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Role of essential oils in preventing hepatotoxicity: A comprehensive review

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Abstract

Hepatotoxicity represents one of the significant and challenging health concerns at the worldwide level. To overcome this condition, essential oil can act as a natural therapeutic in alleviating hepatic disorders caused by toxins, drugs, alcohol, or infections. Various aromatic plants such as Citrus species, Allium species, spices, and rosemary species contain bioactive compounds—mainly terpenes, phenolics, flavonoids, and sulfur-containing compounds. These bioactive compounds possess excellent antioxidant potential to neutralize free radicals and promote the endogenous antioxidant defense system, such as SOD, catalase, Gpx, and others as well. In addition to this, they exhibit anti-inflammatory potential to regulate inflammatory cascades and cytokine levels, while their detoxification mechanism stimulates the liver's capacity to eradicate harmful substances. Although previous research has documented that essential oil exhibits the ability to protect the liver from chronic diseases—mainly fibrosis, non-alcoholic fatty liver disease (NAFLD), and drug-induced hepatotoxicity—by modulating lipid metabolism, hepatocyte integrity, the antioxidant defense system, and pathological factors, future research is still required to evaluate its efficacy, bioavailability, safe doses, and explore synergistic formulations. Keeping these perspectives in mind, the current review is planned to highlight the hepatoprotective properties of essential oils, their underlying mechanisms, and their prospective contribution to the development of natural therapeutics for liver health.

Keywords: Anti-apoptotic; anti-inflammatory; antioxidant; essential oil; hepatotoxicity; liver diseases.

Introduction

Liver disease, including cirrhosis, viral hepatitis, and liver cancer, causes more than two million fatalities a year and accounts for 4% of all deaths globally (1 out of every 25 deaths); one out of three liver-related deaths occurs in women.[1] Recently, liver disease is considered the 11th leading cause of death, but liver deaths may be underreported. The major cause of liver disease is characterized by metabolic abnormalities and histological alterations like zonal necrosis, vascular lesions, granuloma, steatosis, and cholestasis, accounting for 5% of all injuries and consequently prevalent to known injury.[2] Although the pathophysiological processes of hepatotoxicity are still poorly understood, they are primarily linked to the metabolic conversion of xenobiotics into reactive oxygen species (ROS). This contributes to the condition known as "oxidative stress" and, as a result, impairs the macromolecules within cells.[3] In the majority of liver diseases like cirrhosis, hepatitis, and hepatocellular carcinoma (HCC), oxidative stress represents one of the key factors involved in promoting these disorders.[4] Furthermore, overproduction of ROS and a decrease in the antioxidant defense system accelerate free radical formation and, as a result, attack polyunsaturated fatty acids in cellular membranes and promote lipid peroxidation.[5] Apart from that, upregulation in enzymatic markers such as serum alanine aminotransferase (ALT), alkaline phosphatase (ALP), and aspartate aminotransferase (AST) is also interlinked with tissue necrosis and degeneration of hepatic tissues and, therefore, promotes "hepatotoxicity."[6]

As the liver plays a vital role in the metabolism, transport, and clearance of xenobiotics, it is critically susceptible to damage.[7] A wide range of toxicants such as chemicals, antibiotics, steroidal and non-steroidal drugs, viral infections, dietary and herbal supplements contribute to the onset of liver disease by triggering "oxidative stress." It plays a vital role in the pathogenesis and progression of hepatotoxicity by modulating the release of inflammatory mediators such as TNF-α, IL-1β, and apoptotic factors (Bax, Bcl-2, caspase-3, 9, etc).[8] Depending on the toxicity and mechanism of action of toxicants, it can be classified into two types: intrinsic and idiosyncratic.[9] Intrinsic toxicity is typically dose-dependent and frequently detected within hours to days after toxicant exposure. In contrast, idiosyncratic toxicity follows unpredictable behavior with variable latency of onset from weeks to months. However, a variety of synthetic and natural drugs are available on the market to reduce hepatic disease as well as to overcome the challenges associated with these disorders. Due to availability, safety, and efficacy concerns, it is necessary to explore and develop more novel drugs to counteract hepatotoxicity.[10,11]

In the recent era, the consumption of essential oils can be considered a novel approach to evaluate the potential benefits for human health. The volatile nature of essential oil allows its rapid absorption through inhalation or transdermal routes, distinguishing essential oils from non-volatile herbal extracts that rely on larger, often water-soluble molecules. These unique molecular profiles are not only responsible for the diverse pharmacological effects of essential oils but also account for the

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challenges related to their stability, standardization, and formulation. However, it can be extracted from aromatic plants by hydrodistillation, steam distillation, microwave-assisted hydrodistillation, and others as well.[12] They are typically comprised of secondary metabolites and possess oxygenated structures such as alcohols, ketones, aldehydes, and esters. They exhibit a wide range of pharmacological potential such as antioxidant, antibacterial, antiviral, and anticancer activity.[13] Due to these activities, essential oils are utilized in a variety of industries, including pharmaceutical, aroma, and food.[14] For preparing novel drugs, it is essential to consider various aspects like solubility, dose range, dosing methods, and bioactive delivery systems to ensure efficacy, safety, and stability.[15] The current research attempts to assess the composition and mechanisms of essential oils in experimental models and provides deeper insights for futuristic research in the development of folk medicine for treating liver diseases and boosting liver functions.

Essential Oil Composition

The composition of essential oils varies depending on the plant source, extraction method, and environmental factors. However, they primarily consist of volatile organic compounds that contribute to their biological activities.[16] The key components of essential oils include terpenes and their derivatives, phenolic compounds, and sulfur-containing compounds, which offer unique aroma and medicinal qualities.[17]

Pharmacokinetics, Bioavailability, and Drug Interactions

Pharmacokinetics of Essential Oils

Due to the presence of terpenoids and non-terpenoids, essential oils exhibit pharmacokinetic properties required for therapeutic potential. Their hydrophobic nature promotes absorption across biological membranes. Various routes like oral, inhalational, and transdermal allow their entry into the biological system.[18] After entry into the biological system, depending on the solubility, molecular weight, and skin barrier, absorption of essential oil and its components is rapidly distributed into lipid-rich tissues such as the liver, brain, and adipose tissues. However, the liver plays a crucial role in metabolizing the essential oil components through Phase I and Phase II reactions. Different families of cytochrome P450 (CYP450) enzymes, particularly CYP3A4 and CYP2D6, are majorly involved in the biotransformation of major EO components. The resulting metabolites are generally more water-soluble and are eliminated via renal and biliary excretion. In addition, a portion of volatile EO components can be exhaled through the lungs or secreted via sweat, contributing to their characteristic odor even after systemic administration.[19]

Bioavailability of Essential Oils

The poor bioavailability of essential oils limits their usage for therapeutic benefits. This may be due to the fact that essential oils exhibit low aqueous solubility, rapid metabolism, and instability under physiological parameters. However, orally administered EO and its components typically undergo extensive first-pass metabolism, significantly reducing their systemic concentration and therapeutic effect. Essential oil exhibits a short half-life, which limits its duration of action and may necessitate repeated or sustained delivery for therapeutic efficacy.[20] For example, curcumin extracted from turmeric essential oil exhibits significantly low oral bioavailability in response to rapid metabolism and elimination. To address these problems, a number of delivery methods have been designed to increase bioavailability, such as solid lipid nanoparticles, liposomes, and nanoemulsions. These formulations improve solubility, protect volatile constituents from degradation, and facilitate sustained release. Transdermal and sublingual routes have also gained attention as they bypass hepatic metabolism, offering improved bioavailability and prolonged systemic activity. In a previous study, lipid-based formulations of bioactive substances such as carvacrol and thymol can greatly improve their absorption and therapeutic efficacy.[21]

Drug Interactions of Essential Oils

In clinical applications, the possibility of interactions between essential oils and traditional medications is a major concern. A wide variety of EO components may alter the behavior of transport proteins and drug-metabolizing enzymes, which can either make medication combinations more hazardous or less effective. For example, one of the most studied interactions is CYP450 enzyme inhibition or induction. In a previous study, it has been demonstrated that eugenol, a phenolic molecule found in clove oil, inhibits CYP3A4, which in turn affects the activity of calcium channel blockers, statins, and some benzodiazepines. Meanwhile, limonene and other monoterpenes may induce particular CYP isoforms and lower the plasma levels of some medicinal substances.[22] Furthermore, essential oils have the ability to affect the function of efflux transporters like P-glycoprotein (P-gp), which is crucial for pharmacokinetics and drug resistance. For example, peppermint oil can improve the efficacy of NSAIDs in treating irritable bowel syndrome, but it may also prevent the absorption of iron and other minerals. The significance of assessing EO use is highlighted by these interactions, particularly for patients following polypharmacy regimens. This indicates that when EOs and medications having a limited therapeutic index, like immunosuppressants, anticoagulants, and antiepileptics, are taken together, caution is advised.[23]

Mechanism of Hepatoprotective Activity

Antioxidant

During metabolic processes or external signals such as environmental pollutants and other toxicants, the level of reactive oxygen species—mainly superoxide (O_2•−), hydroxyl radical (•OH), and hydrogen peroxide (H_2O_2)—can be increased and, as a result, promote metabolic diseases.[24] However, an increase in ROS production can be neutralized by the antioxidant defense system, or natural antioxidants and dietary supplements, to maintain redox status.[25] The use of essential oils accelerates the process of free radical scavenging to improve liver health and oxidative stress-related conditions. Due to their rich composition of bioactive compounds such as alcohols, ethers, ketones, aldehydes, and monoterpenes, essential oils exhibit significant antioxidant behaviour, preventing cellular damage and apoptosis and therefore act as hepatoprotective agents.[26] In a previous study, treatment with the essential oil of *A. campestris* has substantially reduced oxidative stress, biochemical alterations, and improved histopathological architecture in hepatic tissues of mice intoxicated with chlorpyrifos.[27] Furthermore, administration of essential oil extracted from flowers of *Tagetes patula* can be considered a natural therapeutic for relieving multiple liver disorders associated with oxidative stress. It exhibits antioxidant potential, confirmed by DPPH scavenging assay, nitric oxide, and FRAP assays at a dose of 10 mg/kg body weight in hepatic tissues intoxicated with CCl_4. Meanwhile, *Tagetes patula* essential oil restores liver activities by maintaining histological architecture and lipid profiles at two different doses.[28] This indicates that essential oil can serve as a potent therapeutic for liver illnesses due to its ability to neutralize free radicals and enhance detoxification mechanisms.

Anti-Apoptotic

Apoptosis is characterized as controlled cell death to preserve cellular homeostasis and eliminate damaged or unnecessary cells. However, in the case of certain liver illnesses, an imbalance exists between cell proliferation and death, which promotes pathophysiological conditions.[29] For example, liver diseases like acute and fulminant hepatitis and chronic illnesses like chronic hepatitis, alcoholic liver disease, cholestatic liver disease, and non-alcoholic steatohepatitis are mainly associated with excessive apoptosis.[30] It can be controlled by multiple factors like oncogenes and anti-oncogenes, death receptor–ligand binding, and excessive inflammatory cytokines. The hallmarks of apoptotic cells are membrane blebbing, cellular shrinkage, chromatin condensation and DNA fragmentation, formation of apoptotic bodies, and no release of cellular contents.[31] Collectively, it may further activate a wide range of signalling cascades for cellular apoptosis such as caspase pathways, Bcl-2 gene families, as well as immune-mediated apoptosis.[32] In order to prevent this, there is a need to explore essential oils and their bioactive compounds to evaluate their multifaceted roles in preventing hepatic damage by inhibiting apoptotic cascades. By targeting specific signaling cascades, essential oil promotes its antioxidant and anti-inflammatory potential in protecting against hepatic injuries and, as a result, acts as a novel therapeutic agent for modulating apoptotic mechanisms.[33] In a previous study, treatment with coriander essential oil upregulated the level of antioxidant enzymes and modulated Nrf2/HO-1 as well as anti-apoptotic signaling cascades in hepatic tissues of rats intoxicated with dexamethasone. Furthermore, the administration of essential oil of *Carpesium abrotanoides* L. (CAEO) significantly activated the apoptotic factors such as caspase-3 and -9 and, as a result, declined the ratio of Bcl-2/Bax protein. This suggests that CAEO acts as a potent therapeutic in preventing hepatic cancer by triggering mitochondrial-mediated apoptotic cascades involved in apoptotic processes.[34] Apart from that, the upregulation of mRNA expression of anti-apoptotic factor Bcl-2 and substantial downregulation of the nuclear and cytoplasmic apoptotic mediator p53 in hepatic tissues were observed in hepatocytes administered with thyme oil and thymol. Additionally, it ameliorates lipid peroxidation and declines the concentration of TNF-α, albumin, and IL-4 in hepatic tissues intoxicated with doxorubicin.[35] This may be due to the fact that upregulation in antioxidant enzymes (GST and Gpx) counteracts the inflammatory as well as apoptotic markers and acts as a potent hepatoprotective agent.

Anti-Inflammatory

Inflammation plays a vital role in stimulating hepatic injury by modulating cellular and molecular mechanisms followed by hepatic damage, alteration in liver function, cirrhosis, and fibrosis. Various inflammatory and immune factors such as monocytes, macrophages, neutrophil leukocytes, NK, NKT cells, Th17, and regulatory T cells are responsible for liver inflammation.[36,37] Hepatocytes represent different pattern recognition receptors (PRRs) that identify endogenous or pathogen-derived molecular sequences to enhance intracellular signalling cascades and, as a result, induce inflammatory responses. However, interaction of parenchymal and immune cells with each other produces multiple cytokines and chemokines in the local environment to promote liver inflammation.[38] To overcome this condition, essential oils offer a novel and alternative strategy to treat inflammatory diseases. Various signaling pathways upregulate the level of cytokines and other key transcription factors to activate pro-inflammatory genes and, as a result, induce pathological conditions in hepatocytes. Earlier studies have demonstrated that treatment with grape essential oil induces antioxidant enzymes, upregulates the level of trace elements, and downregulates the enzymatic activity of cytochromes, caspases, and NF-κB expression in hepatic tissues.[39] Additionally, the supplementation of lavender essential oil also minimizes hepatic destruction through downregulation of pro-inflammatory cytokines, nitric oxide (NO), and myeloperoxidase (MPO) activity in mice intoxicated with acetaminophen.[40] Furthermore, acrylamide, a major toxicant and carcinogenic agent, is involved in hepatic injury by downregulating the antioxidant defense system and modulating inflammatory factors such as the NF-κB/NLRP3 inflammasome axis and interleukins. However, treatment with *T. satureioides* essential oil highlights its therapeutic potential by targeting the NLRP3 inflammasome/NF-κB axis, which acts as a promising strategy for preventing acrylamide-induced hepatotoxicity.[41] This indicates that essential oil may serve as complementary or alternative therapy to overcome hepatic diseases by reducing inflammation through targeting a variety of signalling cascades like NF-κB, the NLRP3 inflammasome, and maintaining oxidative stress with minimal side effects (Fig. 1).

Clinical and Pre-clinical Evidences

Spice Essential Oil

Spices are classified as functional foods because they have been shown to improve specific body functions beyond just meeting basic nutritional needs in a variety of flavor, color, and aroma.[42,43] From past centuries, different spices such as bud (clove), bark (cinnamon), aromatic seed (cumin), and others have promoted flavor in foods and are considered culinary agents to preserve food and enhance health benefits.[44] From the previous literature, it has been found that alteration in biochemical parameters, oxidative markers, interleukins, caspases, and histopathological studies can be greatly influenced by the action of spice essential oils.[45,46] However, treatment with clove essential oil substantially downregulated the level of biochemical parameters (ALT, AST, and ALP) and restored histological architecture in hepatic tissues of rats. Meanwhile, it enhanced several changes such as infiltration of inflammatory cells, congestion, hyperplasia, cytoplasmic vacuolation, degeneration, and necrosis.[47] Furthermore, *S. aromaticum* L. oil ameliorated liver injury by downregulating serum biomarkers and MDA levels in rats subjected to levofloxacin. The administration of oil at a dose of 10 mg/kg reduced the level of total bilirubin and hepatic biomarkers and, as a result, acted as a hepatoprotective agent.[48] Another study revealed that chemical-induced liver injury also promotes the formation of hepatic lesions through upregulation of serum biomarkers (ALT, AST, and ALP) and lactate dehydrogenase (LDH) levels in CCl_4-intoxicated rats. Treatment with *Cinnamomum verum* essential oil (CVEO) at a dose of 100 mg/kg exhibited the potential of free radical scavenging and thus downregulated the level of serum biomarkers (ALT, AST, and ALP).[49] However, in a randomized controlled trial, treatment with *Nigella sativa* essential oil improved liver steatosis and injury and blood levels of triglycerides, LDL-C, and HDL-C in NAFLD patients.[50] Essential oils exhibit a variety of bioactive compounds such as cinnamaldehyde, cuminaldehyde, cymene, terpenes (β-pinene, γ-terpinene), eugenol, and thymoquinone, which possess multiple pharmacological activities.[51] In a recent study, it has been demonstrated that treatment with cinnamaldehyde improved liver function by significantly reducing biochemical parameters (ALT, AST, GGT), which in turn alleviates inflammation (TGF-β) and apoptosis in CCl_4-induced liver fibrosis.[52] In non-alcoholic fatty liver disease (NAFLD), the administration of cuminaldehyde, an active constituent of cumin essential oil, enhances the antioxidant defense system and

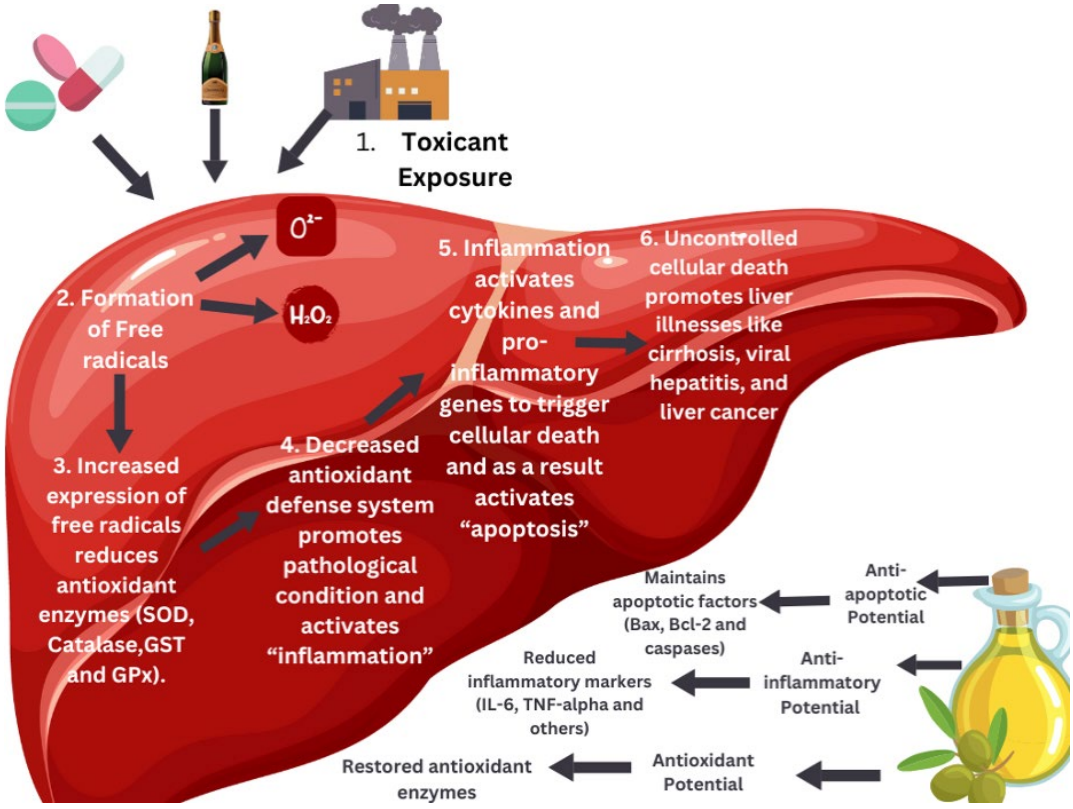

Figure 1. Mechanistic insights of essential oil in preventing hepatocytes.

significantly reduces serum levels of liver enzymes (AST and ALT) as well as hyperlipidemia in experimental rat models.[53] Besides this, other bioactive compounds like p-cymene greatly prevented the infiltration of inflammatory cells in the liver parenchyma of stressed rats. In conclusion, the study found that thymol and p-cymene have a hepatoprotective effect on immobilized rats, likely exerted by suppressing oxidative stress and inflammation, stimulating Nrf2/HO-1 signaling, and inhibiting the TNF-α/NF-κB pathway.[54] In HepG2 cell lines, eugenol protects human liver HepG2 cells from H_2O_2-induced oxidative hepatotoxicity by maintaining ROS homeostasis, increasing IL-10 levels, and upregulating cytochrome gene expression.[55] In summary, these investigations demonstrated that spice essential oils and their bioactive compounds exhibit favorable hepatoprotective benefits and require further investigations to identify safety dosage, biodistribution and potency.

Allium Species Essential Oil

Essential oils derived from *Allium* species, such as garlic (*Allium sativum*), onion (*Allium cepa*), and leek (*Allium porrum*), are renowned for their medicinal properties. These oils are highly rich in organosulfur compounds, which exhibit strong hepatoprotective properties, making them suitable for managing conditions such as drug-induced hepatotoxicity, NAFLD, and liver fibrosis.[56] In a previous study, exposure to deltamethrin upregulated biochemical parameters and downregulated the antioxidant defense system. As a result, it altered the histological architecture of liver tissues, which was confirmed by central vein congestion, necrosis, and infiltration of inflammatory leukocytes. Moreover, administration of *Allium sativum* essential oil (ASEO) significantly reduced hepatic intoxication by restoring the level of antioxidant enzymes and biochemical parameters. This highlighted that ASEO exhibits the potency to minimize hepatic damage induced by deltamethrin.[57] Furthermore, it reduces inflammation, apoptosis, and genotoxicity and modulates histological architecture in hepatic tissues of mice intoxicated with heavy metal.[58] This explains that *Allium sativum* essential oil protects against liver damage via maintaining the inflammatory pathways such as NF-κB signalling cascades and apoptotic pathways (extrinsic and intrinsic) and therefore protects against genotoxicity. Apart from that, in non-alcoholic fatty liver disease, *Allium sativum* essential oil (ASEO) and its bioactive compound DADS promote lipid-lowering and anti-obesity effects by downregulating biochemical parameters in serum and reducing body weight gain in mice exposed to a high-fat diet. However, administration with two doses of ASEO (50 and 100 mg/kg) and its bioactive compound DADS at 20 mg/kg substantially altered the mechanism of fatty acid synthesis. This indicates that ASEO and DADS dose-dependently prevented obesity in mice through minimizing lipid accumulation and oxidative stress and, as a result, protected against inflammation by alleviating metabolic abnormalities in mice fed with a high-fat diet.[59] In the case of acute liver failure, administration of DATS suppressed inflammation and apoptosis by downregulating caspase-3 and the Bax/Bcl-2 ratio in LPS/D-gal–treated mice. Further, it inhibited the increase in CD11b+ Kupffer cells and other macrophages in the liver and tumor necrosis factor-alpha in the blood.[60] Another study demonstrated that allicin exhibits a significant protective effect on CCl_4-induced liver injury via inhibiting the inflammatory response and hepatocyte apoptosis and alleviating oxidative stress associated with the progression of liver damage, highlighting the potential of allicin as a hepatoprotective agent.[61] From these findings, it has been revealed that *Allium sativum* essential oil (ASEO) and its bioactive compounds may act as a promising approach for herbal drug preparation to prevent hepatotoxicity.

Citrus Species Essential Oil

Citrus species such as grapefruit (*Citrus paradisi*), orange (*Citrus sinensis*), lemon (*Citrus limon*), and lime (*Citrus aurantiifolia*) are well-known for their therapeutic and medical qualities. The bioactive compounds such as limonene, linalool, citral, and flavonoids are mainly found in essential oils extracted from peels, leaves, or flowers.[62] One of the noteworthy uses of citrus essential oil is its hepatoprotective potential, protecting against hepatic damage induced by toxins, oxidative stress, or inflammation.[63] However, prolonged consumption of non-steroidal anti-inflammatory drugs, mainly aspirin, induces hepatotoxicity by increasing the level of biochemical parameters (AST, ALT, and LDH) and decreasing the antioxidant defense system. From the literature survey, it has been documented that citrus essential oil (CEO) exhibits antioxidant, anti-inflammatory, and anti-apoptotic potential, contributing to substantial protection against aspirin toxicity by restoring these parameters back to normal. It prevents oxidative stress and NF-κB cells from nuclear localization to restrict the activation of inflammatory genes and, as a result, inhibits inflammation and reduces hepatocyte death to shield the liver from I/R damage.[64] Furthermore, induction of HO-1 prohibits the activation of inflammatory mediators and stimulates iNOS expression and therefore promotes antioxidant defense in hepatocytes. This indicates that modulation of HO-1 can serve as a promising strategy to protect against liver damage; however, CEO treatment significantly restored the mRNA and protein expression of HO-1 to overcome cellular injuries induced by I/R. This suggests that expression of NF-κB and HO-1 signaling cascades can significantly promote liver recovery by altering metabolic abnormalities in I/R-induced liver injuries. Furthermore, in order to modify lipid metabolites and modulate genes related to lipid metabolism, CEO could potentially mediate lipid and cholesterol homeostasis and successfully prevent hypercholesterolemia and hepatic steatosis.[65,66] Bioactive compounds—mainly limonene, linalool, citral, α-terpineol, geraniol, myrcene, γ-terpinene, and β-pinene—are majorly present in citrus species essential oil.[67] In an experimental study, the administration of myrcene significantly inhibited acetaminophen-induced liver damage by normalizing several biochemical characteristics of liver function and oxidative stress and thus improved histopathological parameters due to its antioxidant activity.[68] Meanwhile, treatment with linalool ameliorated lipid accumulation in hepatocytes by promoting fatty acid oxidation, inhibiting lipid biosynthesis, and reducing oxidative stress by regulating Nrf-2/HO-1 signaling cascades.[69] Apart from that, other bioactive compounds like limonene, geraniol, citral, and others as well upregulate the antioxidant defense system and alter pathological conditions such as inflammation, apoptosis, and lipid accumulation in hepatocytes. Previous literature suggested that limonene possesses the capacity to reduce hepatic lipid peroxidation and inhibit pro-inflammatory cytokines such as TNF-α and IL-6. Moreover, geraniol exhibits anti-apoptotic properties by modulating Bcl-2 family proteins, while citral downregulates lipogenic gene expression, thereby reducing lipid accumulation.[70–73] This indicates that CEO and its bioactive compounds hold significant promise for drug development aimed at liver protection. However, further research is necessary to elucidate its precise molecular mechanisms, optimize its dosage and formulation, and evaluate its clinical safety and efficacy.

Rosemary Essential Oil

A well-known medicinal herb, rosemary (*Rosmarinus officinalis*) has been considered for its pharmacological benefits. Essential oil extracted from the plant's leaves is highly rich in bioactive components, mainly carnosol, rosmarinic acid, and carnosic acid. These bioactive compounds exhibit a variety of pharmacological potentials such as antioxidant, anti-apoptotic, anti-inflammatory, and aid in detoxification mechanisms.[74] According to a previous study, it has been indicated that rosemary essential oil (REO) acts as a potent free radical scavenger, determined by DPPH assay and, as a result, activates antioxidant defense mechanisms in hepatocytes.[75] Due to the presence of bioactive compounds such as phenolics and tocols, rosemary oil can be significantly involved in alleviating hepatotoxicity and is considered in pharmaceutical and food industries, particularly in the development of natural drug formulations and functional foods to improve overall health.[76] Moreover, the abnormal behavior of hepatocytes can be assessed by the alterations in hematological parameters, oxidative stress markers (protein carbonyl, TBARS, and H_2O_2), and a significant drop in glutathione (GSH) concentration. For example, in rats, chromium exposure upregulates biochemical parameters (ALP, AST, and ALP), total protein, and albumin levels and causes a significant decline in enzymatic antioxidants (SOD, CAT, GPx, and GST) in hepatocytes. To overcome this, treatment with REO significantly restored these parameters by improving antioxidant status and decreasing lipid peroxidation.[77] Furthermore, the assessment of histological and immunohistochemical expression of PCNA revealed the restoration of hepatic tissues. In conclusion, it has been considered that REO and its bioactive compounds can effectively modulate chromium-induced hepatotoxicity, especially in pretreated rats. Rosemary essential oil exhibits hepatoprotective activity primarily due to its bioactive compounds like 1,8-cineole, α-pinene, camphor, and borneol, which exert antioxidant, anti-inflammatory, and detoxifying effects on liver tissue.[78] In a previous study, treatment with 1,8-cineole prevented liver damage by reducing oxidative stress and inflammation in rats intoxicated with lead acetate. This hepatoprotection is probably achieved by inhibiting TLR4/MyD88/NF-κB signalling cascades.[79] Moreover, administration of alpha-pinene induces liver protective effects against N-acetyl-p-aminophenol (paracetamol, APA) damage by reducing the activity of liver enzymes, improving antioxidant/oxidative status, and reducing inflammation through the regulation of NF-κB and pro-inflammatory cytokines.[80] This indicates that rosemary essential oil and its bioactive compounds can act as promising candidates to prevent and alleviate hepatotoxicity.

Challenges, Limitations, and Contradictory Findings

Despite growing interest in the anticancer potential of essential oils and their constituents, several critical challenges limit their clinical applicability and scientific validation.

Lack of Standardization and Reproducibility

Depending on the plant species, geographical background, and extraction procedures, the chemical composition of essential oils may differ. Various studies have clearly demonstrated that in-depth analysis of compositions by techniques such as gas chromatography–mass spectrometry (GC-MS) is crucial for identifying and measuring bioactive compounds.[81–83] Due to a lack of internationally recognized quality control procedures and substantial batch-to-batch variability, it is difficult to accurately replicate experimental results. This can be a major limitation because it lacks standardization and makes it challenging to draw consistent conclusions across studies. Concerns regarding the safety and effectiveness of essential oils in clinical and therapeutic settings are also raised by this diversity, which restricts the comparability of results between investigations. Thus, standardizing extraction procedures, maintaining quality control standards, and establishing chemical characterization are important for increasing the legitimacy and relevance of essential oil research.

Limited Clinical Evidence

The effectiveness and safety of essential oils in human populations are still not well supported by high-quality clinical data. The majority of the information originates from pre-clinical or *in vitro* research, useful for comprehending mechanisms of action. Still, there is a lack of evidence representing clinical studies to examine the effect of essential oils. Study limitations include sample sizes, study durations, and methodological flaws like blinding, placebo control, or randomization. Furthermore, there is considerable variability in the dosage forms, administration routes (e.g., inhalation, topical, oral), and types of essential oils used across studies, making it difficult to establish standardized treatment protocols. Regulatory oversight is also minimal in many countries, resulting in inconsistent product quality and further complicating clinical translation. To establish essential oils as evidence-based therapeutic agents, there is an urgent need for well-designed, large-scale, and placebo-controlled clinical trials that adhere to rigorous methodological standards. These shortcomings diminish the reliability of the evidence and make it more difficult to reach strong conclusions about treatment efficacy.

Toxicity and Safety Concerns

Essential oils are not always safe and can be extremely toxic or dangerous, especially if used incorrectly or in large quantities. They contain strong bioactive chemicals which impart negative consequences like skin irritation, allergic responses, respiratory discomfort, hepatotoxicity, or neurotoxicity. Due to their lipophilic nature, they facilitate absorption through the skin and increase the risk of poisoning. People with pre-existing diseases are more vulnerable. As essential oils are widely accessible in the consumer market without any regulatory monitoring, this in turn increases the chances of misuse, such as improper dilution and consumption of oils that are not intended for internal use. Therefore, strict toxicological testing, clear labeling, uniform safety regulations, and public education are vital to ensuring the safe and responsible use of essential oils in both commercial and medical contexts. Despite the common belief that essential oils are "natural and safe," they could potentially cause unfavorable side effects.

Contradictory Findings in the Literature

Essential oils present numerous contradictory findings, mainly regarding their mechanisms of action and the establishment of efficacy and effectiveness. Literature studies suggest that essential oils exhibit promising pharmacological benefits such as antimicrobial, antioxidant, anti-inflammatory, or neuroprotective effects, while others show minimal or no activity under similar experimental conditions.[84–86] Variation in plant species, oil extraction techniques, chemical composition, and dosage are the major factors responsible for these discrepancies. Furthermore, different biological models, such as animal models, mammalian cells, or bacterial cultures, may respond differently and produce varied results. It is sometimes possible for the same essential oil to exhibit both cytotoxic and therapeutic effects, depending on the target tissue, concentration, and dosage. Such conflicting results highlight the necessity for established methodology, rigorous quality control, and reproducible techniques in essential oil research.

Conclusion

Essential oil extracted from aromatic plants offers a promising approach to protect the liver from pathological conditions such as oxidative stress, inflammation, and toxin-induced damage. Due to its pharmacological potential, it strengthens the antioxidant defense system, modulates inflammatory and apoptotic cascades to support detoxification processes, and thus serves as a valuable hepatoprotective agent. Despite these advantages, various challenges including dose optimization, oil composition consistency, and possible toxicity at higher concentrations still need to be resolved. According to recent studies, essential oils could potentially be helpful in treating liver problems, but more research is needed before they can be used in clinical settings. By tackling these avenues, essential oils provide enormous promise as sustainable, safe, and efficient alternatives for managing and preventing liver illnesses, facilitating a holistic approach to liver health.

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