

Essential Oils for Liver Diseases

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Abstract

The liver is the largest organ, responsible for over 5,000 critical functions, including metabolism, detoxification, blood clotting, hormonal regulation, and defense against infections. Globally, liver diseases are major contributors to morbidity and mortality. Hepatitis, fatty liver, steatohepatitis, cirrhosis, and carcinoma are the primary causes of liver-related ailments. Despite significant progress in liver disease management, the limitations of current treatments have driven growing interest in natural remedies, such as essential oils, to enhance liver health and mitigate disease progression. Essential oils are potent extracts obtained from various plant parts, such as flowers, leaves, roots, seeds, stems, fruit peels, and bark. They are widely utilized for their therapeutic, aromatic, and flavoring properties in diverse products, including cosmetics, food, and pharmaceuticals. Rich in bioactive compounds, essential oils exhibit numerous biological activities, including antioxidant, anti-inflammatory, anti-diabetic, anti-hyperlipidemic, antimicrobial, antifungal, and antiviral effects. Essential oils derived from ginger, peppermint, rosemary, turmeric, black seeds, and garlic have demonstrated therapeutic potential against liver diseases in clinical studies. However, further research is essential to thoroughly assess their safety and toxicity profiles.

Keywords: Essential oils, Fatty liver diseases, Cirrhosis, Inflammation

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Introduction

The liver, the second largest organ in the human body, performs over 5,000 distinct functions. These include aiding in blood clotting, detoxifying the blood, converting food into nutrients, regulating hormone levels, combating infections and illnesses, and metabolizing substances such as cholesterol, glucose, and iron while maintaining their balance in the body (Sivakrishnan and Pharm, 2019). Chronic liver disease and its related complications, including cirrhosis and liver cancer, contribute substantially to mortality, morbidity, and economic challenges (Younossi et al., 2023). There are more than 100 recognized forms of liver disease, each stemming from various causes. The leading causes of liver-related morbidity and mortality are viral hepatitis, alcoholic liver disease, non-alcoholic fatty liver disease, cirrhosis, and hepatocellular carcinoma (HCC) (Desai et al., 2015). Despite advances in managing liver diseases, treatment limitations have spurred interest in natural therapies like essential oils to support liver health and slow disease progression.

Essential oils are highly dense, fragrant constituents derived from plants through techniques such as hydro-diffusion, steam distillation, or mechanical pressing (Manion et al., 2017). These oils play a vital role in plants by providing their distinctive scent and flavor, attracting pollinators, and deterring pests. Aromatic plants and their extracts are well-known for their biological properties, including anti-septic, bactericidal, fungicidal, and anti-viral activities (Żukowska and Durczyńska, 2023). Gas chromatography, rotary evaporation, steam distillation, freeze drying, and hydrolysis are some methods employed for the extract preparation of essential oils and these all ways boost their therapeutic and bioactive characteristics (Herman et al., 2019). Essential oils are well-recognized in healthcare settings to treat health disorders like Alzheimer's disease, depression, insomnia, cardiovascular ailments, and pain during childbirth (Pezantes-Orellana et al., 2024). This chapter aims to provide a comprehensive understanding of the pathophysiology of liver diseases and the mechanisms of essential oils in the treatment of liver diseases.

Pathophysiology of Liver Diseases

The pathogenic mechanisms of Non-alcoholic fatty-liver disease (NAFLD) and Non-alcoholic steatohepatitis (NASH) is intricate, with numerous mechanisms proposed as potential reasons of fatty-liver infiltration. Clinical manifestations including type-II diabetes, hyperlipidemia and central obesity are well-recognized risk factors of steatosis. These pathological states are associated with both benign liver steatosis and the progression to NASH (Kořínková et al., 2020). Gut microbiota changes the intestinal permeability and the absorption of certain nutrients, and this dysregulation leads to increased supply of microbiota metabolites, nutrients and endotoxins towards the liver, exacerbating inflammation and hepatic fat deposition. Age-related changes in the gut microbiota's composition are linked to a higher incidence and/or severity of NAFLD (Jiang et al., 2020).

The pathogenesis of liver diseases, including NAFLD and NASH, is significantly influenced by the immune system, with Kupper cells as a major contributor. In response to metabolic disorders, these cells produce inflammatory cytokines like TNF and interleukins, and these cytokines worsen the condition further. Typically, there are two possible progressive outcomes to NAFLD: the first one is non-progressive, in which the patient does not advance to NASH, while in the other one, patients progress to NASH and fibrosis over years (Haas et al., 2016). Further, NASH can also advance to two stages; in first stage the insulin resistance leads towards fatty buildup in liver tissues. Whereas, in the second stage there are molecular and cellular modifications like oxidation of fatty acids, oxidative stress, and changes in immune system, increased insulin concentration, cytokine-mediated destructions, and energy disparities (Pouwels et al., 2022).

Cirrhosis is advanced stage of chronic liver diseases, which is distinguished by fibrosis and structural changes in liver architecture which further leads towards liver cancer or failure (Figure 1). Viral hepatitis, NAFLD, NASH, alcohol consumption, and metabolic syndrome can cause degeneration of hepatocytes and necrosis and this can lead to the formation of fibrotic scars. The activation of hepatic stellate cells is a major mechanism involved in liver fibrosis which is occurred by oxidative stress and apoptosis (Huang et al., 2023). These liver disorders can lead to HCC. PNPLA2 I148M, a genetic variant, is linked with increased risk of HCC (Kanda et al., 2020).

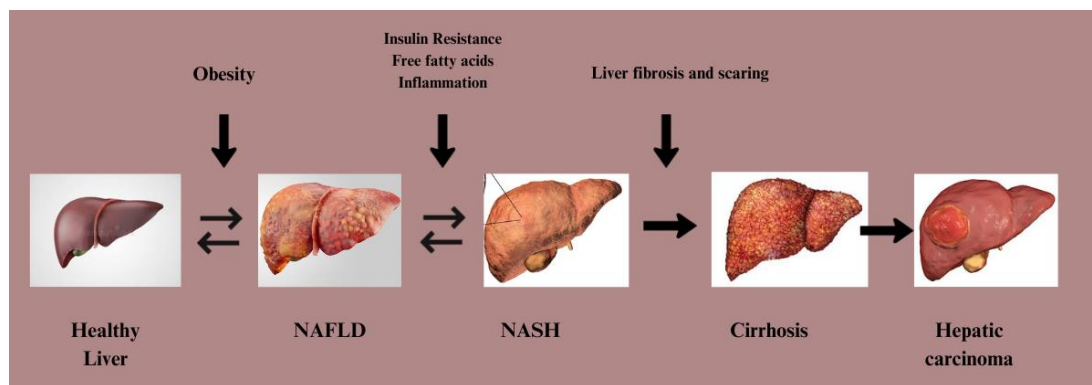


Fig. 1: Stages of liver diseases

1. Key Essential Oils for Liver Disease

1.1. Ginger Essential Oil

Zingiber officinale (ginger) is not only utilized as flavoring in food but also used as herbal drug from decades. The scientific studies extensively showed that its extract and essential oil are used for the treatment of gut disorders, inflammatory diseases, metabolic syndrome, osteoarthritis, and cancers (Alsherbiny et al., 2019). Gingerol, shogaol, beta-bisabolene, and zingerone are some of major bioactive components present in ginger oil and these compounds have been proven to show certain health benefits (Jan et al., 2022). The consumption of ginger essential oil has been proven to reduce serum LDL, ALT, AST, and ALP levels, followed by the increase in concentration of serum HDL and GSH-px level. In addition, ginger oil showed anti-cancerous activities against the liver cell lines (HepG2). The histopathological assessment of liver tissues showed remarkable reduction in abnormalities, indicating its modulating effects (Fahmi et al., 2019). Ginger essential oil also helps to prevent the non-alcoholic steatohepatitis development, by following different mechanism including decreased hepatic inflammation and varying gut microbiota and its metabolic pathways. Moreover, Ginger oil also utilized as dietary supplement as a primary prevention of NASH (Sheen et al., 2023). NASH progression is effectively inhibited by the ginger oil through a variety of mechanism including modification of intestinal microbiota and the suppression of the LPS/TLR4/NF- κ B signaling pathway (Panyod et al., 2024). Ginger also helps to prevent hepatic inflammation, oxidative stress, and apoptosis by increasing the phosphorylation of AMPK pathway and decreasing the mRNA levels of SREBP 1 and SREBP 2 (Mohammed, 2022).

1.2. Turmeric Essential Oil

Curcuma longa (turmeric), a perennial herb, originating in tropical Asia, its rhizomes are widely employed in traditional medicine, as a food, and dye. *Curcuma longa* (turmeric) The *C. longa* is presently taken as a functional food for improving the liver functions. It contains around 5% essential oils, which improve blood flow, reduce inflammation, and include bioactive components such as curcuminoids and curcumin, which have potential anti-tumor, anti-inflammatory, antioxidant, and hypoglycemic effects (Jarhahzadeh et al., 2021). In a high-fat diet-induced hyperlipidemic rat model, turmeric oil (TO) was found to protect against liver diseases by preventing liver tissue damage, as confirmed through histological examinations. It has also enhanced antioxidant enzyme activities and decreased markers of oxidative stress that promote liver function (Ling et al., 2012). Turmeric essential oil contains sesquiterpenes like ar-turmerone, β -sesquiphellandrene, and curcumenol, which have been proven *in vitro* to show cytotoxic effects by preventing cell growth and apoptosis in HepG2 cell lines of liver (Abdel-Lateef et al., 2016).

The pharmacodynamics study of turmeric oil showed the presence of pharmaceutical compounds found in it including curdione, zedoaronidol, curzerenone, curcumenol, germacrone, and β -elemene. These bioactive components have the ability to act as anti-hepatoma such as curcumin can regulate many pathways like YAP, P53, JAK/STAT, VEGF, and NF- κ B. On the other hand, these compounds in combination target the key pathways including HIF-1 signaling. These studies suggest that turmeric oil can be used for the treatment of liver cancer (Li et al., 2022). In another experiment, the research animals were provided turmeric essential oil to evaluate the effect is effect on liver health. The findings of research showed activation of PPAR- α (lipid metabolism gene), while reduced serum values of liver enzymes (ALT, AST), hepatic triglycerides levels, and fat weight. The reduction of fat deposition in hepatic cells was confirmed by the histopathological examination of liver tissues (Watanabe et al., 2023).

1.3. Rosemary Essential Oil

Rosmarinus officinalis is widely utilized in food and pharmaceutical industries because of its anti-oxidant and anti-microbial properties. Rosemary contains many classes of biological compounds such as polyphenols, flavonoids, and diterpenes (Veenstra and Johnson, 2021). The hepato-protective study of rosemary oil showed inhibition of the lipid per-oxidation in liver homogenates caused by carbon tetrachloride. The outcomes of research showed that the activities of anti-oxidant enzymes in liver homogenates such as catalase, glutathione reductase, peroxidase, and glutathione peroxidase were enhanced by the pre-treatment with rosemary oil while the levels of liver enzymes including ALT and AST were reduced (Rašković et al., 2014). The nanoemulsion of rosemary oil was also studied for its hepato-protective effects and similar results regarding liver enzymes were obtained (Pascual-Mathey et al., 2022).

Another research indicated that the administration of curcumin and rosemary oil showed reduction in liver enzyme concentration and lipid per-oxidation, and also improved the anti-oxidative, inflammatory and apoptotic properties. The consumption of these oils also enhanced the over-expression of MEK and ERK proteins, indicating the hepatoprotective effects of these signaling pathway (Mohamed et al., 2022). Rosemary essential oil was found to protect DNA against oxidative damage in HepG2 cells and induced apoptotic cell death. In liver cell extracts from rats fed with rosemary oil, no impact on DNA repair capacity was observed. Differentiated HepaRG cells showed greater resistance to diterpenes like carnosol, carnosic acid, and rosmanol, which significantly altered the cells' metabolome (Rahbardar and Hosseinzadeh, 2024).

1.4. Peppermint Essential Oil

Mentha piperita L. (peppermint) is commonly used as essential oil, food ingredient, and tea infusion, with its extracts and oil having a long history in traditional medicine. Research on cellular and animal models has highlighted its diverse biological and pharmacological properties (Diab et al., 2022). Peppermint essential oil (PEO) demonstrated potential antidiabetic effects in diabetic rats induced by streptozotocin and nicotinamide. Treatment with PEO improved liver health by enhancing antioxidant status and promoting the regeneration of hepatic tissue. Histological analysis showed reduced degenerative changes in the liver, indicating a hepatoprotective effect of PEO in the diabetic rats (Abdellatif et al., 2017).

Hepato-toxicity or liver damage is generally attributed to the production of toxic substances (uric acid, creatinine, carbon tetrachloride) due to the chemical reactions taking place in liver. Moreover, some medicines and viruses also contribute to liver damage (Chakraborty et al., 2022). Several studies showed that the peppermint oil has the ability to protect the liver against carbon tetrachloride (CCl₄) induced liver toxicity. It is thought that CCl₄ promote liver toxicity by reducing the levels of liver enzymes and anti-oxidant enzymes (Khalil et al., 2015). While on the other hand, peppermint essential oil has the ability to reverse this toxicity by improving the levels of liver enzymes and MDA (Batoool et al., 2023). Bellassoued et al. (2018) suggested similar findings that peppermint oil can improve the liver function by reducing the levels of liver enzymes, urea, creatinine, LDH and γGT. In addition, they also concluded that the oil can improve anti-oxidant enzymes activities effectively and also lowered the lipid peroxidation (TBARS) in liver. *Mentha piperita* oil has the ability to effectively mitigate the CCl₄-induced liver fibrosis, as the oils shows potent anti-fibrogenic effects by increasing antioxidant activity, lowering p53 concentration, and altering the expression of transforming growth factor (Ogaly et al., 2018).

1.5. Black Seed Oil

Black seed (*Nigella sativa*) has a long history of use as it has shown many health promoting effects related to fatty liver disease risk factors including metabolic syndrome, diabetes, weight management, and blood pressure in several clinical experiments. Moreover, black seeds are rich source of bioactive components which have strong anti-oxidant and anti-inflammatory properties. These properties play a crucial in the management of fatty liver disease as inflammation and oxidative stress are important key risk factors in the disease development and progression (Hussain et al., 2017). Black seed oil supplementation has the ability to increase the serum high-density lipoprotein concentration while reducing the levels of blood sugar, lipid profile markers (VLDL, TG, TC, LDL), liver enzymes (AST and ALT), and inflammatory markers (hs-CRP, IL-6, and TNF-α) in comparison to placebo group.

These findings imply that supplementation of black seed oil may mitigate the lipid profile and liver enzyme levels in fatty liver patients and provide protective benefits for the liver by lowering the inflammation (Rashidmayvan et al., 2019). In another trial, the consumption of 2.5 mL of standardized black seed oil considerably increase the HDL concentration and lowered the serum levels of TG, LDL-C, AST, and ALT, as well as hepatic steatosis. Additionally, the same dosage and treatment duration considerably alleviate the concentration of liver enzymes, and 3-month ultrasound assessments revealed a noticeable improvement in liver condition compared to the control group (Khonche et al., 2019).

2. Mechanisms of Action of Essential Oils in Liver Disease Treatment

Oxidative stress is a major pathogenic mechanism implicated in the development and advancement of liver damage. Alcohol consumption, radiations, environmental pollutants, and drugs are some risk factors which can result in severe liver conditions such as alcoholic liver disease and non-alcoholic steatohepatitis (Li et al., 2015). Essential oils are abundant source of bioactive compounds which can quench free radicals and can reduce hepatic oxidative stress (Sheweita et al., 2016). Hepatotoxins increase reactive oxygen species (ROS) concentrations and inhibit anti-oxidant enzymes including SOD, GPx, GST, GSH, and CAT, thereby leads towards the development and progression of liver injury (Daoudi and Bnouham, 2020). While essential oils have the ability to enhance the activity of these anti-oxidant enzymes. Essential oils, obtained from herbal drugs helps to improve intestinal health and lipid metabolism by effectively increasing the gut microflora and lowering the endogenous concentrations of TG, TC, FFA, VLDL, and SREBP-1c, and normalizing PPAR-α activity (Xu et al., 2020; Lu et al., 2018). Essential oils exhibit anti-inflammatory effects by targeting and inhibiting several dysregulated signaling pathways associated with inflammation (Figure 2). These include Toll-like receptors (TLR), NLRP3, NF-κB, and MAPKs, as well as auxiliary pathways such as Nrf2/ARE and JAK/STAT signaling pathways (Zhao et al., 2023). Figure 2 shows the different mechanisms through which essential oils contribute to the mitigation of liver diseases.

3. Safety of Essential Oils

Essential oils (EOs) used as food supplements require a toxicological evaluation to determine safe recommended doses, considering genotoxicity and other harmful effects. A tiered approach, based on existing data and safety factors, ensures that the recommended dose has a safety margin of at least 1 for all constituents, avoiding unnecessary new animal testing (Tamburlin et al., 2021). Oral ingestion of essential oils (EOs) should be approached with caution, under the guidance of a healthcare professional, and in minimal doses, as over consumption can lead to liver or kidney damage. In topical applications, EOs should be diluted with some carrier oils to avoid skin irritation. Certain people may be sensitive or allergic to specific essential oils, particularly those containing dense levels of aldehydes or phenols. It is advisable to perform a patch test before using EOs widely. Essential oils can interact with medications, potentially varying their effectiveness or causing negative reactions. For example, oils like lavender and peppermint may interfere with sedative drugs.

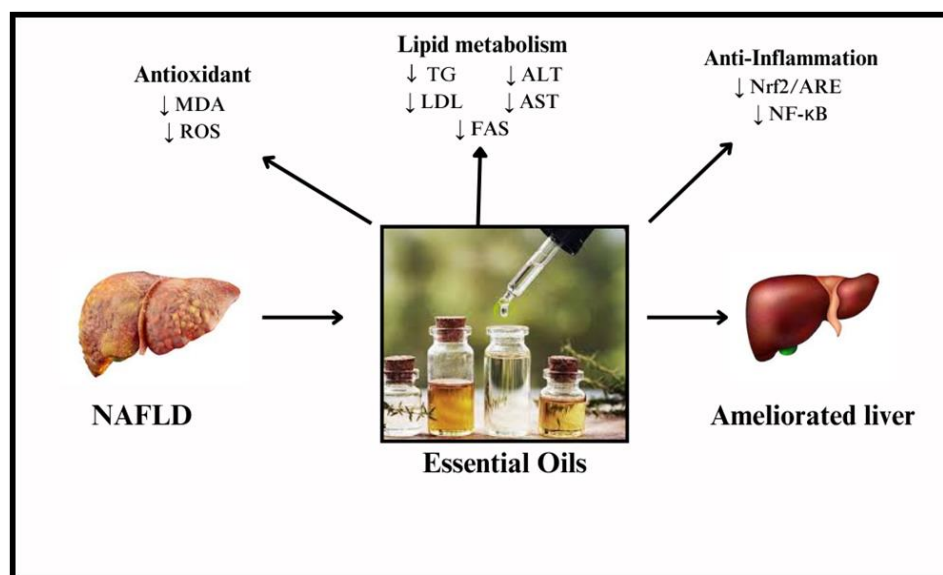


Fig. 2: Mechanism of action of essential oils

Conclusion

Essential oils have several pharmaceutical functions including anti-oxidant, anti-inflammatory and hepatoprotective effects. Essential oils hold a promising therapeutic potential against liver diseases including NAFLD, NASH, and cirrhosis by mitigating lipid metabolism, reducing oxidative stress, and regulating the inflammation. However, their use, requires caution, as improper administration or excessive doses may result in hepatotoxicity. To ensure the safety and efficacy of EOs in managing liver diseases, thorough toxicological assessments, well-defined dosing protocols, and vigorous clinical research are crucial. Conclusively, while EOs show substantial promise, their incorporation into therapeutic applications needs a careful approach that blends traditional knowledge with modern scientific research to optimize liver health outcomes.

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