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Omega 3 Fatty Acids- Clinical Implications

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Abstract: Omega-3 fatty acids are polyunsaturated fatty acids (PUFA) that have in common a final carbon–carbon double bond in the n−3 position; that is, the third bond from the methyl_end of the fatty acid. It can be obtained from various sources such as marine source, vegetable and food sources but sometimes they are not enough to maintain levels of these fatty acids due to some factors like absence of desaturase an enzyme necessary for conversion ALA to EPA and DHA. So to overcome these problems different formulations containing omega 3 fatty acids in the form of tablet, capsules, oils and gels, are available. The review mainly highlights clinical implications of Omega 3 fatty acids. Higher dietary omega-3 fatty acid intakes are associated with reductions in cardiovascular disease risk, cancer, skeletal disorders, problems in pregnancy and child development, diabetes, central nervous system disorders etc.With increasing knowledge about omega 3 fatty acids and its importance in health, it has received increasing awareness in global food companies that launches products enriched in omega-3 fatty acids
Key words: Omega 3 Fatty Acids, Clinical Implications.

Introduction

Omega-3 fatty acids are a family of unsaturated fatty acids that have in common a final carbon–carbon double bond in the n−3 position; that is, the third bond from the methyl_end of the fatty acid. These are also known as polyunsaturated fatty acids (PUFAs), Omega-3 fatty acids are considered essential fatty acids to human health, but cannot be manufactured by the body. For this reason, omega-3 fatty acids must be obtained from other sources such as source, vegetable and food. Omega-3 fatty acids play a crucial role in brain function as well as normal growth and development. Omega-3 fatty acids reduce inflammation and help prevent risk factors associated with chronic diseases such as heart disease, cancer, and arthritis. These essential fatty acids are highly concentrated in the brain and appear to be particularly important for cognitive (brain memory and performance) and behavioral function. Infants who do not get enough omega-3 fatty acids from their mothers during pregnancy are at risk for developing vision and nerve problems. It is important to maintain an appropriate balance of omega-3 and omega-6 (another essential fatty acid) in the diet, as these two substances work together to promote health. Omega-3 fatty acids help reduce inflammation, and most omega-6 fatty acids tend to promote inflammation. An inappropriate balance of these essential fatty acids contributes to the development of disease while a proper balance helps maintain and even improve health. A healthy diet should consist of roughly 2 - 4 times more omega-6 fatty acids than omega-3 fatty acids. It is found that this imbalance is a significant factor in the rising rate of inflammatory disorders.[1]

History

Although omega-3 fatty acids have been known as essential to normal growth and health since the 1930s,

awareness of their health benefits has dramatically increased in the past few years. New versions of ethyl esterized omega-3 fatty acids, such E-EPA and combinations of E-EPA and E-DHA have drawn attention as highly purified and more effective products than the traditional ones. In 1963 it was discovered that the n−6 arachidonic acid was converted by the body into pro-inflammatory agents called prostaglandins.[3] By 1979 more of what are now known as eicosanoids were discovered: thromboxanes, prostacyclins and the leukotrienes. The eicosanoids, which have important biological functions, typically have a short active lifetime in the body, starting with synthesis from fatty acids and ending with metabolism by enzymes. However, if the rate of synthesis exceeds the rate of metabolism, the excess eicosanoids may have deleterious effects. It is found that n−3 is also converted into eicosanoids, but at a much slower rate. Eicosanoids made from n−3 fats are often referred to as anti-inflammatory, but in fact they are just less pro-inflammatory than those made from n−6 fats. If both n−3 and n−6 are present, they will "compete" to be transformed, so the ratio of n−3:n−6 directly affects the type of eicosanoids that are produced.

This competition was recognized as important when it was found that thromboxane is a factor in the clumping of platelets, which leads to thrombosis. The leukotrienes were similarly found to be important in immune/inflammatory-system response, and therefore relevant to arthritis, lupus, and asthma. These discoveries led to greater interest in finding ways to control the synthesis of *n*−6 eicosanoids. The simplest way would be by consuming more *n*−3 and fewer *n*−6 fatty acids.[3]

Chemistry

There are three major types of omega 3 fatty acids that are ingested in foods and used by the body: alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Once eaten, the body converts ALA to EPA and DHA, the two types of omega-3 fatty acids more readily used by the body. The term *n*−3 (also called ω−3 or omega-3) signifies that the first double bond exists as the third carbon-carbon bond from the terminal methyl end (*n*) of the carbon chain. Fig-1, 2 and 3.

These three polyunsaturates have 3, 5 or 6 double bonds in a carbon chain of 18, 20 or 22 carbon atoms, respectively. All double bonds are in the cis-configuration, i.e. the two hydrogen atoms are on the same side of the double bond.[1, 4]

Most naturally-produced fatty acids (created or transformed in animalia or plant cells with an even number of carbon in chains) are in *cis*-configuration where they are more easily transformable. The *trans*-configuration results in much more stable chains that is very difficult to further break or transform, forming longer chains that aggregate in tissues and lacking the necessary hydrophilic properties. This *trans*-configuration can be the result of the transformation in alkaline solutions, or of the action of some bacterias that are shortening the carbonic chains. Natural transforms in plant or animal cells more rarely affect the last *n*−3 group itself. However, *n*−3 compounds are still more fragile than *n*−6 because the last double bond is geometrically and electrically more exposed, notably in the natural *cis* configuraon

The human body cannot synthesize *n*−3 fatty acids de novo, but it can form 20-carbon unsaturated *n*−3 fatty acids (like EPA) and 22-carbon unsaturated *n*−3 fatty acids (like DHA) from the eighteen-carbon *n*−3 fatty acid α-linolenic acid. These conversions occur competitively with *n*−6 fatty acids, which are essential closely related chemical analogues that are derived from linoleic acid. Both the *n*−3 α-linolenic acid and *n*−6 linoleic acid are essential nutrients which must be obtained from food. Synthesis of the longer *n*−3 fatty acids from linolenic acid within the body is competitively slowed by the *n*−6 analogues. Thus accumulation of long-chain *n*−3 fatty acids in tissues is more effective when they are obtained directly from food or when competing amounts of *n*−6 analogs do not greatly exceed the amounts of *n*−3.[3, 4]

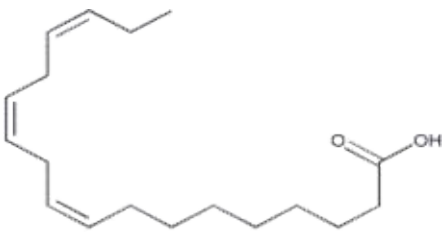

Figure 1 Chemical structure of alpha-linolenic acid, an essential *n*−3 fatty acid.

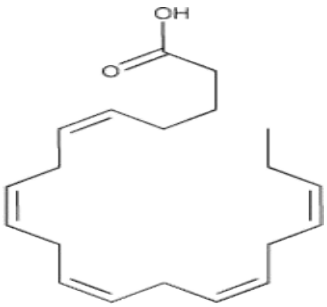

Figure 2-Chemical structure of Eicosapentaenoic acid, essential n-3 fatty acid.

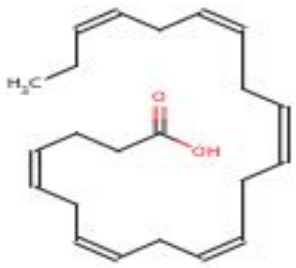

Figure 3-Chemical structure of Docosahexaenoic acid, essential n-3 fatty acids

Figure 4-Botanical sources of omega 3- flax seeds

Table 1- Botanical source of omega 3 fatty acid

Common name	**Alternative name**	Linnaean name	**% *n*−3**
Chia	chia sage	Salvia hispanica	64
Kiwifruit	Chinese gooseberry	Actinidia chinensis	62
Perilla	shiso	Perilla frutescens	58

Dietary Sources

Daily values:-
Macronutrients have AI (Acceptable Intake) and AMDR (Acceptable Macronutrient Distribution Range) instead of RDAs. The AI for *n*−3 is 1.6 grams/day for men and 1.1 grams/day for women while the AMDR is 0.6% to 1.2% of total energy.
Because the physiological potency of EPA and DHA is much greater than that for α-linolenic acid, it is not possible to estimate one AMDR for all *n*−3 fatty acids. Approximately 10 percent of the AMDR can be consumed as EPA and/or DHA.

Fish:-
Although fish is a dietary source of *n*−3 fatty acids, they do not synthesize these fatty acids and obtain from the algae or plankton in their diet. The most widely available source of EPA and DHA is cold water oily fish such as salmon, herring, mackerel, anchovies and sardines. Oils from these fish have a profile of around seven times as much *n*−3 as *n*−6. Other oily fish such as tuna also contain *n*−3 in somewhat lesser amounts. Consumers of oily fish should be aware of the potential presence of heavy metals and fat-soluble pollutants like PCBs and dioxin which may accumulate up the food chain. The FDA recommends that total dietary intake of *n*−3 fatty acids from fish not exceed 3 grams per day, of which no more than 2 grams per day are from nutritional supplements.[3]

Flax seeds: - fig-4
Flax Seeds produce linseed oil, which has very high *n*−3 content about six times richer than most fish oils in *n*−3, flax (or linseed) (Linum usitatissimum) and its oil are perhaps the most widely available botanical source of *n*−3. Flaxseed oil consists of approximately 55% ALA (alpha-linolenic acid). Table 1

Eggs:-
Eggs produced higher levels of *n*−3 fatty acids (mostly ALA) than chickens fed corn or soybeans.

Meat:-
The *n*−6 to *n*−3 ratio of grass-fed beef is about 2:1, making it a more useful source of *n*−3 than grain-fed beef, which usually has a ratio of 4:1. In most countries, commercially available lamb is typically grass-fed and thus higher in n−3 than other grain-fed or grain-finished meat sources.

Vegetable:-
Some Vegetables contain higher amount of *n*-3, including strawberries and broccoli. Walnuts are one of few nuts that contain appreciable *n*−3 fat, with approximately a 1:4 ratio of *n*−3 to *n*−6. Acai palm fruit also contains *n*−3 fatty acids.

Other sources:-
The microalgae Crypthecodinium cohnii and Schizochytrium are rich sources of DHA (22:6 *n*−3) and can be produced commercially in bioreactors. This

is the only source of DHA acceptable to vegans. Oil from brown algae (kelp) is a source of EPA.[3, 4]

Clinical Implications [9, 13]

Clinical studies suggest that omega-3 fatty acids is helpful in treating a variety of health conditions.The biological effects of the n−3 are largely mediated by their interactions with the n−6 fatty acids. A small amount of *n*−3 in the diet (~1% of total calories) enable normal growth. Omega 3 fats also play an important role in the production of powerful hormone-like substances called prostaglandins. Prostaglandins help regulate many important physiological functions including blood pressure, blood clotting, nerve transmission, the inflammatory and allergic responses, the functions of the kidneys and gastrointestinal tract, and the production of other hormones. In essence, all prostaglandins perform essential physiological functions

All dietary fatty acids are incorporated into cell membranes, and the type of fatty acids dictates how a cell responds and grows.

Topical- EPA supplements are found better than those treated with the medications alone in psoriasis In addition, many clinicians believe that flaxseed (which contains omega-3 fatty acids) is helpful for treating acne.

Omega-3 exerts neuroprotective action in Parkinson's disease and exhibit a protective effect (much like it did for Alzheimer's disease as well). The scientists found that high doses of omega-3 completely prevente the neurotoxin-induced decrease of dopamine that ordinarily occurs. A recently identified lipid (fat) product make from EPA, called resolvins, has anti-inflammatory effects on joints and improves blood flow.

Role of Omega 3 Fatty acids:-

Cardiovascular disease

EPA and DHA found in fish oil help reduce risk factors for heart disease including high cholesterol and high blood pressure. There is also strong evidence that these substances can help prevent and treat atherosclerosis by inhibiting the development of plaque and blood clots, each of which tends to clog arteries. Daily omega-3 fatty acid supplements dramatically reduce the risk of death, subsequent heart attacks, and stroke. Similarly, people who eat an ALA-rich diet are less likely to suffer a fatal heart attack.[7]

Omega-3 fatty acid intake (primarily from fish) helps protect against stroke caused by plaque buildup and blood clots in the arteries that lead to the brain. In fact, eating at least 2 servings of fish per week can reduce the risk of stroke by as much as 50%. However, eating more than 3 grams of omega-3 fatty acids per day (equivalent to 3 servings of fish per day) may lead to increased risk for hemorrhagic stroke, a potentially fatal type of stroke in which an artery in the brain leaks or ruptures.

EPA had a statistically significant decrease in the thickness of the carotid arteries along with improvement in blood flow. Purified EPA improves the thickness of carotid arteries along with improving blood flow in patients with unhealthy blood sugar levels.

High amounts of *n*−3 fatty acids from fatty fish also tend to have higher proportions of *n*−3, increased HDL cholesterol and decreased triglycerides (fatty material that circulates in the blood) and less heart disease. In addition, fish oil supplements containing eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) helps to reduce low density lipoprotein (LDL or "bad") cholesterol and triglyceride levels. Finally, walnuts (which are rich in alpha linolenic acid or ALA) have been reported to lower total cholesterol and triglycerides in individuals with high cholesterol levels.[5, 7]

Precautions:-

Persons with congestive heart failure, chronic recurrent angina pectoris or evidence that their heart is receiving insufficient blood flow are advised to talk to their doctor before taking *n*−3 fatty acids. There have been concerns if such persons take *n*−3 fatty acids or eating foods that contain them in substantial amounts in congestive heart failure, cells that are only barely receiving enough blood flow become electrically hyperexcitable. This, in turn, can lead to increased risk of irregular heartbeats, which, in turn, can cause sudden cardiac death. *n*−3 fatty acids seem to stabilize the rhythm of the heart by effectively preventing these hyperexcitable cells from functioning, thereby reducing the likelihood of irregular heartbeats and sudden cardiac death.

High blood pressure:-

Diets or supplements rich in omega-3 fatty acids lower blood pressure significantly in individuals with hypertension. Fish oil supplements found that supplementation with 3 or more grams of fish oil daily can lead to significant reductions in blood pressure in individuals with untreated hypertension. Omega 3 oils help to emulsify (break up) fats and plaques that build up in our arteries. If these fats are emulsified (or broken up into tiny pieces), it's easier for bodies to get rid of them.

Central Nervous System

Psychiatric disorders:-

Omega 3fatty acids are known to have membrane-enhancing capabilities in brain cells. One medical

explanation is that *n*−3 fatty acids play a role in the fortification of the_myelin sheaths a benefit of *n*−3 fatty acids is helping the brain to repair damage by promoting neuronal growth. In the prefrontal cortex (PFC) of the brain, low brain *n*−3 fatty acids are thought to lower the dopaminergic neurotransmission in this brain area, possibly contributing to the negative and neurocognitive symptoms in schizophrenia. This reduction in dopamine system function in the PFC may lead to over activity in dopaminergic function in the limbic system of the brain which is suppressively controlled by the PFC dopamine system, causing the positive symptoms of schizophrenia.This is called the *n*−3 polyunsaturated fatty acid/dopamine hypothesis of schizophrenia. Consequently, the past decade of *n*−3 fatty acid research has procured interest in *n*−3 fatty acids as being a legitimate 'brain food. An even more significant focus of research however, lies in the role of *n*−3 fatty acids as a non-prescription treatment for certain psychiatric and mental diagnoses and has become a topic of much research and speculation.[5, 7]

Attention deficit/hyperactivity disorder (ADHD):- [15]

Children with attention deficit/hyperactivity disorder (ADHD) may have low levels of certain essential fatty acids (including EPA and DHA) in their bodies. Children's those with lower levels of omega-3 fatty acids have more learning and behavioral problems (such as temper tantrums and sleep disturbances) than boys with normal omega-3 fatty acid levels. In animals low levels of omega-3 fatty acids have been shown to lower the concentration of certain brain chemicals (such as dopamine and serotonin) related to attention and motivation. At this point in time, eating foods high in omega-3 fatty acids is a reasonable approach for someone with ADHD. Increase in omega-3 and omega-6 fatty acid supplementation in children with ADHD found significant improvements in reading, spelling, and behavior in the children over the 3 months of therapy. Another clinical study found that omega-3 fatty acid supplementation helped to decrease physical aggression in school children with ADHD.

Depression: - [10]

People who do not get enough omega-3 fatty acids or do not maintain a healthy balance of omega-3 to omega-6 fatty acids in their diet may be at an increased risk for depression. The omega-3 fatty acids are important components of nerve cell membranes. They help nerve cells communicate with each other, which is an essential step in maintaining good mental health. In particular, DHA is involved in a variety of nerve cell processes.

Levels of omega-3 fatty acids were found to be measurably low and the ratio of omega-6 to omega-3 fatty acids were particularly high in a clinical study of patients hospitalized for depression. Those who ate a healthy diet consisting of fatty fish 2 - 3 times per week for 5 years experienced a significant reduction in feelings of depression and hostility.

Schizophrenia: - [14]

Preliminary clinical evidence suggests that people with schizophrenia experience an improvement in symptoms when given omega-3 fatty acids. However, a recent well-designed study concluded that EPA supplements are no better than placebo in improving symptoms of this condition. The conflicting results suggest that more research is needed before conclusions can be drawn about the benefit of omega-3 fatty acids for schizophrenia. Similar to diabetes, individuals with schizophrenia may not be able to convert ALA to EPA or DHA efficiently.

Cancer

When omega 3 fatty acids are incorporated into cell membranes they help to protect against cancer. They are suggested to promote cancer cell apoptosis via several mechanisms including: inhibiting a pro-inflammatory enzyme called cyclooxygenase 2 (COX 2), which promotes breast cancer; activating a type of receptor in cell membranes called peroxisome proliferator-activated receptor (PPAR)-ã, which can shut down proliferative activity in a variety of cells including breast cells; and, increasing the expression of BRCA1 and BRCA2, tumor suppressor genes that, when functioning normally, help repair damage to DNA, thus helping to prevent cancer development. Researchers found that omega-3 fatty acids affect cell growth by activating an enzyme called sphingomyelinase, which then generates the release of ceramide, a compound that induces the expression of the human tumor suppressor gene p21, which ultimately causes cancer cell death.

Breast cancer:-

Omega-3 fatty acids found in cold water fish-docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)-help protect against breast cancer development.

Colon cancer:-

Consuming significant amounts of foods rich in omega-3 fatty acids appears to reduce the risk of colorectal cancer. Those who tend to follow a high-fat diet but eat significant amounts of fish rich in omega-3 fatty acids, have a low rate of colorectal cancer. It is found that omega-3 fatty acids prevent worsening of colon cancer while omega-6 fatty acids promote the growth of colon tumors. Daily consumption of EPA and DHA also appeared to slow or even reverse the

progression of colon cancer in people with early stages of the disease. Low levels of omega-3 fatty acids in the body are a marker for an increased risk of colon cancer.

Prostate cancer:-
Omega-3 fatty acids (specifically, DHA and EPA) inhibit the growth of prostate cancer. Omega-3 fatty acids reduced prostate tumor growth, slow histopathological progression, and increases survival. Similarly, studies suggest that a low-fat diet with the addition of omega-3 fatty acids from fish or fish oil help prevent the development of prostate cancer. ALA, however, may not offer the same benefits as EPA and DHA. among n-3 fatty acids, neither long-chain nor short-chain forms were consistently associated with breast cancer risk.

Skeletal system
Arthritis:-
It is found that use of omega-3 fatty acid supplements for inflammatory joint conditions have focused almost entirely on rheumatoid arthritis. Omega-3 fatty acid supplements reduce tenderness in joints, decrease morning stiffness, and allow for a reduction in the amount of medication needed for people with rheumatoid arthritis.
Omega-3 fatty acids decrease inflammation and reduce the activity of enzymes that destroy cartilage.

Osteoporosis:-
Omega-3 fatty acids such as EPA help increase levels of calcium in the body, deposit calcium in the bones, and improve bone strength. In addition, people who are deficient in certain essential fatty acids (particularly EPA and gamma-linolenic acid [GLA], an omega-6 fatty acid) are more likely to suffer from bone loss than those with normal levels of these fatty acids. In osteoporosis, those given EPA and GLA supplements experienced significantly less bone loss over 3 years than those who were given a placebo. Many of these women also experienced an increase in bone density.[5]

Pregnancy and Fetal/Infant Development:-
Omega 3 fatty acids can promote an easier birth ,can prevent preterm delivery, help baby, sleep through the night at a younger age, can reduce the chances of child developing allergies, increase baby's brain functions and eyesight while in the womb, decrease chances of developing post-partum depression.
Omega-3 fatty acids (DHA and EPA) are very important for proper nutrition during pregnancy. DHA is particularly important because the fetus and/or premature infants cannot produce DHA efficiently.

Women, those with the highest dietary intake of omega-3 fatty acids had the mildest symptoms, such as hot flashes and increased sweating, during menstruation.[9]

Diabetes
Individuals with diabetes tend to have high triglyceride and low HDL levels. Omega-3 fatty acids from fish oil can help lower triglycerides and apoproteins (markers of diabetes), and raise HDL, so people with diabetes may benefit from eating foods or taking supplements that contain DHA and EPA. ALA (from flaxseed, for example) may not have the same benefit as DHA and EPA because some people with diabetes lack the ability to efficiently convert ALA to a form of omega-3 fatty acids that the body can use readily. There have been slight increases reported in fasting blood sugar levels in patients with type 2 diabetes while taking fish oil supplements.

Weight loss:-
Many individuals who are overweight suffer from poor blood sugar control, diabetes, and high cholesterol. Clinical studies suggest that overweight people who follow a weight loss program that includes exercise tend to achieve better control over their blood sugar and cholesterol levels when fish rich in omega-3 fatty acids (such as salmon, mackerel, and herring) is a staple in their low-fat diet.

Eating disorder:-
Studies suggest that men and women with anorexia nervosa have lower than optimal levels of polyunsaturated fatty acids (including ALA and GLA). To prevent the complications associated with essential fatty acid deficiencies, it is recommend that treatment programs for anorexia nervosa include PUFA-rich foods such as fish and organ meats (which include omega-6 fatty acids).

Burns:-
Essential fatty acids have been used to reduce inflammation and promote wound healing in burn victims. Omega-3 fatty acids help promote a healthy balance of proteins in the body by recovery after sustaining a burn.

Inflammatory bowel disease (IBD):-
When added to medication, such as sulfasalazine (a standard medication for IBD), omega-3 fatty acids may reduce symptoms of Crohn's disease and ulcerative colitis.

Asthma:-
Omega-3 fatty acid supplements (in the form of perilla seed oil, which is rich in ALA) may decrease

inflammation and improve lung function in adults with asthma.

Formulation and Dosage Form

Need of formulation:-

Although varieties of sources are available there are some factors which might contribute to a deficiency of omega 3 fatty acids such as the conversion of alpha-linolenic acid to EPA and DHA.This conversion involves a series of chemical reactions. One of the first reactions in this series is catalyzed by the enzyme delta-6 desaturase. Further down the line is a reaction that is catalyzed by the enzyme delta-5 desaturase. These enzymes do not function optimally in many people, and, consequently, only a small amount of the alpha-linolenic acid consumed in the diet is converted to EPA, DHA, and ultimately to the anti-inflammatory prostaglandins.

To increase the activity of desaturase enzymes it is necessery that diet includes a sufficient amount of vitamin B6, vitamin B3, vitamin C, magnesium and zinc. In addition, intake of saturated fat and partially hydrogenated fat should be limited, as these fats are known to decrease the activity of delta-6 desaturase. Therefore to include a direct source of EPA and DHA in diet, different formulations of omega fatty acids are available.

Pharmaceutical formulation:-

The omega-3 fatty acid formulations are available in various oral dosage forms such as pills, gel, capsules, syrup, suspensions, sublingual, candy, and chewable tablets etc. However, the administration could also be through any other route where the active ingredients may be efficiently absorbed and utilized, e.g. intravenously, subcutaneously, rectally, vaginally or topically. Also included are pharmaceutical compositions, comprising pharmaceutical formulations in a unit dosage form. In such dosage forms, the formulation is subdivided into suitably sized unit doses containing appropriate quantities of the omega-3 fatty acids, an effective amount to achieve the desired purpose.

Omega-3 dosage forms are provided in blister packages together with over the counter medical use information and/or nutritional information. Such packages may contain, for example 30, 60, or 180 omega-3 fatty acid unit dosage forms. Packaged pharmaceutical formulations contains only active agent or in which an omega-3 formulation is packaged in combination with one or more other active agents.[11]

Dose:-

The amounts of omega-3 formulation contained in an oral unit dose form for adult human patients may be generally varied or adjusted from about 400 mg to about 1000 mg of omega 3 fatty acids. For pediatric use an oral use the amount of omega 3 fatty acid contained in an oral unit dosage form will typically be less. Unit dosage forms for pediatric patients provide 10 mg/kg to about 30 mg/kg omega 3 fatty acid per day in one or two oral unit dosage forms. Thus, a unit dosage form for a child aged 2 to 6 years contains about 50 mg to about 500 mg, or preferably about 150 to about 180 mg, omega-3 fatty acids.

Combination Administration, Possible Interaction, and Precaution:-

The Omega-3 fatty acid formulations and dosage forms may be used alone or in combination with one or more other active agents which show either increased or decreased effects. They may be used with other psychotropic agents including, for example, lithium, pharmaceutical antidepressants, herbal antidepressants (e.g., St. John's Wort, S-adenosylmethionine), anti-convulsants, mood stabilizers, antipsychotic agents, benzodiazepines, psychostimulants, and alpha-2 agonists, active agent used to treat cardiovascular disorders, vitamins or herbal supplements. These other agents may either be given together with omega-3 fatty acid in a single dosage form, or they may be administered separately.

The addition of omega-3 fatty acids (specifically EPA) to the drug therapy etretinate and topical corticosteroids may improve symptoms of psoriasis.

In fact, people who eat more than three grams of omega-3 fatty acids per day (equivalent to 3 servings of fish per day) may be at an increased risk for hemorrhagic stroke, a potentially fatal condition in which an artery in the brain leaks or ruptures. Fish oil can cause flatulence, bloating, belching, and diarrhea

Manufacturing:-

Manufacture under Nitrogen:-

The manufacturing process is carried out under nitrogen conditions, with packing under vacuum, to limit any oxidation of the fish oil by its exposure to air. This process preserves the freshness of the Omega-3 product and eliminates the emergence of any oxidative contaminants. This process includes refinement of crude fish oil. Crude fish oil is obtained by methods known to those of ordinary skill in the art.

Degumming, Deacidifcation and Bleaching:-

The crude fish oil undergoes a pre-treatment prior to other steps in the refining process. This might be considered a `general pre-treatment` of the crude fish oil. In this process, phospholipids, metals, pigments, carbohydrates, proteins, fatty acids, sulfur, oil-insoluble, and oxidation products are removed.

Adsorbent Treatment:-
Adsorbent treatment is carried out by methods know to those of ordinary skill in the pharmaceutical arts. In this process heavy metals (such as mercury, cadmium, arsenic, copper and lead), organo-chlorins, and dioxins are removed.

Ethyl-Esterification:-
In this process, the triglyceride (TG) form of fish oil is converted into the ethyl-ester form of fish oil to concentrate the EPA and/or DHA in the fish oil. Methods for converting triglyceride form of fish oil to the ethyl ester form.
For example, crude fish oil may be diluted with ethanol, and then refluxed in the presence of catalytic amounts of concentrated sulfuric acid. After extraction with hexane, the transesterification mixture is subjected to silica gel chromatography, then to a two-step molecular distillation process, with a vacuum of about 10-3 mm Hg and at an evaporation temperature ranging from 65°-70° C. to 105°-125° C. and a condenser at 5° C.
This process optimizes Omega-3 purity and provides maximal concentrations of EPA and DHA, the Omega-3 essential fatty acids with demonstrated clinical benefits.

Recrystallization:-
Recrystallization is used to increase the concentration of omega-3 fatty acids in the fish oil by removing saturated fatty acids.

Molecular Distillation:-
Molecular distillation is effected by heating the recrystallized fish oil to a temperature sufficient to evaporate unnecessary fatty acids. The process environment is less than a 0.1 tore vacuum. This process step increases the concentration of EPA and/or DHA and removes potential environmental contaminants such as heavy metals.

High Vacuum Distillation:-
This step is a type of fractionation process, in which ethyl esters in the fatty acids are separated and purified. This unique process allows for provides purified omega 3 fatty acids having and EPA to DHA ration of over 4:1.

Conclusion:-

The importance of omega 3 fatty acids in health promotion and disease prevention has received awareness. Thus Omega-3 fatty acids play an important modulatory role in the immune and inflammatory responses, vascular reactivity and BP control, cell membrane function and omega-3 supplementation may offer a host of benefits in Cardiovascular diseases, Central nervous disorders, skeletal disorders, cancer and pregnancy and child development.
Number of food products enriched in omega-3 fatty acids has increased.*n*−3 supplementation in food has been a significant recent trend in food fortification, with food companies launching *n*−3 fortified bread, mayonnaise, pizza, yogurt, orange juice, children's pasta, milk, eggs, confections and infant formula. Many companies add fish oil or flax oil into their final product to enrich it in omega-3 fatty acids. Some animal products, such as milk and eggs, can be naturally enriched for omega-3 fatty acids by feeding the animals a diet that is rich in omega-3 fatty acids.
Since there are few adverse effects due to imbalance with omega 6 fatty acids, a large, long-term, randomized controlled study is needed in order to determine if there is a significant therapeutic effect and to assess the influence of disease severity, dosage and duration of treatment.

References:-

1. J.L McGuire, “Pharmaceutical classes, Therapeutic Agents, Area of application.”

Vol-IV, (Miscellaneous drug Related Technology) Page no-344, 2046

2. Albert Lehniger, David L. Nelson, Micheal M. Cox, “Principles of biochemistry” Second edition, Page no-655,656.

3. Vinod. D. Rangari, “Pharmacognosy & phytochemistry”, Career Publication, First Edition, PartII, Page no-6, 77

4. Dr A.C.Deb, “fundamental of biochemistry”, Sixth Edition 1996, Page no-39-40

5. Hu FB, Stampfer MJ, Manson JE et al. Dietary intake of alpha-linolenic acid and risk of fatal ischemic heart disease among women. Am J Clin Nutr. 1999;69:890-897.

6. Newcomer LM, King IB, Wicklund KG, Stanford JL. The association of fatty acids with prostate cancer risk. *Prostate*. 2001; 47(4):262-268.

7. Iso H, Rexrode KM, Stampfer MJ, Manson JE, Colditz GA, Speizer FE et al. Intake of fish and omega-3 fatty acids and risk of stroke in women. JAMA. 2001; 285(3):304-312.Ed macular

degeneration. Arch Opthalmol. 2001; 119(8):1191-1199.

8. Arita M, Bianchini F, Aliberti J, Sher A, Chiang N, Hong S, Yang R, Petasis NA, Serhan CN. Stereochemical assignment, antiinflammatory properties, and receptor for the omega-3 lipid mediator resolvin E1. J Exp Med. 2005 Mar 7; 201(5):713-22. 2005. PMID: 15753205.

9. http://en.wikipedia.org/wiki/Omega-3_fatty_acid.

10.http://www.umm.edu/altmed/articles/omega-3-000316.htm

11.http://www.softecare.com/omega3/omega3-pregnancy.php

12. http://www.faqs.org/patents/app/20080268042

13. http://www.whfoods.com/genpage.php?tname=nutrient&dbid=84

14.http://www.nlm.nih.gov/medlineplus/druginfo/natural/patient-fishoil.html

15. http://nutrition.about.com/od/therapeuticnutrition1/tp/omega3oils.htm

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