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Review

Hepatoprotective effects of rosmarinic acid: Insight into its mechanisms of action

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ABSTRACT

Liver diseases such as hepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma are one of the major health challenges in the world and many conditions such as inadequate nutrition, viral infection, ethanol and drug abuse, xenobiotic exposure, and metabolic diseases have been implicated in the development and progression of liver diseases. Several factors including lipid peroxidation, production of reactive oxygen species (ROS), peroxynitrite formation, complement factors and proinflammatory mediators, such as cytokines and chemokines, are involved in hepatic diseases. Rosmarinic acid (RA) is a natural phenolic compound found mainly in the family Lamiaceae consisting of several medicinal plants, herbs and spices. Several biological activities have been reported for RA and these include antioxidant properties as a ROS scavenger and lipid peroxidation inhibitor, anti-inflammatory, neuroprotective and antiangiogenic among others. This review is aimed at discussing the effects of RA on the liver, highlighting its hepatoprotective potential and the underlying mechanisms.

1. Introduction

The normal liver contains resident and migratory lymphocytes, macrophages and leukocytes (infiltrated monocytes and neutrophils) that provide immune surveillance against foreign antigens [1]. However, cell types such as hepatocytes parenchymal, the Kupffer, sinusoidal endothelial and stellate (fat-storing or Ito) are also present in the liver [2]. The cells of the liver are primary targets for oxidative stress and toxicity induced by a variety of agents. This is because the liver is a major site for drug metabolism coupled with the proliferative response of the hepatocytes.

Liver injury is one of the major health challenges in the world. Dysregulation of the liver function leads to pathologies including hepatitis, fibrosis, cirrhosis, hepatocellular carcinoma etc. Usually, liver disease progresses from histological and biochemical changes such as hepatocyte death, hepatic stellate cell (HSC) activation, Kupffer cell (KC) activation, peripheral inflammatory cell infiltration and activation, free radical generation, proinflammatory cytokine production, and extracellular matrix protein expression and deposition to irreversible cirrhosis and hepatocellular carcinoma (HCC) [3–5]. Several factors such as inadequate nutrition, viral infection, ethanol and drug abuse, xenobiotic exposure, and metabolic diseases have been implicated in the development and progression of liver diseases [3,6]. However, it's been documented that the main causative agents for hepatic injury that triggers the onset of liver failure in a particular area depends on the prevalent hepatotropic virus infections and patterns of drug use [6–8].

Cholestasis has relatively high morbidity and mortality rates worldwide [9,10] and is caused by the impairment of bile formation and/or bile flow [9]. The most chronic cholestatic diseases result from hepatocellular functional defects or obstructive lesions of the small intrahepatic bile ducts [10]. On the other hand, hepatitis A, B, C, D, and E are viral infections of the liver with different viruses responsible for each type and high incidence of Hepatitis A infection has been linked with poor hygiene and sanitation [11]. However, drug-induced injury which is the second main cause of acute liver failure is very common in the developed world [12]. Paracetamol-induced hepatoxicity is the most common example and other drugs implicated in liver injury vary by location and prevailing drug use with anti-infectives, anticonvulsants, and anti-inflammatory drugs being the most common while herbal or adulterated traditional or complementary medications have been implicated in East Asia [13,14].

Fibrogenesis, a normal physiological repairs process after injury or inflammation, can be dysregulated after chronic injury thus leading to abnormal accumulation of the extracellular matrix which results into fibrosis [13] and eventual loss of functional cells and impaired function of the liver [15,16]. Transforming growth factor-β (TGF-β) is the major pro-fibrotic factor in liver fibrosis which means that inhibition of TGF-β or blocking its downstream signaling pathway will lead to prevention of

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the fibrotic process in the liver [15]. However, because TGF-β is also an important anti-proliferative and anti-inflammatory agent, its inhibition may have positive or negative effect [16]. Thus, connective tissue growth factor (CTGF), which acts as a down-stream mediator of TGF-β1 induced fibrosis is an alternative target for therapy [19] since its inhibition result in a potent reduction of fibrosis [17].

Consumption of alcohol has also been linked to liver disease (alcoholic liver disease, ALD) that manifest as an acute (alcoholic hepatitis) or chronic (steatosis, steatohepatitis, fibrosis and cirrhosis) form [18]. Oxidative stress [19] and changes in lipid metabolism [20] resulting in damage to cell membranes and organelles (especially mitochondria) are implicated in ALD. Individual susceptibility, presence of other liver disease involvement such as viral hepatitis [21], obesity and metabolic syndrome [22] are also contributing factors. Classical mechanisms of fibrogenesis in ALD are alcohol metabolism, oxidative stress, methionine metabolism abnormalities, hepatocyte apoptosis and increased serum lipopolysaccharide (LPS) level that activates KC [23]. However, at the early stages of ALD, lipogenesis has been implicated as a risk factor for the progression of cirrhosis. This makes newer mechanisms involve stimulation of lipogenesis and inhibition of fatty acid oxidation, osteopontin, IL-1 signaling and genetic variations [23]. ALD can present in many disease states including asymptomatic fatty liver, steatohepatitis, progressive fibrosis, end-stage cirrhosis, and HCC [24,25].

Hepatocellular carcinoma is one of the most common and lethal cancers worldwide [24] and it is the fifth leading cause of cancer, ranking third in cancer mortality [25]. Inflammation is closely linked to carcinogenesis [26] as exemplified by HCC [27] and both chemically or genetically induced HCC depends on inflammatory signaling [28]. Different signaling pathways are involved in injury-inflammation-regeneration response and in human HCC development. Out of these signaling pathways, inhibitor of κB kinase β (IKKβ)-dependent classical nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling and signal transducer and activator of transcription 3 (STAT3) were found to be critical for compensatory liver regeneration and chemically-induced HCC development [29].

The use of complementary and alternative medicine that includes dietary supplementation with plant-derived phytochemicals is on the increase for health promotion and therapy. Rosmarinic acid (RA, Fig. 1), an ester of caffeic acid and 3,4-dihydroxyphenyl lactic acid, is a major constituent of Chinese and oriental herbal medicines and is commonly found in species of the Boraginaceae and the subfamily Nepetoideae of the Lamiaceae. The presence of RA in medicinal plants, herbs and spices has been associated with beneficial and health promoting effects. In plants, RA is supposed to act as an accumulated defense compound and in humans, it has a number of biological activities such as antiviral, antibacterial, anti-inflammatory, anti-mutagenicity and antioxidant [30]. RA has very low toxicity and is rapidly eliminated from the blood circulation after intravenous administration [31]. The goal of the present review is to provide a comprehensive literature survey on the effects of RA on liver and discuss its possible mechanism of action vis-à-vis hepatoprotection

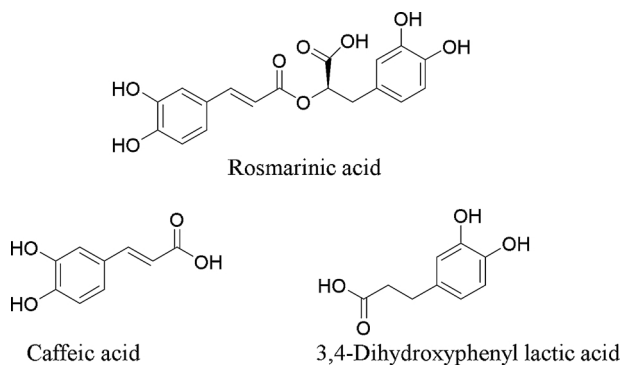

Fig. 1. The structure of rosmarinic acid and its precursors.

2. Mechanism of hepatotoxicity

2.1. Hepatotoxicity resulting from mitochondrial dysfunction

Inhibition of mitochondrial β-oxidation causes deprivation of cellular energy during fasting [32]. Nonesterified fatty acids (NEFAs) and their metabolites also impair mitochondrial energy production [32]. This deficiency of energy causes liver failure, pancreatitis, coma, and even death [32]. Many drugs are known to impair mitochondrial β-oxidation and cause microvesicular steatosis through various mechanisms [2]. These include nonsteroidal antiinflammatory drugs [33], tetracycline derivatives [34] glucocorticoids [35], antianginal cationic amphiphilic drugs [36], as well as female sex hormones or pregnancy [37]. β-oxidation and respiration are also inhibited by cationic amphiphilic drugs which concentrates in the mitochondria [36]. The inhibition of respiration leads to production of ROS by mitochondria and cause lipid peroxidation of fat deposits [36]. Both lipid peroxidation and ROS induce release of cytokine such as TGF-β, tumor necrosis factor alpha (TNF-α), and interleukin-8 (IL-8) which contributes to the development of nonalcoholic steatohepatitis (NASH) [38]. Also, cytolytic hepatitis, a severe liver lesion that can cause liver failure results from mitochondrial uncoupling, respiratory inhibition and mitochondrial permeability transition (MPT) caused by opening of permeability transition (PT) pores in the mitochondrial inner membrane [2].

2.2. Apoptosis induced by bile acids

The liver produces bile and failure of bile production is referred to as cholestasis. Retention of bile constituents within the hepatocyte during cholestasis results in hepatocyte apoptosis [39] and failure to secrete bile acids into bile results in liver injury, cirrhosis, and death from liver failure [40]. Experimentally using cultured rat hepatocytes, the hydrophobic bile acid glycochenodeoxycholate, GCDC, at appropriate concentrations (20–100 mM) can induce apoptosis. This is evidenced by cell shrinkage, nuclear condensation and lobulation, caspase activation, DNA fragmentation, and phosphatidylserine externalization [41]. Hepatocytes apoptosis occurs by either death receptor pathway or the mitochondrial pathway [42]. Tumor necrosis factor-receptor 1 (TNF-R1) and first apoptosis signal receptor (FasR) are the predominant death receptors expressed by hepatocytes [43]. Ligand-independent Fas-mediated apoptosis is also an implicated mechanism in bile acid-related liver injury [44]. The potential mechanisms for bile acid-induced Fas activation include alterations in Fas synthesis, Fas compartmentation, and Fas trimerization in the plasma membrane. Bile acid also promotes rapid transport of cytoplasmic vesicular Fas to the plasma membrane in a microtubule-dependent manner [45].

2.3. CYP2E1-dependent toxicity in HepG2 cells

The ethanol-inducible form of cytochrome P4502E1 (CYP2E1), activates and metabolizes many toxicologically important substrates, such as ethanol, carbon tetrachloride, acetaminophen, and N-nitrosodimethylamine, to more toxic products [46]. CYP2E1-dependent metabolism of ethanol generates ROS leading to oxidative stress [47]. Ethanol-induced liver pathology correlates with CYP2E1 levels and elevated lipid peroxidation, which is blocked by inhibitors of CYP2E1. The hypothesis of the role of CYP2E1 in alcohol-induced oxidative stress and hepatotoxicity suggests that though several mechanisms may contribute, the linkage between CYP2E1-dependent oxidative stress, mitochondrial injury, and increased collagen formation by stellate cells are important mechanistic contributions to the toxic action of ethanol on the liver [2].

2.4. Liver toxicity involving peroxynitrite

Acetaminophen produces centrilobular hepatic necrosis when taken in overdose [48]. The initial step in acetaminophen toxicity is metabolism to N-acetyl-*p*-benzoquinone imine (NAPQI) and this causes depletion of the reduced form of glutathione (GSH) and covalent adduct formation. In wild type mice, induction of nitric oxide (NO) synthesis and superoxide anion generation occurs subsequently, leading to peroxynitrite formation. However, in inducible nitric oxide synthase (iNOS) knockout mice, superoxide increases after acetaminophen but not NO synthesis. Superoxide anion then causes lipid peroxidation. Thus, acetaminophen toxicity may be mediated by nitration in wild type mice and by lipid peroxidation in iNOS knockout mice. Cosequently, hepatotoxins like acetaminophen, bromobenzene, chloroform, and allyl alcohol that deplete hepatic GSH and encourages peroxynitrite formation will promote hepatic toxicity. However, with hepatotoxins that cause lipid peroxidation but do not deplete GSH, such as carbon tetrachloride, NO may scavenge superoxide by forming peroxynitrite, which is then detoxified by GSH [2].

2.5. Inflammation, oxidative stress and adhesion molecules in liver diseases

Systemic and local inflammation, with recruitment of macrophages and neutrophils into the liver vasculature characterizes certain pathologies such as sepsis, alcoholic hepatitis, ischemia-reperfusion injury, and some drug-induced liver toxicities [49,50] The functions of these macrophages and neutrophils are to destroy invading organisms as well as remove dead cells and debris in preparation for tissue regeneration. In the course of this function however, healthy cells might be affected, which can aggravate the original liver injury [2]. Events such as drug toxicity, tissue trauma, ischemia-reperfusion, sepsis, and other pathophysiological conditions activate both neutrophils and KC either directly or through activation of complement. KC then releases cytotoxic mediators, such as ROS, and proinflammatory mediators such as cytokines and chemokines. Complement factors (e.g., C5a) and cytokines activate neutrophils to promote their recruitment into the hepatic vasculature. Neutrophils, when chemotactically stimulated then extravasate and adhere to parenchymal cells, which induces necrotic cell death through release of ROS and proteases [2]. The adhesion and subsequent infiltration of leucocytes to extravascular tissues is a result of induced expression of several key adhesion molecules on the surface of inflammatory cells (leucocytes, endothelial cells, etc.). The overall mechanism of liver disease pathology is depicted in Fig. 2.

3. Rosmarinic acid (RA)

Rosmarinic acid (Fig. 1) is a natural phenolic compound with many biological activities. It consists of two phenolic rings, both of which contain two hydroxyl groups in *ortho*-position. Joining the two rings are an unsaturated double bond, a carbonyl group, and a carboxylic acid group.

RA was first isolated from *Rosmarinus officinalis* in 1958 by Italian chemists, Scarpati and Oriente hence the name [51] and it is mainly found in species of the family Boraginaceae and subfamily Nepetoidae (family Lamiaceae) [31]. Examples of other plants containing RA are *Origanum vulgare* (oregano), *Thymus* vulgaris (thyme), *Mentha spicata* (spearmint), *Perilla frutescens* (perilla), *Ocimum basilicum* (sweet basil) and several other medicinal plants, herbs and spices [52]. The level of production of RA depends on the natural source from which it is obtained [53] and this may range from 1.5 (in *R. officinalis*) to 20.0% w/w (in *Perilla frutescens*) [54]. RA has been shown to possess many biological activities like antitumor [55], antiangiogenic [56], antidepressive [57], anti-inflammatory [58], anti-allergic [59] antimicrobial [60], neuroprotective [61] and HIV-1-inhibiting properties [62]. It has also been reported to have antioxidant properties as a reactive species scavenger and lipid peroxidation inhibitor [63]. Its antimutagenic activity effect has been documented by several authors [59,64].

4. Effect of rosmarinic acid on liver

Several researches involving different experimental models have reported the effects of RA on the liver.

4.1. RA on lipopolysaccharide (LPS) and D-galactosamine ($_D$GalN)-induced liver failure

LPS) and $_D$GalN-induced liver failure is a well-established experimental model [65–69] which capitalizes on the ability of $_D$-GalN, a transcriptional inhibitor, to potentiate the toxic effects of LPS in producing typical hepatic necrosis and apoptosis followed by fulminant hepatitis [70,71]. LPS activates KC which then secrete various cytokines such as interleukin 1 (IL-1), interleukin 6 (IL-6), and TNF-α [68]. TNF-α appears to be the major inflammatory cytokine implicated in liver injury induced by LPS and $_D$-GalN [72–74]. The induction of apoptosis by TNF-α also involves the activation of the cysteine protease caspases [68]. Furthermore, NO overproduction resulting from upregulation of iNOS expression, is also implicated to the induction of apoptosis in a number of different cell types [75–77]. All these events can be studied *in vivo* using the LPS and $_D$GalN model [73].

RA from *Perilla frutescens* was shown to possess protective effect against the LPS-induced liver injury in $_D$-GalN-sensitized mice [78]. The mechanism of RA protection was confirmed by investigating the effects of anti–TNF antibody, SOD, and aminoguanidine in this model. RA treatments significantly reduced the elevation of plasma asparatate aminotransferase (AST) levels, as well as had anti-TNF and SOD effect compared with controls as confirmed by histological examination (Table 2). However, increase in TNF-mRNA expression in liver and in plasma TNF levels were not significantly reduced by RA. RA also did not reduce iNOS mRNA expression or plasma nitrate/nitrite levels suggesting that its liver protective effect might be due to scavenging or reducing activities of superoxide or peroxynitirite rather than to inhibition of TNF [78].

4.2. RA on Tert-butyl hydroperoxide (t-BHP)-induced oxidative liver damage

Butyl hydroperoxide (BHP) is a popular compound used to induce acute oxidative stress *in vitro* and *in vivo* [79–81]. It is usually metabolized by cytochrome P450 to free radical intermediates like *t*-butoxyl and – *t*-methyl radicals, [76] which can cause lipid peroxidation [77], GSH depletion [82] and DNA damage [79]. *t*-BHP-induced hepatotoxicity is a reaction involving GSH peroxidase which converts GSH to glutathione disulfide (GSSG). With the expense of NADPH oxidation, GSSG is reduced back to GSH by GSH reductase. Decreased GSH and oxidized NADPH contribute to altered Ca^{2+} homeostasis, which is considered to be a major event in *t*-BHP-induced hepatotoxicity [80].

The hepatoprotective effects of RA alone and in combination with caffeic acid (CA) was reported in *t*-BHP-induced oxidative liver damage [83]. In an *in vitro* study, CA remarkably reduced the oxidative damage more than RA. However, in an *in vivo* experiment involving administration of CA or RA alone for five days prior to treatment with a single dose of *t*-BHP (0.5 mmol/kg b.w., i.p.), there was a significant reduction of indicators of hepatic toxicity, such as AST, ALT, GSSG, lipid peroxidation. The activities of antioxidant enzymes (catalase, glutathione peroxidase and SOD) were also enhanced by RA (Table 2) [83] though the hepatic protection appears to be additive with CA [83].

4.3. RA on Carbon tetrachloride (CCL_4)-induced rat liver fibrosis model

Carbon tetrachloride (CCl_4) intoxication is the most common study model of liver injury [81]. CCl_4 is activated by hepatic microsomal cytochromes to form the trichloromethyl radical, $\cdot CCl_3$ which induces

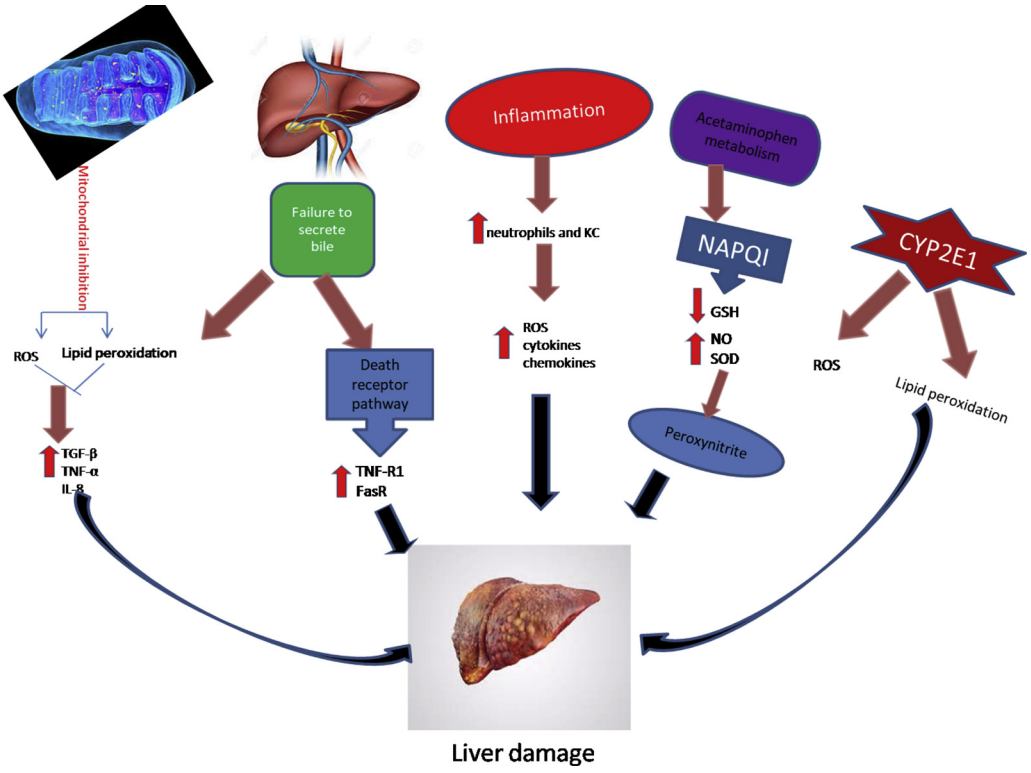

Fig. 2. Different mechanisms leading to liver diseases. Inhibition of mitochondrial β-oxidation leads to lipid peroxidation and generation of ROS. Both lipid peroxidation and ROS cause the release of cytokines (TGF-β, TNF-α, and IL-8) which precipitate liver dysfunction. CYP2E1 and bile acid dependent (in addition to the receptor death pathway) also go through the mitochondrial pathway to induce liver injury. Peroxynitrite formation through depletion of GSH as well as increased SOD and NO synthesis results from the metabolism of such drugs as acetaminophen and lead to liver injury.

oxidative stress by binding to biological molecules. This leads to impairment of numerous cellular processes that culminate in necrotic cell damage, inflammation and apoptosis [84]. Nonlethal intoxication triggers liver tissue remodeling and healing through the activation of trichloromethyl radical and produce liver fibrosis [85]. CCl_4 intoxication causes hepatic necrosis and increase serum alanine aminotransferase (ALT) activity [86]. The oxidative/nitrosative stress caused by CCl_4 in the liver usually leads to increased 3-nitrotyrosine (3-NT) and thiobarbituric acid reactive substances (TBARS) formation and a significant decrease in Cu/Zn superoxide dismutase (SOD) activity. CCl_4 administration also triggers inflammatory response in mice livers by activating NF-κB, which coincided with the induction of TNF-α and cyclooxygenase-2 (COX-2) [86]. Usually, CCl_4 induces typical necrosis but this can be accompanied by increased apoptosis of hepatocytes [87]. While TGFs pushes toward fibrosis, TNF-α appear to direct toward activation of caspases and apoptosis [81]. Thus, CCl_4 destroys not only plasma membrane but also phospholipid bilayer in mitochondria [88] and this triggers caspase-3-dependent apoptosis [89].

The *in vitro* and *in vivo* antifibrotic effects of RA on experimental liver fibrosis have also been reported. In the CCl_4-induced rat liver fibrosis model, liver fibrosis grade and histopathological changes, as well as immunohistochemical detected liver TGF-β1 and connective transforming growth factor (CTGF) expression were noted [17]. In this study, RA inhibited (HSCs) proliferation, TGF-β1, CTGF and α-smooth muscle actin (α-SMA) expression in cultured HSCs (Table 1). It also reduced fibrosis grade, ameliorated biochemical indicator and histopathological morphology [17].

Similar study also documented that severe acute liver damage caused by CCl_4 administration could be significantly ameliorated by RA [86]. The study reported that though the increase in relative liver weight persisted even with RA treatment, the body weight loss in experimental animals was greatly reduced, suggesting a less deleterious effect of CCl_4. It was also observed that RA dose-dependently decreased hepatic histopathological changes and serum ALT levels in CCl_4-intoxicated mice. RA also substantially reduced the necrotic area, expression of active caspase-3 and suppressed oxidative/nitrosative liver damage [86]. Furthermore, liver inflammation caused by CCl_4 intoxication was significantly ameliorated by RA treatment. The study also showed that suppression of inflammation by RA was mediated through the inhibition of the NF-κβ pathway and down-regulation of TNF-α and COX-2 and submitted that RA has antifibrotic effects which were achieved through inhibition of TGF-β1.

4.4. RA on Extrahepatic cholestasis rat model by bile-duct ligation (BDL)

Bile acids are required for intestinal nutrient absorption as well as hepatic metabolism. They are dynamically balanced by intrahepatic biliary tree through secretory and reabsorptive processes under normal condition. Any obstruction of the hepatobiliary system leads to elevation of biliary pressure, disruption of intrahepatic bile duct integrity, and leakage of bile into the liver thus predisposing the liver to cholestasis [3,52]. This results into stimulatory effects on biliary cholangiocytes, hepatocytes, HSC, and KC which causes many biochemical consequences like hepatocyte death and hepatic inflammation, oxidative stress, and fibrosis [51–53]. Surgical ligation of bile ducts in rodents can induce extrahepatic cholestasis and has been used as a model for pathophysiological and therapeutic studies of cholestatic liver injury [90,54–56].

Dietary RA supplementation has been reported to have hepatoprotective benefits using a BDL model of cholestasis in rats [3]. The cholestatic hepatoprotective effect of RA was due to its improvement in serum biochemicals and hepatic histopathological changes, fibrosis, inflammation, and oxidative stress. RA inhibited the development of hepatic fibrosis and suppressed the activation of matrix producing cells and fibrogenic changes. On cultured HSC, it also inhibited TGF-β1-induced stellate cell mitogenic and fibrogenic activation by suppressing post-receptor TGF-β1 signaling, fibrogenic molecule expression, and cell cycle regulator expression. The study also showed that RA improved BDL-induced oxidative stress as well as an induction of hepatic toll-like receptor 4 (TLR4) signaling in BDL rats and its reversal by RA [3].

Table 1
In vitro hepatoprotective effect of rosmarinic acid.

Experimental model used	Concentration/dose applied	Major outcomes	References
Effects on XME in rat liver.	0.5% (w/w)	WSE containing RA, flavones and monoterpenes enhanced CYP 1 A1, 2B1/2, 2E1and GST but no modification of XME	[97]
The *in vitro* antifibrotic effect of RA on experimental liver fibrosis in CCL_4-induced rat liver fibrosis model.	Dose range 2.5 mg/kg to 10 mg/kg	RA inhibited HSCs proliferation and inhibited TGF-β1, CTGF and α-SMA expression in cultured HSCs.	[17]
Ex vivo study using (fPCLS)	120-270 μM	RA inhibited TGF-β1 signaling and reduced collagen expression in liver slices.	[50]
Effect of RA on HSC	8 mg/ml RA	RA inhibited proliferation and induce apoptosis in HSC-T6 by the down-regulation of CyclinD1 and Bcl-2 mediated by the phosphorylation of STAT3.	[64]
Effect of RA on t-BHP-induced oxidative liver damage	RA 26.84 μg/mL	RA reduced indicators of hepatic toxicity, such as AST, ALT, oxidized GSH, lipid peroxidation and enzyme activities related to antioxidant such as catalase, glutathione peroxidase and SOD.	[83]

4.5. RA on precision-cut liver slices

The *ex vivo* experimental method for liver damage involves the use of precision-cut liver slices from fibrotic rat livers (fPCLS) to study antifibrotic drugs [91,92]. The major advantage of PCLS cell culture systems is the presence and viability of all cell types of the liver and also, this model uses the original cell–cell and cell–matrix contacts are retained [51]. Compared to *in vivo* experiments however, there is a significant reduction in the numbers of animals required because about 250 slices of 5-mm diameter and 250-μm thickness can be prepared from a normal rat liver and up to 40–45 from a normal mouse liver [93]. Different culturing systems for PCLS are also available [91] making the model easy to use. The dynamic organ culture system and the 6–12 wells plate incubation systems have been used successfully for the studies of liver fibrosis [65,94,95]. Moreover, slices of healthy liver have been used to study the mechanisms of early onset of fibrosis and the efficacy of antifibrotic drugs while slices from fibrotic tissue have been utilized to study the effect of antifibrotic drugs in fully developed fibrotic liver tissue [96].

The effect of RA was also investigated in an *ex vivo* study using fPCLS [50]. RA had no effect on ATP values of fPCLS, but had a concentration-dependent reduction of the gene expression of the fibrosis markers (Table 1). It also decreased the total collagen content as detected by the hydroxyproline content [50].

4.6. Other mechanisms of RA effect on the liver

The effects of RA and water-soluble extract (WSE) of rosemary (containing 1,2% RA) after dietary administration, on xenobiotic metabolizing enzymes (XME) were studied in rat liver [108]. This was done by evaluating the modulation of phase I enzymes such as cytochrome P450 (CYP) 1 A, 2B, 2E1, 3 A, and phase II enzymes such as glutathione *S*-transferase (GST), quinone reductase (QR) and UDP-glucuronosyltransferase (UGT) by measuring enzyme activities with specific substrates. Protein levels of CYPs and rGST A1/A2, A3/A5, M1, M2 and P1 were also measured using antibodies in Western blots. The extract containing RA, flavones and monoterpenes enhanced CYP 1 A1, 2B1/2, 2E1 and GST (especially rGST A3/A5, M1 and M2), QR and UGT. However, RA and caffeic acid (CA) did not modify XME (except for a slight increase of UGT activity after CA treatment) thus the induction of XME by WSE could be attributed to flavones, monoterpenes or an additive effect of all components (Table 1). On the whole, WSE of rosemary strongly enhanced detoxification enzymes in rat liver [97].

The liver regeneration potential of RA has been reported by Lou et al., [98]. RA stimulated hepatocyte proliferation during liver regeneration processes. Specifically, RA activated the mechanistic target of rapamycin (mTOR) signaling pathway during liver regeneration and rescued partial hepatectomy (PH) impaired liver functions [98]. Treatment with RA resulted in an increase in body weight and stimulation of proliferating cell nuclear antigen (PCNA) protein expression from days 2 to 4 in mice due to the activation of the mTOR/S6K pathway during the early period of hepatic regeneration. It also significantly increased the level of binuclear hepatocytes in the treated group. The study showed that RA stimulated hepatocyte proliferation during liver regeneration through the mTOR signaling pathway (Table 2).

The effect of RA on liver ischemia/reperfusion (I/R) injury has also been reported [19]. It was observed that RA reduces hepatocellular injury following liver I/R. I/R induced extensive areas of coagulation necrosis with disintegration of hepatocyte cords and inflammatory cell infiltration. These histologic and serum parameters of hepatocellular injury were significantly attenuated in animals treated with RA [99]. RA also protects the hepatic parenchyma from I/R-induced oxidative stress. RA treatment reduced considerably lipid hydroperoxide levels in the liver parenchyma. Also, the total hepatic antioxidant capacity and the hepatocellular reserves of GSH were partially preserved by RA administration [99]. The study also found that RA decreases hepatic NO content and nitrosative stress after I/R. RA-treated animals showed a dramatic decrease of nitrotyrosine staining, exhibited decreased NO levels and reduced the levels of both eNOS and iNOS in the liver [99]. RA also attenuated I/R-induced inflammatory response in liver. It down regulated polymorphonuclear leukocytes recruitment into the livers of rats subjected to I/R and remarkably diminished the accumulation of phagocytes in the liver. It also markedly down-regulated I/R-induced p65 nuclear translocation and substantially decreased hepatic mRNA levels of pro-inflammatory cytokines [99].

The suppressive effects of RA on cell proliferation has also been reported [64]. HSC-T6 cells treated with RA grew at a significantly slower rate in a dose and time dependent manner compared to non-treated cells with the most effective dose being 8 mg/ml [64]. The effect of RA on the growth of CCC-HEL was also investigated in order to check if it has selective growth inhibition on abnormal cells. It was observed that RA did not inhibit the growth of CCC-HEL [64]. The researchers also investigated the ability of RA to induce apoptosis in HSC-T6 over a period of 48 h and observed that treated cells underwent serial changes, such as autophagosome, enlarged rough endoplasmic reticulum (RER), porphytitic chromatin and lower density of mitochondrial matrix, which are characteristic of apoptosis in cells [64]. Also in an attempt to find out whether the effect of RA on HSC-T6 was partly due to the Janus kinase (JAK)/STAT3 signal pathway, they observed that compared with glyceraldehyde-3-phosphate dehydrogenase (GAPDH) protein level, the expression of phosphorylated STAT3 had a high degree of correlation in the expression pattern of genes encoding apoptosis inhibitors (Bcl-2) and cell cycle regulators (CyclinD1) protein in HSC-T6 cells treated with RA while the level of STAT3 protein showed no significant changes [64]. A report on the suppressing effect of RA acid on hepatic fibrogenesis via suppression of HSC activation/proliferation and induction of apoptosis was given [100]. In the study, RA-treatment mitigated the proliferation of HSC-T6 cells in a time and concentration-dependent manner with no impact on hepatocytes. It also had a concentration-

Table 2
In vivo hepatoprotective effect of RA.

Experimental model used	Concentration/dose applied	Major outcomes	References
LPS induced liver injury in D-GalN-sensitized mice	135 mg/kg RA	RA showed liver protection which was due to the scavenging or reducing activities-superoxide or peroxynitirite rather than to inhibition of TNF-production.	[78]
t-BHP-induced oxidative liver damage	26.84 mg/kg body weight (BW) of RA	RA protects the liver against oxidative hepatic damage.	[83]
PH model in mice.	0.2 g/kg BW	RA activated the mTOR signaling pathway during liver regeneration and rescued PH-impaired liver functions	[98]
Normothermic I/R model in the rat liver.	50 mg/kg BW	RA protects liver parenchymal cells against normothermic I/R injury by anti-inflammatory and antioxidant properties. It also inhibited NF-κβ signaling pathway and reduced hepatic iNOS and eNOS expressions and NO levels.	[99]
Thioacetamide (TAA)-intoxicated rats	Various concentrations of RA (0, 25, 50, 100, 200, 400 mg/mL)	RA impeded the progression of liver fibrosis through inhibition of HSCs activation/proliferation and induction of apoptosis with preservation of hepatic architecture.	[100]
Extrahepatic cholestasis in rats induced by BDL	20 mg/kg	RA improves cholestasis-related liver injury via mechanisms involving resolution of oxidative burden and down-regulation of HMGB1/TLR4, NF-kβ, AP-1, and TGF-β1/Smad signaling.	[3]
PCLS and PCIS prepared from human, mouse, and rat tissue.	RA (100 μM – 500 μM)	RA decreased the gene levels of Fn2 and PAI-1 in murine PCLS, and Fn2 in murine PCIS but had no effect on the gene expression of fibrosis markers in human and rat PCIS.	[101]
Acute liver damage and fibrogenesis in CCl_4-intoxicated mice	RA at 10, 25 and 50 mg/kg	RA improved histological and serum markers of liver damage and ameliorated oxidative/nitrosative stress and inflammatory response in liver tissue. It also suppressed profibrotic response by preventing TGF-β1 and α-SMA expression. It inhibited CCl_4-induced apoptosis as well as enhanced Nrf2 and heme oxygenase-1 (HO-1) expression.	[86]
CCl_4-induced liver fibrosis	2,4,8,16 and 32 μM	RA inhibited HSCs proliferation, TGF-β1, CTGF and α-SMA expression in cultured HSCs. It reduced fibrosis grade, ameliorated biochemical indicator and histopathological morphology, as well as reduced liver TGF-β1 and CTGF expression.	[17]
HSCs *in vitro* and TAA-induced fibrosis *in vivo*.	RA (0, 25, 50, 100, 200, 400 μg/mL)	RA had anti-proliferative effects on cultured HSCs with IC_{50} of 276 mg/mL and 171 mg/mL for 24 h and 48 h, respectively. It also reversed activated stellate cell morphology to quiescent form and improved ALT, AST, oxidative stress markers as well as reduced TIMP-1, HP levels, inflammatory markers and fibrosis score.	[102]
Liver I/R injury.	150 mg/kg BW	RA decreased hepatocellular damage, neutrophil infiltration and all oxidative/nitrosative stress parameters. It also reduced the liver content of eNOS/iNOS and NO, attenuated NF-κB activation, and down-regulated inflammatory gene expression.	[99]
Tumor-bearing mice	RA at 75, 150 and 300 mg/kg	RA suppressed tumor growth by regulating the secretion of cytokines associated with inflammation and angiogenesis, and suppressing the expression of NF-kβ p65 in the xenograft microenvironment.	[103]
Hepatic stellate cells in response to ROS	10 μM RA	RA reverses activated HSCs to quiescent cells. It inhibited MMP-2 activity and suppressed ROS generation and lipid peroxidation. It also increased antioxidant response element (ARE)-mediated luciferase activity, nuclear translocation Nrf2 and catalytic subunits from glutamate cysteine ligase (GCLc) expression.	[104]
Liver injury induced by LPS in D-GalN-sensitized mice	135 mg/kg RA	RA reduced the elevation of plasma AST levels, as well as anti-TNF and SOD. It also reduced the expression of TNF-α mRNA in liver and plasma	[78]
Sepsis induced wistar albino rats	100 mg/kg b.w.	RA reduced DNA damage in the lymphocytes, livers, and kidneys. It also decreased malondialdehyde (MDA) and TNF-α levels while increasing GSH levels as well as SOD and GSH-Px activities in the livers and kidneys.	[105]
Liver ischaemia–reperfusion	25 mg/kg (i.v.) 30	RA caused a reduction in the serum concentration of AST, ALT, and LDH.	[106]
Human dermal fibroblasts	1-40 μM	RA inhibited the expression of CCL11 and CCR3 by suppressing the IKK-β activity in NF-κβ activation signaling.	[107]
BDL- induced cholestatic liver fibrosis	0.1 mg / 25 g BW	RA inhibited HSC activation and progression of liver fibrosis.	[108]
Alcohol-induced hepatotoxicity in rats	RA 10 mg/kg	RA prevented ethanol-induced prooxidant and antioxidant imbalance in liver. It also prevented an increase in the serum levels of ALT, AST, LDH, TNF-α, and IL-6 and caused a reduction in necrosis and infiltration of inflammatory cells in liver parenchyma.	[109]
Aging mice	50, 100 or 200 mg/ kg	RA caused an increase in the activity of SOD, CAT and GSH-Px with a decrease in MDA	[110]
Strepotozotocin-induced diabetic rats	10 mg/kg	RA prevented increase of TBARS levels and alteration in SOD and CAT activity. It also reversed the decrease in ascorbic acid and non-protein-thiol (NPSH) levels in diabetic rats.	[111]
Type 1 diabetic mice	0, 25, and 50 mg/ml	RA decreased the hepatic level of IL-6, TNF-Alpha, and PGE_2, as well as the activity of COX-2 It also decreased hepatic RAGE and sorbitol levels, and GLO-1 activity	[112]
Acetaminophen-induced liver damage	10, 25 and 50 mg/kg	RA showed insignificant hepatoprotective activity against acetaminophen-induced liver damage.	[113]
Fructose-fed mice		RA diminished oxidative stress and reduced mitochondrial function	[114]
Activated HSC-T6		RA inhibited proliferation and induce apoptosis in HSC-T6 by inhibiting phosphorylation in STAT3, which enhanced the reversal of hepatic fibrosis.	[115]
Cobalt chloride ($CoCl_2$) hypoxia-induced injury in rat hepatocytes		RA protects primary cultured rat hepatocytes against $CoCl_2$-induced cell injury through inhibition of ROS-activated p38MAPK and COX-2/PGE2 pathway.	[116]

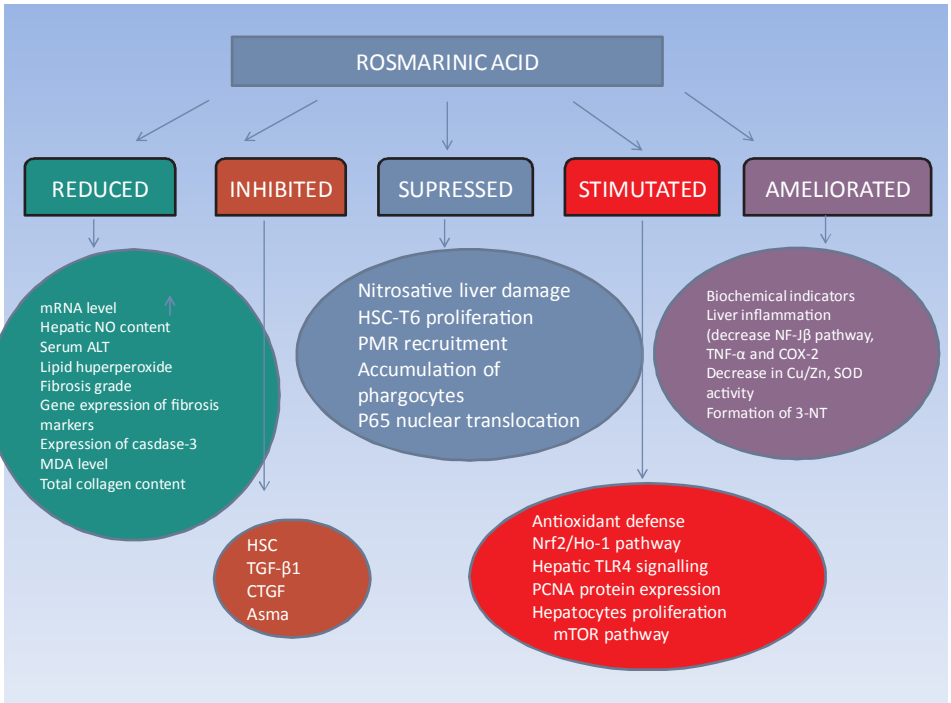

Fig. 3. Mechanisms of hepatoprotective action of rosmarinic acid.

dependent reduction in HSCs activation, elevation in caspase-3 expression, and concentration-dependent-inhibition in TGF-β1 production. [100]. Administration of RA restored AST depletion and reduced lipid peroxidation in the treated group as well as normalized hepatic levels of TGF-β1 and restored hepatic architecture of treated rat liver [100]. A summary of the various hepatoprotective mechanisms of RA is as shown in Fig. 3 below.

5. Discussions

About 29 million people in the Europe still suffer from a chronic liver condition despite the progress made in the knowledge and management of liver disease in the past few years, with cirrhosis and primary liver cancer cases being the highest [117]. Approximately 14–26 new cases of cirrhosis, per 100,000 inhabitants per year and an estimated 170,000 deaths per year has been suggested [118]. In the US, the prevalence of chronic liver disease ranged from 3.9% in African Americans and Native Hawaiians to 4.1% in whites, 6.7% in Latinos, and 6.9% in Japanese [119] and more than 1 million deaths due to liver cirrhosis occurs annually [120]. Several management strategies ranging from diet/lifestyle modification to surgery including various medications have been used to combat liver problems. In this review, the role of RA in liver diseases through different mechanisms is examined.

5.1. Antioxidant and anti-inflammatory

Oxidative stress is considered as a key mechanism of hepatocellular injury and disease progression. It is partly responsible for some pathological findings in compromised liver as well as serve as a prognostic indicator. Oxidative stress is known to trigger the consumption of tissue antioxidant reserves and induces massive lipid peroxidation in cellular membranes. Over the years, both ROS and reactive nitrogen species (RNS) have been shown to lead to loss of liver function. Production of harmful substances and reduction of bile and redox reaction as well as oxidative damage can lead to diseases like subclinical hepatitis, inflammatory necrotic hepatitis, liver cirrhosis and cancer.

The link between oxidation and various liver diseases has been unambiguously reported. For instance in alcoholic liver disease, CYP2E1-dependent oxidative stress, mitochondrial injury, and GSH homeostasis contributes to the toxic actions of ethanol on the liver [121]. In chronic liver cirrhosis and hepatitis, SOD and glutathione peroxidase (GSH-PX) are significantly reduced and this correlates negatively with serum ALT level [122]. In chronic hepatitis the concentration of MDA [123] are higher than normal values and oxidative damage is closely related to the pathological damage of hepatic fibrosis [123,124]. Also, increase in intracellular oxygen free radicals production in HSC promotes the activation of HSC leading to liver fibrosis [125]. High level of 8-Hydroxydeoxyguanosine (8-OHdG) expression in chronic hepatitis can also cause DNA mutations and induce liver cancer [126]. There is also a higher serum level of oxidation protein products like NO and the activities of myeloperoxidase (MPO), arylesterase (AE) and paraoxonase-1 (PON1) in chronic hepatitis [127,128]. Several authors have reported RA as having strong antioxidant effect in different experimental models [129–134]. With particular reference to liver diseases however, RA was reported to significantly reduce plasma ALT as well as had anti-TNF and SOD activity [135]. This effect of RA on ALT, SOD, GSH as well as other enzymes related to antioxidant was also corroborated by other reports [136]. Specifically, RA also protects hepatic parenchyma from I/R-induced oxidative stress, reduced lipid hydroperoxide levels in liver parenchyma and preserved the total hepatic antioxidant capacity as well as the hepatocellular reserves of GSH [99].

Inflammation is closely linked to oxidative stress due to the fact that free radicals can affect intracellular signal transduction and gene regulation, resulting in cytokine production essential to inflammatory process. In alcoholic liver disease, lipid peroxidation causes inflammation and organ fibrosis [137] and in chronic hepatitis the concentration of TNF-α and TGF-β [123] are higher than normal values. NF-κB also plays a major role in inflammatory processes [138]. NF-κB activation, triggered by reactive oxygen species, modulates liver injury by producing cytotoxic cytokine such as NF-κB -p65 and TNF-α [139], and inducing several other inflammatory mediators like COX-2 and iNOS [140]. RA has been implicated in a number of inflammatory responses [58,101,106,141–143]. It significantly ameliorated CCl_4 induced liver inflammation [6] through the inhibition of COX-2 [144] and inhibition of production of inflammatory cytokines [145]. It has also showed that suppression of inflammation by RA can be mediated

through the inhibition of NF-κB pathway as well as down-regulation of TNF-α and COX-2 [6], a submission which agrees with other reports [146,147]. In summary, several studies have shown the therapeutic potential of RA against acute liver toxicity through amelioration of hepatic oxidative/nitrosative stress and suppression of inflammation,

5.2. Anti-fibrotic

The effect of RA as an anti-fibrotic agent was reported in CCl_4-induced liver fibrosis [17] where biochemical parameters, histopathological changes and immunohistochemical factors were assessed. In the study that RA inhibited HSCs proliferation, TGF-β1, CTGF and α-SMA expression in cultured HSCs. Furthermore, it ameliorated biochemical indicator, histopathological morphology and reduced fibrosis grade [17]. In an *ex-vivo* study using fPCLS [148], RA reduced the gene expression of the fibrosis markers and decreased the total collagen content as detected by the hydroxyproline content in a concentration dependent manner. Also, reports from an extrahepatic cholestasis rat model [3] showed that RA inhibited BDL-induced biliary fibrosis through mitogenic and fibrogenic inhibition by targeting matrix-producing hepatic stellate cells [3]. In this model, there was an observed improvement in hepatic function, parenchymal structure, ductular reaction, and fibrosis and this correlated well with the suppression of NF-κB and AP1 activities, leukocytes infiltration/activation, and cytokine overproduction [3]. Previous reports have also documented the involvement of NF-κB inhibition in the anti-inflammatory action of RA [103,149–151] thus making NF-κB an important targets in the pharmacological effects of RA [3].

5.3. Cholestasis

In an *in vivo* experiment in rats, RA was reported to have cholestatic hepatoprotective effect observed as an improvement in serum biochemical and hepatic histopathological parameters [3]. The same study corroborated the antioxidant, anti-inflammatory and anti-fibrotic effect of RA. The researcher observed that the anti-fibrotic effect was mediated by suppression of TGF-β1-provoked mitogenic and fibrogenic activation while the cholestatic hepatoprotective effect was due to the reduction of total bile acid level in BDL rats thus showing that a decrease in bile acid level is associated with RA-mediated hepatoprotection The study also suggested that RA target of action might be hepatic primary bile acid synthesis, intestinal secondarily metabolism, and biological activities [3]. Furthermore, the study showed that RA improved BDL-induced oxidative stress and oxidative stress has been documented to play a pathogenic role in cholestatic liver injury by modulating mitogenic and fibrogenic gene expression as well as cell activities involving NF-κB and AP-1 mechanisms [152–154]. The researchers therefore suggested that the resolution of oxidative burden is a mechanism through which RA suppresses redox-sensitive NF-κB and AP-1 action thus leading to hepatoprotection [3]. Also from the study, an induction of hepatic TLR4 signaling in BDL rats and its reversal by RA was demonstrated pointing to the role of HMGB1/TLR4 signaling pathway in cholestasis associated NF-κB and AP1 activities and suggesting that the interference of HMGB1/TLR4-derived signals could be another mode of action of RA in cholestatic liver injury [3]. On the whole, it can be seen that the steps of bile acid synthesis/ metabolism, hepatic stellate cell mitogenic and fibrogenic activation, the axis of HMGB1/TLR4, and free radical generation are targets for intervention by RA.

5.4. Liver damage

RA has also been shown to have a positive effect on general liver damage. For instance, in a CCl_4 induced liver damage, a less deleterious effect was reported with RA administration in mice [86]. In the study, RA dose-dependently decreased hepatic histopathological changes and serum ALT levels. It also significantly reduced the necrotic area, expression of active caspase-3 and suppressed oxidative/nitrosative liver damage [86] as well as inhibited lipid peroxidation thus agreeing with previous findings [155]. Lipid peroxidation leads to destruction of plasma membrane and intracellular organelles resulting in massive destruction of hepatocytes and tissue necrosis which is central to the toxicity of CCl_4. [86]. RA has also been reported to decrease eNOS/iNOS and NO content [99]. Increased production of nitric oxide and superoxide anion in injured liver could result in the formation of peroxynitrite [156] and subsequent nitration of protein tyrosine residues [157], which plays an important role in the pathogenesis of hepatic necrosis [158]. The effect of RA on liver damage due to ischemia/reperfusion has also been reported [99]. Liver damage due to ischemia and reperfusion is common in many surgical procedures involving the liver. In such I/R injuries, cellular damage as a result of hypoxia is increased after the restoration of blood supply and oxygen delivery. This leads to acute inflammatory response within the liver parenchyma immediately after blood flow restoration and it is the major mechanism of injury during the reperfusion phase. The activation of KC and sinusoidal endothelial cells (SEC), CD4 + T lymphocyte and neutrophil recruitment to the hepatic interstitium, and the subsequent generation of ROS, RNS and cytokines have been identified as the most relevant events in the pathogenesis of liver damage due to I/R. ROS affects the pathophysiology of the liver indirectly by supporting protease activity through the inactivation of antiproteases and by acting as second messengers in signal transduction pathways involved in the regulation of genes encoding adhesion molecules and pro-inflammatory mediators [2,159,160]. NF-κB, a key transcription factor that is activated during reperfusion following an ischemic event in diverse organs is made up predominantly of a p50 and p65 heterodimer associated with regulatory proteins called inhibitors of κB (IκB) and has been implicated in neuronal inflammation. [161]. The effects of RA on both ROS [104,116] and NF-κB [99,103,107] have been documented.

5.5. Xenobiotic metabolizing enzymes

RA in combination with other flavonoids has been shown to enhance detoxication enzymes in rat liver [97]. This was done by evaluating the modulation phase I enzymes such as cytochrome P450 (CYP) 1 A, 2B, 2E1, 3 A, and phase II enzymes such as glutathione S-transferase (GST), quinone reductase (QR) and UDP-glucuronosyltransferase (UGT). The activities of these enzymes were measured using specific substrates and thus used to determine the effect of RA on them. Extract containing RA only enhanced CYP 1 A1, 2B1/2, 2E1 and GST (especially rGST A3/A5, M1 and M2), QR and UGT. It however had no effect on drug metabolizing enzymes probably due to the fact that following oral administration, RA gets metabolized before reaching the liver and the resulting metabolites have no effect on drug metabolizing enzymes [97].

5.6. Cell proliferation

The effects of RA on cell proliferation was investigated both in rat activated hepatic stellate cells (HSC-T6) and normal CCC-HEL cells [64]. RA significantly lowered HSC-T6 cell growth rate in a dose and time dependent manner but had no effect on CCC-HEL cells showing it had selective growth inhibition on abnormal cells. The study further suggested that the RA inhibitory effect on HSC-T6 proliferation may be associated with G1/S cell cycle arrest [64] and concluded that RA inhibited proliferation of HSC-T6 without significant toxicity and evident adverse function on normal cells [64]. Inhibition of HSCs activation and proliferation as well as the induction of its apoptosis is important in the prevention and treatment of hepatic fibrosis.

5.7. Liver regeneration

Removal of the liver is a common therapy for liver fibrosis or tumor patients and the ability of the liver to regenerate is important for liver homeostasis [144]. Liver regeneration however is a very complex process involving multiple pathways operating simultaneously and/or sequentially [162]. The potential of RA on liver regeneration was studied by Lou et al., [98]. In the study, it was observed that RA stimulated hepatocyte proliferation. Specifically activated the mTOR signaling pathway during liver regeneration and rescued PH-impaired liver functions [98]. Thus, it was concluded that RA stimulates the proliferation of hepatocytes through the mTOR signaling pathway hence supporting the potential usage of RA in liver regeneration [98].

6. Concluding remark

There is a current interest in natural products in general and dietary supplements in particular. This might be due to the fact that several studies suggest that diets rich in phytochemicals are beneficial to human health. RA is a di-phenolic compound common in many herbs and spices and it is regarded as a potential pharmaceutical natural product. Very many reports have proven the hepatoprotective effect of RA through various mechanisms. These mechanisms include scavenging or reducing activities-superoxide or peroxynitirite, reduction of indicators of hepatic toxicity, such as aspartate aminotransferase, alanine aminotransferase, oxidized glutathione, lipid peroxidation as well as enzyme activities related to antioxidant such as catalase, glutathione peroxidase and superoxide dismutase. RA also inhibited hepatic stellate cells proliferation, TGF-β1, CTGF and α-SMA expression in cultured HSCs. It reduced fibrosis grade, ameliorated biochemical indicator and histopathological morphology. It also had profound effect on inflammation and several inflammatory mediators. In this review we have outlined various mechanisms involved in liver toxicity, experimental models for liver damage and the effects of RA in the different models that support its hepatoprotective potential. It is hoped that further studies in future will harness all these research findings and lead ultimately to the use of RA against liver diseases in a precise and beneficial way.

Conflict of interest

The authors declare no conflict of interest.

References

[1] P.F. Lalor, P. Shields, A.J. Grant, D.H. Adams, Recruitment of lymphocytes to the human liver, Immunol. Cell Biol. 80 (1) (2002) 52–64.
[2] H. Jaeschke, G.J. Gores, A.I. Cederbaum, J.A. Hinson, D. Pessayre, J.J. Lemasters, Mechanisms of hepatotoxicity, Toxicol. Sci. 65 (2) (2002) 166–176.
[3] S.Y. Lin, et al., Hepatoprotective activities of rosmarinic acid against extrahepatic cholestasis in rats, Food Chem. Toxicol. 108 (2017) 214–223.
[4] D. Schuppan, N.H. Afdhal, Liver cirrhosis, Lancet 371 (9615) (2008) 838–851.
[5] P. Ichai, D. Samuel, Etiology and prognosis of fulminant hepatitis in adults, Liver Transplant. 14 (S2) (2008).
[6] V. Bhatia, A. Singhal, S.K. Panda, S.K. Acharya, A 20-year single-center experience with acute liver failure during pregnancy: is the prognosis really worse? Hepatology 48 (5) (2008) 1577–1585.
[7] R. Liu, et al., Conjugated bile acids promote cholangiocarcinoma cell invasive growth through activation of sphingosine 1-phosphate receptor 2, Hepatology 60 (3) (2014) 908–918.
[8] K. Tajiri, Y. Shimizu, Recent advances in the management of pruritus in chronic liver diseases, World J. Gastroenterol. 23 (19) (2017) 3418.
[9] A.E. Kremer, et al., Serum autotaxin is increased in pruritus of cholestasis, but not of other origin, and responds to therapeutic interventions, Hepatology 56 (4) (2012) 1391–1400.
[10] C. Jüngst, F. Lammert, Cholestatic liver disease, Dig. Dis. 31 (1) (2013) 152–154.
[11] A. Wasley, A. Fiore, B.P. Bell, Hepatitis A in the era of vaccination, Epidemiol. Rev. 28 (1) (2006) 101–111.
[12] W. Bernal, G. Auzinger, A. Dhawan, J. Wendon, Acute liver failure, Lancet 376 (9736) (2010) 190–201.
[13] M. Guarino, A. Tosoni, M. Nebuloni, Direct contribution of epithelium to organ fibrosis: epithelial-mesenchymal transition, Hum. Pathol. 40 (10) (2009) 1365–1376.
[14] T.A. Wynn, Cellular and molecular mechanisms of fibrosis, J. Pathol. 214 (2) (2008) 199–210.
[15] D. Leask, A. Abraham, TGF-beta signaling and the fibrotic response, FASEB J. 18 (2004) 816–827.
[16] G.S. Li, W.L. Jiang, J.W. Tian, G.W. Qu, H.B. Zhu, F.H. Fu, In vitro and in vivo antifibrotic effects of rosmarinic acid on experimental liver fibrosis, Phytomedicine 17 (3–4) (2010) 282–288.
[17] Y. Li, G. Xie, Q. Shi, Y. Li, D. Zhang, M. Jiang, S. Zhou, H. Lu, H. Jin, Inhibition of connective tissue growth factor by siRNA prevents liver fibrosis in rats, J. Gene Med. 8 (2006) 889–900.
[18] R. Bruha, K. Dvorak, J. Petrtyl, Alcoholic liver disease, World J. Hepatol. 4 (3) (2012) 81.
[19] M. Yin, et al., Essential role of tumor necrosis factor α in alcohol-induced liver injury in mice, Gastroenterology 117 (4) (1999) 942–952.
[20] T.M. Donohue Jr, Alcohol-induced steatosis in liver cells, World J. Gastroenterol. WJG 13 (37) (2007) 4974.
[21] R. Bhattacharya, M.C. Shuhart, Hepatitis C and alcohol: interactions, outcomes, and implications, J. Clin. Gastroenterol. 36 (3) (2003) 242–252.
[22] S. Naveau, V. Giraud, E. Borotto, A. Aubert, F. Capron, J. Chaput, Excess weight risk factor for alcoholic liver disease, Hepatology 25 (1) (1997) 108–111.
[23] H. Fujii, N. Kawada, Fibrogenesis in alcoholic liver disease, World J. Gastroenterol. WJG 20 (25) (2014) 8048.
[24] N. Oishi, T. Yamashita, S. Kaneko, Molecular biology of liver cancer stem cells, Liver Cancer 3 (2) (2014) 71–84.
[25] M. Rantala, M.J. Van de Laar, Surveillance and epidemiology of hepatitis B and C in Europe–a review, Eurosurveillance 13 (21) (2008) 18880.
[26] F. Balkwill, A. Mantovani, Inflammation and cancer: back to Virchow? Lancet 357 (9255) (2001) 539–545.
[27] M. Karin, F.R. Greten, NF-κB: linking inflammation and immunity to cancer development and progression, Nat. Rev. Immunol. 5 (10) (2005) 749.
[28] T. Sakurai, S. Maeda, L. Chang, M. Karin, Loss of hepatic NF-κB activity enhances chemical hepatocarcinogenesis through sustained c-Jun N-terminal kinase 1 activation, Proc. Natl. Acad. Sci. 103 (28) (2006) 10544–10551.
[29] G. He, M. Karin, NF-κB and STAT3–key players in liver inflammation and cancer, Cell Res. 21 (1) (2011) 159.
[30] M. Petersen, M.S.J. Simmonds, Rosmarinic acid, Phytochemistry 62 (2) (2003) 121–125.
[31] S.M. Petersen, Rosmarinic acid, Phytochemistry. 62 (2) (2003) 121–125.
[32] B. Fromenty, D. Pessayre, Inhibition of mitochondrial beta-oxidation as a mechanism of hepatotoxicity, Pharmacol. Ther. 67 (1) (1995) 101–154.
[33] E. Freneaux, et al., Stereoselective and nonstereoselective effects of ibuprofen enantiomers on mitochondrial beta-oxidation of fatty acids, J. Pharmacol. Exp. Ther. 255 (2) (1990) 529–535.
[34] G. Labbe, et al., Effects of various tetracycline derivatives on in vitro and in vivo beta-oxidation of fatty acids, egress of triglycerides from the liver, accumulation of hepatic triglycerides, and mortality in mice, Biochem. Pharmacol. 41 (4) (1991) 638.
[35] P. Letteron, N. Brahimi-Bourouina, M.A. Robin, A. Moreau, G. Feldmann, D. Pessayre, Glucocorticoids inhibit mitochondrial matrix acyl-CoA dehydrogenases and fatty acid beta-oxidation, Am. J. Physiol. Liver Physiol. 272 (5) (1997) G1141–G1150.
[36] A. Berson, et al., Steatohepatitis-inducing drugs cause mitochondrial dysfunction and lipid peroxidation in rat hepatocytes, Gastroenterology 114 (4) (1998) 764–774.
[37] S. Grimbert, et al., Decreased mitochondrial oxidation of fatty acids in pregnant mice: possible relevance to development of acute fatty liver of pregnancy, Hepatology 17 (4) (1993) 628–637.
[38] D. Pessayre, A. Berson, B. Fromenty, A. Mansouri, Mitochondria in steatohepatitis, Semin. Liver Dis. 21 (1) (2001) 57–70.
[39] T. Patel, L.R. Roberts, B.A. Jones, G.J. Gores, Dysregulation of apoptosis as a mechanism of liver disease: an overview, Semin. Liver Dis. 18 (2) (1998) 105–114.
[40] S.S. Strautnieks, et al., A gene encoding a liver-specific ABC transporter is mutated in progressive familial intrahepatic cholestasis, Nat. Genet. 20 (3) (1998) 233.
[41] T. Patel, S.F. Bronk, G.J. Gores, Increases of intracellular magnesium promote glycodeoxycholate-induced apoptosis in rat hepatocytes, J. Clin. Invest. 94 (6) (1994) 2183–2192.
[42] D.R. Green, Apoptotic pathways: ten minutes to dead, Cell 121 (5) (2005) 671–674.
[43] W.A. Faubion, G.J. Gores, Death receptors in liver biology and pathobiology, Hepatology 29 (1) (1999) 1–4.
[44] H. Miyoshi, C. Rust, P.J. Roberts, L.J. Burgart, G.J. Gores, Hepatocyte apoptosis after bile duct ligation in the mouse involves Fas, Gastroenterology 117 (3) (1999) 669–677.
[45] T. Sodeman, S.F. Bronk, P.J. Roberts, H. Miyoshi, G.J. Gores, Bile salts mediate hepatocyte apoptosis by increasing cell surface trafficking of Fas, Am. J. Physiol. Liver Physiol. 278 (6) (2000) G992–G999.
[46] D.R. Koop, Oxidative and reductive metabolism by cytochrome P450 2E1, FASEB J. 6 (2) (1992) 724–730.
[47] S.C. Bondy, Ethanol toxicity and oxidative stress, Toxicol. Lett. 63 (3) (1992) 231–241.
[48] J.R. Mitchell, D.J. Jollow, W.Z. Potter, D.C. Davis, J.R. Gillette, B.B. Brodie, Acetaminophen-induced hepatic necrosis. I. Role of drug metabolism, J. Pharmacol. Exp. Ther. 187 (1) (1973) 185–194.
[49] I.M. Westra, D. Oosterhuis, G.M.M. Groothuis, P. Olinga, The effect of antifibrotic drugs in rat precision-cut fibrotic liver slices, PLoS One 9 (4) (2014) 1–10.

[50] M. van de Bovenkamp, et al., Precision-cut liver slices as a new model to study toxicity-induced hepatic stellate cell activation in a physiologic milieu, Toxicol. Sci. 85 (1) (2005) 632–638.
[51] G. O, M.L. Scarpati, Isolation and constitution of rosmarinic acid from Rosmarinus officinalis, Science 28 (1958) 2329–2333.
[52] K. Shetty, R.E. Shetty, K. Paliyath, G. Pometto, A.L. LevinIII (Eds.), Food Biotechnology, second ed., CRC Press, Boca Raton, 2005, pp. 825–845.
[53] R.A.F. Michelle Andrade Furtado, Lenita Caetano Fernandes de Almeida, D.C.T. Wilson Roberto Cunha, Antimutagenicity of rosmarinic acid in Swiss mice evaluated by the micronucleus assay, Mutat. Res. 657 (2008) 150–154.
[54] J. Terao, S. Baba, N. Osakabe, M. Natsume, A. Yasuda, Y. Muto, T. Hiyoshi, H. Takano, T. Yoshikawa, Absorption, metabolism, degradation and urinary excretion of rosmarinic acid after intake of Perilla frutescens extract in humans, Eur. J. Nutr. 44 (1) (2005) 1–9.
[55] J. B, D.L. McKay, A review of the bioactivity and potential health benefits of peppermint tea (Mentha piperita L.), Phyther. Res. 20 (8) (2006) 619–633.
[56] R. Z, S.S. Huang, Rosmarinic acid inhibits angiogenesis and its mechanism of action in vitro, Cancer Lett. 239 (2) (2006) 271–280.
[57] T. M, H. Takeda, M. Tsuji, M. Inazu, T. Egashira, Rosmarinic acid and caffeic acid produce antidepressive-like effect in the forced swimming test in mice, Eur. J. Pharmacol. 449 (3) (2002) 261–267.
[58] T. Y, N. Osakabe, A. Yasuda, M. Natsume, Rosmarinic acid inhibits epidermal inflammatory responses: anticarcinogenic effect of Perilla frutescens extract in the murine two-stage skin model, Carcinogenesis 25 (4) (2004) 549–557.
[59] N. Takano, N. Osakabe, C. Sanbongi, R. Yanagisawa, K. Inoue, A. Yasuda, M. Natsume, S. Baba, E. Ichiishi, T. Yoshikawa, Extract of Perilla frutescens enriched for rosmarinic acid, a polyphenolic phytochemical, inhibits seasonal allergic, rhinoconjunctivitis in humans, Exp. Biol. Med. 229 (2004) 247–254.
[60] S. Moreno, T. Scheyer, C. Romano, Antioxidant and antimicrobial activities of rosemary extracts linked to their polyphenol composition, Free Radic. Res. 40 (2006) 223–231.
[61] K. Ono, L. Li, Y. Takamura, Phenolic compounds prevent amyloid B protein oligomerization and synaptic dysfunction by site-specific binding, J. Biol. Chem. 287 (2012) 14631–14643.
[62] P. C, M. Dubois, F. Bailly, G. Mbemba, J.F. Mouscadet, Z. Debyser, M. Witvrouw, Reaction of rosmarinic acid with nitrite ions in acidic conditions: discovery of nitro-and dinitrorosmarinic acids as new anti-HIV-1 agents, J. Med. Chem. 51 (8) (2008) 2575–2579.
[63] K. CB, M. Koşar, F. Göger, In vitro antioxidant properties and phenolic composition of Salvia virgata Jacq. from Turkey, J. Agric. Food Chem. 56 (7) (2008) 2369–2374.
[64] J.-J. Zhang, Y.-L. Wang, X.-B. Feng, X.-D. Song, W.-B. Liu, Rosmarinic acid inhibits proliferation and induces apoptosis of hepatic stellate cells, Biol. Pharm. Bull. 34 (3) (2011) 343–348.
[65] K. Keppler, D. Lesch, R. Reutter, W. Decker, Experimental hepatitis induced by D-galactosamine, Exp. Mol. Pathol. 9 (1968) 279–290.
[66] A.F. Martich, G.D. Danner, R.L. Ceska, M. Suffredini, Detection of interleukin 8 and tumor necrosis factor in normal humans after intravenous endotoxin: the effect of anti-inflammatory agents, J. Exp. Med. 173 (1991) 1021–1024.
[67] A. Gantner, F. Uhlig, S. Wendel, Quinine inhibits release of tumor necrosis factor, apoptosis, necrosis and mortality in a murine model of septic liver failure, Eur. J. Pharmacol. 294 (1995) 353–355.
[68] M. Blanco, F.J. Ochs, R.L. Schwarz, H. Lotz, Chondrocyte apoptosis induced by nitric oxide, Am. J. Pathol. 146 (1995) 75–85.
[69] V. Mignon, A. Rouquet, N. Fabre, M. Martin, S. Pages, J.C. Dhainaut, J.F. Kahn, A. Briand, P. Joulin, LPS challenge in D-galactosamine-sensitized mice accounts for caspase-dependent fulminant hepatitis, not for septic shock, Am. J. Respir. Crit. Care Med. 159 (1999) 1308–1315.
[70] C. Lehmann, V. Freudenberg, M.A. Galanos, Lethal toxicity of lipopolysaccharide and tumor necrosis factor in normal and Dgalactosamine- treated mice, J. Exp. Med. 165 (1987) 657–663.
[71] H. Watanabe, N. Miura, S. Zeki, S. Ishii, Hepatocellular oxidative DNA injury induced by macrophage-derived nitric oxide, Free Radic. Biol. Med. 30 (2001) 1019–1028.
[72] T.R. Taylor, B.S. Alarcon, L.H. Billiar, Inducible nitric oxide synthase in the liver: regulation and function, Biochem. 63 (1998) 766–781.
[73] J.H. Wang, H.P. Redmond, Q.D. Wu, Bouchier-Hayes, Nitric oxide mediates hepatocyte injury, Am. J. Physiol. 275 (1998) G1117–G1126 D. A. J. P. 275: G. 1998.
[74] W.R. Rush, G.F. Gorski, J.R. Ripple, M.G. Sowinski, J. Bugelski, P. Hewitt, Organic hydroperoxide-induced lipid-peroxidation and cell-death in Isolated hepatocytes, Toxicol. Appl. Pharmacol. 78 (1985) 473–483.
[75] Y.J. Yen, G.C. Yeh, C.T. Chen, Protective effect of Mesona procumbens against tert-butyl hydroperoxide-induced acute hepatic damage in rats, J. Agric. Food Chem. 52 (2004) 4121–4127.
[76] P.J. Hogberg, J. Orrenius, S. Obrien, Further studies on lipid-peroxide formation in isolated hepatocytes, Eur. J. Biochem. 59 (1975) 449–455.
[77] J.L. Masaki, N. Kyle, M.E. Farber, Tert-butyl hydroperoxide kills culture-dhepatocytes by peroxidizing membrane-lipids, Arch. Biochem. Biophys. 269 (1989) 390–399.
[78] T. Y, N. Osakabe, A. Yasuda, M. Natsume, C. Sanbongi, Y. Kato, T. Osawa, Rosmarinic acid, a major polyphenolic component of Perilla frutescens, reduces lipopolysaccharide (LPS)-induced liver injury in D-galactosamine (D-GalN)-sensitized mice, Free Radic. Biol. Med. 33 (6) (2002) 798–806.
[79] O. Guidarelli, A. Clementi, E. Brambilla, L. Cantoni, Mechanism of the antimycin A-mediated enhancement of t-butylhydraperoxide-induced single strand breakage in DNA, Biochem. J. 328 (1997) 801–806.
[80] R. Recknagel, Carbon tetrachloride hepatotoxicity, Pharmacol. Rev. 19 (1967) 145–208.
[81] A. Weber, L.W. Boll, M. Stampfl, Hepatotoxicity and mechanism of action of haloalkanes: carbon tetrachloride as a toxicological model, Crit. Rev. Toxicol. 33 (2003) 105–136.
[82] A. Chance, B. Sies, H. Boveris, Hydroperoxide metabolism in mammalian organs, Physiol. Rev. 59 (1979) 527–605.
[83] S.Y. Yang, C.O. Hong, G.P. Lee, C.T. Kim, K.W. Lee, The hepatoprotection of caffeic acid and rosmarinic acid, major compounds of Perilla frutescens, against t-BHP-induced oxidative liver damage, Food Chem. Toxicol. 55 (2013) 92–99.
[84] C. Sun, F. Hamagawa, E. Tsutsui, Evaluation of oxidative stress during apoptosis and necrosis caused by carbon tetrachloride in rat liver, Biochim. Biophys. Acta 1535 (2001) 186–191.
[85] S. Friedman, Molecular regulation of hepatic fibrosis, an integrated cellular response to tissue injury, J. Biol. Chem. 275 (2000) 2247–2250.
[86] R. Domitrović, M. Škoda, V. Vasiljev Marchesi, O. Cvijanović, E. Pernjak Pugel, M.B. Štefan, Rosmarinic acid ameliorates acute liver damage and fibrogenesis in carbon tetrachloride-intoxicated mice, Food Chem. Toxicol. 51 (1) (2013) 370–378.
[87] Z. Meng, Y. Wang, L. Wang, et al., FXR regulates liver repair after CCl4-induced toxic injury, Mol. Endocrinol. 24 (2010) 886–897.
[88] K. Megli, F.M. Sabatini, Mitochondrial phospholipid bilayer structure is ruined after liver oxidative injury in vivo, FEBS Lett. 573 (2004) 68–72.
[89] S.Y. Sun, P. Yue, J. Zhou, Overexpression of Bcl2 blocks TNF-related apoptosis-inducing ligand (TRAIL)-induced apoptosis in human lung cancer cells, Biochem. Biophys. Res. Commun. 280 (2001) 788–797.
[90] S.-Y. Lin, Y.-Y. Wang, W.-Y. Chen, Y.-H. Chuang, P.-H. Pan, C.-J. Chen, Beneficial effect of quercetin on cholestatic liver injury, J. Nutr. Biochem. 25 (11) (2014) 1183–1195.
[91] M. Van de Bovenkamp, G.M.M. Groothuis, D.K.F. Meijer, P. Olinga, Liver fibrosis in vitro: cell culture models and precision-cut liver slices, Toxicol. In Vitro 21 (4) (2007) 545–557.
[92] A.E.M. Vickers, et al., Organ slice viability extended for pathway characterization: an in vitro model to investigate fibrosis, Toxicol. Sci. 82 (2) (2004) 534–544.
[93] I.M. Westra, B.T. Pham, G.M.M. Groothuis, P. Olinga, Evaluation of fibrosis in precision-cut tissue slices, Xenobiotica 43 (1) (2013) 98–112.
[94] I.M. Westra, D. Oosterhuis, G.M. Groothuis, P. Olinga, Induction Of Fibrotic Markers In An in Vitro model Of Liver Fibrosis, Hepatology 54 (4) (2011) 754A–755A.
[95] A. Bohlinger, I. Leist, M. Gantner, F. Angermuller, S. Tiegs, G. Wendel, DNA fragmentation in mouse organs during endotoxic shock, Am. J. Pathol. 149 (1996) 1381–1393.
[96] M. van de Bovenkamp, G.M.M. Groothuis, D.K.F. Meijer, P. Olinga, Precision-cut fibrotic rat liver slices as a new model to test the effects of anti-fibrotic drugs in vitro, J. Hepatol. 45 (5) (2006) 696–703.
[97] P. Debersac, M.F. Vernevaut, M.J. Amiot, M. Suschetet, M.H. Siess, Effects of a water-soluble extract of rosemary and its purified component rosmarinic acid on xenobiotic-metabolizing enzymes in rat liver, Food Chem. Toxicol. 39 (2) (2001) 109–117.
[98] K. Lou, et al., Rosmarinic acid stimulates liver regeneration through the mTOR pathway, Phytomedicine 23 (13) (2016) 1574–1582.
[99] L.N.Z. Ramalho, et al., Rosmarinic acid attenuates hepatic ischemia and reperfusion injury in rats, Food Chem. Toxicol. 74 (2014) 270–278.
[100] N.M. El-Lakkany, et al., Rosmarinic acid attenuates hepatic fibrogenesis via suppression of hepatic stellate cell activation/proliferation and induction of apoptosis, Asian Pac. J. Trop. Med. 10 (5) (2017) 444–453.
[101] R. Iswandana, et al., Organ- and species-specific biological activity of rosmarinic acid, Toxicol. In Vitro 32 (2016) 261–268.
[102] N.M. El-Lakkany, et al., Rosmarinic acid attenuates hepatic fibrogenesis via suppression of hepatic stellate cell activation/proliferation and induction of apoptosis, Asian Pac. J. Trop. Med. 10 (5) (2017) 444–453.
[103] W. Cao, C. Hu, L. Wu, L. Xu, W. Jiang, Rosmarinic acid inhibits inflammation and angiogenesis of hepatocellular carcinoma by suppression of NF-κB signaling in H22 tumor-bearing mice, J. Pharmacol. Sci. 132 (2) (2016) 131–137.
[104] C. Lu, Y. Zou, Y. Liu, Y. Niu, Rosmarinic acid counteracts activation of hepatic stellate cells via inhibiting the ROS-dependent MMP-2 activity: involvement of Nrf2 antioxidant system, Toxicol. Appl. Pharmacol. 318 (2017) 69–78.
[105] M. Bacanlı, et al., Does rosmarinic acid treatment have protective role against sepsis-induced oxidative damage in Wistar Albino rats? Hum. Exp. Toxicol. 35 (8) (2016) 877–886.
[106] J. Rocha, et al., Anti-inflammatory effect of rosmarinic acid and an extract of Rosmarinus officinalis in rat models of local and systemic inflammation, Basic Clin. Pharmacol. Toxicol. 116 (5) (2015) 398–413.
[107] J. Lee, et al., Rosmarinic acid as a downstream inhibitor of IKK-β in TNF-α-induced upregulation of CCL11 and CCR3, Br. J. Pharmacol. 148 (3) (2006) 366–375.
[108] M.D. Yang, et al., Rosmarinic acid and baicalin epigenetically derepress peroxisomal proliferator-activated receptor γ in hepatic stellate cells for their antifibrotic effect, Hepatology 55 (4) (2012) 1271–1281.
[109] P. Hasanein, R. Seifi, Beneficial effects of rosmarinic acid against alcohol-induced hepatotoxicity in rats, Can. J. Physiol. Pharmacol. 96 (1) (2017) 32–37.
[110] Y. Zhang, X. Chen, L. Yang, Y. Zu, Q. Lu, Effects of rosmarinic acid on liver and kidney antioxidant enzymes, lipid peroxidation and tissue ultrastructure in aging mice, Food Funct. 6 (3) (2015) 927–931.
[111] N. Mushtaq, et al., Protective effect of rosmarinic acid against oxidative stress biomarkers in liver and kidney of strepotozotocin-induced diabetic rats, J. Physiol.

Biochem. 71 (4) (2015) 743–751.
[112] Y.-J. Wen, M.-C. Yin, The anti-inflammatory and anti-glycative effects of rosmarinic acid in the livers of type 1 diabetic mice, Biomedicine 7 (3) (2017).
[113] R. Lucarini, et al., Hepatoprotective effect of Rosmarinus officinalis and rosmarinic acid on acetaminophen-induced liver damage, Emirates J. Food Agric. 26 (10) (2014) 878.
[114] B. Vanithadevi, C.V. Anuradha, Effect of rosmarinic acid on insulin sensitivity, glyoxalase system and oxidative events in liver of fructose-fed mice, Int. J. Diabetes Metab 16 (2008) 35–44.
[115] J.-J. Zhang, Y.-L. Wang, X.-B. Feng, X.-D. Song, W.-B. Liu, Rosmarinic acid inhibits proliferation and induces apoptosis of hepatic stellate cells, Biol. Pharm. Bull. 34 (3) (2011) 343–348.
[116] Y.J. Jeon, K.S. Song, H.J. Han, S.H. Park, W. Chang, M.Y. Lee, Rosmarinic acid inhibits chemical hypoxia-induced cytotoxicity in primary cultured rat hepatocytes, Arch. Pharm. Res. 37 (7) (2014) 907–915.
[117] M. Blachier, H. Leleu, M. Peck-Radosavljevic, D.-C. Valla, F. Roudot-Thoraval, The burden of liver disease in Europe: a review of available epidemiological data, J. Hepatol. 58 (3) (2013) 593–608.
[118] W.A. Zatoński, et al., Liver cirrhosis mortality in Europe, with special attention to Central and Eastern Europe, Eur. Addict. Res. 16 (4) (2010) 193–201.
[119] V.W. Setiawan, D.O. Stram, J. Porcel, S.C. Lu, L. Le Marchand, M. Noureddin, Prevalence of chronic liver disease and cirrhosis by underlying cause in understudied ethnic groups: the multiethnic cohort, Hepatology 64 (6) (2016) 1969–1977.
[120] I.A. Rowe, Lessons from epidemiology: the burden of liver disease, Dig. Dis. 35 (4) (2017) 304–309.
[121] A.A. Caro, A.I. Cederbaum, Oxidative stress, toxicology, and pharmacology of CYP2E1, Annu. Rev. Pharmacol. Toxicol. 44 (2004) 27–42.
[122] H.G. Osman, O.M. Gabr, S. Lotfy, S. Gabr, Serum levels of bcl-2 and cellular oxidative stress in patients with viral hepatitis, Indian J. Med. Microbiol. 25 (4) (2007) 323.
[123] G. Poli, Pathogenesis of liver fibrosis: role of oxidative stress, Mol. Aspects Med. 21 (3) (2000) 49–98.
[124] O. Rogowski, S. Shnizer, R. Wolff, B.S. Lewis, O. Amir, Increased serum levels of oxidative stress are associated with hospital readmissions due to acute heart failure, Cardiology 118 (1) (2011) 33–37.
[125] S. Zhan, et al., Phagocytosis of apoptotic bodies by hepatic stellate cells induces NADPH oxidase and is associated with liver fibrosis in vivo, Hepatology 43 (3) (2006) 435–443.
[126] R. Zhu, Y. Wang, L. Zhang, Q. Guo, Oxidative stress and liver disease, Hepatol. Res. 42 (8) (2012) 741–749.
[127] E.M.M. Ali, H.H. Shehata, R. Ali-Labib, L.M.E. Zahra, Oxidant and antioxidant of arylesterase and paraoxonase as biomarkers in patients with hepatitis C virus, Clin. Biochem. 42 (13–14) (2009) 1394–1400.
[128] Ö. Seren, G.E. Rler, Ö.B. Özlem Gülbahar, Serum levels of advanced oxidation protein products, malonyldialdehyde, and total radical trapping antioxidant parameter in patients with chronic hepatitis C, Turk. J. Gastroenterol. 22 (1) (2011) 47–53.
[129] Y. Lu, L.Y. Foo, Antioxidant activities of polyphenols from sage (Salvia officinalis), Food Chem. 75 (2) (2001) 197–202.
[130] M.J. del Baño, et al., Phenolic diterpenes, flavones, and rosmarinic acid distribution during the development of leaves, flowers, stems, and roots of Rosmarinus officinalis. Antioxidant activity, J. Agric. Food Chem. 51 (15) (2003) 4247–4253.
[131] A. Wojdyło, J. Oszmiański, R. Czemerys, Antioxidant activity and phenolic compounds in 32 selected herbs, Food Chem. 105 (3) (2007) 940–949.
[132] N. Erkan, G. Ayranci, E. Ayranci, Antioxidant activities of rosemary (Rosmarinus Officinalis L.) extract, blackseed (Nigella sativa L.) essential oil, carnosic acid, rosmarinic acid and sesamol, Food Chem. 110 (1) (2008) 76–82.
[133] M.S. Afonso, et al., Phenolic compounds from Rosemary (Rosmarinus officinalis L.) attenuate oxidative stress and reduce blood cholesterol concentrations in diet-induced hypercholesterolemic rats, Nutr. Metab. (Lond). 10 (1) (2013) 19.
[134] S. Fazel Nabavi, G. Carlo Tenore, M. Daglia, R. Tundis, M. Rosa Loizzo, S. Mohammad Nabavi, The cellular protective effects of rosmarinic acid: from bench to bedside, Curr. Neurovasc. Res. 12 (1) (2015) 98–105.
[135] N. Osakabe, A. Yasuda, M. Natsume, C. Sanbongi, Y. Kato, T. Osawa, T. Y, Rosmarinic acid, a major polyphenolic component of Perilla frutescens, reduces lipopolysaccharide (LPS)-induced liver injury in D-galactosamine (D-GalN)-sensitized mice, Free Radic. Biol. Med. 33 (6) (2002) 797–806.
[136] K.-W. Lee, Sung-Yong Yang, Chung-Oui Hong, Gung Pyo Lee, Cheong-Tae Kim, The hepatoprotection of caffeic acid and rosmarinic acid, major compounds of Perilla frutescens, against t-BHP-induced oxidative liver damage, Food Chem. Toxicol. 55 (2013) 92–99.
[137] W.E. Stehbens, Oxidative stress in viral hepatitis and AIDS, Exp. Mol. Pathol. 77 (2) (2004) 121–132.
[138] P.P. Tak, G. Firestein, NF-jB: a key role in inflammatory diseases, J. Clin. Invest. 107 (2003) 7–11.
[139] T. Luedde, R. Schwabe, NF-jB in the liver-linking injury, fibrosis and hepatocellular carcinoma, Nat. Rev. Gastroenterol. Hepatol. 8 (2011) 108–118.
[140] M.A. Rosillo, M. Sanchez-Hidalgo, A. Cárdeno, Protective effect of ellagic acid, a natural polyphenolic compound, in a murine model of Crohn's disease, Biochem. Pharmacol. 82 (7) (2011) 737–745 de L. L. C. B. pharmacology. 2011 O. 1;82(7):737-45.
[141] V. Swarup, J. Ghosh, S. Ghosh, A. Saxena, A. Basu, Antiviral and anti-inflammatory effects of rosmarinic acid in an experimental murine model of Japanese encephalitis, Antimicrob. Agents Chemother. 51 (9) (2007) 3367–3370.
[142] W. Boonyarikpunchai, S. Sukrong, P. Towiwat, Antinociceptive and anti-inflammatory effects of rosmarinic acid isolated from Thunbergia laurifolia Lindl, Pharmacol. Biochem. Behav. 124 (2014) 67–73.
[143] A.B. Kunnumakkara, et al., Chronic diseases, inflammation, and spices: how are they linked? J. Transl. Med. 16 (1) (2018) 14.
[144] G.K. Michalopoulos, Liver regeneration, J. Cell. Physiol. 213 (2) (2007) 286–300.
[145] T. Y, C. Sanbongi, H. Takano, N. Osakabe, N. Sasa, M. Natsume, R. Yanagisawa, K.I. Inoue, Y. Kato, T. Osawa, Rosmarinic acid inhibits lung injury induced by diesel exhaust particles, Free Radic. Biol. Med. 15 (34) (2003) 1060–1069.
[146] D. R, R. Domitrović, H. Jakovac, V.V. Marchesi, I. Šain, Ž Romić, Preventive and therapeutic effects of oleuropein against carbon tetrachloride-induced liver damage in mice, Pharmacol. Res. 65 (4) (2012) 451–464.
[147] G. K, D.O. Moon, M.O. Kim, J.D. Lee, Y.H. Choi, Rosmarinic acid sensitizes cell death through suppression of TNF-α-induced NF-κB activation and ROS generation in human leukemia U937 cells, Cancer Lett. 288 (2) (2012) 183–191.
[148] I.M. Westra, D. Oosterhuis, G.M.M. Groothuis, P. Olinga, The effect of antifibrotic drugs in rat precision-cut fibrotic liver slices, PLoS One 9 (4) (2014) p. e95462.
[149] R. Domitrović, I. Potočnjak, Ž. Crnčević-Orlić, M. Škoda, Nephroprotective activities of rosmarinic acid against cisplatin-induced kidney injury in mice, Food Chem. Toxicol. 66 (2014) 321–328.
[150] Y.-T. Fan, et al., Rosmarinic acid attenuates sodium taurocholate-induced acute pancreatitis in rats by inhibiting nuclear factor-κB activation, Am. J. Chin. Med. 43 (6) (2015) 1117–1135.
[151] Y. Han, et al., Consumption of some polyphenols reduces fecal deoxycholic acid and lithocholic acid, the secondary bile acids of risk factors of colon cancer, J. Agric. Food Chem. 57 (18) (2009) 8587–8590.
[152] G. Svegliati Baroni, et al., Fibrogenic effect of oxidative stress on rat hepatic stellate cells, Hepatology 27 (3) (1998) 720–726.
[153] T.-Z. Liu, K.-T. Lee, C.-L. Chern, J.-T. Cheng, A. Stern, L.-Y. Tsai, Free radical-triggered hepatic injury of experimental obstructive jaundice of rats involves overproduction of proinflammatory cytokines and enhanced activation of nuclear factor κB, Ann. Clin. Lab. Sci. 31 (4) (2001) 383–390.
[154] G. Poli, M. Parola, Oxidative damage and fibrogenesis, Free Radic. Biol. Med. 22 (1–2) (1997) 287–305.
[155] Z. Özgen, U. Mavi, A. Terzi, Relationship between chemical structure and antioxidant activity of luteolin and its glycosides isolated from Thymus sipyleus subsp. sipyleus var. sipyleus, Rec. Nat. Prod. 5 (2011) 12–21.
[156] W.A. Pryor, G.L. Squadrito, The chemistry of peroxynitrite: a product from the reaction of nitric oxide with superoxide, Am. J. Physiol. 268 (1995) L699–rL722.
[157] J. Beckman, Oxidative damage and tyrosine nitration from peroxynitrite, Chem. Res. Toxicol. 9 (1996) 836–844.
[158] A. Jaeschke, H. Gores, G.J. Cederbaum, Mechanisms of hepatotoxicity, Toxicol. Sci. 65 (2002) 166–176.
[159] H. Jaeschke, Reactive oxygen and mechanisms of inflammatory liver injury, J. Gastroenterol. Hepatol. 15 (7) (2000) 718–724.
[160] C. Peralta, M.B. Jiménez-Castro, J. Gracia-Sancho, Hepatic ischemia and reperfusion injury: effects on the liver sinusoidal milieu, J. Hepatol. 59 (5) (2013) 1094–1106.
[161] C. Fan, R.M. Zwacka, J.F. Engelhardt, Therapeutic approaches for ischemia/reperfusion injury in the liver, J. Mol. Med. 77 (8) (1999) 577–592.
[162] N. Fausto, J.S. Campbell, K.J. Riehle, Liver regeneration, Hepatology 43 (S1) (2006).