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REVIEW ARTICLE

A comprehensive overview of hepatoprotective natural compounds: mechanism of action and clinical perspectives

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Abstract Hepatoprotective effects of natural compounds have been frequently attributed to their antioxidant properties and the ability to mobilize endogenous antioxidant defense system. Because of involvement of oxidative stress in virtually all mechanisms of liver injury, it is a reasonable presumption that antioxidant properties of these compounds may play a key role in the mechanism of their hepatoprotective activity. Nevertheless, growing evidence suggests that other pharmacological activities of natural compounds distinct from antioxidant are responsible for their therapeutic effects. In this review, we discussed currently known molecular mechanisms of the hepatoprotective activity of 27 most intensively studied phytochemicals. These compounds have been shown to possess anti-inflammatory, antisteatotic, antiapoptotic, cell survival and antiviral activity through interference with multiple molecular targets and signaling pathways. Additionally, antifibrotic properties of phytochemicals have been closely associated with apoptosis of hepatic stellate cells and stimulation of extracellular matrix degradation. However, although these compounds exhibit a pronounced hepatoprotective effects in animal and cell culture models, the lack of clinical studies remains a bottleneck for their official acceptance by medical experts and physicians. Therefore, controlled clinical trials have an imperative in confirmation of the therapeutic activity of potentially hepatoprotective compounds. Understanding the principles of the hepatoprotective activity of phytochemicals could guide future drug development and help prevention of clinical trial failure. Also, the use of new delivery systems that enhances bioavailability of poorly water soluble compounds may improve the results already obtained. Most importantly, available data suggest that phytochemicals possess a various degree of modulation of specific signaling pathways, pointing out a need for usage of combinations of several hepatoprotective compounds in both experimental studies and clinical trials.

Keywords Phytochemicals · Hepatoprotection · Chemopreventive · Liver inflammation · Hepatic steatosis · Hepatic fibrosis

Abbreviations

4E-BP	eIF4E-binding protein
A2AR	Adenosine A2A receptor
AA	Arachidonic acid
ABC	ATP-binding cassette transporter
ACAT	Acyl-CoA:cholesterol acyltransferase
ACC	Acetyl-CoA carboxylase
ACE	Angiotensin-converting enzyme
ACOX	Acyl-coenzyme A oxidase
ACS	Acetyl-CoA synthetase
AdipoR	Adiponectin receptor
AhR	Aryl hydrocarbon receptor
AIF	Apoptosis-inducing factor
AKR	Aldo–keto reductase
ALT	Alanine transaminase
AMPK	5′ AMP-activated protein kinase
Ang	Angiotensin
AP	Activator protein
aP	Adipocyte fatty acid-binding protein
Apaf	Apoptotic protease-activating factor
AR	Amphiregulin
ARE	Antioxidant response element
ARNT	Aryl hydrocarbon nuclear translocator

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ASC	Apoptosis-associated speck-like protein containing a carboxy-terminal CARD
ASK	Apoptosis signal-regulating kinase
AT1R	Angiotensin II type 1 receptor
ATF	Activating transcription factor
BA	Bile acid
Bambi	Bone morphogenetic protein and activin membrane-bound inhibitor
Bax	Bcl-2-associated X protein
Bcl-2	B-cell lymphoma 2
BDL	Common bile duct ligation
Bid	Bcl-2 homology 3 (BH3) interacting-domain death agonist
Bim	Bcl-2-interacting mediator of cell death
BiP	Immunoglobulin binding protein
C/EBP	CCAAT/enhancer-binding protein
CAMKK	Ca^{2+}-calmodulin dependent protein kinase kinase
cAMP	Cyclic adenosine monophosphate
casp	Caspase
CAT	Catalase
CBR	Cannabinoid receptor type
CD	Cluster of differentiation
Cdk	Cyclin-dependent kinase
c-FLIP	(FADD-like IL-1β-converting enzyme)-inhibitory protein
CHOP	C/EBP homologous protein
cIAP	Cellular inhibitor of apoptosis
CPT	Carnitine palmitoyltransferase
CREB	CAMP-response element-binding protein
CRP	C-reactive protein
CTGF	Connective tissue growth factor
Cx43	Connexin 43
CXCR	Chemokine (CXC motif) receptor
CXCL	Including chemokine (C-X-C motif) ligand
CYP	Cytochrome P450
DAG	Diacylglycerol
DEN	Diethyl nitrosamine
DGAT	Diacylgycerol acyltransferase
ECM	Extracellular matrix
EGF	Epidermal growth factor
EGFR	EGF receptor
EGR	Early growth response protein
eIF	Eukaryotic initiation factor
EMR	EGF-like module-containing mucin-like hormone receptor
eNOS	Endothelial nitric oxide synthase
ER	Endoplasmic reticulum
ERK	Extracellular regulated kinase
ESR	Estrogen receptor
ET	Endothelin
FA	Fatty acid
FABP	Fatty acid-binding protein
FADD	Cellular Fas-associated death domain
FAK	Focal adhesion kinase
FAS	Fatty acid synthase
FasL	Fas ligand
FATP	Fatty acid transport protein
FOXO	Forkhead box protein O
FXR	Farnesoid X receptor
GalN	D-Galactosamine
GCLC	Glutamate-cysteine ligase, catalytic subunit
GJIC	The gap junctional intercellular communication
GLI	Glioma-associated oncogenes
GPx	Glutathione peroxidase
GR	Glutathione reductase
GRP78	78 kDa glucose-regulated protein
GSH	Glutathione
GSK	Glycogen synthase kinase
GST	Glutathione-S-transferase
H_2O_2	Hydrogen peroxide
HAV	Hepatitis A virus
HBeAg	Hepatitis B e antigen
HBsAg	HBV surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCMV	Human cytomegalovirus
HCV	Hepatitis C virus
HDAC	Histone deacetylase
HFD	High-fat diet fed
HGF	Hepatocyte growth factor
HIF	Hypoxia-inducible factor
HMGB	High-mobility group protein box
HMGCR	HMG-CoA reductase
HNF	Hepatocyte nuclear factor
HO	Heme oxygenase
HSCs	Hepatic stellate cells
HSL	Hormone-sensitive lipase
ICAM	Intracellular adhesion molecule
IFN	Interferon
IGF	The insulin growth factor
IGF-1R	IGF 1 receptor
IKK	IkappaB kinase
IL	Interleukin
iNOS	Inducible nitric oxide synthase
IP_3	Inositol 3-phosphate
IR	Insulin receptor
IRAK	IL-1R-associated kinase
IRE	Inositol-requiring enzyme
IRES	Internal ribosome entry site
IRF	IFN regulatory factor
IRS	IR substrate
IκBα	IkappaBalpha
JAK	Janus-activated kinase
JNK	c-Jun N-terminal kinase
Keap	Kelch-like ECH-associated protein

KLF	Krueppel-like factor
LC3	Microtubule-associated protein light chain 3
LDL	Low-density lipoprotein
LDLR	LDL receptor
LKB	Liver kinase B
LPS	Lipopolysaccharide
LXR	Liver X receptor
MAPK	Mitogen-activated protein kinase
MCP	Monocyte chemoattractant protein
MD	Myeloid differentiation factor
Mdm2	Mouse double minute 2 homolog
MDR	Multidrug resistance protein
MEK	Mitogen-activated protein/extracellular signal-regulated kinase kinase
MKK	Mitogen-activated protein kinase kinase
MMP	Matrix metalloproteinase
MRP	Multidrug resistance protein
mTOR	Mammalian target of rapamycin
MT	Metallothionein
MTTP	Microsomal triglyceride transfer protein
MyD	Myeloid differentiation factor
MYPT	Myosin phosphatase target subunit
NAFLD	Nonalcoholic fatty liver disease
NALP	NACHT, LRR and PYD domains-containing protein
NAMPT	Nicotinamide phosphoribosyltransferase
NASH	Nonalcoholic steatohepatitis
NFAT	Nuclear factor of activated T cells
NO	Nitric oxide
NQO	NAD(P)H:quinone oxidoreductase
Nrf	Nuclear factor-erythroid-2-related factor
NS	Nonstructural protein
OATP	Organic anion-transporting polypeptide
$p70^{S6K}$	70 kDa ribosomal S6 kinase
PAI	Plasminogen activator inhibitor
PARP	Poly (ADP-ribose) polymerase
PCNA	Proliferating cell nuclear antigen
PC-PLC	Phosphatidylcholine-specific phospholipase C
PCSK	Proprotein convertase subtilisin/kexin
PDE	Phosphodiesterase
PDGF	Platelet-derived growth factor
PDGFRβ	PDGF receptor beta
PERK	PKR-like ER kinase
PG	Prostaglandin
PGC	PPARγ coactivator
PGF	Placental growth factor
PI3K	Phosphoinositide 3-kinase
PKA	Protein kinase A
PKC	Protein kinase C
PKD	Protein kinase D
PKR	Protein kinase R
PLA	Phospholipase A
PP2A	Protein phosphatase 2A
PPAR	Peroxisome proliferator-activated receptor
Prx	Peroxiredoxin
PTP	Protein tyrosine phosphatase
PUMA	p53-up-regulated modulator of apoptosis
PXR	Pregnane X receptor
RAGE	Receptor for advanced glycation end-products
RAS	Renin–angiotensin system
ROCK	Rho-associated coiled coil-forming protein kinase
ROS	Reactive oxygen species
RSK	Ribosomal S6 kinase
RXR	Retinoid X receptor
S1P	Sphingosine-1-phosphate
SCD	Stearoyl-CoA desaturase
SESN	Sestrin
SIRT	Silent mating type information regulation 2 homolog
Smo	Smoothened
SOCS	Suppressor of cytokine signaling
SOD	Superoxid dismutase
SP	Specificity protein
SphK	Sphingosine kinase
SREBP	Sterol regulatory element-binding protein
STAT	Signal transducers and activators of transcription
TAB	TGF-β-activated kinase
TAG	Triacylglycerol
TAK	TGF-β-activated kinase
TGF	Transforming growth factor
TIMP	Tissue inhibitor of matrix metalloproteinase
TLR	Toll-like receptor
TNFR	TNF-α receptor
TNF	Tumor necrosis factor
TRADD	Receptor-associated death domain
TRAF	TNFR-associated factor
TRPV	Transient receptor potential vanilloid subfamily
Trx	Thioredoxin
TrxR	Thioredoxin reductase
TXNIP	Thioredoxin-interacting protein
Tβ-R	TGF-β receptor
UCP	Uncoupling protein
ULK	UNC-51-like kinase
uPA	Urokinase-type plasminogen activator
VEGF	Vascular endothelial growth factor
VEGFR	VEGF receptor
XBP	X-box binding protein
XIAP	X-linked inhibitor of apoptosis protein
SMA	Smooth muscle actin

Introduction

The liver has a crucial role in the regulation of multiple metabolic functions and physiological processes, such as the metabolism of nutrients, bile secretion and synthesis of

proteins, lipids and carbohydrates as well as vitamin storage. Its ability to detoxify xenobiotics makes it particularly important in the maintenance of body health. Hepatic diseases are among leading causes of morbidity and mortality worldwide. Unhealthy lifestyles, related to obesity and the excessive consumption of alcohol, drugs and soft drinks are a common cause of hepatic injury. Hepatic diseases can also be induced by biological factors (bacteria, virus and parasites) and autoimmune disorders (immune hepatitis and primary biliary cirrhosis) (Nseir et al. 2010). However, this is just one arm of the balance, which is counterweighted by liver's capacity to metabolize toxic compounds and prevent liver impairment. Moreover, the self-healing and regenerative potential of the liver could result in an excessive accumulation of extracellular matrix (ECM) proteins such as collagen, followed by progressive tissue scarring, development of cirrhosis and loss of liver function.

Despite advances in modern medicine, there is no successful therapeutical approach regarding stimulation of hepatic function, liver protection or enhancement of hepatic cell regeneration (Madrigal-Santillan et al. 2014). Current drugs, such as pegylated interferon-alpha (IFN-α) and ribavirin used in the treatment of hepatitis virus infection, are not effective in all patients and some of them will not tolerate this therapy. Similarly, silymarin, the most known hepatoprotective substance, has shown limitations regarding treatment of chronic liver impairment such as cirrhosis. Thus, it is imperative to identify highly effective pharmaceuticals for the treatment of hepatic disorders, with the accent on their low toxicity. The use of natural products in the treatment of hepatic diseases has a long history. These products emerged as a promising source of relatively nontoxic hepatoprotective compounds. However, despite the numerous evidence of hepatoprotective effects of these compounds in vitro and in vivo, it should be emphasized that studies using animal models of diseases, although generally accepted by the scientific community, cannot be easily translated to humans due to differences between species, such as genomic response to acute inflammatory stresses (Seok et al. 2013) or the activity of hepatic metabolizing enzymes (Cheung and Gonzalez 2008). Similarly, in vitro studies could not completely reflect in vivo metabolic conditions. Therefore, controlled clinical trials have an imperative in defining the therapeutic activity of potentially hepatoprotective compounds.

In this review, we gathered data based on studies conducted in animal models of hepatic disease as well as liver cell cultures, which explored hepatoprotective properties of naturally occurring phytochemicals. We focused on the possible molecular mechanisms of hepatoprotective activity of pure substances and standardized formulas, such as silymarin, rather than crude plant extracts or their fractions, which contain numerous constituents, making it difficult to attribute biological activity and its mechanism to a specific compound. Data were collected by using search engines PubMed and Scopus, with keywords "compound name"[Title/Abstract] AND (liver*[Title/Abstract] OR hepato*[Title/Abstract] OR hepati*[Title/Abstract]). Also, we excluded studies on tumor-bearing animals or tumor cell lines, since we have not reviewed antitumor properties of natural compounds, although chemopreventive activity was discussed. Additional reason to exclude such studies was ambivalent use of human hepatocellular carcinoma (HCC) cell lines for studying both cytotoxic and cytoprotective effects of tested compounds, resulting in controversial results. Some studies demonstrated a beneficial effect of natural compounds through the proapoptotic effect or sensibilization of HCCs to apoptosis, promoting these compounds as "promising chemotherapeutic agents"(Abou El Naga et al. 2013; Gao et al. 2014; Nishikawa et al. 2006; Yan et al. 2015a) while others showed antiapoptotic activity and were suggested as "protective against hepatocyte apoptosis" (Wu et al. 2008; Jung et al. 2014; Wang et al. 2014a). This imposes a following question: is it a goal to destroy or preserve HCCs in the culture? Moreover, some studies demonstrated opposed effects of tested compounds on apoptosis induced in primary hepatocytes and HCC cells, suggesting the potential use of the compound as both "hepatoprotective drug and adjuvant in anti-cancer therapy" (Ansorena et al. 2002; Karimian et al. 2012). Similarly, HCCs are frequently used as a research model for study of hepatoprotective effect of natural compounds against oxidative stress-induced hepatocellular damage (Al-Sheddi et al. 2015; Wang et al. 2015b). However, oxidative stress, including increased generation of lipid peroxidation products, is involved in both cell proliferation and growth arrest of cancer cells (Barrera 2012). Moreover, manipulation with intracellular reactive oxygen species (ROS) level is proposed as a way to selectively kill cancer cells without causing a significant toxicity to normal cells (Schumacker 2006).

We also commented on the effect of natural compounds discussed in this review on the cytochrome P450 (CYP) induction. The cytochromes P450 (CYPs) are a multigene family of microsomal hemoproteins. These enzymes are most prominent in the liver, where they play the vital role in the biotransformation of exogenous compounds such as drugs, pesticides and carcinogens (Watkins et al. 1987). However, these enzymes are involved in metabolical activation of biologically inert compounds to electrophilic derivatives that can cause toxicity and liver pathologies from alcoholic liver disease to nonalcoholic steatohepatitis, but also cellular transformation which could result in cancer (Gonzalez 2005).

Virtually all classes of natural compounds have their representative compounds which exhibit a beneficial effect against liver diseases. We reviewed 27 most intensively studied natural compounds for the mechanisms of hepatoprotective activity, belonging to nine classes, including flavonoids, terpenoids, phenolic acids, stilbenes,

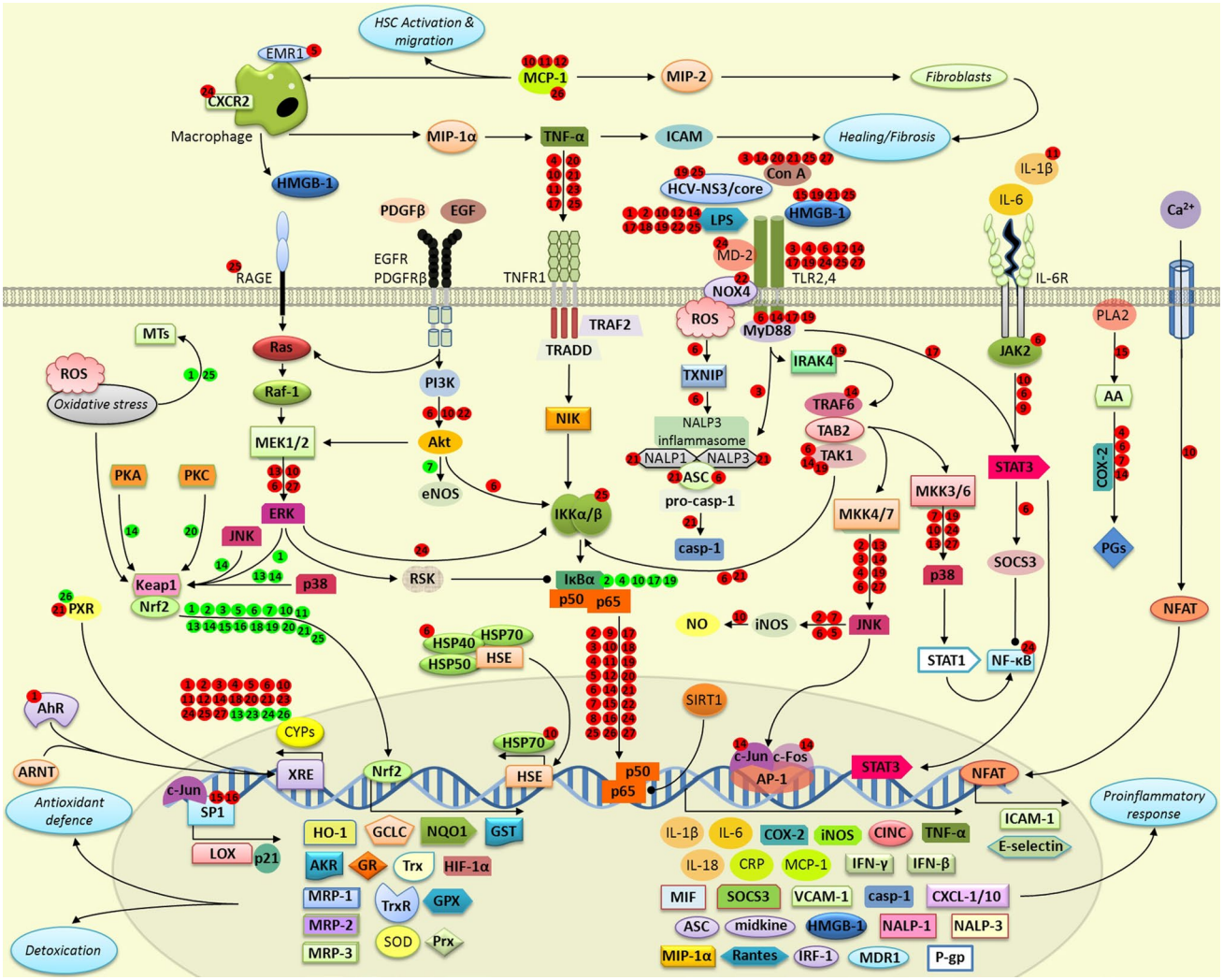

Fig. 1 Mechanisms of antioxidant and anti-inflammatory activities of phytochemicals in the liver. (**1**) luteolin, (**2**) baicalein, (**3**) baicalin, (**4**) genistein, (**5**) naringenin, (**6**) quercetin, (**7**) rutin, (**8**) troxerutin, (**9**) morin, (**10**) (–)-epigallocatechin-3-gallate, (**11**) silymarin, (**12**) thymoquinone, (**13**) andrographolide, (**14**) ginsenosides, (**15**) glycyrrhizin, (**16**) 18β-glycyrrhetinic acid, (**17**) betulinic acid, (**18**) ursolic acid, (**19**) chlorogenic acid, (**20**) salvianolic acid, (**21**) resveratrol, (**22**) berberine, (**23**) caffeine, (**24**) emodin, (**25**) curcumin, (**26**) capsaicin, (**27**) ellagic acid. *Red circle* denotes inhibitory effect; *green circle* denotes stimulatory effect. For abbreviations, see the abbreviation list

alkaloids, antraquinones, curcuminoids, capsaicinoids and chromenes. The mechanisms of their hepatoprotective actions are summarized in Figs. 1, 2, 3 and 4.

Flavonoids

Flavonoids are the largest group of naturally occurring phenolic compounds present in high concentrations in many foods, such as tea, apples, grapes and their processed beverages (Parvez et al. 2006). Flavonoids share a common 15-carbon skeleton consisting of two benzene rings linked via a heterocyclic pyrane ring. These compounds can be divided into several classes, including flavones, isoflavones, flavanones, flavonols (including flavan-3-ols and polymeric flavonolos, proanthocyanidins), flavanonols and anthocyanins. They are generally considered nontoxic for humans, exhibiting numerous pharmacological effects in vitro and in vivo. Still, their ability to modulate the activity of xenobiotic-metabolizing enzymes, particularly phase I enzymes, may have pharmacological and/or toxicological significance.

Flavones

Hepatoprotective activity of luteolin (3′,4′,5,7-tetrahydroxyflavone) (**1**), as well as virtually all hepatoprotective

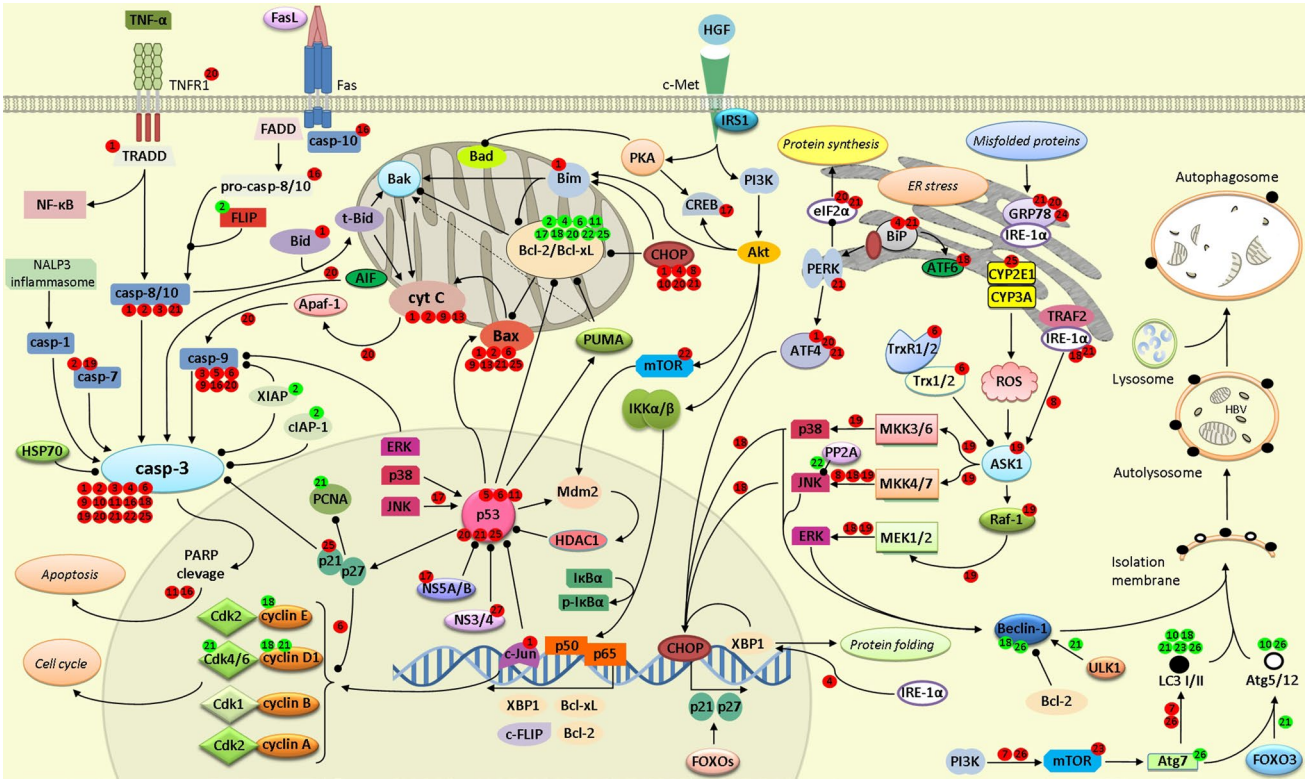

Fig. 2 Mechanisms of antiapoptotic activity of phytochemicals in injured liver tissue. (**1**) luteolin, (**2**) baicalein, (**3**) baicalin, (**4**) genistein, (**6**) quercetin, (**7**) rutin, (**8**) troxerutin, (**9**) morin, (**10**) (–)-epigallocatechin-3-gallate, (**11**) silymarin, (**13**) andrographolide, (**16**) 18β-glycyrrhetinic acid, (**17**) betulinic acid, (**18**) ursolic acid, (**19**) chlorogenic acid, (**20**) salvianolic acid, (**21**) resveratrol, (**22**) berberine, (**24**) emodin, (**25**) curcumin, (**26**) capsaicin. *Red circle* denotes inhibitory effect; *green circle* denotes stimulatory effect. For abbreviations, see the abbreviation list

compounds reviewed in this article, has been associated with improvement in antioxidant defense, such as the increase in superoxid dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) activity and glutathione (GSH) levels (Domitrovic et al. 2008, 2009a; Balamurugan and Karthikeyan 2012). It has been suggested that luteolin and other flavones, such chrysin and apigenin, inhibit hepatic oxidative stress through up-regulation of the extracellular signal-regulated kinase (ERK) 2/nuclear factor-erythroid-2-related factor 2 (Nrf2)/antioxidant response element (ARE) pathway (Huang et al. 2013). Luteolin has also been shown to modulate the expression of xenobiotic-induced phase I and phase II drug-metabolizing enzymes in several liver cell lines (Zhang et al. 2014f). Thus, luteolin inhibited the expression of NAD(P)H:quinone oxidoreductase-1 (NQO1) and aldo-keto reductases (AKRs) through the Nrf2 pathway and the expression of CYP1A1 and glutathione-S-transferase (GST) through the aryl hydrocarbon receptor (AhR) pathway. Moreover, luteolin inhibited CYP3A4 and CYP3A5 enzymes in human liver microsomes, suggesting a potential of pharmacokinetic interaction with co-administered drugs (Quintieri et al. 2008). Furthermore, this flavone attenuated chemically induced endoplasmic reticulum (ER) stress through suppression of activating transcription factor (ATF) 4 and CCAAT/enhancer-binding protein (C/EBP)-homologous protein (CHOP) signaling (Tai et al. 2015).

Hepatic fibrosis is a pathological condition that occurs as response to persistent liver injury, resulting in progression toward cirrhosis or resolution if an insult has been withdrawn. The reversion of hepatic fibrosis by luteolin has been accompanied by enhanced expression of matrix metalloproteinase (MMP)-9 and removal of collagen deposits, with attenuation of hepatic stellate cells (HSCs) activation (Domitrovic et al. 2009b). Li et al. (2015a) showed that luteolin may also induce apoptosis and G1 arrest in HSCs through inhibition of the platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGF-β) signaling pathways, potent stimulators of fibrogenesis. Luteolin inhibited PDGF-BB-stimulated expression of phosphorylated Akt, its downstream target mammalian target of rapamycin (mTOR), as well as the mTOR substrate 70 kDa ribosomal S6 kinase ($p70^{S6K}$). Additionally, luteolin attenuated TGF-β1-stimulated hepatic Smad2 phosphorylation, suggesting its potential to inhibit synthesis of fibrogenic mediators, such as connective tissue growth factor (CTGF). Moreover, these changes led to increased p53 expression and caspase-3

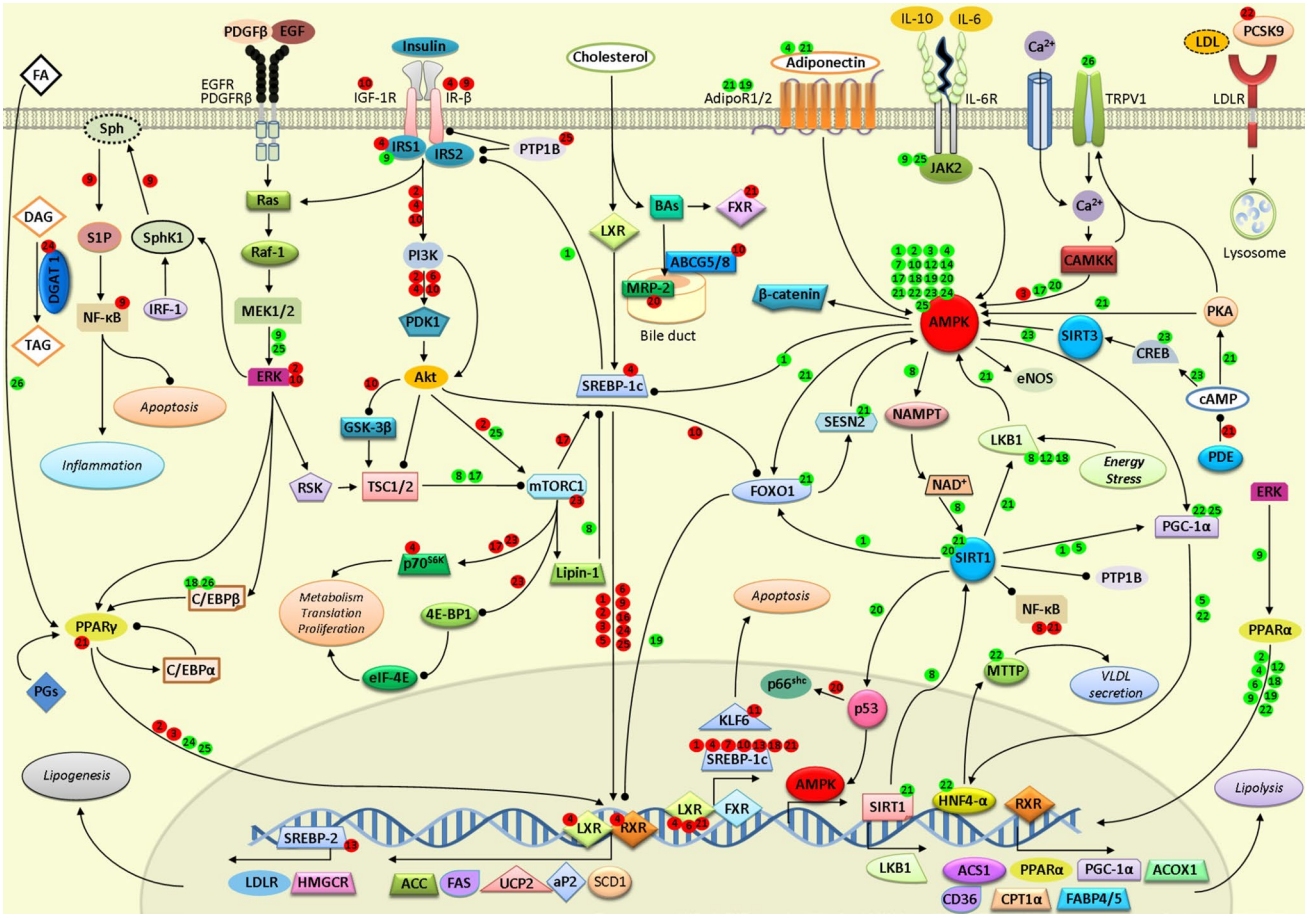

Fig. 3 Mechanisms of antisteatotic activity of phytochemicals in fatty liver disease. (**1**) luteolin, (**2**) baicalein, (**3**) baicalin, (**4**) genistein, (**5**) naringenin, (**6**) quercetin, (**7**) rutin, (**8**) troxerutin, (**9**) morin, (**10**) (–)-epigallocatechin-3-gallate, (**11**) silymarin, (**12**) thymoquinone, (**13**) andrographolide, (**14**) ginsenosides, (**16**) 18β-glycyrrhetinic acid, (**17**) betulinic acid, (**18**) ursolic acid, (**19**) chlorogenic acid, (**20**) salvianolic acid, (**21**) resveratrol, (**22**) berberine, (**23**) caffeine, (**24**) emodin, (**25**) curcumin. *Red circle* denotes inhibitory effect, *green circle* denotes stimulatory effect. For abbreviations see the abbreviation list

activity, with concomitant inhibition of the cell cycle through decrease in the expression of cyclin E and phosphorylated cyclin-dependent kinase (Cdk) 2, resulting in HSCs apoptosis and cell cycle arrest. On the other hand, luteolin protected against lipopolysaccharide (LPS)/D-galactosamine (GalN)-induced apoptotic liver damage in mice, which was accompanied by decrease in hepatic expression of tumor necrosis factor-alpha (TNF-α) receptor-associated death domain (TRADD) (Lee et al. 2011). Protection of hepatocytes was achieved by suppression of caspase-3 and caspase-8 activity and expression of proapoptotic B-cell lymphoma 2 (Bcl-2) family, including Bcl-2-associated X protein (Bax), Bcl-2 homology 3 (BH3) interacting-domain death agonist (Bid) and Bcl-2-interacting mediator of cell death (Bim).

The potential of luteolin to inhibit hepatic lipogenesis and improve hepatosteatosis was demonstrated in ethanol and high-fat diet fed (HFD) mice (Liu et al. 2014a; Kwon et al. 2015). Activation of peroxisome proliferator-activated receptor gamma (PPARγ) has emerged as a potential strategy for blocking HSCs activation and differentiation. In both models, luteolin increased PPARγ protein expression in adipose tissue and reduced hepatic expression of lipogenic genes, including sterol regulatory element-binding protein (SREBP)-1c, the master regulator of lipid synthesis, fatty acid synthase (FAS), acetyl-CoA carboxylase (ACC) and stearoyl-CoA desaturase (SCD) 1. Luteolin abrogated ethanol-induced SREBP-1c phosphorylation via stimulation of 5′ AMP-activated protein kinase (AMPK) activity, the negative regulator of lipogenesis. In addition, luteolin improved hepatic insulin sensitivity in diet-induced obese mice by suppressing the expression of SREBP-1c and up-regulating insulin receptor (IR) substrate (IRS)-2 expression through its negative feedback (Kwon et al. 2015). Moreover, luteolin supplementation in diethylnitrosamine (DEN) and ethanol-intoxicated mice significantly reversed reduced silent mating type information regulation

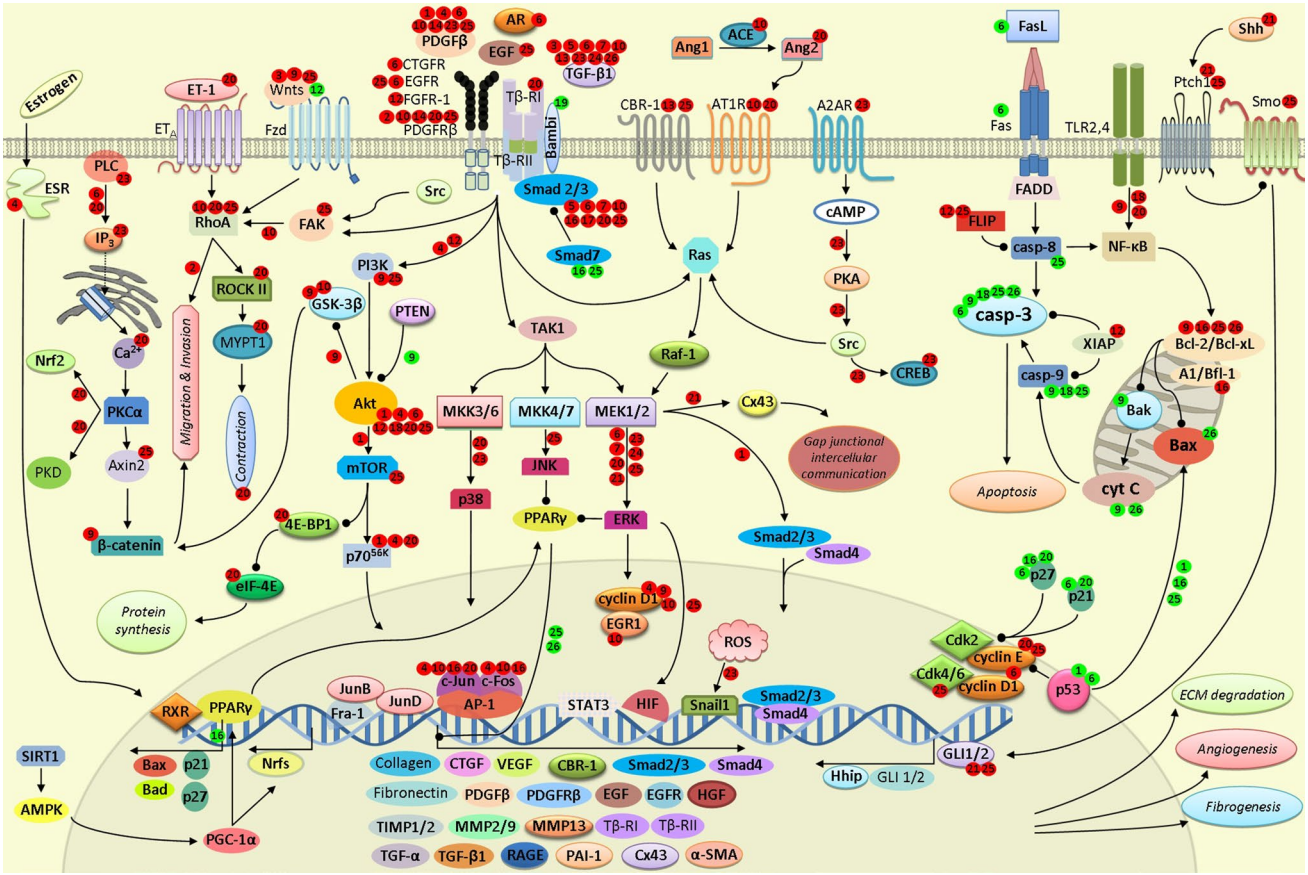

Fig. 4 Mechanisms of antifibrotic activity and HSCs apoptosis by phytochemicals in liver fibrosis. (**1**) luteolin, (**2**) baicalein, (**3**) baicalin, (**4**) genistein, (**5**) naringenin, (**6**) quercetin, (**7**) rutin, (**9**) morin, (**10**) (–)-epigallocatechin-3-gallate, (**12**) thymoquinone, (**13**) andrographolide, (**14**) ginsenosides, (**16**) 18β-glycyrrhetinic acid, (**18**) ursolic acid, (**19**) chlorogenic acid, (**20**) salvianolic acid, (**21**) resveratrol, (**23**) caffeine, (**24**) emodin, (**25**) curcumin, (**26**) capsaicin. *Red circle* denotes inhibitory effect; *green circle* denotes stimulatory effect. For abbreviations, see the abbreviation list

2 homolog 1 (SIRT1) activity assessed by modulating the expression of forkhead box protein O (FOXO) 1 and SIRT1 target PPARγ coactivator 1 alpha (PGC1α), substantially preventing pre-neoplastic lesions in the liver (Rafacho et al. 2015). Usage of the phospholipid complex of luteolin has been proposed as an enhanced drug delivery system for oral administration of luteolin with increased bioavailability and hepatoprotective potential (Khan et al. 2015).

Flavones baicalein (5,6,7-trihydroxyflavone) (**2**) and baicalin (baicalein 7-O-glucuronide) (**3**) inhibited pro-oxidant-induced liver injury in vitro by scavenging ROS in hepatocytes (Zhao et al. 2006). Baicalein improved metabolic syndrome induced by HFD in mice through the inhibition of ERK1/2 and c-Jun N-terminal kinase (JNK)1/2/3 mitogen-activated protein kinases (MAPKs) phosphorylation and activation of the IRS-1/phosphoinositide 3-kinase (PI3K)/Akt pathway (Pu et al. 2012b). The lipid-lowering effect was attributed to the suppression of SREBP-1c, PPARγ and their target genes, including FAS, ACC, uncoupling protein (UCP) 2 and adipocyte fatty acid-binding protein (aP), with concomitant induction of lipolytic enzymes such as PPARα, cluster of differentiation (CD) 36 and carnitine palmitoyltransferase (CPT) 1. All these effects were dependent on AMPK activation. Interestingly, the same effect was observed by flavanone naringin (Pu et al. 2012a). Baicalein also prevented nonalcoholic steatohepatitis (NASH) through enhancement of Nrf2/heme oxygenase (HO)-1 pathway and suppression of NF-κB activation (Xin et al. 2014). In LPS/D-GalN-induced acute liver failure in mice, baicalein ameliorated gene expression of TNF-α, inducible nitric oxide synthase (iNOS), vascular endothelial growth factor (VEGF), VEGF receptor (VEGFR) and monocyte chemoattractant protein (MCP)-1, inhibiting hepatic inflammation and HSCs migration (Cheng et al. 2007; Wu et al. 2010; Chen et al. 2013a). Concomitantly, it inhibited hepatic apoptosis by suppressing phosphorylation of ERK and JNK (Wu et al. 2010). Moreover, baicalein activated cellular Fas-associated death domain (FADD)-like IL-1β-converting enzyme-inhibitory protein (c-FLIP), X-linked

inhibitor of apoptosis protein (XIAP) and cellular inhibitor of apoptosis (cIAP) 2 proteins while reducing nuclear levels of RelA, suggesting attenuation of the NF-κB signaling. Similarly, the inhibition of MAPKs activation by this compound significantly improved the survival of mice with polymicrobial sepsis-induced liver injury (Liu et al. 2015a). Furthermore, baicalein prevented CCl_4-induced liver fibrosis in rats and inhibited HSCs activation and proliferation by down-regulation of PDGF receptor beta (PDGFRβ) (Sun et al. 2010). In addition, baicalein increased gene expression of TGF-α, hepatocyte growth factor (HGF) and epidermal growth factor (EGF), well-known regulators of liver regeneration.

Similarly to baicalein, its glucoronide conjugate, baicalin, exhibited protection against oxidative liver injury (Kim et al. 2010c; Zhang et al. 2012). Baicalin also suppressed toll-like receptor (TLR) 4-mediated inflammatory response after ischemia/reperfusion-induced liver injury in rats (Kim and Lee 2012) which was associated with the inhibition of myeloid differentiation factor 88 (MyD88) protein expression and the nuclear translocation of NF-κB. Additionally, baicalin up-regulated cytoprotective HO-1 expression, which is suggesting the activation of the Nrf2 pathway (Kim et al. 2010c). Moreover, baicalin suppressed apoptosis in concanavalin A-treated mice livers by inhibiting TNF-α-induced JNK phosphorylation and suppressing caspase-3 and caspase-9 activation (Liu et al. 2007). Studying the antifibrotic potential of baicalin, several authors showed attenuation of CCl_4-intoxication in rats through suppression of TGF-β1 and PPARγ activation (Peng et al. 2009; Qiao et al. 2011). Yang et al. (2012) showed that the mechanism of PPARγ-mediated suppression of fibrotic response by baicalin, as well as rosmarinic acid, could be mediated through the suppression of signaling by canonical Wnts. Furthermore, Guo et al. (2009) demonstrated that baicalin had beneficial effect on development of hepatic steatosis by reducing hepatic lipid accumulation through enhancement of AMPK phosphorylation and down-regulation of genes involved in lipogenesis, including FAS and its upstream regulator SREBP-1c. Additionally, baicalin could attenuate HFD-induced obesity and fatty liver disease through the inhibition of Ca^{2+}-calmodulin dependent protein kinase kinase (CAMKK)/AMPK/ACC pathway (Xi et al. 2015).

Both compounds, baicalein and baicalin, were able to modulate the activity of hepatic CYP system. Baicalein inhibited CYP1A2 and CYP3A4 activity in human liver microsomes and CYP2E1 and CYP3A expression in mice liver (Ueng et al. 2000; Kim et al. 2002). Baicalin inhibited hepatic CYP3A and CYP2D activity in rats (Tian et al. 2013; Gao et al. 2014) and CYP1A2 in both human and rat livers (Cheng et al. 2014). These findings suggest that baicalein and baicalin may modulate the activity of drug-metabolizing enzymes.

Isoflavones

The inhibition of NF-κB and MAPK signaling was suggested as a mechanism of the anti-inflammatory activity of genistein (4′,5,7-trihydroxyisoflavone) (**4**) (Ji et al. 2011; Lin et al. 2014b; Saleh et al. 2014; Ganai et al. 2015). This soy estrogenic isoflavone showed the ability to improve liver fibrosis induced by chronic CCl_4 administration through the increase in expression and proteolytic activity of urokinase-type plasminogen activator (uPA), a potent inductor of collagenases and ECM degradation (Salas et al. 2007). Antifibrotic activity of genistein has also been associated with reduced levels of PDGF-BB (Demiroren et al. 2014), which acts via its cell surface tyrosine kinase receptors, inducing proliferation of HSCs via PI3K/Akt and ERK pathways (Fang et al. 2013). In hepatic fibrosis induced by chronic administration of alcohol in rats, genistein promoted extracellular matrix (ECM) degradation by reducing tissue inhibitor of matrix metalloproteinase (TIMP)-1 and increasing MMP-2 mRNA levels, with concomitant inhibition of TGF-β1 expression. In addition, genistein exhibited potency to attenuate PDGF-induced c-Fos, c-Jun and cyclin D1 expression and inhibit HSCs proliferation (Liu et al. 2002d). Genistein also acted as a selective agonist for the beta isoform of the estrogen receptor (ESRβ), which is highly expressed by active HSCs (McCarty et al. 2009).

Genistein has also been shown to possess inhibitory effect on hepatic steatosis in HFD-induced nonalcoholic fatty liver disease (NAFLD) in mice through down-regulation of genes associated with lipogenesis, including SREBP-1c, liver X receptor alpha (LXRα), retinoid X receptor alpha (RXRα), PPARγ and ACC2, with concomitant up-regulation of genes involved in β-oxidation, including AMPK and PPARα (Kim et al. 2010b). Additionally, genistein augmented the expression of anti-steatohepatitic adiponectin, an adipocyte-derived hormone, and reduced levels of pro-inflammatory cytokine TNF-α. Moreover, this isoflavone inhibited expression of TLR4, a member of a class of proteins involved in regulation of IkappaB kinase (IKK) activity and downstream NF-κB activation (Ambade and Mandrekar 2012), leading to attenuation of production of proinflammatory cytokines in diet-induced NAFLD (Yoo et al. 2015). Concomitant reduction in CHOP, X-box binding protein 1 (XBP-1) and ER chaperone immunoglobulin binding protein (BiP) mRNA expression suggested attenuation of ER stress in hepatocytes. Genistein-treated younglings showed lower hepatic expression of FAS and SREBP-1, but higher expression of PPARα, indicating lower rates of lipid synthesis and higher rates of β-oxidation (Huang et al. 2011). Moreover, genistein was able to sensitize hepatic insulin signaling by improving insulin-stimulated tyrosine phosphorylation of IR-β and IRS-1 as well as downstream PI3K and Akt phosphorylation in the mouse

model of metabolic syndrome (Arunkumar et al. 2013). Genistein treatment also resulted in the increase in AMPK and the decrease in $p70^{S6K}$ phosphorylation, suggesting its beneficial effect in amelioration of both hepatic steatosis and metabolic syndrome.

Nevertheless, caution with intake of higher doses of genistein has been suggested, since they can produce several undesirable effects by affecting multiple cellular pathways (Okazaki et al. 2002; Singh et al. 2014). Specific tyrosine kinase inhibitory properties of genistein resulted in dose-dependent inhibition of the recombinant human HGF-mediated stimulation of DNA synthesis by hepatocytes, which could have negative impact on liver repair and regeneration (Arakaki et al. 1992; Kaibori et al. 2006). The potential for diet–drug interactions of genistein and several other dietary flavonoids has also been demonstrated. Thus, these flavonoids acted as modulators of organic anion-transporting polypeptide (OATP) 1B1, a liver-specific uptake transporter important in hepatic drug disposition (Wang et al. 2005). In addition, genistein was shown to inhibit the activity of several CYPs, including CYP1A2 and CYP2E1, in a non-competitive manner (Roberts-Kirchhoff et al. 1999).

Flavanones

The most intensively studied citrus flavonoid, naringenin (4′,5,7-trihydroxyflavanone) (**5**), exhibited protective activity against hepatic oxidative injury (Pari and Gnanasoundari 2006; Lv et al. 2013). Naringenin has been showing a potential to attenuate inflammation in several experimental models of liver injury. The suppression of CCl_4- and cholesterol-induced hepatic inflammation in rats was mediated by down-regulation of proinflammatory genes, including NF-κB, TNF-α, IL-1 β, IL-6, iNOS and EGF-like module-containing mucin-like hormone receptor 1 (EMR1, the macrophage-specific gene) (Esmaeili and Alilou 2014; Chtourou et al. 2015). In addition, naringenin up-regulated the cytoprotective Nrf2/HO-1 pathway. Several studies showed that naringenin may be useful in preventing the ECM accumulation and development of hepatic fibrosis. This flavone inhibited gene expression of the antifibrotic targets MMP-2 and MMP-9 and prevented ECM remodeling (Liu et al. 2006). Mechanistically, the antifibrotic activity of naringenin was accompanied by inhibition of TGF-β1-induced production of Smad3 at both mRNA and protein levels. In HFD-fed mice, naringenin reduced hepatic triglyceride concentration and gene expression of hepatic lipogenic enzymes and up-regulated hepatic fatty acid oxidation genes, suggesting inhibition of SREBP-1c and induction of SIRT1/PGC-1α pathways (Assini et al. 2015). In docking study, naringenin and quercetin exhibited minimum binding energy with nonstructural hepatitis C virus (HCV) NS2 protease, suggesting inhibitory potential against the viral replication (Lulu et al. 2015). As seen in similar studies, usage of naringenin-loaded nanoparticles system could improve hepatoprotective effects of the flavonoid after oral administration (Yen et al. 2009). Nanoformulation improved the bioavailability of the compound, which resulted in more potent antioxidant and antiapoptotic activities.

The ability of naringenin to modulate the activity of CYPs has also been demonstrated. Naringenin was potent inhibitor of CYP1A1, CYP1A2, CYP2B1, CYP2D6, CYP2E1 and CYP3A1/2 and relatively weak inhibitor of CYP3A4 activity in vitro (Fuhr et al. 1993; Bear and Teel 2000; Ho et al. 2001; Motawi et al. 2014; Arinc et al. 2015). Thus, the possibility of modulation of drug and other xenobiotic metabolism exists, which should be further investigated, particularly in light of protection against xenobiotic-induced carcinogenesis.

Flavonols

Quercetin (3,3′,4′,5,7-pentahydroxyflavone) (**6**) is one of the most studied natural products, showing numerous beneficial effects, such as hepatoprotection. It has been found that quercetin could ameliorate oxidative livery injury by reducing lipid peroxidation and increasing GSH levels and the activity of antioxidant enzymes (Casella et al. 2014; Surapaneni and Jainu 2014; El-Shafey et al. 2015). Several studies demonstrated that protective activity of quercetin against oxidative hepatocyte injury was mediated through activation of the Nrf2/HO-1 pathway (Liu et al. 2012, 2015b; Li et al. 2013c). The mechanism of induction involved p38 and ERK activation and nuclear translocation of Nrf2. Antioxidant activity of quercetin was also associated with expression of other oxidative stress-related genes, including peroxiredoxin (Prx) 1, 2, 3, 5, 6, thioredoxin reductase (TrxR) 1 and 2 and thioredoxin (Trx) 1 and 2 (Zhang et al. 2014c). We showed that expression of Nrf2 and HO-1 was more potently suppressed by rutin, quercetin 3-O-rutinoside, than its aglycone quercetin (Domitrovic et al. 2012). In contrast, quercetin more potently attenuated the expression of TGF-β1, suggesting strong impact of structure–activity relationship between these two compounds on amelioration of liver injury. Several studies also demonstrated antiapoptotic activity of quercetin in chemically intoxicated rats (de David et al. 2011; Sekaran et al. 2012; Sarkar and Sil 2014). The mechanism involved down-regulation of p53-inducible apoptotic proteins (Bax, caspase-9, caspase-3) and up-regulation of the pro-survival ERK1/2 pathway. In contrast, quercetin initiated proapoptotic events in DMN-induced hepatocarcinogenesis in rat livers (Casella et al. 2014) and induced the cell cycle arrest by reducing expression of cyclins and Cdk1.

Quercetin suppressed nuclear import of NF-κB in diet-induced hepatic inflammation in mice (Das et al. 2013; Sikder et al. 2014). The inhibition of NF-κB was accompanied by suppression of TNF-α, iNOS, cyclooxygenase-2 (COX-2), interleukin (IL)-1β and C-reactive protein (CRP), as well as suppression of IKKα and prevention of IkappaBalpha (IκBα) degradation, both involved in NF-κB activation (Dias et al. 2005; Martínez-Flórez et al. 2005; García-Mediavilla et al. 2007; Ponmari et al. 2014). Moreover, quercetin has been shown to decrease protein expression of TLR4, an upstream inductor of NF-κB (Marcolin et al. 2013). Quercetin also suppressed arsenite-induced expression of COX-2 and PGE_2 production by blocking the activation of the PI3K/Akt/$p70^{S6K}$ signaling pathway and phosphorylation of ERK1/2 (Lee et al. 2010b). The inhibition of heavy metal-induced hepatic injury could be, at least in part, attributed to inhibition of the p38/STAT1/NF-κB signaling pathway (Liu et al. 2015b). Furthermore, quercetin suppressed nonalcoholic steatohepatitis in mice induced by methionine/choline-deficient diet, which was associated with the reduction of the mRNA levels of inflammatory mediators and the decrease in protein expression of JNK and p65 NFκB subunit (Marcolin et al. 2012). Zhang et al. (2015b) demonstrated that quercetin could ameliorate high-fructose diet-induced caspase-1 expression in rat hepatocytes and activation of proinflammatory cytokines, such as IL-18 and IL-1β, through inhibition of thioredoxin-interacting protein (TXNIP)-mediated NACHT, LRR and PYD domains-containing protein 3 (NALP-3) inflammasome. In addition, quercetin inhibited activation of janus-activated kinase 2/signal transducers and activators of transcription 3 (JAK2/STAT3)-mediated inflammatory signaling and altered the expression of lipid metabolism-related enzymes, including PPARα, SREBP1 and SCD1, thus preventing lipid accumulation in the liver. An amelioration of metabolic syndrome in rats by this phenolic was mediated through the suppression of NF-κB and caspase-3 activation, with increased expression of Nrf2, HO-1 and CPT1 (Panchal et al. 2012).

Antifibrotic potential of quercetin has been shown in rat common bile duct ligation (BDL) and CCl_4 models of hepatic damage (Bona et al. 2012; Lin et al. 2014a). Quercetin attenuated BDL-induced NF-κB activation and the expression of MyD88 and TGF-β-activated kinase 1 (TAK1), critical for linking TLR and NF-κB. Quercetin also reduced Smad2/3 activity critical for the fibrogenic potential of TGF-β1 and HSCs activation (Lin et al. 2014a; Wan et al. 2014). In addition, this compound down-regulated the expression of inflammatory genes and proteins related to precancerous conditions, such as glioma-associated oncogenes (GLI)-1 and -2 (Cuevas et al. 2011). Suppression of amphiregulin (AR)/EGF receptor (EGFR) axis was associated with the inhibition of Akt and ERK1/2, major survival signals. In CCl_4-induced cirrhosis model in rats, quercetin was shown to decrease MMP-2 levels (Bona et al. 2012) and ameliorate HSCs activation by reducing the levels of inflammatory cytokines. Moreover, quercetin decreased the hepatic gene expression of PDGF-BB, HSCs mitogen, CTGF and TGF-β1, potent stimulators of ECM production, and the EGFR ligand AR, suggesting inhibition of multiple profibrotic gene pathways (Marcolin et al. 2012). Further, quercetin induced G_1 arrest and impaired the proliferation of activated rat HSCs by increasing levels of p53, p21 and p27 and decreasing expression of cyclins D_1, D_2, A and E (Wu et al. 2011). Additionally, quercetin prevented HSCs activation by reducing the levels of inflammatory cytokines, including chemokine (C-X-C motif) ligand (CXCL)-1 and midkine. Quercetin also stimulated HSCs apoptosis, which was accompanied by increased expression of Fas/Fas ligand (FasL) and caspase-3 activity. Previously, Kawada et al. (1998) showed that resveratrol, and more potently, quercetin, may suppress inositol phosphate (IP_3) production, receptor-tyrosine kinase phosphorylation and ERK1/2 activation in PDGF/BB-stimulated HSCs, indicating a complex role of quercetin in hepatoprotection.

Further, quercetin showed inhibitory effect on HCV replication in vitro, which was attributed to inhibition of HCV nonstructural protein (NS) protease activity and reduction of HSP40 and HSP70 expression (Gonzalez et al. 2009; Bachmetov et al. 2012). The HCV genome is translated through an internal ribosome entry site (IRES) before its conversion into individual mature viral proteins and NS5A has been implicated in the regulation of viral genome replication. Quercetin has been shown to reduce IRES activity and its augmentation by NS5A (Gonzalez et al. 2009). Interestingly, inhibition of the PI3K/Akt/LXRα-dependent lipogenesis also contributed to suppression of the viral replication (Pisonero-Vaquero et al. 2014).

It should be mentioned that some studies indicated that quercetin may exhibit prooxidant activity and exacerbate toxic liver injury (Meng et al. 2013; Pietsch et al. 2014). Nevertheless, doses used in these studies were relatively high compared to average dietary intake. Quercetin has been mostly shown to inhibit the activity of various CYPs, including CYP1A1, CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19 and CYP3A4 (Walsky et al. 2005; He et al. 2006; Tiong et al. 2010; Rastogi and Jana 2014; Arinc et al. 2015). It also reduced CYP2E1 levels and activity and decreased CYP1B1 expression (Choi et al. 2012; Tang et al. 2013; Surapaneni et al. 2014). The inhibitory potential against gene expression of CYP2B9, CYP2B10, CYP2B13 and CYP3A59 in mice livers has also been demonstrated (Marcolin et al. 2012). In addition, among several flavonoids tested, including resveratrol and curcumin, only quercetin induced accumulation of CYP3A4 mRNA in primary human hepatocytes (Raucy 2003), indicating the potential for adverse reactions by this compound.

Rutin, a quercetin-rutinoside (**7**), exhibited the hepatoprotective effect through modulation of the antioxidant genes expression and improvement in antioxidant status in several models of liver injury (Khan et al. 2012; Al-Rejaie et al. 2013). In mice fed high-cholesterol diet, rutin, as well as quercetin, attenuated the increase in expression of redox sensitive transcription factor NF-κB and inflammatory markers such as CRP and TNF-α (Sikder et al. 2014). Similarly, inflammatory response in cyclophosphamide-intoxicated mice was inhibited through down-regulation of COX-2 and p38 MAPK expression (Nafees et al. 2015). Rutin administration also attenuated the increase in expression of hepatic iNOS in ischemia-/reperfusion-injured rat livers, while increasing endothelial nitric oxide synthase (eNOS) expression (Lanteri et al. 2007) and nitric oxide (NO) production (Yagnik et al. 2002). Moreover, rutin supplementation completely reversed CCl_4-induced increase in the gene expression of EGF, FADD, Bcl-xL, IL-6, STAT3 and JAK and decrease in Bcl-2 expression, suggesting attenuation of hepatotoxicity through several signaling pathways (Hafez et al. 2015). The beneficial effects of rutin in cholestatic liver injury were associated with down-regulation of inflammatory NF-κB and profibrotic TGF-β1/Smad2/3 signaling pathways, most likely via suppression of ERK and AMPK activation as well as enhancement of Nrf2 and HO-1 expression (Pan et al. 2014). Additional suggestion for antifibrotic mechanism of rutin came from another study, which demonstrated that rutin, as well as curcumin, may stimulate microtubule-associated protein light chain 3 (LC3) protein expression and autophagy of activated HSCs via stimulation of the PI3K/Akt/mTOR-dependent pathway (Lee et al. 2014c). The hepatoprotective effects of rutin against fatty acid-induced inflammation and obesity were associated with the suppression of transcriptional activation of SREBP-1c and CD36 in the liver and amelioration of fatty liver disease (Gao et al. 2013a).

Troxerutin, a trihydroxyethylated derivative of rutin (**8**), has been shown to exert hepatoprotective activity through amelioration of hepatic oxidative stress and inflammation by restoring the activity of antioxidant enzymes and suppressing NF-κB, iNOS and COX-2 expression (Zhang et al. 2009, 2015e). Troxerutin could reduce hepatic oxidative stress-mediated NAD^+-depletion in intoxicated mice and restored SIRT1 protein expression and activity (Zhang et al. 2015e), which was accompanied by suppression of NF-κB nuclear translocation and inflammatory genes induction. The same authors demonstrated that troxerutin could inhibit hepatocyte apoptosis by alleviating oxidative stress-mediated proteasome dysfunction and restoring ER stress-mediated apoptotic pathway (Zhang et al. 2015d). Mechanistically, troxerutin blocked TNF-α receptor (TNFR)-associated factor (TRAF) 2/apoptosis signal-regulating kinase (ASK) 1/JNK and CHOP-mediated signaling. Troxerutin could also prevent liver steatosis by blocking oxidative stress and restoring dysfunction of lipin 1 signaling in high-fat diet-treated mice, improving lipid homeostasis by enhancing fatty acid oxidation and triglyceride secretion while suppressing lipogenesis (Zhang et al. 2014g). The authors demonstrated that troxerutin suppressed oxidative stress-mediated NAD^+-depletion by increasing nicotinamide phosphoribosyltransferase (NAMPT) protein expression and decreasing poly (ADP-ribose) polymerase (PARP)-1 protein expression and activity in mice livers. Consequently, troxerutin restored hepatic SIRT1 protein expression and activity, thus promoting AMPK activation and subsequent inhibition of mTOR complex 1 (mTORC1) signaling. This resulted in reduced cytoplasmic and increased nuclear localization of lipin 1, where it could serve as a component of a transcriptional complex with PPARα and PGC-1α to regulate fatty acid metabolism in liver (Finck et al. 2006).

Morin (3,5,7,2′,4′-pentahydroxyflavone) (**9**), a flavonoid isolated from herbs of the *Moraceae* family, showed hepatoprotective activity by reducing hepatic oxidative stress (Shankari et al. 2010; Merwid-Lad et al. 2014). Morin prevented acute liver damage induced by CC_4 by inhibiting the expression of NF-κB and the production of inflammatory cytokines (Heeba and Mahmoud 2014). High-glucose-induced oxidative stress and apoptosis in primary rat hepatocytes, evidenced by increased Bax, caspase-3 and caspase-9 expression and cytochrome c cytoplasmic translocation, were attenuated by morin (Kapoor and Kakkar 2012). Morin could also be employed as a chemopreventive compound in attenuation of fibrogenesis. Morin demonstrated the ability to inhibit hepatic fibrosis in rats and induce apoptosis of HSCs by suppressing canonical NF-κB signaling (MadanKumar et al. 2015). Those authors demonstrated the inhibition of DEN-induced liver fibrosis in rats by this compound through the down-regulation of glycogen synthase kinase-3 beta (GSK-3β), β-catenin and cyclin D1 expressions, which was accompanied by the inhibition of Wnt signaling (MadanKumar et al. 2014). Using the same model of hepatic fibrogenesis, other authors also showed the suppression of TGF-β1 expression by this compound (Lee et al. 2009). Moreover, oral supplementation of morin down-regulated NF-κB nuclear translocation and MMP-2 and MMP-9 expression in DEN-intoxicated rats, indicating the potential of morin to prevent inflammation and carcinogenesis (Sivaramakrishnan and Niranjali Devaraj 2009). Morin administration also resulted in inhibition of the PI3K/Akt-mediated suppression of GSK-3β (Sivaramakrishnan and Devaraj 2010).

Further, morin attenuated hepatosteatosis in high-fructose fed rats by inhibiting NF-κB activation (Wang et al. 2013). Fructose feeding activated sphingosine kinase 1 (SphK1)/sphingosine-1-phosphate (S1P) signaling

pathway, which in turn caused activation of the NF-κB pathway and inflammation in rat livers. Subsequently, hepatic leptin and insulin signaling impairment resulted in liver lipid accumulation. Morin restored high-fructose-induced changes in mice by increasing phosphorylation of IR, IRS-1(Tyr), ERK, JAK and reducing phosphorylation of the long form of leptin receptor (Ob-RL), STAT3, suppressor of cytokine signaling (SOCS) 3 and IRS-1(Ser), with the decrease in SphK1 activity and S1P production. Additionally, the level of lipolytic PPARα and CPT1 was increased by morin treatment. Taken together, these data showed the potential of morin to ameliorate hepatic inflammation and metabolic syndrome.

Flavan-3-ols

(–)-Epigallocatechin-3-gallate ((–)-cis-3,3′,4′,5,5′,7-hexahydroxy-flavane-3-gallate, EGCG) (**10**), the major catechin found in green tea, *Camellia sinensis* L., showed protective effects against oxidative damage in hepatic cells through the increase in SOD, CAT, GPx and GR activity and vitamin C and E levels (Kaviarasan et al. 2008; Ren et al. 2011; An et al. 2014), which was attributed to activation of the Nrf2 pathway (Wang et al. 2015a). Numerous studies indicated potentially therapeutic role of EGCG against various kinds of impairment of liver function. Thus, EGCG reduced caspase-3 expression and apoptosis in the ischemia/reperfused rat livers through down-regulation of NF-κB and c-Jun expression (Giakoustidis et al. 2010). Pretreatment with EGCG reduced LPS-induced production of inflammatory mediators, including TNF-α, Rantes, MCP-1, intracellular adhesion molecule (ICAM)-1, VEGF, NO and MMP-2 by inhibiting NF-κB, Akt and MAPK pathways (Liu et al. 2014c).

EGCG prevented NASH-related preneoplastic lesions in obese and hypertensive rats by decreasing the mRNA expression of angiotensin-converting enzyme (ACE) and angiotensin II receptor type 1 (AT1R), components of the renin–angiotensin system (RAS), which is closely associated with liver fibrosis and carcinogenesis (Kochi et al. 2014). Additionally, EGCG attenuated the mRNA expression of liver fibrosis-related MMP-2, MMP-9, TIMP-1, TIMP-2, alpha-smooth muscle actin (α-SMA), TGF-β1 and plasminogen activator inhibitor type 1 (PAI-1). In addition, this compound decreased levels of hepatic phospho-JNK and reduced mRNA expression of inflammatory mediators. EGCG also prevented DEN-induced liver steatosis and tumorigenesis in obese and diabetic mice by activating AMPK and inhibiting the insulin growth factor (IGF)/IGF 1 receptor (IGF-1R) axis (Shimizu et al. 2011). EGCG inhibited the phosphorylation of IGF-1R, ERK, Akt, GSK-3β, STAT3 and JNK in mice livers. Furthermore, EGCG ameliorated hepatic preneoplastic lesions induced by DEN and HFD by decreasing hepatic gene expression of proinflammatory mediators and cyclin D1 and suppressing hepatocyte proliferation (Sumi et al. 2013). In rat liver epithelial cells, the gap junctional intercellular communication (GJIC), which is strongly associated with carcinogenesis, particularly the tumor promotion process, was inhibited by EGCG (Kang et al. 2008). EGCG treatment increased phosphorylation of ERK1/2 and connexin 43 (Cx43), the major regulator of GJIC, whereas inhibition of ERK by a pharmacological inhibitor U0126 completely reverted inhibition of GJIC. Interestingly, the GJIC inhibitory properties of EGCG were attributed to its prooxidant activity. EGCG has also been reported as an in vitro inhibitor of several CYP isoforms, including CYP1A1, CYP1A2, CYP2B1/2, CYP2B6, CYP2C8 and CYP3A (Yun et al. 2007; Weng et al. 2012; Misaka et al. 2013), which could contribute to its cytoprotective potential.

Treatment with EGCG attenuated hepatic inflammation and fibrosis in the CCl_4, BDL and NASH models in vivo and HSCs in vitro (Zhen et al. 2007; Tipoe et al. 2010; Xiao et al. 2014; Yu et al. 2015; Ding et al. 2015). EGCG ameliorated expression of inflammatory and fibrotic markers such as NOS, COX-2, TNF-α, collagen α1(I), MMP-2, MMP-9, TIMP-1 and α-SMA, which was associated with down-regulation of the TGF-β1/Smad2/3, PI3K/Akt/FOXO1 and NF-κB pathways. Further, EGCG ameliorated the mRNA expression of IGF-1R and the mRNA and protein levels of PDGFRβ in the liver of fibrotic rats (Yasuda et al. 2009). Moreover, EGCG interrupted TGF-β signaling by reducing the gene expression of TGF-β receptors (Tβ-R) I and II and Smad4, resulting in reduced the mRNA levels of CTGF, collagen and fibronectin, which was dependent on the induction of *de novo* synthesis of GSH (Fu et al. 2008b; Yumei et al. 2006). This compound also inhibited HSCs growth, which was attributed to the suppression of the tyrosine phosphorylation and the gene expression of PDGFRβ by blocking the activation of transcription factors AP-1 and NF-κB (Chen and Zhang 2003). In cultured human HSCs, EGCG inhibited the PDGF-BB-induced HSCs proliferation and collagen α1(I) and (IV) mRNA expression (Sakata et al. 2004). Furthermore, EGCG regulated HSCs growth through Rho-signaling pathway, which is implicated in activation and proliferation of HSCs (Higashi et al. 2005). Activated Rho (the GTP-bound state) was inhibited by ECGC, which was accompanied by suppression of phosphorylation of focal adhesion kinase (FAK), an regulator of Rho-signaling pathways. Moreover, EGCG was found to suppress HSCs invasiveness, through inhibition of MMP-2 activation (Zhen et al. 2006). EGCG also interrupted EGF signaling in activated HSCs by reducing the trans-activation of early growth response protein (EGR)-1 and suppressing gene expression of EGFR (Fu and Chen 2006; Hirsova

et al. 2012), which plays an important role in differentiation and mitogenesis.

EGCG administration to hypercholesterolemic rats diminished induction of acyl-CoA:cholesterol acyltransferase ACAT and SREBP-1 mRNA and raised reduced levels of ATP-binding cassette transporter (ABC) G5 and G8 (Hirsova et al. 2012). Moreover, EGCG supplementation reduced the TNF-α-mediated Ca^{2+}-dependent nuclear factor of activated T-cell (NFAT) expression and its downstream targets, including ICAM-1 and E-selectin, and NF-κB-mediated downstream targets such as VCAM-1 and P-selectin, thus inhibiting high-cholesterol-induced macrophage infiltration and hepatic steatosis (Krishnan et al. 2014). Similarly, the beneficial effects of EGCG on HFD-induced fatty liver in mice were associated with reduced levels of inflammatory cytokines (Chen et al. 2011) and down-regulation of lipogenesis-related genes, including ACC, FAS and SCD1 (Friedrich et al. 2012). The reduction of hepatosteatosis was accompanied by increased expression of LC3-I/II and phosphorylation of AMPK, one of major regulators of autophagy (Zhou et al. 2014). In addition, EGCG was shown to down-regulate uncoupling protein (UCP) 2 expression (Jamal et al. 2015), which is involved in development of steatohepatitis.

EGCG has been shown to suppress the expression of HBV surface antigen (HBsAg) and hepatitis B e antigen (HBeAg), the hepatitis B virus (HBV) antigens, and to reduce extracellular HBV DNA production and intracellular HBV DNA replication in vitro, although it had weaker efficacy compared to green tea extract (Xu et al. 2008). EGCG also demonstrated inhibitory activity on HCV viral protein, NS5B, which possesses the key function of replicating HCV viral RNA (Roh and Jo 2011). Moreover, EGCG opposed HBV-induced incomplete autophagy via enhancing lysosomal acidification, which seems to be unfavorable for HBV replication (Zhong et al. 2015). EGCG also inhibited HCV attachment to hepatocytes, disrupting the initial step of cell entry (Ciesek et al. 2011), which was attributed to impairment of HCV envelope glycoproteins E1 and E2 (Calland et al. 2012). Other catechins, such as (+)-epicatechin and (−)-epicatechin, also showed significant anti-HCV activity, protecting against HCV replication and attenuating virus-induced inflammation (Lin et al. 2013).

Recent study of Church et al. (2015) indicated that hepatotoxicity reports of green tea extract consumption in humans could be related to differences in sensitivity to EGCG, which emerge from the genetic background. Research conducted by James et al. (2015) may also partly explain the observed variation in hepatotoxic response to EGCG and green tea-containing dietary supplements. Thus, dietary pretreatment with EGCG may limit the bioavailability and hepatotoxicity of successive oral bolus doses of the catechin. Most importantly, randomized, double-blind, placebo-controlled study demonstrated that oral doses of EGCG of up to 800 mg per day for 10 days were safe and very well tolerated (Ullmann et al. 2004). Interestingly, the authors found the increase in accumulation factor for EGCG in the high-dosage group, suggesting dose-dependent saturation of capacity-limited excretion routes or an increase of hepato-duodenal recirculation, which should be taken into consideration.

Flavonolignans

Silymarin (**11**) is a natural substance isolated from *Silybum marianum* L., commonly known as Milk thistle. This substance contains several flavolignans including silybin, isosilybin, silychristin and silydianin, and flavonoids such as taxifolin and quercetin (Zhu et al. 2013). Silymarin has been extensively studied for its hepatoprotective effects in the last decade. However, surprisingly small number of studies investigated the underlying mechanisms of hepatoprotective activity of silymarin or its components. Generally, silymarin has been shown to modulate enzymatic and nonenzymatic markers of oxidative injury in the liver (Pradeep et al. 2007; Tzeng et al. 2013) and induce Nrf2 expression (Kim et al. 2012). Silymarin also exhibited anti-inflammatory activity in several models of liver damage. In the alcoholic fatty liver model in rats silymarin down-regulated expression of NF-κB, ICAM-1 and IL-6 (Zhang et al. 2013a). Silymarin also attenuated chemically induced hepatocellular damage by increasing the expression of antiapoptotic Bcl-xL protein and reducing p53 expression, caspase-3 activity, PARP activity and DNA fragmentation (Patel et al. 2010; Sherif and Al-Gayyar 2013). Inhibition of TGF-β1 and PDGF signaling has also been involved in the hepatoprotective effects of silymarin (Chen et al. 2012a; Clichici et al. 2015). In chronic liver fibrosis in mice silymarin down-regulated hepatic TGF-β1, MMP-2, MMP-13, TIMP-1, TIMP-2, AP-1, tumor suppressor Krueppel-like factor 6 (KLF6) and collagen α1 expression with significant reduction of hepatic hydroxyproline content (Chen et al. 2012a; El-Lakkany et al. 2012). Moreover, Polyak et al. (2010) demonstrated that silymarin could inhibit HCV cell infection through suppression of TNF-α-induced activation of NF-κB and its nuclear translocation.

Major constituent of silymarin, silybin, exhibited antioxidant effect in nonalcoholic steatohepatitis (Haddad et al. 2011). Silibinin, a mixture of silybin A and silybin B, and more bioavailable silibinin-phosphatidylcholine complex, significantly inhibited IL-1β-induced production of proinflammatory markers PGE_2, IL-8 and MCP-1 in hepatocytes (Au et al. 2011). Mechanistically, both compounds attenuated NF-κB activation and its nuclear translocation. Yao et al. (2011) suggested that inhibition of oxidative stress,

stabilization of mitochondrial membrane and improved insulin resistance may be the key mechanisms for the hepatoprotective effect of silibinin against NAFLD.

Silymarin has a good safety profile and is well tolerated by patients (National Toxicology 2011). In individuals occupationally exposed to hydrogen sulfide, treatment with 140 mg of silymarin, three times per day for 1 month, resulted in a significant decrease in serum aminotransferases and alkaline phosphatase levels (Mandegary et al. 2013). Nevertheless, the effectiveness of silymarin was modulated by the TNF-α polymorphisms. Schrieber et al. (2008) showed the correlation between the severance of hepatic disease (HCV noncirrhosis, NAFLD and HCV cirrhosis) and the level of total silymarin flavonolignans in the blood. Current research provides optimistic data regarding improvement of physicochemical property of silymarin. Silymarin-loaded solid lipid nanoparticles have been proposed as a useful system for the delivery of poorly water-soluble compounds such as silymarin, showing enhanced antioxidant and hepatoprotective activity compared to a crude silymarin (Hsu et al. 2012; Hwang et al. 2014; Cengiz et al. 2015).

Interaction between silymarin or its components and CYPs activity has not been intensively studied. A few data available suggested that silybin ameliorated CYP3A expression and activity in thioacetamide-injured rat liver (Xie et al. 2013). Studying the effect of the anti-Alzheimer drug tacrine and silibinin, Chen et al. (2012c) showed that the co-drug administration diminished tacrine-induced hepatotoxicity and induction of CYPs. These studies indicated that silymarin or its component may not be involved in CYP activation.

Terpenoids

Monoterpenoids

Thymoquinone (**12**), a monoterpenoid quinone, the major active compound derived from the *Nigella sativa* L. seeds, has been reported to protect experimental animals against oxidative hepatic injury by improving hepatic antioxidant status (Sayed-Ahmed et al. 2010; Prabhakar et al. 2014). In addition, thymoquinone treatment has been shown to significantly suppress CYP1A2, CYP3A4 but not CYP2E1 activity in rabbits (Elbarbry et al. 2012).

Chemically induced hepatic fibrosis and inflammation in mice were attenuated by thymoquinone through suppression of protein and mRNA expression of collagen I and TIMP-1 and reduction of ECM accumulation (Bai et al. 2014; Ghazwani et al. 2014). Thymoquinone down-regulated the expression of TLR4 and decreased proinflammatory cytokine levels (Bai et al. 2014). In addition, it also inhibited PI3K phosphorylation, enhanced the phosphorylation AMPK and liver kinase B (LKB)-1. In rats injected with cisplatin, thymoquinone reduced the expression of NF-κB and proinflammatory proteins TNF-α, iNOS and IL-1β (Al-Malki and Sayed 2014). Investigating the mechanism of antifibrotic activity in several HSC lines, Ghazwani et al. (2014) showed that the inhibition of LPS-induced mRNA expression of IL-6 and MCP-1 was associated with the inactivation of NF-κB pathway and down-regulation of mRNA expression of several fibrosis-related genes. This quinone also showed the inhibitory potential toward TLR4 and PI3K/Akt signaling pathways in activated HSCs and proapoptotic activity, as shown by decreased XIAP and c-FLIP expression (Bai et al. 2013). Moreover, thymoquinone administration in rats fed HFD diminished metabolic syndrome by preventing reduction in hepatic mRNA levels of PPAR-α and PPAR-γ (Prabhakar et al. 2014).

Diterpenoids

Andrographolide

Andrographolide (**13**) is a diterpenoid lactone isolated from *Andrographis paniculata* L., which possesses antioxidant effects against chemically induced liver injury (Trivedi et al. 2007; Chen et al. 2014a). It up-regulated protein and gene expression of oxidative stress response genes such as hypoxia-inducible factor-1 alpha (HIF-1α), SOD-1, HO-1 and GST, which was associated with increased nuclear Nrf2 content and its DNA-binding activity (Ye et al. 2011; Shi et al. 2012; Chen et al. 2014a). Similarly, the anti-HCV activity of andrographolide has been mediated by up-regulation of HO-1 via the p38 MAPK/Nrf2 pathway (Lee et al. 2014a).

Andrographolide suppressed thioacetamide-induced hepatic inflammation, angiogenesis and fibrosis in mice (Lee et al. 2014a, d). Andrographolide treatment decreased TNF-α and COX-2 expression and reduced liver hypoxia, as shown by the down-regulation of hypoxia-inducible genes, such as VEGF. In addition, andrographolide treatment resulted in the decrease in Tβ-RI expression and hepatic fibrogenesis. Similarly, andrographolide attenuated hepatic apoptosis and fibrosis after BDL in rats (Lee et al. 2010c). The compound decreased serum levels of TNF-α and IL-1β and hepatic expression of TGF-β, cannabinoid receptor type 1 (CBR1) and Bax. The effect was mediated by suppression of JNK and ERK phosphorylation. Andrographolide was also able to down-regulate cellular lipid accumulation in HFD-fed mice (Ding et al. 2014). The compound reduced the hepatic protein and mRNA levels of SREBP-1 and its downstream targets, such as FAS, ACC and SCD-1 as well as SREBP-2 and its target genes involved in cholesterol biosynthesis.

Nevertheless, andrographolide showed a potential to induce CYP1A1, CYP2A4, CYP2B9 and CYP2B10 expression in mice hepatocytes (Chatuphonprasert et al. 2009). In a similar way, andrographolide decreased CYP2C and CYP3A expression and activity in human hepatocytes, but without the effect on CYP2E1 (Pekthong et al. 2008, 2009), suggesting a potential to interact with drug metabolism.

Triterpenoids

Ginsenosides (**14**) are the major steroid compounds in ginseng root, which belong to the genus *Panax* of the family *Araliaceae*. These compounds reduced ROS generation in chemically injured hepatocytes by increasing SOD, GPx and CAT activity and restoring GSH levels (Park et al. 2012; Li et al. 2014b), while suppressing ERK and JNK MAPKs. Ginsenoside Rg3, but not other tested ginsenoides (Rb1, Rc and Rg1), increased acetaminophen-induced GSTA2 protein expression and the transcriptional activation by the multiple cellular signaling, including PI3K, JNK and protein kinase A (PKA) (Gum and Cho 2013b). Ginsenoside Rg3 ameliorated chemical toxicity in hepatic cells by inducing Nrf2-mediated gene expression of multidrug resistance protein (MRP) 1 and 3, involved in a detoxification process (Gum and Cho 2013a). Further, ginsenosides were effective in attenuation of hepatic fibrosis induced by alcohol and CCl_4. Ginsenoside Rb1 attenuated liver inflammation and fibrosis by suppressing hepatic PGE_2 and TIMP-1 expression (Hou et al. 2014). Similarly, ginsenoide Rg1 protected against hepatic fibrosis by increasing nuclear translocation of Nrf2 and the expression of antioxidant enzymes, including HO-1 and NQO1 (Li et al. 2014b). In addition, ginsenoside Rg1 down-regulated the expression of PDGFRβ in cultured HSCs by reducing the NF-κB activity, which resulted in the inhibition of PDGF-BB-stimulated cell proliferation and activation (Geng et al. 2010). In H_2O_2-activated HSCs, ginsenoside Rb1 suppressed the mRNA and protein expression of TGF-β1, MMP-2, TIMP-1 and collagen (Lo et al. 2011), suggesting that Rb1 may exert an antifibrotic effect by inhibiting HSCs activation and proliferation.

Ginsenoside Rb1 reduced fatty liver in obese rats by activating hepatic AMPK (Shen et al. 2013). In primary rat hepatic cells, activation of AMPK consistently stimulated the expression of genes encoding fatty acid oxidative enzymes, including PGC-1α, PPARα, and peroxisomal acyl-coenzyme A oxidase 1 (ACOX1) and increased the activity of CPT1, a key enzyme in fatty acid β-oxidation. In a similar fashion, ginsenoside Re lowered hepatic lipid levels via activation of the AMPK pathway and protected against hepatic steatosis in HFD-fed mice (Quan et al. 2012).

Furthermore, ginsenoides were shown to suppress hepatic inflammation through the inhibition of NF-κB signaling in several experimental models. Ginsenosides Rd1 and Rg1 protected mouse liver against ischemia–reperfusion injury through down-regulation of NF-κB expression and reduced production of proinflammatory cytokines, including TNF-α and ICAM-1 (Wang et al. 2008; Tao et al. 2014). Similarly, ginsenoside Rg1 attenuated concanavalin A-induced hepatitis in mice through the inhibition of IκBα and p65 phosphorylation as well as ICAM-1 and CXCL-10 mRNA expression and cytokine secretion (Cao et al. 2013). Ginsenoides Rd and Rg3 also attenuated hepatic NF-κB, COX-2 and iNOS protein expression in LPS-challenged murine (Kang et al. 2007; Kim et al. 2013). Moreover, ginsenoside Rd suppressed NO production and PGE_2 synthesis (Kim et al. 2013).

Ginsenoside Rg1 and Rb1 showed the potential to decrease hepatitis A virus (HAV) titer in infected hepatocytes (Lee et al. 2013b). Moreover, ginsenoside Rg3 was shown to attenuate HBV replication (Kang et al. 2013). Rg3 inhibited the expression of TRAF6 and TAK1, adaptor molecules that signal through the TLR/MyD88-dependent pathway. Furthermore, Rg3 inhibited MAPK signaling in hepatic cells by inhibiting JNK phosphorylation. In addition, it reduced the expression of AP-1 transcription factors c-Jun and JunB and inhibited AP-1 promoter activity, resulting in reduced gene and protein expression of proinflammatory cytokines.

It has been shown that ginsenoside Rd, as well as quercetin, have a potential to inhibit CYP2C9 and CYP3A4 in human liver microsomes (He and Edeki 2004). However, available data suggest that ginsenosides Rb1, Rb2, Rc and Rd are not likely to interact with conventional medicines that are metabolized by CYP2C19 and CYP2D6 (He et al. 2006). Similarly, in another study, ginsenosides Rb1, Rb2, Rc, Rd, Re, Rf and Rg1 showed only weak inhibition of CYP1A1, CYP1A2 and CYP1B1 activity (Chang et al. 2002). These data suggest that ginsenosides have relatively low CYP-modulating effect.

Glycyrrhizin (**15**), a triterpenoid glycoside isolated from the roots of licorice plant (*Glycyrrhiza glabra* L.), has been shown to increase antioxidant defense in the liver (Rahman and Sultana 2006; Orazizadeh et al. 2014). Glycyrrhizin may also protect against liver injury by reducing the expression of high-mobility group protein box 1 (HMGB1), an early mediator of inflammation (Mabuchi et al. 2009; Ogiku et al. 2011) and interrupting HMGB1 binding to GSTO1 promoter region (Kuroda et al. 2014). Glycyrrhizin and its metabolite, glycyrrhetinic acid, inhibited collagen αI(I) gene expression and progression of liver fibrosis induced by CCl_4 (Moro et al. 2008). The compounds significantly decreased mRNA expression of TGF-β1, Smad2/3 and specificity protein-1 (SP-1) in the liver

(Qu et al. 2015). Further, glycyrrhizin down-regulated pro-inflammatory mediators and induced expression of HO-1 (Lee et al. 2007a). The potential of this compound to accelerate recovery from hepatic injury has been demonstrated in vitro. Glycyrrhizin suppressed activation of HSCs and induced their apoptosis by blocking nuclear translocation of NF-κB (Qu et al. 2012). Importantly, glycyrrhizin and its metabolites may induce growth of hepatocytes by binding to EGFR and stimulating ERK2-mediated hepatocyte DNA synthesis and proliferation (Kimura et al. 2001), which could contribute to acceleration of liver regeneration.

Antiviral activity of glycyrrhizin has been demonstrated both in vitro and in vivo. Glycyrrhizin treatment of HCV-infected hepatic cells resulted in reduced release of infectious HCV particles through inhibitory effect on phospholipase A2 (PLA2), whereas a co-treatment with glycyrrhizin augmented antiviral effect of IFN-α (Matsumoto et al. 2013). A similar effect on HAV antigen expression and infectivity has also been reported (Crance et al. 1990). Moreover, glycyrrhizin modified the intracellular transport and suppressed sialylation of HBsAg in vitro (Takahara et al. 1994), which was also observed in patients with chronic HBV infection (Sato et al. 1996).

Although mechanistically modestly investigated, glycyrrhizin has been intensively studied in clinical trials. In patients who failed previous IFN-α-based therapy, intravenous administration of glycyrrhizin significantly reduced serum alanine transaminase (ALT) level after 12 weeks of therapy and improved necro-inflammation and fibrosis after 52-week treatment (Manns et al. 2012). In another study, a 6-month co-treatment with IFN-α2b and glycyrrhizin was less effective in reducing ALT levels compared to IFN-α2b and ribavirin co-administration; however, the treatment was associated with significantly lower frequencies of leukopenia and anemia (Acharya et al. 2012). Interestingly, the decrease in ALT levels after 26 months treatment in a smaller group of patients treated with glycyrrhizin did not translate in a significant histological improvement (Orlent et al. 2006). Nevertheless, glycyrrhizin injection therapy showed effectiveness in prevention of progression from HCV-related cirrhosis to HCC, particularly in a group of older patients (Ikeda 2007; Ikeda et al. 2014). Similar effect of this compound was observed in another study on 1093 patients nonresponding to IFN (Veldt et al. 2006). Importantly, usage of the suppositories of glycyrrhizin improved quality of life for chronic hepatitis C patients similarly to intravenously treated patients, with greater benefit in those who did not respond to IFN therapy (Fujioka et al. 2003).

18β-Glycyrrhetinic acid (**16**), a hydrolytic product of glycyrrhizin, has also been shown to possess a wide range of pharmacological and biological activities, including hepatoprotection (Hasan et al. 2015). 18β-Glycyrrhetinic acid decreased oxidative stress and expression of inflammatory markers both in vivo and in vitro models of hepatocyte injury, which coincided with down-regulation of NF-κB and up-regulation of Nrf2 target genes (Chen et al. 2013b; Hasan et al. 2015). Importantly, this compound inhibited hepatic expression and activity of CYP2E1 in CCl_4-intoxicated mice (Jeong et al. 2002) and the activity of CYP2C9, CYP2C19 and CYP3A4 in rat and human liver microsomes (Zhao et al. 2012). 18β-Glycyrrhetinic acid but not glycyrrhizin inhibited PARP, caspase-3, caspase-9 and caspase-10 activation and suppressed phosphorylation of JNK in a model of cholestatic liver injury, protecting hepatocytes against necrosis and apoptosis (Gumpricht et al. 2005). In human and rat HSCs, the compound inhibited mRNA and protein expression of collagen type I and III, which was attributed to down-regulation of Smad3, up-regulation of Smad7 and inhibition of DNA-binding activities of NF-κB as well as SP-1 and AP-1, both involved in the synthesis of ECM (Moro et al. 2008; Zong et al. 2012). Additionally, proliferation of activated HSCs was inhibited and apoptosis was induced, as evidenced by decreased expression of cyclin D1 and the pro-survival Bcl-2 homolog A1/Bfl-1, with simultaneous increase in Bax and PPARγ-mediated expression of p27 (Zong et al. 2013).

Betulinic acid (**17**), a natural pentacyclic lupane-type triterpenoid found in various plants, especially bark of the birch tree (genus *Betula,* family *Betulaceae*), showed hepatoprotection against ethanol-induced oxidative stress and steatohepatitis in mice (Wan et al. 2013b; Yi et al. 2014). The amelioration of steatohepatitis involved decrease in TLR4 expression and increased phosphorylation of STAT3, signaling molecule involved in regulation of cell survival (Wan et al. 2013b). Furthermore, the potential role of betulinic acid in prevention of hepatic inflammation and fibrosis has also been demonstrated in thioacetamide-intoxicated rats (Wan et al. 2012). Mechanistically, betulinic acid induced suppression of the TLR4/MyD88/NF-κB signaling pathway.

Other studies showed that betulinic acid and betulin could inhibit ethanol-induced activation of HSCs at different levels (Szuster-Ciesielska et al. 2011; Wan et al. 2013b). Both compounds inhibited the production of ROS by HSCs, inhibited their migration and down-regulated ethanol-induced TIMP-1, TIMP-2 and MMP-2 activity (Szuster-Ciesielska et al. 2011). Additionally, betulin inhibited the activation of the p38 MAPK and the JNK transduction pathways, while betulinic acid inhibited the JNK transduction pathway only. Nevertheless, both compounds inhibited phosphorylation of IκB and Smad3 and attenuated the activation of TGF-β1 and NF-κB transduction signaling. Betulinic acid also showed several other hepatoprotective activities. This compound was also able to prevent hepatic apoptosis induced by LPS/D-GalN through

suppression of apoptosis-related JNK1/2 and ERK1/2 signaling (Zheng et al. 2011). Further, the inhibitory effect of betulinic acid on lipid accumulation and amelioration of NAFLD in mice involved suppression of SREBP-1 activity via down-regulation of the CAMKK/AMPK/mTOR/$p70^{S6K}$ signaling pathway (Quan et al. 2013b). Moreover, betulinic acid exhibited antiviral properties. In hepatocytes from HBV-transgenic mice, betulinic acid mediated inhibitory effect on HBV replication through down-regulation of manganese SOD expression via attenuation of cAMP-response element-binding protein (CREB) phosphorylation and inhibition of its transcriptional activity (Yao et al. 2009). Moreover, betulinic acid inhibited HCV replication, acting synergistically with IFN-α and NS5B polymerase inhibitor. The compound down-regulated HCV-induced COX-2 expression through reducing the phosphorylation of NF-κB and ERK1/2 (Lin et al. 2015a), suggesting betulinic acid as a promising compound for treatment of hepatitis virus-infected patients.

Ursolic acid (**18**), a pentacyclic triterpenoid acid found in various plants, suppressed oxidative stress in various models of liver injury (Kazmi et al. 2013; Ma et al. 2014). Ursolic acid modestly inhibited CYP2C19 in vitro, while other CYPs, including CYP2C8, CYP2C9, CYP3A4, CYP2E1, CYP1A2 and CYP2D6, showed weak inhibition by this triterpene or no inhibition at all (Kim et al. 2004), suggesting low potential of interaction with drugs and activation of pro-carcinogens.

Ursolic acid was shown to activate autophagy in mice model of hepatic steatosis in the NAFLD model in rodents, by inducing the expression of LC3-II and beclin 1 (Jia et al. 2015). It also activated PPARα and expression of genes involved in fatty acid uptake and β-oxidation, such as fatty acid transport protein 4 (FATP4), acetyl-CoA synthetase 1 (ACS1), CPT1 and peroxisomal acyl-coenzyme A oxidase 1 (ACOX1), while down-regulating genes involved in lipogenesis, such as SREBP-1c, FAS and ACC1 (Li et al. 2014e; Sundaresan et al. 2014; Jia et al. 2015). Moreover, ursolic acid treatment significantly decreased hepatic steatosis in db/db mice by modulating β-oxidation and ER stress in the liver (Li et al. 2015b). Mechanistically, it reduced expression of the unfolded protein response sensor inositol-requiring enzyme-1alpha (IRE-1α) expression and activation of ERK, JNK and CHOP, while increasing PPARα levels. In addition, ursolic acid decreased palmitic acid-induced intracellular lipid accumulation in L02 cells, with concomitant inhibition of ATF6, IRE-1α and CHOP gene expression.

Wang et al. (2011) and Yang et al. (2015) demonstrated the beneficial effect of ursolic acid against hepatic fibrosis. In culture-activated HSCs, ursolic acid activated caspase-3 and caspase-9, decreased phosphorylation of Akt and diminished nuclear localization of NF-κB (Wang et al. 2011), suggesting their apoptosis and suppression of survival mechanisms. Treatment of hepatocytes with ursolic acid in the presence of LPS dose-dependently inhibited ROS production and NF-κB activation. The improvement of liver functions in mice was associated with activation of the LKB1/AMPK pathway, involved in cell growth and control of metabolism. Ursolic acid also prevented CCl_4-induced hepatotoxicity and fibrosis in mice, at least in part, through modulation of the Nrf2/ARE signaling pathway (Ma et al. 2015a). In addition, this compound suppressed hepatic production of proinflammatory and proapoptotic markers, including TNF-α, IL-1β, COX-2 and caspase-3, while increasing antiapoptotic Bcl-2 expression (Ma et al. 2014). The underlying mechanisms of ursolic acid action involved suppression of MAPKs activation and the suppression of immunoregulatory transcription factor NF-κB. Ursolic acid also enhanced hepatic cell proliferation in partially hepatectomized mice, which was associated with increased cyclin D1, cyclin E and C/EBPβ protein expression (Jin et al. 2012), suggesting its potential to facilitate liver regeneration.

Phenolic acids

Chlorogenic acid (5-O-caffeoylquinic acid) (**19**) ameliorated liver injury in several models of experimentally induced oxidative stress (Shi et al. 2013a; Koriem and Soliman 2014). It should be also mentioned that chlorogenic acid may exhibit in vitro inhibitory effect on the activity of hepatic metabolizing enzymes, including CYP1A1, CYP1A2 and CYP2B (Baer-Dubowska et al. 1998).

Treatment of animals with this compound inhibited acetaminophen-induced activation of caspase-3 and caspase-7, ERK1/2, JNK and p38 MAPKs upstream molecular signals, including ASK1, c-Raf and mitogen-activated protein kinase kinases MEK1/2, MKK4 and MKK3/6 (Ji et al. 2013), suggesting inhibition of apoptosis. Concomitantly, chlorogenic acid restored glutamate-cysteine ligase, catalytic subunit (GCLC), Trx1/2 and TrxR1 expression (Ji et al. 2013). Several studies demonstrated anti-inflammatory action of chlorogenic acid in the liver (Xu et al. 2010; Yun et al. 2012; Park et al. 2015). Chlorogenic acid inhibited various TLR agonist-, IL-1α- and HMGB1-stimulated activation of IL-1R-associated kinase 4 (IRAK4) in mice peritoneal macrophages of LPS-intoxicated mice via directly affecting the kinase activity of IRAK4, a signal transducer in the TLR/MyD88-mediated signaling cascade (Park et al. 2015). In addition, it significantly suppressed the expression of phospho-IκBα, phospho-TAK1, phospho-JNK1/2 and phospho-p38. This resulted in reduction of protein and mRNA levels of NF-κB/AP-1 target genes encoding TNF-α, IL-1α, IL-6 and HMGB-1,

resulting in attenuation of acute hepatic inflammation. Chlorogenic acid also suppressed hepatic expression of TLR3 and TLR4-dependent nuclear translocation of NF-κB in inflammatory liver injury (Yun et al. 2012; Zheng et al. 2015). Concomitantly, the compound restored mRNA level of transcriptional coactivator PGC-1α and inhibited activity of IFN regulatory factor-1 (IRF-1), with enhanced Nrf2 nuclear translocation and HO-1 expression. Chlorogenic acid ameliorated the development of HFD-induced hepatic steatosis and insulin resistance in mice by suppressing the expression of genes for fatty acid-binding protein (FABP), PPARγ and CD36, a scavenger receptor that mediates internalization of low-density lipoprotein (LDL) particles (Ma et al. 2015b). In addition, treatment by chlorogenic acid attenuated hepatic inflammation by decreasing the mRNA levels of macrophage inflammatory genes. The gene expression of PPARα in diet-induced hypercholesterolemia in rats was up-regulated by this compound, suggesting decreased risk for development of complications such as NAFLD (Wan et al. 2013a). Moreover, the expression of adiponectin receptors (AdipoR) 1/2, the phosphorylation of AMPK and the mRNA and protein levels of PPARα in the liver were significantly higher in chlorogenic acid-treated diabetic db/db mice, suggesting a potential to alleviate obesity-related metabolic syndrome (Jin et al. 2015).

Chlorogenic acid has also been shown to attenuate CCl_4-induced liver inflammation and fibrosis in rats via inhibition of the TLR4/MyD88/NF-κB pathway, which coincided with the inhibition of collagen I, α-SMA, iNOS and COX-2 expression and concomitant increase in bone morphogenetic protein and activin membrane-bound inhibitor (Bambi) expression, which is expressed in quiescent HSCs, blocking Tβ-RI activity (Shi et al. 2013b). In addition, chlorogenic acid suppressed mRNA levels of profibrotic inductors such as VEGF and TGF-β1 (Shi et al. 2009). In cultured HSCs, this compound inhibited LPS-induced IκBα phosphorylation, nuclear translocation of NF-κB and the gene expression of inflammatory mediators (Shi et al. 2013a). Chlorogenic acid, as well as quinic acid and caffeic acid, also showed inhibitory potential against HBV DNA replication and HBsAg production (Wang et al. 2009a), suggesting a potential against viral hepatitis infection.

A combined nutraceutical containing chlorogenic acid, berberine and tocotrienols improved a large number of metabolic and liver parameters in a double-blind cross-over trial in 40 overweight subjects with mixed hyperlipidaemia (Cicero et al. 2015).

The antioxidant activity of salvianolic acid (**20**) (*Salvia miltiorrhiza* L. active component), a rosmarinic acid dimer, has been associated with amelioration of drug-induced hepatotoxicity (Gao et al. 2012; Lin et al. 2015b). Salvianolic acid B attenuated hepatocyte apoptosis by regulating ER stress, death receptor-mediators and mitochondrial pathways (Yan et al. 2015b). The compound markedly decreased TNF-α/D-GalN-induced levels of phospho-eukaryotic initiation factor (eIF) 2α, ATF4, 78 kDa glucose-regulated protein (GRP78), CHOP, cleaved-caspase-3 and caspase-9, apoptosis-inducing factor (AIF) and apoptotic protease-activating factor 1 (Apaf-1), with concomitant increase in cytochrome c release. In addition, salvianolic acid B reduced TNFR1 and restored Bcl-2 expression in apoptotic cells (Yan et al. 2010). In acetaminophen-intoxicated mice, salvianolic acid B pretreatment induced the expression of Nrf2 and phase II enzymes via activation of the PI3K and protein kinase C (PKC) pathways (Lin et al. 2015b). Further, pretreatment with salvianolic acid A and B ameliorated ethanol and concanavalin A-induced liver injury in murine by SIRT1-dependent mechanism (Xu et al. 2013; Li et al. 2014d). Mechanistically, salvianolic acid B increased the expression of SIRT1, a NAD^+-dependent deacetylase which plays an important role in protection against acute hypoxia damage and metabolic liver diseases through modulation of NF-κB and p53 expression. The increase in SIRT1 by salvianolic acid B was accompanied by the decrease in acetyl-p53 expression (Li et al. 2014d) and down-regulation of the p66 isoform of the growth factor adapter Shc (Xu et al. 2013). Additionally, both salvianolic acid A and B decreased cytotoxic cytokine levels and abrogated the increase in NF-κB and cleaved caspase-3 as well as decrease in Bcl-xL expression. Interestingly, in both type 1 and type 2 diabetic animals, salvianolic acid A activated AMPK phosphorylation through CaMKKβ/AMPK signaling pathway, independent of LKB1/AMPK pathway (Qiang et al. 2015).

Both salvianolic acid A and B showed the inhibitory effect on the PDGF-BB-induced signaling in HSCs through different signaling pathways (Tsai et al. 2011). Thus, salvianolic acid A and B diminished PDGF-induced activation of protein kinase D (PKD), Nrf2, Trx and HO-1. In addition, salvianolic acid A inhibited an expression of Akt, $p70^{S6K}$ and related proteins such as eIF-4E and translation repressor eIF-4E-binding protein 1 (4E-BP1). In contrast, salvianolic acid B attenuated PDGF-induced JNK, p38 and PKC-δ phosphorylation. Further, salvianolic acid A attenuated PDGF-BB-stimulated proliferation of HSCs by inducing the cell cycle inhibitory proteins p21 and p27, down-regulating cyclins D1 and E and suppressing Akt and PDGFRβ phosphorylation (Lin et al. 2006). The inhibition of TGF-β1 signaling by the compound in isolated rat HSCs was associated with down-regulation of Smad2/3 protein expression and suppression of collagen production (Liu et al. 2002a; Zhao et al. 2004). The down-regulation of Tβ-RI activity in vitro and TGF-β1 autosecretion were contributing mechanism of salvianolic B antifibrotic activity (Liu et al. 2002c; Tao et al. 2013). In primary rat HSCs, this compound inhibited ERK1/2 and p38 MAPK pathways

via inhibition of MEK and MKK3/6 phosphorylation (Lv et al. 2010). Interestingly, the effect was independent on TGF-β1 stimulation. The antifibrotic effect of salvianolic acid B was mediated by direct inhibition of p38 signaling and inhibition the cross-talk between the Smad and ERK signaling (Lv and Xu 2012). Furthermore, salvianolic acid B abrogated DMN-induced hepatic fibrosis in rats, which coincided with down-regulation of angiotensin (Ang) II-stimulated HSCs activation and proliferation (Li et al. 2012). The mechanism involved down-regulation of TGF-β gene and AT1R protein expression, as well as suppression of ERK1/2 and c-Jun phosphorylation. Moreover, salvianolic acid B reduced portal hypertension in rats with DMN-induced cirrhosis (Xu et al. 2012). *In vitro* study showed that this compound decreased endothelin (ET) 1-induced contraction of activated HSCs by reducing intracellular Ca^{2+} increase, the actin cytoskeleton regulator RhoA expression and activation of Rho-associated coiled coil-forming protein kinase (ROCK) II, a major downstream effector of the RhoA. This resulted in reduced phosphorylation of the myosin phosphatase target subunit 1 (MYPT1), which is involved in regulation of the contraction and relaxation of vascular smooth musculature. In addition, salvianolic acid B reduced CCl_4-induced hepatic fibrosis in rats by inhibiting nuclear translocation of NF-κB (Wang et al. 2012b).

In the double-blind randomized study, salvianolic acid B reversed serum markers of liver fibrosis in patients with chronic hepatitis B, more effectively than IFN-γ after 6 months of treatment, with no obvious side effects (Liu et al. 2002b). The drug delivery system based on salvianolic acid B loaded mesoporous silica nanoparticles was significantly more effective than free salvianolic acid B in suppressing the ROS level and proliferative activity of LX-2 cells (He et al. 2010), suggesting a promising novel application route of this compound in patients. Salvianoic acid B was found as a relatively weak inhibitor of CYP1A2 (Qiu et al. 2008), suggesting low impact on hepatic drug-metabolizing enzymes.

Stilbenes

Resveratrol (3,5,4′-trihydroxy-trans-stilbene) (**21**), well known as grape polyphenol, has been shown to possess hepatoprotective activity through attenuation of oxidative stress in the liver (Das 2011; Dalaklioglu et al. 2013; Ahmad and Ahmad 2014). Resveratrol protected hepatocytes against oxidative injury by modulating the expression of nuclear transcription factors Nrf2 and NF-κB and down-regulating HO-1 and iNOS gene expression (Sahin et al. 2012), which led to increased expression of antioxidant and phase II enzymes (Rubiolo et al. 2008; Cerny et al. 2009). Interestingly, resveratrol behaved as an antioxidant during the dark span and as a pro-oxidant during the light span, suggesting a day/night rhythm-dependent antioxidant activity of the compound (Gadacha et al. 2009). Wong et al. (2009) demonstrated that resveratrol treatment attenuated oxidative stress in mice tissues with prominent age-related oxidative damage accumulation, but prolonged treatment resulted in nephrotoxicity.

Resveratrol possesses the ability to modulate a number of signaling pathways involved in liver diseases, emerging as a promising therapeutic agent for prevention or treatment of hepatic disorders in humans.

Pretreatment with resveratrol was able to ameliorate the pathologic effects of concanavalin A-induced autoimmune hepatitis, significantly inhibiting proinflammatory cytokines such as IL-2, IL-6 and TNF-α (Zhou et al. 2015). In addition sonic hedgehog (Shh), patched (Ptch) and GLI-1 expression was decreased, suggesting suppression of the Shh-Ptch-GLI pathway that is involved in regulation of the cell cycle, apoptosis and angiogenesis. Administration of resveratrol resulted in decreased accumulation of bile acids through up-regulation of hepatic transporters gene expression, including farnesoid X receptor (FXR) and MRP2, which play a central role in the bile acid metabolism (Wang et al. 2014c). The protective effect of resveratrol in cholestatic liver injury was mediated by up-regulation of autophagy and suppression of proapoptotic proteins Bax and caspase-3 and caspase-8 (Chan et al. 2011; Lin et al. 2012b; Chan et al. 2014). Further, resveratrol, a well-known SIRT1 agonist, ameliorated hepatic inflammation in vivo and in vitro by reducing NF-κB activation (Andrade et al. 2014). Resveratrol also enhanced SIRT1-mediated suppression of HMGB1 translocation, which is an essential step in response to sepsis-induced liver injury (Xu et al. 2014b). Further, hepatotoxicity induced by isoniazid and rifampicin was reduced with resveratrol by modulating SIRT1 mRNA expression in mice liver, which was accompanied by decreased hepatic oxidative stress, cytokine production and PPARγ gene expression (Nicoletti et al. 2014). Resveratrol also prevented acetaminophen-induced hepatotoxicity through induction of SIRT1expression and negative regulation of p53 signaling, inducing cyclin D1, Cdk4 and proliferating cell nuclear antigen (PCNA) expression and promoting hepatocyte proliferation and liver regeneration (Wang et al. 2015d). Moreover, resveratrol modulated HFD-induced alterations in SIRT pathway and activation of NALP-3 inflammasome, involved in maturation of proinflammatory cytokines (Yang and Lim 2014). Interestingly, resveratrol reduced COX-2 expression and mRNA levels of NALP-3 inflammasome components, including NALP-1, NALP-3, apoptosis-associated speck-like protein containing a carboxy-terminal CARD (ASC) and its downstream target caspase-1 in old but not young mice (Tung et al.

2015), suggesting its beneficial effect in elderly population. Other researchers showed that prevention of NAFLD development by resveratrol in rats fed a HFD was associated with up-regulated expression of hepatic UCP2, the inhibitor of mitochondrial ROS production and oxidative stress regulator (Poulsen et al. 2012). In human hepatocytes, resveratrol ameliorated ethanol-induced activation of signaling pathways associated with ER stress, including GRP78, IRE-1α, eIF2α, translational regulator RNA-dependent protein kinase R (PKR)-like ER kinase (PERK) and ATF4 (Liu et al. 2014b). In addition, resveratrol inhibited apoptosis by decreasing cleaved caspase-3 as well as CHOP and Bax expression, which was associated with restoration of SIRT1 levels and suppression of phosphodiesterase (PDE) activity. Similarly, resveratrol prevented hepatic steatosis and dyslipidemia by attenuating ER stress in rat livers (Pan et al. 2015). Mechanistically, the compound down-regulated HFD-induced increase in ATF4, CHOP and BiP levels.

Resveratrol also showed a potential to inhibit cell growth of activated HSCs by inducing cell cycle arrest in sub-G1 phase and to modulate the SIRT1/PPARγ ratio (de Souza et al. 2015). This compound reduced collagen I, TGF-β and NF-κB mRNA expression in cirrhotic rat livers (Di Pascoli et al. 2013) and decreased the secretion of MMP-2 in human liver myofibroblasts (Godichaud et al. 2000), suggesting the ability to deactivate HSCs. Nevertheless, the up-regulation of profibrotic genes in human HSCs by resveratrol in the presence of free fatty acids, suggests the possibility of fibrogenic activity in obese patients (Bechmann et al. 2009).

SIRT-1 has also been identified as a regulator of hepatocyte lipid metabolism via activation of AMPK. Activation of the SIRT1/LKB1/AMPK pathway has been suggested as a key mechanism by which resveratrol counteracts hepatic lipid accumulation, hyperlipidemia and atherosclerosis (Hou et al. 2008). Resveratrol ameliorated HFD-induced hepatic steatosis and decrease in gene expression of SIRT1 in mice liver, with a concomitant suppression of liver lipogenic genes, including ACC, PPARγ and SREBP-1 (Andrade et al. 2014). The SREBP-1 inhibitory effect of resveratrol was accompanied by activation of PGC-1α, increased circulating levels of adiponectin and enhanced mRNA expression of hepatic AdipoR1/2 (Ajmo et al. 2008). Jin et al. (2013) demonstrated that resveratrol may inhibit SREBP-1c-inducing ability of LXRα, a regulator of *de novo* fatty acid synthesis, consequently impairing the expression of target genes and hepatic steatosis. This effect was not dependent on AMPK and SIRT1 but involved up-regulation of sestrin 2 (SESN2) expression. Interestingly, in normally fed mice, resveratrol treatment did not change the expression of LXR target genes but activated AMPK and increased phosphorylation of ACC (Gao and Liu 2013). In contrast to steatosis, resveratrol treatment had no consistent therapeutic effect on amelioration of experimental steatohepatitis (Heeboll et al. 2015). Furthermore, resveratrol showed the ability to inhibit the expression of SREBP1 via SIRT1-FOXO1 signaling pathway in vitro (Wang et al. 2009b). Members of the FOXO family of transcription factors have been shown to regulate the expression of numerous genes involved in the cell cycle, apoptosis, differentiation and cellular response to oxidative stress. Resveratrol treatment could attenuate hepatic steatosis and lipid metabolic disorder in mice by up-regulating the levels of SIRT1, phospho-AMPK and phospho-FOXO1 expression (Zhu et al. 2014). It should be mentioned that treatment with this compound enhanced ethanol-induced expression of autophagy-related genes in mouse hepatocytes via increased deacetylation of FOXO3a, which seems to play a critical role in ethanol-induced autophagy (Ni et al. 2013). Experimental NAFLD in a murine was also improved through regulation of autophagic mediator UNC-51-like kinase 1 (ULK1) and NF-κB pathways, which coincided with amelioration of inflammation and insulin resistance (Li et al. 2014c). Moreover, most recent study demonstrated resveratrol-mediated induction of autophagy in the steatotic liver via the cAMP-PKA-AMPK-SIRT1 signaling pathway (Zhang et al. 2015c).

In HBV X protein (HBX) transgenic mice, resveratrol exhibited chemopreventive activity by reducing the incidence of HBV-associated HCC (Lin et al. 2012b). It inhibited LXRα expression and down-regulated lipogenic genes, with concomitant stimulation of AMPK and SIRT1 activity. In human hepatic cells HBX up-regulated β-catenin, which plays important role in cell–cell adhesion and maintenance of epithelial cell layers, by sequestering SIRT1 deacetylase (Srisuttee et al. 2012). Interestingly, resveratrol significantly enhanced HCV RNA replication and attenuated antiviral effects of IFN-α2b and ribavirin (Nakamura et al. 2010), suggesting a need for further investigation of HCV therapeutic potential in patients.

Finally, resveratrol was found to exert a chemopreventive activity against DEN-induced rat liver tumorigenesis. It reduced gene expression and production of hepatic inflammatory cytokines (Mbimba et al. 2012), while up-regulating protein and mRNA expression of Nrf2 (Bishayee et al. 2010). The stilbenoid also attenuated HSCs activation and reduced hydroxyproline content and TGF-β1 gene expression in DEN-treated rats (Lee et al. 2010a). Administration of resveratrol after warm ischemia and reperfusion in rat liver attenuated gene expression of HIF-1α and VEGF, associated with development of tumors and their metastases (Zhang et al. 2014d). Moreover, resveratrol blocked phosphorylation of ERK1/2 and ERK1/2-induced connexin 43 (Cx43), a critical regulator of GJIC, which has been involved in carcinogenesis (Kim et al. 2009). Interestingly, resveratrol has been shown to prevent deregulation of GJIC

by toxicants that act only through MEK1/2- or phosphatidylcholine-specific phospholipase C (PC-PLC)-dependent pathways (Sovadinova et al. 2015). The inhibitory effect of resveratrol on chemically induced hepatocarcinogenesis may be also attributed to down-regulation of CYPs, such as CYP2E1 (Wu et al. 2013). Interestingly, Kim et al. (2009) showed that protective effect of resveratrol against H_2O_2-induced inhibition of GJIC in rat epithelial cells is not mediated through its free radical-scavenging activity.

The inhibition of CYP activities as a common feature of resveratrol has been demonstrated in a number of studies. Among several flavonoids, including quercetin, naringenin, hesperidin and rutin, resveratrol was the most potent inhibitor of CYP1A1 in vivo (Arinc et al. 2015). Resveratrol suppressed pregnane X receptor (PXR)-mediated CYP3A4 and CYP3A11 mRNA and protein expression in primary mouse hepatocytes (Deng et al. 2014) and CYP2D2 activity in isolated rat livers (Zendulka et al. 2009). It also inhibited CYP1A1 and CYP1A2 mRNAs in primary human hepatocytes (Dvorak et al. 2008). The inhibition of expression of CYP1A1 and CYP1B1 by resveratrol was mediated by inhibition of the recruitment of AhR and aryl hydrocarbon nuclear translocator (ARNT) (Beedanagari et al. 2009). Resveratrol inhibited chemically induced human CYP1 enzymes in vitro by two distinct mechanisms: direct inhibition of CYP1B1 and CYP1A1 and irreversible NADPH-dependent inactivation in case of CYP1A2 (Chang et al. 2001). Interestingly, resveratrol showed over 50-fold selectivity for CYP1A1 over CYP1A2 (Chun et al. 1999).

Double-blind, randomized, placebo-controlled trial in relatively small group of patients indicated that resveratrol supplementation decreased serum alanine aminotransferase, HOMA-IR, TNF-α, cytokeratin 18 fragment and FGF21 levels, while increasing adiponectin level, suggesting a beneficial effect in amelioration of NALFD in humans (Chen et al. 2015).

Alkaloids

Berberine (**22**), a quaternary ammonium salt from the protoberberine group of isoquinoline alkaloids, possesses antioxidant properties which could suppress oxidative stress in the liver (Li et al. 2014a; Othman et al. 2014). DEN- and CCl_4-induced HCC development was prevented by berberine and even more potently with a combination of berberine and S-allyl-cysteine (Sengupta et al. 2014). Carcinogen-stimulated induction of Akt-dependent mouse double minute 2 homolog (Mdm2)/histone deacetylase 1 (HDAC1) interaction led to p53 deacetylation and its subsequent degradation. This resulted in increased expression of antiapoptotic Bcl-xL and decreased levels of proapoptotic p53-up-regulated modulator of apoptosis (PUMA), Bax and Bak proteins. Berberine alone or in combination with S-allyl-cysteine diminished these effects and induced apoptosis by stimulating protein phosphatase 2A (PP2A) and inhibiting JNK activation. Furthermore, amelioration of the early phase of DEN and phenobarbital-induced hepatocarcinogenesis by berberine was accompanied by suppression of iNOS expression and inhibition of CYP2E1 and CYP1A2 activities (Zhao et al. 2008). Berberine also ameliorated apoptosis in ischemia-/reperfusion-injured rat livers by increasing the Bcl-2/Bax ratio and inhibiting caspase-3 cleavage. The mechanism of its action involved up-regulation of Akt, with concomitant inhibition of mTOR expression (Sheng et al. 2015). Moreover, berberine protected against ethanol-induced steatosis in mice by restoring PPARα/PGC-1α and hepatocyte nuclear factor 4 alpha (HNF4α)/microsomal triglyceride transfer protein (MTTP) pathways, involved in secretion of lipoproteins (Zhang et al. 2014e).

Berberine pretreatment in LPS-induced inflammation in mice reduced the expression of hepatic proprotein convertase subtilisin/kexin type 9 (PCSK9), a cholesterol homeostasis regulator, and decreased IFN-γ, TNF-α, IL-1α and 8-isoprostane levels (Xiao et al. 2012). CCl_4-induced acute liver injury was ameliorated by berberine through suppression of TNF-α, COX-2 and iNOS expression, with concomitant attenuation of oxidative/nitrosative stress (Domitrovic et al. 2011). In experimental liver fibrosis, berberine decreased TGF-β1 expression, increased MMP-2 levels and stimulated elimination of fibrous deposits (Domitrovic et al. 2013). Moreover, berberine treatment attenuated liver fibrosis via activation of AMPK and decreased expression of NOX4 and phosphorylated Akt (Li et al. 2014a).

In hyperlipidemic patients with HBV, HCV and liver cirrhosis, treatment with 500 mg of berberine hydrochloride orally twice a day for 3 months has been shown to markedly improve serum indicators of liver injury and lipid parameters (Zhao et al. 2008), suggesting its beneficial potential in hepatic viral infections.

Caffeine (1,3,7-trimethylxanthine) (**23**), is a well-known ingredient of coffee, a brewed drink prepared from roasted coffee (genus *Coffea*) beans. Caffeine has been recognized as a protector against hepatic oxidative damage since 1990s (Devasagayam et al. 1996). It has been shown that conventional coffee and caffeine intake provide better beneficial effects than decaffeinated coffee against liver injury in male animal model (Furtado et al. 2012). However, the hepatoprotective effects of coffee cannot be directly attributed to caffeine but also to other compounds present in the coffee, such as diterpenes kahweol and cafestol (Lee et al. 2007b). Thus, inflammatory cytokine IL-1β gene expression in the liver of mice fed HFD was reduced by simultaneous intake of either regular of decaffeinated coffee (Fukushima et al.

2009). Most of the studies investigating hepatoprotection by this compound were focused on its antifibrotic potential and prevention of steatohepatitis. Second line of studies was oriented toward CYP-modulating effects of caffeine and a possible risk of indicating activation of carcinogens. Caffeine has been frequently reported as CYP1A2 inductor in mice and rats (Goasduff et al. 1996; Kuribayashi et al. 2006); however, this induction was not observed in human hepatocytes (Vaynshteyn and Jeong 2012). Interestingly, a recent study in mice demonstrated that caffeine acted as an inhibitor of CYP1A2 activity and an enhancer of CYP3A activity, decreasing APAP hepatotoxicity (Wolf et al. 2005).

Caffeine protected against alcoholic liver injury by attenuating production of ROS and TNF-α in Kupffer cells (Lv et al. 2010). It also inhibited TNF-α-induced apoptosis of hepatocytes but had no significant effect on anti-Fas antibody-induced hepatitis and apoptosis, which suggest that caffeine differentially affects TNFR- and Fas-mediated liver injury in mice (Sugiyama et al. 2001). Further, caffeine reduced hepatosteatosis in mice fed a HFD and concomitantly stimulated the autophagy-lysosomal pathway. Caffeine inhibited mTOR and its downstream targets $p70^{S6K}$ and 4E-BP1 (Sinha et al. 2014). 4E-BP1 acts as a repressor of mRNA translation, suggesting restoration of transcriptional activity in hepatic cells. Inhibition of mTOR was closely associated with increased LC3-II levels and enhanced lipid accumulation in autolysosomes. Caffeine also attenuated lipid accumulation in hepatic cells by inhibiting lipogenesis and stimulating lipolysis through modulation of the AMPK signaling pathway. Mechanistically, caffeine increased phosphorylation of AMPK and decreased the mRNA level of lipogenesis-associated genes, including SREBP-1c, SREBP-2, FAS, SCD and HMG-CoA reductase (HMGCR) (Quan et al. 2013a). Caffeine could also improve high-energy diet-induced hepatic steatosis by promoting lipid metabolism via the cAMP/CREB/SIRT3/AMPK/ACC pathway (Zhang et al. 2015a).

Caffeine was found to increase HSCs apoptosis and cyclic adenosine monophosphate (cAMP) expression in human HSCs (Shim et al. 2013). However, although pharmacological activity of caffeine was usually attributed to inhibition of phosphodiesterase enzymes and elevation of cAMP levels, some studies have shown that caffeine may act via inhibition of receptor-stimulated inositol 3-phosphate (IP_3) formation and direct inhibition of the IP_3-sensitive Ca^{2+}-release channel in a cAMP-independent way (Combettes et al. 1994). Other mechanisms of hepatoprotective actions of caffeine were also investigated. Thus, caffeine protected against alcohol-induced liver fibrosis, which was associated with inhibition of the cAMP/PKA-dependent activation of CREB, one of the major stimulators of liver fibrosis (Wang et al. 2015c). CREB acts as a regulator of PPARγ expression, which in turn down-regulates CTGF expression. Caffeine down-regulates TGF-β-induced expression of CTGF in hepatocytes by stimulating degradation of TGF-β effector Smad2, inhibition of Smad1/3 phosphorylation and up-regulation of PPARγ-receptor (Gressner et al. 2008). Study in rats demonstrated that caffeine could also diminish thioacetamide-induced liver fibrosis by impairing the expression of profibrogenic and proinflammatory genes such as TNF-α, PDGF and TGF-β1 (Gordillo-Bastidas et al. 2013; Arauz et al. 2014). Concomitantly, caffeine reduced expression of transcriptional factor Snail1, which is involved in fibrotic processes. Further, caffeine inhibited activation of HSCs and reduced levels of collagen mRNA, with concomitant inhibition of MMP-2 and MMP-9, main tissue remodelators (Arauz et al. 2014). Moreover, this compound inhibited HSCs activation via adenosine A2A receptor (A2AR) mediated by the cAMP/PKA/Src/ERK1/2 and p38 MAPK signaling pathways (Wang et al. 2014b), which play an important role in the pathogenesis of hepatic cirrhosis (Chan et al. 2006).

Investigating dietary behavior in NAFLD patients, an association between caffeine intake and lower risk for NAFLD (Birerdinc et al. 2012), reduced liver fibrosis among patients with NASH or chronic hepatitis C virus infection (Modi et al. 2010; Molloy et al. 2012; Khalaf et al. 2015), as well as reduced risk of HCC (Johnson et al. 2011), the severity of chronic hepatitis C (Costentin et al. 2011) or chronic liver disease (Ruhl and Everhart 2005) was established. Hepatoprotective effect of caffeine was clearly dependent on daily intake, showing beneficial effects in patients consuming more than two cups of coffee per day.

In HBV-infected HCC cells, ROS accumulation induced DNA damage that activated the ATM-Chk2 pathway, resulting in the inhibitory phosphorylation of Cdc25C phosphatase and Cdk1 (Kim et al. 2015), suggesting the inhibitory potential of caffeine against the viral replication.

Antraquinones

Emodin (1,3,8-trihydroxy-6-methyl-anthraquinone) (**24**), is an anthraquinone derivative isolated from *Rheum* species. Emodin protected against acetaminophen and CCl_4-induced oxidative stress and acute liver injury in rats (Dang et al. 2008; Bhadauria 2010). Attenuation of fulminant hepatitis and proinflammatory response by this compound was associated with inhibition of the p38 MAPK/NF-κB pathway and blockade of TLR4/myeloid differentiation factor (MD) 2 complex expression (Yin et al. 2014; Xue et al. 2015). Emodin partially protected against cholestatic injury in rats (Zhao et al. 2009) by exerting anti-inflammatory activity through decreased nuclear translocation of NF-κB (Ding et al. 2008). Emodin also alleviated alcohol-mediated

oxidative stress and liver steatosis in mice by down-regulating hepatic CYP2E1 expression (Liu et al. 2014d).

Emodin has been shown to ameliorate dyslipidemia in HFD-fed rats by activating AMPK and its downstream targeting enzyme, ACC (Tzeng et al. 2012). Concomitant up-regulation of gene expression of CPT1 and down-regulation of SREBP-1 and FAS protein levels in hepatocytes suggested attenuation of lipid accumulation by decreasing lipogenesis and increasing fatty acid β-oxidation. Emodin also ameliorated NAFLD in rats induced with a high caloric diet by suppressing GRP78-mediated SREBP-1c pathway in the liver and restoring reduced expression of PPARγ gene expression (Dong et al. 2005; Li et al. 2015c). In steatotic hepatic cells, emodin down-regulated HMGCR and diacylgycerol acyltransferase 1 (DGAT1), key enzymes in the synthesis of cholesterol and triglycerides, while up-regulating expression of CYP7A, involved in hepatic bile acid biosynthesis (Wang et al. 2014d).

Protection against CCl_4-induced fibrogenesis by emodin was mediated by the reduction of the mRNA levels of TGF-β1 and Smad4 and inhibition of myofibroblastic differentiation (Dong et al. 2009). In immortalized rat HSCs, emodin reduced AP-1 DNA-binding activities and attenuated JunD mRNA expression (Gui et al. 2007). Emodin also markedly inhibited TGF-β1-induced ERK1/2 phosphorylation as well as the expression of TIMP-1.

However, some concerns arise from available data on chronic usage of this compound. A comprehensive study by National Toxicology (2001) showed that chronic administration of emodine resulted in sex and species-dependent low but significant carcinogenic activity of emodin and increased incidences of nephropathy in female mice. CYP-modulating activity of emodin was not intensively studied. However, one available study demonstrated activation of the metabolism of midazolam, a CYP3A4/5 substrate, in human liver microsomes by emodin (Li et al. 2014f). Biotransformation of emodin by the microsomal enzymes, which resulted in several metabolites, demonstrated that at least one of them, 2-hydroxyemodin (1,2,3,8-tetrahydroxy-6-methyl-anthraquinone), possessed a direct mutagenic activity to the test strain, *Salmonella typhimurium* (Masuda and Ueno 1984). These findings suggest potential adverse effects of emodin by long-term exposure in patients. In addition, emodin showed severe cytotoxicity against human liver cell line L-02 (Yu et al. 2011).

Curcuminoids

Curcumin, diferuloylmethane (**25**), is a major polyphenolic compound of the spice turmeric obtained from rhizomes of *Curcuma* species. The mechanism of hepatoprotection seems to be related at least in part to antioxidant activity and activation of the Nrf2/Kelch-like ECH-associated protein 1 (Keap1)/ARE pathway, with concomitant induction of phase II detoxifying/antioxidant enzymes such as HO-1 and NQO1 (Farombi et al. 2008; Gao et al. 2013b; Garcia-Nino and Pedraza-Chaverri 2014; Xu et al. 2014a). Moreover, curcumin administration in diet-induced oxidative stress reduced CYP2E1 as well as Prx1 expression, while up-regulating Prx6 expression (Lee et al. 2015). Oxidative stress induced with hepatotoxins is closely related to hepatic inflammatory response through activation of several signaling pathways, including MAPKs, NFκB and STAT3 (Ambade and Mandrekar 2012). Nevertheless, numerous studies demonstrated decreased hepatic expression of NF-κB and its downstream targets by curcumin (Bisht et al. 2011; Tu et al. 2012b; Xu et al. 2014a). It has also been shown that curcumin could decrease the expression of TLR2 and TLR4 and their ligand molecule HMGB1 in the rat model of fibrogenesis (Tu et al. 2012b) and T-cell-mediated hepatitis in concanavalin A-challenged mice (Tu et al. 2012a, 2013), suggesting a potential to attenuate inflammatory processes in the liver. Moreover, curcumin could ameliorate LPS/D-GalN-induced liver injury through reduction of hepatic mRNA levels of SIRT1 (Zhang et al. 2014b).

Furthermore, curcumin treatment resulted in alleviation of hepatic inflammation in steatohepatitis. Fructose is a dietary compound known to decrease tyrosine phosphorylation of insulin-induced IRS1 and inhibit activation of Akt and ERK1/2 in peripheral tissues. Administration of curcumin in rats increased phosphorylation of hepatic JAK2 and stimulated Akt and ERK1/2 activation in the model of fructose diet-induced steatohepatitis (Li et al. 2010). Overexpression and hyperactivity of hepatic protein tyrosine phosphatase 1B (PTP1B) was reduced by curcumin, with subsequent improvement of insulin and leptin signaling. Further, this compound suppressed HFD-mediated increase in SREBP-1, ACC1, FAS and CD36 expression, thus attenuating hepatic steatosis (Um et al. 2013). Curcumin also inhibited gene expression of receptor for advanced glycation end-products (RAGE) in HSCs in vitro by elevating the PPARγ activity and attenuating oxidative stress, leading to elimination of the AGE effects on HSCs activation (Lin et al. 2012a). Moreover, it decreased the hepatic gene expression of inflammatory cytokines, procollagen I and TIMP-1 in experimental steatohepatitis in mice (Vizzutti et al. 2010).

Curcumin has been shown to target multiple pathways to inhibit hepatic fibrosis. Hedgehog (Hh) signaling becomes activated in chronic liver injury and plays a role in the pathogenesis of hepatic fibrosis. Therefore, targeting Hh signaling may represent a novel therapeutic strategy for treatment of liver fibrosis. HSCs are Hh-responsive cells and activation of the Hh pathway may promote transdifferentiation of HSCs into myofibroblasts. Curcumin

down-regulated Ptch and smoothened (Smo), two key elements in Hh signaling, simultaneously restoring Hhip expression in fibrotic rat livers and cultured HSCs (Lian et al. 2015). Curcumin also prevented the nuclear translocation, DNA binding, and transcription activity of GLI-1. Additionally, this compound arrested the cell cycle, induced mitochondrial apoptosis, restored lipid accumulation, reduced fibrotic gene expression and inhibited invasion and migration in HSCs. Further, curcumin inhibited HSCs activation in CCl_4-intoxicated rat livers by activating PPARγ and reducing expression of mRNA and proteins involved in cell proliferation, including PDGF, PDGFRβ and EGFR, as well as genes related to fibrogenesis, including TGF-β, Tβ-RI/II and fibronectin (Fu et al. 2008a). As the result, curcumin inhibited proliferation of HSCs in the G2/M phase of the cell cycle (Shu et al. 2009). Furthermore, this compound activated AMPK and increased expression of PGC-1α, a coactivator for PPARγ, resulting in increased PPARγ activity and reduced collagen α1(I) gene expression (Zhai et al. 2015). In addition, curcumin has been shown to down-regulate Wnt signaling pathway, including the expression of Axin2 and Fra1 (Shin et al. 2009), both involved in HSCs activation (Jiang et al. 2006). During hepatic fibrogenesis, suppression of PPARγ is negatively associated with PDGF and EGF mitogenic signaling in HSCs. Curcumin could interrupt PDGF and EGF signaling by inhibiting gene expression and phosphorylation of PDGFRβ and EGFR and suppression PI3K, ERK and JNK signaling (Zhou et al. 2007; Fu et al. 2008a; Lin and Chen 2008). Curcumin also impaired production of ECM proteins in alcohol-stimulated HSCs and CCl_4-induced liver by suppressing the TGF-β/Smad2/3 signaling and inducing Smad7 (Chen et al. 2014b). Activation of PPARγ by curcumin was required for inhibition of both VEGF expression and angiogenic properties of HSCs (Zhang et al. 2014a). VEGF plays a crucial role in the initial stages of new vessel formation and endothelial cell proliferation (Carmeliet 2005). Mechanistically, curcumin inhibited PDGFRβ/ERK and PI3K/Akt/mTOR pathways in activated HSCs via PPARγ signaling, thus inhibiting VEGF mRNA and protein expression (Zhang et al. 2014a). Inhibition of PDGFRβ also blocked FAK/RhoA cascade, resulting in reduced HSCs motility. Moreover, curcumin ameliorated hepatic angiogenesis and sinusoidal capillarization in fibrotic livers through suppression of proangiogenic factors, including HIF-1α, VEGFR-1, placental growth factor (PGF) and COX-2 (Yao et al. 2013). The inhibition of HIF-1α expression was at least in part mediated through inhibition of the ERK pathway (Zhao et al. 2014). Induction of CTGF in activated HSCs is another mechanism for increased production of ECM during fibrogenesis. Activation of PPARγ by curcumin resulted in interruption of TGF-β signaling by suppressing gene expression of Tβ-Rs, ultimately leading to inhibition of CTGF gene expression and decreased production of ECM proteins (Zheng and Chen 2006). Moreover, this compound inhibited CTGF expression in activated HSCs via inhibition of TLR-mediated NF-κB activation (Chen and Zheng 2008). Curcumin not only could impair HSCs activation and proliferation, but also blocked antiapoptotic protein c-FLIP and increased Bax expression, resulting in caspase-3 activation and induction of HSCs apoptosis (Priya and Sudhakaran 2008; Shin et al. 2009; Bisht et al. 2011). Curcumin also protected HSCs against leptin-induced activation in vitro and increased AMPK activity, leading to increased expression of genes relevant to lipid accumulation, including PPARγ, SREBP-1 and C/EBPα (Tang and Chen 2010). Finally, the inhibition of CBR1 can be added to a broad spectrum of antifibrotic activities of curcumin (Zhang et al. 2013b). Curcumin reduced the mRNA and protein abundance of CBR1 in cultured HSCs and inhibited ECM production. This compound also alleviated hepatic injury in parasitic infestation. In hamsters infected with a trematode parasite *Opisthorchis viverrini*, curcumin decreased the mRNA expression of TIMP-1, TIMP-2 and TNF-α, while increasing MMP-13 and MMP-7 levels (Pinlaor et al. 2010), suggesting degradation of ECM and improvement of liver fibrosis.

DEN-induced hepatocarcinogenesis was another pathological process which was prevented by curcumin administration. Beneficial effect of curcumin was associated with decreased levels of oncogenic p21 and p53 as well as cell cycle-related proteins, including PCNA, cyclin E and Cdc2 but not Cdk2 or cyclin D1 (Chuang et al. 2000a, b). In DNE-induced HCC, mice treatment with doxorubicin and curcumin co-delivery lipid nanoparticles (doxorubicin/curcumin-NPs) induced increase in caspase-3 activation and Bax/Bcl-2 ratio, and PCNA and VEGF (Zhao et al. 2015). On the other hand, doxorubicin/curcumin-NPs exhibited the synergistic effect on the apoptosis, proliferation and angiogenesis of HCC by decreasing the levels of multidrug resistance protein 1 (MDR1), P-gp, Bcl-2 and HIF-1α, indicating that curcumin might reverse multidrug resistance through these pathways. These findings suggested that doxorubicin/curcumin-NPs may be a promising treatment for HCC. Furthermore, curcumin treatment protected against acetaminophen-induced hepatocyte apoptosis via decreasing expression of pro-apoptotic genes Bax and caspase-3, while inducing antiapoptotic genes such as Bcl-xL and increasing Bcl-2/Bax ratio (Bulku et al. 2012; Li et al. 2013a). Interestingly, curcumin was able to up-regulate p53 protein expression and down-regulate Bcl-2 mRNA expression in thioacetamide-induced cytotoxicity, forcing the damaged cells to undergo apoptosis, thus suppressing hepatic inflammatory response and fibrogenesis (Wang et al. 2012a).

Additionally, curcumin protected mice against human cytomegalovirus (HCMV) infection through its anti-inflammatory and antioxidant effects (Lv et al. 2014). Curcumin also inhibited Rift Valley fever virus replication in infected human cells by inhibiting phosphorylation of NFκB p65 subunit via inhibition of kinase activity of the IKKβ2 complex (Narayanan et al. 2012). Curcumin could also inhibit HBV and HCV replication via down-regulation of metabolic coactivator PGC-1α and the Akt/SREBP-1 pathway, respectively (Kim et al. 2010a; Rechtman et al. 2010). Additionally, it inhibited HCV entry independently of the genotype in primary human hepatocytes, without effect on HCV RNA replication or viral assembly/release (Anggakusuma et al. 2014). Nevertheless, another study demonstrated inhibition of HCV replication through suppression of PI3K/Akt and induction of HO-1 (Chen et al. 2012b).

Administration of curcumin has been shown to decrease activity of CYP2B1/2 and CYP1A1 in mice liver (Sehgal et al. 2013) and inhibit activation of CYP2E1 in chronic alcohol and high-fat diet-induced liver injury in mice (Lee et al. 2013a). Similarly, microsomal CYP2C and CYP3A activities in bovine hepatocytes were inhibited by treatment with curcumin (Lemley and Wilson 2010). It has also been reported that curcumin inhibited activation of carcinogens metabolized by rat CYP isozymes, namely, CYP1A1, 1A2 and 2B1 (Thapliyal and Maru 2001). Interestingly, minimal to no induction of CYP1A2, CYP2B6, CYP3A4, CYP2C8/2C9 or CYP2D6 in human hepatocytes studies was observed (Price et al. 2008; Mach et al. 2010), with no effect on CYP2B1 and CYP2E1-mediated activation of carcinogenic *N*-nitrosamines in mice liver, kidney or intestine (Mori et al. 2006). Taken together, available data suggest low potential for CYP-mediated drug interactions at physiological serum concentrations of curcumin.

Capsaicinoids

Capsaicin (8-methyl-*N*-vanillyl-6-nonenamide) (**26**) protected against liver injury by reducing hepatic oxidative stress (Manjunatha and Srinivasan 2007; Hassan et al. 2012). However, capsaicin was able to induce CYP3A4 expression via PXR and C/EBPβ activation in rat livers and in human liver microsomes (Takanohashi et al. 2010; Han et al. 2012), suggesting a potential of causing drug–drug interactions.

Several studies revealed that capsaicin efficiently reduced liver fibrosis, inhibited HSCs proliferation and promoted cell apoptosis. Thus, capsaicin reduced gene expression of TGF-β1 and TIMP-1 in HSCs (Yu et al. 2014). Moreover, this compound induced apoptosis of HSCs, which was associated with increased expression of cytochrome c, Bax and caspase-3 and reduced levels of Bcl-2. Capsaicin also inhibited culture-induced activation of mouse HSCs by preventing the up-regulation of several activation markers such MMP-2, MMP-9 and TIMP-1 (Bitencourt et al. 2012). In addition, capsaicin inhibited PDGF-induced chemotaxis and proliferation of HSCs. Moreover, mice receiving capsaicin after BDL showed a significant improvement of liver fibrosis accompanied by a decrease in collagen deposition (Bitencourt et al. 2015). In CCl_4-intoxicated mice, capsaicin prophylactically inhibited up-regulation of profibrogenic markers, but it could not attenuate already established fibrosis. Additionally, capsaicin inhibited autophagic process during HSCs activation. The same authors have shown induction of quiescent phenotype in HSCs via PPARγ activation, with the decrease in COX-2 and type I collagen mRNA expression (Bitencourt et al. 2012). These events preceded the suppression of TGF-β1 and collagen secretion.

Further, capsaicin stimulated hepatic lipolysis by increasing levels of phosphorylated hormone-sensitive lipase (HSL), CPT1 and PPARδ in mice liver (Li et al. 2013b). Activation of transient receptor potential vanilloid subfamily, member 1 (TRPV1), a capsaicin-specific receptor, and a concomitant PPARδ activation, prevented NAFLD through induction of autophagy-related proteins, such as LC3-II, Beclin1, Atg5 and Atg7. In addition, capsaicin suppressed inflammatory responses in obese mice fed a HFD by decreasing mRNA and proteins levels of TNF-α, MCP-1 and IL-6 in adipose and liver tissue (Kang et al. 2010). Concomitantly, capsaicin increased hepatic PGC-1α and TRPV1 expression in adipose tissue.

Chromenes

Ellagic acid (2,3,7,8-tetrahydroxy-chromeno[5,4,3-cde] chromene-5,10-dione) (**27**), a natural phenol antioxidant, also exhibited protection against hepatic oxidative injury (Pari and Sivasankari 2008; Girish et al. 2009). Administration of ellagic acid to rats increased NQO1, CAT, GPX and GST activity in the liver, while reducing CYP1A, 2B, 2C and 2E activity, suggesting impact on the metabolism of chemical carcinogens and drugs by affecting the activity of enzymes involved in xenobiotic activation and detoxification (Celik et al. 2013). Further, administration of ellagic acid prevented experimental liver cancer induced by DEN through activation of Bax and caspase-9 (Srigopalram et al. 2014). Concomitant down-regulation of NF-κB, cyclin D1, cyclin E1, MMP-2, MMP-9 and PCNA expression suggested inhibition of the cell cycle and activation of tissue remodeling process. Ellagic acid also decreased the expression of MMPs and TIMP-2 induced by alcohol consumption, resulting in amelioration of hepatic fibrosis (Devipriya et al. 2007).

Further, ellagic acid decreased concanavalin A-induced expression of TLR2 and TLR4 at both mRNA and protein level. This led to decrease in phosphorylation of JNK, ERK1/2 and p38 and suppression of NF-κB activation (Lee et al. 2014b). In addition, ellagic acid treatment decreased the expression of proinflammatory cytokines, including TNF-α, IL-6 and IL-1β, suggesting protection against T-cell-mediated hepatitis through the inhibition of TLR/MAPK/NF-κB signaling pathway. The suppression of metabolic syndrome by ellagic acid was also mediated through inhibition of NF-κB activation and induction of hepatoprotective Nrf2, HO-1 and CPT1 enzymes (Panchal et al. 2013). In addition, ellagic acid reduced serum resistin level and up-regulated mRNA expression of lipolytic genes, leading to improvement in hepatic steatosis (Yoshimura et al. 2013).

Treatment with ellagic acid has also been shown to overcome host immune tolerance induced by HBeAg during HBV infection (Kang et al. 2006) and block HBeAg secretion in infected hepatic cells, suggesting its beneficial effect on immune tolerance in HBV-infected individuals (Shin et al. 2005). Moreover, ellagic acid blocked the HCV NS3/4A protease activity in vitro. Structural analysis showed that ellagic acid interacted with the catalytic and substrate binding residues of NS3/4A protease, leading to its inhibition (Reddy et al. 2014).

Conclusion and future perspectives

Although all reviewed compounds showed a clear potential to alleviate different liver pathologies through multiple signaling pathways that reach beyond their antioxidant activity, the lack of clinical studies could not promote them as the hepatoprotective drugs. Interestingly, although silymarin gained a reputation as the hepatoprotective gold standard, glycyrrhizin has been a clinically most investigated natural compound, with a considerable amount of mechanistical evidence which support its hepatoprotective activity.

It is known that natural compound may directly bind to cellular molecules such as proteins or DNA (Walle et al. 2003), which could mediate their cellular actions. It has been found that quercetin binds directly to the BH3 domain of Bcl-2 and Bcl-xL proteins, inhibiting their activity (Primikyri et al. 2014). The molecular docking studies with quercetin showed bonded interaction within iNOS active site region, although quercetin analogues exhibited more favorable interaction than quercetin (Singh and Konwar 2012). Some natural compounds, such as genistein, have been shown to function as inhibitors of tyrosine protein kinases, which play an important role in the activation and proliferation of HSCs (Liu et al. 2002d). Resveratrol has been shown to directly interact with numerous protein molecules involved in signal transduction, such as PI3K, IKK and COX-2 (Pirola and Frojdo 2008). Dietary flavonoids luteolin, naringenin, eriodictyol and daidzein may stimulate the DNA-binding activity of NodD1 transcriptional regulator (Peck et al. 2006). Similarly, in silico docking studies indicated that morin was a better PI3K inhibitor than the classical inhibitor LY294002 (Sivaramakrishnan and Devaraj 2010). Therefore, the use of computational docking studies could lead to development of more potent hepatoprotective compounds.

The optimistic data based on the current knowledge of the mechanisms of hepatoprotective activity of natural compounds may result in therapeutic approaches with enhanced bioavailability and increased effectiveness of these compounds. Nevertheless, these compounds have to be evaluated in pre-clinical and clinical assays to determine their safety for humans. Generally, natural compounds have a low potential of interaction with drugs and activation of pro-carcinogens. However, since interaction between these compounds and pharmaceutical drugs has not been thoroughly examined, particularly at the level of CYPs, co-administration of these compounds by health-care practitioners requires caution.

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