



# Short Review: Nrf2 and Omega 3 for Human Health

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## Abstract

Oxidative stress is exhilarated through pollution and is the major cause of chronic diseases. The nuclear factor erythroid 2-related factor 2/ antioxidant response element (Nrf2/ARE) pathway is vital in the up-regulation of cytoprotective genes and enzymes in response to oxidative stress. Omega 3 fatty acids are well known and well researched for their use in coronary diseases, brain nutrition, reducing inflammation and many more benefits. Regular consumption of omega 3 fatty acids may prevent diseases as Omega 3 fatty acids can activate Nrf2 pathways which are known to activate natural defense against free radicals and inflammation and thus achieving better health.

**Keywords:** Nrf2, Essential fatty acids; Omega 3 fatty acids; Antioxidants; Inflammation

## Introduction

Inflammation is the cause of many chronic diseases such as Alzheimer's disease, multiple sclerosis, epilepsy, cerebral injury, cancer, allergy, psoriasis, depression, and fatigue. Several factors such as stress, less exercise, sleeping disorders, unhealthy eating habits, dehydration, ultraviolet (UV) exposure, pollution, smoking and medication for certain diseases can trigger or accelerate oxidation and inflammation in the body. The inflammation in body initiates carcinogenesis mediated by Reactive oxygen Species (ROS) may be direct (oxidation, nitration, halogenation of nuclear DNA, RNA, and lipids), or mediated by the signaling pathways activated by ROS. To control the balance between production and removal of ROS, a variety of DNA repair enzymes exist, although antioxidants are more specific and efficient in protecting cells from radicals [1]. Use of Lipids in diet serves several functions such as providing energy, carrier for fat soluble vitamins and supply

of essential fatty acids necessary for nutrition and wellbeing of human body. These essential fatty acids are not only precursors of important compounds such prostaglandins but they also modulate eicosanoids synthesis and thus play a major role for amelioration of various diseases [2].

Nuclear factor-erythroid 2-related factor 2 (Nrf2) is a transcriptional signaling pathway that plays a crucial role in numerous clinical complications. The Nrf2/ARE (Nuclear factor (erythroid-derived 2)-like 2/antioxidant response element) pathway is one of the most important cellular defense mechanisms against oxidative stress. It controls gene expression in which produced proteins are involved in detoxification and elimination of reactive species. Nrf2 is a family member of the transcription factors that activate the battery of cytoprotective genes through ARE, participating in bio transformation, antioxidant reactions,

and inflammation [3]. Pivotal roles of Nrf2 have been proved in cancer, autoimmune diseases, neurodegeneration, cardiovascular diseases, diabetes mellitus, renal injuries, respiratory conditions, gastrointestinal disturbances, and general disorders related to oxidative stress, inflammation, apoptosis, gelatinolysis, autophagy, and fibrogenesis processes.

Nrf2 up-regulates the expression of cytoprotective genes involved in antioxidant and anti-inflammatory responses, including heme oxygenase-1 (HO-1), SOD, NADPH Quinone oxydoreductase enzyme (NQO1), catalase, and enzymes involved in glutathione metabolism such as glutathione S-transferase (GST), glutathione cysteine ligase Modifier (GCLM) subunit, and glutathione cysteine ligase catalytic (GCLC) subunit. It initiates the protein expressions involved in response to oxidative stress i.e., reduces oxidative stress [3,4].

### Omega 3 And Nrf2 Activation

Essential fatty acids are found in the membrane of every cell in the body, where they serve a structural function. Essential fatty acids in the cell membranes serves as stores from which prostaglandins are formed. The prostaglandins regulate heart function and regulation, the kidneys, the brain and reproduction and skin condition [5]. Primary essential fatty acids are omega 3 and omega 6. Several studies have concluded that omega-3 fatty acids are readily incorporated into lipid membranes and modify cellular signaling through multiple mechanisms. Omega-3 fatty acid membrane enrichment occurs mainly at expense of arachidonic acid (AA), resulting in reduced production of AA-derived pro-inflammatory prostaglandins and leukotrienes [6,7]. Omega 3 fatty acids alter membrane fluidity and leads to the disruption of lipid raft-related pro-inflammatory signaling. Omega 3 fatty acids are converted into oxygenated bioactive derivatives to promote the resolution of inflammation. Once incorporated into cell membranes, omega 3 fatty acids become available for conversion into bioactive oxidized derivatives via enzymatic and non-enzymatic pathways and uses both free and esterified fatty acids as substrates. In particular, electrophilic oxo-derivatives are generated during oxidative reactions. These species are released by the cell during oxidative stress and inflammation to exert autocrine and paracrine signaling. Omega 3 fatty acids electrophilic derivatives appear to be the active mediators that transduce the beneficial actions observed [7].

**Antioxidant Pathway:** A recent study by Meijuan et al. [8] demonstrate that omega 3 fatty acids are highly effective in protecting the brain, and that the protective mechanisms involve Nrf2 activation and HO-1 upregulation by 4-HHE. Omega 3 fatty acids have a well described antioxidant capacity which could alleviate oxidative stress. Omega 3 fatty acids stimulate Nrf2 translocation from the cytoplasm into the nucleus, where it binds to ARE and initiates the expression of antioxidant enzymes, including Ho-1, Nqo1 and Cat, in IMS32 cells. The preventive effects of Omega 3 fatty acids against the oxidative stress-induced cell death. The antioxidant effects are induced by omega 3 fatty acids in HUVECs

and 3T3-L1 adipocytes. Omega 3 fatty acids suppress inflammatory responses by inhibiting the arachidonate cascade in neutrophils, and the stimulation of the G protein-coupled receptor 120 by DHA exerts anti-inflammatory effects in macrophages. Recent studies report the antioxidant effects of 4-hydroxy-2-hexanal (4-HHE), resolvin E1 and protectin D1, which are intracellular metabolites of Omega 3 fatty acids [9].

Study done by Ling Gao et al. [10] demonstrate a requirement for free radical-mediated oxidation of DHA and EPA for the process of Nrf2 stabilization, ARE-directed reporter gene expression, as well as for expression of endogenous HO1 and GCLC. These data identify the association of Keap1 with Cullin3 as a key regulatory step in Nrf2 biology with respect to activation by J3-IsoPs and, by extension, other cyclopentenone-containing IsoPs.

These studies emphasis on the necessity of omega 3 fatty acids in human health and also opens new avenues to use omega 3 in preventive wellness products. Most of omega 3 fatty acids products consumed for health and wellness comprises of fish oil or its derivatives. Depending on source and processing conditions of such products, they may content oxidized and polymerized by products [11] which can be carcinogenic as well as toxic. With increased awareness about fish oils quality issues and preference to vegan products, consumers are switching to plant-based omega 3 products based on vegetable oils such as flax seed oil or algal oil. Use of such omega 3 rich oils in wellness applications is restricted due to its oxidative stability. Therefore, with decades of experience in lipids research, we have developed a unique technology of internal stabilization using only natural herbs to overcome challenges of oxidative stability. With internal stabilization technology, we enhance oxidative stability of lipids multi-fold thus increasing its shelf life and safety during applications [12]. We have also developed a vegan omega 3 oil blend which has high content of omega 3 fatty acids, and it is stabilized with internal stabilization to have longer shelf life and effective in many applications internal as well external such as encapsulation, ointments, food preparations.

### Concluding Remarks and Further Directions

Thus, benefits of Omega 3 fatty acids in alleviating oxidative stress and inflammation using activation of Nrf2 pathway will help to broaden applications of Omega 3 uses in food, cosmetics as well as nutraceuticals. Furthermore, plant derived bio actives present a broad spectrum of biological effects and their antioxidants, anti-inflammatory and more recently antiaging effect combined together will provide a hot topic for medical and scientific communities. Finally, efforts should be made to develop more health products from plant based Omega 3 fatty acids which are not only safe but also environmental friendly and sustainable provided they are made stable.

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### Conflict of Interest

No Conflict of interest.

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