



Polyphenols and terpenoids derived from *Ocimum* species as prospective hepatoprotective drug leads: a comprehensive mechanistic review

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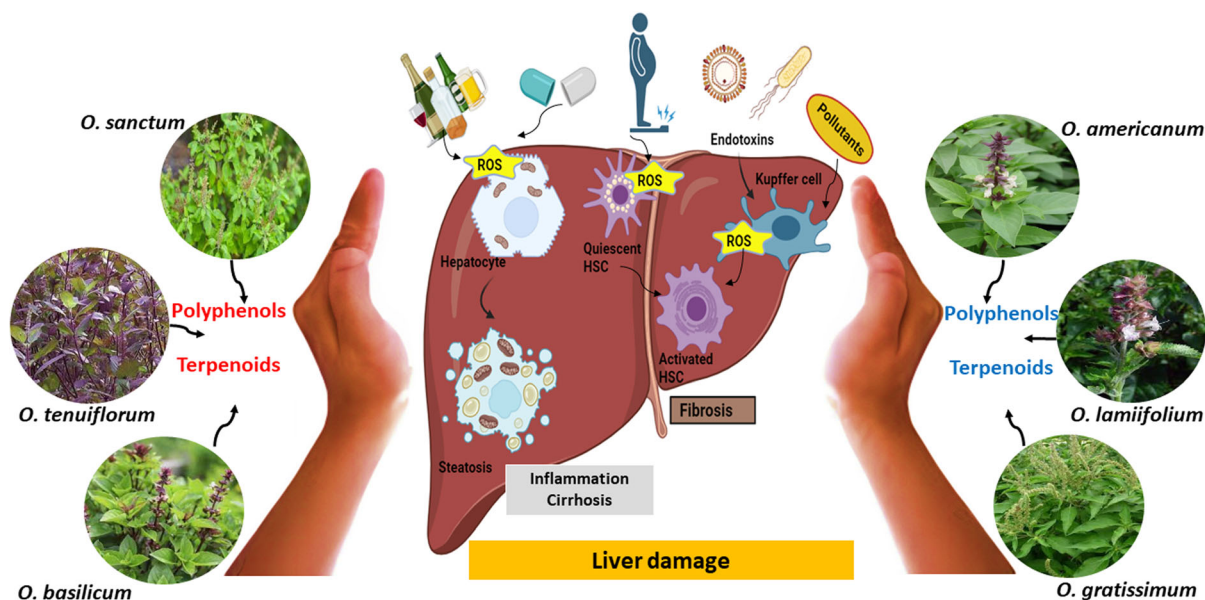
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Abstract The hepatic regulatory role in metabolism involves exposure to a diverse array of xenobiotic compounds leading to the potential accumulation of harmful toxins and subsequent manifestation of hepatic conditions such as steatosis, fibrosis, and cirrhosis. Herbs as part of culinary and traditional uses have demonstrated therapeutic effects against such conditions. Predominant among the dietary constituents are polyphenols and terpenoids, which are known for their liver-protective efficacies. Evident from their antioxidant and anti-inflammatory properties and modulation of antioxidant enzymes this class of phytochemicals regulates pivotal liver biomarkers. *Ocimum* species, notably Tulsi, are recognized for their abundant repertoire of terpenoids and polyphenols. From time immemorial, owing to its diverse biological properties, the *Ocimum* species has made its way into our culinary habits and traditions. Clinical findings have indicated the beneficial effects of

Ocimum sanctum on the biochemical parameters of the liver in young overweight/obese subjects. However, despite several pre-clinical, and clinical studies elucidating the hepatoprotective potential of *Ocimum* species, a comprehensive understanding of the molecular mechanism underlying the actions of phenolic and terpenoid phytoconstituents is lacking till date. Consequently, targeted molecular therapies involving *Ocimum* species are yet to be developed. Thus, this mechanistic review was aimed at elucidating the intricate molecular pathways through which polyphenols and terpenoids derived from *Ocimum* species exert their hepatoprotective effects. By correlating these molecular mechanisms, insights into the hepatoprotective abilities of polyphenols and terpenoids found in *Ocimum* species were provided, which may pave the way for potential targeted therapeutic interventions.

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Graphical abstract



Keywords Hepatoprotective · *Ocimum* · Polyphenols · Terpenoids · Cellular targets

Introduction

The liver, being the largest glandular organ, assumes a pivotal role in biotransformation, as well as the synthesis and storage of carbohydrates, lipids, alcohol, and toxins, while concurrently executing the detoxification of xenobiotics and toxic by-products (Saha et al. 2019). Despite its protective mechanisms, the liver remains continuously exposed to harmful substances and bio-transformed toxic products, many of which accrue within its confines, thereby instigating pathological manifestations such as hepatic steatosis, fibrosis, and cirrhosis (Fig. 1). Hepatic pathology contributes to over two million fatalities annually, constituting 4% of global mortality, with a notable prevalence among females (Devarbhavi et al. 2023). Alcohol consumption escalates the hazard of hepatopathy-associated death by a staggering factor of 260. Excessive alcohol consumption leads to liver damage, including fatty liver, alcoholic hepatitis, and cirrhosis (Lieber 2020). The worldwide frequency of

alcohol-induced hepatitis has surged in recent times, particularly among adolescents and females, concomitant with a heightened susceptibility to alcohol-induced hepatic cirrhosis. Hepatic cirrhosis precipitates a 5- to tenfold elevation in mortality risk, primarily attributable to complications such as ascites, variceal hemorrhage, hepatic encephalopathy, renal impairment, and infections, alongside instances of acute-on-chronic hepatic failure (Wu et al. 2024). Sametime, non-alcoholic fatty liver disease (NAFLD) afflicts 32.4% of the global populace, affecting one-fourth of adults worldwide, and ranks as the second principal etiology of end-stage hepatic afflictions and transplantation surgeries across Europe and the Americas (Le et al. 2024). Notably, 75% of hepatocellular carcinomas manifest in Asia, are primarily linked to hepatitis B virus (HBV) and hepatitis C virus (HCV) infections. HBV constitutes a predominant catalyst for hepatic mortality across numerous nations, with China, India, and Nigeria bearing the brunt of HBV-associated hepatic morbidity (Balakrishnan and Rehm 2024).

The liver plays a vital role in alcohol detoxification, especially in processing ethanol. Ethanol, the primary psychoactive component in alcoholic beverages, is metabolized in the liver by alcohol dehydrogenase

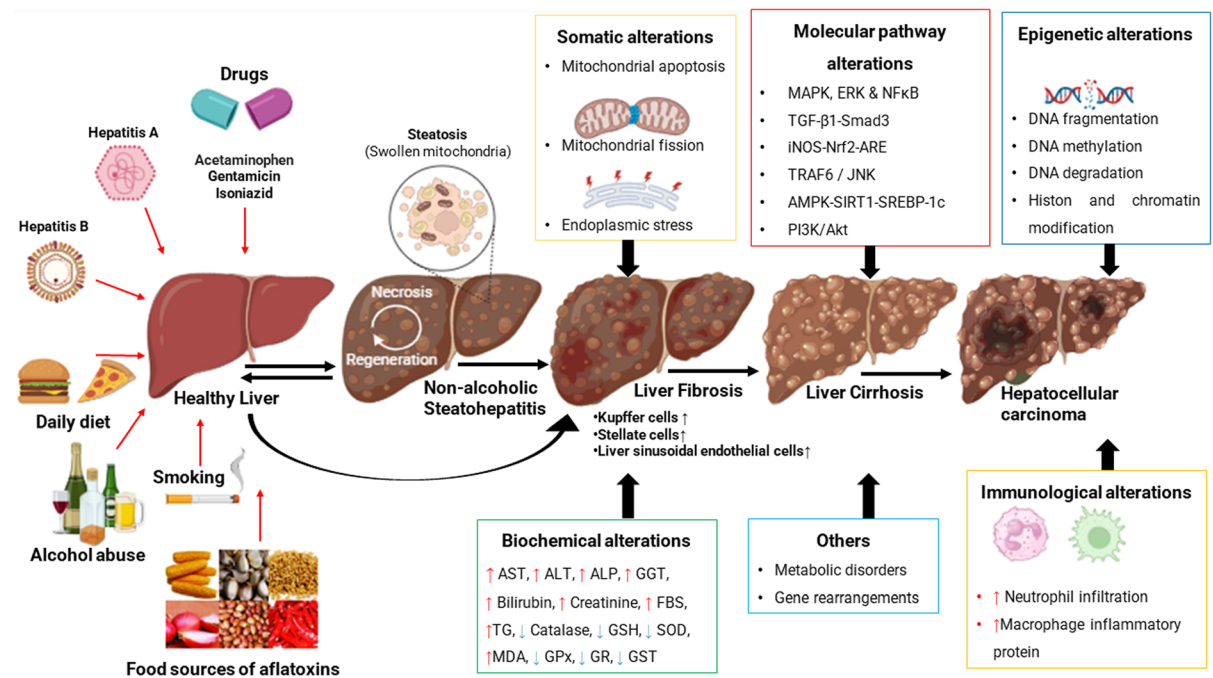


Fig. 1 Etiology of hepatotoxicity (Meżyńska et al. 2019). Persistent chronic exposure to hepatic insults caused by environmental factors (such as viral hepatitis, alcohol abuse, non-alcoholic steatohepatitis (NASH), exposure to toxins, and drug metabolites) repeatedly damages hepatocytes and induces inflammation, ultimately leading to liver cirrhosis. At this stage,

the liver is prone to genomic instability. Consequently, hepatocytes are more likely to accumulate somatic changes, epigenetic modifications, and gene rearrangements, resulting in metabolic changes and alterations in molecular pathways. These dysregulations drive tumor progression and metastasis. ↓ Decrease, ↑ Increase

(ADH) and other enzymes [cytochrome P450 2E1 (CYP2E1) and catalase] into acetaldehyde, which is further metabolized into acetate by aldehyde dehydrogenase (ALDH). Acetate is further broken down into water and carbon dioxide facilitating the elimination from the body. Alike alcohol liver also processes toxicants like acetaminophen and aflatoxins. Acetaminophen, a common over-the-counter antipyretic and pain reliever, causes liver damage primarily through the production of a toxic metabolite, N-acetyl-p-benzoquinone imine (NAPQI). The liver normally detoxifies NAPQI by conjugating it with glutathione. However, in overdose situations, stored glutathione can become depleted, leading to liver injury (McGill and Jaeschke 2020; Ramachandran and Jaeschke 2021). Aflatoxins are toxic metabolites produced by certain fungi, such as *Aspergillus flavus* and *Aspergillus parasiticus*, which commonly contaminate food crops like peanuts, corn, and cereals. Continuous exposure to this toxin can cause liver damage and increase the risk of liver cancer. The liver metabolizes aflatoxins through a process involving

cytochrome P450 enzymes, leading to the formation of reactive intermediates that can bind to DNA and proteins, causing cellular damage (Guengerich et al. 1996).

All these factors primarily function as prooxidants, instigating the generation of reactive oxygen species (ROS) or reactive nitrogen species (RNS), consequently inducing oxidative stress. In the context of chronic alcohol intoxication, the hydroxyethyl radical ($\text{CH}_3\text{C}\cdot\text{HOH}$), in conjunction with ROS, has the potential to initiate oxidative liver damage (Unsal et al. 2021). Cytochrome P450 isozymes significantly elevate endogenous production of $\text{CH}_3\text{C}\cdot\text{HOH}$ in the endoplasmic reticulum. Free radicals can initiate cellular damage through diverse mechanisms, including lipid peroxidation (LPO), covalent binding, depletion of glutathione and protein thiols, disruption of intracellular free calcium homeostasis, and DNA fragmentation (Poli, 1993). LPO has emerged as a pivotal mechanism instigating irreversible hepatocyte damage and eliciting fibrotic responses induced by haloalkanes (Recknagel et al. 2020).

Dietary interventions have emerged as efficacious antioxidant strategies for mitigating and neutralizing the detrimental effects of ROS/RNS. A diet enriched in natural antioxidants (polyphenols, carotenoids, lignans, etc.) augments endogenous antioxidant enzyme defense including superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GR), and catalase, or the fortification of non-enzymatic defenses, such as glutathione and vitamins. Antioxidants exhibit the capability to delay, inhibit, or prevent oxidation by scavenging free radicals and attenuating oxidative stress. However, in pathological conditions, the defense against ROS is compromised or impaired, leading to an increased oxidant load. Under such circumstances, an external supply of antioxidants becomes imperative to counteract the deleterious consequences of oxidative stress (Vladimir-Knežević et al. 2012).

While synthetic hepatoprotective drugs demonstrate adeptness in scavenging free radicals, their prolonged usage can induce toxicity, resulting in inflammation and carcinogenicity. Consequently, herbal therapeutic approaches are consistently regarded as alternatives, capable of targeting diseases with minimal side effects. The current utilization of plants to derive “lead molecules” in drug development underscores their potential as natural bioactive compounds or structural analogs, holding promise as drug candidates for hepatoprotection (Saha et al. 2019).

Natural phenolics and terpenoids represent prevalent components in plant-based diets globally. Polyphenols, renowned as leading antioxidants, exhibit mechanisms for scavenging free radicals, breaking free radical chain reactions, suppressing free radical formation by enzyme activity regulation, and chelating metal ions involved in free radical production (Vladimir-Knežević et al. 2012; Simón et al. 2020). Many of these activities are effective in mitigating oxidative liver damage. Similarly, terpenoids, naturally occurring hydrocarbon compounds, and their oxygenated derivatives like alcohols, aldehydes, and ketones (Gutiérrez-del-Río et al. 2021), showcase hydrogen-donating or radical-scavenging activities. Monoterpenes and diterpenes, along with their effectiveness in inhibiting LPO, protect the liver by binding

with ions of toxic metals (Simón et al. 2020). In some instances, this can be attributed to their phenolic content, including carnosol, carnosic acid, carvacrol, or thymol (Graßmann, 2005). Thus, a diet rich in both polyphenols and terpenoids stands as an alternative to hepatoprotective drugs.

The genus *Ocimum*, or Tulsi, holds a sacred status in Hindu belief. It has secured its place in ancient Ayurvedic medical literature due to its myriad therapeutic values. Various species within the *Ocimum* genus possess medicinal properties, including hypoglycemic, antibacterial, antimicrobial, antifungal, cardiac, and hepatoprotective effects, pain management, and alleviation of depression and general stress. Traditionally, Tulsi is consumed in various forms such as herbal tea, dried powder, or fresh leaves for treating common colds, headaches, stomach disorders, inflammation, and various forms of poisoning (Zahran et al. 2020). Due to their diverse properties various marketed herbal formulations of Tulsi are available, such as Tulsi Hill capsules, Tulsi Ghanwati tablets, Tulasi Respiratory Wellness Tablets (Himalaya, Himalaya Wellness Company, Makali, Bangalore—562,162, Karnataka, India), Baidyanath Tulsi Tablets (Pandey et al. 2015).

Among the 150 species of the *Ocimum* genus, Krishna Tulsi or purple Basil (*O. tenuiflorum*), Green Tulsi or Rama Tulsi (*O. sanctum*), African Basil or clove Basil (*O. gratissimum*), Sweet Basil (*O. basilicum*), Damakese (*O. lamifolium*), Rosary Tulsi (*O. canum*), and Hoary basil or (*O. americanum*) are the most prevalent. While these species are distributed widely across temperate zones globally, a majority is concentrated in Africa, cultivated throughout the Indian subcontinent, and Southeast Asia for their nutraceutical values and essential oil content (Pandey et al. 2014; Zahran et al. 2020; Gurav et al. 2022).

The *Ocimum* genus is recognized for its abundance of polyphenols (Apigenin, Quercetin, Rutin, Rosmarinic acid, Ferulic acid) and terpenoids (α -copaene, β -elemene, β -caryophyllene, α -humulene, and germacrene D). Various *Ocimum* species have undergone investigation for their hepatoprotective potential in diverse in vivo models of hepatotoxicity. Nevertheless, the precise molecular mechanisms underlying hepatoprotection attributed to the phenolic or

terpenoid metabolites remain undefined thus far. Similarly, there exists a knowledge gap concerning the mechanistic insights into various other therapeutic compounds present in *Ocimum*. Consequently, this review aims to establish a correlation between the polyphenolic and terpenoid compounds within *Ocimum* species and their respective molecular mechanistic pathways involved in the prevention of hepatotoxicity.

Review strategy

To assess the real scenarios of polyphenolics and terpenoids from *Ocimum* for the treatment of different liver illnesses, a literature search was conducted for papers published till December 2023, without any restriction of time, using online databases including Science Direct, Springer, Wiley online library, Pubmed, Google Scholar, Web of Science and Scopus. Following search terms were used either alone or in combination: medicinal plants, herbal medicine, *Ocimum* species, hepatotoxicity, hepatoprotective, phytochemicals present in *Ocimum* species, polyphenols present in *Ocimum* species, terpenoids present in *Ocimum* species, polyphenols as antioxidant, polyphenols in hepatotoxicity, terpenoids in oxidative stress, terpenoids in hepatoprotection, *Ocimum* species hepatoprotection study. The accurate scientific designation of the plant was determined by consulting The Plant List database (theplantlist.org). Utilizing ChemDraw Professional v.17.1 software, the chemical structures of naturally transpiring metabolites previously recognized in *Ocimum spp.* were delineated.

The papers that were excluded were those written in any language other than English, conference proceedings, research involving non-phenolics and non-terpenoids from *Ocimum*, and articles without information on liver toxicity. Counting of research publications whose complete text or abstract is unavailable was avoided, well-illustrated, cited as well as recent full-text articles were chosen after careful consideration. The chosen studies were acquired, and pertinent papers were picked for full-text analysis. Following such a specific search, polyphenols and terpenoid compounds present in *Ocimum* have been reported from 40 reports, 40 pre-clinical and 2 clinical studies with *Ocimum* imparting hepatoprotective potential, over 86 recent studies of phenolic and terpenoid

compounds present in *Ocimum* that can treat hepatic disorders were brought to light.

Natural molecules from *Ocimum*

Phenolic compounds and terpenoids are prominent classes of compounds abundantly found in *Ocimum* species (Pandey et al. 2016). Plant phenolics encompass simple phenols, phenolic acids, and flavonoids. Phenolic acids, deriving primarily from benzoic acid, cinnamic acid, and phenylacetic acid, exhibit a pharmacophore in the form of a methyl ester within the phenol ring, facilitating interaction with various protein targets in cell membranes. Bioactive flavonoids such as apigenin, luteolin, baicalin, quercetin, rutin, and kaempferol have been identified in *Ocimum* species (Table 1). Flavonoids, synthesized from cinnamic acid, exhibit a structural diversity that can undergo modifications such as skeleton dimerizations, oligomerizations, prenylations, glycosidations, and conjugation with other ring systems. *O. tenuiflorum*, or Krishna Tulsi, serves as a rich source of plant pigments, including seasonally varying quantities of anthocyanins and anthocyanidins, with peonidin, cyanidin, and delphinidin derivatives being common.

Terpenoids, distinguished by their diverse chemical structures, are categorized based on the number of isoprene units, encompassing monoterpenes, sesquiterpenes, diterpenes, sesterterpenes, triterpenes, tetraterpenes, and polyterpenes (Fox et al. 2011). *Ocimum* species contain various monoterpenes, such as camphor, pinene, thymol, eucalyptol, geraniol, and limonene. Additionally, hepatoprotective terpenoid compounds present in *Ocimum* species include linalool, borneol, ursolic acid, β -elemene, germacrene D, β -caryophyllene, epimaslinic acid, α -copaene, oleanolic acid, and humulene (Table 1; Fig. 2). The copious presence of phenolic compounds and terpenoids in *Ocimum sp.* imparts hepatoprotective effects (Table 2).

Hepatoprotective properties of *Ocimum* species

Hepatic steatosis, fibrosis, and cirrhosis constitute sequential manifestations of liver impairment induced by exposure to alcohol, pharmaceuticals, and environmental pollutants. These exposures lead to hepatocellular necrosis and heightened levels of various

Table 1 continued

Name of Species	Geographical sources	Polyphenols		Phenolic acids	Other Polyphenols	Medical Significance	References
		Flavonoids	Flavonols				
<i>O. sanctum</i>	South-east Asia, Australia, West Africa, and some Arab Countries	<p>Quercetin, kaempferol, rutinoidse, kaempferol-3-O-rutinoside, quercetin-3-O-glucoside, quercetin-3-O-malonylglycoside, Quercetin-3-O-xylosyl (1'' → 2'') Galactoside</p> <p>Flavones - Apigenin, Apigenin-7-O-glucuronide, Luteolin, Galuteolin, Orientin, Vicenin 2, Luteolin-7-O-glucuronide, Isorientin, Vitexin, Isovitexin, Cirsimaritin, gardenin, salvigenin, crisilineol, eupatorin, isothymunin, xanthomicrol, Cosmosiin, Molludislin, Genkwanin, Hymenoxin, Demethylinobiletin, apigenin-7-O-rutinoside, luteolin-7-O-glucoside, Eupalitin, apigenin-7, 4'-dimethyl ether, nevadensin, acacetin, Luteolin-7-O-β-D-glucopyranoside, Cirsiliol, Eupatorin, 3'-Methoxy eupatorin, 4',5-Dihydroxy-3',7,8-Trimethoxy-flavone, Chrysoeriol</p>	<p>Flavonols - Quercetin, kaempferol, rutinoidse, kaempferol-3-O-rutinoside, quercetin-3-O-glucoside, quercetin-3-O-malonylglycoside, Quercetin-3-O-xylosyl (1'' → 2'') Galactoside</p>	<p>Hydroxybenzoic acids - 4-hydroxybenzoic acid, Gallic acid, gallic acid methyl ester, gallic acid ethyl ester, Vanillic acid, Protocatechuic acid, syringic acid</p> <p>Hydroxy-phenylacetic acids- 3,4-Dihydroxyphenylacetic acid</p> <p>Hydroxy-cinnamic acids and esters- Rosmarinic acid, Rabdosin, Caffeic acid, Nepetoidin, chlorogenic acid, sinapic acid, p-coumaric acid, ferulic acid, vanillic acid, Ethyl caffeate</p>	<p>Hydroxy-cinnamaldehides -Ferulaldehide, Coniferaldehide</p> <p>Hydroxy-coumarins— Ocimarin, Aesculin, Aesculetin</p> <p>Hydroxy-benzaldehide- 4-Hydroxybenzaldehyde, vanillin</p> <p>Phenolic terpenes- Camosic acid, carvacrol</p> <p>Alky/phenols- 1, 2, 4- tri-vinyl Cyclohexane</p> <p>Hydroxy phenylpropenes- Eugenol, methyl eugenol, Estragole</p> <p>Neolignans- Tulsinols A-G</p>	<ul style="list-style-type: none"> • Expectorant • Analgesic • Anticancer • Antiasthmatic • Antiemetic • Diaphoretic • Antidiabetic • Antifertility • Hepatoprotective • Hypotensive • Hypolipidmic • Antistress • Anti-arthritis • Antiepileptic 	<p>Zahran et al. (2020) Verma, (2016), Anandjiwala et al. (2006); Gupta et al. (2007), Chaudhary et al. (2020) Singh and Chaudhuri, (2018) Venuprassad et al. (2017) Hussain et al. (2017) Pandey and Kumar, (2016) Borah and Biswas, (2018) Chaudhary et al. (2020)</p>

Table 1 continued

Name of Species	Geographical sources	Polyphenols		References
		Flavonoids	Other Polyphenols	
<i>O. gratissimum</i>	Africa, Madagascar, southern Asia, Mexico, Panama, the West Indies, Brazil, and Bolivia	Flavones – Isoorientin, orientin, isovitexin, vitexin, luteolin, isothymusin, apigenin, cirsiolol, cirsimaritin, cirsilineol, nevaadensin, acacetin, 5-desmethylinsetin, salvigenin, apigenin-7-O-rutinoside, luteolin-7-O-glucuronide, luteolin-7-O-glucoside, apigenin-7-O-glucoside, apigenin-7-O-glucuronide, gardenin B, apigenin-7, 4'-dimethyl ether	Hydroxy-cinnamic acids and esters- Rosmarinic acid, coniferyl aldehyde, caffeic acid, chlorogenic acid, Vanillic acid, p-Coumaric acid, Hydroxy benzoic acid, Caffeic acid, Ferulic acid, Cinnamic acid, Dihydroxy phenyllactic acid, Sinapic acid, Ethyl caffeate	Venuprasad et al. (2014), Ugbogu et al. (2021), Lisboa et al. (2020), Mohr et al. (2017), Zahran et al. (2020) Lima et al. (2018) Hakkim et al. (2008), Pandey and Kumar. (2016)
		Flavonols- Quercetin, kaempferide, kaempferol, quercetin-3-O-rutinoside, kaempferol-3-O-rutinoside, quercetin-3-O-glucoside, quercetin-3-O-malonylglucoside	Hydroxy-benzoic acids- Gallic acid, methyl gallate, protocatechuic acid, syringic acid, p-hydroxybenzoic acid, Lithospermic acid	
<i>O. basilicum</i>	Tropics of Asia and Africa	Flavonols - Dihydrokaempferol-3-O-glucoside, quercetin-, kaempferol, quercetin-3-O-rutinoside, kaempferol-3-O-rutinoside, quercetin-3-O-glucoside, quercetin-3-O-malonylglucoside, Isoquercetin, Quercetin-3-O-2'-galate	Hydroxy-cinnamic acids esters- Caffeic acid, caffeoyl ester, p-Coumaric acid, chlorogenic acid, ferulic acid, caffeoyl -3-O-rutinoside, p-coumaryl acid, Ethyl caffeate, chlorogenic acid, sinapic acid, Rosmarinic acid	Strazzer et al. (2011), McCance et al. (2016), Zahran et al. (2020), Tawallali et al. (2020), Hajdari et al. (2020) Pandey and Kumar, (2016) Stanojevic et al. (2017)
Flavanols – Catechin	Hydroxybenzoic acids and esters- Gentisic acid, ethyl protocatechuate, methyl protocatechuate, gallic acid, protocatechuic acid, syringic acid, p-hydroxybenzoic acid, methyl gallate, vanillic acid	Phenolic terpenes- carnosic acid, Methyl chavicol, Carvacrol, Thymol	<ul style="list-style-type: none"> • Anti-cancer activity • Radioprotective activity • Anti-microbial activity • Anti-inflammatory activity • Immunomodulatory activity • Anti-stress • Anti-Diabetic • Anti-Pyretic • Anti-Arthritic • Anti-Oxidant • Cardiovascular disease 	
Flavone	Flavanones- Naringenin, eriodictyol hexoside, tetrahydroxy flavanone		Phenolic terpenes- carnosic acid, Methyl chavicol, Carvacrol, Thymol	Strazzer et al. (2011), McCance et al. (2016), Zahran et al. (2020), Tawallali et al. (2020), Hajdari et al. (2020) Pandey and Kumar, (2016) Stanojevic et al. (2017)
			Alkylphenols- Catechol derivatives	
			Hydroxy phenylpropenes- Eugenol, Methyl eugenol, methoxy eugenol	Strazzer et al. (2011), McCance et al. (2016), Zahran et al. (2020), Tawallali et al. (2020), Hajdari et al. (2020) Pandey and Kumar, (2016) Stanojevic et al. (2017)
			Hydroxy cinnamaldehydes –Coniferaldehyde	
			Lignans	Strazzer et al. (2011), McCance et al. (2016), Zahran et al. (2020), Tawallali et al. (2020), Hajdari et al. (2020) Pandey and Kumar, (2016) Stanojevic et al. (2017)
			(-) rabdosiin, Shimobashiric acid A	
			Hydroxycoumarins	Strazzer et al. (2011), McCance et al. (2016), Zahran et al. (2020), Tawallali et al. (2020), Hajdari et al. (2020) Pandey and Kumar, (2016) Stanojevic et al. (2017)
			Ocimarin, Aesculin, Aesculetin, Coumarin	

Table 1 continued

Name of Species	Geographical sources	Polyphenols		Phenolic acids	Other Polyphenols	Medicinal Significance	References
		Flavonoids	Flavones				
<i>O. americanum</i>	Tropical Africa, Indian Subcontinent, China, Southeast Asia, tropical America	<p>Flavones- Jacosidin, Nevadensin, Salvigenin, Cirsiliinol, Genkwanin, Xantho microl, Vicianin 2, isoorientin, orientin, Isovitexin, vitexin, luteolin, isothymusin, apigenin, Cirsiliol, Cirsimaritin, acacetin, 5-desmethylisnensetin, gardenin B, apigenin-7, 4'-dimethyl ether, luteolin-7-O-glucuronide, apigenin-7-O-glucoside, apigenin-7-O- glucuronide, 5-Desmethyl-nobiletin</p> <p>Flavonols- Quercetin, kaempferide, kaempferol, quercetin-3-O-rutinoside, kaempferol-3-O-rutinoside, quercetin-3-O-glucoside, quercetin-3-O-malonylg lucoside</p>	<p>Hydroxybenzoic acids and esters- Gallic acid, methyl gallate, protocatechuic acid, syringic acid, p-hydroxybenzoic acid, methyl protocatechuate, methyl protocatechuate, Lithospermic acid, Vanillic acid Hydroxy-cinnamic acids and esters- Rosmarinic acid, p-Coumaric acid, Caffeic acid, Ethyl Caffeate, Ferulic acid, Cinnamic acid, Sinapic acid, chlorogenic acid</p>	<p>Hydroxy- phenylpropenes- Eugenol, Iso eugenol, methyl eugenol, methoxy eugenol, methyl chavicol Hydroxy cinnamaldehydes - conifer aldehyde</p>	<ul style="list-style-type: none"> • Antifungal activity • Anti-microbial activity • Anti-oxidant activity • Analgesic and Anti-inflammatory activity • Immunomodulatory activity • Hepatoprotective activity 	<p>Sutlii et al. (2016), Bhatt et al. (2018), Silva et al. (2018), Zahran et al. (2020), Hakkim et al. (2008), Pandey and Kumar, (2016)</p>	
<i>O. canum</i>	Tropical and West Africa, Indian Subcontinent, China, Southeast Asia, tropical America, Brazil	<p>Flavones- Nevadensin, Pflotin, Salvigenin, Genkwanin, Scutellarein, Hspidulin</p>	<p>Hydroxy- phenylpropenes- eugenol, Methyl eugenol Phenolic terpenes- Carvaerol, methyl thymol, Thymol</p>	<ul style="list-style-type: none"> • Anthelmintic Activity • Antisickling Activity • Antimicrobial Activity • Antifungal Activity • Antulcer • Antioxidant • Wound Healing Effects • Anthypertensive effects • Hepatoprotective activity 	<p>Mith et al. (2016), Silva et al. (2018), Usman et al. (2017), Adjou et al. (2019), Zahran et al. (2020)</p>		

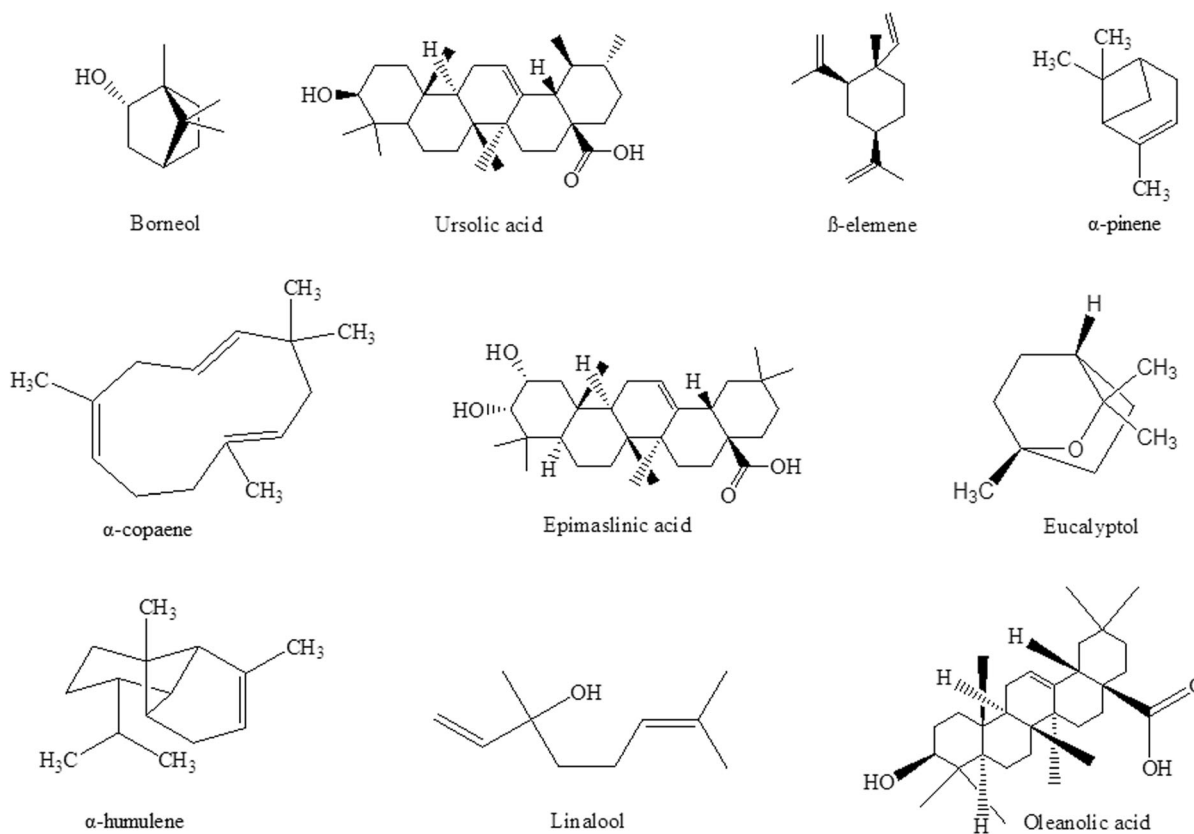


Fig. 2 Structure of some hepatoprotective terpenoid compounds present in *Ocimum* species

liver biomarkers and metabolites, indicative of pathological deviations (Leathers et al. 2019). Alcohol-induced impairment manifests in alterations to mitochondrial morphology and functionality, along with disruption of the antioxidant defense system. Concurrently, a conjugation process unfolds, resulting in escalated Caspase levels and diminished adenosine triphosphate (ATP) levels. These clinical manifestations precipitate hepatotoxicity and apoptosis accumulation (Madrigal-Santillán et al. 2015). When hepatocytes undergo injury, transaminases and glutathione enzymes emerge as primary indicators of bile metabolism. The quantification of alkaline phosphatase, alanine transaminase, and aspartate transaminase, pivotal hepatic enzymes in the serum, serves as a means to discern the clinical status of the hepatic milieu (Teofilović et al. 2021). Numerous studies involving *Ocimum* sp. have demonstrated the protection of the liver cells and their functions against hepatotoxic agents like drugs, chemicals, viral toxins, and apoptotic changes (Table 3).

In vitro and in vivo studies against drug-induced liver injury

Pre-treatment with Tulsi extracts proved instrumental in preserving hepatic antioxidant defenses, as evidenced by the downregulation of malondialdehyde levels and upregulation of catalase, glutathione S-transferase (GST), glutathione reductase (GR), glutathione peroxidase (GPx) levels (Table 3). Genfi et al. (2020) proposed that leaf and stem extracts of *O. americanum* 250 mg/kg BW administered orally in rats for 7 days, conferred substantial protection to the liver against acetaminophen-induced damage. An increased production of glutathione (GSH) and superoxide dismutase (SOD), inhibiting malondialdehyde (MDA) production, and downregulating the expression of nuclear factor-kappa B (NF- κ B) and interleukin-1 (IL-1).

During hepatic injury, the formation of fibrous tissues attempts to repair the damage, impeding crucial functions of the liver such as drug detoxification, protein secretion, and albumin formation.

Table 2 List of terpenoids present in the various *Ocimum* species

Name of species	Terpenoids	Medicinal significance	Reference
<i>O. tenuiflorum</i>	β -caryophyllene, β -elemene, Germacrene D, borneol, n-butyl benzoate, caryophyllene oxide, cis- α -terpineol, cubenol, limonene, linalool, oleic acid, phytol, α -pinene, β -pinene, α -thujene, ursolic acid, methyl isovalerate, ethyl isovalerate, tricyclene, camphene, Myrcene, Phellandrene, Eucalyptol, Ocimene, Sabinene hydrate, Terpinolene, Carene, Fenchone, Camphor, Isoboreneol, Terpineol, Bourbonene, Elemene, Guaiene, Bergamotene, Sesquiphellandrene, Farnesene, Sesquisabinene, Humulene, Longipinene, Bisabolene-z, Muurolene, β bisabolene, Cadinene, α bisabolene, Cubebene, Amorphene, oleanolic acid	<ul style="list-style-type: none"> • Hypoglycemic and anti-hyperglycemic activity • Hepatoprotective activity • Fibroblast and keratinocyte gene expression activity • Analgesic activity • Anticancer activity • Anticataract activity • Wound healing effect • Anti-oxidant activity • Anti-microbial activity 	Yamani et al. (2016), Upadhyay et al. (2015)
<i>O. sanctum</i>	Ursolic acid, oleanolic acid, Betulinic acid, stigmasterol, α -pinene, camphene, Sabinene, β -pinene, Limonene, 1,8-cineol, cis-sabinenehydrate, Linalool, Camphor, Borneol, α -terpinenol, D-carvone, Anethole γ -elenene, β -elemene, α -gurjunene, β -caryophyllene, β -cubebene, β -gurjunene, Alloaromadendrene, Germacrene D, β -selinene, α -selinene, β -bisabolene, δ -cadinene, 1–4, cadinadiene, α -calacorene, Nerolidol, Spathulenol, Caryophyllene oxide, α -cadinol, Aromadendrene oxide, α -humulene, Farnesol, Elemol, α -copaene, Hedycaryol, Palmitic acid, α – Farnesene	<ul style="list-style-type: none"> • Anticancer • Antioxidant • Hepatoprotective activity • Anti-Inflammatory • Leishmanicidal • Radiation Protective • Mosquitocidal • Antimicrobial • Antistress 	Zahran et al. (2020), Verma., (2016), Anandjiwala et al. (2006), Singh and Chaudhuri, (2018), Hussain et al. (2017), Borah and Biswas, (2018)
<i>O. gratissimum</i>	Linalool, Camphor, Fenchone, Limonene, 1,8-Cineole, (Z)- β -ocimene, E-caryophyllene, γ -murolene, (E)- β -ocimene, α -Thujene, Camphene, α -Pinene, Sabinene, β -Pinene, Myrcene, α -Phellandrene, α -Terpinene, p-Cymene, γ -Terpinene, Terpinolene, p-Mentha-1,3,8-triene, Borneol, Terpinen-4-ol, p-Cymen-8-ol, α -Terpineol, β -Elemene, (E)-Caryophyllene, α -Humulene, Germacrene D, β -Selinene, Viridiflorene, β -Curcumene, Spathulenol, α -Cadinol, oleanolic and ursolic acid	<ul style="list-style-type: none"> • Antibacterial activity • Antioxidant activity • Antifungal activity • Anti-malarial activity • Anti-helminthic activity • Anti-leishmanial activity • Anti-hepatic fibrosis • Apoptotic activity in human osteosarcoma cells • Cerebroprotective effect • Antidiarrhoeal activity • Anti-trypanosomal activity 	Venuprasad et al. (2014), Lisboa et al. (2020), Mohr et al. (2017), Zahran et al. (2020), Lima et al. (2018)

Table 2 continued

Name of species	Terpenoids	Medicinal significance	Reference
<i>O. basilicum</i>	Betulinic acid, 3-epimaslinic acid, Alphitolic acid, Euscaphic acid, 1,8-cineole, β -ocimene, Linalool, β -elemene, β -caryophyllene, α -Pinene, β -Pinene, Myrcene, cubenol, α -humulene, Germacrene-D, γ -cadinene, α -amorphene, β -cubebene, octyl acetate, nerol, neral, cis-isocitral, geraniol, trans-isocitral, neryl acetate, α -farnesene, cis- α -bisabolene, Borneol, p-Cymene, oleanolic acid, ursolic acid, α -Bisabolol, β -Bisabolol, Bulnesol, Trans cadinol, β -Eudesmol, Farnesol, Nerolidol, Ledol, Spathulenol, Calamenene, Betulin	<ul style="list-style-type: none"> • Antioxidant and Antimicrobial activity • Insecticidal activity • Hepatoprotective activity • Antifungal activity • Anti-convulsant and Hypnotic activity • Anti-convulsant 	Strazzer et al. (2011), McCance et al. (2016), Zahran et al. (2020), Tavallali et al. (2020), Hajdari et al. (2020) Stanojevic et al. (2017)
<i>O. americanum</i>	γ -terpinene, linalool, γ -cadinene, Copaene, Germancrene D, Trans- α -Bergamotene, α -caryophyllene, β -caryophyllene, α -phellandrene, α -pinene, sabinene, α -Thujene, myrcene, α -terpinene, limonene, terpinen-4-ol, β - selinene, α - selinene, caryophyllene oxide, Eucalyptol, cis- β -ocimene, Camphor, farnesene, oleanolic and ursolic acid	<ul style="list-style-type: none"> • Hemolytic activity • Antifungal activity • Bactericidal activity • Anti-microbial activity • Anti-oxidant activity • Analgesic and Anti-inflammatory activity • Immunomodulatory activity • Anesthetic activity • Hepatoprotective activity 	Sutli et al. (2016), Bhatt et al. (2018), Silva et al. (2018), Zahran et al. (2020)
<i>O. canum</i>	γ -terpinene, linalool, γ -cadinene, caryophyllene oxide, Copaene, Trans- α -Bergamotene, α -Caryophyllene, β -Caryophyllene, α -phellandrene, α -pinene, sabinene, α -Thujene, myrcene, Germacrene-D, α -Farnesene, Thujone, oleanolic acid, α -terpinene, limonene, terpinen-4-ol, β - selinene, α - selinene, β -phellandrene, Eucalyptol, cis- β -ocimene, m-cymenene, α -terpinolene, Octylacetate	<ul style="list-style-type: none"> • Antimicrobial Activity • Antifungal Activity • Antiulcer • Insecticidal and Larvicidal Activity • Wound Healing Effects • Hepatoprotective activity 	Mith et al. (2016), Silva et al. (2018), Usman et al. (2017), Adjou et al. (2019) Zahran et al. (2020)

Notably, the substantial bile acid production during ethanol oxidation induces cholestatic syndrome by activating Fas, an apoptotic element, and its expression on the plasma membrane. Consequently, total protein, bilirubin, albumin, urea, and creatinine levels serve as pivotal markers for assessing liver function (Cederbaum 2017). The majority of studies investigating the hepatoprotective effects of Tulsi extract against drug-induced liver injury have reported an

elevation in total protein and albumin levels, coupled with a reduction in bilirubin, urea, and creatinine levels (Table 3). Teofilović et al. investigated the hepatoprotective potential of *Ocimum basilicum* (sweet basil) extract administered orally at a dose of 200 mg/kg for seven days in a model of acetaminophen-induced hepatotoxicity. The hepatoprotective effects were evidenced by an increase in the activity of antioxidant enzymes (catalase, GST, GR, and GPx),

Table 3 List of some preclinical studies with *Ocimum* species imparting hepatoprotective activity

Plant Species	Extract and plant part	Effective dose & route of administration	Duration	Preclinical Model (in vitro or in vivo)	Findings/ Outcomes in the treated groups	Reference
A. Hepatoprotective activity against drug-induced liver injury						
<i>O. basilicum</i>	Decoction of whole plant part	200 mg/kg BW, orally	7 days	Acetaminophen-induced hepatotoxicity in male Wistar rats	↓AST, ↓ALT, ↓ALP, ↓direct bilirubin, ↑GST, ↑GSH, ↑CAT, ↑GPx, ↑GR, ↓LPO In Liver tissue histopathology, the treated group had a significantly lower degree of parenchymal damage than the disease group	Teofilović et al. (2021)
	Methanol, ethanol, aqueous, and ethyl acetate extracts of the dried leaves and inflorescence	20 and 200 µg/ mL	Pre-incubation of extract + microsomes + co-factors at 37 °C for 30 min. before efavirenz or rifampicin addition	Human liver microsomes and HepG2 cells	Reversible and time dependant inhibition of cytochrome P450 enzymes CYP2B6 and 3A4	Kumar et al. (2020)
<i>O. sanctum</i>	Aqueous extract of leaves	2% w/w and 4% w/w of powdered leaves as diet supplement	30 days	Gentamicin-induced hepatotoxicity in albino rats	↓AST, ↓ALT, ↓ALP, ↓ACP, ↓bilirubin, ↓LPO, ↑SOD, ↑GSH, ↑CAT	Patidar et al. (2019)
<i>O. canum</i>	Aqueous and ethanolic extract of leaves	400 mg/kg of BW, orally	7 days	Acetaminophen-induced acute liver toxicity in male Wistar albino rats	Both in aqueous and ethanolic extract- ↓ALT, ↓ALP, ↑TP, ↑Albumin, ↓TB, ↓DB, ↓JB In ethanolic extract-↑SOD, ↑CAT, ↑GPx Histopathology showed- normal hepatic lobular structure restoration	Enemali & Udedi, (2018)
<i>O. gratissimum</i>	Aqueous and methanolic extract of leaves n-hexane, ethyl acetate, ethanol and water fraction of dried leaves	100, 200, and 400 mg/kg BW orally 400 mg/kg BW, orally	28 days 28 days	Gentamicin-induced liver injury in adult male Wistar rats Paracetamol-induced hepatotoxicity in Wistar albino rats	↓AST, ↓ALT, ↓ALP, ↓TB, ↑GSH, ↑SOD, ↑CAT, ↓MDA, ↓TP In all fractions ↓AST, ↓ALT, ↓ALP, ↓TB, ↓DB In aqueous and hexane fraction ↑TP Histopathology showed that- extract minimized congestion, mononuclear infiltration, and cytoplasmic vacuolation of the hepatocytes caused by Paracetamol intoxication	Ogundipe et al. (2021) Chigozie and Monanu, (2016)

Table 3 continued

Plant Species	Extract and plant part	Effective dose & route of administration	Duration	Preclinical Model (in vitro or in vivo)	Findings/ Outcomes in the treated groups	Reference
B. Hepatoprotective activity against chemical-induced liver injury						
<i>O. basilicum</i>	Rosmarinic Acid-Rich Extract of leaves	200 mg/kg BW, orally	7 days	CCl ₄ induced hepatotoxicity in Wistar albino rats	↓AST, ↓ALT, ↓ALP, ↓bilirubin, ↓LDH, ↓MDA, ↓Urea, ↓Creatinine	Touiss et al. (2021)
	Hydro-distilled essential oil obtained from leaves	200 mg/kg BW IP	8 weeks	CCl ₄ induced liver fibrosis in male albino rat	↓AST, ↓ALT, ↑GSH, ↑SOD, ↑CAT, ↓MDA, ↑TAC, ↓Protein expression (HGF mRNA, Cytochrome CYP2E1 mRNA), ↓α-SMA expression Histopathology showed- a reduction in centrilobular necrosis and fatty degeneration of the hepatocytes along with decreased collagen deposition. Pseudo-lobules were formed	Ogaly et al. (2015)
<i>O. sanctum</i>	Alcohol extract from leaves	300 mg/kg BW, orally	30 days	Aspartame-induced hepatotoxicity in Wistar albino rats	↓Weight loss Histopathology showed- hepatocyte cell regeneration from the portal area to the central vein. Restoration of a few granular cells along with a lot of kupffer cells was observed	Suryani and Lubis, (2019)
	Hydro-alcoholic and alcoholic extract (Containing rutin, epicatechin, ellagic acid, kaempferol, quercetin)	100 and 200 mg/kg body weight/day	7 days	Galactosamine (400 mg/kg) i.p. induced in albino rats	↓AST, ↓ALT, ↓ALP, ↓TBARS, ↑SOD, ↑CAT and ↑GSH Histopathology showed- an absence of necrosis and the development of normal hepatic cells in the treated group	Kamel et al. (2023)
	Hydro-alcoholic extract of leaves	Pre-treated with daily administration of 100 and 200 mg/kg BW	40 days	Cadmium-induced liver injury in male Wistar rats	↓TBARS, ↑GSH, ↑SOD, ↑CAT, ↑GPx, and ↑Ascorbate	Ramesh and Satakopan (2010)
<i>O. americanum</i>	Aqueous extract of leaves and stem	250 mg/kg BW, orally for 7 days	20 days	CCl ₄ and acetaminophen-induced hepatotoxicity in albino rats	↓AST, ↓ALT, ↓ALP, ↓bilirubin, ↓γGT, Pro-inflammatory cytokine ↓NF-κβ, ↓IL-1	Genfi et al. (2020)

Table 3 continued

Plant Species	Extract and plant part	Effective dose & route of administration	Duration	Preclinical Model (in vitro or in vivo)	Findings/ Outcomes in the treated groups	Reference
<i>O. canum</i>	70% methanolic extract of the whole plant	80 mg/kg BW and 120 mg/kg BW, orally	30 days	Ethanol-induced oxidative stress in male Wistar rats	↓TBARS, ↑GSH, ↑SOD, ↑CAT, ↑Vit. C, ↑Vit. E, ↓AST, ↓ALT	George and Chaturvedi, (2008)
<i>O. gratissimum</i>	Aqueous extract of leaves	0.2 mg/kg, BW, orally	12 weeks	CCl ₄ -induced hepatic injury in male Wistar rats	↑CAT, ↑DPPH, ↓Protein expressions – (HSP70, iNOS, MMP-9, uPA), ↓Signalling pathways (ERK & NFκB)	Chiu et al. (2012)
	Aqueous extract of leaves	0–40 mg/kg BW, orally	8 weeks	Primary hepatic stellate cell (HSC) culture and CCl ₄ -induced hepatic injury in male Wistar rats	↓AST, ↓ALT, ↑CAT, ↓MDA, ↓α-SMA, ↓Collagen α (I) expression	Chiu et al. (2012)
	Aqueous extract of leaves	200 mg/kg and 400 mg/kg BW, orally	2 weeks	Phenylhydrazine-induced toxicity in rats	↓AST, ↓ALT, ↓ALP	Akara et al. (2021)
	Aqueous extract of leaves	Pre-treated with daily administration of 400 and 800 mg/kg BW	2 weeks	Cadmium-induced liver injury in male Wistar rats	↓AST, ↓ALT, ↓ALP, ↓bilirubin, ↓Urea, ↓Creatinine, ↓TBARS, ↑GSH, ↑SOD, ↑CAT	Ebhohon et al. (2023)
	Polyphenol extract	Daily administration of 12 mg/kg BW	8 weeks	CCl ₄ induced liver fibrosis in male Wistar rats	↓AST, ↓ALT, ↓ALP, ↓TBARS, ↑CAT, ↓α-SMA	Chen et al. (2015)

Table 3 continued

Plant Species	Extract and plant part	Effective dose & route of administration	Duration	Preclinical Model (in vitro or in vivo)	Findings/ Outcomes in the treated groups	Reference
<i>O. sanctum</i> (OS), <i>O. americanum</i> (OA), <i>O. basilicum</i> (OB) and <i>O. gratissimum</i> (OG)	95% ethanolic extract of the whole plant	250, 500, 750 mg/kg BW, orally	7 days	CCl ₄ -induced hepatotoxicity in Wistar rats of either sex	↓AST, ↓ALT, ↓ALP, ↓TB, According to phenolic content- OA > OS > OG > OB Antioxidant activity- Ascorbic acid > OS > OA > OB > OG ALT level and % protection- OS > OA > OB > OG	Green et al. (2013)

↓Decreased and ↑Increased compared with the diseased control group

AST; Aspartate transaminase, ALT; Alanine transaminase, ALP; Alkaline phosphatase, TP; Total protein; TB; Total bilirubin, DB; Direct bilirubin, IB; Indirect bilirubin, CRT; Creatinine, FBS; fasting blood sugar; TG; triglyceride, BW; body weight, IP; Intraperitoneally, DPPH; 2,2-diphenyl-1-picrylhydrazyl, H₂O₂; Hydrogen peroxide, CCl₄; Carbon tetrachloride, CAT; Catalase, GSH; glutathione reductase, SOD; Superoxide Dismutase, LPO; Lipid peroxidation, MDA; Malondialdehyde, TBARS; Thiobarbituric acid reacting substance, GPx; glutathione peroxidase, GR; Glutathione reductase, GST; Glutathione S-transferase, PPO; Polyphenol oxidase, TAA; Total ascorbic acid, γGT; gamma-glutamyl transferase, mPCEs; Micro nucleated polychromatic erythrocyte cells, PCV; Packed cell volume, WBC; White blood cells, RBC; Red blood cells, TAC; Total antioxidant capacity, HGF; hepatocyte growth factor, α-SMA; α-smooth muscle actin

a reduction in lipid peroxidation, and a decrease in serum liver transferase enzyme activities. Additionally, the excretory liver function was preserved in animals pre-treated with the basil extract. Histopathological examination and morphometric analysis of the surface density of hepatic tissue damage corroborated the ameliorative effects of the aqueous basil extract in acetaminophen-induced liver injury as it showed a lower degree of parenchymal damage than the disease group (Teofilović et al. 2021).

ROS, potentiated by pro-inflammatory chemokine activity, are discharged through both neutrophil infiltration and Kupffer cell activation (Suraweera et al. 2015). This circumstance additionally facilitates the activation of hepatocellular stellate cells and triggers pro-fibrogenic pathways. The heightened activity of neutrophils, dormant under normal conditions but increasingly active with elevated cytokine levels, contributes to hepatic necrosis. Chronic inflammation and the concomitant ROS generation lead to hepatotoxicity, ultimately culminating in the development of the lethal condition known as hepatic cirrhosis. Nuclear involvement is evident in this condition, as numerous inflammation-associated transcription factors are upregulated. The combination of ROS and cell membrane adhesion molecules further propels liver fibrosis. Activated Kupffer cells contribute to elevated cytokine levels in circulation by inducing prostaglandin activation through COX-2, with arachidonic acid playing a pivotal role. The collective outcome of these actions results in inflammatory disorders and subsequent fibrogenesis (Zhang et al. 2019; Kanda et al. 2020; Yang et al. 2020). Histopathological examinations demonstrate that Tulsi extracts inhibit Kupffer cell stimulation leading to proinflammatory cytokine production and downregulating neutrophil infiltration (Suryani and Lubis 2019). Kumar et al. investigated the impact of methanol, ethanol, aqueous, and ethyl acetate extracts from the dried leaves and inflorescence of *O. basilicum* on the activity of cytochrome P450 enzymes (CYP2B6 and CYP3A4) and the esterase-mediated metabolism of rifampicin to 25-O-desacetyl rifampicin. Inhibition assays were conducted using human liver microsomes, while HepG2 cell assays were employed to measure the induction of CYP2B6/3A4 mRNA expression. These findings suggest that *O. basilicum* extracts have the potential to cause clinically significant herb-drug interactions (HDI) with CYP2B6 and the metabolism of rifampicin in vivo. The study identified phenolic and

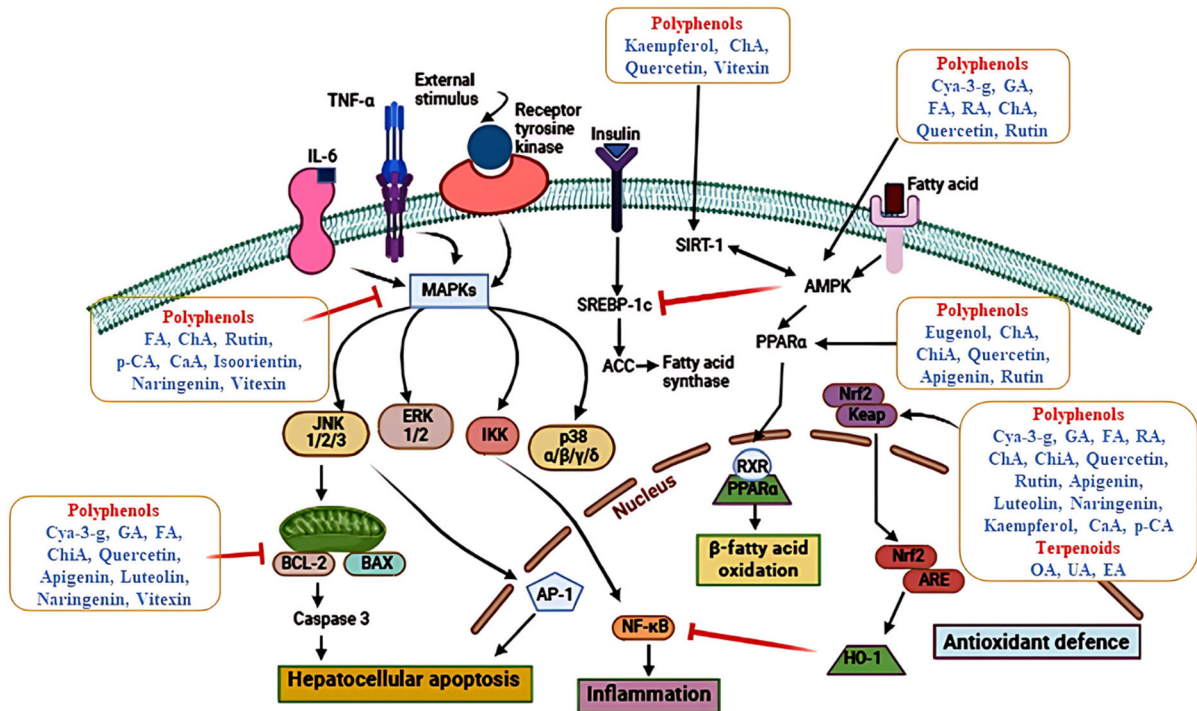


Fig. 3 Intracellular signaling transduction mediated by polyphenols and terpenoids for the treatment of hepatocellular inflammation. Polyphenols may prevent injury in hepatocytes through several signaling pathways: (i) suppressing activation of MAPKs pathway to inhibit apoptosis; (ii) increasing β-fatty acid oxidation by upregulating PPARα; (iii) inhibiting lipogenesis via downregulation of SREBP-1c by AMPK and SIRT-1 activation; (iv) enhancing antioxidant defense through Nrf2-ARE pathway; (v) Bax, Caspase 3 suppression and Bcl 2 upregulation to promote antiapoptotic action CaA; Caffeic acid, p-CA; p- Coumaric acid, ChA; Chlorogenic acid, ChiA; Chicoric acid, RA; Rosmarinic acid, FA; Ferulic acid, GA; Gallic acid, Cya-3-g; Cyanidin-3-glucoside, OA; Oleanolic acid, UA; Ursolic acid, EA; Epimaslinic acid, AMPK; AMP-

activated protein kinase, IL-6; Interleukin-6, MAPK; Mitogen-activated protein kinase, AP-1; activator protein 1, PARP; Poly (ADP-ribose) polymerases, ERK; Extracellular signal-regulated kinase, Nrf2; Nuclear erythroid related factor 2, ARE; Antioxidant response element, Keap1; Kelch like—ECH-associated protein 1, HO-1; Heme oxygenase 1, NQO1; NAD (P) H quinone oxidoreductase 1, SREBP-1c; Sterol regulatory element-binding protein 1c, ACC; Acetyl-CoA carboxylase, Bcl-2; B-cell lymphoma-2, Bax; Bcl-2-associated X protein, TNF; Tumor Necrosis Factor, NF-κB; Nuclear factor kappa B, JNK; c-Jun N-terminal kinase, IKK; Inhibitor of nuclear factor-κB kinase; RXR; Retinoid X receptor.

—| Inhibition; —→ Upregulation

terpenoid compounds including rosmarinic acid (approximately 2298 mg/L in aqueous extract), caftaric acid, salvigenin (approximately 1855 mg/L in ethanolic extract), eupatorin (668.772 mg/L in ethanolic extract), rutin, and isoquercetin potentially responsible for the inhibitory effects. The predicted in vivo inhibition percentile was highest for the aqueous extract on CYP2B6 (96.7%) (Kumar et al.2020).

In vitro and in vivo studies against chemical-induced liver injury

Carbon tetrachloride is a toxic chemical compound that was historically used in cleaning agents and as a

solvent. It is metabolized in the liver by cytochrome P450 enzymes, leading to the formation of highly reactive free radicals that can cause liver damage and fibrosis (Unsal et al. 2021). Nitric oxide (NO), one of those free radicals plays a regulatory role in organelle biogenesis and mitochondrial respiration. Simultaneously, nuclear factor-kappa B (NF-κB), a pro-inflammatory transcription factor, is activated and binds to the promoter of inducible nitric oxide synthase (iNOS), a crucial NO producer. iNOS, in turn, amplifies hepatic fibrosis and inflammatory cytokine expression (Cassini-Vieira et al. 2015). The aqueous extract of *O. gratissimum* leaves (OGE) at a dose of 0.2 mg/kg BW of male Wistar rats administered orally

Table 4 Role of some polyphenols present in *Ocimum* species on the metabolites and associated genes that regulate hepatoprotection

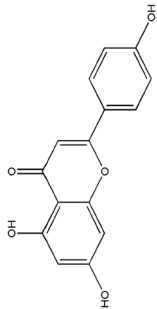
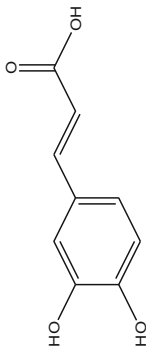
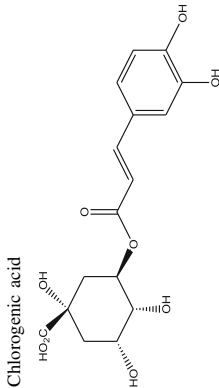
Compounds	Study type	Effect on Targets	Involved in gene expression and signaling pathway modulation	Clinical condition	Reference
 <p>Apigenin</p>	<p>In vivo</p> <p>In silico, in vitro, in vivo and <i>clinical</i></p>	<p>Anti-apoptotic and necrotic activity by</p> <ul style="list-style-type: none"> • Upregulation of Bcl-2 level • Downregulation of STAT-3 and Caspase-3 expression • Prevention of high-fat diet-induced NLRP3 inflammasome activation • Suppression of COL1A1, Xanthine Oxidase, and Platelet Derived Growth Factor β (PDGFRB) • Up-regulation of C1QTNF2 mRNA expression • Reduction of pro-inflammatory cytokine (IL-1β, IL-18) release and uric acid production <p>Activation of apoptotic proteins-c-FLIPL, XIAP, CIAP2</p>	<p>Protects against hepatocyte mitochondrial dysfunction and LFO</p> <p>Down-regulation of PDGFRB</p> <p>Prevention of hepatic stellate cell activation</p>	<p>Hepatic ischemia</p> <p>Non-alcoholic fatty liver disease</p>	<p>Mohamed et al. (2020)</p> <p>Hicks et al. (2017), Lv et al. (2019)</p>
 <p>Caffeic acid</p>	In vivo	<p>Upregulation of Phase II detoxification genes like GCL, NQO1, and HO-1</p>	<p>Pro-inflammatory cytokines NF-κB, TNFα, IL-6, IL-1β down-regulation</p> <p>Prevention of ROS-induced DNA base modification</p>	Acute liver failure	<p>Kim et al. (2018); Owumi et al. (2022)</p>
 <p>Chlorogenic acid</p>	in vitro, in vivo	<ul style="list-style-type: none"> • Downregulation of NFκB, ERK1/2, TLR4, MyD88 • Up-regulation of Nrf2 and HO-1 gene expression 	<p>Upregulation of Phase II detoxification genes like GCL, NQO1, and HO-1</p> <p>Upregulation of c-JNK and ERK leading to MAPK activation</p> <p>Downregulation of NOX/ROS/MAPK pathway and MMP-2 and MMP-9 leading to inhibition of proliferation and suppression of profibrotic action</p>	<p>Acute liver failure</p> <p>Fatty liver disease, Hepatic inflammatory fibrosis and Alcoholic hepatic steatosis</p>	<p>Pang et al. (2016); Yang et al. (2019); Ajiboye et al. (2019); Chatterjee et al. (2024)</p> <p>Shi et al. (2016), Wei et al. (2018), Bako et al. (2021)</p>

Table 4 continued

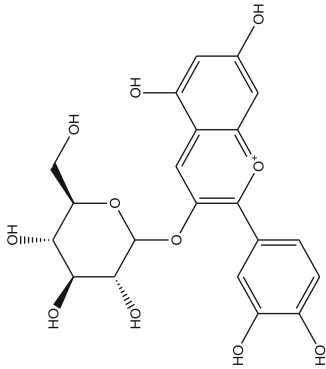
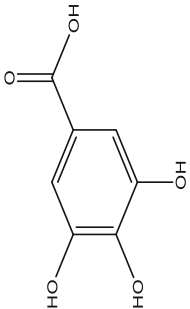
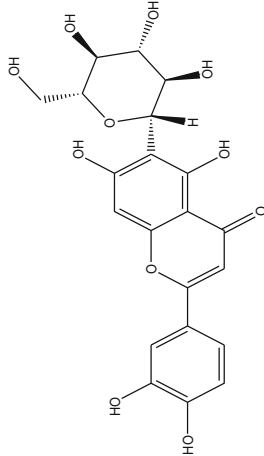
Compounds	Study type	Effect on Targets	Involved in gene expression and signaling pathway modulation	Clinical condition	Reference
<p>Cyanidin-3-glucoside</p> 	In vitro, in vivo	<ul style="list-style-type: none"> Increased expression of antioxidant enzymes like SOD, MDA, and GPx Activation of AMPK leading to up-regulation in the expression of Nrf2, HO-1, and NQO-1 Reduction of apoptotic proteins like cleaved Caspase-3, cleaved PARP, and pro-apoptotic proteins like Bax Elevation of anti-apoptotic proteins like Bcl-2 	Up-regulation of AMPK/Nrf2, ERK and PI3K/Akt pathways	Acute Hepatocellular injury	Yu et al. (2020), Park et al. (2017), Jiang et al. (2014)
<p>Gallic acid</p> 	In vitro, in vivo	<ul style="list-style-type: none"> Increase Caspase-3, Caspase-9, Bcl-2-like protein 4, HO-1 expression, antioxidant enzyme GSH Decrease COX-2 and iNOS protein levels via NF-κB down-regulation Down-regulation of IL-6, COX-2, TNF-α, IL-1β 	Regulation of mitochondria-mediated pathways resulting in inhibition of proliferation by apoptosis induction Up-regulation of Nrf2-ARE pathway	Hepatocarcinoma or Liver fibrosis	Latief et al. (2016), Sun et al. (2016), Tanaka et al. (2020)
<p>Isoorientin</p> 	In vitro	<ul style="list-style-type: none"> Up-regulation of Caspase-3, Caspase-9, antioxidant enzymes Activation of JNK and p38 kinases along with deactivation of ERK1/2 kinase expression 	Regulation of cell cycle gene expressions via inhibition of mitochondrial membrane potential leading to apoptotic change (Down-regulation of PI3K/Akt pathway and up-regulation of MAPK signaling pathway)	Hepatocellular carcinoma	Yuan et al. (2013)

Table 4 continued

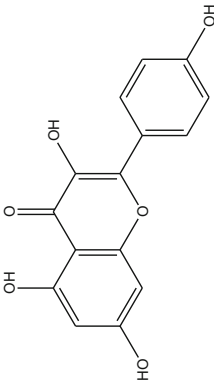
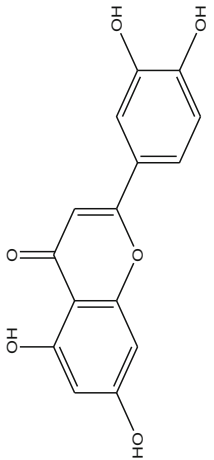
Compounds	Study type	Effect on Targets	Involved in gene expression and signaling pathway modulation	Clinical condition	Reference
 Kaempferol	In vivo	<ul style="list-style-type: none"> Down-regulation of cytoplasmic adaptor proteins (IRS-1) (IKKα) and (IKKβ) which acts as a pro-inflammatory mediator Down-regulation of pro-inflammatory cytokines IL-6, TNFα, iNOS Activation of Nrf2, dose-dependent upregulation of other antioxidant genes HO-1 and NQO-1 Down-regulation of Keap1, NF-κB 	NF- κ B down-regulation	Hepatic fibrosis	Luo et al. (2015), Khlifi et al. (2020)
	In vitro and in vivo	<ul style="list-style-type: none"> Acetylation of PARP1, p53, NF-κB, FOXO-1 Down-regulation of cell cycle regulatory proteins CDK9, Cyclin B1, MCM2, Cyclin D1 and c-myc Inhibition of both endogenous and TGF-β induced expression of extracellular matrix proteins like α-SMA, Collagen I, and fibronectin Hepatic matrix metalloprotein-9 level, metallothionein (MT) I/II expression, and glial fibrillary acidic protein 	PI3K/Akt-regulated Nrf2 pathway stimulation	Acute liver inflammation	Rajendran et al. (2020), Alshehri et al. (2022)
 Luteolin	In vivo	<ul style="list-style-type: none"> Increase cellular antioxidant enzymes Nrf2, HO-1, NOQ1 Suppression of p53, NFκB, TNFα, iNOS, IL-6 protein level 	Upregulation of SIRT1 activity	Intrinsic hepatocellular apoptosis	BinMowyn and AlFaris, (2021)
	In vitro	<ul style="list-style-type: none"> Down-regulation of cell cycle regulatory proteins CDK9, Cyclin B1, MCM2, Cyclin D1 and c-myc Inhibition of both endogenous and TGF-β induced expression of extracellular matrix proteins like α-SMA, Collagen I, and fibronectin Hepatic matrix metalloprotein-9 level, metallothionein (MT) I/II expression, and glial fibrillary acidic protein 	Suppression of STAT3 Down-regulation of c-myc leads to MT-mediated strong enhancement of hepatic regenerative capability leading to hepatic stellate cell deactivation	Hepatic fibrosis	Cummins et al. (2018), Domitrović et al. (2009)
	In vivo	<ul style="list-style-type: none"> Increase cellular antioxidant enzymes Nrf2, HO-1, NOQ1 Suppression of p53, NFκB, TNFα, iNOS, IL-6 protein level 	Up-regulation of Nrf2 signaling pathway leading to hepatic stellate cell deactivation	Drug (Acetaminophen) and chemical (mercuric chloride) induced acute liver failure	Zhang et al. (2017), Tai et al. (2015)

Table 4 continued

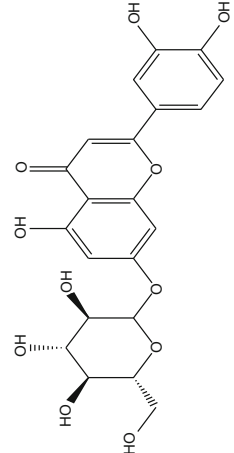
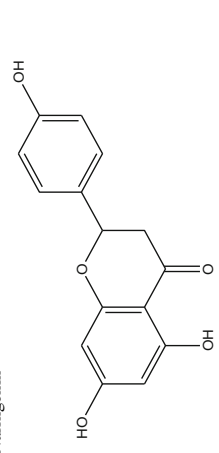
Compounds	Study type	Effect on Targets	Involved in gene expression and signaling pathway modulation	Clinical condition	Reference
<p>Luteolin-7-O-glucoside</p> 	In vitro	<ul style="list-style-type: none"> JNK up-regulation followed by G2/M phase cell cycle arrest Reduction in NF-κB and COX-2 expression 	Caspase-independent apoptotic signaling pathways activation followed by Inhibit proliferation via inducing apoptosis	Hepatocellular carcinoma	Hwang et al. (2013), Witowska-Banaszczak et al. (2020)
<p>Naringenin</p> 	In vitro, in vivo	<ul style="list-style-type: none"> Reduction in the activation of hepatic stellate cells via increased expression of antioxidant enzymes like GPx, SOD, CAT, and GSH Down-regulation of the expression of TNF-α and MMP-2 and MMP-9 Down-regulation of the mRNA expressions of IL-1β, IL-6, iNOS, AP-1, COX-2, HMGGB-1 and NF-κB Elevation of anti-apoptotic proteins like Bcl-2 and depletion in the mRNA levels of Bax, Bak, Cas3 and Cas9 	<p>Up-regulation of PI3K/AKT and Nrf2- ARE pathway</p> <p>Down-regulation of NF-κB, JNK-Smad3, TGF-β-Smad3, and VEGF pathways, TLR, and MAPK signaling pathway</p>	DNA fragmentation, apoptosis, and mitochondrial injury leading to Non-alcoholic fatty liver disease and Hepatocellular carcinoma	Arafah et al. (2020), Hernández-Aquino & Muriel (2018)

Table 4 continued

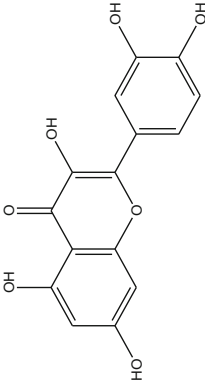
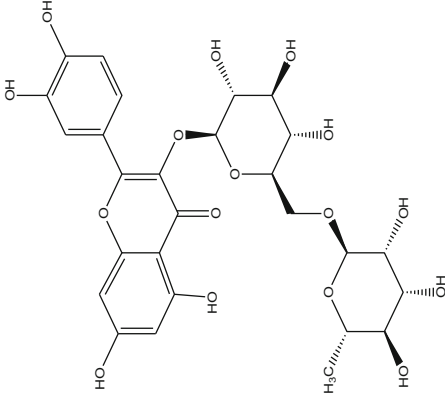
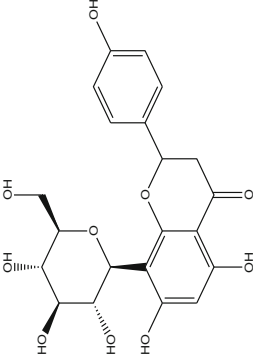
Compounds	Study type	Effect on Targets	Involved in gene expression and signaling pathway modulation	Clinical condition	Reference
 <p>Quercetin</p>	<p>In vivo</p> <p>In vivo and in vitro</p>	<p>Down-regulation of pro-inflammatory cytokine & mediator iNOS, COX-2, and CRP protein level</p> <ul style="list-style-type: none"> • Increase Cu/Zn SOD activity • Down-regulation of NF-κB, TNF-α and COX-2 • Suppression of NOX₁, NOX₂, and NOX₄ leading to inhibition of profibrogenic responses of TGF-β1/Smads and nitrotyrosine formation • Up-regulation of Nrf2 and HO-1 expression 	<p>NF-κB down-regulation</p> <p>Activation of PI3K/Akt signaling pathway</p> <p>Activation of ERK and JNK pathway</p> <p>Down-regulation of NF-κB and TGF-β signaling pathway via up-regulation of Nrf2-ARE pathway</p>	<p>Hepatic fibrosis</p> <p>Liver fibrosis</p>	<p>Wu et al. (2017)</p> <p>Domitrović et al. (2012), Mohammadiaghvaei et al. (2021)</p>
 <p>Rutin</p>	<p>In vitro and In vivo</p> <p>In vitro and In vivo</p>	<p>Down-regulation of metastasis mediators' activity like PPARα, AMPK, NF-κB, TNF-α, and TGF-β1</p> <p>Down-regulation of SREBP-1, ROS and COX-2</p> <p>Up-regulation of Nrf2, HO-1, and AMPK expression</p> <p>Down-regulation of α-SMA protein, TGF-β1, IL-1β, connective tissue growth factor and collagen expression</p>	<p>Down-regulation of PKC, PI3K, MAPK, NF-κB signalling pathways</p> <p>Down-regulation of NF-κB and TGF-β/Smad signaling pathway</p> <p>Up-regulation of Nrf2-ARE pathway and ERK activation</p>	<p>Hepatocellular carcinoma</p> <p>Cholestatic hepatic fibrosis</p>	<p>Liu et al. (2017a, b), Liu et al. (2022)</p> <p>Al-Rejaie et al. (2013), Pan et al. (2014), Singh et al. (2019)</p>

Table 4 continued

Compounds	Study type	Effect on Targets	Involved in gene expression and signaling pathway modulation	Clinical condition	Reference
 Vitexin	<p>In vitro and In vivo</p> <p>In vitro and In vivo</p>	<ul style="list-style-type: none"> • Up-regulation of Caspase-3 • Down-regulation of Bcl-2 • Upregulation of Hepatic SIRT1 protein and mRNA expression • Down-regulation of the activation of acetylated-p53, and Cleaved-Caspase3, Bax expression, MDA level, and TNF-α • Increase Bcl2 • Increase SOD level • Suppression of pro-inflammatory cytokines TNF-α, IL-6, and IL-1β • Down-regulation of TLR4 expression • Decrease the activation of IκBα and NF-κB p65 	<p>Induces apoptosis via up-regulation of JNK and MAPK signaling pathways</p> <p>Regulation of SIRT1/p53 mediated mitochondrial apoptotic pathway</p>	<p>Hepatocellular carcinoma</p> <p>Alcoholic fatty liver disease</p>	<p>He et al. (2016)</p> <p>Yuan et al. (2020)</p>
	In vivo		Down-regulation of TLR4/NF- κ B signaling pathway	Chronic liver inflammation	Duan et al. (2020)

AMPK; adenosine monophosphate-activated protein kinase, c-FLIP; Cellular FLICE –inhibitory protein, TGF- β 1; Transforming growth factor β 1, IL-1 β ; Interleukin-1 β , IL-6; Interleukin-6, MAPK; Mitogen-activated protein kinase, TLR; Toll-like receptor, VEGF; Vascular endothelial growth factor, AP-1; activator protein 1, PARP; Poly (ADP-ribose) polymerases, I κ B α ; inhibitor of nuclear factor kappa B- α , PI3K/Akt; Phosphatidylinositol 3 Kinase, MMP; Matrix metalloproteinase, ERK; Extracellular signal-regulated kinase, Nrf2; Nuclear erythroid related factor 2, ARE; Antioxidant response element, Keap1; Kelch like – ECH-associated protein 1, HO-1; Heme oxygenase 1, GCL; Glutamate-cysteine ligase, NQO1; NAD (P) H quinone oxidoreductase 1, SREBP-1c; Sterol regulatory element-binding protein 1c, HMGCoA; High mobility group box 1, CAT; Catalase, GSH; glutathione reductase, SOD; Superoxide Dismutase, LPO; Lipid peroxidation, MDA; Malondialdehyde, TBARS; Thiobarbituric acid reacting substance, GPx; glutathione peroxidase, GR; Glutathione reductase, GST; Glutathione S-transferase, ACC; Acetyl-CoA carboxylase, Bcl-2; B-cell lymphoma-2, Bax; Bcl-2-associated X protein, iNOS; Inducible nitric oxide synthase, COX; cyclooxygenase, TNF; Tumor Necrosis Factor, NF- κ B; Nuclear factor kappa B, PKC; Protein kinase C, JNK; c-Jun N-terminal kinase, MyD88; Myeloid differentiation primary response 88, Sirt 1; Sirtuin 1, MCM2; Mimichromosome maintenance protein 2, IKK; Inhibitor of nuclear factor- κ B kinase, NOX; Nitrogen Oxides, FOXO; Forkhead box O

for 12 weeks, aids in managing acute liver injury by reducing hepatic heat shock protein 70 (HSP70) and iNOS proteins in the livers of CCl₄-administered rats. Moreover, it diminishes the matrix metalloproteinases (MMP)-9/MMP-2 ratio, urokinase-type plasminogen activator (uPA) protein levels through ERK signaling, and NF- κ B phosphorylation. MMP-9, a member of the MMP family, is crucial for fibrogenesis and malignancies in various liver diseases. The uPA further enhances MMP-9 expression, and ERK 1/2 and NF- κ B signaling are pivotal for MMP-9 up-regulation (Chiu et al. 2012). A comparable study evaluated the in vivo and in vitro efficacy of OGE in a model of carbon tetrachloride (CCl₄)-induced hepatocellular fibrosis in rats. Male Wistar rats were administered CCl₄ via intraperitoneal injection and received varying oral doses of OGE (0–40 mg/kg body weight) for 8 weeks. The results demonstrated that OGE significantly attenuated liver damage, including steatosis and fibrosis, in a dose-dependent manner. Additionally, OGE inhibited the formation of lipid peroxidation products during CCl₄ treatment. Furthermore, OGE reduced CCl₄-induced hepatic collagen deposition and enhanced the expression of catalase, an antioxidant enzyme. Inhibition of fibrosis markers, specifically α -SMA expression, was also observed. In primary hepatic stellate cell (HSC) cultures, OGE significantly suppressed serum-induced activation and decreased both the protein and gene expression of α -SMA and type I collagen α (Chiu et al. 2012). Additionally, essential oil from *O. basilicum* (OBE), comprising primarily monoterpene hydrocarbons (70.3%), notably iso-menthone (38%), 1,8-cineole (13.9%), trans-sabinene (12%), and pulegone (6.4%), along with minor quantities of terpenoids (L-carvone) and sesquiterpenes (cis- α -bisabolene, trans- α -bergamotene, α -farnesene, α -humulene, trans-caryophyllene, δ -cadinene, and α -morphene) and methyl eugenol (7.5%), has been documented to stimulate hepatocyte growth factor (HGF) while concurrently downregulating CYP2E1 expression. This intervention (200 mg/kg BW IP for 8 weeks) results in reduced collagen deposition, and a decrease in α -smooth muscle actin (α -SMA) immunopositive cells, signifying mitigation of hepatic stellate cell activation by OBE in CCl₄-induced liver fibrosis in rats (Ogaly et al. 2015). In another study, CCl₄-induced liver fibrosis in male Wistar rats was treated with *Ocimum gratissimum* polyphenol extract (OGPE) at a dosage of 12 mg/kg body weight for

8 weeks. The results indicated that OGPE containing catechin, caffeic acid, and epicatechin preserved liver weight, significantly ameliorated CCl₄-induced steatosis, and mitigated other histopathological alterations. Additionally, OGPE maintained serum levels of liver function markers like alanine aminotransferase (ALT) and aspartate aminotransferase (AST), as well as the levels of MDA, catalase, and α -SMA in hepatic tissues, counteracting the effects induced by CCl₄. These findings suggest that the polyphenolic components present in OGPE were the primary factors for preventing fibrotic changes (Chen et al. 2015). Kamel et al. conducted a study on the hepatoprotective potential of *Ocimum sanctum* L. against galactosamine-induced hepatotoxicity and investigated the bioactive compounds present in its extract, alongside identifying serum metabolites. Hepatotoxicity was induced in adult albino rats through an intraperitoneal injection of galactosamine (400 mg/kg). The hydroalcoholic and alcoholic extracts of *Ocimum sanctum* L. (administered at 100 and 200 mg/kg body weight/day) containing bioactive compounds such as rutin, ellagic acid, kaempferol, caffeic acid, quercetin, and epicatechin were evaluated for their hepatoprotective potential. A significant reduction in serum enzymes and MDA was observed, indicating hepatoprotective effects. The study further fractionated the hydroalcoholic extract based on polarity into hexane, chloroform, and ethyl acetate fractions and assessed their hepatoprotective activity in vitro using Chang liver cells exposed to CCl₄ toxicity (40 mM). Among these, the ethyl acetate fraction exhibited the highest hepatoprotective activity. This fraction contained substantial amounts of rutin (0.34% w/w), ellagic acid (2.32% w/w), kaempferol (0.017% w/w), caffeic acid (0.005% w/w), quercetin (0.038% w/w), and epicatechin (0.057% w/w), which were identified as key contributors to hepatoprotection. When compared to standard silymarin, the isolated bioactive molecules demonstrated significant hepatoprotective activity in Chang liver cells subjected to CCl₄-induced toxicity (Kamel et al. 2023). To assess cytotoxicity in both malignant and non-malignant cells, specifically hepatocytes, a study was conducted utilizing HepG2 (human hepatocellular carcinoma) and freshly isolated porcine liver cells (PLP2). Among the aqueous and hydroethanolic extracts tested, the hydroethanolic extract of *Ocimum citriodorum* exhibited cytotoxic effects against the human tumor cell lines.

Additionally, this extract demonstrated cytotoxicity towards non-malignant hepatocytes, although it presented a higher GI_{50} (concentration that inhibits 50% of cell growth) value compared to that observed for the cancer cell lines (Majdi et al. 2020). Selvarani et al. 2015 conducted a cytotoxicity study of silver nanoparticles synthesized using ethanol leaf extract from the stem of *Ocimum kilimandscharicum* against HepG2 cells. The study demonstrated an excellent IC_{50} value of 49 $\mu\text{g}/\text{mL}$ and recommended the use of these silver nanoparticles for the effective control of liver cancer cell lines.

Clinical study against metabolic disorder-induced liver injury

A randomized, parallel-group, open-label pilot study was conducted to evaluate the effects of *Ocimum sanctum* on metabolic and biochemical parameters in thirty overweight/obese subjects, divided into two groups: Group A and Group B. Group A ($n = 16$) received one 250 mg capsule of *O. sanctum* extract twice daily on an empty stomach for 8 weeks, while Group B ($n = 14$) received no intervention. Statistically significant improvements were observed in Group A for serum triglycerides, low-density lipoprotein (LDL), high-density lipoprotein (HDL), very low-density lipoprotein (VLDL), and Body Mass Index (BMI) after 8 weeks. The increase in HDL in the intervention group compared to the control group was also statistically significant. No significant changes were noted in liver enzymes, specifically serum glutamic-oxaloacetic transaminase (SGOT) and serum glutamic-pyruvic transaminase (SGPT), in either group. These findings indicate the beneficial effects of *O. sanctum* on various biochemical parameters in young overweight/obese subjects (Satapathy et al. 2017).

In vitro and in vivo studies against apoptotic changes in hepatocellular carcinoma

The in vitro and in vivo study by Huang et al. 2020, treatment with aqueous *Ocimum gratissimum* leaf extract (400, 600, 800 $\mu\text{g}/\text{mL}$ for 24 h) in SK-Hep1 and HA22T cells demonstrated a dose-dependent reduction in apoptosis mediator caspase 3, poly (ADP-ribose) polymerase (PARP), cyclin-dependent kinase 4 (CDK4), and phosphorylated extracellular

signal-regulated kinase 1/2 (p-ERK1/2) expressions, resulting in attenuated hepatocellular carcinoma (HCC) tumor growth. The in vivo study showed significant suppression of tumor weight in the treatment group (60 mg/kg daily oral administration for one month) compared to the control group.

In vitro and in vivo studies against viral hepatitis

Viral hepatitis is an infection that results in hepatic inflammation and damage. The various types of viral hepatitis include hepatitis A, B, C, D, and E. Hepatitis A and E are primarily transmitted via fecal–oral routes, typically through ingestion of food or water contaminated by an infected individual’s feces. Hepatitis B, C, and D are transmitted through exposure to infected blood. Hepatitis B and D can also be transmitted through other bodily fluids. These transmissions can occur through activities such as sharing needles or engaging in unprotected sexual intercourse. Hepatitis A and E viruses generally cause acute infections, which are short-term and typically resolve as the immune system clears the virus. In contrast, hepatitis B, C, and D viruses can lead to both acute and chronic infections. Chronic hepatitis arises when the immune system fails to eliminate the virus, leading to persistent infection. Chronic hepatitis can result in severe complications, including cirrhosis, hepatic failure, and hepatocellular carcinoma. Studies have investigated the antiviral properties of *O. basilicum* extracts and its purified components against the hepatitis B virus (HBV). Results indicate that crude aqueous and ethanolic extracts, along with specific purified components such as apigenin, linalool, and ursolic acid, demonstrate significant antiviral activity. Apigenin exhibited the highest efficacy against the hepatitis B surface antigen, with a 50% effective concentration (EC_{50}) of 7.1 mg/L, and against the hepatitis B e antigen with an EC_{50} of 12.8 mg/L (Chiang et al. 2005). Further research by Kubiça et al. (2014) explored the antiviral activity of *O. basilicum* essential oil and the monoterpenes camphor, thymol, and 1,8-cineole against the hepatitis C virus (HCV). The study assessed plaque inhibition percentages, expressed through metrics such as CC_{50} (50% cytotoxic concentration), IC_{50} (inhibitory concentration for 50% of plaques), and SI (selectivity index = CC_{50}/IC_{50}). Camphor ($CC_{50} = 4420.12 \mu\text{g}/\text{mL}$) and 1,8-cineole ($CC_{50} = 2996.10 \mu\text{g}/\text{mL}$) exhibited the lowest

cytotoxicity and the most potent antiviral activities, with selectivity indices of 13.88 and 9.05, respectively, in the virucidal assay. These findings suggest that the monoterpenes exert their antiviral effects by acting directly on the viral particles. Apart from *O. basilicum*, other species, and their compounds need to be evaluated for their viral hepatitis protective efficacy.

Despite comprehensive investigations into the hepatoprotective efficacy of diverse *Ocimum* species against toxic agents, the majority of the research highlighted in Table 3 predominantly employed *Ocimum* extracts. A limited number of studies conducted phytochemical characterization to identify the specific compounds accountable for the observed protective effects. Furthermore, scant attention has been given to delineating the molecular mechanisms that underlie the hepatoprotective properties of these *Ocimum* species. The polyphenolic and terpenoid compounds identified in characterization studies of various *Ocimum* species were observed to demonstrate extensive associations with proteins and genes implicated in hepatoprotection in separate investigations.

Hepatoprotective polyphenols present in *Ocimum* species

Various polyphenols present in different *Ocimum* species have been studied for their signaling pathways, associated proteins, and genes involved in hepatoprotection. The outcomes of these studies correlate that phenolic compounds have protective potentials against hepatotoxicity (Table 4; Fig. 3). This section extensively explores and elucidates the broad molecular mechanisms of hepatoprotection by some polyphenols present in *Ocimum* species.

Eugenol

Eugenol, belonging to the phenylpropanoid class of essential oils, is prominently present in various *Ocimum* species. Notably, substantial concentrations of eugenol are discerned in the leaves of *O. gratissimum* (79% or 0.0445 mg/g), *O. sanctum* (55% or 0.0943 mg/g), *O. americanum* (0.145 mg/g), *O. basilicum* (0.034 mg/g), and *O. tenuiflorum* (0.043 mg/g) (Pandey et al. 2016).

Recent investigations have explored the hepatoprotective potential of eugenol, unveiling its impact on molecular pathways. Fathy et al. (2019) demonstrated that eugenol activates peroxisome proliferator-activated receptor-gamma (PPAR- γ), mitigating CCl₄-induced hepatotoxicity in vivo. PPAR- γ , a ligand-inducible nuclear hormone receptor, plays a pivotal role in regulating adipogenesis and metabolism. Activated PPAR- γ exhibits hepatocarcinogenesis and fibrosis-mitigating effects by downregulating NF κ B, subsequently reducing the generation of profibrogenic factors, such as kupffer cells, leading to diminished NO formation and reactive species production.

In a parallel mechanism, eugenol was found to ameliorate cadmium toxicity in the liver, showcasing its versatility in hepatoprotection (Kumar et al. 2021). Additionally, eugenol contributes to a reduction in the activation of the microsomal enzyme CYP2E1, resulting in a decreased capacity for toxicant biotransformation within the liver (Yogalakshmi et al. 2010).

Rosmarinic acid

Rosmarinic acid (RA), classified as a phenolic acid within the hydroxy-cinnamic acid subclass, manifests hepatoprotective attributes, particularly evident in its ability to counter hepatic ischemia and reperfusion injury. This protective mechanism involves the inhibition of the NF κ B signaling pathway, leading to a subsequent reduction in iNOS, endothelial nitric oxide synthase (eNOS), and NO levels (Ramalho et al. 2014).

Abundantly present in various *Ocimum* species, RA is notably found in *O. tenuiflorum* (8 mg/g of dried leaf extract), *O. sanctum* (1.653 mg/g of dried leaf extract or 0.27%), *O. gratissimum* (7.866 mg/g of dried leaf extract), *O. basilicum* (7.6 mg/g of dried leaf extract or 15.76%), *O. americanum* (10.966 mg/g of dried leaf extract), and *O. lamiifolium* (0.10 mg/g of dried leaf extract) (Pandey et al. 2016; Sundaram et al. 2012; Ibrahim et al. 2020; Rady and Nazif 2005).

RA exhibits remarkable efficacy in preventing oxidative stress-induced fibrogenesis by reducing the activity of MMPs and tissue inhibitors of metalloproteinases (TIMPs), both of which are NF κ B-dependent and regulate extracellular matrix protein deposition (Lin et al. 2017). This antifibrotic effect is closely associated with the modulation of the hepatic transforming growth factor β 1 (TGF- β 1) pathway. RA

reduces extracellular matrix-producing cells, such as portal myofibroblasts and hepatic stellate cells, linked with α -smooth muscle actin (α -SMA) immunoreactivity. Furthermore, RA downregulates TGF- β 1 levels and its effectors, including hepatic protein phosphorylation of Smad 2/3, procollagen I, III, and connective tissue growth factor (CTGF) gene expression (Lin et al. 2017). In addition, RA diminishes oxidative stress by stimulating the antioxidant defense mechanism of the nuclear erythroid-related factor 2 (Nrf2)-Antioxidant response element (ARE) signaling pathway (Li et al. 2019; Lu et al. 2022). Under oxidative stress conditions, Nrf2 disassociates from the repressor protein Keap1, translocates into the nucleus, and activates ARE, leading to the upregulation of stress response-iron metabolism genes and antioxidant enzyme synthesis. RA also engages in hepatoprotection through the activation of AMP-activated protein kinase (AMPK) phosphorylation, which subsequently decreases the expression of the transcription factor sterol regulatory element-binding protein 1c (SREBP-1c), resulting in reduced fatty acid biosynthesis (Touiss et al. 2021). Moreover, studies by Khalaf et al. (2020) isolated RA from *Rosmarinus officinalis* L. plant leaves, demonstrating its activation of Nrf2 signaling, reduction in malondialdehyde (MDA) levels, and elevation of glutathione (GSH) concentration to attenuate hepatorenal oxidative damage induced by chromium.

The multifaceted mechanisms of hepatoprotection attributed to RA include its role in promoting antioxidant responses, modulating fibrogenic pathways, and regulating lipid metabolism, thereby positioning *Ocimum* species rich in RA as promising agents for liver protection (Guo et al. 2020).

Ferulic acid

Ferulic acid (FA), a prominent hydroxycinnamic acid within the phenolic compound group, is notably present in *O. basilicum* (1% or 0.546 mg/g of dried leaf extract), *O. tenuiflorum* (0.356 mg/g of dried leaf extract), *O. sanctum* (4.367 mg/g of dried leaf extract), *O. gratissimum* (0.446 mg/g of dried leaf extract), and *O. americanum* (0.336 mg/g of dried leaf extract) (Ibrahim et al. 2020).

FA exhibits hepatoprotective properties through multifaceted mechanisms. It upregulates AMP-activated protein kinase (AMPK) phosphorylation,

thereby mitigating drug-induced acute liver injury via AMPK-mediated protected autophagy. Additionally, FA prevents both intrinsic and extrinsic apoptosis pathways by inhibiting TNF α -mediated Caspase-8 activation and suppressing the hepatic protein expression of pro-apoptotic Bcl-2 family members, including Bax, tBid, and Biml (Kim and Lee 2012). Furthermore, FA demonstrates antiapoptotic efficacy by preventing mitochondrial membrane potential reduction, increasing the Bax/Bcl2 ratio, and suppressing Caspase-3 expression (Wu et al. 2022). It enhances the antioxidant defense mechanism by upregulating the Nrf2-ARE signaling pathway and concurrently suppressing inducible nitric oxide synthase (iNOS), nuclear factor kappa B (NF κ B), and other proinflammatory cytokine expressions (Mahmoud et al. 2020). In the context of hepatic ischemia/reperfusion-induced apoptosis, FA exerts protective effects by preventing the phosphorylation of Jun N-terminal Kinase-1 (JNK 1) and JNK 2 (Kim and Lee 2012). JNK, a member of the mitogen-activated protein kinase (MAPK) sub-family responsive to oxidative stress, regulates cellular processes such as migration, proliferation, and apoptosis. JNK 1 signaling induces activator protein-1, leading to Caspase-dependent hepatocellular apoptosis, while JNK 2 promotes TNF-induced apoptosis (Kim and Lee 2012).

Chicoric acid

Chicoric acid, another hydroxycinnamic acid abundantly present in *O. basilicum* (1.01% or 3.19–6.03 mg/g of dried aerial part extract) (Ibrahim et al. 2020), has been documented for its efficacy in preventing drug-induced hepatotoxicity. Its hepatoprotective mechanisms involve the prevention of oxidative stress and inflammation through the upregulation of hepatic Nrf2, HO-1, NQO-1, and PPAR γ . Chicoric acid further inhibits apoptosis by upregulating Bcl-2 expression and suppressing Bax, cytochrome C (Cyt-C), and Caspase-3, highlighting its potential therapeutic role in safeguarding against liver damage (Hussein et al. 2020).

Luteolin

Luteolin, a bioactive flavone abundantly found in *O. sanctum* (1.116 mg/g of dried leaf extract), *O. basilicum* (5.94% or 0.683 mg/g), *O. tenuiflorum*

(ranging from 0.031% to 0.046% or 1.530 mg/g), as well as 0.643 mg/g in *O. gratissimum* and *O. americanum*, among other *Ocimum* species (Pandey et al. 2016; Ibrahim et al. 2020), exhibits hepatoprotective properties. Luteolin effectively mitigates liver apoptosis by diminishing the expression of Bax, Cyt-C, Caspase-3, and Caspase-9, while concurrently elevating Bcl-2 expression.

In the context of mycotoxin-induced liver injury, Luteolin demonstrates protective effects by upregulating the Nrf2-ARE pathway and enhancing the activity of antioxidant enzymes such as catalase, GSH-Px, and SOD (Rajput et al. 2021). Its dietary intake proves beneficial in shielding against chronic liver injury induced by mercuric chloride, where it enhances the FoxO3a transcription factor, subsequently influencing the localization control of the tumor suppressor gene p53 by FoxO3a (Zhang et al. 2017). Moreover, Luteolin exhibits protective effects against acetaminophen-induced acute liver failure by combating endoplasmic stress. It achieves this by downregulating activating transcription factor 4 (ATF4) and C/EBP Homologous Protein (CHOP), as these proteins are notably elevated during endoplasmic stress (Tai et al. 2015).

Quercetin

Quercetin, the principal representative of flavonols, is discerned in varying concentrations across *Ocimum* species, including *O. basilicum* (0.047 mg/g of dried leaf extract), *O. tenuiflorum* (0.040 mg/g of dried leaf extract), *O. sanctum* (0.039 mg/g of dried leaf extract), *O. gratissimum* (0.067 mg/g of dried leaf extract), and *O. americanum* (0.039 mg/g of dried leaf extract) (Pandey et al. 2016). Differing from Luteolin by only one hydroxy group, quercetin emerges as a potent therapeutic agent in addressing liver fibrosis, liver steatosis, fatty hepatitis, and liver cancer. Its efficacy lies in its modulation of various targets and pathways integral to the pathogenesis and treatment of liver diseases. Quercetin exhibits preventive actions against liver steatosis, a disorder linked to lipid metabolism, often induced by excessive caloric intake or alcohol consumption. Mechanistically, it diminishes fat accumulation by downregulating both AMP-activated protein kinase (AMPK) and Sirtuin 1 (SIRT1), recognized targets in metabolic syndrome (Cao et al. 2023). Additionally, quercetin normalizes

hepatic steatosis-related gene expressions by reducing the expression of peroxisome proliferator-activated receptor alpha (PPAR α), which subsequently controls sterol regulatory element-binding protein 1c (SREBP1c) and fatty acid synthase (Zhao et al. 2021). Quercetin induces autophagy through the mammalian target of rapamycin (mTOR), influencing the expression of autophagy marker proteins such as microtubule-associated protein 1 and autophagic autophagosome bridging p62. Furthermore, it reduces oxidized low-density lipoprotein (Ox-LDL) accumulation in mice fed a high-fat diet. Quercetin also demonstrates anti-apoptotic effects by inhibiting factors such as p53 and Bax, while increasing the expression of Bcl-2 (Liu et al. 2017a, b; Lan et al. 2019).

In the context of hepatotoxicity induced by Tripotolide, a potent hepatotoxic agent, Quercetin has been found to protect the liver by blocking Toll-like receptor 4 (TLR4). This protective effect is further emphasized by its modulation of T-cell immunoglobulin and mucin domain-containing protein 3, reduction of myeloid differentiation primary response gene 88, NF κ B, and pro-inflammatory cytokines interleukin-17 (IL-17) and IL-6 related to T helper 17 (Th17) cells (Wei et al. 2017). Quercetin plays a pivotal role in regulating the balance between Th17 and T regulatory (T reg) cells, thereby maintaining T reg dominance and contributing to liver protection.

Quercetin exhibits notable efficacy in mitigating acute autoimmune hepatitis by suppressing the TNF receptor-associated factor 6 (TRAF6) / JNK pathway, thereby impeding autophagy and apoptosis processes (Wu et al. 2017). Rats treated with quercetin displayed reduced levels of 8-hydroxy guanosine, a marker indicative of oxidative damage to 2'-deoxy guanosine, suggesting the flavone's protective role against DNA damage (Ansar et al. 2016). In an *in-vivo* model of bile duct ligation-induced fibrosis in rats, quercetin demonstrated significant downregulation of TGF- β 1 and miR-21 gene expression, while concurrently elevating miR-122 expression. This modulation supports the assertion that quercetin is effective in preventing liver fibrosis and cirrhosis (Nozari et al. 2020). A recent study revealed that quercetin downregulates the Hedgehog pathway, an emerging target for hepatocellular damage repair. It attenuates the mRNA expressions of key Hedgehog pathway mediators and pro-inflammatory cytokines, including

Serum sonic hedgehog (Shh), Patched-1 (Ptch-1), Gli-3, TNF- α , NF κ B, and suppressor of cytokine signaling-3 (Socs-3) (Aslam et al. 2022).

Pérez-Ramírez et al. (2017) reported that *O. sanctum* flower extract, containing quercetin as a primary compound, exhibited anti-inflammatory and hypoglycemic potential by not up-regulating Glut4, IRS1, and PI3K genes while decreasing the levels of TNF- α and IL-6 compared to the negative control. A recent computational study focusing on quercetin from *O. basilicum* and *O. tenuiflorum* aimed at identifying anti-inflammatory responses through a non-steroidal mechanism. The study revealed that this flavonol modulates the carbonic anhydrase family and several key proteins from the arachidonic pathway, providing further insights into its anti-inflammatory properties (Beltrán-Noboa et al. 2022).

Rutin

Rutin, a significant flavonol, manifests in varying concentrations across different *Ocimum* species, including *O. americanum* (10.9 mg/g), *O. basilicum* (1.653 mg/g), *O. gratissimum* (0.920 mg/g), *O. sanctum* (0.074 mg/g), and *O. tenuiflorum* (0.173 mg/g) (Pandey et al. 2016). Its hepatoprotective properties extend to countering the adverse effects of toxic insecticides, exemplified by deltamethrin-induced hepatocellular inflammation, apoptosis, and necrosis. Küçükler et al. 2021, elucidated Rutin's role in attenuating lipid peroxidation (LPO) and downregulating proinflammatory cytokines, including TNF- α , NF κ B, IL-1 β , p38 α MAPK, COX 2, iNOS, beclin 1, Bax, and Caspase 3. Rutin's impact also extends to reducing mRNA expression of PARP-1 and VEGF, indicating its potential in mitigating oxidative stress-associated DNA damage and promoting hepatic regeneration. Moreover, Rutin demonstrates efficacy in ameliorating cadmium-induced hepatotoxicity by inhibiting key members of MAPK and NF κ B pathways such as JNK, ERK, and TNF- α . Liu et al. (2022) reported Rutin's ability to suppress stress response products, including HSP27, HSP40, HSP60, HSP 70, and HSP 90. Rutin's modulation of the iNOS-Nrf2 signaling pathway underscores its potential to maintain intracellular redox homeostasis (Singh et al. 2019). Choi et al. 2021, explored Rutin's protective effects on mitochondrial dynamics and alcohol-induced liver steatosis. The study revealed that Rutin

inhibits lipid absorption in alcoholic fatty liver disease of zebrafish by suppressing *c/ebp α* and *PPAR γ* mRNA expression. Additionally, Rutin restores mitochondrial morphology by inhibiting the *drp1* expression-dependent mitochondrial fission mechanism.

p-Coumaric acid

p-Coumaric acid (*p*-CA) serves as a prominent hydroxycinnamic acid within *O. basilicum*, exhibiting a concentration of 1.653 mg/g. In *O. sanctum* and *O. tenuiflorum*, the quantities are 0.02 mg/g, 0.01 mg/g, and 0.06 mg/g respectively, in the entire plant extract (Pandey et al. 2016). Sabitha et al. (2020) elucidated the protective mechanisms of *p*-CA against alcohol-induced severe liver injury by mitigating reactive oxygen species (ROS) production, mitochondrial depolarization, and nuclear fragmentation in in-vitro cell lines L-02 and HepG2. Notably, *p*-CA treatment suppressed the expression of Bax, Caspases, and lipid biomarkers in rat liver tissue, thereby ameliorating hepatic injury. The inhibitory effect extended to mitogen-activated protein kinases (MAPKs) such as JNK, ERK, and p38 phosphorylation, while concurrently enhancing the antioxidant defense mechanism via upregulation of Nrf2 and HO-1. Additionally, *p*-CA treatment demonstrated efficacy in attenuating liver injury caused by the bioaccumulation of fipronil, a broad-spectrum insecticide. In the context of inflammation, *p*-CA exhibited anti-inflammatory properties by suppressing pro-inflammatory cytokines (TNF- α , IL-1 β , IL-10) and myeloperoxidase (MPO) activity. Furthermore, it modulated antioxidant enzymes, contributing to the reduction of oxidative stress-mediated inflammation, as reported by Bal et al. (2022).

Apigenin

Apigenin (1,4', 5,7-trihydroxy flavone), a compound ubiquitously present in various *Ocimum* species such as *O. americanum* (0.094 mg/g dried leaf extract), *O. basilicum* (0.134 mg/g of dried leaf extract), *O. gratissimum* (0.123 mg/g of dried leaf extract), *O. sanctum* (0.700 mg/g of dried leaf extract), and *O. tenuiflorum* (0.443 mg/g of dried leaf extract) as reported by Pandey et al. (2016). In the context of alcohol-induced liver injury, apigenin demonstrates efficacy in mitigating damage through the regulation

of hepatic CYP2E1 enzyme, thereby mitigating oxidative stress. Additionally, it modulates lipogenic gene expression by upregulating hepatic PPAR α (Wang et al. 2017). Furthermore, apigenin exhibits anti-inflammatory properties in hepatocytes, facilitating the translocation of Nrf2 from the cytoplasm to the nucleus. This results in the reduction of NF κ B, TNF α , and intracellular nuclear factor- κ B (I κ B- α) protein expression (Zhou et al. 2020).

Caffeic acid and Chlorogenic acid

Similar to their counterparts, Caffeic acid (CA) and Chlorogenic acid (ChA) belong to the hydroxycinnamic acid class and are found in various *Ocimum* species. CA, a major phenolic acid in *O. americanum*, *O. basilicum*, *O. gratissimum*, *O. sanctum*, and *O. tenuiflorum*, occurs in quantities of 1.080, 0.920, 2.433, 0.390, and 1.006 mg/g of dried leaf extract, respectively (Pandey et al. 2016). Supplementation with CA has been shown to prevent hepatotoxicity induced by xenobiotics, such as fluoride, by modulating the expression of Bax and Caspase-3p20. CA exhibits protective effects on the liver, mitigating apoptosis and oxidative damage through the suppression of mitochondrial stress-associated factors like NADPH oxidase 4 (Nox4), p38 α MAPK, Hsp 60, and the upregulation of Hsp 27 (Kanagaraj et al. 2015). Furthermore, CA plays a role in restoring energy metabolism, including hepatic fatty acid oxidation. This is achieved by upregulating transcriptional coactivators such as Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1 α (PGC-1 α), PPAR α , farnesoid X receptor (FXR), and Liver X receptor (LXR) through the induction of SIRT 1 protein regulation (Xu et al. 2010; Zhu et al. 2018). Additionally, CA exhibits regulatory effects on bilirubin and bile acids, reducing their uptake and synthesis while accelerating their metabolism and efflux. This is accomplished by downregulating uptake transporters Ntcp, Oatp1a4, and Oatp1b2, and upregulating efflux transporters like Bsep and Mrp 2/3/4 (Buko et al. 2021).

Chlorogenic acid is found in varying quantities in *O. americanum*, *O. basilicum*, *O. gratissimum*, *O. sanctum*, and *O. tenuiflorum*, with concentrations of 0.460, 0.180, 0.803, 1.113, and 0.320 mg/g of dried leaf extract, respectively, as reported by Pandey et al. 2016. This compound exhibits anti-inflammatory and

anti-apoptotic effects on hepatocytes and Kupffer cells by suppressing TLR4, TNF α , NF- κ B p65, iNOS, COX-2, Bax mRNA expressions, as well as Caspase 3 and 9 activities. Additionally, ChA enhances mRNA expressions of AMPK- α , nuclear respiratory factor 1, and mitochondrial DNA transcription factor A. It plays a role in repairing mitochondrial dysfunction associated with acute or chronic hepatic injury by promoting ATP production and mitochondrial oxidative phosphorylation (Zhou et al. 2016).

Gallic acid

Ocimum species is a rich source of another small phenolic acid, 3,4,5- trihydroxy benzoic acid or gallic acid (GA). It is a major phenol present in leaves of *O. americanum*, *O. basilicum*, *O. gratissimum*, *O. sanctum*, and *O. tenuiflorum* at a quantity of 0.396, 0.255, 0.366, 0.282, 0.315 mg/g respectively (Pandey et al. 2016). GA serves as a key component in various Ayurvedic herbal formulations designed for diverse liver ailments. Its efficacy extends to mitigating hepatic damage induced by the anti-TB medications isoniazid and rifampicin, accomplished through the activation of Nrf2 and its downstream proteins or genes. When coadministered with these anti-TB drugs, GA effectively hinders the upregulation of the NF κ B–TLR4 axis, as demonstrated in a study by Sanjay et al. 2021. In a separate investigation, gallic acid demonstrated its ability to alleviate hepatic lipid accumulation and impede the progression of non-alcoholic steatohepatitis by activating AMPK. This was achieved through the suppression of transcription factors ACC α , SREBP-1c, and LXR α , which play pivotal roles in fatty acid synthesis. The protective effects of GA were further evidenced by its prevention of apoptotic changes, as indicated by a decrease in Caspase 3/7 activity and ATF3 transcription factor levels, which regulate Bax/Bcl2 mRNA expression (Tanaka et al. 2020). Moreover, GA exhibited a notable impact on liver fibrosis markers, including the reduction of TIMP-1, TGF β -1, platelet-derived growth factor B (PDGF-B), and hydroxyproline, while concurrently restoring expressions of α -SMA and Proliferating Cell Nuclear Antigen (PCNA) (El-Lakkany et al. 2019).

Apart from the mentioned polyphenols, many other similar compounds are present in *Ocimum* species in traces. However, not all have yet been evaluated for

their oxidative stress-modulating potentials. In a recent *in silico* study by Rahayu et al. 2024 flavonoids (apigenin, rutin, and quercetin) and essential oils (α -bergamotene, α -cadinol, methyl cinnamate, and methyl eugenol) from *O. basilicum* were investigated for their involvement in the Keap1/SIRT1/NF κ B pathway. The study demonstrated that apigenin, rutin, α -bergamotene, α -cadinol, and methyl cinnamate exhibit low toxicity. Pharmacokinetic analysis indicated that compounds from *O. basilicum* are primarily absorbed in the human intestine. Protein network analysis revealed the participation of NF κ B and Nrf2 in the inflammatory response and regulation of the stress response. Rutin exhibited the highest binding affinity for Keap1, while α -bergamotene and α -cadinol showed the strongest binding affinities for NF κ B and SIRT1, respectively. Further preclinical studies need to be conducted. The leaves of *O. basilicum* contain about 79% methyl chavicol, a phenylpropanoid group of compounds (Maurya and Sangwan 2020). This compound has been studied for less number of pharmacological activities. Santos et al. 2018 evaluated the *In vitro* antioxidant and anticipated activities of methyl chavicol, which may be promising molecular targets for the treatment of diseases associated with oxidative damage like hepatotoxicity.

Hepatoprotective terpenoids present in *Ocimum* species

A large number of terpenoids present in various *Ocimum* species (Table 2) have been studied for their mechanistic pathways in hepatoprotection. This can be corroborated by the fact that these terpenoids may be responsible for the protective role of *Ocimum* species against hepatotoxicity.

Ocimum species are rich in sesquiterpenoid compounds, including α -copaene, β -elemene, β -caryophyllene, α -humulene, and germacrene D, as reported by Maurya and Sangwan 2020. These compounds are recognized for their hepatoprotective potential. Paukku et al. (2009) have provided a comprehensive quantitative structure–activity relationship analysis of hepatoprotection by sesquiterpenoids, the largest class within the terpenoid category. The analysis outlines essential molecular variables associated with the hepatoprotective activity

of sesquiterpenoid compounds. Notably, the hepatoprotective potency of these compounds is influenced by or can be inferred from specific variables, elucidating molecular electronic and geometrical components.

The variable dipole moment (μ) underscores the observation that the smallest charge separation or lowest μ corresponds to the highest hepatoprotective activity. Steric effects, attributed to the overall size of the molecule and functional groups with secondary sp³ hybridized carbons, contribute to a lowering effect on hepatoprotective activity. Additionally, compounds exhibiting the highest molecular walk count or a substantial number of substituted carbons demonstrate the most robust hepatoprotective activity (Paukku et al. 2009; Vinholes et al. 2014).

The following sections contain a detailed discussion of the hepatoprotective mechanisms of some terpenoids present in *Ocimum* species (Fig. 3).

β -elemene

B-elemene, a sesquiterpenoid compound identified at a concentration of 21% in the stem of *O. sanctum* (Maurya and Sangwan 2020), demonstrates inhibitory effects against liver fibrosis, inflammation, and hepatocellular cancer in various *in vivo* and *in vitro* experimental models. The protective mechanism of β -elemene against CCl₄-induced hepatic fibrosis in Wistar rats involves the down-regulation of the serum angiotensin II-hepatic angiotensin II type 1 (ANGII-AT1) receptor pathway, thereby suppressing hepatic collagen deposition. Additionally, β -elemene down-regulates the lipopolysaccharide signal transduction pathway (Zhu et al. 2009) and decreases TNF- α , plasma endotoxins, and hepatic CD14 expression (Liu et al. 2011). Furthermore, β -elemene exhibits inhibitory effects on the cell proliferation of the murine hepatocellular carcinoma cell line (H22) by elevating histone H1 protein levels (Bao et al. 2012). Supporting this finding, a study by Dai et al. 2013 delved into the anti-proliferative and apoptotic mechanisms of β -elemene on the human hepatoma (HepG2) cell line. The results revealed that β -elemene upregulates Fas/Fas L protein and gene expression, leading to the arrest of the cell cycle in the G2/M phase.

β -caryophyllene

β -Caryophyllene, a bicyclic sesquiterpene present in *O. tenuiflorum*, *O. sanctum*, *O. basilicum*, and *O. americanum*, serves as a natural antioxidant with the ability to inhibit hepatic stellate cell activation. This inhibition is achieved by reducing the activity of the fibrogenesis enzyme 5-lipoxygenase, subsequently suppressing the overproduction of extracellular matrix proteins and the expression of fibrotic marker genes such as COL1a1, TGF β 1, and TIMP1 (Calleja et al. 2013). In a study by Cho et al. 2015, the hepatoprotective mechanism of β -caryophyllene against D-galactosamine and lipopolysaccharide-induced liver injury was explored. It was revealed that β -caryophyllene down-regulates toll-like receptor (TLR4) and receptor for advanced glycation end products (RAGE) protein expression, as well as the phosphorylation of NF κ B, ERK, p38, and c-JNK. Additionally, it inhibits the production of pro-inflammatory cytokines, reduces early growth response protein 1, and suppresses macrophage inflammatory protein 2 expression. Moreover, β -caryophyllene has been identified as a potential remedy for non-alcoholic steatohepatitis, as demonstrated by Arizuka et al. 2017. The compound achieves this by down-regulating the expression of the monocyte chemoattractant and activating factor 1 gene. Chronic treatment with β -caryophyllene, as reported by Varga et al. 2018, also shows promise in improving alcoholic steatohepatitis. This improvement is attributed to the attenuation of kupffer cell-mediated pro-inflammatory cytokine response, up-regulation of PPAR- α , and suppression of neutrophil infiltration.

α -humulene/ α -caryophyllene

α -Humulene, alternatively recognized as α -caryophyllene, emerges as a prolific compound within *O. tenuiflorum*, *O. sanctum*, *O. basilicum*, and *O. gratissimum*. In a recent investigation, this 11-membered monocyclic terpene demonstrated the capability to impede Akt activation and facilitate Caspase 3 activation, thereby inducing mitochondrial apoptosis in hepatocellular carcinoma cells, both in vitro and in vivo contexts (Chen et al. 2019).

α -pinene

α -Pinene, a monoterpene present in *O. tenuiflorum*, *O. sanctum*, *O. basilicum*, *O. gratissimum*, *O. americanum*, *O. lamiifolium* and *O. canum* (Table 2) was found to have a similar apoptotic mechanism with β -elemene. α -pinene acts by suppressing human hepatoma tumor progression by down-regulating CDK1 and miR-221 levels (Xu et al. 2018).

Borneol

Borneol, a lipophilic monoterpene found in *O. tenuiflorum*, *O. sanctum*, *O. basilicum*, *O. lamiifolium*, and *O. gratissimum*, protects rat hepatocytes against exogenous oxidative DNA damage (Horváthová et al. 2012).

Oleanolic acid

Oleanolic acid (OA), a pentacyclic triterpenoid akin to the one reported in *O. tenuiflorum*, *O. sanctum*, *O. basilicum*, and *O. canum*, up-regulates multidrug resistance-associated proteins 2, 3, and 4. This action contributes to the reduction of cholestasis, facilitating normal bile flow from the liver (Sen 2020). Additionally, oleanolic acid demonstrates the ability to enhance the expression of various proteins and their associated genes. It elevates metallothionein, Nrf2, HO-1, and NQO1 expression, while also stimulating the potential of antioxidant enzymes such as SOD, GPx, and glutamate–cysteine ligases (Iranshahy et al. 2018). Notably, oleanolic acid increases the glutathione content in the liver, showcasing its antioxidant potential and promoting hepatic cell regeneration.

Epimaslinic acid

Epimaslinic acid, a member of the pentacyclic triterpenoid class found in *O. basilicum*, demonstrates a significant capacity to up-regulate Nrf2 in hepatocytes (Sen 2020).

Linalool

Linalool, a significant acyclic monoterpene compound identified in *O. tenuiflorum*, *O. sanctum*, *O. basilicum*, *O. gratissimum*, *O. americanum*, *O. lamiifolium*, and *O. canum* (Table 2), activates

cytoprotective genes. This activation occurs through the inhibition of D-galactosamine/lipopolysaccharide-induced NF- κ B up-regulation, as demonstrated in the study by Jadeja et al. 2016.

Eucalyptol

1,8-cineole, also known as eucalyptol and classified as a monoterpene oxide, is a significant compound present in *O. tenuiflorum*, *O. americanum*, and *O. lamiifolium*, exhibiting hepatoprotective activity. Identified as a potent drug candidate for treating non-alcoholic steatohepatitis, eucalyptol achieves this through the inhibition of the PI3K/Akt pathway. Notably, it hinders the progression of liver fibrosis by down-regulating collagen 1a1 expression (Murata et al. 2015). Additionally, eucalyptol has been found to effectively reduce myeloperoxidase activity, malondialdehyde (MDA) levels, and pro-inflammatory cytokines such as TNF- α , IL-8, IL-6, and IL-1 β . Simultaneously, it increases the levels of the anti-inflammatory cytokine IL-10 and the antioxidant enzyme GSH (Lima et al. 2013). Furthermore, eucalyptol enhances PPAR- γ expression, leading to the down-regulation of NF κ B (Linghu et al. 2019). These collective findings suggest that eucalyptol can mitigate oxidative stress within the liver through its anti-inflammatory mechanisms.

Ursolic acid

Ursolic acid (UA), a prominent pentacyclic triterpenoid, is found in significant quantities in *O. basilicum*, *O. gratissimum*, *O. sanctum*, *O. tenuiflorum*, and *O. americanum*, with concentrations of 8.033, 6.933, 1.473, 4.800, and 0.373 mg/g of dried leaf extract, respectively (Pandey et al. 2016). Research indicates its effectiveness in safeguarding against chronic alcoholic liver damage. This protection is achieved through the modulation of glutathione homeostasis and the downregulation of the NQO1 gene and protein expression, as NQO1 is a Phase II detoxifying enzyme belonging to the GST family and associated with Nrf2 activation (Yan et al. 2022). UA treatment has been observed to significantly impede the activation of CASP3 and cleavage of PARP, mitigating DNA degradation and apoptosis, thereby reducing the risk of alcoholic liver injury (Ma et al. 2021). Furthermore, UA treatment suppresses the

phosphorylation of PI3K, Akt, and NF κ B signaling processes, along with the associated cytokine oncostatin M production, contributing to the alleviation of hepatic inflammation (Han et al. 2022).

The molecular mechanistic pathways of numerous other terpenoids within *Ocimum* species have not been thoroughly explored. The 3D-QSAR model has been employed to analyze the molecular structure of α -copaene, a sesquiterpenoid found in *O. sanctum* and *O. americanum*. The analysis revealed that α -copaene possesses a compact structure with less molecular symmetry and electronegative substitution. Although the results of hepatoprotective activity analysis suggest its potential efficacy in liver protection (Vinholes et al. 2014), the specific molecular mechanisms underlying its hepatoprotective effects remain unknown.

Toxicity profile of the compounds preeet al.,t in *Ocimum* species

To develop a safe and targeted phytomedicine, the toxicity profile of phenols and terpenoids in *Ocimum* species has been studied. *Ocimum basilicum* powder, identified as having the lowest toxicological risk, was extracted using various solvents, including n-hexane, dichloromethane, ethanol, and water. The ethanolic basil leaf extract was selected for further analysis due to its lower toxicological effects. Phytochemical analysis of the ethanolic extract identified rosmarinic acid, ellagic acid, catechin, liquiritigenin, and umbelliferone. Additionally, aqueous extracts of basil, at concentrations ranging from 10 to 1000 μ g/mL, exhibited no toxicity (Nadeem et al. 2022). Ajayi et al. (2017) observed the acute toxicity effects of crude methanol extracts of *Ocimum gratissimum* leaves. Comparative acute toxicity tests revealed no mortality in rats administered doses of 2 and 5 g/kg. The extracts did not produce significant changes in the behavioral patterns, skin color, diarrhea, food intake, water consumption, or body weights of the treated animals immediately after administration or during the 14-day observation period. In another study, a 28-day subacute oral toxicity test of an aqueous extract of *Ocimum basilicum* leaves, containing phenolic acids (p-hydroxybenzoic, vanillic, caffeic, and rosmarinic acids) and flavonoids (naringenin, rutin, quercetin, and kaempferol), revealed no toxic effects in rats at doses

of 50, 200, and 500 mg/kg (Housse et al. 2023). Ali et al. (2022) demonstrated the potential cytotoxicity of all crude extracts and fractions of *Ocimum americanum* L. on Clarkson's scale, indicating low median lethal concentration (LC₅₀) values. The chloroform and ethyl acetate fractions of the hydroethanolic crude extract exhibited the highest toxicological profiles against brine shrimp larvae. The chloroform fraction (LC₅₀ 0.59 µg/mL) had a lower median lethal concentration compared to the standard drug vincristine (LC₅₀ 11.83 µg/mL), suggesting a high potential for this fraction as a novel compound warranting further bioprospecting. Similarly, the ethyl acetate fraction (LC₅₀ 44.65 µg/mL) was highly toxic according to Clarkson's criteria. The acetonic crude extract and fractions, as well as the aqueous fractions, exhibited moderate toxicity (LC₅₀ 303.39 µg/mL). The aqueous crude extract was slightly toxic (LC₅₀ 559.71 µg/mL), supporting the observation that acute use of herbal decoctions does not show toxicity in patients.

Conclusion

The effectiveness of phytomedicine is influenced by key groups of phytoconstituents present in plants, comprising alkaloids, terpenoids, tannins, flavonoids, saponins, quinones, and polyphenolics. Natural compounds, especially plant phenolics and terpenoids, have gained prominence due to their efficacy, minimal side effects, and protective properties. Polyphenols and terpenoids comprise the major share of all the phytoconstituents present in various *Ocimum* species. Pharmacological reports support the hepatoprotective properties of *Ocimum* species. Sametime, diverse polyphenols and terpenoids found in various *Ocimum* species have been investigated to understand their impact on signaling pathways, proteins, and genes associated with hepatoprotection. The findings of these investigations consistently demonstrated the effectiveness of terpenoids and phenolic compounds against hepatotoxicity. This mechanistic review provided a comprehensive exploration and clarification of the extensive molecular mechanisms involved in hepatoprotection by specific polyphenols present in *Ocimum* species. However, the limitations are that most of these hepatoprotective studies presented in this review have used different extracts of *Ocimum*, without identifying the individual compounds present

in them. So, the specific mechanistic activities elicited by these individual phytochemicals remain unstudied and the antiviral properties of *Ocimum* in treating viral hepatitis remain largely unexplored. Consequently, targeted clinical trial investigations are necessary to unlock the full potential of *Ocimum* species for developing hepatoprotective therapies. As a result, various marketed herbal formulations of Tulsi are available as immunity boosters, and vitamin and nutrition supplements but no hepatoprotective herbal formulation from crude Tulsi or any of its isolated compounds has been marketed till now.

Future directions

Finally, to derive a potent hepatoprotective medication from this species, focused studies are required to elucidate the cellular molecular targets. Despite a rich reservoir of polyphenols and terpenoids, not all the species of *Ocimum* have been studied for hepatoprotective properties. Additionally, the natural variations of these compounds across different species are influenced by environmental factors such as weather and nutrients, posing a challenge in isolating lead molecules. Thus modern techniques, including tissue culture, biotransformation, and fermentation, need to be employed to overcome these challenges and extract hepatoprotective phytochemicals effectively. Information derived from human trials is also inconclusive regarding the use of *Ocimum*. In a parallel, randomized, single-blind trial to evaluate the effects of *O. basilicum* (dosage of 10 g/ day or a control group without a placebo for 12 weeks) in patients of NAFLD with hepatic steatosis did not produce significant anthropometric changes (Akbarian et al. 2016). Consequently, further research is required for the separation and isolation of phytoconstituents along with assessments of chronic toxicity, and clinical studies of the active biomolecules.

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Declarations

Conflict of interest The authors declare no conflict of interest.

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