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ROLE OF ECOSAPENTAECONIC ACID (EPA) AND DECOSAHEXAENOIC ACID (DHA) AS ADD-ON TREATMENT OF MAJOR DEPRESSIVE DISORDER (MDD).

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ABSTRACT

Depression or Major Depressive Disorder (MDD) is a pervasive, recurrent mental disorder. Worldwide, roughly 350 million people of all ages are affected by depression. Depression is a main global burden as a fourth leading cause of disability among the list of ten by the world health organization in 2012 survey Male, female depression affect ratio is 1:2, worst of which lead to suicide. The human brain comprises of roughly 60% of fat. Grey matter contain 50% of polyunsaturated fatty acids (PUFAs) among which 30% belong to omega-3 polyunsaturated fatty acids (PUFAs) family, and accordingly are taken through diet. Over the last two decades mounting attention has been given to the role of omega-3 polyunsaturated fatty acids (PUFAs) regarding the etiology and treatment of psychiatric disorders. This review aims to explore the scientific evidence to support the hypothesis on the role of omega-3 polyunsaturated fatty acids (PUFAs) in the treatment of depression. For this purpose PubMed and science direct, databases were used to search the non-duplicate studies published from September 2012 to September 2016. Clinical trials, observational studies, and randomized double and single blind placebo controlled trials (RCTs) were searched by staying within the realm of original studies, role of omega-3 in depression in human, and role of omega 3 purely on depression. Articles were rejected on first sight which were inadequate to inclusion consideration, non-human studies, role of omega 3 in bipolar depression, pilot studies, role of omega 3 in co-morbid depression and role of omega 3 along with omega 6 in depression. This review is different from others as it focuses on role of Ecosapentaeconic Acid (EPA) and Decosahexaenoic Acid (DHA) exclusively in depression

Keywords: Eicosapentaenoic acid (EPA), Decosahexaenoic acid (DHA), Randomized controlled trial (RCTs), Alpha linolenic acid (ALA)

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INTRODUCTION

Depression is a medical abnormality, evidenced by low mood, loss of pleasure, feelings of guilt and thoughts of suicide. Globally affecting the people of all ages, from all communities.[1] The Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV), describes the diagnostic criteria for major depressive disorder as low mood, anhedonia and anergia, lasting for a period of at least two weeks.[2] According to world health organization, more than 4.5% people throughout the world are affected by depression.[3] Depression is connected to a variable prognosis and chronic pathway; the median period of an episode is reported to be 23 weeks.[4,5]

Currently depression is the fourth leading cause of disability and till 2020 it will become second among ten leading causes of disability.[6] Social and economic effects of depression and suicide are getting very high in present decades.[7] Further more other medical condition associated to depression are suicide, type-2 diabetes, coronary heart disease, and complications regarding recovery from chronic disease.[8] The 20 times increase in depression post 1945 cannot be

explained by changes in attitude of health professionals and society, criteria of diagnosis, and reporting bias.[9] Despite of advancement in pharmacology and increasing focus on cognitive/ behavioral intervention, there is prominent treatment resistance[10] Omega-3 fatty acids are long chain poly unsaturated fatty acids, sources are plants and marine of our diet.[2] Omega-3 PUFAs named due to presence of first carbon bond on third atom from methyl end of chain. [11,12] EPA and DHA members of omega-3 PUFAs family originate from α-linolenic acid (ALA), ALA however, cannot be produced by human body.[13] Hence must be obtained from diet.[14]

Human body can synthesize the long chain omega-3 PUFAs, but biological availabilityis slow and inefficient, hence diet an important source of these fatty acids.[15] Dietary origins of α-linolenic acid (ALA) are seeds and certain nuts, like walnut, flaxseeds and rapeseed oil. Dietary origins of the omega-3 PUFAs as EPA and DHA consist of fatty fish, some white fish, shellfish, and other seafood.[16,18]

Combination therapy with omeg-3 fatty acids found to be effective in decreasing the symptoms of depression.[19] In past, several research into understanding the etiology and pathophysiology of depression has focused on genetic and environmental factors, while, pharmacological treatment were based on the monoamine hypothesis of depression.[20] Till now, selective serotonin reuptake inhibitors (SSRIs) are mainly prescribed drugs for treatment of depression.[21] Omega-3 fatty acids are emerging as a potential agent in the area of research for the depression treatment. [22,23] Combining Omega-3 fatty acids with SSRIs is beneficial in the treatment of depression.[24]

METHODS

A review of literature from last 7 years was made. Original studies, published from July 2011 to July 2017 were included. Randomized single and double blinded clinical trials and cross sectional studies were reviewed. Pub Med, science direct and Cochrane databases were used. Two sets of keywords were used to search **(**Omega-3 polyunsaturated fatty acids, eicosapentaenoic acid EPA and docosahexaenoic acid DHA**)**and **(**Depression, Major Depressive Disorder MDD**).**

The following search limits were considered **(**role of omega-3 in depression in human and role of omega 3 purely on depression**).** Following studies were rejected,**(**inadequate to inclusion consideration, role of omega 3 in bipolar depression, pilot studies, role of omega 3 in co morbid depression and role of omega 3 along with omega 6 in depression). This search strategy found 66 non duplicate articles and among these 15 were found to be compatible to criteria. These selected studies were conducted throughout the worldwide. Potential role of omega 3 in treatment of depression was investigated by 10 double blind placebo controlled trials, 4 single blind placebo controlled trials and 1 cross sectional studies. Among 15 studies 11 explored potential role of omega 2 polyunsaturated fatty acid in treatment of depression. While other four found mild role in treatment of depression.

Omega 3 PUFA:

Three naturally occurring fats which are named according to the number of double bonds between carbon-carbon atoms, in their fatty acid side chains and categorized as saturated, monounsaturated, and polyunsaturated.

Moreover these fatty acids are ranked as (monounsaturated and polyunsaturated containing one or more carbon-carbon double bonds). This is based on the isomeric configuration on the carbon-carbon double bond, Trans or cis fatty acids. These differences in fatty acid structural configuration are known to affect changes in LDL and HDL serum cholesterol levels in humans.[25]

Table 1: RCTs from July 2011 to July 2017 for Effect of EPA and DHA in the management of depression.

Authors & years of publication	Country	Study design	N	Age (years)	Case EPA DHA /Day	Control	Duration of study	P value
Binod Thapa Chittrietal. April 2016	USA	Non-Randomized before and after control trials	28	22-50	EPA 1.6g DHA 0.8g	placebo	6 weeks	= 0.008
Annie, T.etal. June 2015	USA	Double blind randomized control trial	23	18-21	EPA 1g DHA 400 mg	Corn oil	21 days	= < 0.04
Yongsoon park etal. March 2015	Korea	Double blind randomized control trial	35		EPA 1140mg DHA 600mg	Olive oil	12weeks	= 0.519
Mischowon D.etal. Jan 2015	Boston USA	Double blind randomized control trial	154		EPA 1gm DHA 1gm		8weeks	=< 0.o5
K.P.su etal. Oct 2014	UK	Double blind randomized control trial	152		EPA 1.7gm DHA 3.5 gm	Oleic oil	2 weeks	=0.02
Mozaffari et al, July 2013	Iran	Double blind randomized control trial	81		1gm EPA 1gm DHA	Coconut oil	12 Weeks	< 0.001
Gersticketal. Feb 2012	US California	Single blind placebo control trail	42	18-65	EPA 900mg DHA 200 mg	Olive oil	8weeks	= 0.018
Sinn N etal Sep 2011	Australia	Double blind randomized control trial	40	>65	EPA 400mg DHA 1500mg	Omega-6 safflower	6 months	=0.02
S.L.duffyetal April 2015	Australia	Double blind randomized control trial	80	60-82	EPA 12mg DHA 800mg	Paraffin oil	12 weeks	=< 0.05
Shiraishi M et al. jun 2015	Japan	Cross sectional	371	34+- 4.1	EPA+DHA 1gm	Placebo	2010-2012	= 0.01
Dashti et al jul 2014	Iran	randomized control trial	40		EPA 1.8g DHA 1.2g	Placebo	4 months	0.008
MH Rapaport et al, Jan 2016	USA	Double blind randomized control trial	40		EPA 1060mg DHA 3900mg	placebo	8 weeks	0.04
LY Freund et al, Apr 2014	Sweden	randomized control trial	40		EPA 1.7gm DHA 0.6 gm	Placebo	6 months	<0.05
BJ Meyer sep 2013	Australia	randomized control trial	95		EPA 0.6 g DHA 2 g	Corn oil	16 weeks	0.001
Mazereeuw et al oct 2016	Canada	Double blind randomized control trial	79	45 80 years	EPA 1.2g DHA 0.6g	Placebo	12 weeks	0.002

Moreover Polyunsaturated fats are categorized into two types based on the position of the first carbon - carbon double bond from the end of chain as in n-3 first double bond is present at third carbon atom and in n-6 double bond present at sixth carbon atom. There are two important n-6 PUFA in human diet, arachidonic acid (AA), and linoleic acid (LA). Arachidonic acid (AA), is obtained from animal side like meat, eggs, and dairy products, while linoleic acid (LA) is come from vegetable source.

Vegetable sources such as oils of corn, safflower, and soybean, and in commercially baked goods as well as from fried foods. Western diet mainly consist of arachidonic acid (AA) poly unsaturated fatty acid (PUFA), is also converted from linoleic acid (LA) in human body, comprises of more than 85% of poly unsaturated fatty acid (PUFA) (Suntrap 2006). n-3 poly unsaturated fatty acids (PUFAs) comes from alpha linolenic acid (ALA)

which is found in canola, hemp, walnuts as well as flaxseed which contains the highest concentrations.[22] Alpha linoleic acid is converted in vivo to (EPA) and docosahexaenoic acid (DHA).[22] Sea food like oily fish such as tuna, salmon, mackerel, and sardines is a concentrated source of EPA and DHA. ALA and LA which are essential fatty acids, because they cannot be synthesized by the body and must be derived from dietary sources.[26]

Possible mechanisms of n-3 PUFAs in depression:

Double bonds in long-chain PUFAs consist of at least twenty c-atoms, are portion of phospholipids that make the cell membrane.[27] Phospholipids of brain composed of high amount of these fatty acids, Docosahexaenoic acid and arachidonic acid occupied most of brain structure, representing approximately 15% and 10% respectively of total fatty acids in brain.[28,29] There is higher concentration of DHA in frontal cortex and other cortical regions, whereas the lowest concentration is found in midbrain areas of brain.[30,31]

To explain the mechanism of omega-3 PUFA in treatment of depression, there are two main neuro-physical pathways. Mounting studies, support the relationship between depression and pro-inflammatory cytokines.[32] Some studies suggested that cytokines decreases neurotransmitter precursor availability, activation of the HPA (hypothalamic pituitary adrenalaxis) and altered neurotransmitter metabolism.[22] There is not just association between depression and pro-inflammatory cytokines, but also act as indicator of severity of depression.[33] Pro-inflammatory cytokines bring about an enzymes activity named indole amine 2,3-dioxygenase, this enzyme originates metabolism of tryptophan and kynurenine in the central nervous system and chemically deteriorate serotonin.[34]

The presence of pro-inflammatory cytokines especially PGE2 and thromboxane B2 found associated with depression by many research studies. Omega-3 PUFAs are good documented inhibitors of both pro-inflammatory cytokines and inflammatory eicosanoids.[35] Another pathway of action of omega-3 PUFAs is maintains of membrane integrity and fluidity which is indispensable for neurotransmitter binding and signaling within the cell.[36] Furthermore, omega-3 polyunsaturated fatty acids (PUFAs) affects brain derived neurotrophic factor (BDNF), which promotes synaptic plasticity, hence provide neuro protection and promotes neurotransmission , has an antidepressant effects.[22]

CONCLUSION

Most of these studies indicated potential role of Ecosapentaeconic acid (EPA) and docosahexaenoic acid (DHA), while very few studies were found to have no association. Although present study concluded potential role of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in the treatment of depression, more observation and interventions are needed to exclude the clinically affective dose of ecosepantaecnic acid (EPA) and docosahexaenoic acid (DHA) in treatment of major depressive disorder (MDD).

Transparency Declaration

It is affirmed that this manuscript is an honest, accurate, and transparent account of the study being reported, no important aspects of the study have been omitted. All authors and co-authors worked honestly.

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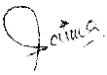
2	Saima Kouser	Co-Author	
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