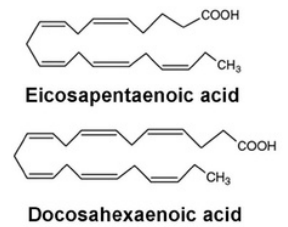


COMMON NAME: Fish oil

CHEMICAL CLASS: Polyunsaturated Fatty Acids (PUFAs)

ACTIVE INGREDIENTS: Fish oil contains two Omega-3s called docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA)

DIETARY SOURCES: Fatty fish, such as salmon, mackerel, and trout, and shellfish, such as mussels, oysters, and crabs.



CLINICAL PROPERTIES

- Anti-inflammatory (4)
- Neuroprotective (5)
- Gastroprotective (6)
- Cardioprotective (10)

CLINICAL SAFETY AND ADVERSE EFFECTS

SAFETY: The US Food and Drug Administration recognizes doses of up to 3 g/day as safe and the European Safety Union up to 5 g/day as safe. (3)

ADVERSE EFFECTS: Side effects of fish oil supplements or EPA + DHA ethyl esters include fishy burps, dyspepsia, gas, and diarrhea. (3)

CLINICAL APPLICATIONS IN ONCOLOGY

- Omega-3 fatty acid supplementation could improve overall survival and progression-free survival of cancer patients undergoing standard treatment. (7)
- Omega-3 fatty acids seem to reduce the incidence and severity of oxaliplatin-related neurotoxicity, and improve the quality of patients' life, indicating it is expected to be a potential drug for the treatment of oxaliplatin-related neurotoxicity. (8)
- Omega-3 fatty acids may reduce some adverse cardiometabolic and inflammatory risk factors in children with ALL. (10)
- Fish oil may lead to a better performance status for gastrointestinal cancer patients undergoing chemotherapy. (11)
- High-dose fish oil supplementation may reduce bone resorption in post-menopausal breast cancer survivors. (12)
- Nutritional support enriched omega-3-fatty acids may improve immune cell functions in surgical cancer patients resulting in a reduction of infectious complications, length of hospital stays and morbidity. (13)

MECHANISM OF ACTION

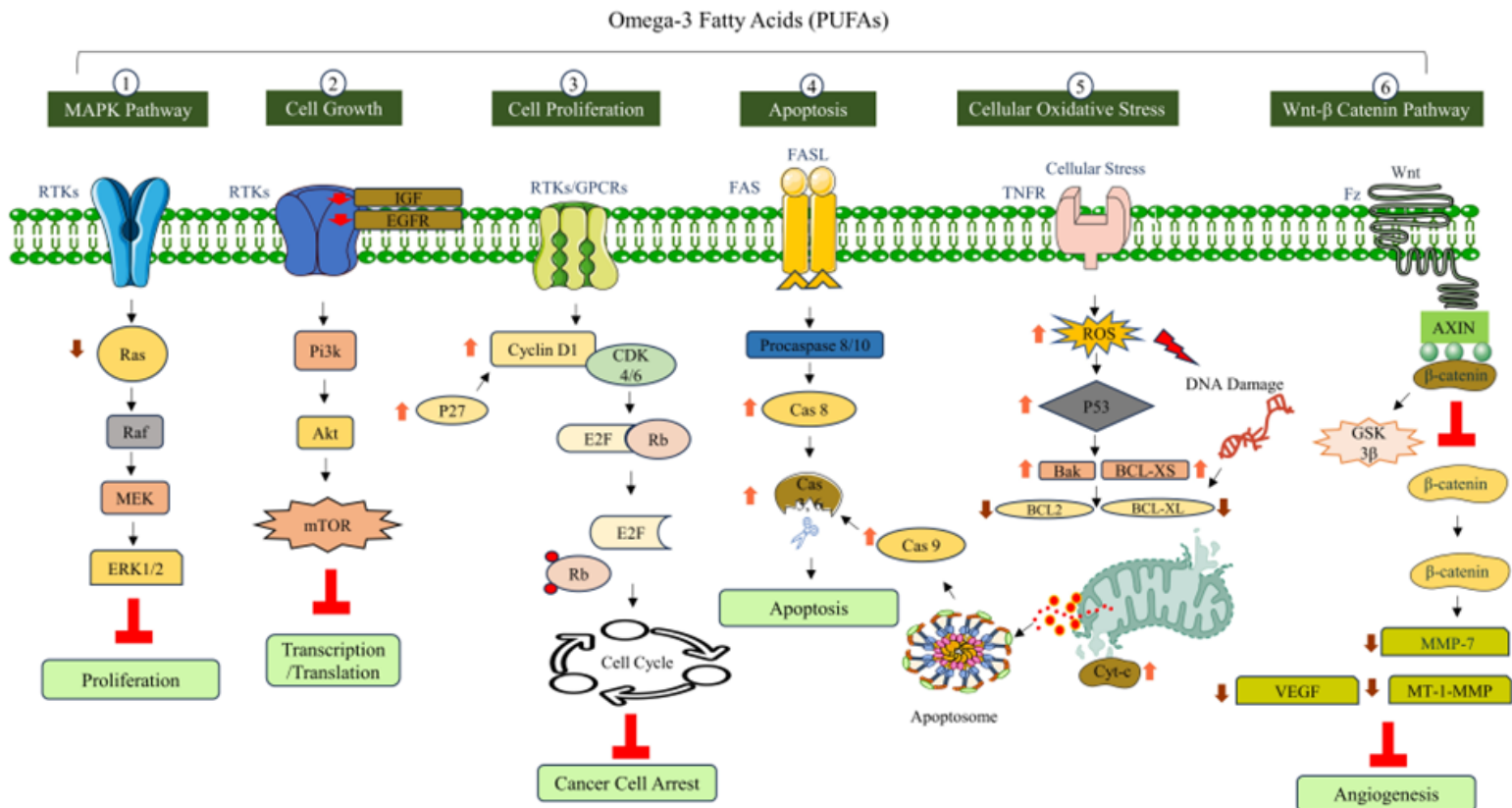


FIGURE A: The effect of Omega-3 fatty acids on multiple targets to exert antitumor effect

1. MAPK Pathway:

Omega-3 reduced the levels of the phosphorylated MAP-kinases, especially ERK1/2 and p38 in the pathway decreasing cell proliferation of tumor cells. (14)

2. Growth Factor Receptor Pathways:

EPA and DHA decrease EGFR levels causing growth inhibition in cancer cells. (15), (16) Omega-3 diet decreases IGF receptor levels in vivo. (17)

3. Effects of ω-3 PUFAs on Cell Proliferation Signals:

DHA and EPA triggered G0/G1 cell cycle arrest in

cancer cells. (18) Specifically, DHA increased cyclin D1 by 40% and increased p27KIP1 levels by 300% in cancer cell lines. (19)

4. Apoptosis:

Omega-3 fatty acids induce apoptosis in cancer cells by both extrinsic and intrinsic pathways. (20), (21)

5. Cellular Oxidative Stress:

ω-3 PUFAs are highly peroxidizable and it is hypothesized that their incorporation into plasma and mitochondrial membrane phospholipids may sensitize cells to reactive oxygen species (ROS), resulting in tumor cell death. (22)

6. Wnt/Beta-catenin signalling Pathway:

Omega 3 decreases concentration of β-catenin protein in the cells. (23), (24)

OMEGA-3 FATTY ACIDS AND CHEMOTHERAPY DEBRIS

- Cancer therapy reduces tumor burden by killing tumor cells but creates tumor cell debris.
- This debris promotes tumorigenesis by stimulating the release of a cytokine storm (Fig B)
- Omega 3 fatty acids help in the clearance of cellular debris resulting from chemotherapy through its active metabolites: resolvins and maresins.
- Resolvins, derived from omega-3 fatty acids EPA and DHA, are known as Resolvin E (RvE) and Resolvin D (RvD), respectively, (Fig C).
- These mediators enhance the clearance of debris via macrophage phagocytosis in multiple tumor types. (25)
- Maresins (MaR's) also called macrophage mediators, are synthesized from DHA by the 12-LOX enzyme (Fig C).

1- MARESINS

Maresins can:

- Inhibit neutrophil recruitment and promote macrophage efferocytosis.
- Negatively regulate the synthesis of pro-inflammatory cytokines, such as IL-1 β , IL-6, and TNF- α , to induce the resolution of inflammation and tissue regeneration. (26)

2. RESOLVINS

DHA and EPA derived active metabolites resolvins (RvD2, and RvE1) clear cellular debris by acting on macrophages(3)

A- RvD2 and Macrophages

- Inside a tumor microenvironment, RvD2 binds to the DRV2 receptor. (28)
- The RvD2 and DRV2 interaction initiates the G α S coupling leading to activation of the cAMP/PKA signaling pathway and phosphorylation of STAT3. (28)
- All this process contributes to macrophage phagocytosis and thereby reduces the pro-inflammatory cytokines i.e. MPC1, TNF, IL-6 and CXCL10 production and promotes 1 macrophage phagocytosis, survival, proliferation and infiltration. (26), (29)

B- RvE1 and Macrophages

- Other type of resolvins i.e. RvE1 derived from EPA, also acts to enhance phagocytosis.
- The ligand RvE1 binds to the ChemR23 receptor of the macrophage membrane.
- This leads to PI3k activation which promotes Akt phosphorylation at SER473.
- The downstream signaling in the macrophage further causes the mTOR activation and it promotes the phosphorylation of Ribosomal Protein S6 at SER235/236(30).
- This process then enhances the phagocytosis through macrophages(30)

“PUROBEST OMEGA-3”

FORMULATION

EACH (1255MG) CAPSULE OF PUROBEST OMEGA-3 CONTAINS 540MG EPA AND 360MG DHA. QUALITY OF ACTIVE INGREDIENT IS ENSURED VIA THIRD PARTY TESTING.

Chemotherapy-Stimulated Cancer

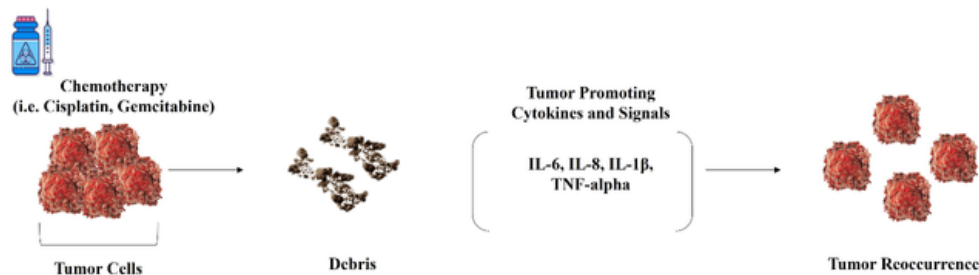


FIGURE B: Chemotherapy debris and tumor recurrence

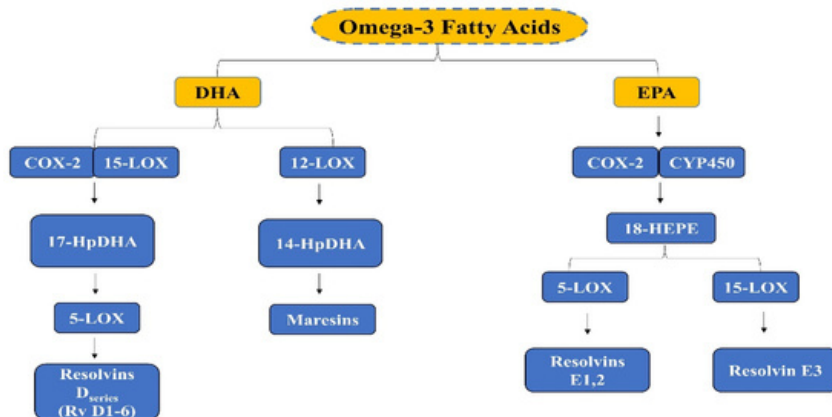


FIGURE C: Biosynthesis of Maresins and Resolvins

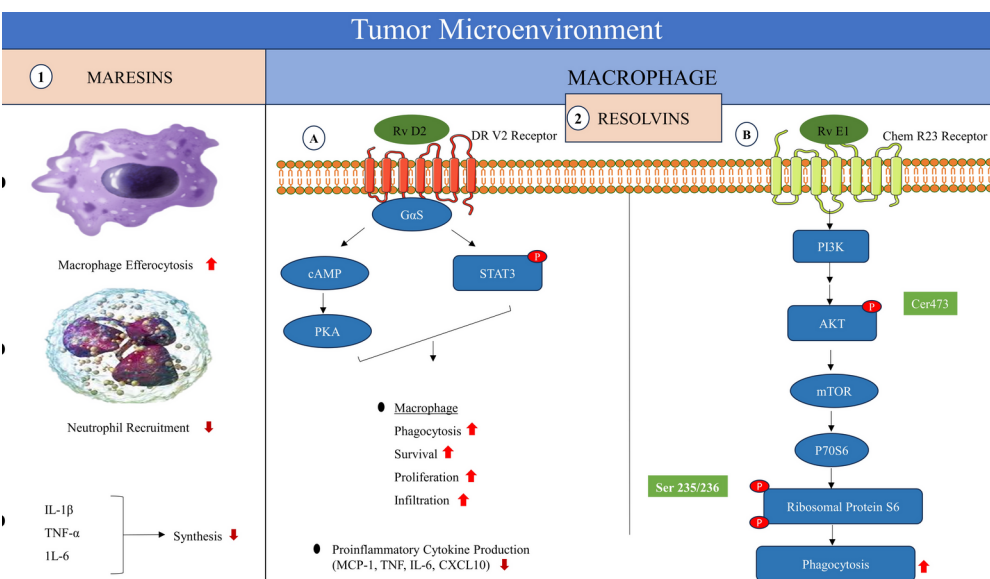


FIGURE D: Mechanism of action of Maresins and Resolvins

SYNERGY WITH CHEMOTHERAPY/RADIOTHERAPY ACCORDING TO CLINICAL TRAILS

- Improvement of survival when used alongside CAF chemotherapy (7)
- Reduction of Oxaliplatin induced neurotoxicity (8)
- Ameliorative effect on Doxorubicin-induced cardiotoxicity (9)
- Improvement of immunosuppression caused by Radiochemotherapy (13)

DOSE ACCORDING TO PUBLISHED CLINICAL TRAILS OF CANCER

Omega-3 is safe up to 52 weeks above 1.5 g/day without any adverse effects. (1) Fish oil capsules are safe for consumption in cancer patients. (2)

“PUROBEST OMEGA-3” RECOMMENDED DOSAGE

1-2 CAPSULES TWICE A DAY WITH FATTY FOOD OR AS RECOMMENDED BY THE HEALTH CARE PRACTITIONER.

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