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Anti-inflammatory and antioxidant mechanisms of bioactive oils in the pathophysiology of NAFLD

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Abstract
Liver has a crucial role in the human body**.** It has multiple functions like bile production and metabolism, carbohydrate metabolism, storehouse of several vitamins and minerals, detoxification and many more. Liver disease is responsible for more than two million deaths each year, including those caused by cirrhosis, viral hepatitis, and liver cancer. It accounts for 4% of all global deaths, meaning 1 in every 25 deaths. Additionally, one-third of liver-related deaths occur in women. NAFLD is a condition characterized by excessive fat build up in liver leads to steatosis, fibrosis, cirrhosis and even liver cancer. It is closely associated with obesity, metabolic syndrome, and poor dietary habits. Dietary fat quality, not just quantity, plays a crucial role in NAFLD pathogenesis and progression. This review evaluates the role of various nuts and seed oils walnut, sesame, cottonseed, hemp seed, olive, and wheat germ oil—in mitigating hepatic steatosis and inflammation. Each oil offers distinct bioactive compounds and fatty acid profiles contributing to their hepatoprotective effects. In this review, we have seen different nuts and seeds oils, there bioactivity, antioxidant activity, and that how the right choice of oil can help in liver disease. Overall, these oils show promise in NAFLD prevention and management, primarily through lipid modulation, oxidative stress reduction, and anti-inflammatory actions. However, limitations such as the paucity of large-scale human trials and heterogeneity in study protocols call for further clinical research. This paper supports the incorporation of specific dietary oils as part of comprehensive lifestyle interventions for NAFLD management and highlights the potential of seed oils as nutraceutical agents.

Keywords: NAFLD, dietary fats, seed oils, monounsaturated fatty acids, polyunsaturated fatty acids, oxidative stress, liver steatosis

Introduction
Liver is the largest gland, weighs 1-1.5 kg, consists of 4 lobes. It has multiple functions like bile production and metabolism, carbohydrate metabolism, storehouse of several vitamins and minerals, detoxification and many more. There are different liver diseases such as hepatitis, cirrhosis, nonalcoholic fatty liver disease (NAFLD), alcohol induced liver disease, cirrhosis, liver cancers and autoimmune liver disease like primary cholangitis [1-2].

Liver disease causes over two million deaths annually (cirrhosis, viral hepatitis, and liver cancer) and accounts for 4% of all deaths worldwide (1 out of every 25 deaths); 1 out of 3 liver-related deaths occur among females. In this estimate, liver cancer is responsible for 600,000 to 900,000 deaths. Liver disease ranks as the eleventh leading cause of death, though the number of liver-related deaths may be underreported. Cirrhosis is the tenth leading cause of death in Africa (up from thirteenth in 2015), the ninth leading cause in Southeast Asia and Europe, and the fifth leading cause in the Eastern Mediterranean [3,4].

Non-alcoholic fatty liver disease (NAFLD) refers to a range of conditions marked by the presence of hepatic steatosis (macro-vesicular steatosis) observed through imaging or histology, without the involvement of secondary causes like excessive alcohol consumption, long-term use of medications known to induce hepatic steatosis, or genetic disorders. It has several phases of progression, which include simple steatosis, steatohepatitis, fibrosis, cirrhosis, and ultimately could even progress to hepatocellular carcinoma. The occurrence of this disorder is closely linked to various risk factors of metabolic syndrome (MetS), including obesity, dyslipidemia, hypertension, and type 2 diabetes [7]. The prevalence of adult NAFLD in India has been reported to range from 6.7% to 55.1%. In fact, obesity plays a significant role in determining the severity of NAFLD, contributing to the worsening of

liver fibrosis and the progression of liver diseases [10]. The presence of NAFLD is also effective in the development of cardiovascular diseases (CVD) [5]. A lack of physical activity and poor dietary habits are commonly linked to the development of NAFLD. As a result, lifestyle changes and dietary modifications are regarded as the primary non-medical treatment for NAFLD. [6]. Dietary fatty acids play an important role in hepatic lipogenesis and may have a dual effect on the development of liver steatosis, both contributing to its progression and potentially helping to prevent or reverse fat accumulation in the liver. The composition of dietary fatty acids is a crucial factor in the development of NAFLD, as 15% of liver triacylglycerol is derived from them. A high-fat diet is well recognized as a factor in the advancement of hepatic steatosis. Alterations in dietary fatty acids may be significant in preventing and treating conditions like coronary heart disease, hypertension, and fatty liver disease. Specifically, high-fat diets induce biochemical and structural changes in the liver, such as steatosis, collagen deposition, and changes in plasma lipoprotein levels and serum aminotransferases (ALT, AST) [1]. These features are affected not only by the quantity but also by the composition of the dietary fat Monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs) are parts of a complete diet that have beneficial effects in preventing NAFLD [5]. Perisinusoidal stellate cells (PSCs), also referred to as Ito cells or fat-storing cells, are liver pericytes that participate in the metabolism of lipoproteins, the production of extracellular matrix proteins, and the release of certain hepatocyte growth factors. As a result, they play a crucial role in various liver conditions, including hepatic fibrosis and nonalcoholic steatohepatitis. [1].

Objective

Different types of fat may play an important role in NAFLD pathophysiology in addition to the total fat content of the diet. Saturated fat has been linked with diabetes, cardiovascular disease and metabolic syndrome [12]. Polyunsaturated fatty acids, particularly n-3 polyunsaturated fatty acids (PUFAs) and monounsaturated fatty acids (MUFAs), may help protect against increases in intrahepatic triglyceride (IHTG) levels. N-3 PUFAs promote the expression of genes related to fatty acid oxidation, while reducing the expression of genes involved in lipogenesis, such as SREBP-1 [3]. This review is an attempt to demonstrate the different biological activities and medical properties of different seeds oil like sesame oil, cotton seed oil, sunflower oil, wheat germ oil and walnut oil and its components in animal studies and some human trials. Particularly, focused on the mechanisms underlying their effects on hepatic steotosis and NAFLD also its antioxidant properties.

Materials and Methods

- **Search strategy:** Databases searched (PubMed, Scopus, Google Scholar, Sci-Hub); search keywords listed.
- **Inclusion criteria:** Animal experiments or human intervention studies investigating seed oil effects on hepatic outcomes.
- **Data extraction:** Details on oil type, model (animal/human), dosage, key outcomes (liver enzymes, histology, oxidative/inflammatory markers).

Result

Walnut Oil

Walnut oil, derived from *Juglans regia*, is rich in polyunsaturated fatty acids (PUFA), with a notable 4:1 n-6/n-3 ratio, and is also high in antioxidants like tocopherols, phytosterols, and ellagitannins. Studies suggest that walnut oil, especially in a diet where it comprises 14% of the total fat, offers significant health benefits. It has been shown to improve liver lipid metabolism, reducing steatosis (fat accumulation in the liver) and influencing hepatic fatty acid composition. Walnut oil's bioactivity is attributed to its PUFA content, tocopherols, and phytosterols, which can help in reducing liver triglyceride content and have anti-inflammatory effects, potentially preventing atherosclerosis and chronic inflammation. [7]

Sesame Oil

Extracted from *Sesamum indicum*, sesame oil is a rich source of MUFAs and PUFAs, along with essential vitamins and minerals like B6, B12, E, calcium, and magnesium. It also contains bioactive lignans such as sesamin and sesamolin [13]. In clinical studies, sesame oil demonstrated positive effects on fatty liver disease (NAFLD), improving fatty liver severity and liver enzyme levels like ALT and AST. Additionally, sesame oil's antioxidant content, including phenols and sesamin, plays a key role in reducing hyperlipidemia, lipid peroxidation, and inflammation, showing superior hepatoprotective effects compared to sunflower oil [1].

Cottonseed Oil

Cottonseed oil (CSO) is known for its potential to improve plasma and liver lipid profiles, particularly in the context of a high-fat diet. CSO contains bioactive compounds, including dihydrosterculic acid (DHSA), which helps reduce lipid synthesis by promoting oxidation and suppressing lipogenic gene expression. Studies have shown that CSO can reduce liver fat accumulation and improve lipid metabolism, making it a valuable dietary oil for combating fatty liver and hyperlipidemia [8-11].

Hemp Oil

Hemp oil, derived from *Cannabis sativa*, is rich in PUFAs, particularly omega-3 fatty acids like linolenic acid. The oil has been shown to help alleviate symptoms of Non-Alcoholic Steatohepatitis (NASH) by reducing liver fatty acid content, improving insulin resistance, and decreasing liver inflammation. Studies with nanoemulsions of hemp oil have demonstrated enhanced biological activity, with a reduction in hepatic steatosis, fibrosis, and free fatty acids, suggesting that hemp oil is a promising candidate for future liver disease treatments [9]

Olive Oil

Olive oil, particularly extra virgin olive oil, is central to the Mediterranean diet and is known for its beneficial effects on metabolic syndrome and liver health. It is rich in MUFAs, especially oleic acid, and contains bioactive compounds like oleocanthal, which has anti-inflammatory properties similar to ibuprofen. Olive oil has been shown to reduce serum aminotransferase levels, indicating improvement in liver function. Studies suggest that olive oil may be more effective than sunflower oil in treating hepatic steatosis due

to its lower susceptibility to oxidative stress, making it a valuable fat source in liver disease management [8].

Wheat germ oil

Wheat germ oil (WGO) has shown potential benefits for managing fatty liver disease (FLD), particularly non-alcoholic fatty liver disease (NAFLD). Study suggest that WGO, which is rich in essential fatty acids, antioxidants, and bioactive compounds, can have a positive impact on liver health. WGO contains linoleic acid (omega-6 fatty acid) and oleic acid (omega-9 fatty acid), which have been found to help reduce liver fat accumulation, a hallmark of fatty liver disease. By improving lipid metabolism, WGO can help prevent or reduce the build-up of fat in liver. WGO is rich in vitamin E, particularly in the form of tocopherols, which are powerful antioxidants. By neutralizing free radicals, WGO can help protect liver cells from damage and inflammation.

It can lower the levels of pro-inflammatory cytokines, such as TNF-α and IL-6, which are commonly elevated in individuals with fatty liver disease. This anti-inflammatory effect may help prevent the transition from simple steatosis (fatty liver) to more severe forms of liver disease, such as non-alcoholic steatohepatitis (NASH). Improves liver enzymes AST and Alt. WGO can upregulate the expression of antioxidant genes like Nrf2 and HO-1, which help the liver cope with oxidative damage and reduce lipid peroxidation [5].

Table 1: Effects of different dietary fats in NAFLD

S. no.	Authors (Year)	Disease	Target	Seed Oil	Main Results
1	Hernández (2005)	NAFLD	Rat	Olive oil	Increased glial fibrillary acidic protein (GFAP) expression, Decreased serum ALT and AST levels
2	Fink *et al*. (2014)	NAFLD	Zucker rat	Walnut oil	Decreased hepatic triglyceride levels, Reduced oxidative stress, Lower SDC activity
3	Atefi *et al*. (2022)	NAFLD	Women	Sesame oil	Decreased ALT and AST levels
4	Son *et al*. (2023)	NAFLD	Mice	Cottonseed oil	Improved plasma and liver lipid profiles
5	Elgendy *et al*. (2022)	Alcoholic Fatty Liver Disease	Rats	Wheat germ oil	Reduced oxidative damage, Modulated genes linked to antioxidants and inflammation, Restored caspase-3 and Bcl2 response
6	Qushawy *et al*. (2022)	NASH	Rats	Hemp seed oil	Protective role via NEF4 in lipid degeneration and insulin resistance• Reduced fibrosis, Decreased liver enzyme levels

Discussion

Non-Alcoholic Fatty Liver Disease (NAFLD) is rapidly becoming the most prevalent chronic liver condition worldwide, closely linked with the metabolic syndrome, obesity, and sedentary lifestyles [7]. Dietary fats, especially the type and source, play a crucial role in the pathogenesis and management of NAFLD [1, 5]. This review evaluated the hepatoprotective properties of different nuts and seed-derived oils—including walnut oil, sesame oil, cottonseed oil, hemp seed oil, olive oil, and wheat germ oil—based on their bioactive components, lipid-modulating potential, and antioxidant capacity [1,5,7,9,11,13]. The comparative effectiveness of various nut and seed oils in NAFLD management is largely attributed to their distinct fatty acid profiles and bioactive compounds, which act through overlapping yet unique mechanisms [3,5]. Walnut oil, rich in PUFAs and tocopherols, effectively reduces hepatic triglyceride accumulation and oxidative stress by enhancing fatty acid oxidation and suppressing lipogenesis [7]. Sesame oil demonstrates strong clinical benefits due to its lignans, sesamin and sesamolin, which modulate lipid metabolism and down regulate inflammatory cytokines, improving liver enzyme profiles [1,13]. Olive oil, abundant in MUFAs like oleic acid and polyphenols such as oleocanthal, offers potent anti-inflammatory and antioxidant actions, stabilizing hepatocyte membranes and reducing stellate cell activation [8]. Hemp seed oil, high in omega-3 fatty acids, improves insulin sensitivity and attenuates liver fibrosis by inhibiting pro-inflammatory signaling pathways and promoting lipid clearance, especially when administered in nanoemulsion form for enhanced bioavailability [9]. Wheat germ oil, with its high vitamin E and essential fatty acid content, upregulates endogenous antioxidant genes such as Nrf2 and HO-1, protecting against oxidative and inflammatory liver damage [5]. Cottonseed oil, although less studied clinically, has shown potential in animal models to reduce liver fat via dihydrosterculic acid-mediated inhibition of lipogenesis and promotion of β-oxidation [11]. These oils exert their beneficial effects through multifactorial mechanisms—ranging from lipid regulation and inflammation control to oxidative stress reduction—making them promising components in dietary strategies for preventing and managing NAFLD [1,3,5,7-9,11,13].

Clinical Relevance and Translation

From a clinical perspective, sesame and olive oils show the strongest evidence from human trials. Walnut, wheat germ, and hemp oils show high potential based on robust preclinical data. Cottonseed oil's effect, although promising in animal models, lacks sufficient human data and warrants further investigation. Most current evidence points toward the superiority of oils high in MUFAs and PUFAs, with minimal saturated fat content and high antioxidant load.

Additionally, the form of oil delivery (e.g., Nano emulsions in the case of hemp oil) may significantly influence its absorption and bioactivity. Such formulations should be explored in future clinical trials.

Limitations and Gaps

While the collective data strongly support the hepatoprotective role of these oils, several limitations must be acknowledged:

- **Lack of large-scale clinical trials:** Most findings come from animal models or small clinical studies.
- **Heterogeneity in dosage and intervention durations:** Makes cross-comparison difficult.
- **Limited post-transplant studies:** The impact of these oils on liver transplant outcomes remains unexplored.

Conclusion

Non-Alcoholic Fatty Liver Disease (NAFLD) is a progressively prevalent health concern worldwide,

intimately associated with contemporary dietary patterns, sedentary lifestyles, and the incidence of metabolic syndrome. Research indicates that not all fats are equivalent; monounsaturated and polyunsaturated fatty acids, prevalent in specific seed and nut oils, can markedly affect the progression and possible reversal of fatty liver. Oils such as walnut, sesame, cottonseed, hemp, olive, and wheat germ are abundant in advantageous compounds including tocopherols, lignans, phytosterols, polyphenols, and essential fatty acids, which collectively aid in regulating blood lipids, diminishing inflammation, and countering oxidative stress—crucial elements in the management of NAFLD. Walnut and hemp seed oils, rich in omega-3 fatty acids, facilitate fat metabolism in the liver, whereas sesame and wheat germ oils, abundant in antioxidants, reduce inflammation and enhance liver enzyme activity. Olive oil, an essential component of the Mediterranean diet, has significant anti-inflammatory and metabolic advantages, whereas cottonseed oil has demonstrated potential in animal tests for diminishing hepatic fat. Although these findings are encouraging, further rigorous human trials are necessary to validate their efficacy and ascertain optimal usage of these oils. Incorporating high-quality oils abundant in MUFAs and PUFAs into a balanced lifestyle presents a promising, evidence-based strategy for the prevention and management of NAFLD.

Conflict of Interest
None declared.

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