

## Potential Fish Oil as Acute Hepatitis Candidate by Hepatoprotective Mechanism: A-review

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**Abstract:** Acute hepatitis is a health concern that emerged during the COVID-19 outbreak. Toxic drugs, infections, autoimmune diseases, and other causes may induce acute hepatitis, which is deadly. Acute hepatitis isn't treatable. Renewable natural products, such as fish, are used in complementary treatment. This paper mentions current preclinical and clinical studies of omega-3 fatty acids (N-3 FAs) for hepatoprotection. The mechanism of inhibition of oxidative stress and inflammation in the liver is the subject of discussion associated with its potential as a treatment for acute hepatitis. This review article on acute hepatitis treatment analyzed original articles, books, and other relevant material from the Web of Science, Scopus, and PubMed. The literature search was conducted in April-July 2022. The keywords explored during the literature investigation were "omega-3 or EPA or DHA or fish oil," "hepatoprotective," "acute hepatitis," "inflammatory", and "stress oxidative". The study's results show that N-3 FAs can protect against liver damage through inflammation and oxidative stress pathways. Enzyme parameters of liver damage, proinflammatory cytokines, and oxidative stress can be inhibited by the administration of fish oil and its derivatives. Even though not all clinical trial parameters are directly related to animal tests, the results of this study show that omega-3 fatty acids should be considered a treatment option for acute hepatitis.

**Keywords:** Acute hepatitis; inflammatory; omega-3; stress oxidative

### 1. Introduction

Acute hepatitis is evidence of a health issue that arises when the world focuses on COVID-19. Acute hepatitis may be caused by toxic substances, viruses, autoimmune disorders, and other factors, all of which have a bad prognosis and a high mortality rate (Shalimar *et al.*, 2020; Sallam *et al.*, 2022). It's a worldwide health concern. There are no acute hepatitis drugs. New effective treatments for acute hepatitis are a global research priority (Huang *et al.*, 2022). Renewable natural materials are an option for complementary therapy (Bruce *et al.*, 2021), especially those sourced from marine and inland waters such as fish (Sasongko *et al.*, 2022).

Fish is a well-known source of high-quality polyunsaturated fatty acids (PUFAs) (Gómez-Limia *et al.*, 2020; Sasongko *et al.*, 2019). Seafood is rich in critical unsaturated fatty acids, including docosahexaenoic (DHA), eicosapentaenoic (EPA), and docosapentaenoic (DPA), which have several health benefits (Al-Obaidi & Al-Izzi, 2021). In the current research development, there have been many uses of nutrients from food as medicine (Sasongko *et al.*,

2017). The utilization of fatty acids, especially EPA and DHA, from fish sources as medicine has been developed for complementary therapy (AbuMweis *et al.*, 2021). Omega-3 fatty acids (N-3 FAs), especially EPA and DHA, are known to affect anti-inflammatory, antioxidant, anticancer positively, cardiovascular disease, hepatoprotective and immunomodulatory activities El-Mowafy *et al.*, 2022). Although some clinical trials consider EPA and DHA as placebo-like and even prove that these fatty acids have no effect, the dose, duration, patient adherence to taking the drug, and source of omega-3 are key factors for effect (Sasongko *et al.*, 2022). Animal investigations show that EPA or DHA influences cardiac function by modifying fatty acid content in the rat heart (Yamanushi *et al.*, 2014). Omega-3 fatty acids inhibit heart fibrosis in pressure-overloaded mice. Omega-3 PUFA, EPA and DHA are well-documented to have hepatoprotective effects by regulating fatty acid metabolism, preventing lipogenesis, and reducing inflammation and oxidative stress (Wang *et al.*, 2017).

In the future, people's perspectives on the use of food as medicine might be changed by this approach. The significant aspect of this review is the use of N-3 FAs from fish oil to treat acute hepatitis with signs of oxidative stress and inflammatory pathways. This article aims to provide information on recent developments in preclinical and clinical trials of N-3 FAs as a treatment for acute hepatitis. Furthermore, practical aspects addressing the effects of N-3 FAs supplementation on acute hepatitis, including dosage, method of administration, treatment duration, population, and biomarkers, will be explored.

## 2. Material and Methods

This review article on acute hepatitis therapy was prepared by identifying, studying, and compiling some original papers, books, and other relevant literature from credible international databases such as Scopus and PubMed. The literature search was conducted between April and July 2022. The keywords investigated during the literature review were "omega-3 or EPA or DHA or fish oil," "hepatoprotective," "acute hepatitis," "inflammatory", and "stress oxidative." The inclusion criteria to select the papers were: (1) studies regarding the treatment of hepatitis using fish oil containing omega-3 polyunsaturated fatty acids and their derivatives between 2012–2022; (2) omega-3 polyunsaturated fatty acid mechanisms of action in hepatitis between 2012–2022; (3) the use of omega-3 polyunsaturated fatty acids to treat hepatitis is supported by both in-vivo and human clinical trials; and (4) all papers written in English. The exclusion criteria of the papers were (1) not open access journal, (2) the article is a review, and (3) does not accurately describe the variables or experimental procedure.

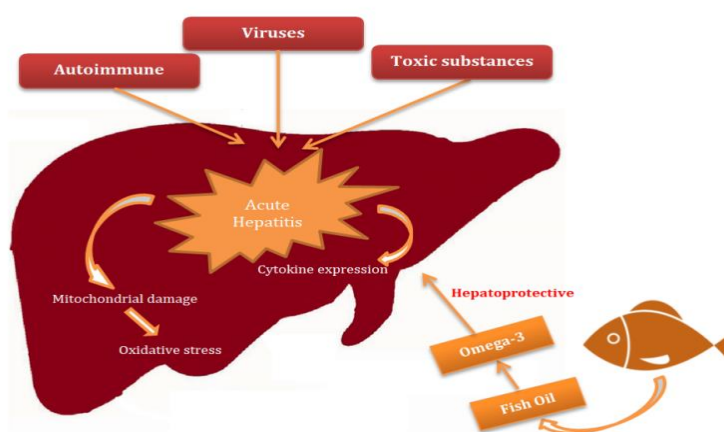
### 3. Acute Hepatitis

Children with severe acute hepatitis with no clear cause have been getting sicker worldwide recently (Chen *et al.*, 2022). Hepatitis is a liver inflammation caused by infectious agents such as bacteria or non-infectious agents such as medications, alcohol, or hepatotoxic chemicals. Acute viral hepatitis (AVH) is usually caused by hepatitis A or E virus infection and may vary from preclinical illness to liver failure (Benzamin *et al.*, 2019). Age (>40) and previous liver disease are associated with more severe acute hepatitis A. Some people can have unusual clinical signs, like recurrent hepatitis, prolonged cholestasis, or even signs outside of the liver (Shin & Jeong, 2018). Marsh *et al.* (2022) reported five infants with severe acute hepatitis of an unknown cause in April 2022. In prior years, the number of instances surpassed the whole year (Marsh *et al.*, 2022). In Alabama, USA, 9 incidents were found retrospectively from October 2021 to February 2022 (Baker *et al.*, 2022). As of April 18, 2022, 6 out of 24 nations reported at least 3 times more instances than the 5-year norm (van Beek *et al.*, 2022). The causes of the present epidemic of severe acute hepatitis are unclear and are being investigated. All of the possible causes that have been written about and are presented here are still just hypotheses that need to be tested (Chen *et al.*, 2022). Clinical symptoms include acute hepatitis with elevated aspartate or alanine transaminases. The disease progresses quickly. Jaundice (71%), nausea (63%), and pale stools (50%). Early symptoms include diarrhea (45%), stomach discomfort (42%), and nausea (31%). 31% have a fever, and 19% have respiratory problems (van Beek *et al.*, 2022). Hepatomegaly is more prevalent than splenomegaly. Hepatic encephalopathy may arise during hospitalization (Baker *et al.*, 2022). Pathogens may be collected from whole blood, serum, respiratory droplets, faeces, urine, or other bodily fluids. There is currently a shortage of data about potential therapeutic options. The treatment plan below is based on current research and what our hospital has learned from treating children with severe hepatitis (Chen *et al.*, 2022). The use of hepatoprotective is one solution to overcome acute hepatitis. Studies have shown that omega-3 fatty acids, which are found in fish oil, have anti-inflammatory and antioxidant properties that could protect the liver from toxic substances, viruses or autoimmune disease (Figure 1).

### 4. Fish Oil as Hepatoprotective

Acute hepatitis is a serious disease with a high death rate. It can be caused by toxic drugs, infections, autoimmune diseases, and other things. A substance or material used to protect or damage the liver is called a hepatoprotector (Sasongko & Sugiyarto, 2018). The health benefits of fish oil containing N-3 FAs, particularly-linolenic acid (ALA), EPA, and DHA, have been well-established in human studies (Sasongko *et al.*, 2022). A recent study indicates that N-3

FAs may have a preventive role in various cardiometabolic risk factors, including hepatoprotection (El-Mowafy *et al.*, 2022). Randomized and non-randomized clinical studies in adults have indicated that supplementing with N-3 FAs, particularly EPA and DHA, reduces liver disease (Sangouni *et al.*, 2021). DHA supplementation reduces hepatic steatosis, lowers blood alanine aminotransferase (ALT) and lipid levels, and increases insulin sensitivity in children (Nobili *et al.*, 2013). Fish oil and its ingredients may be utilized as a hepatoprotective and antioxidant dietary supplement, especially in individuals taking anti-tubercular medication who are at risk for hepatotoxicity (Basheer *et al.*, 2017). N-3 FAs effectively slowed down acetaminophen overdose caused by acute liver injury. Mechanically, this protective action appears to reduce C-jun N-terminal kinase (JNK) through the apoptosis signal-regulating kinase 1 (ASK1)-mitogen kinase 4 (MKK4) signalling pathway and stopping inflammation caused by nuclear factor kappa B (NF- $\kappa$ B) (Feng *et al.*, 2018). The previous study shows that N-3 FAs from fish oil may function as an antioxidant against thioacetamide-induced hepatic fibrosis, suggesting its application in treatment (Al-Attar & Al-Rethea, 2017). A Randomized Controlled Trial (RCT) study in children aged 2 to 19 years with nonalcoholic fatty liver disease (NAFLD) found that N-3 FAs aspartate aminotransferase and gamma-glutamyl transpeptidase levels improved when compared to placebo (Janczyk *et al.*, 2015). Table 1 and Table 2 are a summary of the clinical trials and animal studies that have been done on the use of fish oil and its derivatives to treat liver injury.



**Figure 1.** Effects of toxic substances on acute hepatitis and fish oil as hepatoprotective by anti-inflammatory and antioxidant pathways adapted by Scorletti & Byrne (2018).

**Table 1.** The clinical trials studies of fish oil enriched with omega-3 and its derivatives in liver injury. Description: symbols ↑ or ↓ = significantly different compared with the control group; ↔ = not significantly different compared with the control group, ALT = alanine aminotransferase, AST = aspartate aminotransferase, ALP = alkaline phosphatase, TB: Total bilirubin, MDA = malondialdehyde, TAC: Total antioxidant capacity, GPX = glutathione peroxidase, CAT = catalase, SOD = superoxide dismutase, GSH = glutathione, Nox = nitric oxide, TNF-α = Tumor necrosis factor alpha, IL-6 = interleukin-6, IL-10 = interleukin-10, NF-Kb = nuclear factor kappa B.

Sample	Study design	Study population	Duration	Dose	Clinical liver outcomes	Reference
DHA	Double-blind, parallel-group, placebo-controlled randomized trial	<18 years old (N=58)	29 months	250 mg/day p.o	↓ ALT	(Pacifico <i>et al.</i> , 2015)
Fish oil (Omegaven 10%)	Baseline and follow-up clinical trial	20-45 years old (N=15)	4 week	10 g/ day or 0.15–0.2 g/kg p.n.	↓TB, ↓ALT, ↓cholestasis and inflammation observation in liver histology biopsy	(Xu <i>et al.</i> , 2012)
Omega-3 (1000 mg/capsule contained 180 mg EPA and 120 mg DHA)	Double-blind, randomized controlled clinical trial	18-65 years old (N=56)	12 week	2 g/day p.o	↑ GGT and ↑ FLI	(Sangouni <i>et al.</i> , 2021)
Fish oil containing omega-3 LC-PUFA (DHA and EPA in a 3:2 proportion)	Multicenter, randomized, double-blind, placebo-controlled clinical trial	2-19 years old (N=64)	24 week	450-1300 mg/day p.o	↓AST and ↓GGTP	(Janczyk <i>et al.</i> , 2015)
Fish oils contained 900 mg EPA and 600 mg DHA	Single-center, double-blind, randomized controlled trial	18-65 years old (N=104)	2 week	5 gr/day via nasogastric tube	↔ liver enzymes	(Rashidi <i>et al.</i> , 2020)
Fish oil 1000 mg (180 mg EPA and 120 mg DHA)	Double-blind, randomized, placebo-controlled trial	≤16 years old (N=70)	6 months	1000 mg/day p.o	↓ALT, ↓AST, ↓ALP, ↓Direct bilirubin, and ↓GGT	(Elbarbary <i>et al.</i> , 2016)
Omega-3 0.315 g (64% ALA, 16% EPA, and 21% DHA)	Randomized, double-blind, placebo-controlled trial	18-75 years old (N=50)	6 months	three capsules daily containing 0.315 g of omega-3 p.o	↔ liver enzymes	(Nogueira <i>et al.</i> , 2016)

**Table 2.** The animal studies of fish oil enriched with omega-3 and its derivatives in liver injury. Description: symbols ↑ or ↓ = significantly different compared with the control group; ↔ = not significantly different compared with the control group, ALT = alanine aminotransferase, AST = aspartate aminotransferase, ALP = alkaline phosphatase, TB = Total bilirubin, MDA = malondialdehyde, TAC = Total antioxidant capacity, GPX = glutathione peroxidase, CAT = catalase, SOD = superoxide dismutase, GSH = glutathione, Nox = nitric oxide, TNF-α = Tumor necrosis factor alpha, IL-6 = interleukin-6, IL-10 = interleukin-10, NF-Kb = nuclear factor kappa B.

Sample	Animals	Duration	Dose	Outcomes	Reference
EPA and DHA	Male Sprague-Dawley rats	2 weeks	250 mg/kg DHA and 300 mg/kg EPA separately, p.o	DHA = liver enzymes: ↓ALT, ↓ALK, ↓γ-GT, and ↑albumin; antioxidant marker: ↑GSH and ↓MDA; inflammatory marker: ↓TNF-α and ↓IL-6 EPA = liver enzymes: ↓ALT, ↓ALK, ↓γ-GT, and ↔albumin; antioxidant marker : ↔ GSH and ↓MDA; inflammatory marker : ↓TNF-α and ↓IL-6	(El-Mowafy <i>et al.</i> , 2022)
Fish Oil	Male Wistar rats	2 week	4 ml/kg, i.p	liver enzymes: ↓ALT, ↓AST, and ↓ALP; antioxidant marker: ↑GSH and ↓MDA; inflammatory marker: n/a	(Basheer <i>et al.</i> , 2017)
Omega-3 (EPA and DHA in a 3:2 ratio)	Male Sprague-Dawley rats	8 weeks	150 mg/kg/day, p.o	liver enzymes: ↓AST, ↓total bilirubin, ↑albumin, ↑total protein, and ↔ ALT, antioxidant marker: ↓MDA; inflammatory marker: NF-κB	(Abo El-Magd <i>et al.</i> , 2015)
Omega-3	Male Sprague-Dawley rats	7 day	Omega-3 (270 mg/kg EPA and 180 mg/kg DHA) /day, p.o	liver enzymes: ↓ALT, ↓AST antioxidant marker: ↓MDA and ↑TAC inflammatory marker: ↓TNF-α and ↓IL-10	(Eraky & Abo El-Magd, 2020)
Omega-3 (EPA and DHA in a 3:2 ratio)	Male Wistar rats	3 week	100 and 300 mg/kg/day, p.o	liver enzymes: ↓ALT, ↓AST, ↓ALP, and ↓TB bilirubin antioxidant marker: ↓MDA, ↑GPX, ↑CAT, ↑TAC, and ↑SOD	(Olayaki <i>et al.</i> , 2018)
DHA	Male Sprague-Dawley rats	8 week	1000 nmol/kg/ day, i.p.	liver enzymes: ↓ALT, ↓AST, and ↓ALP antioxidant marker: ↓MDA and ↑GSH inflammatory marker: ↓TNF-α and ↓IL-6	(He <i>et al.</i> , 2017)
Fish oil	Male Wistar rats	4 week	20% on feed formula (200 g/kg/ day)	liver enzymes: ↓ALT, ↓AST antioxidant marker: ↓MDA, ↑GPX, ↑CAT, and ↑SOD	(Daidj & Lamri-Senhadji, 2021)
Fish oil	Female albino rats	4 week	117.6 mg/kg, p.o	liver enzymes: ↓ALT, ↓AST, and ↓ALP antioxidant marker: ↓MDA, ↑CAT, and ↑GSH	(Refaie <i>et al.</i> , 2021)
Omega-3	Female Wistar albino rats	3 week	50 and 100 mg/kg/day, p.o.	liver enzymes: ↓ALT, ↓AST antioxidant marker: ↔MDA, ↓NOx, and ↑GSH inflammatory marker: ↓TNF-α and ↓IL-6	(El-Gendy <i>et al.</i> , 2021)
Omega-3	Female Wistar albino rats	4 week	25; 50 and 100 mg/kg /day, p.o.	liver enzymes: ↓ALT, ↓AST, ↓total billirubin, ↓direct bilirubin antioxidant marker: ↓MDA and ↑GSH inflammatory marker: ↓TNF-α	(Saleh <i>et al.</i> , 2022)

## 5. Inflammation Targets

Inflammation is the underlying cause of several physiological and pathological processes in disease. Effective acute inflammation is the consequence of the inflammatory response, which aims to eliminate or avoid the source of the disturbance and restore function and balance. If abnormal conditions continue, however, a persistent inflammatory state develops (Mariqueo & Zúñiga-Hernández, 2020). Chronic liver disorders are characterized by inflammation. Prolonged inflammation from liver injury deposits fibrous proteins, glycoproteins, and proteoglycans as extracellular matrix (Shoieb *et al.*, 2020). Due to hepatocytes' failed attempts to cure the liver injury, fibrosis developed. As tissue damage persists, healing slows, and extracellular matrix deposition continues (Bataller & Brenner, 2005). Eicosanoids are a group of powerful chemical messengers that play a role in immune and inflammatory responses. They are made from PUFAs with 20 carbons and oxygen. Most of the time, they are not stored in cells. Instead, they are made when needed. In the liver, N-3 FAs are turned into bioactive eicosanoids by a series of enzymes. These bioactive eicosanoids help control inflammation and balance the body's systems (Igarashi *et al.*, 2007). The hepatoprotective benefits of N-3 FAs are related to the anti-inflammatory environment and the rise of M2 polarization, which work through a fatty acid receptor in Kupffer cells, providing the hepatic with decreased sensitivity to inflammation (Raptis *et al.*, 2014). Omega-3 FAs promote cell development and decrease inflammation, cytokine release, and hepatocyte death. This is connected to liver kinase b1 (LKB1)- adenosine monophosphate-activated protein kinase (AMPK) signals that govern bile canalicular development, hepatocyte polarization, and proliferation. N-3 FAs may assist trigger cellular regeneration pathways (Qiu *et al.*, 2012).

## 6. Oxidative Stress Targets

Liver injury causes redox homeostasis imbalance, characterized by an increase in ROS and a loss in antioxidant defenses, resulting in the oxidation of DNA and other macromolecules, including lipids and liver damage (Alasmari *et al.*, 2021). The past oxidative stress theory was validated by assessing additional major oxidative markers, including reduced GSH in the liver and TAC in the blood (El-Mowafy *et al.*, 2022). Omega-3 FAs decreased oxidative stress in the liver by reducing MDA and NO and increasing GSH, GPX, CAT, and SOD (Daidj & Lamri-Senhadji, 2021). Despite the benefits of N-3 FAs supplementation, PUFAs in the diet lead to increased amounts of oxidizable substrate that may de-regulate redox regulation and promote oxidative stress (Liu *et al.*, 2000). Omega-3 FAs upregulate superoxide dismutase enzyme expression and diminish superoxide anion, peroxynitrite, and hydroxyl radical production (Shaaban *et al.*, 2014).

## 7. Conclusion

As a result of their anti-inflammatory and anti-oxidative properties, N-3 FAs may prevent liver damage. Fish oil and its derivatives may reduce liver damage enzyme markers, proinflammatory cytokines, and oxidative stress. This research suggests that N-3 FAs may be useful as a therapy for acute hepatitis. However, not all characteristics of human trials are directly comparable to animal experiments. It is necessary to study the combination therapy of N-3 FAs with anti-viral agents or other drugs in treating acute hepatitis, both in vivo and in clinical trials.

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## Conflict of Interest

All authors declared that there was no conflict of interest.

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