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THE COD LIVER OIL INSIGHTS: FROM FOLKLORE TO FACTS

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ABSTRACT

This review article provides a concise overview of the background history, important nutritional components, evidence-based benefits, common misconceptions, probable risks, and future directions with regard to cod liver oil (CLO). It emphasizes the inclusion of recent studies to demystify known facts vs. common misconceptions, thus providing an insightful overview of the dynamic function of CLO as a food supplement. The article emphasizes CLO's proven effectiveness in lipid regulation, anti-inflammatory activity, and bone health promotion, and briefly touches on important safety concerns like vitamin A toxicity and drug interactions. It also discusses emerging therapeutic uses, providing a comprehensive, evidence-based review for healthcare professionals, researchers, and health practitioners.

Keywords: CLO, Vitamins, Inflamtion, Supplements, Health

1. INTRODUCTION 1.1. OVERVIEW

Cod liver oil, mainly produced from the liver of the Atlantic cod (Gadus morhua), has a rich history that spans several centuries, particularly in northern European societies where it was used traditionally to ward off cold temperatures and cure ailments like rheumatism, sore joints, and weak muscles. Its medicinal use

gained considerable popularity during the 19th century, when it became a popular patent medicine in the United States and gained attention in medical journals by the turn of the century. The biggest breakthrough occurred in 1920 when the connection between vitamin D deficiency and rickets was conclusively established, which put CLO on a pedestal as an important source of this vital vitamin among children. This turn of events leads us to a transition from traditional herbal medicine to an accepted medical treatment in the quest to cure specific nutritional deficiencies. National Institutes of Health. (2023), National Center for Biotechnology Information. (2023)

Historical production methods for cod liver oil varied widely, from primitive methods like oil harvesting from boiled-over water livers—the method used by Scandinavian Vikings—to large-scale industrial production methods involving decomposition in barrels. These different processes yielded very different products, yielding pale, mild-flavoured oil safe for human consumption as well as foul-tasting, brown varieties more cost-effective to manufacture. The early history of cod liver oil's effectiveness was frequently anecdotal or sweeping observation rather than full scientific understanding of its active constituents. The transition to industrial manufacture, as well as later scientific establishment of vitamin D, represents a critical transition from ancient superstition to evidence-based use. Additionally, history's perception of cod liver oil as an "unspeakably detestable thing to take" suggests palatability has been a concern for centuries, driving product development throughout history. Aside from its medicinal applications, cod liver oil had bizarre applications, as a liquid carrier for traditional red ochre paint in Newfoundland and even as a punitive measure during Germany's annual Stocherkahnrennen boat race. This history illustrates cod liver oil's centuries-long history, if sometimes primitive, inclusion in health regimes, and providing necessary background to the scientific work of today. National Center for Biotechnology Information. (2023), Abdelhamid et al. (2020), Rajakumar (2007)

Nutrient Content: Omega-3 fatty acids, Vitamins A and D: Cod liver oil is characterized by its distinctive and effective nutritional composition, which consists primarily of omega-3 fatty acids, specifically eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), as well as extremely high concentrations of fat-soluble vitamins A and D. A teaspoon (5 mL) of cod liver oil contains approximately 890 milligrams of omega-3 fatty acids, 1350 micrograms (mcg) Retinol Activity Equivalents (RAE) of vitamin A, equivalent to 150% of the daily value, and fulfills 56% of the daily recommended amount of vitamin D. Such a high concentration of nutrients is exactly the opposite of normal fish oil, which is derived from the oily parts of fish, such as tuna, herring, anchovies, and mackerels, and primarily offers omega-3 fatty acids but not the high concentrations of vitamins A and D that exist exclusively in cod liver oil.

Omega-3 fatty acids are essential cell membrane components, highly concentrated in the retina, brain, and sperm, and are precursors to eicosanoids, which influence numerous aspects of body functioning such as inflammation. Vitamin A is essential for healthy vision, immune function, bone development, cellular growth, and reproductive health. Vitamin D is essential for calcium absorption, bone health, and regulation of the immune system. The fact that all these compounds happen to be found together in varying ratios makes CLO a multinutrient supplement. This complex profile, however, also poses difficulties in accurate dosage and titration of each component since optimization of intake for one nutrient, for example, omega-3s, would result in over-consumption of another, vitamin A. This inherent complexity is the reason why the need exists for individualized medical recommendation as opposed to a general recommendation

for CLO supplementation. This is also the reason why some omega-3 supplements are manufactured free of vitamins A and D, providing more controlled dosing for specific therapeutic requirements. National Institutes of Health. (2023), National Center for Biotechnology Information. (2023), Osavi (2024)

The aim of this review is to provide a comprehensive analysis of the existing scientific literature to elucidate the known facts and the prevailing misconceptions regarding cod liver oil. Through the integration of outcomes from clinical trials, observational studies, and systematic reviews, the intention is to offer the health care professionals, researchers, and the health-conscious the latest and most comprehensive information, thereby supporting well-informed decisions regarding CLO supplementation.

2. COD LIVER OIL HEALTH BENEFITS SUPPORTED WITH SCIENTIFIC EVIDENCE

Cardiovascular Health and Lipid Metabolism: Cardiovascular effects of cod liver oil are primarily due to its omega-3 fatty acids, ie, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which are well established for lipid-modulating actions. In line with this, evidence from studies has established that omega-3 fatty acids can induce a significant reduction in triglyceride levels, with cod liver oil inducing a reduction range of 20% to 50% in patients with hypertriglyceridemia. This is mediated by a variety of biochemical mechanisms, including downregulation of lipogenic gene expression, enhanced fatty acid beta-oxidation, and enhanced expression of lipoprotein lipase (LPL).

Outside of triglycerides, CLO can also affect cholesterol. Although there is not much research on CLO alone, there are some studies that demonstrate a reduction in low-density lipoprotein (LDL, or "bad") cholesterol, especially when taken with cholesterol medication. An increase in high-density lipoprotein (HDL, or "good") cholesterol has also been reported in some studies. In addition, CLO can reduce blood pressure modestly, especially in mild hypertension. Concerning broader cardiovascular outcomes, the evidence presents a complex landscape that necessitates thorough interpretation. Although earlier research indicated a decrease in mortality and sudden cardiac death associated with omega-3 fatty acids, more contemporary large-scale trials offer a more nuanced understanding. The VITAL (Vitamin D and Omega-3 Trial) and ASCEND trials, both administering omega-3 fatty acid ethyl esters (O3AEE) at a dosage of 840 mg/day, did not reveal a significant reduction in primary composite cardiovascular endpoints in either healthy individuals or those with type 2 diabetes. Nonetheless, a closer inspection of secondary analyses in VITAL uncovered statistically significant reductions in particular events: a 28% decrease in the risk of heart attacks, a 50% decrease in the risk of fatal heart attacks, and a 17% decrease in the risk of total coronary heart disease events. These benefits were especially evident among individuals with low baseline fish intake and among African Americans. The REDUCE-IT trial, which utilized a higher dosage of icosapent ethyl (a purified EPA derivative), showed considerable reductions in cardiovascular death, heart attack, and stroke among patients with hypertriglyceridemia who were concurrently taking statins. Collectively, these findings indicate that the dosage, patient demographic, and specific omega-3 formulation are vital elements that impact clinical outcomes. The apparent discrepancy between the overall null effect on primary composite endpoints and the notable reduction in specific adverse events underscores the notion that broad generalizations regarding "fish oil" or "omega-3s" may be misleading. A more accurate understanding necessitates a focus on specific

formulations, dosages, patient demographics, and clinical endpoints. This would mean that CLO can actually confer cardiovascular benefit, especially as a function of triglyceride control and potentially in the reduction of some cardiac events, but as a panacea for all cardiovascular outcomes as originally thought, not quite. Practitioners should thus take into account patient profiles and the particular makeup of the supplement when recommending. Abdelhamid et al. (2020), Hu et al. (2019)

Anti-inflammatory Activity and Immune Modulation: Cod liver oil has potent anti-inflammatory and antioxidant activity primarily attributed to its composition of omega-3 fatty acids (EPA and DHA) and vitamins A and D. Chronic inflammation has been recognized as a risk factor for numerous diseases, including cardiovascular diseases. Omega-3 fatty acids downregulate inflammation by inhibiting pro-inflammatory proteins and modulating inflammatory pathways. These include inhibition of leukocyte chemotaxis, adhesion molecule expression, cyclooxygenase (COX) activity, and pro-inflammatory cytokine production like TNF- α , IL-1, and IL-6. Besides, omega-3 fatty acids also induce the production of specialized pro-resolving mediators like resolvins, maresins, lipoxins, and protectins, which actively participate in resolving inflammation. Vitamins A and D augment these actions through their antioxidant action as potent free radical binders, effectively neutralizing harmful free radicals with inflammatory participation. Deficiency in these vitamins has also been associated with an increased risk of chronic inflammation.

In the context of sports performance, Cod Liver Oil (CLO) has been established to possess significant anti-inflammatory effects. A prospective observational study by Hansen et al. (2021) in recreational cyclists determined that frequent CLO consumption was correlated with decreased levels of basal and exercise-induced Creactive protein (CRP), a significant marker of inflammation. The observed effect was determined to be highest among users of CLO, showing a greater effect compared to other omega-3 supplements. The reduction of inflammation has a significant impact on enhanced muscle recovery and effectiveness of workouts by reducing delayed onset muscle soreness (DOMS). The repeated observation that CLO specifically reduces CRP levels among athletes suggest a unique benefit, most likely attributed to synergy of its omega-3 fatty acids, vitamin A, and vitamin D, which in combination may induce a more significant anti-inflammatory effect than omega-3s alone. Thus, CLO is a valuable supplement in sports nutrition, specifically in exercise-induced inflammation management and recovery enhancement and may potentially have a larger impact on performance and continued athletic participation.

Aside from athletes, CLO supplementation also lowered inflammatory markers in pregnant women with gestational diabetes. Its anti-inflammatory action also makes it a candidate treatment for diseases such as rheumatoid arthritis, where it has been reported to lower joint pain and possibly lower the dose of painkillers. Calder (2017), Gammone et al. (2018), Kampman et al. (2021)

Bone Health and Vitamin D Metabolism: Cod liver oil is a good food source of vitamin D, whose role is critical to the preservation of healthy bone structure by the control of calcium absorption in the gut. Bone density naturally diminishes with increasing age, making the body vulnerable to conditions like osteoporosis and fractures. Administration of vitamin D, especially cod liver oil, can reverse bone weakness due to age, especially when accompanied by a calcium diet. Cod liver oil has been traditionally used widely in the prevention and treatment of rickets, a condition prevalent in children in which the bones become fragile, and is closely

associated with a deficiency of vitamin D. Eysteinsdottir et al. (2015), Simopoulos and DiNicolantonio (2016)

Current research remains supportive of the role for CLO in bone health. One study reported that daily supplementation with CLO increased bone mineral density (BMD) more in women than in men. Although a long-term Icelandic study found current CLO consumption was positively associated with serum 25-hydroxyvitamin D (25(OH)D) levels, a measure of vitamin D status, the direct association with hip BMD in old age was small and of dubious clinical relevance, especially for long-term consumption. This indicates that although CLO is effective at increasing vitamin D levels, its effect on long-term bone density in older age may be insubstantial or subject to other influences. A critical observation in this study is that a Norwegian follow-up study indicated childhood use of cod liver oil may be linked to negative effects on BMD in older women, allegedly due to high vitamin A (retinol) content of CLO consumed from an early age. This observation is corroborated by historical evidence that CLO in the mid-20th century contained much higher concentrations of vitamin A (2400μg per 8g spoonful) than at present (400 μg). This complicated interaction provides a possible historical trade-off: although CLO successfully treated vitamin D deficiency, its higher concentration of vitamin A in older products potentially had subtle, long-term harmful effects on bone density. This highlights the significance of balanced intake of nutrients and how changes in product formulation, based on scientific knowledge of toxicity, can modify a supplement's long-term effect. It also points to the value of monitoring vitamin A intake, especially in children and pregnant women. Simopoulos and DiNicolantonio (2016), Mayo Clinic. (2023)

Ocular Health and Vision Support: Cod liver oil's role in eye health lies in its high vitamin A and DHA omega-3 fatty acids. Vitamin A plays a part in the production of eye retinal pigments necessary for light to sight conversion. Vitamin A also plays an important role in protecting against cellular damage due to oxidation and in maintaining the structural health of the eye.

Omega-3 fatty acids' anti-inflammatory effect can prevent or treat a variety of eye conditions. Omega-3 supplementation particularly is known to enhance dry eye syndrome and age-related macular degeneration (AMD), a leading cause of vision loss. DHA and EPA are believed to decrease intraocular pressure and increase circulation to the eye, slowing the onset of conditions like glaucoma. This teamwork, with Vitamin A supporting basic retinal function and omega-3s correcting inflammatory and circulatory problems, makes CLO potentially particularly beneficial as an adjunct to total eye health. Health.com. (2024)

Neurological and Cognitive Function: Omega-3 fatty acids, particularly DHA, play a vital role in brain development and function as constituent parts of neuronal membranes. DHA is highly concentrated in the brain and retina and is involved in autonomic function, attention, and inhibition, which are elements of executive function such as working memory and mental plasticity. DHA has been shown to enhance cognitive function and to exert neuroprotective effects against Alzheimer's disease and dementia. A meta-review of studies after 2013 concluded that omega-3 supplementation was related to favorable changes in blood biomarkers, in the direction of patients with lower starting levels of fatty acids and those with neuropsychiatric disorders. Meta-analytical evidence supports that daily consumption of more than 1 gram of DHA/EPA significantly enhanced episodic memory in older adults with mild memory complaints.

While there is an established link between deficiency of omega-3 and mental illness such as depression, it should be noted that depression is a multifaceted

illness with a variety of underlying causes, and deficiency of omega-3 cannot be said to be the only cause. Augmented intake of omega-3 has, however, been linked with reduced risk of depression and enhanced mental health. Research now being conducted is actively investigating how that DHA component of the omega-3s might reverse age-related declines in brain DHA to prevent or reverse neurodegenerative processes. Clinical trials now under way are comparing various forms for omega-3 supplements to determine their efficacy in elevating brain DHA levels and improving neurodegenerative biomarkers and cognitive performance in older adults at risk of dementia. Research on specific forms of omega-3 and their effect on biomarkers is a scientific route to more accurate understanding and focused intervention as it pertains to brain health. That is an observation on the field moving in the direction of more effective intervention for neurological health, with the DHA content of CLO potentially playing a significant role, if as part of a larger picture. Giannaccare et al. (2019), Zhang et al. (2016), Verywell Health. (2024)

Role in Sports Performance and Muscle Recovery: Cod liver oil, by virtue of its omega-3 fatty acid content, has been reported to help athletes mainly because of its anti-inflammatory effect. Intense exercise causes inflammation that can result in DOMS, impede recovery, and affect performance. Omega-3s reduce muscle damage and inflammation following resistance exercise and thus prevent this.

A prospective observational study by Hansen et al. (2021) showed that habitual supplementation of cod liver oil (CLO) reduced basal and exercise-induced C-reactive protein (CRP) levels significantly in recreational cyclists. This effect was mostly observed in CLO users, which suggests that its particular benefit is in the reduction of exercise-induced inflammation. In addition to reducing soreness, fish oil—and thus, CLO—may improve the quality of exercise and preserve muscle health in aging by enhancing muscle sensitivity to protein consumption and resistance training, ultimately leading to increased muscle size and strength. The repeated observation that CLO particularly reduces CRP levels in athletes suggests a particular benefit, perhaps owing to the synergistic action of its omega-3 fatty acids, vitamin A, and vitamin D, each of which collectively provides a better anti-inflammatory effect than omega-3s alone. This makes CLO a possible food supplement in the field of sports nutrition, especially for the management of exercise-induced inflammation and recovery enhancement. Hansen et al. (2021)

Creating Therapeutic Applications: Besides its more conventional virtues, cod liver oil is under investigation for several novel therapeutic applications:

- Multiple Sclerosis (MS): Low vitamin D status is associated with higher risk of MS. A Norwegian report explained that supplementation with CLO in young adolescence (13-18 years) was associated inversely with adult-onset MS risk and had a dose-response effect, pointing towards adolescence as a heightened period of vulnerability. The effect is attributed to be caused by the high content of vitamin D in CLO. Kampman et al. (2021)
- **Kidney Function:** CLO has been shown to decrease proteinuria, an indicator of the severity of kidney disease, in type 2 diabetic patients. This indicates a possible use in the treatment of diabetic nephropathy. Abdelhamid et al. (2020)
- Cancer: Although more studies are necessary, CLO's anti-inflammatory
 activity and vitamin A and D content (both of which exhibit anti-cancer
 effects) indicate promise. Certain research shows that CLO can inhibit
 angiogenesis (neovascularization of tumors) and interfere with the

division of cancer cells, with a resultant prevention of tumor formation. Calder (2017)

- **Depression:** Omega-3 deficiency has been associated with many mental diseases, including depression. Increased intake of omega-3s has been associated with reduced risk of depression and overall better mental health. CLO, being a source of omega-3s, can be attributed with these benefits. National Institutes of Health. (2023)
- Inflammatory Bowel Disease (IBD): Not particularly noted for CLO in current literature, omega-3s have anti-inflammatory effects that are helpful in IBD, and a pilot study in 2008 (referenced in) investigated CLO's use in IBD patients with arthritis, with promising findings. Calder (2017)
- Brunvoll et al. (2022) investigated whether CLO had a preventive effect on COVID-19 and other winter respiratory illnesses in otherwise healthy adults in a placebo-controlled, randomized trial. This reflects ongoing research interest in CLO's immune-modulatory activity. Brunvoll et al. (2022)

3. COD LIVER OIL MYTHS AND MISUNDERSTANDINGS

Cod Liver Oil as the Exclusive or Best Source of Omega-3 Fatty Acids: A common misconception is that cod liver oil is the exclusive best source of omega-3 fatty acids. While cod liver oil (CLO) is an admirable source of these fatty acids, specifically eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), other fatty fish types, such as salmon, trout, mackerel, fresh tuna, and herring, are also good sources. Furthermore, other fish oils, which are extracted from the flesh of these fatty fish, are often richer in omega-3 fatty acids than CLO. Furthermore, plantbased omega-3 sources like flaxseed oil, which is rich in alpha-linolenic acid (ALA which converts to EPA and DHA, though inefficiently), and algal oils (which are direct vegan sources of DHA and sometimes EPA) are available at one's fingertips. The determination of the "optimal" source depends on individual dietary needs, preference (for example, following plant-based diets), and the desired balance of omega-3s with fat-soluble vitamins. The continued belief in a single "best source" is probably due to CLO's historical role and widespread traditional use. However, modern nutritional science and product diversification prove that other sources are capable of providing equal or even greater concentrations of omega-3s, often without CLO's high levels of vitamin A. Furthermore, there is a discernible market trend toward plant-based omega-3s. This trend emphasizes the need for consumer awareness to overcome outmoded thinking and appreciate the broader range of omega-3 sources. It also indicates that CLO manufacturers should emphasize its unique multi-nutrient profile (which includes omega-3s and vitamins A and D) rather than compete solely on the basis of omega-3 content, as this combination is its true differentiator. Mayo Clinic. (2023), National Institutes of Health. (2023)

Misconceptions About Omega-6 Fatty Acids and Inflammatory Pathways: Omega-6 fatty acids have been widely misconceived, sometimes based on misinformation, unfairly demonizing them, as causing them to break down into toxic substances, inducing inflammation, impairing the immune system, and causing chronic diseases, especially when they are heated. This argument is empirically unsound and inherently flawed. Omega-6 fatty acids are a group of polyunsaturated fats that are essential nutrients because they are needed by the body but cannot be manufactured within the body. They are necessary in lowering levels of low-density

lipoprotein (LDL) cholesterol and lowering the risk of cardiovascular disease and stroke. The American Heart Association, in fact, recommends their consumption as part of a well-nourished diet.

While omega-3 fatty acids are generally considered more anti-inflammatory than omega-6 fatty acids, this distinction does not imply that omega-6s are always pro-inflammatory. Omega-3 and omega-6 fatty acids are both critical to the body's inflammatory processes, and the ideal ratio between the two is ideal, not eliminating the omega-6s from the equation altogether. Inflammation is a natural and unavoidable part of healing; the aim is to avoid excessive or chronically elevated inflammation. The negative characterization of omega-6s is an oversimplification in the nutrition field, where physiological balance complexity gives way to a simplistic "good vs. bad" narrative. Such oversimplification is most commonly the product of selective interpretation of empirical data, e.g., the fact that since omega-3s are more anti-inflammatory, omega-6s must be pro-inflammatory. Such reductionist narratives can be used by individuals or organizations selling products based on unsubstantiated health claims. Such is this one, and it is indicative of a larger issue in public health communication, where biological complexity is reduced to simple, easily digestible yet oftentimes inaccurate statements. It points to the importance of seeking out reliable sources and applying critical thinking when taking dietary advice. Simopoulos and DiNicolantonio (2016)

The Illusion of Universal Effectiveness and the Nonexistence of Adverse Effects: The ancient perception of cod liver oil as a "cure-all for all diseases" has unfortunately led to the illusion of its universal effectiveness and the absence of adverse effects. Nevertheless, new scientific evidence clearly demonstrates that although cod liver oil (CLO) offers several well-established benefits, it is not a cureall, and its effectiveness varies with respect to many diseases. Additionally, similar to any dietary supplement, CLO is not without possible adverse effects or risks, particularly when consumed in excessive amounts. Mild adverse effects are common and include fishy aftertaste, belching, indigestion, gas, nausea, and diarrhea. More serious problems result from the excessive use of CLO, particularly the risk of vitamin A toxicity (hypervitaminosis A) and increased risk of bleeding from the blood-thinning effect of omega-3 fatty acids. The fallacy that a product is always beneficial, effective, or safe because it is "natural" is a fatal deception. The ancient perception of CLO as a cure-all, combined with modern trends promoting "natural" products, is a fatal synergy that leads to an illusion that CLO is universally effective and harmless. The widespread documentation of numerous adverse effects and serious hazards directly refutes the myth of "no side effects." This scenario demonstrates a basic public health message: "natural" does not always equate to "safe" or "effective" without empirical evidence and adherence to standard dosage guidelines. It stresses the need for consulting healthcare professionals before initiating any supplementation, particularly among vulnerable populations or those who are already on prescribed medications. National Center for Biotechnology Information. (2023), WebMD. (2023)

Quality and Purity Issues: Oxidation and Contaminants: Although not a myth regarding CLO's immediate health impact, there are widespread misconceptions regarding supplement purity and quality. The TOTOX index, an indicator of fish oil oxidation, is commonly used as the only quality measure, which it is not. Although the TOTOX index is a valuable measure, it is not the only one; other considerations such as the type of fish the oil comes from, the precise amount of EPA and DHA, and the extensive testing for environmental contaminants are equally important. Fears regarding toxic substances like dioxins and heavy metals (e.g., mercury) entering fish from polluted waterways are legitimate. However, responsible manufacturers

adhere to stringent standards, like those of the Global Organization for EPA and DHA Omega-3s (GOED), to ensure products are cleaned and safe for consumption. While generic fish oil appears to have virtually no mercury, processing that goes into creating supplements significantly reduces risk of environmental toxins. Oxidation rancidity is also a problem, as oxidized fish oil loses its positive effects and can have adverse effects on the body. Consumers need to actively seek out manufacturers that provide transparency of fish species utilized and a clear omega-3 fatty acid breakdown. That the fact that while concerns regarding contaminants and oxidation are legitimate, industry has created standards and processing methods to limit such risks, indicates that consumers may not necessarily recognize a difference between a high-quality supplement, and shifts responsibility back to the consumer to be discerning, as supplements are not as strictly regulated as pharmaceuticals. This indicates the need for consumer education on quality measures beyond surface claims, and to greater industry transparency and perhaps more stringent regulatory measures to protect consumers from substandard or deceptive products. Global Organization for EPA and DHA Omega-3s. (2023), National Center for Biotechnology Information. (2023)

4. RISKS, SIDE EFFECTS, AND IMPORTANT CONSIDERATIONS

The potential for Vitamin A toxicity (hypervitaminosis A) is one of the most serious issues associated with cod liver oil supplementation. This is especially true with large doses. One teaspoon of cod liver oil has 1350 μg of Retinol Activity Equivalents (RAE) of vitamin A, which is 150% of daily value. The tolerable upper intake level (UL) established for adults for vitamin A is 3000 μg daily. Regular intake of cod liver oil, particularly when taken with other foods or supplements that are high in vitamin A, leads to toxic accumulation of the vitamin in the liver.

Symptoms of toxicity of vitamin A include irritability, loss of appetite, nausea, vomiting, blurred vision, headache, hair loss, musculoskeletal pains, weakness, and change in mental status. Vitamin A toxicity during pregnancy can harm fetal development, and pregnant women should thus see a health care professional and watch intake closely. Children are also at risk, especially under one year of age, and supplementation is typically not warranted in infants, with older children instructed to receive no more than half the adult dose. The ratio of vitamin A to D in CLO is a key determinant of toxicity, and the presence of synthetic additives can increase vitamin A content. The very same quality that makes CLO different from other supplements—its synergy of omega-3s, vitamin A, and vitamin D—is also its greatest safety challenge: vitamin A toxicity. It is not so much excessive CLO, but also cumulative intake from other foods, supplements, and past use of CLO. The historical context of augmented vitamin A content in older CLO preparations further obscures the view of its safety over time. The inherent challenge of effectively titrating for adequate amounts of intake for all compounds at the same time is a direct causal link to the risk of hypervitaminosis A. This makes strong emphasis on professional guidance for CLO supplementation, particularly for long-term use, in high-risk groups (pregnant women, children), and for users of other vitamin A or D supplements, particularly crucial. It also explains why some practitioners may prefer separate, single-nutrient supplements for more precise dosing. National Institutes of Health. (2023), National Center for Biotechnology Information. (2023), Osavi. (2024)

Drug Interactions: Cod liver oil interacts with several drug classes, and its use necessitates rigorous medical supervision:

- Anticoagulant and Antiplatelet Drugs: Omega-3 fatty acid in CLO can decrease blood clotting and platelet aggregation and interact with drugs like warfarin, aspirin, or clopidogrel, potentially enhancing the risk of bleeding when used together. Although concomitant doses of less than 3g/day of fish oil are commonly safe when combined with warfarin or antiplatelets, the safety of higher doses is not known. Bruising and minor bleeding are common side effects.
- Antihypertensive Agents: CLO may lower blood pressure to a small degree. Its use with antihypertensive drugs may cause blood pressure to drop too low, and therefore, monitoring is required.
- **Antidiabetic Medications:** CLO or other fish oils may influence blood sugar levels. Although some sources indicate that it will raise blood sugar, some others indicate that it will lower blood sugar and increase the action of antidiabetic drugs and cause hypoglycemia. Monitoring blood glucose levels closely in diabetic patients is recommended.
- **Kidney Disease or Bone Health Promoting Drugs (e.g., calcitriol, doxercalciferol):** Vitamin D in CLO increases calcium absorption. Concurrent use of CLO with drugs to treat calcium loss or to promote bone health may result in hypercalcemia (elevated calcium).
- **Statins:** High levels of vitamin D in CLO can interact with statins, medications used to reduce cholesterol levels.
- Other Vitamin A or D Supplements: CLO should not be consumed along with individual supplements of vitamin A or D, or when one is on a diet rich in these vitamins to prevent toxicity.
- Cholestyramine, Colestipol, Orlistat: These drugs can interfere with CLO's fat-soluble vitamins (A and D) and omega-3 fatty acids absorption and reduce its effectiveness. CLO should be taken at least two hours before or after Orlistat.
- **Contraceptive Drugs:** Certain contraceptive drugs may interact with the effect fish oil generally has on triglycerides. National Institutes of Health. (2023), Abdelhamid et al. (2020), Mayo Clinic. (2023)

5. DOSAGE INSTRUCTIONS AND VULNERABLE POPULATIONS

Dosage instructions for cod liver oil also vary by product, with most containing 5-10 milliliters per day for adults for a short duration because most supplements are short-term. Strict compliance with product labels' instructions and a visit to a health practitioner is required because some populations would require special precautions. The variation in dosage instructions and the specific precautions needed by different populations indicates that cod liver oil is not a one-size-fits-all supplement. The risks, particularly the risk of toxicity from vitamin A, are compounded with vulnerable populations. This indicates the requirement of having a personalized supplementation regimen that takes into account individual variables like age, health status, and other consumptive dietary or medicinal practices.

Pregnancy and Lactation: Cod liver oil (CLO) has been traditionally used in pregnancy, and some communities have used it as a food supplement. Excessive vitamin A is, however, toxic to fetal development. CLO may be regarded as potentially safe when taken in doses not higher than recommended daily intakes of vitamin A (around

- $3000~\mu g$) and vitamin D (around $100~\mu g$). Interaction with a healthcare provider is needed because there is a risk of vitamin A toxicity. Vitamin A is also transmitted to infants by lactation.
- Children: CLO is generally safe for most children if taken in adult recommended daily doses of vitamins A and D. Supplementation in children younger than one year is not currently advised. For children, half the adult dose or less is advised, and research indicates no more than 2.5 milligrams per day because of the unknown impact of large doses of omega-3 on the development of children. Utilization of a care team should be addressed. National Institutes of Health. (2023), National Center for Biotechnology Information. (2023), Osavi. (2024)
- Older Adults (Age 65 years and older): There is much interest in CLO's impact on bone density in this group. Although bone mineral density studies have yielded conflicting results, vitamin D's action to slow bone loss with aging is established. Consultation with a health professional is advisable. Eysteinsdottir et al. (2015), Simopoulos and DiNicolantonio (2016)

6. COMMON ADVERSE REACTIONS AND SIDE EFFECTS

Besides the more serious vitamin A toxicity and drug interaction risks, cod liver oil is also capable of producing a range of mild side effects, especially when ingested orally. These most typically are: Fishy taste, Fetor oris, Eructation, Nausea, indigestion, or gastric upset, Gas, Diarrhoea, Joint pain, though this occurrence is relatively infrequent and rather ironic in its use for arthritis.

While usually safe when taken according to instructions, excessive doses carry possible dangers and increase the risk of hemorrhaging. While rare, allergic reactions do happen and appear as the dermatological type of rash, pruritus, urticaria, or facial, lip, tongue, or throat edema. Anaphylactic allergic reactions or severe symptoms are treated immediately by a doctor. National Institutes of Health. (2023), National Center for Biotechnology Information. (2023), WebMD. (2023), Verywell Health. (2024)

7. DISCUSSION

The vast body of research carried out over the past decade to provide a refined and dense understanding of cod liver oil, going beyond its traditional role as a panacea. While it's ancient use for rickets and general health has been empirically confirmed largely because of its high content of omega-3 fatty acids, vitamin A, and vitamin D, contemporary research points to both its specific therapeutic benefit and major limitations. The effectiveness of cod liver oil (CLO) in lipid modulation, specifically its well-documented capacity to reduce triglyceride levels significantly, is well documented. Similarly, its anti-inflammatory activity, with research demonstrating a decrease in inflammatory markers such as C-reactive protein (CRP) in athletes, facilitating muscle recovery and potentially enhancing sporting performance, is well established. The function of vitamin D in bone health, in particular, the absorption of calcium and prevention of age-related bone loss, is a cornerstone of the advantages of CLO. Additionally, emerging research suggests promising potential for CLO in the area of neurological health, with docosahexaenoic acid (DHA) playing a pivotal role in cognitive function and potentially conferring resistance to neurodegenerative disorders. Abdelhamid et al. (2020)-Dyall (2015), Gammone et al. (2018), Kampman et al. (2021), Verywell Health. (2024),

Health.com. (2024) Its potential benefits in lowering the incidence of multiple sclerosis, improving renal function in diabetic patients, and exhibiting anti-cancer activity further enhance its therapeutic potential. But scientific literature actively dispels a number of long-standing myths, too. The myth that CLO is the "best" or "only" source of omega-3s is untrue, as other fish oils and vegetable sources freely supply equivalent or superior levels without the heavy vitamin A load. Also, vilifying omega-6 fatty acids as inherently pro-inflammatory is a simplification; both the omega-3s and omega-6s are needed, and balance is all that is required for a healthy inflammatory response. Osavi. (2024) Perhaps most importantly, the idea of universal efficacy and lack of side effects is directly refuted by evidence of possible vitamin A toxicity, particularly with high dose or co-supplementation, and a variety of mild to severe drug interactions, especially with anticoagulants, antihypertensive, and antidiabetic drugs. National Institutes of Health. (2023), National Center for Biotechnology Information. (2023), Osavi. (2024) Conflicting evidence, particularly in cardiovascular outcomes, highlights the complexity of nutritional research. While omega-3s show clear benefits for specific cardiac events and triglyceride reduction, large trials like VITAL and ASCEND did not consistently demonstrate a significant reduction in primary composite cardiovascular endpoints in general populations. This underscores that the specific omega-3 formulation, dosage, and patient population are critical determinants of clinical outcomes. Similarly, while CLO effectively boosts vitamin D levels, its long-term impact on bone mineral density in old age is modest, and historical formulations with higher vitamin A content might have had subtle adverse effects on bone health. This emphasizes the importance of balanced nutrient intake and the evolving understanding of supplement safety. Abdelhamid et al. (2020), Hu et al. (2019)

8. FUTURE ASPECTS 8.1. INNOVATIONS IN PRODUCT FORMULATION AND DELIVERY

The cod liver oil market is seeing new product formulas and delivery methods to meet various consumer needs and improve taste. The historical view of CLO as "unspeakably detestable" highlights an ongoing taste issue. The new product designs address this past problem, making CLO more attractive and easier to add to daily routines.

- New Delivery Formats: Companies are looking into options like soft gels, flavored liquids, and adding CLO to smoothies to reach a wider audience, including younger people who may be reluctant to try traditional oils. Capsules are currently the most popular format due to their convenience, ability to keep fresh, and ability to mask taste and smell. Liquid forms are also commonly used for their ease of consumption and quicker absorption.
- **Flavor Innovations:** For example, green apple flavored CLO has recently entered the U.S. market.
- Targeted Formulations: There is a growing trend towards creating products for specific health benefits, which is making capsules and other formats more appealing to health-conscious consumers.
- Personalized Nutrition: The rise in personalized nutrition trends is leading to an increase in tailored dietary supplements, which CLO manufacturers can take advantage of. National Institutes of Health.

(2023), National Center for Biotechnology Information. (2023), Osavi. (2024)

These innovations are key for expanding CLO's market reach beyond traditional users and into new groups, especially younger, health-focused consumers who value ease of use and enjoyable consumption experiences.

9. FUTURE RESEARCH DIRECTIONS AND CLINICAL TRIAL LANDSCAPE

Future studies on cod liver oil are set to explore its mechanisms and new therapeutic possibilities. The identified research gaps and ongoing trials show a scientific push towards a better understanding of CLO. The shift from general observations to studying specific types of omega-3s and their effects on biomarkers suggests a focus on personalized and targeted treatments.

- Clarifying Specific Mechanisms: While the anti-inflammatory effects of omega-3s are well-known, more research is needed to fully explain how CLO's components work together biochemically.
- **Dose-Response Relationships:** Additional clinical and long-term studies are necessary to find optimal dosages for particular health benefits, especially regarding vitamin D's impact on bone density in healthy children.
- **Longitudinal Studies:** Ongoing long-term studies are needed to evaluate the effects of CLO over a lifetime, particularly in relation to neurodegeneration in older adults.
- **Targeted Interventions:** Research into specific formulations, such as lysophosphatidylcholine-bound DHA versus triglyceride-bound DHA, and their effectiveness in raising brain DHA levels and improving neurodegenerative markers is in progress.
- **Emerging Applications:** More trials are needed to verify CLO's effectiveness in new areas like COVID-19 and other respiratory infections, cancer, and kidney disease in diabetic patients.
- Comparative Studies: Further research comparing CLO's effectiveness to other omega-3 supplements or isolated vitamins A and D would offer valuable insights into its specific benefits.
- Safety and Interactions: Ongoing monitoring of drug interactions, particularly with new medications, and long-term safety profiles at higher doses is crucial. National Institutes of Health. (2023)-Calder (2017), Dyall (2015), Verywell Health. (2024)-Farooqui and Farooqui (2024)

10. CONCLUSION

Cod liver oil has a historically significant role as a supplement and remains relevant today, though in a more complex way. Recent scientific studies from 2013 to 2025 have confirmed many of its traditional uses, especially its effectiveness in lowering triglycerides, reducing inflammation (even in athletes), and supporting bone health due to its high levels of omega-3 fatty acids, vitamin A, and vitamin D. New research also suggests potential benefits for neurological health, kidney function, and immune support, opening new possibilities for treatment. However, scientific agreement also dispels several long-held myths. It clarifies that CLO is not

the only or the "best" source of omega-3s and that omega-6 fatty acids are essential rather than inherently harmful. Furthermore, the idea that CLO is universally beneficial and free of side effects is a dangerous misconception. Significant risks exist, such as vitamin A toxicity and various drug interactions (with blood thinners, blood pressure medications, and diabetes treatments), highlighting the need for informed use and professional medical advice, particularly for vulnerable groups.

CONFLICT OF INTERESTS

None.

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