A, McKeown NM. The Disease Burden Associated with Overweight and Obesity. In: De Groot LJ, Chrousos G, Dungan K, et al., eds. *Endotext*. South Dartmouth (MA): MDText.com, Inc.; 2000
- 11. Monteiro R, Azevedo I. Chronic inflammation in obesity and the metabolic syndrome. Mediators Inflamm.2010;2010
- 12. Jung UJ, Choi MS. Obesity and its metabolic complications: the role of adipokines and the relationship between obesity, inflammation, insulin resistance, dyslipidemia and nonalcoholic fatty liver disease. *Int J Mol Sci.* 2014;15(4):6184-223
- 13. Howe P, Buckley J. Metabolic health benefits of long-chain omega-3 polyunsaturated fatty acids. *Mil Med*.2014;179(11 Suppl):138-43
- 14. Kurt A, Andican G, Siva ZO, et al. The effects of n-3 long-chain polyunsaturated fatty acid supplementation on AGEs and sRAGE in type 2 diabetes mellitus. *J Physiol Biochem.* 2016;72(4):679-87
- 15. Gonzalez-Acevedo O, Hernandez-Sierra JF, Salazar-Martinez A, et al. [Effect of Omega 3 fatty acids on body female obese composition]. *Arch Latinoam Nutr.* 2013;63(3):224-31
- 16. Haghravan S, Keshavarz SA, Mazaheri R, et al. Effect of Omega-3 PUFAs Supplementation with Lifestyle Modification on Anthropometric Indices and Vo2 max in Overweight Women. *Arch Iran Med.* 2016;19(5):342-7
- 17. Kaliannan K, Wang B, Li XY, et al. Omega-3 fatty acids prevent early-life antibiotic exposure-induced gut microbiota dysbiosis and later-life obesity. *Int J Obes (Lond)*. 2016;40(6):1039-42
- 18. Fisman EZ, Tenenbaum A. Adiponectin: a manifold therapeutic target for metabolic syndrome, diabetes, and coronary disease? *Cardiovasc Diabetol.* 2014;13:103
- 19. van Greevenbroek MM, Schalkwijk CG, Stehouwer CD. Obesity-associated low-grade inflammation in type 2 diabetes mellitus: causes and consequences. *Neth J Med.* 2013;71(4):174-87
- 20. Pohl M, Mayr P, Mertl-Roetzer M, et al. Glycemic control in patients with type 2 diabetes mellitus with a disease-specific enteral formula: stage II of a randomized, controlled multicenter trial. *JPEN J Parenter Enteral Nutr.* 2009;33(1):37-49
- 21. Milic S, Lulic D, Stimac D. Non-alcoholic fatty liver disease and obesity: biochemical, metabolic and clinical presentations. *World J Gastroenterol.* 2014;20(28):9330-7
- 22. Available at: http://www.merckmanuals.com/professional/hepatic-and-biliary-disorders/approach-to-the-patient-with-liver-disease/nonalcoholic-steatohepatitis-nash. Accessed November 14, 20147
- 23. Scorletti E, Bhatia L, McCormick KG, et al. Effects of purified eicosapentaenoic and docosahexaenoic acids in nonalcoholic fatty liver disease: results from the Welcome* study. *Hepatology*. 2014;60(4):1211-21
- 24. Sofi F, Giangrandi I, Cesari F, et al. Effects of a 1-year dietary intervention with n-3 polyunsaturated fatty acid-enriched olive oil on non-alcoholic fatty liver disease patients: a preliminary study. *Int J Food Sci Nutr*.2010;61(8):792-802

- 25. Pacifico L, Bonci E, Di Martino M, et al. A double-blind, placebo-controlled randomized trial to evaluate the efficacy of docosahexaenoic acid supplementation on hepatic fat and associated cardiovascular risk factors in overweight children with nonalcoholic fatty liver disease. *Nutr Metab Cardiovasc Dis.* 2015;25(8):734-41
- 26. Boyraz M, Pirgon O, Dundar B, et al. Long-Term Treatment with n-3 Polyunsaturated Fatty Acids as a Monotherapy in Children with Nonalcoholic Fatty Liver Disease. *J Clin Res Pediatr Endocrinol*.2015;7(2):121-7
- 27. Nobili V, Bedogni G, Alisi A, et al. Docosahexaenoic acid supplementation decreases liver fat content in children with non-alcoholic fatty liver disease: double-blind randomised controlled clinical trial. *Arch Dis Child.* 2011;96(4):350-3
- 28. Nobili V, Alisi A, Della Corte C, et al. Docosahexaenoic acid for the treatment of fatty liver: randomised controlled trial in children. *Nutr Metab Cardiovasc Dis.* 2013;23(11):1066-70
- 29. Li YH, Yang LH, Sha KH, et al. Efficacy of poly-unsaturated fatty acid therapy on patients with nonalcoholic steatohepatitis. *World J Gastroenterol*. 2015;21(22):7008-13
- 30. de Castro GS, Calder PC. Non-alcoholic fatty liver disease and its treatment with n-3 polyunsaturated fatty acids. *Clin Nutr.* 2017
- 31. Yassine HN, Braskie MN, Mack WJ, et al. Association of Docosahexaenoic Acid Supplementation With Alzheimer Disease Stage in Apolipoprotein E epsilon4 Carriers: A Review. *JAMA Neurol.* 2017;74(3):339-47
- 32. Bourre JM, Bonneil M, Clement M, et al. Function of dietary polyunsaturated fatty acids in the nervous system. *Prostaglandins Leukot Essent Fatty Acids*. 1993;48(1):5-15
- 33. Dyall SC, Michael GJ, Whelpton R, et al. Dietary enrichment with omega-3 polyunsaturated fatty acids reverses agerelated decreases in the GluR2 and NR2B glutamate receptor subunits in rat forebrain. *Neurobiol Aging*. 2007;28(3):424-39
- 34. Pifferi F, Dorieux O, Castellano CA, et al. Long-chain n-3 PUFAs from fish oil enhance resting state brain glucose utilization and reduce anxiety in an adult nonhuman primate, the grey mouse lemur. *J Lipid Res*. 2015;56(8):1511-8
- 35. Giusto NM, Salvador GA, Castagnet PI, et al. Age-associated changes in central nervous system glycerolipid composition and metabolism. *Neurochem Res.* 2002;27(11):1513-23
- 36. Thomas J, Thomas CJ, Radcliffe J, et al. Omega-3 Fatty Acids in Early Prevention of Inflammatory Neurodegenerative Disease: A Focus on Alzheimer's Disease. *Biomed Res Int.* 2015;2015:172801
- 37. Robinson JG, Ijioma N, Harris W. Omega-3 fatty acids and cognitive function in women. *Womens Health* (Lond). 2010;6(1):119-34
- 38. Kulzow N, Witte AV, Kerti L, et al. Impact of Omega-3 Fatty Acid Supplementation on Memory Functions in Healthy Older Adults. *J Alzheimers Dis.* 2016;51(3):713-25
- 39. Bo Y, Zhang X, Wang Y, et al. The n-3 Polyunsaturated Fatty Acids Supplementation Improved the Cognitive Function in the Chinese Elderly with Mild Cognitive Impairment: A Double-Blind Randomized Controlled Trial. *Nutrients*. 2017;9(1)
- 40. Freeman MP, Hibbeln JR, Silver M, et al. Omega-3 fatty acids for major depressive disorder associated with the menopausal transition: a preliminary open trial. *Menopause*. 2011;18(3):279-84
- 41. Ginty AT, Conklin SM. Short-term supplementation of acute long-chain omega-3 polyunsaturated fatty acids may alter depression status and decrease symptomology among young adults with depression: A preliminary randomized and placebo controlled trial. *Psychiatry Res.* 2015;229(1-2):485-9
- 42. Rapaport MH, Nierenberg AA, Schettler PJ, et al. Inflammation as a predictive biomarker for response to omega-3 fatty acids in major depressive disorder: a proof-of-concept study. *Mol Psychiatry*. 2016;21(1):71-9
- 43. Dang R, Zhou X, Tang M, et al. Fish oil supplementation attenuates neuroinflammation and alleviates depressive-like behavior in rats submitted to repeated lipopolysaccharide. *Eur J Nutr.* 2017
- 44. Rakoff-Nahoum S. Why cancer and inflammation? Yale J Biol Med. 2006;79(3-4):123-30
- 45. Yum HW, Na HK, Surh YJ. Anti-inflammatory effects of docosahexaenoic acid: Implications for its cancer chemopreventive potential. *Semin Cancer Biol.* 2016;40-41:141-59
- 46. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell. 2010;140(6):883-99
- 47. Molfino A, Amabile MI, Monti M, et al. The Role of Docosahexaenoic Acid (DHA) in the Control of Obesity and Metabolic Derangements in Breast Cancer. *Int J Mol Sci.* 2016;17(4):505
- 48. Chagas TR, Borges DS, de Oliveira PF, et al. Oral fish oil positively influences nutritional-inflammatory risk in patients with haematological malignancies during chemotherapy with an impact on long-term survival: a randomised clinical trial. *J Hum Nutr Diet*. 2017
- 49. Djuric Z, Aslam MN, Simon BR, et al. Effects of fish oil supplementation on prostaglandins in normal and tumor colon tissue: modulation by the lipogenic phenotype of colon tumors. *J Nutr Biochem.* 2017;46:90-9
- 50. Park M, Kim H. Anti-cancer Mechanism of Docosahexaenoic Acid in Pancreatic Carcinogenesis: A Mini-review. *J Cancer Prev.* 2017;22(1):1-5
- 51. Dawczynski C, Dittrich M, Neumann T, et al. Docosahexaenoic acid in the treatment of rheumatoid arthritis: A double-blind, placebo-controlled, randomized cross-over study with microalgae vs. sunflower oil. *Clin Nutr.* 2017
- 52. Sorto-Gomez TE, Ortiz GG, Pacheco-Moises FP, et al. Effect of fish oil on glutathione redox system in multiple sclerosis. *Am J Neurodegener Dis.* 2016;5(2):145-51
- 53. Veselinovic M, Vasiljevic D, Vucic V, et al. Clinical Benefits of n-3 PUFA and -Linolenic Acid in Patients with Rheumatoid Arthritis. *Nutrients*. 2017;9(4)
- 54. Barden A, O'Callaghan N, Burke V, et al. n-3 Fatty Acid Supplementation and Leukocyte Telomere Length in Patients with Chronic Kidney Disease. *Nutrients*. 2016;8(3):175

- 55. Panahi Y, Dashti-Khavidaki S, Farnood F, et al. Therapeutic Effects of Omega-3 Fatty Acids on Chronic Kidney Disease-Associated Pruritus: a Literature Review. *Adv Pharm Bull.* 2016;6(4):509-14
- 56. Golden Omega. Golden Omega Direct to the Source Corporate proprietary literature 2016
- 57. Dyall SC. Interplay Between n-3 and n-6 Long-Chain Polyunsaturated Fatty Acids and the Endocannabinoid System in Brain Protection and Repair. *Lipids*. 2017;52(11):885-900
- 58. Manzanares J, Julian M, Carrascosa A. Role of the cannabinoid system in pain control and therapeutic implications for the management of acute and chronic pain episodes. *Curr Neuropharmacol.* 2006;4(3):239-57
- 59. Menni C, Zierer J, Pallister T, et al. Omega-3 fatty acids correlate with gut microbiome diversity and production of N-carbamylglutamate in middle aged and elderly women. *Sci Rep.* 2017;7(1):11079
- 60. Golkhalkhali B, Rajandram R, Paliany AS, et al. Strain-specific probiotic (microbial cell preparation) and omega-3 fatty acid in modulating quality of life and inflammatory markers in colorectal cancer patients: A randomized controlled trial. Asia Pac J Clin Oncol. 2017