An Overview of Analeptic Applications of Omega-3 Fatty Acids

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ABSTRACT
This article is an examination of the Analeptic Applications of Omega-3. The scientific development and subsequent clinical applications of Omega-3 in Healthcare continue to influence researchers all over the globe today. This article examines the research done and published by researchers and scientists. Consideration of current trends and data in scientific queries and demonstrates further aspects of the applications of Omega-3 on various health backgrounds, including.

Cardiovascular Health: The study addresses the comparison of Omega-3 and Omega-6 in cardiovascular diseases. Higher intake of dietary Omega-3 helps activation, inhibition, and alteration of metabolic and signaling pathways which is associated with better cardiovascular health, while Omega-6 decreases the risk of coronary heart diseases and cardiovascular disease mortality.

Immunology: Omega-3 Polyunsaturated Fatty Acids (PUFAs) have been found to show an anti-inflammatory effect in the body by downregulating the activation of various immune cells. They regulate immunological functions via eicosanoids and resolvins which are anti-inflammatory. External supplementation can reduce chronic and acute inflammation as well as reduce the chances of graft rejection. The regulatory effect is shown by modifying gene expression and/or

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signal transduction in human cells. They are also involved in altering the membrane composition of Fatty Acids (FA) and as a result, they affect the lipid raft structure and also membrane trafficking.

**Joint Health:** The study shows the effects of omega-3 and other fatty acid consumption in Rheumatoid Arthritis (RA), bone marrow lesions, and knee cartilage lesions. It notes the interrelations between synovitis, plasma levels of Omega-3 and Omega-6 PUFAs in OsteoArthritis (OA) patients along with risk factors for OA, which could help consider liable treatments for improvement of OA. The study highlights the importance of the Omega-6:Omega-3 PUFA ratio and clinical and functional outcome measures which can help us in better understanding the role of PUFAs and possible treatments for people with knee osteoarthritis while showing the effect of Omega-3 fatty acids on muscle health in RA.

**Skin Disorders:** Fish oils rich in PUFAs are reported to improve several inflammatory disorders, including rheumatoid arthritis and psoriasis. They have also been broadly reported as a potential supplement to ameliorate the severity of some skin disorders such as photoaging, skin cancer, allergy, dermatitis, cutaneous wounds, and melanogenesis. The significance of omega-3 in skin structure was proved by describing a syndrome caused by stringent fat reduction in the diet that leads to erythema with scaling, hair loss, itching, and increased water loss.

**Keywords:** Analeptic; resolvins; leukotrienes; protectins; linoleic acid; nutraceuticals.

1. **INTRODUCTION**

Fatty acids are saturated, monounsaturated, and polyunsaturated. The main physical difference between them is that saturated fatty acids are solid at room temperature, while unsaturated fatty acids are liquid [1-6]. Linoleic acid, a precursor of the omega-6 series of fatty acids, and α-linolenic acid (ALA), a precursor of the omega-3 series of fatty acids, are considered to be the two essential fatty acids. They make up the fatty acid profiles of cells of our body and Eicosanoids, which are formed by either Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) which are a part of the Omega-3 FA family, or Arachidonic acid (AA) which is a part of Omega-6 FA family. Omega-3 and Omega-6 both have 18 carbon chains and the structural similarity leads to competition between the two for enzymes [7-16].

Mammals cannot synthesize Linoleic and α-Linolenic from Oleic acid since they lack Δ12-desaturase and Δ15-desaturase enzyme, but they can convert α-linolenic acid obtained in diet to EPA and DHA [17-25]. However, most marine plants can form EPA and DHA which are transferred to fishes via the food chain. This makes fish oil a rich source of Omega-3 PUFAs.

The 'Western diet' today reflects a fatty acid breakdown of 20% arachidonic acid (AA), 1% EPA, and 2.5% DHA which indicates that the diet is rich in saturated and Omega-6 PUFA at the cost of Omega-3 PUFAs. Omega-3 FAs as anti-inflammatory nutraceuticals. As a result, human cells are rich in AA as compared to DHA or EPA [25-32].

Vegetable oils, another source of Omega-3 FA have been used for a plethora of health benefits by their incorporation in foods, cosmetics, and pharmaceutical products, especially those intended for skincare which has in turn led upto 86% of dermatology patients to modify their diet to improve the condition of their skin. The cure of skin conditions like Psoriasis and atopic dermatitis is accelerated by the dietary intake of Omega-3 Fatty Acids. Moreover, many studies and clinical trials have proven the triglyceride reducing property of omega-3 fatty acids [32-38].

Omega-3 FA reduces the AA contents of inflammatory cells which utilizes a class of mediators called specialized pro-resolving lipid mediators (SPMs), thus lowering the production of AA-derived inflammation mediator molecules. This is due to their competition with w-6 PUFAs, principally arachidonic acid, as substrates for the cyclooxygenase component of Prostaglandin H2 (PGH 2) synthase, leading to the formation of less active prostanoids. Hence, the change in the FA composition (increases Omega-3:Omega-6 ratio in cells) causes changes in immune functions like phagocytosis, lipid mediator production, T cell reactivity, and antigen-presentation capabilities. It is also associated with increased inflammation and decreased immunity, in a dose-dependent manner, and can alter gene expression to negatively affect organ function. While high omega-6 in diet shifts the metabolism towards the synthesis of Arachidonic acid which increases inflammatory mediators, Omega-3 having antiinflammatory properties changes the fluidity of platelets and inhibits their aggregation.
Both of them are components of phospholipids and are therefore found in cell membranes. The incorporation of omega-3 into cell membranes alters its property. It can modify the Na+ and Ca++ channels and avoid cholesterol domain formation. They can also reduce the number of triglycerides in the blood by activating liver uptake of triglycerides. It can bind to nuclear receptors and transcription factors involved in lipid metabolism and can also regulate gene expression of inflammatory molecules.

While the cardioprotective effects of Omega-3 are not based on just one mechanism but involve various interrelated working pathways, they are largely due to its aggregation and inflammation resistive effects. These involve activation, inhibition, and alteration of different metabolic and signaling pathways. Higher dietary intake of omega-3 is associated with better cardiovascular health and higher plasma concentration of omega-6 has been associated with decreased risk of coronary heart disease and cardiovascular disease mortality.

Human exposure to UVR has increased over the past 50 years and is largely attributable to behavioral changes relating to sun exposure. Omega-3 PUFA are multi-active agents that may convey photoprotection through a range of mechanisms including alterations in membrane fluidity, modification of signal transduction, transcription factor activation, modulation of oxidative stress, and production of bioactive lipid mediators sunburn, nutrients may provide a lower level of protection against chronic, repeated UVR insults.

Apart from these benefits, Omega-3 PUFAs also reduce the development of OsteoArthritis and Rheumatoid Arthritis. Osteoarthritis is a common joint inflammatory disease that leads to the destruction of joint cartilage. Intervertebral Disc (IVD) degeneration is a usual cause of lower back pain. It involves the breakdown of Nucleus Pulposus (NP) leading to defects in Annulus Fibrosus and Disc endplates. OA with synovial inflammation can vary from between the joints to within individual joints to between two joints. Knee Osteoarthritis includes inflammation, chronic pain, and psychosocial distress. Rheumatoid Arthritis (RA) is an inflammatory disease that causes joint destructions and functional impairment. Insulin resistance, metabolic syndrome, and sarcopenia are some co-occurring diseases that are associated with RA. Sarcopenia is caused by changes in the muscle leading to changes in muscle strength and mass. Prevention of agitations like lipotoxicity, mitochondrial dysfunctions, and insulin resistance can help in improving muscle health.

The efficacy of omega-3 fatty acid is still under a lot of discussion, but in most cases, the benefits have been proven by various experimental and observational studies. Hence its use as a therapeutic agent has been increasing rapidly. It is seen in the cases of homeostasis, maintenance of skin health, and treatment of skin disorders like sunburn, cancer, photosensitivity, and photoaging. In the case of anti-inflammation, the exact mechanism of action of Omega-3 FAs remained unknown for a very long time, but despite that, its use as a therapeutic agent has rapidly increased. On external supplementation, cell membranes of most immune cells including phagocytes like neutrophils and monocytes take up PUFAs especially Omega-3 PUFAs more rapidly than other unsaturated fatty acids. This uptake causes a change in the physical properties of the membrane and increases the phagocytic capacity of cells. Additionally, the anticancer effect of Omega-3 PUFAs is ascribed to the capability of downregulating proinflammatory eicosanoid synthesis from cyclooxygenase-2 (COX-2).

There are different products available on the market containing omega-3 and omega-6 oils from different sources. Some of these products are Food and Drug Administration (FDA) approved and are used as supportive or therapeutic medication but most other products are used only as dietary supplements. This paper aims to investigate the Analeptic Applications of Omega-3.

2. METHODS

The study was conducted using four databases Google Scholars SAGE, DOAJ, and PubMed. The selection of papers was done based on keywords and themes relevant to this area. Further, the published papers from these databases were arranged in systematic order concerning the year of publication.

3. RESULT AND DISCUSSION

3.1 Cardiovascular Diseases

3.1.1 Benefits of omega-3

The cardioprotective effects of Omega-3 are not based on just one mechanism but involve various
interrelated working pathways. These mechanisms have been proven by various clinical trials such as the REDUCE-IT and OPERA trials. Some of the effects include.

3.1.2 Effects on triglycerides

Omega-3 decreases TG by inhibiting hepatic Very-low-density lipoprotein (VLDL) to TG synthesis and secretion. It can also decrease the activity of certain enzymes that catalyzes TG synthesis. It also decreases low-density lipoprotein (LDL) and chylomicrons. The REDUCE-IT trial found that people with very high blood triglycerides who were given a high dose of EPA, had a reduced blood AA: EPA ratio, decreased high sensitivity c-reactive protein (hs-CRP), remnant-like particle cholesterol (RLP-C), apolipoprotein C-III (ApoC-III), and oxidized LDL-C (oxLDL) concentrations compared to placebo controls. DHA reduced more than 25% of postprandial TG in diabetic men. EPA had a much better triglyceride reducing effect than DHA or EPA/DHA combined. These properties of omega-3 can be achieved only if the right dosage is taken for the right duration. At lower concentrations, the effects do not show and can vary between populations.

EPA and DHA, both have the efficacy in reducing triglyceride levels. However, the structural dissimilarities between EPA and DHA cause them to have varied effects in-vivo. In most cases, EPA has been proven more potent while DHA remains either equally potent or less potent than EPA. In some cases, DHA has shown detrimental effects due to its intrinsic structural properties. These cases, however, need more research to determine the safety of DHA as a dietary supplement.

3.1.3 Effects on inflammation

Omega-3 FAs can produce signaling molecules that can reduce inflammation whereas omega-6 FAs have a pro-inflammatory effect. In a meta-study, it was observed that omega-3 had a cardiovascular risk reduction effect but not omega-6. Several bioactive compounds are a derivative of omega-3. These include resolvins, leukotrienes, and protectins. These compounds promote the resolution of inflammation and reduction in reactive oxygen species (ROS).

So, it can be said that the anti-inflammatory effects of EPA/DHA can further increase effectiveness. The dosage and duration of therapy is also a major determining factor for efficacy. For hemostatic parameters, a minimum of 2 weeks with 4g daily of omega-3 is needed. People with a lower intake of omega-3 based food may require more than 4g/day for 6 weeks for considerable effect on hemostasis.

3.1.4 Effects on membrane fluidity

The property of the cell membrane is altered when omega-3 is incorporated into it. It can alter the properties of lipid rafts and caveolae that act as signaling platforms for lipid transport, endocytosis, and signal transduction thereby modulating downstream signaling pathways. Multiple mechanisms of this function have been hypothesized. One direct mechanism is the reduction in membrane excitability potential in Na+ channels which increases the refractory period after excitation.

3.1.5 Effects on endothelial function

Omega-3 can decrease endothelial function by inactivating inflammatory cytokines that activate the endothelial. It shifts eicosanoid production towards anti-thrombotic mediators and causes the release of NO (cellular relaxant) in endothelial cells. A study done on mice deficit in an endothelial isoform of nitric oxide synthase (eNOS) enzyme showed insulin resistance and reduced nitric oxide (NO) production. Vascular smooth muscle cells (VSMC) can overgrow in arteries which can lead to arterial damage. EPA and DHA to some extent can inhibit VSMC growth by blocking cytokines from activating them. A study showed that DHA and EPA can alter DNA synthesis by reacting with cyclins and cyclin-dependent kinases.

3.1.6 Effect on atherosclerosis

The development of Atherosclerosis is mediated primarily by oxidized low-density lipoprotein (LDL). This causes the build-up of plaque in the arteries due to the coagulation of platelets. Omega-3 can both, directly and indirectly, respond to inflammation by rapidly regulating transcription factors and by producing signaling molecules and lipid-based anti-inflammatory mediators. In a study done on transgenic rabbits, an increase in levels of LXA4 (LXA4 is a resolvin molecule that is released during inflammation) reduced atherosclerosis, and biosynthesis of LXA4 reduced the number of cytokines that cause the development of atherosclerosis. Protectins, which are a derivative of EPA, is another anti-inflammatory compound that blocks neutrophil recruitment and activating by blocking TNF-α secretion.
Mechanisms involving the cardioprotective effects of n-3 PUFA

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<td>Inflammation</td>
<td>Decrease TNE-α, IL-1β, IL-6, IL-8, CRP, SAA, PPARα, PPARγ, iNOS</td>
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<td>Increase Two- and four-series eicosanoids (derived from n-6 PUFA)</td>
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Stimulation

Proresolving mediators

Stabilization of atherosclerotic plaques

TC lowering

Changes in membrane lipid composition

Fig. 1. Structural view of fatty acid

Fig. 2.
Omega-3 can modulate gene transcription, mRNA processing, and PTM of proteins thereby altering gene expression. Peroxisome proliferator-activated receptors (PPAR) are a group of nuclear receptors. PPARα and PPARδ can inhibit the expression of proinflammatory genes by inhibiting NF-κB activation. EPA and DHA have been deemed as agonist molecules for both these receptors.

### 3.1.7 Antioxidative effects

EPA and DHA have different cellular properties due to their structural dissimilarities. This molecular difference causes them to have different types of interactions. EPA can get incorporated into lipoprotein particles and react with ROS. A study showed that patients treated with EPA had significantly lower oxidized LDL (oxLDL) levels. These molecules can be harmful to health because they can cause foam cell formation. In contrast, the antioxidative property of DHA declines more quickly than EPA due to its longer carbon chain and extra double bonds that cause isomerization.

### 3.1.8 Hematological effects

EPA inhibits the activity of thromboxanes and thus reduces platelet activity. A study conducted on normal patients used EPA supplements for 25 days and found a >60% decrease in platelet adhesion to fibrinogen and collagen. There were concerns regarding the excessive bleeding effect of omega-3 but most researchers believe that these effects are theoretical but practically are safe to use.

### 3.1.9 Electrophysiological effects

Omega-3 can stabilize cardiac membrane systems by inactivating fast sodium channels and increasing cytosolic retention of calcium. Apart from this, omega-3 can reverse or inhibit physiological processes such as oxidative stress, inflammation, and endothelial dysfunction.

### 3.1.10 Effect on haemostasis

Several studies have shown that omega-3 has anti-platelet activity and can lower the concentration of thrombin and factor V coagulation factors. The effect of fish oils on hemostasis was observed in studies done on cardiovascular disease patients along with healthy control. It was concluded from the study that for patients with CVD, a higher dose is required. People who consume on average two fatty fish per week have a much lower chance of getting any such diseases. Higher consumption of omega-3 had a significant effect on the inhibition of inflammatory markers without affecting platelet reactivity. For this reason, the antithrombotic effect of omega-3 can be used as a combined therapy for the prevention of venous thromboembolism (VTE) in post-surgery patients of total knee arthroplasty. However, there is not much evidence on the optimal dosage of fish oils. The effect of omega-3 can also vary among populations and further studies are required on this aspect.

Fishes are a rich source of Omega-3. Studies were conducted to determine the effects of omega-3 by comparing the consumption of fish and cardiovascular risk reduction.
Cohort studies done on Inuit and Japanese fishermen and farmers without coronary artery disease (CAD) found that people who consumed more than 30g daily had a much lower risk (more than 50%) of getting CAD. Studies done on high-risk vs. low-risk populations for CAD found the cardio-protective nature of fish oil only in high-risk people while the low-risk people did not show any considerable effects.

Moreover, in two independent studies, it was found that people who consumed fish at least twice a week had a 17% less chance of getting fatal CAD than people who ate very little or no fish while people who ate fish more than 5 times a week had 38% lower risk. This inverse relationship was however not observed for myocardial infarction (MI). Control studies were done on patients with primary cardiac arrest who consumed 185mg of EPA/DHA per day (corresponding to eating fatty fish once a week) showed a 50% lower risk. Similar results were obtained for sudden cardiac death in men who consumed one fish meal per week. Meta studies were done on patients with peripheral vascular diseases, hypercholesterolemia, and implanted cardioverter defibrillators (ICDs) beside complications such as MI, CAD or heart failure found that administering 1-3g of omega-3 fatty acids daily reduced the risk of severe arrhythmia by 10%, cardiac death by 20% and sudden cardiac death by 26%.

3.1.11 Krill oil and its effect on dislipidemia

Cholesterol is a component of the mammalian cell membrane and essential in maintaining a lipid barrier between cells. Too much cholesterol can however cause accumulation in blood vessels leading to cardiovascular complications. A study was conducted on cynomolgus monkeys to observe the long-term effects of EPA and DHA as well as choline on blood levels of cholesterol, LDL, HDL, and triglycerides.

3.1.12 Plasma concentration of EPA, DHA, and DPA

Administration of the fatty acids increased the plasma concentrations of EPA and DHA, dose-wise. With a low dose, the concentration increased by a smaller fraction than what was obtained with a high dose. In the control group, there was no significant increase in EPA and a slight increase in DHA and DPA.

3.1.13 Omega-3 index

The EPA+DHA in erythrocyte membranes was compared to the total amount of fatty acids in the membrane. This is called the omega-3 index. We observed a dose-dependent increase in the omega-3 index. The baseline was 5-6%. With low dose, intermediate, and high dose, the
omega-3 index increased to 9.2%, 13.1%, and 18.3% respectively. The control group remained at 6%. After stopping the treatment, the omega-3 index dropped as rapidly as it increased.

3.1.14 Blood lipids and apolipoproteins
Total cholesterol, LDL-c, and non-HDL cholesterol decreased when intermediate and high doses were given. HDL-c and HDL increased during this time. After stopping the treatment, total cholesterol and LDL-c increased while HDL-c decreased. Triglycerides were reduced but the treatment did not significantly affect apolipoproteins.

3.1.15 Biomarkers of diabetes and inflammation
This treatment did not have any noticeable effect on diabetes-related parameters- Glucose and insulin. No significant changes in inflammation markers were observed either. C reactive protein concentrations remained consistent hinting at the absence of any systemic inflammation.

3.1.16 Biosafety markers
There were no changes in parameters indicative of liver function, kidney function, or coagulation. This meant that there was no damage to the subject’s vital functions.

3.1.17 Omega-3 and CVD diagnosis using pulse wave velocity
Arterial stiffness is a risk factor for cardiovascular disease. It can be determined using PWV and can be further improved with the consumption of omega-3 fatty acids. Previous research has shown an inverse relationship between consumption of omega-3 and arterial stiffness. This was based on the anticoagulatory and anti-inflammatory effects as well as Nitric Oxide (NO) stimulation of endothelial cells and atherosclerotic plaque growth inhibition properties of omega-3.

In a study, the baseline plasma concentration of omega-3 [EPA, DHA and DPA], omega-6 [LA and AA], and Δ6-linoleic acid were correlated with arterial stiffness by measuring with cf-PWV after a 5 year follow up examination.

3.1.18 PUFA compared to cf-PWV
It was found that omega-3 consumption was associated with lower cf-PWV values. This established the inverse relation of plasma EPA and DHA with lower cf-PWV.

Omega-6 however was associated with higher cf-PWV values.

3.1.19 Fish oil intake compared to cf-PWV
No significant connections were noted between fish consumption in early life with cf-PWV values but there was a significant association during midlife. These results were negated after covariate analysis. In late life, occasional fish intake was associated with lower cf-PWV values.

3.1.20 Sensitivity analysis
It was done to check if the cf-PWV association was affected by the baseline values. This study confirmed that omega-3 consumption was associated with lower cf-PWV values and omega-6 consumption was associated with higher cf-PWV values.

3.1.21 Omega-3 in improving AAA
Abdominal aortic aneurysm (AAA) affects older men and can be diagnosed by various non-invasive techniques (e.g. Pulse wave velocity [PWV]) as well as blood monitoring (eg. Erythrocyte sedimentation rate and red blood cell distribution width [RDW]). The cause for AAA is believed to be vascular stiffness.

A study observed vascular stiffness in 30 random men with AAA and was compared to 20 healthy white men. Patients were given Omega-3 capsules (1.8g with 5:1 DHA: EPA) or placebo capsules for 12 weeks. These patients did not eat more than 3 fish meals per week or use any fish or krill oil-based supplements. They were all aged between 60-86 with a BMI > 39kg/m2 and have no other cardiac issues other than AAA.

It was seen that

1. The vascular stiffness in patients increased due to AAA.
2. PWV data correlated to the extent of vascular stiffness.
3. PWV negatively correlated to omega-3 index and positively correlated to RDW.
4. Omega-3 supplementation improved vascular stiffness in patients with AAA.
3.1.22 Omega-3 in improving AVS

Aortic valve stenosis (AVS) can significantly reduce the cardiac outflow and increase valve narrowing by thickening the valve leaflets. EPA/DHA produces the E and D series resolvins. They mediate signal transduction through G-protein coupled receptors ChemR23, GPR18, ALX/FPR2, and GPR32. Resolvin E1 (RvE1) through ChemR23 has been shown in the case of atherosclerosis, intimal hyperplasia, and vascular calcification.

Tissues from human donors with AVS as well as animal models (mice) having and devoid of the RvE1/ChemR23 axis were compared and studied.

3.1.23 Omega-3 content in the human heart

The lipid content of the human aorta was determined using gas chromatography. It was found that omega-3 was higher in noncalcified parts than calcified parts. Additionally, patients with slow progression of AVS had higher omega-3 content in the noncalcified parts compared to a patient with a rapid progression case.

3.1.24 Resolvins in aortic tissue

Two omega-3 derived SPMs-DHA derived RvD3 and EPA derived RvE1 were compared in both calcified and noncalcified parts. It was found that both RvE1 and RvD3 levels were lower in calcified regions than in noncalcified regions. However, omega-6 derived lipid mediator leukotriene B4 was significantly higher in the calcified region compared to noncalcified regions.

3.1.25 Role of RvE1 in aortic valve

To determine the local effects of these SPMs, mRNA levels of the SPM receptors in the tissue were determined. It was found that ChemR23 was the predominant of them all in both the calcified and noncalcified parts.

3.1.26 Omega-3 and omega-6 ratio in the tissue

The aortic root was analyzed. It showed the presence of phosphatidylethanolamine on the tissue surface, cholesterol in the plaque, and heme in the tissue-free area. Analysis of fatty acids showed a higher relative concentration of omega-3 and a much lower concentration of omega-6 fatty acids in the transgenic mice compared to the knockout mice.

3.1.27 ChemR23 increases echocardiographic progression

The ChemR23/RvE1 axis was removed in the knockout mice to study the mechanism. It was found that omega-3 was able to provide a protective effect on the aortic valve. To check the significance of omega-3 biosynthesis, the omega-3 synthesizing enzyme was introduced in the knockout mice. The results showed no difference when compared to the knockout mice.

3.1.28 ChemR23/RvE1 axis is related to the aortic valve leaflet area

On inspection, the aortic valve leaflet area was smaller in the transgenic mice when compared to normal mice. In contrast, the knockout mice have a larger leaflet area compared to normal mice. Moreover, the leaflet area was significantly correlated with aortic valve thickness.

3.1.29 Leaflet calcification

The omega-3 content is decreased in the calcified region w.r.t to noncalcified parts. It was noted that the transgenic mice had reduced calcification while the knockout mice had higher levels of calcification.

3.1.30 ChemR23 deletion causes valve thickening

Because ChemR23 reduced calcification, the knockout mice were found to have more amount of calcified tissue. The aortic valve leaflet thickness was much more in the knockout mice than normal mice.

Hence, the study conducted on RvE1/ChemR23 mice shows that increased omega-3 content caused lower calcification. It can be concluded that this can prevent AVD progression. More clinical evaluation is needed to prove the efficacy of this therapeutic alternative for the slowing of AVD progression.

3.1.31 Omega-3: Supplements vs. Prescription drugs

Fish oil supplements are available from fish, algal, or mostly unregulated plant sources. Different varieties of supplements have different ratios of DHA/EPA. Omega-3 are also available...
as prescription medicines with fixed dosage and are FDA approved.

3.1.32 Prescription omega-3 fatty acid products

Based on different studies companies have introduced prescription medicines that are directed towards the treatment of high serum triglycerides among others. These drugs are primarily of 4 types:

1. Omega-3 acid ethyl esters
2. Omega-3 acid ethyl esters A
3. Omega-3 carboxylic acids
4. Icosapent ethyl

All of these except icosapent ethyl contain DHA. These drugs have a specific amount of EPA/DHA with a strict dosage. In randomized, placebo-control trials, patients with a very high baseline triglyceride and residually high triglycerides have shown a decrease after administration of DHA/EPA products. However, EPA-only products were much more effective than a combination of the two.

3.1.33 Omega-3 dietary supplements

Dietary supplements are only appropriate in supplementing a diet since they contain a very low dose of omega-3 fatty acids and are therefore not suitable for treating disease. Furthermore, the dose mentioned on the label may not be consistent with the actual product, which varies between batches. There might be contaminating agents present in them which can be detrimental to health. Whereas, the triglyceride-lowering effects of prescription drugs have been proven by clinical trials. They are heavily regulated and contain a precise dosage of omega-3 fatty acids. These drugs are meant to be used to treat disease and should not be replaced with supplements.

Most omega-3 dietary supplements contain DHA and EPA except the plant-based (which contains ALA). These products are not regulated and as such have a different composition than what is specified on the label. In an analytical study, the EPA and DHA contents ranged from 51-153% of the amounts written on the label. Some products even contain saturated fats and cholesterol along with omega-3 FA. Some products also contain high oxidized omega-3. In a Canadian study, 50% of the omega-3 supplement products contained oxidized form. Oxidized lipids can alter cholesterol metabolism, increase uptake of cholesterol and decrease their metabolism in the liver causing high serum cholesterol levels. The actual EPA/DHA content of these supplements is low and a high pill burden is required to achieve the same effect as that of prescription medicine.

4. IMMUNOLOGY

4.1 Immunoregulatory and Anti-inflammatory Effect

The effect of two n-3 PUFA i.e. EPA and DHA on the functioning of immune cells and other immunological processes were monitored, and it was found that they regulate their activity by affecting the gene expression and signal transduction pathways. Overall, they show an anti-inflammatory effect and can be used as supplements to lessen the effects of inflammation. The anti-inflammatory activity of fish oil, while thought to be beneficial, prove to be detrimental in certain bacterial infections. On the contrary, they have proven to be very effective in auto-immune and acute and chronic inflammatory disorders like rheumatoid arthritis, ulcerative colitis, and psoriasis. This has been discussed in detail.

Based on animal studies previously performed, consumption of fish oil suppresses lymphocyte proliferation stimulated by mitogens, decreases the activity of Cytotoxic T-lymphocyte and spleen NK cells, suppresses the chemotaxis of neutrophils & monocytes towards chemoattractants, and diminishes the expression of MHC II and other antigens on dendritic cells. EPA replaces the AA in cell membranes which leads to reduced production of AA-derived eicosanoids which are responsible for causing inflammation and for regulating immune cell functions. It is highlighted that supplementation of n-3 PUFAs in the diet significantly reduces the IL-1α, IL-1β, IL-2, and TNFα production and diminishes Delayed-type hypersensitivity. The cytokine production remains suspended for a few weeks even after the termination of supplementation. Fish oil administration also leads to increased release of NO from the endothelial cells.

Inclusion of fish oil in the diet of mice showed reduced levels of mRNA for IL-1β, IL-6, TNF-
and CD106 due to their impaired synthesis. This is thought to be the mechanism for regulating the immune response. N-3 PUFA administration affects gene expression by interfering with signal transduction pathways or binding to transcription factors. Changes in FA supplemented in diet also lead to a change in lymphocyte and monocyte composition of phospholipid and DAG. n-3 consumption leads to “reduced PLC activity, resulting in reduced DAG and IP3 generation, resulting in turn in a reduced intracellular free calcium rise and a reduced activation of PKC isoforms.” PKC is also responsible for phosphorylation of I-κB (inhibitory κB) which in turn activates NF-κB (nuclear transcription-factor κB). The synthesis of various cytokines is regulated by NF-κB.

A paper published by P. Calder in 2002 highlighted the clinical studies performed which show the antagonistic effect of omega-3 PUFAs on the action of PGE2 and 4-series LT which are derivatives of AA.

In vitro studies have shown that DHA exhibits stronger inhibitory function on superoxide production, phagocytosis, and cytokine-induced cell-surface expression of MHC II than EPA. The study also found that EPA and DHA diminish the antigen presentation ability of monocytes and lymphocytes.

Certain animal-feeding studies concluded that n-3 PUFAs not only downregulated the production of superoxide and hydrogen peroxide by macrophages but also decreased TNF-α, IL-1β, and IL-6 production. Another study found that dietary fish oil supplementation hampers the phagocytosis of pathogenic bacteria. “These studies suggest that dietary fish oil might impair the cell-mediated immune response by decreasing the activity of antigen-presenting cells and by decreasing the sensitivity of macrophages to T lymphocyte–derived cytokines.”

Human studies found that EPA+DHA reduced neutrophil function and decreased monocyte chemotaxis indicating its anti-inflammatory action. It has also been concluded that only high doses of EPA and DHA mimic the effects of fish oils. Lower concentrations show no immunological action. EPA is a stronger immunomodulator as compared to DHA. The studies performed to demonstrate the effect of fish oil on bacterial susceptibility have shown no conclusive results, but it has been noted that it does impair the cell-mediated immunity of the host.

Omega-3 PUFAs decrease cytokine-induced adhesion molecule expression which has a cascading effect on the migration of leukocytes. They also shift the lipid homeostasis towards energy-supplying pathways. Owing to these effects, n-3 PUFAs show a beneficial effect in immunodeficient and hyperinflammatory states. Under normal conditions, EPA is preferentially metabolized at the cost of AA. Besides, unlike AA, lipid mediators derived from EPA (like PG, TX, LT), upregulate vasodilation, bleeding time, and insulin insensitivity but have a down-regulatory effect on blood viscosity, platelet aggregation, VLDL formation, TNFα & IL-1β generation, and inflammatory & allergic response. EPA and DHA interfere and inhibit the GPCR signaling pathway by directly or indirectly affecting the activation of PLC and PKC. n-3 PUFAs also act as fuel partitioners by promoting lipid oxidation and thermogenesis, hence increasing energy supply which is essential for maximal immune cell functioning. “PUFA and their metabolites upregulate genes of FA oxidation and thermogenesis as ligands for PPARα” (peroxisome proliferator-activated receptors are involved in lipid homeostasis). They govern lipogenic genes by suppressing the expression and translocation of sterol regulatory binding proteins(SREBP). They also shift the production of adhesion molecules (like ICAM-1 and VCAM-1) which are generally involved in leukocyte-endothelial interaction and hence the migration of leukocytes.

4.2 Effect on Immune Cell Migration via Regulation Metalloendopeptidase-9(MMP-9) Production

Many studies established the role of omega-3 PUFAs on immune modulation but their mode of action in most cases remains uncertain hence, before being considered as a treatment option for Multiple sclerosis, it is necessary to establish the optimal dose to avoid any complications.

Experimental studies performed by G. Marracci et al. demonstrated that both, DHA and EPA, treatments to Peripheral Blood mononuclear cells (PBMC) result in significantly lower levels of MMP-9 with increasing concentrations. EPA showed a stronger effect as compared to DHA. OA which was used as a control showed no noticeable reduction in MMP-9 levels. A similar trend was observed while measuring MMP-9.
activity; DHA and EPA showed an inverse relation with the activity of MMP-9, although the effect of both was almost equivalent. DHA and EPA increasingly reduced Jurkat cell (CD4+ t cell line) migration with their increasing concentrations. Cell migration was reduced by 46.2% and 83.9% at 30 µg/ml and 100 µg/ml concentrations of DHA respectively. Similarly, Jurkat cell migration reduced by 46.9%, 51.8%, and 83.1% at 10, 30, and 100 µg/ml concentrations of EPA respectively. Matrix metalloproteinase-9 (MMP-9) is associated with compromised blood-brain barrier (BBB) and T-cell migration in Multiple sclerosis (MS) and this study implicates that the use of omega-3 supplements can alleviate the condition of patients with this disease.

4.3 Effect of Parental n-3 Exposure on the Immunity of Offsprings

A mice-feeding study in 2014 experimentally concluded the role of parental n-3 PUFA supplementation on the gut microbiome and immunity of their offspring. In this study involving parent or breeder mice, the offspring of n-3 breeder mice reflected an altered gut microbiome and also suggested an increased anti-inflammatory response. Using a Low-fat diet as a control, the parent mice were fed with varying concentrations of fat diet. As compared to LF(low fat) breeders, pups from Omega-3 breeders were found to have an increased Firmicutes to Bacteroidetes ratio which correlates to deleterious inflammation but on the contrary, these pups do not show increased inflammation against LPS. These pups also exhibited heightened IL-10 levels but decreased IL-2 levels. Against peanut anaphylaxis, Omega-3 breeder offspring showed a ‘small but significant difference in peanut-specific IgE’. As compared to LF pups, they were also protected from temperature drop during the test. N-3 breeder pups had increased fatality against E.coli sepsis test and larger lesion sizes during MRSA skin infection. The Omega-3 pups demonstrated no significant changes in microbial load in skin lesions but they had an impaired inflammatory response (reduced IL-17A mRNA and markers of neutrophil infiltration). The speculated mechanisms for this regulation include (1) increased production of resolvins and protectins on n-3 exposure which explains the decreased inflammatory cytokines (2) enhanced Treg cells as a result of n-3 consumption and the altered gut microbiome. Increased Treg function also justifies the reduced inflammatory action and protection against allergies.

Since the relationship between the gut microbiome, immune response, and n-3 PUFAs has been established, they can be used to alter a wide range of immunological conditions. Since they have proven to be effective in treating cancer, similar results can be expected from studies on other inflammatory disorders. It has been mentioned that before being used in immunotherapies, optimal levels of n-3 required for eliciting the growth of good bacteria, and as a result control inflammation need to be experimentally determined.

4.4 Effect on Gut Microbiota and Role in Cancer Modulation

Optimal levels of LC-PUFA promote the growth of certain gut microbes which enhance immune checkpoint (PD-1 receptor) inhibitors and help in overcoming immunosuppressive tumor microenvironment. Acute forms of inflammation are perceived positively and can help in boosting the immune system to fight infections but Prolonged or chronic inflammation can negatively affect diseases like cancer and diabetes.

Metabolism of n-6 PUFA releases pro-inflammatory eicosanoids and cytokines which can help in combating any injury or infection whereas metabolites of n-3 PUFA are involved in countering this mechanism by producing anti-inflammatory eicosanoids and lipid mediators (resolvins and protectins).

Harmful gut bacteria promote inflammation by producing metabolites that suppress the immune system, whereas probiotics like Bifidobacteria produce metabolites that strengthen the gut barrier. Cytokines activate the immune cells to fight the tumor cells, “however, the failure of the immune system to resolve inflammation can lead to the genesis of the tumor microenvironment.” On the persistence of inflammation, more cytokines are activated and this turns into a cycle that eventually leads to tissue damage and chronic diseases. It is hypothesized that a higher n-3/n6 ratio promotes the growth of a healthy gut microbiome and this results in enhanced immune activity against tumors. “The current body of evidence suggests that n-3 PUFAs perform a balancing act where it has both pro-inflammatory functions (overcome immunosuppression in the tumor microenvironment), as well as anti-inflammatory functions (modulate neoplastic progression).”

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has been established, they can be used to alter a wide range of immunological conditions. Since they have proven to be effective in treating cancer, similar results can be expected from studies on other inflammatory disorders. It has been mentioned that before being used in immunotherapies, optimal levels of n-3 required for eliciting the growth of good bacteria, and as a result control inflammation need to be experimentally determined.

4.5 Effect on Lipid Raft Composition and T-cell Signaling

N-3 PUFAs have been found to affect the lipid raft and CD4+ T-cells. Lipid rafts are formed through the interaction of lipids with other lipids and also with proteins. Certain signaling proteins essential for T-cell activation and differentiation are found in the lipid rafts. Nanoscale lipid rafts are found to be involved in signal transduction; They organize the proteins to increase their signaling capacity. A stabilized lipid raft phase (size or lifetime) is achieved either by the ‘associate and disassociate’ mechanism of rafts or because of the actin cytoskeleton. Actin filaments interact with proteins like PI(4,5)P2 which upon hydrolysis release DAG and IP3 and are hence thought to be important signaling molecules. An increase in PI(4,5)P2 leads to cytoskeletal remodeling. DHA and EPA can get incorporated into the nano-scale lipid rafts and alter their size and stability. They decrease bilayer stiffness, increase the lifetime of gramicidin channels and decrease free energy for channel formation.

T-cell differentiation is also regulated by the membrane order - low membrane order cells show increased apoptosis whereas high membrane order is linked with increased IL-4 production. n-3 PUFAs also affect T-cell differentiation by inhibiting polarization of TH1 And TH17 cells but do not affect the polarization of TH2 or Treg cells.

It has been suspected that protein complexes are a potential mechanism by which n-3 PUFAs might exhibit their effect, but this is yet to be studied. It should also be noted that not all n-3 PUFAs show a similar effect on the plasma membrane or in lipid raft regulation. Before being used in humans, the exact mechanism of action and the dosage required for suppressing T-cell activation or differentiation needs to be established.

4.6 Autocrine Mediation by n-3 Epoxides

n-3 epoxides are derived from mast cells which are produced by type II platelet-activating factor acetylhydrolase (PAF-AH2: oxidized phospholipid- selective phospholipase A2). Y. Shimanaka et al. performed a study on mouse bone marrow-derived mast cells using comprehensive lipidomics and the effect of PAF-AH2 deletion on omega-3 epoxide production and mast cell activation was established.

Mouse bone marrow-derived mast cells (BMMCs) were used to study the release of metabolites of AA, EPA, and DHA. Stimulation of BMMCs with IgE-antigens increased release of AA and EPA metabolites which were dependent on group IVA cytosolic PLA2. In the case of no antigen stimulation, negligible AA-derived metabolites were detected but substantial concentrations of oxygenated EPA and DHA metabolites were found due to PAF-AH2. In vivo studies on mice, models found that deletion of PAF-AH2 attenuates FccRI(IgE receptor)-dependent activation. PAF-AH2 affects the catalytic activity of FccRI (Lyn and Fyn kinase activation). Lyn is responsible for the activation of central kinase Syk12 and Fyn activates Gab2. It was also concluded that expression of PAF-AH2 affects IgE antigen-dependent activation of mast cells but doesn’t affect their proliferation and maturation. The study also proved that out of all other n-3 metabolites, n-3 epoxides are responsible for the activation of mast cells this is because PAF-AH2 preferentially hydrolyzes phospholipids that contain n-3 epoxides. It was concluded that activities of n-3 epoxides were
similar to those of PPARγ inhibitors and it acts by inhibiting PPARγ. PPARγ is a receptor that negatively regulates mast cell activation. N-3 epoxides also reduce activities of Src kinase signaling inhibitor 1 (Sric1). “Taken together, these results suggest that Sric1 blocks phosphorylation of FcεRI by inhibiting Lyn and Fyn and that PAF-AH2-driven ω-3 epoxides downregulate Sric1 expression by counteracting PPARγ signaling to ensure full activation of mast cells.”

4.7 Effects on Various Immune Cells

n-3 PUFAs regulate immune function by getting incorporated in the cell membranes of the immune cells and causing an increase in membrane fluidity and affecting the lipid raft assembly.

The change in the composition of immune cell fatty acids occurs in a dose-dependent manner (linear relation) and it reaches its peak in humans within 4 weeks. The increased amount of EPA and DHA in cell membranes leads to increased production of eicosanoids-PGE3 and 5-series LT’s (instead of PGE2 and 4-series LT’s which are derived from AA) and also resolvins through cyclooxygenase and lipoxygenase enzyme-mediated pathways.

SPM’s - Specialized pro-resolving molecules i.e. derivatives of n-3 and n-6 metabolism, also show certain immune-regulatory functions. These derivatives, along with n-3 PUFAs, act as signaling molecules to elicit their function. EPA regulates the cell cycle regulator genes in macrophages whereas DHA affects the genes controlling immune response pathways. The timing of the addition of omega-3 plays a crucial role in determining its effect; they show anti-inflammatory effect only when pre-incubated and then stimulated with LPS. In general, EPA and DHA pre-treatment leads to decreased cytokine production by macrophages, suppressed inflammasome-mediated inflammation, decreased ROS and NO production, and increased localization of TLR4 and CD14. It also promotes M2 polarization in macrophages and increases their phagocytic capacity. In-vivo n-3 FA administration promotes the endothelial cells to produce prostaglandin D3 instead of D2. DHA is involved in increasing the phagocytic and fungicidal capacity of neutrophils. Apart from this, n-3 supplementation in humans leads to increased ROS production.

It was also found that n-3 PUFAs have a suppressive effect on T-cell activity but no changes in the percentage of T-cells or T-cell population have been found. They inhibit T cell proliferation by altering plasma membrane protein composition, modifying eicosanoid mediators, and by affecting transcription factor activation. n-3 PUFAs selectively cause the displacement of acylated proteins from the lipid leaflet but do not affect GPI-anchored proteins. They also inhibit phosphorylation of LAT (linker of activated T cells) and this is a mechanism to inhibit T cell responses. EPA and DHA also affect antigen presentation by decreasing the expression and antigen presentation of MHC II. “AA and DHA were shown to decrease cell surface MHC I expression by slowing flow of new class I molecules from the endoplasmic reticulum to the Golgi.”

Omega-3 FAs induce an alteration in the lipid rafts of the cells which are necessary for activation of CD4+ T-cells. This inhibits the differentiation of CD4+ cells into Th1 cells and also reduces IFN-γ and interleukin(IL) secretion. Similarly, Th17 differentiation and activation are also diminished. On the other hand, dietary omega-3 PUFAs up-regulate the proliferation and accumulation of Treg cells and this finds its application in treating arthritis and atopic dermatitis.

n-3 FAs decrease B-cell activation but show no effect on the proportion of B cells that get activated. It also downregulates the production or activation of most immune cells and decreases IgE-mediated activation of mast cells, circulating levels of basophils, and the recruitment of eosinophils. Omega-3 supplementation has shown no conclusive results on the activation and activity of NK cells.

5. JOINT HEALTH

Many studies have tried to prove the effectiveness of Omega-3 consumption on various joint diseases. In a study,17 articles were finalized for the meta-analysis. Six pain outcomes were identified: patient assessed pain, physician assessed pain, duration of morning stiffness, number of painful and/or tender joints, Ritchie articular index, and NSAID consumption. At 3-4 months,13 studies reported patient assessed pain, 8 reported morning stiffness,10 reported number of painful and/or tender joints, and 3 reported NSAID consumption. It was observed that in all the above studies, patients
receiving Omega-3 fared better than placebo. In studies reporting outcomes for 5 months or more, improvement was observed in physician-assessed pain, the number of painful and/or tender joints, morning stiffness, and NSAID consumption. In studies reporting for 2 months or less, improvement was observed in Ritchie articular index. Studies that reported high dose Omega-3 showed improvements in morning stiffness, the number of painful and/or tender joints, and patient assessed pain. Studies reporting non-olive oil placebo showed improvements in patient assessed, pain morning stiffness than olive-oil placebo.

In a study, Cartilage was removed from the Bovine metacarpal - metatarsophalangeal joints and digested. Uptake into chondrocytes was done with different fatty acids. No Difference was observed in the total uptake between the four fatty acids (ALA, EPA, DHA, and arachidonic acid [AA]). The morphology of the chondrocytes was carried out by using light microscopy. Plate 1 - no morphological difference was observed as the cultures were placed in serum-free media. Plate2 and 4- chondrocytes changed their shape over 96 h, to more spindle-like, cell debris and cell death were observed. Plate3- They were pre-treated with EPA and were morphologically for 48 hrs of IL-1 treatment. At 72hrs, fibroblastic cells, cell debris, and cell death were observed. It suggests that preincubation of chondrocytes with n-3 PUFA, EPA has a protective effect. Lactate production by chondrocytes was unaffected for 96hrs by an 8hrs pre-incubation with fatty acids. Fatty acids were added to ADAMTS-4 (that causes cartilage damage in OA) for an 8hrs period. It was observed that fatty acids did not change the expression level of ADAMTS-4. Reduction of mRNA levels by EPA was observed during inflammation. No change in COX-1 mRNA levels was found on treatment of the chondrocyte with any PUFA. mRNA for TNF-α was induced by inflammatory stimulation and was reduced strongly by pre-exposure to EPA. Exposure to the n-6 PUFA, arachidonate, did not affect mRNA levels for TNF-α.

According to the authors, 12 Sprague Dawley rats were introduced to IVD degeneration by puncturing lumbar discs of L3/4 and L5/6. They were randomly placed in the n-3 fatty acids diet group and control diet group. The n-3 fatty acids diet group was given n-3 fatty acids along with sucrose solution, whereas the control diet group was given only sucrose solution, for 2 months. After 1 month post-surgery, disc hydration was analyzed using micro-MRI. In the control diet group, a reduction in disc hydration was observed. In the n-3 fatty acid diet group, the disc was reduced compared to the control diet group. After 2 months, the disc tissue was taken for histological analysis, and 0.1ml of blood was collected for AA/EPA ratio. The disc spines were decalcified, sectioned, and stained using hematoxylin and eosin for analysis. It was observed that disc degeneration in the injured and uninjured IVDs was less in the n-3 fatty acids diet group than compared to the injured discs of the control diet group, pre, and post-surgery, whereas in the n-3 fatty acids group the AA/EPA ratios were different (Fig. 1). The authors note that consumption of fibers with simple sugars, fats and proteins, and sodium chloride induces pro-inflammatory reactions. The dietary courses taken during rheumatic diseases are based on the Mediterranean diet which includes vegetables, olives, fish, fruit, nuts, meat, dairy, alcohol, and eggs as they include n-3, n-6, n-9 fatty acids.

In another study, a total of 167 individuals with knee OA (53% African American, 47% non-Hispanic white adults) have participated in the study. Pressure pain sensitivity was tested on the index knee and ipsilateral forearm by an algometer at a rate of 30 kPa. The average verbal rating and change score was calculated as an index of temporal summation. The samples were prepared by the addition of an internal standard to the sample and were centrifuged to pelletize the protein which was dissolved in acetonitrile and methanol in a 1:1 ratio. LC-MS/MS analysis was done by liquid chromatography-tandem mass spectrometry. Selected reaction monitoring(SRM) was used in detecting DHA, EPA, and AA whereas single ion monitoring (SIM) was used in detecting ALA and LA. Low and high ratio groups were created by Quartile splits, group differences in variables were tested using ANOVA F-test or Chi-square test. BMI, smoking status, and exercise were added as covariates. Smoking status showed a relation with n-6:n-3 ratio, BMI, and negative affect score. The high ratio group included African Americans with smoking and greater BMI compared to the low ratio group. The high ratio group showed greater clinical pain, pain intensity, and functional limitations along with stress and negative effects, while the pressure pain thresholds were similar between the two groups. The low ratio group included low knee pain symptoms, less psychosocial stress, and improved physical functioning. The authors note
that individuals with higher n-3 PUFAs show lower levels of pain, stiffness, and functional limitations. Supplementation of n-3 PUFAs showed decreased anxiety, improved performance, and chronic headaches. Authors also observe that ethnicity doesn't play any role in the n-6:n-3 PUFAs ratio.

Similar studies were conducted for various joint diseases. In a study, RA patients were divided into 3 groups. Group 1 was given 6 capsules of olive oil, group 2 was given 3 capsules of fish oil and group 3 was given 6 capsules of fish oil each for 12 months. No changes were observed in the duration of morning stiffness in any group. Reductions were seen in Ritchie's articular index of pain and for the number of painful joints. Worsening of grip strength was observed in group 1, while an improvement of grip strength was observed in group 3. An increase in the RF titer was observed in group 1 and 2. Group 3 showed an improvement and a reduction in pain score and 47% of patients were able to reduce their medications, while 29% of patients in roup2 could decrease their medications. A reduction of disease activity and symptoms was observed in group 3.

In a study conducted in Melbourne Collaborative Study (MCCS) with 297 participants, BMI was calculated and an MRI was performed by each participant. It resulted in tibial cartilage volume and the presence of tibiofemoral cartilage defects and bone marrow lesions. The authors stated that intake of Omega-6 PUFA and monounsaturated fatty acids were related to the presence of bone marrow lesions whereas intake of saturated fatty acids and Omega-3 PUFAs and n-6/n-3 ratio weren't. None of the fatty acids were related to the presence of tibiofemoral cartilage defects before and after the adjustment of age, gender, BMI. Whereas all fatty acids were related to tibial cartilage volume except the n-6/n-3 ratio. But no relations were seen after the adjustment of age, gender, and BMI. No relations were observed between intakes of dairy products, meat, fish, etc, with bone marrow lesions or knee cartilage volume after adjusting for potential confounders. The addition of other lifestyle factors such as physical activity, smoking did not change the results. (Fig. 3).

According to the authors, Baker et al. investigated the relations between plasma levels of long-chain Omega-6 and Omega-3 fatty acids and synovitis in knees of osteoarthritis patients. Synovial thickening on the knees was observed in MRI studies of patients in the early stages of OA. Baker calculated an odds ratio from moderate to severe synovitis and found that there was no correlation found between synovitis and omega-3 PUFAs but an inverse association between patellofemoral cartilage was seen. The study by Baker suggested that observation of plasma levels of PUFAs could help in the identification of chronic diseases. Authors also state that providing an Omega-3 rich diet to Dunkin –Hartley strain guinea pigs improves OA closely to the OA resistant Bristol strain. It is stated that gene polymorphisms and enzyme efficiencies could influence profiles of plasma and tissue Omega-6 and Omega-3 fatty acids.

Juvenile idiopathic arthritis is an inflammatory autoimmune joint disease that can be seen under 16 years of age. observe increased levels of TNF-α, INF-γ, IL-6, and IL-1b in serum and synovial fluids in patients with JIA. Patients with JIA were given 2g of Omega-3 fatty acids a day for 12 weeks. After 12 weeks, a reduction in the number of swollen joints and Juvenile Arthritis Disease Score on 27 joints (JADAS-27) was observed.

Ankylosing Spondylitis: It is included in axial spondyloarthropathies. I can be observed before the age of 40. It causes chronic pain and fatigue. In a randomized trial, two groups of patients taking a small dose, and a large dose. Reduced disease activity was observed in the group taking a large dose.

Psoriatic arthritis: It affects the facet joints in patients under 40 years of age and peripheral joints in patients above 40 years. Other diseases can be seen in patients with psoriatic arthritis such as Dyslipidemia, hypertension, obesity, and type 2 diabetes. A trial with 145 PA patients was given 3g of Omega-3 acids or olive oil per day. It was observed that patients taking Omega-3 showed a reduction in disease activity and the number of painful joints. Reduction in intake of NSAID and acetaminophen was also observed.

Rheumatoid Arthritis: It is the most common inflammatory rheumatic disease. A study including 727 patients with RA following an omega-3 rich diet responded positively towards disease-modifying antirheumatic drugs (DMARDs) therapy and Methotrexate (MTX). A double-blind study with 60 RA patients was given 3 capsules of EPA and DHA along with DMARDs resulted in reduced morning stiffness, reduced number of painful and
swollen joints. A group of 139 patients with RA for less than 12 months were given 3 DMARDs therapy. Patients who showed greater disease activity were given 25g of MTX per week. They were divided into a 2:1 ratio taking small and large doses of fish oil for a year. A decrease was seen in 61% of patients taking large doses and 33% of patients taking small doses. A study included 60 patients with RA who were divided into 3 groups. Group 1 was given 5 capsules containing 1g of fish oil, group 2 was given 2 capsules of fish oil and 1 capsule of evening primrose oil, and group 3 continued their recommended therapy. It was observed that groups 1 and 2 showed a reduction in platelet aggregation and decreased disease activity.

Sjögren’s syndrome: It is an inflammatory autoimmune disease causing inflammation to exocrine glands and inflammatory lesions in multiple organs. The authors state that intake of Omega -3 acids for 3 months resulted in increased production of saliva, while the combination of Omega-3 and Omega -6 acids showed decreased disease activity and improved ocular lesions. Sjögren’s syndrome is believed to affect women more often than men.

Gout: It is a crystal deposition disease in which deposition of monosodium urate crystals causes inflammation. A polynsaturated fatty acids-rich diet influences the uric acid level leading to decreased risks of gout attacks. A study including 724 patients with 22% patients was given an Omega -3 rich diet. It was observed that a high Omega-3:Omega-6 ratio showed reduced gout attacks, a neutral Omega-3:Omega-6 ratio showed no impact, and a low Omega-3: Omega-6 ratio showed a greater risk of gout attacks.

5.1 Omega-3 and Muscle Health

The authors state that during sarcopenic obesity, changes in muscle density, and fat accumulation are observed leading to changes in muscle performances and intensified muscle loss and fat deposition. Lipid paradox in RA patients leads to a reduction in total cholesterol and low-density lipoprotein cholesterol (LDL-c). Increased levels of hs-C-reactive protein(CRP) and proinflammatory cytokines could cause muscle loss and reduction in muscle mass and strength. Insulin resistance is associated with the activity and severity of the disease. Lower levels of insulin-like growth factor -1(IGF-1) are related to the reduction of muscle cross-sectional area, muscle density, and high severity of RA. Changes in insulin action causes decreased muscle protein synthesis. Tardif showed that muscle fat deposition could lead to anabolic resistance in sarcopenic rats. Peterson treated muscle cells of a mouse with palmitate increased cell death which led to the reduction of the regenerative capacity of muscle cells. Age-related sarcopenia is related to mitochondrial dysfunction. Oxidative stress causes chronic inflammation and skeletal muscle dysfunction in animal models of RA. Authors state that insulin resistance, lipid homeostasis, inflammation, and mitochondrial activity could be involved in sarcopenia in RA. A study on Fat-1 mice included the conversion of Omega-6 fatty acids to Omega-3 fatty acids. A reduction in ankle joint inflammation, bone damages, and reduced production of IL-17, IL-6, and IL-23 was observed. Authors also note that intake of 2.4 g/day of EPA and DHA in arthritic patients resulted in increased concentration of resolvins, and decreased inflammatory markers leading to reduced pain and inflammation. Consumption of fish oil for 3 years showed a reduction in the concentration of the omega 6 inflammatory mediators and circulating autoantibodies. High doses of fish oil resulted in reduced pain, morning stiffness, tender joint, and swelling joint count. In vivo studies have shown that Omega-3 fatty acids reduced circulating oxidized LDL and improved endothelial functions in patients. It was shown that high EPA and DHA plasma levels reduced metabolic syndrome and insulin resistance. Omega-3 supplementation could reduce lipotoxicity, insulin resistance, and anabolic resistance.

A C57BL/6 mouse was given DHA- enriched diet for 8 weeks and preservation of tibialis anterior muscle mass was seen after fasting for 48 hrs. An improvement in muscle protein anabolic response and muscle protein rate and improved muscle metabolism was observed in older adults with Omega-3 fatty acids supplementation. Studies that involved fish oil consumption by RA patients showed the reduction of CD4+T cells and pro-inflammatory cytokines - TNF-α, IL-1β, and IL-6 which improved clinical signs and symptoms of RA. In an experiment, Fat-1 transgenic mice which could produce Omega-3 internally were able to reduce the levels of inflammatory cytokines, reducing the effect of arthritis, whereas wild mice could not do so. Studies have shown that intake of Omega-3 in mice resulted in delayed onset, reduced inflammation, and knee joint injuries in experimentally induced arthritis. Early studies which investigated the effect of Omega-3 on RA patients by fish oil consumption...
found out that high consumption of Omega-3 fatty acids resulted in a lower number of tender or swollen joints, the production of neutrophil leukotriene B4, macrophage IL-1, and plasma 1β decreased. In a study, RA patients were given Omega3 along with their standard treatment. An improvement was seen in the patients along with the reduction of their medication. There was no change in their weights.

In another study, a group of RA patients was given an infusion of fish oil emulsion and another group was given an oral treatment of fish oil capsules. It was observed that patients who received oral treatment showed better results than those who received an infusion. They showed a reduction in the number of swollen and tender joints. NSAIDs (Non- Steroidal Inflammatory Drugs) consumption was reduced and an improvement was observed in the patient's physical functions.

To conclude the studies, the authors suggest that intake of high doses of Omega-3 supplementation in Rheumatoid arthritis patients reduces the pain outcomes. 20-25% improvement was observed in patients receiving a high dose of Omega-3 PUFA. The authors compare the results reported by Kremer to reports by Sperlington's study of fish oil supplementation for 6-24 weeks and state that olive oil may truly not be a placebo as it contains unsaturated fats. Even though a major improvement was not observed, a reduction was seen in their medications. It suggests that long-term consumption of Omega-3 supplements could help in reduction in NSAIDs and DMARDS intake. The authors compare their study with studies by Maclean and Fortin. There were only six studies available for 6-month analysis which decreases the power of the study. Each study uses different methods, materials, and time duration, which could prove to be difficult in reaching one conclusion. Including associated analgesics could help know the true effect of Omega-3 supplementation. It is suggested that the intake of fatty acids affected knee bone rather than knee cartilage. However, the authors did not measure knee alignment, which is associated with bone marrow lesions. The authors also suggest we shift towards foods rich in Omega-3 Polysaturated fatty acids to maintain a balance between Omega-3 and Omega-6 PUFAs. n-3 PUFAs can reduce mRNA expression for cartilage-degrading proteases and inflammatory cytokines and expression of the inflammatory compound COX-2 but not COX-1 and Omega-3 fatty acids have direct effects on gene expression. Example: signaling pathways using MAP kinases such as ERK. n-3 PUFAs can have a beneficial effect on the inflammation and cartilage degradation associated with OA. The study by Baker suggests that the availability of Arachidonic acid for the production of inflammatory cytokines can be a liable factor for synovitis in early osteoarthritis. The authors also note that the ratios of Arachidonic Acid to Omega-3 PUFA might correlate with synovitis even when there were no correlations found between synovitis and Omega-3. The authors suggest that the analysis of fatty acids needs to be more efficient and effective to guide the fatty acid treatment. Studies suggest that intake of n-3 fatty acids could prove effective for IVD degeneration. It can reduce the consumption of NSAIDs, leading to fewer gastrointestinal and cardiovascular side effects. The treatments could be very helpful in curing IVD degeneration and would prove less cost-effective than others. But the study still needs further analysis of human discs including histology and radiography to improve the results of the studies further. Omega-3 fatty acids affect inflammatory diseases by decreasing disease activity, pain and reducing cardiovascular risks. The authors suggest that gamma-linolenic acid(GLA) should be added to the omega-3 supplementation which helps in the anti-inflammatory effect. Omega-3 and GLA can prove beneficial in treatments for Juvenile Idiopathic Arthritis(JIA), Ankylosing Spondylitis, arthritis, Sjögren's syndrome, and other inflammatory diseases. This was an initial study of the n-6:n-3 PUFA ratio, a prospective interventional study with other functional measures which lead us to a healthy lifestyle. The study did not include the evaluation of NSAIDs or any other pain medications. A further study including the relation between lifestyle behaviors, diet, and n-6:n-3 ratio with larger sample sizes can help in the identification of treatments for knee OA. Supplementation of Omega-3 fatty acids in RA could reduce lipotoxicity and anabolic resistance. But a nutritional approach regarding omega-3 supplementation for lipotoxicity in aging, obesity and other chronic inflammatory diseases is needed. Further studies need consideration of nutrients like protein but also physical activity and other medications. As physical activity helps preserve lean body mass, muscle anabolic response, and muscle function, proteins prove beneficial on muscle protein metabolism, muscle mass, and quality. These can prove effective in therapies for muscle health in RA patients. The
authors note that Omega3 fatty acids help in improving the conditions of patients with joint diseases.

6. SKIN DISORDERS

6.1 The Methods Involved to Test the Skin Disorders Include

1. The Sunburn Response: This is an inflammatory reaction characterized clinically by erythema and edema, and histologically by thickening of the stratum corneum, apoptotic epidermal cells (‘sunburn cells’), and dermal leukocyte infiltration. A pathway of pivotal importance in inflammation production is the metabolism of AA by COX-2, producing pro-inflammatory lipid mediators. Increased concentrations of pro-inflammatory eicosanoids are seen in the skin, including PGE2 and a range of HETE, which contribute to the regulation of vasodilatation and leukocyte infiltration, respectively. Photoprotective effects of n-3 PUFA were confirmed in a double-blind randomized study in healthy volunteers using 4 g of purified (95%) EPA supplements; % EPA/total fatty acids in epidermal phospholipids increased 8-fold and the minimal erythematous dose (MED) increased by 36%. Application of sardine oil (11.2% EPA, 23.6% DHA) to human skin after UVB reduced erythema by 24.5% compared to control (89). However, topical ALA proved unsuccessful in reducing UV erythema.

6.2 VA Provocation

This test apparatus used was a specially constructed "UVA arm-box" (Medical Engineering Department, Carlisle Hospital Is Inc. Cumbria) comprises IS Philips Cleo R-UVA 100-W fluorescent lamps mounted in a cylindrical arrangement, with a central irradiance of 26 mW/cm². The emission spectrum of the lamps was 313-370 nm, peaking at 362 nm; 0.7% of the UVR was less than 315 nm.

6.3 Statistical Method

Results of erythemal sensitivity to UVB irradiation and prostaglandin levels were analyzed by Student paired test, and arc presented. as mean (SEM). Data from UV A challenges were analyzed by Wilcoxon’s paired rank-sum test, and arc presented as median (interquartile range).

Evidence For Participation Of Dietary PUFAs In Uvr -induced Skin Cancer: A role of omega-3 FA in carcinogenesis has recently been acquired from studies with a transgenic mouse model designated fat-1. The fat-1 transgenic mice are capable of producing omega-3 FA from omega-6 FA, i.e., the transgenic has received a gene encoding an omega-3 FA desaturase that converts omega-6 FA to omega-3 FA. This results in abundant omega-3 FA and reduced omega-6 FA in the animals’ tissues without the need for omega-3 FA supplementation and eliminates many of the confounding variables encountered in dietary studies. dramatic reduction of melanoma formation and growth when fat-1 mice were injected with B16 melanoma cells, compared to their non-transgenic littermates.

Immunopathogenesis of Psoriasis: The immunopathogenesis of psoriasis involves changes in the innate and acquired (T lymphocytes) immune system. The cells of the innate immune system when activated produce growth factors, cytokines, and chemokines that act on cells of the acquired immune system and vice versa. The skin renewal occurs around 28 to 30 days with the formation of new cells on its lower layer and with the ripening, migrates to the top layer of skin dropping in an unnoticed way. In psoriasis, the cell cycle changes fast and can be reduced to 4 days. These altered cells accumulate composing whitish plates with erythroderma originating typical lesions of the disease. Several environmental factors such as mechanical trauma, infections, drugs, emotional stress, or even change of the own skin in the constitution of keratinocytes are considered triggers of the disease.

6.4 Photoaging

Photoaging is activated via human skin damage attributable to repeated ultraviolet (UV) exposure from sunlight. UV irradiation elicits both acute and chronic adverse effects on the skin. Which includes sunburn, photosensitivity, inflammation, immunosuppression, and photocarcinogenesis. UV exposure to the skin creates reactive oxygen species (ROS), leading to the massive infiltration of immune cells such as neutrophils and macrophages in viable skin. Omega-3 PUFAs can decrease the production of proinflammatory eicosanoids through direct competition with the metabolism of AA. The other mechanisms of omega-3 PUFAs for suppressing UV-induced keratinocyte damage can be the regulation of COX-2, NF-Êb, and nitrogen-activated protein kinase(MAPK)/extracellular-signal-regulated kinase (ERK) pathways.
6.5 Measurement of Cytokines

Quantification of TNF-α and IL-6 production in the supernatant of LPS-activated murine macrophages RAW 264.7 after photodermatoses were determined by enzyme-linked immunoabsorbent assay (ELISA) using specific antibodies (purified and biotinylated) and cytokine standards.

6.6 Photoreception

The effect of ultraviolet radiation (UVR) on the skin following supplementation with O3FA.18-24 The studies varied in their primary objectives, measuring outcomes including photoaging, sunburn threshold, and disease activity of a variety of photo dermatoses. One cross-sectional study examined the relationship between solar elastosis and dietary O3FA. O3FA supplementation, a significant increase in sunburn threshold was observed, with the sunburn threshold continuing to trend upwards for the duration of treatment until follow-up at 6 months. A subsequent RCT of 45 subjects supported these results, again proving significantly increased MED as well as a significant decrease in p53 gene expression as a marker for UVR-associated DNA damage. Immunohistochemical analysis of skin biopsies demonstrated significant O3FA epidermal lipid content compared to controls and a reduction in p53 gene expression by 50% at 24 hours after UVR vs controls. The photoprotective role of O3FA was further supported by Pilkington et al.25 who reported preservation of cell-mediated immunity following UVR exposure.

Metabolism Of PUFAs: The cell membrane composition and consequent cell membrane homeostasis maintenance obtained by the membrane balance of FAs, but also FAs detachment of the PL for becoming signaling mediators. Nutrition, metabolism, external and internal stressors with consequent oxidative stress, and lifestyle factors all cause FAs changes that result in impaired cell membrane homeostasis. PUFAs derived from LA are GLA, dihomo-gamma-linolenic acid (DGLA), and ARA. On the other hand, the ω-3 family is derived from ALA, and the most notable among them are EPA and DHA. In the enzymatic cascades, eicosanoids are produced.

Mouse Model Of Psoriasis: Mice received a daily topical application of 62.5 mg 5% IMQ cream on the shaved back skin (nape area of 2 × 2 cm) for 7 consecutive days, whereas control mice were treated similarly but with a control vehicle cream (Vaseline). Spontaneous itch, alloknesis, and skin inflammation were assessed daily or on day 2 and/or 7. For spontaneous itch, mice were habituated to the testing environment daily for at least two days before testing and itch assessed 20 to 22 hours after each topical application by videotaping the mice for 30 min. The spontaneous itch was determined by the number of scratching bouts, was defined as one rapid back-and-forth hind paw motion directed toward and contacting the treated area, ending with licking or biting of the toes or placement of the hind paw on the floor. Hind paw movements directed away from the treated area (e.g., ear scratching) and grooming movements were not counted. The presence or absence of a positive response (a hind limb scratching bout directed to the site of mechanical stimulation) was noted for each stimulus. The alloknesis score was the total number of positive responses elicited by the five stimuli (0-5). For skin inflammation, we evaluated erythema and scaling based on our and other similar studies.

In the tests, the Threshold for Provocation of PLE by UV A Increases on Dietary Fish Oil at baseline, the provocation test was positive in 10 of the 13 subjects. Following 3 months of fish oil supplementation, there was evidence of reduced sensitivity to lesion provocation in nine of these 10 subjects. Seven patients showed an increased threshold for provocation of lesions and two had a mild response at 10 j/cm² when previously they had shown a severe reaction. The median provocation score is released from 2 (interquartile range 0.5-3) to 0 (0-2.5) on fish oil, p < 0.001. Also, topical EPA (98% EPA ethyl ester) to murine skin reduced local UVB immune suppression, evidenced by increased response to difluorornitrobenzene compared to control oil. PPAR activators may directly downregulate or inhibit cyclooxygenase-2 (COX-2) expression which is increased in cutaneous squamous cell carcinoma (SCC).60-62 The therapeutic potential of the link between COX-2 and the PPARs may be used to inhibit UV-induced skin tumor progression. Omega-3 FA inhibits certain genotoxic markers of UVR-induced DNA damage, e.g., UV-induced cutaneous p53. The n-3 polyunsaturated fatty acids, mainly of marine origin, have beneficial effects and can be utilized as adjuvant therapy in psoriasis treatment. Both oral and intravenous. The administration of fish oil in n-3 polyunsaturated fatty acids gives positive effects. The ideal quantity of fish oil to be
utilized, the effect on different forms and severity of psoriasis, and last, but not least, the consequences of using fish oil n-3 polyunsaturated fatty acids on the cardiovascular features of patients with psoriasis. The fatty acids found in fish oil used in skin-related diseases include therapies for skin cancer, dermatitis, wound healing, and melanogenesis. The use of PUFAs ameliorates the symptoms of in diseases. Some fatty acids have been approved for clinical use or are under clinical trial for preventive or therapeutic use. Besides, some fish oil-containing formulations are approved to manage various skin diseases in cell-based and animal studies. The quantities of fatty acids with healing effects are highlighted as oleic fatty acid, linoleic acid, and linolenic acid. O3FA plays a significant role in skin health and may prove particular importance for adjuvant therapy in psoriasis and eczema, chemotherapy and retinoid-induced cutaneous side effects, and systemic photoprotection. Fish oil, which contains EPA and DHA, is reported to be useful for improving dermatitis symptoms, due to the Omega-3 PUFAs which suppress, anti-inflammatory effects like inhibition of lymphocyte proliferation, cytokine and antibody production, adhesion molecules expression, NKC activity, and triggering apoptosis. Both TRPV1 and ALX/FPR2 are critically used for the regulation of immunity and skin inflammation in which TRPV1 plays a major role in psoriasiform skin inflammation and potentially in chronic itch. The commonly used antihistamine olopatadine significantly lowered the number of spontaneous scratching bouts in only 2 days, but not 7 days after IMQ application. Intrathecal injection confines RvD3 to the nervous system, we hypothesized that RvD3 may attenuate psoriasiform itch solely through neuronal actions.

To further look into the matter we can say that the protective effect of dietary fish oil extends from the sunburn response to an inflammatory disease process. Reduction of PGE2 levels on dietary fish oil could be due to interference with prostaglandin synthesis at more than one step by w-3 PUFAs. w-3 PUFAs compete with w-6 PUFAs for metabolism by cyclooxygenase, leading to the production of less active prostaglandins. LC n-3 PUFA, particularly EPA, is capable of reducing UV-induced inflammation in human skin, it also offers protection against photo immunosuppression, photocarcinogenesis, photoaging, and photosensitivity disorders. Ultimately, combined dietary and standard topical sunscreen measures may optimize human skin protection from sunlight. The photoprotective properties of SC n-3 PUFA are less explored but may hold potential for skin protection. PPARs represent a major research target for the treatment of many skin diseases. A large number of PPAR ligands (i.e., long-chain fatty acids, thiazolidinediones, fibrates) have been identified. Some of them are already registered and clinically used for other diseases. Omega-3 FAs have a high safety profile and a daily intake of circa 4 g/day as employed in previous photoprotection studies is in adequate amounts. Because of the promising evidence from animal and clinical studies. ALA is fundamental to visual and brain functions through its effect on membrane fluidity because PUFAs and their derivatives are principally located in the cell membrane made of the phospho-lipid layer. The derivatives of ALA can modify the immune response of the epidermis via affecting the T cells, acting on Toll-like receptors, and stimulating caspase cascades that relieve inflammatory dermatoses such as acne, psoriasis, dermatitis, lupus, and skin cancers. The fatty acid composition, enhancing the commercial application, and producing new specific products with a desired biological property, in general, at affordable prices. They are easily accessible and a relatively inexpensive option for skincare including their therapeutic potential to positively influence cutaneous wound healing. It has emollient properties, many natural oils possess specific compounds with antimicrobial, antioxidant, and anti-inflammatory activities. It m lipids which derived from topically applied emollients and to utilize them as nutritional building blocks for the formation of a healthy and functional epidermal barrier. RvD3 significantly alleviated psoriasiform itch and skin inflammation in the IMQ-animal model of psoriasis via activation of the ALX/FPR2 receptor, inhibition of TRPV1 activity, and reduction in CGRP release. RvD3 can control mouse and human DRG neuronal functions (i.e. TRPV1 activity and CGRP release) and significantly attenuate psoriasiform itch and skin inflammation.

7. CONCLUSION

This research review’s purpose is to help the reader understand different aspects posed by the research on the Analgesic Effects of Omega-3. This is significant because it gives insights into its aspects of cardiovascular diseases, immunology, Joint diseases, and Skin Disorders. There has been much research and discussion
conducted on these opinions of using Omega-3 as a treatment and a health supplement for various diseases. Most of the research found was on the anti-inflammatory effects more research and testing are required to gain a better understanding of the Analeptic Applications of Omega-3 Polyunsaturated Fatty Acids.

CONSENT AND ETHICS APPROVAL TO PARTICIPATE

It is not applicable

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are based on this research.

AVAILABILITY OF DATA AND MATERIALS

The author confirms that the data supporting the findings of this research are available within the article.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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