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"PRAISEWORTHY ASPECTS AND SHORTCOMINGS OF OMEGA-3 POLYUNSATURATED FATTY ACID ON MAJOR DEPRESSIVE DISORDER – A REVIEW"

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ABSTRACT :

Depression is a leading cause of disability worldwide, significantly impacting quality of life and overall health. While pharmacological and psychotherapeutic interventions remain the cornerstone of treatment, growing evidence suggests that nutritional factors, particularly omega-3 polyunsaturated fatty acids (PUFAs), may play a critical role in the modulation of depressive symptoms. This dissertation explores the relationship between omega-3 fatty acids and depression, focusing on the biological mechanisms, clinical outcomes, and potential therapeutic applications. A comprehensive review of epidemiological studies, randomized controlled trials, and meta-analyses is undertaken to assess the effectiveness of omega-3 supplementation in various populations. Particular attention is given to the differential effects of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) on mood regulation, inflammatory pathways, and neurotransmission. The findings suggest that higher intake or supplementation of omega-3 fatty acids, especially EPA-rich formulations, may offer a modest but clinically meaningful benefit in the management of depression, particularly in individuals with treatment-resistant symptoms or those with low baseline omega-3 levels. However, inconsistencies across studies highlight the need for standardized methodologies and further investigation into optimal dosages, treatment duration, and patient selection criteria.

Keyword: Depression, EPA, DHA, Omega 3 fatty acid

INTRODUCTION

MAJOR DEPRESSIVE DISORDER (MDD):

Mental pain is less dramatic than physical pain, but it is more common and also harder to bear.
------ C.S.Lewis [1]

According to WHO, Major Depressive Disorder (MDD) is a very renowned part of common mental illness, which has some characteristics and the most dangerous effect of depression is, it hampers daily life activity [2]. In recent days depression is one of the main cause of disability and leading contributor to disease burden Globally [3]. It is costly disorder associated with severe and persistent symptoms which lead to social role impairment and increased mortality [4]. It exists as a greatest non-communicable [5] mood disorder, can be mild, moderate, severe, psychogenic or recurrent in nature [6], contributing to health loss and risk of suicide [5]. Irrespective of age, sex, race, occupation, depression can enter anyone's life and snatching the quality of life; even the doctors can suffer from depression. Severe depression may provoke suicidal tendency and attempts [2,6].

TYPES OF DEPRESSION:

Major Depressive Disorder have some characteristic types. These are as follows below-

1.MAJOR DEPRESSION- It is manifested by symptoms include- loss of ability to work, sleep, do not get pleasure in such things that give lots of enjoyment in past. This episode of depression occurs once and twice in a life time [7].

2.DYSTHYMIA- It is less severe, long-term type of depression that does not severely disable a person.in this type, people are able to perform daily life function but not to a "Feeling satisfied" level. People with dysthymia may also experience major depressive disorder/episode [2,7].

3.MANIC DEPRESSIVE OR BIPOLAR- It has no similarity with other types of depression. Generally, this involves a cyclic process of depressive

episode and mania. When the depressed cycle continues, one can have all symptoms of a depressive illness. When manic cycle continues, any or all symptoms of mania may be experienced. Mania usually affect thinking, judgement and social behaviour in such a way that may create social embarrassment [7].

SYMPTOMS OF DEPRESSION: [2,6,7]

Emotional, behavioral and somatic changes are seen in depression. Many symptoms are there but some common symptoms are included below-

- Loss of interest
- Mood changes
- Low self-esteem and confidence
- Loss of appetite
- Sadness without any reason
- Anxiety, insomnia, libido
- Reduced motivation
- Tiredness in minimal activity
- Guilt feeling

CAUSES OF DEPRESSION:

1.GENETIC FACTOR- It is seen that depression can run in families, but until the fairly research, it is not fully known. Some researchers are also able to determine that to some extent depression can be inherited.

Bipolar disorder has a strong genetic influence, 50% of patients of bipolar disorder have a strong history of parent with clinical depression. 25% chance of developing bipolar disorder in children when mother or father has a history of having this. If both parents have bipolar disorder, the chance of their child also developing bipolar disorder is between 50% - 75% [7].

2.SOCIAL FACTOR – There are some social factors include- unemployment, separation, social stigma, poverty, death of close ones, conflict with family and friends, alcohol and drug abuse may also contribute for developing depression [2,6].

3.HORMONAL AND ENVIRONMENTAL FACTOR- Sometimes depression may develop due to changes in hormonal and physiological process.

Many study reported that many persons are suffered from depression due to seasonal changes e.g. in spring and fall season.

High maladaptation in coping adverse situations and low social support increase the rate of development of depression.

Everyone tries to cope up with the evil but all the time situations are not favourable. Sometimes tolerance give up in front of occurrence. Interaction of all the events (unwanted or unpleasant) may be a crucial for developing depression [6].

PREVALENCE RATE OF DEPRESSION :

WORLDWIDE- Globally 300 Million[5] people are suffered from depression which is 4.4% of World's population.

AMONG GENDE – Though depression can not obey anything about its occurrence, but from study, it is seen that women are more prone to depression than men [2]. Life long prevalence rate of depression is about 20-25% in women and 7-12% in men [3]. Though women are suffered more but suicidal attempts are 3 times more in male [6].

IN INDIA – According to WHO, in the list of depressed countries, India got the first position as the most depressed country followed by China and USA.

As per the study report of WHO, In India, 6.5% of total countries population suffer from serious mental illness. 10.9 for every one lakh people are committed suicide and the most important thing is that the majority of people who committed are below 44 years of age [1].

- **TREATMENT:**

Conventional treatment procedure of depression are – pharmacological and psychological treatment. But now-a-days research can also open the door of nutritional therapy [5]

OMEGA-3 POLYUNSATURATED FATTY ACID:

Polyunsaturated fatty acid (PUFA) are the fatty acids which have more than one double bond in their backbone. Polyunsaturated fatty acid mainly are of two types – 1. Omega-3 Polyunsaturated Fatty Acid (n-3 PUFA), 2. Omega-6 Polyunsaturated Fatty Acid (n-6 PUFA) [8]. There are over 30 different types of PUFAs. In addition to n-3 and n-6, there are n-5, n-7, n-9 PUFAs. n-3 and n-6 play the most important biological roles and the quantitative balance between n-3 and n-6 believed to be a crucial factor [9].

Omega-3 Polyunsaturated Fatty Acid was discovered by George Burr and Mildred Burr in 1929 [10]. Name of polyunsaturated fatty acid, determined by the presence of first double bond from the tail end / omega end [8] (Omega is the last letter in Greek alphabet [9]) / n-end [8] (Another nomenclature used, the Latin letter 'n' instead of Greek Omega [9]). So, on omega-3 PUFA, first C-C double bond present in between C3 and C4 [8].

Omega-3 fatty acids are also known as 'Vitamin F', F from fatty acid [8].

FUNCTION OF OMEGA-3 PUFA:

After the discovery of omega-3 PUFA, researches after researches were done to find out the effectiveness of this element and they found out the effective role of omega-3 PUFA on cardiovascular health, neuropsychiatric pathologies and neurodegenerative disease [10]. A study by Swanson et al. reported that with other potent beneficial effect of DHA and EPA (most common bio-active forms of omega-3 PUFA) in cardiovascular function, fetal development, they are both important for Alzheimer's Disease as they improve cognitive function in mild form of this disease [11]. Omega-3 fatty acids are important component of diet which can only be supplemented through diet. Along with the above, it plays some other important role in human body. These are as follows-

- Maintain cell wall integrity, membrane fluidity, and cell to cell connection.
- Anti-inflammatory property
- Significant role in chronic illness- coronary heart disease, artharitis, cancer.
- Regulates blood pressure, haematic clotting etc [8]
- Lowering serum triglycerides
- Suppression of lipogenesis, increase mitochondrial β-oxidation [12]

- **<u>TYPES OF OMEGA-3 PUFA:</u>**

There are 3 focused types of omega-3 PUFAs-

1. α- Linolenic Acid (ALA)
2. Docosahexaenoic Acid (DHA)
3. Eicosapentaenoic Acid (EPA) [8]

EPA and DHA are known as 'Conditionally Essential Fatty Acid ' [9] as most of the mammals can not able to synthesize them by their own, they always be taken up by diet as short chain omega-3 fatty acid, α-linolenic acid (ALA) , consisting of 18 carbons and 3 double bonds. Then within the body ALA is converted to eicosapentaenoic acid (EPA), is more important one, consisting of 20 carbons and 5 double bonds in their structure. From EPA, Docosahexaenoic Acid (DHA) is formed, more crucial fatty acid, 22 carbons and 6 double bonds are present in it's structure [13]. Some study reported that conversion rate of ALA to EPA are 0.2%-6% and DHA 0.05% or less in human. Women seem to possess a higher capacity of conversion than men [9].

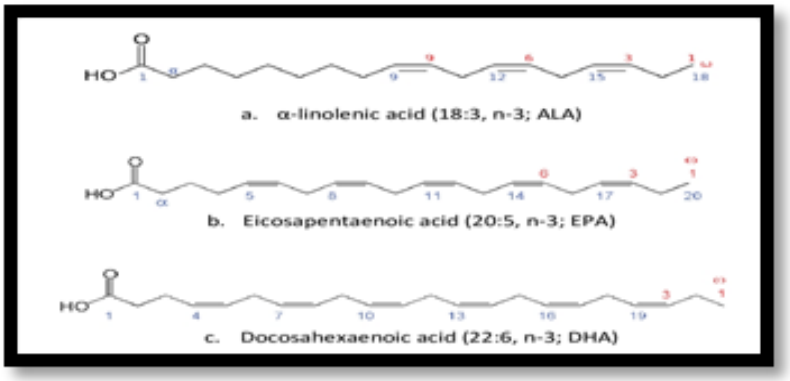

Figure: Chemical structure of Omega-3 PUFAs [14]

SOURCES:

Common name [8]	Source [8]	Lipid name [9]
ALA	Flax seed, Canola (rapeseed), Soyabean, Walnut etc.	18:3n3
EPA	Main Sources- cold water fishes (sardine, salmon, tuna, halibut, crustacean) Alternative Sources- krill oil, algae, sponges, autotrophic macroalgae and microalgae, brown and red algae	20:5n3
DHA		22:6n3

EPA/ DHA containing Fish/seafood	Total EPA and DHA content (mg/100g)
Mackerel	2300
Herring	1700

Sardine	1400
Chinok salmon	1900
Coho salmon	1200
halubut	400
Spinly lobster	500
Shrimp	300
Cod	200

Table: EPA and DHA content in sea fishes [15]

Fish oil is derived from tissues of oily fishes. But those fish do not produce these fatty acids in their body, they store these from their feedings. Marine and cold water fish mainly contain various amounts of omega-3 fatty acids [12].

ALA containing oils	Percentage of ALA
Soyabean	7
Canola	9
Walnut	10
Flaxseed oil	57

Table: Percentage of ALA in ALA containing oils [15]

METHODOLOGY

In this revie purpose, E-library and library have played an important role to collect various information from different national and international journals about the topic that I have chosen.

REVIEW OF LITERATURE

OMEGA-3 PUFA AND DEPRESSION

The role of nutrition for preventing and treating neuropsychiatric disorders is increasingly being recognized and recently based on situation it is stated that "nutrition and neutraceuticals should now be considered as mainstream elements of psychiatric practice" [9]. It is predicted that by the year 2030, Major Depressive Disorder would be leading cause of burden of diseases Worldwide [16], so along with many natural and synthetic antidepressants, omega-3 fatty acids gained special attention now-a-days for the treatment of depression [13]. Omega-3 PUFA composed of EPA and DHA, essential part of cell membrane, important component of brain and retina [17] and they are important for lowering the inflammation markers : C-reactive protein, TNF-α and IL-6 in blood stream . A study by He et al. proposed that as omega-3 PUFAs are able to change cell signalling and cell membrane structure, thus, omega-3 PUFA can act like an antidepressants [13].

Central Nervous System (CNS) is a place where a large amount of lipids are present after the adipose tissues. 15% of total fatty acids (including saturated, monounsaturated, polyunsaturated fatty acids) is accounted by DHA in both male and females. Reduced dietary supply of omega-3 PUFAs to brain is associated with many brain diseases – depression and anxiety [10]. Various preclinical studies suggested that omega-3 fatty acids influence various neurobiological mediators that appears to be beneficial in treating the pathophysiology of depression [16]. Omega-3 PUFAs are known for inhibiting endothelial cell proliferation and increase in glucose uptake and utilization by the brain cells [18].

Some study stated that the EPA content in RBC phospholipid is negatively correlated with severity of depression. Some other studies also suggested that suicidal tendency might be associated with low level of EPA in RBC [15]. K.P.Su et al. stated that patients with major depressive disorder have a lower level of n-3 PUFA in tissues of blood [19]

Cognitive deficits are often observed in depressed individuals. Omega-3 fatty acids have an important role in improving cognitive function in a variety of population ranging from infant to elderly, and from healthy individuals to patients with psychiatric, neurodegenerative or neurodevelopment disorders [20].

POSSIBLE BIOLOGICAL MECHANISM OF ACTION OF OMEGA-3 FATTY ACID ON MAJOR DEPRESSIVE DISORDER

Human brain is highly enriched with omega-3 PUFAs and it regulates several biological processes such as – neurotransmission, cell survival [19]. Omega-3 fatty acids and their bioactive metabolites have anti-inflammatory and inflammation resolving properties, these properties may have a broader implications for understanding the role of omega-3 fatty acid bio-status and proinflammatory cascade in the pathophysiology of depression disorder [21].

K.P.Su et al. stated that among the beneficial function of omega-3 PUFA, what are the exact mechanism behind the psychotropic effect of omega-3 PUFA ae not fully understood. But various study gave some possible hypothesized explanation about that [19].

- ***OMEGA-3 PUFA IN NEUROTRANSMISSION*** - Chronic dietary omega-3 deficiency, change the omega-3 concentration in brain, this situation could lead to an increase in Serotonin 2 (5-HT2) and decrease in Dopamin 2 (D2) receptors density in frontal cortex. The upregulation of serotonin 2 and downregulation of Dopamin 2 receptors might play a role in pathophysiology of depression [19].

  Biochemical studies prove that omega-3 PUFA increases the level of 5-HIAA (5-Hydroxy-Indoleatic Acid) in cerebrospinal fluid, is a metabolite of serotonin and that mechanism indicates a good brain serotonin turnover [19]. High concentration of 5-HIAA in CSF and somatotropin release are associated with improvement of depression symptoms [22].

  Omega-3 fatty acid may exert antidepressant effect via. Cytokinin modulation. Many research documented the association between cytokines and occurrence of depression. Psychological stress can cause an elevation of cytokines, which are pro-inflammatory immune

chemicals, have a direct effect on Central Nervous System, lowered neurotransmitters precursor availability activation of Hypothalmic-Pituitary-Axis, alteration of metabolism of neurotransmitters [15].

Depression and related mental health conditions are caused by low serotonin level. Serotonin, is a neurotransmitter (a messenger chemical that carries signals between nerve cells in the brain). After carrying message, serotonin usually reabsorbed by nerve cells (this process known as Reuptake). Selective Serotonin Reuptake Inhibitor (SSRI), a widely used type of antidepressants, work by blocking or inhibiting reuptake, meaning more serotonin is available to pass further message between near by nerve cells [23]. SSRI called selective because they mainly affect serotonin, not other neurotransmitters [24]. To rise serotonin level for improving depressive symptoms [23] 0mega-3 fatty acids now-a-days can be supplemented with combination with Selective Serotonin Reuptake Inhibitor (SSRI) and considered more standard treatment procedure by clinicians [13].

- ***OMEGA-3 PUFA IN ANTI-INFLAMMATION –*** Some studies showed that EPA highly correlated with inflammation, so, EPA supplementation might be beneficial for only MDD patients with inflammation as a part of their syndrome and also thought that EPA supplementation may be harmful for MDD patients with different physiological disturbance other than inflammation [25].

Both EPA and DHA reduce the occurrence of inflammation by decrease the production of pro-inflammatory cytokines – Tumour Necrosis Factor -alpha (TNF-α), IL-1, IL-6, IL-2, Interferon-gamma [25,15].

EPA and DHA reduce inflammation through another way, they both can combine with Arachidonic Acid [25], an omega-6 fatty acid [22], for amalgamation into membrane-based phospholipid leading to a decline in both cellular and plasma concentration of arachidonic acid. Another possibility, EPA may compete with arachidonic acid and help in blocking the synthesis process of Eicosanoids (Prostaglandins, Thromboxane, leukotrienes) from arachidonic acid (AA) [25].

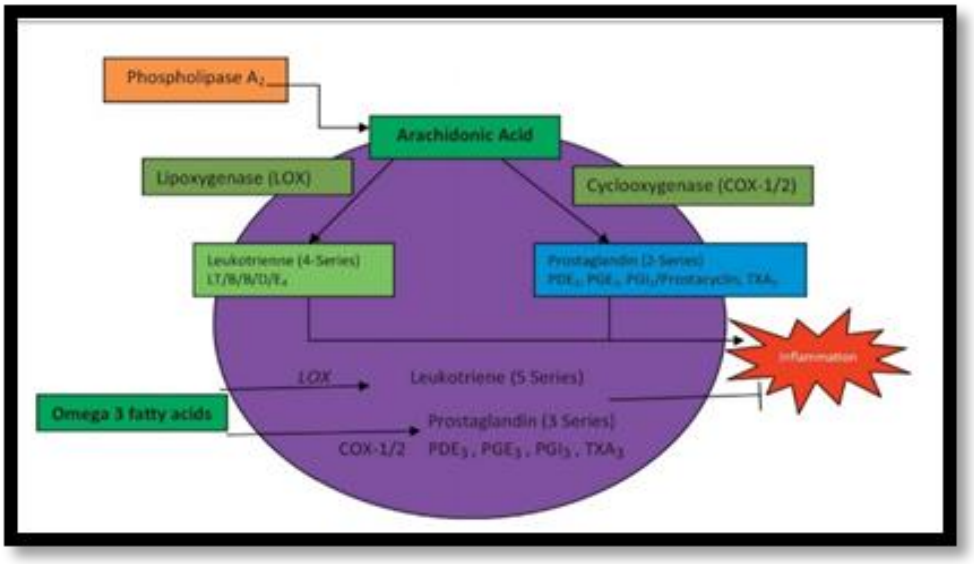

Figure: Possible pathway of omega-3's role in anti-inflammation [13]

In addition, resulted that individual who have high Interferon -alpha (IFN-α) after receiving INF-α therapy for chronic Hepatitis-C (HCV) infection or cancers almost all patients meet the operational diagnostic criteria for depression or experience of an acute-cytokine induced behaviour [25,22]. Lower EPA levels are found at early stage of IFN-α in those patients and developed more IFN-α - induced sickness behaviour. Symptoms of cytokine-induced behaviour are mediated by prostaglandins (PGs). PGs are produced from Arachidonic Acid (AA) and cause anxiety behaviour. EPA can supress the pro-inflammatory effect of AA, there by reducing PG-E2 synthesis and attenuating Interleukin-1-β induced activation of PG-E2 [22].

- ***NEUROTROPHIC EFFECT OF OMEGA-3 PUFA*** – In many studies it was noticed that EPA may exerts a greater neurotropic effect than DHA, as it was shown that supplementation of EPA increased Brain Derived Neurotropic Factor (BDNF) after traumatic brain injury [25]. BNDF is a polypeptide which supports the survival and growth of neurons through development and negatively correlate with depressive symptoms [15]. Antidepressants and voluntary exercise enhance BDNF while diet high in saturated fatty acids (SFAs), Sucrose and psychological stress may inhibit BDNF production [15].
- ***OMEGA-3 IN ANTI-OXIDATION –*** In patients with MDD, there are a causative fact of oxidative stress and lipid peroxidation [15]. Upon activation of resident macrophages of brain, upregulate the expression of determinant factors of Reactive Oxygen Species (ROS) such as – Nitric Oxide through inducible nitric oxide synthase and induce oxidative stress and this may contribute to pathogenesis of neuropsychiatric diseases. Omega-3 PUFA which may be associated in the activation of anti-oxidative enzymes like – Heme-oxygenase-1 (HO-1) can reverse oxidative stress and may characterise antidepressant mechanism [19].
- ***OMEGA-3 PUFA IN NEUROPLASTICITY*** - In a small study, it was seen that EPA has ana effect to increase cortical concentration of N-

acetyl aspartate, is an important marker of neuronal integrity [19] and neuronal homeostasis [25], there by protect against Excitotoxic Apoptosis [19], hence give neuroprotection [25]. Omega-3 PUFA modulate neurotrophins that might induce neuroplasticity and neurogenesis as various antidepressants [19].

- EPA supplementation also increase the ratio of cerebrospinal monoester to phosphodiester, that is a major indicator of phospholipid turnover and reverse brain atrophy of subjects with MDD [25]. As an important component of CNS membrane phospholipid acyl chain, omega-3 PUFA take a critical part to maintain the dynamic structure and function of neuronal membrane. Omega-3 PUFA can alter and maintain optimal fluidity of membrane and made a good path for neurotransmitter binding and helps in good signaling [15].
- Some study found an association between depression and high cortisol level in blood due to hyperactivity of HPA axis, largely due to hypersecretion of Corticotrophin Releasing Hormone (CRH) [18] or Corticotrophin Releasing Factor (CRF) [22]. Omega-3 PUFA may control the regulation of CRF/CRH, thus may give a betterment from depressive symptoms [22].

SOME STUDY BASED CLINICAL AND EPIDEMIOLOGICAL EVIDENCE OF OMEGA-3 PUFA ON DEPRESSION

Studies by Harvard University stated that, in different mechanism omega-3 PUFA exert their action like they can easily move to the brain cell and interact with mood related molecule and they have also certain anti-inflammatory action that may help to relief from depression. Most of the studies, use typically EPA or DHA or both altogether at a doses of 0.5-1g/day to 6-10g/day and gave their conclusion that omega-3 PUFA may act as an add-on therapy for people who are being under the prescribed antidepressant therapy with limited or no benefit [26].

Luo et al. (2020) reported that the efficacy of high doses of omega-3 PUFA is more than that of low doses. Various study and ISNPRP guideline suggested 1-2 g or ≥2 g/day EPA is recommended dose for EPA supplementation. Luo et al. considered ≥2000 mg /day as a high dose and ≤ 2000 mg/ day as low dose and conduct their study. Then they conclude that, treatment enhanced with EPA increased the level of Eicosapentaenoyl Ethanolamide in plasma, which may lead a greater importance in MDD. Another finding from their study, that EPA monotherapy and EPA+DHA combined therapy significantly reduce the depressive symptoms, compared to DHA monotherapy, from this it could be concluded that EPA might be the main antidepressant component [27].

Liao et al. (2019) concluded from their research study that supplementation of EPA in range of 720-1000 mg/ day may be more effective in improving depression episode, mediated by the known mechanism of omega-3 PUFA at the cellular level. A study by *Song et al.* found that the most effective EPA and DHA ratio would be 2:1 or 3:1 for improvement in depression [25].

An increase in Omega-3 Index reduces the risk and severity of depressive symptoms. One of the clinical studies found that 1% increase in Omega-3 Index, the risk of developing depression was reduced by 28% [9].

RJT Mocking et al. (2016) concluded a data from meta analysis study is that beneficial effect of omega-3 PUFA (mainly EPA) supplementation is larger in patients with MDD when taking at the same time some antidepressant medication [28].

Markthus et al. (2013) stated the women who have the risk of omega-3 deficiency in pregnancy period, nearly 10% of them may experience postpartum depression. A stydy by *Mc Namera et al*. (2007, 2008, 2013) reported that post-mortem reports of persons who had committed suicide, a reduced level of DHA in prefrontal cortex of those who were suffering from depression [10].

A logistic regression analysis reported that 1% rise in plasma DHA was associated with 59% reduction in the reporting depression symptoms. A case report documented with the use of 4g EPA / 2 g DHA per day during pregnancy, improved the depressive symptoms measured in Hamilton Rating Scale for Depression (HRSD) within 4 weeks of supplementation EPA+DHA therapy and all symptoms were resolved by 6 weeks. In another case study, a patient with treatment resistant depression, benefitted after one month supplementation of 4 g pure EPA /day basis, resolved the problem of social phobia. After 9 month after that treatment it was reported that patient was completely free from all the symptoms [15].

There are some Epidemiological data gave special attention that people who usually consume a diet rich in omega-3 fatty acid are at lower risk of developing depression as well as other mental illness. In USA, among adult and children omega-3 PUFA gained the attention as most common Non-vitamin supplementation [13].

In a study by *Maes et al.* stated a significant strong association between reduced level of EPA and overall omega-3 PUFA and increased Omega-6: Omega-3 proportion in phospholipids and choleteryl esters were found in individual who had an experience of MDD. It was observed in many studies that, increased amount of EPA+DHA consumption related to increased grey matter in brain with an important role in regulating depression and mood disorder [13].

Controlled and open labelled trials found that omega-3 fatty acid supplementation administered adjunctively or as monotherapy, significantly reduce depression symptoms. A prospective surveillance study stated that, patients with chronic hepatitis C during the treatment with pro-inflammatory Interferon-α, have a lower baseline DHA level or a higher baseline AA/EPA+DHA ratio were significant predictors of development of depression. A higher baseline AA/EPA+DHA ratio was also associated with profuse production of cytokines during IFN-α treatment [21].

The omega-3 fatty acid Subcommittee assembled by the Committee on research on psychiatric treatment advice that "patients with mood, impulse-control or psychiatric disorder should consume 1 g of EPA+DHA per day." A supplementation of 1-9 g/ day may be useful for patients with mood disorders [29].

In another hand, some study provide evidence about omega-3 PUFA have not been so far provided as a significant monotherapy though omega-3 PUFA plays a very closely linked supplementation for depression and other mental illness [13]. *Arne et al.* reported that the efficacy of omega-3 PUFA in special subpopulation such as – children, adolescents, elderly with underlying co-morbidities, are only incompletely studied [9]. A study stated that high doses of EPA supplementation had a prohibitory [13] effect in the activity of CYP2D6 and CYP2A4, are the major hepatic enzymes involving in the metabolism of antidepressant drugs such as – some Selective Serotonin Reuptake Inhibitors, SSRI [25]. Along with positive effect, many meta-analysis and review study showed that omega-3 PUFA is effective for depression in adults but nothing such special effect on depression of children and adolescents [30]. With regard to DHA or combination of EPA and DHA have been reported for many negative outcomes. In a study, DHA monotherapy (2 g pure DHA) was administered on 36 patients with MDD for 6 weeks. Significant result was not found in Montgomery- Asberg Depression Rating Scale between the groups who were on DHA therapy and who were not on DHA therapy [15].

OMEGA-3 AND OMEGA-6 PUFA RATIO AND EFFECT ON DEPRESSION

Several sources suggested that in human diet omega-3 to omega-6 ratio should be in 1:1, where as in modern Western diet the ratio is 1:20. Arachidonic Acid (AA),an omega-6 fatty acid further converted into prostaglandin and leukotrienes which are responsible for proinflammatory effect which can contribute for developing the symptoms of depression, n-6 are also responsible for pathogenesis of many diseases, where as omega-3 fatty acid reduce the synthesis of pro-inflammatory mediators by acting as competitive inhibitor to n-6 and n-3 showed suppressive effect of pathogenesis of many disease.

Along with anti-inflammatory effect, omega-3 PUFA affect serotonin and dopamine neurotransmitters by altering the phospholipid composition. Thus decrease in omega-3 fatty acid level in diet influence both somatic and neuropsychiatric function through several mechanism [29].

Lots of clinical and epidemiological studies focused the link between mood disorders and blood and/ cellular level PUFA content. It was shown that subjects diagnosed with depression, had a lower level of omega-3 PUFA and relative a higher content of omega-6 in their blood compared to healthy subjects matching for age and sex [10].

Another study report found that, in depressed aged patients there is a high AA, n-6: n-3, AA/EPA, and AA/DHA ratios were observed than healthy volunteers [19].

A study was done by *Adams et al.* to find out the relationship between depression and ratio of omega-3 PUFA and omega-6 PUFA concentration in erythrocyte and plasma. The study was conducted on 20 moderate to severe depressed patients and in this study both positive and negative correlation were found. So, the author conclude that only dietary intake of fatty acid cannot explain the result. But in another study concluded that a increased level of omega-6 fatty acid and compromised intake of omega-3 fatty acid may boost the rate of depression and alter the functioning neurons [13].

RELATIONSHIP BETWEEN CARDIOVASCULAR DISEASE, MAJOR DEPRESSIVE DISORDER AND OMEGA-3 PUFA [18]

The increased prevalence of depression over last few decades in Western countries has been parallelly accompanied with prevalence of cardiovascular disease. Several studies reported that depression may share common pathological characteristics and risk factors with cardiovascular disease such as – production of pro-inflammatory cytokines, endothelial dysfunction and elevated plasma homocysteine level. One factor could explain the reason behind two parallelly increased diseases over the last Century is that there was a devastating increase in saturated fats and increase in the ratio of omega-6 and omega-3 in diet. Increased amount of n-6 PUFA, saturated fat and a high n-6 to n-3 ratio may predispose the pathogenesis of inflammatory related disease, neuropsychiatric disorders, cardiovascular disease and cancer where as high amount of omega-3 and low n-6 to n-3 ratio may exert suppressive and anti-inflammatory effects.

In both diseases, it is seen that glucose metabolism is hampered and there are an abnormal flow of blood that lead to hypoperfusion in the limbic system and prefrontal cortex and low glucose utilization in brain negatively correlating with severity of depression. Omega-3 PUFAs are very famous for inhibiting endothelial cell proliferation and increase in glucose uptake and utilization by brain cells.

Prospective secondary prevention studies suggested that EPA/DHA supplementation ranging from 50-180 mg/day and ALA intake of 150-300 mg/day seems to be beneficial and may reduce all kinds of mortality from cardiac and psychiatric illness.

RELATIONSHIP BETWEEN FISH-OIL CONSUMPTION AND DEPRESSION

As fish from specially marine sources are richest source of omega-3 PUFA, several epidemiological studies investigated the association between fish consumption and occurrence of MDD in many countries – New Zealand, France, Northern Iceland, Norway, Netherlands etc. Also many epidemiological studies revealed that high fish consumer countries from Asia like – Japan, Korea, Taiwan, people form these countries suffered less from depression. On the other hand, Western countries like – New Zealand, Canada, United States, Germany, France, people from those countries consumes relatively less fish and had a higher depression prevalence rate. Other studies revealed that subjects who consume less fish (lower than once per week, including seafood) presented with a higher score of depression. There all data suggest that there may be a close association between fish consumption and prevalence of depression [10].

A double-blind placebo control trial was done over 2 months in 28 MDD patients with high doses of fish oil (9.6 g/day) along with standard antidepressant therapy. In this study, the result was revealed that patients who had received omega-3 fish oil supplementation, got a significantly low score in HRSD scale compared to those who were not on that therapy [15].

Suominen -Taipale et al.(2010) stated that their study gave some support to the hypothesis that high fish consumption protect against depression, but this holded true for men but not for women. In this study, higher association between fish consumption and reduced risk for depression in men indicates a complex association between depression and lifestyle. They also reported that high fish consumption seems to protect against MDD particularly in men with high alcohol consumption. Alcohol intake has been suggested to be an effective modifier of the relationship between folate intake and plasma homocysteine. Ethanol may affect the absorption and metabolism of folate, leading to reduction of the potential beneficial effect of folate intake on depression in men [31].

EFFECT OF ETHYL-EICOSAPENTAENOIC ACID (E-EPA) ON DEPRESSION

Ethyl – EPA(E-EPA) is a synthetic derivative of EPA, which is widely used now-a-days and believed to exhibit its anti-psychotic and anti-depressive effect and get the special attention in the field of psychiatry.

Many randomized double blind, place-control studies proved the beneficial effect of E-EPA on improving depressive episodes and symptoms. It was known for effective and well-tolerated intervention in Bipolar psychiatry [13].

A 12 week, randomized, double-blind, placebo-control study was done with various doses of E-EPA – 1g, 2g, 4g of EPA respectively to 70 patients with persistent depression along with ongoing standard antidepressant pharmacotherapy. The result of this study was “less is more” i.e. patients who were on 1g/ day group, 53% of them achieved a 50% reduction in HRSD (Hamilton Rating Scale for Depression) score with dramatic improvement in depression, anxiety, sleep disturbances and suicidal ideas [15].

INFLUENTIAL ROLE OF OTHER DIETARY FACTORS ON INCREASING THE EFFICACY OF OMEGA-3 PUFA ON MAJOR DEPRESSIVE DISORDER [15]

There are some nutrients which can influence the Omega-3 PUFA status within the human body; among them 4 dietary factors gained the special attention, these are – **Zinc, Selenium, Folic acid and Dietary antioxidants,** hence these are closely related to MDD.

In many studies it was shown that lower level of **Zinc** are found among MDD patients. Interestingly, in another study, 25mg of zinc supplementation for 2 months improved the depressive symptoms and increase omega-3 status in plasma phospholipid of patients.

Selenium, plays a significant role in Anti-oxidant Defence System. Its deficiency can interfere with the normal conversion of ALA to EPA and then DHA and results in increase in n-6: n-3 ratio and negatively affect mood and predispose the criteria for developing depression.

A growing body of research documented that low **Folic acid** level were noticed in depressed individuals. Some small studies gave evidence about beneficial effect of folic acid in depression and enhance the effectiveness of antidepressant drugs at just 500 µg. it is shown that, folic acid supplementation improve the folic acid status in animal model, but when not supplemented no such improvement was found out. Last but not the least, folic acid deficiency can lead lipid peroxidation.

In patients with MDD, there are a causative fact of oxidative stress and lipid peroxidation and antidepression medications reverse the situation. **Dietary antioxidants** are known to influence Antioxidant Defence System. Many research work also found that antioxidants influence omega-3 fatty acid status and omega-3 PUFAs are shown to decrease lipid peroxidation.

EFFECT OF OMEGA-3 PUFAs ON DEPRESSION IN VARIOUS STAGES HUMAN LIFE SPAN

- ***OMEGA-3 PUFA AND PERINATAL DEPRESSION*** - Perinatal depression is onset of depression during pregnancy or postpartum within 1 year after delivery. It can be severe and persistent if it untreated or ignored. One thing must be kept in mind that perinatal depression is different from "Maternity Blues [17] or Postpartum Blues, is the occurrence of mild depressive symptoms like – anxiety, decreased concentration, insomnia etc, which typically developed 2-3 days after child birth and resolved by one-self (Self-limited) within 1-2 weeks of onset [17,31]. Postpartum blues is milder self-limiting whereas postpartum depression is more severe and need proper treatment [31].

  Symptoms of postpartum depression include - lack of pleasure, insomnia, guilt feeling, self-harm or even suicide. Depression during pregnancy can harm the baby including small size, preterm birth, defect in cognitive development and may have a risk of depressive behaviour or development of criminal activities in adolescence and adulthood.

  More or less all antidepressants cross the placental barrier. Mothers are also refuse to take medication during pregnancy period in fear of serious side effects on offspring like – cardiovascular malformation, maladaptive syndrome etc.

  Mi-Mi-Zhang et al. stated that omega-3 with specially higher ratio of EPA/DHA (≥1.5) has significant efficacy in MDD, hence, considering the safety issue in perinatal period, omega-3 fatty acids are supposed to be a very effective alternative therapy [17].

- ***EFFECT OF OMEGA-3 PUFAs IN POSTPARTUM DEPRESSION –*** Postpartum depression is characterized by low mood, anxiety, fatigue, low motivation in one word all the symptoms of clinical depression but different from Postpartum blues [31] or Baby blues [32]. The characteristic symptoms of postpartum depression may arise from 1 month to 1 year after child birth or delivery [32]. Around one in seven women may develop postpartum depression [33]. Prevalence rate of postpartum depression is between 5%-60.8% Worldwide [34].

  It was seen that women who had multiple pregnancy or a sort interval (less than 24 weeks) between two pregnancies had a higher risk of having postpartum depression.

  Many studies were conducted on human and rats, the result revealed that after a single pregnancy plasma DHA level is decreased by 50% and erythrocyte and liver DHA levels also depleted significantly. So, if the DHA supplementation were not done properly, it would affect the baby as they would not get enough DHA from mother's milk.

  A study was conducted and concluded the result that if diet low in DHA was fed to a mother, the mother's brain phospholipid content was reduced roughly by 25% and associated with altered fatty acid composition in brain.

  Many epidemiological and clinical studies reported that pregnancy associated changes in omega-3 fatty acid status may be a sole cause of developing postpartum depression. Also some studies concluded that higher fish consumption was reflected in high DHA content in breast milk and a lower incidence of postpartum depression [35].

- ***OMEGA-3 PUFAs AND DEPRESSION AMONG CHILDREN AND ADOLESCENTS –*** The prevalence of paediatric depression is high, with approximately 2.8% in children, 5.6% in adolescents Worldwide [30]. The fact is that, prevalence rate of MDD is low in prepubertal children but it increases substantially through the adolescent period. Females have a three times more chance of facing first depression episode than male in age group of 12-17 years [20]. There is a 70% chance of relapse of paediatric depression within 5 years and half of the young people may experience of recurrence of at least once during their adult life. Depression causes great harm to young people's social activity and a major risk factor for suicidal tendency in adolescents [30]. It is seen that 20% of childhood onset MDD will recover within 3 months and about 60% within 9 months, thus a mean length of recovery of childhood onset MDD is about 9 months. Another study stated that mean duration of recovery from depressive episode about 27 weeks. But it is seen that most of the cases this disorder is not recognized by professionals but it should be kept in mind that the findings are alarming and if undiagnosed and untreated might cause disability between 10-24 years.

  Dramatic changes in lifestyle and dietary pattern specially practice of Western lifestyle and food pattern does not balance between omega-6 and omega-3 fatty acid ratio in today's young generation. Omega-6 fatty acids are present abundantly in processed foods and at the same time fish consumption rate is very poor. many epidemiological studies provide some evidence that high intake of fish seems to be a protective factor against the development of depression [20].

  Mainly two widely used type of therapies used for depression are – Pharmacotherapy and Psychotherapy. For the first line treatment of depression, psychotherapy is carried out mild effect. Antidepressants are used in clinics for treating moderate to severe paediatric depression along with psychotherapy. But in 2004, US Food and Drug Administration (FDA) alert clinicians about antidepressants as these were associated with increased risk of suicidal tendency in adolescents.

  Omega-3s are known for its widespread effect on cognitive function improvement but there are no such effect on depression. Many small scale epidemiological studies, clinical trials provide data towards beneficial effect of omega-3 PUFAs on paediatric depression but large scale studies did not give evidence on such thing. Many studies reported no or small beneficial effect of omega-3 fatty acid ion

depression. A recent meta-analysis study reported about beneficial effect omega-3 fatty acid in infants upto 18 months of age but no such effect on children, adolescents, although some questions were raised about the validation of the result [20]. Thus, Zhang et al. concluded about the topic, omega-3 fatty acid on depression, is that many more studies should be conducted in future for gather evidence that omega-3 fatty acid is greatly effective for paediatric depression (specially) and depression among all age groups [30].

- ***EFFECT OF OMEGA-3 PUFAs ON GERIATRIC DEPRESSION*** – Ji-Hyun et al. (2018,Feb) reported that omega-3 fatty acid supplementation is effective in mild to moderate depression in elderly people [37].

  M. Rondanelli et al. (2011) designed a two month, randomized, double-blind, placebo-control trial in an Italian nursing home among 46 depressed females, aged between 66-95 years to find out relationship between Omega-3 PUFA and geriatric depression. The study result concluded that long chain polyunsaturated fatty acid supplementation reduce the occurrence of depressive symptoms, change phospholipid fatty acid concentration and overall improvement in health related quality of life [38].

SOME STUDY BASED EVIDENCE OF EFFECTIVENESS OF OMEGA-3 PUFA IN VARIOUS MENTAL DISORDERS AMONG SOME OCCUPATIONAL GROUP [13]

A fairly good amount of omega-3 fatty acid in military diet, will help in rebalancing the essential fatty acid composition, help in reducing psychiatric disorders mainly depression and suicidal tendency etc.

A study was conducted in nurses as they are considered to be the most vulnerable to depression; the author evaluated that omega-3 fatty acid and mindfulness-based stress management was recommended and it gave an amazing result in maintenance of healthy mental state, coping with depression, stress management etc.

ADVERSE EFFECT OF OMEGA-3 PUFA SUPPLEMENTATION [16]

Many evidence prove that long term supraphysiological deses of omega-3 PUFA supplementation may lead unwanted side effects.

The more common adverse effects of fish-oil preparations, particularly high dose may cause nausea, fishy burping and loose stool. Because of these effects, the effectiveness of fish oil in treatment of mental illness, is in front of question.

Several potential risks need to be considered when natural natural omega-3 PUFAs are administered. Marine fish and seafood, a rich and renowned source of omega-3 PUFAs, may be contaminated with methylmercury dioxins, polychlorinated biphenyls, can increase the risk of some cancers and may cause harm to a growing foetus when these consumed with marine fishes and seafoods by a pregnant woman.

Fish oil supplements may contain antioxidants and omega-3 PUFA's oxidation products, both of these can lead to adverse reactions. The possible long-term effect of Vitamin E, which is added as an antioxidant to fish oil supplements, large scale trials have proved that alpha-tocopherol supplementation have a link with elevated rates of prostate cancers.

DISCUSSION AND CONCLUSION

In this Review it is seen that, omega-3 polyunsaturated fatty acid are a type of polyunsaturated fatty acids which are known as "Essential Fatty Acids" as they are not produced in the body of most of mammals and because of that reason they should be consumed through diet and they have a wide range of functions in human psychological systems like- improve cognitive function , anti-inflammatory effect , maintain cell wall integrity, membrane fluidity etc. and omega-3 PUFAs are effective against various chronic diseases such as- cancer, arthritis etc. besides these all now-a-days a very cultivated topic about omega-3 PUFAs, is relationship with depression. Depression in last few decades spread like a terrifying thing irrespective of age, sex, occupation, race, living standard, telling in one line that anyone from any place any background can be affected by depression. We all know that pharmacotherapy for depression are very costly and antidepressant drugs can cause a no. of side effects , whereas as an alternative or add-on therapy of Omega-3 PUFA has a very limited or no side effects. Some studies said that in long term use there is a lesser chance of side-effect of Omega-3 supplementation. Some studies stated that as omega-3 PUFAs are nature derived source, in general those do not cause any harm if there not contaminated by somethings like- marine fishes are a rich source of omega-3 PUFAs, so if they are contaminated with heavy metals they will cause harm to those who will consume these contaminated fishes. In general omega-3 supplementation are combined with anti-oxidants, so in this cases long term use of antioxidants may create problematic effects. As a whole if omega-3 PUFAs are consumed or supplemented in a permitted or prescribed level it will give its beneficial effect rather than adverse effect.

EPA and DHA are the main bio-active forms of Omega-3 PUFA and they are both may show antidepressant property but some studies stated that only EPA possess antidepressant effect. Ethyl EPA(E-EPA) is a synthetic derivative product of EPA, very effective for lowering the depressing outcomes. In which mechanism omega-3 PUFAs are act like antidepressant are not clearly known but some hypothesized mechanisms are revealed the possible mechanism of action like- antiinflammation and antioxidation property, a part of proper neurotransmission, neuroplasticity etc.

Studies proved a strong correlation between fish consumption and occurrence of depression. In many studies reported that those countries where fish consumption rate is high there was a less prevalence of depression and on other hand, people of those countries consume less fish study report showed a high prevalence of depression in them.

Omega-3 to Omega-6 PUFA ratio is a very effective point for depression. Increased level of Omega-6 PUFAs are responsible for the production of pro-inflammatory cytokines which are thought to predispose the criteria for development of depression where as Omega-3 has a suppressive effect against pro-inflammatory cytokines and thought to protect from depression occurrence or decrease the depressive symptoms.

Many studies showed both mainly positive and some not such fruitful type of result about the role of omega-3 fatty acid against depression in various stages of life like- perinatal period, postpartum period, adulthood, geriatric population but no such effective result were found for depression in children and adolescent age group.

So, as a whole, from this review study we may conclude that Omega-3 PUFAs in general is effective for cognitive development and to a very greater extent effective against depression with or without traditional antidepressant therapy. Many studies and clinical and epidemiological trials have done in favour if omega-3 fatty acid against depression. Very few studies has given positive evidence about successful omega-3 supplementation as monotherapy against depression, but omega-3 fatty acid supplementation therapy as an add-on therapy with antidepressant therapy is found to be more promising.

It will be helpful to the common people if many more studies will be done on omega-3 PUFA supplementation as monotherapy for prevention as well as treatment of depression, a major health problem in this modern era.

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