Redox Biology 17 (2018) 274–283

Contents lists available at ScienceDirect

Redox Biology

journal homepage: www.elsevier.com/locate/redox

Mechanisms of acetaminophen-induced liver injury and its implications for therapeutic interventions

Mingzhu Yan[a], Yazhen Huo[b], Shutao Yin[a], Hongbo Hu[a,*]

[a] Beijing Advanced Innovation Center for Food Nutrition and Human Health, Beijing Key Laboratory for Food Non-thermal Processing, National Engineering Research Centre for Fruit and Vegetable Processing, College of Food Science and Nutritional Engineering, China Agricultural University, No. 17 Qinghua East Road, Haidian District, Beijing 100083, China

[b] State Key Laboratory of Biomacromolecules, Institute of Biophysics, Chinese Academy of Sciences, Beijing, China

ARTICLE INFO

Keywords:
Acetaminophen
Mitochondrial oxidative stress
Endoplasmic reticulum stress
Autophagy
Sterile inflammation
Liver regeneration

ABSTRACT

Acetaminophen (APAP) overdose is the leading cause of drug-induced acute liver failure in many developed countries. Mitochondrial oxidative stress is considered to be the predominant cellular event in APAP-induced liver injury. Accordingly, N-acetyl cysteine, a known scavenger of reactive oxygen species (ROS), is recommended as an effective clinical antidote against APAP-induced acute liver injury (AILI) when it is given at an early phase; however, the narrow therapeutic window limits its use. Hence, the development of novel therapeutic approaches that can offer broadly protective effects against AILI is clearly needed. To this end, it is necessary to better understand the mechanisms of APAP hepatotoxicity. Up to now, in addition to mitochondrial oxidative stress, many other cellular processes, including phase I/phase II metabolism, endoplasmic reticulum stress, autophagy, sterile inflammation, microcirculatory dysfunction, and liver regeneration, have been identified to be involved in the pathogenesis of AILI, providing new targets for developing more effective therapeutic interventions against APAP-induced liver injury. In this review, we summarize intracellular and extracellular events involved in APAP hepatotoxicity, along with emphatic discussions on the possible therapeutic approaches targeting these different cellular events.

1. Introduction

Acetaminophen (APAP) is one of the most frequently used drugs for its analgesic and antipyretic properties. It is safe and effective at recommended doses, whereas overdose may lead to hepatotoxicity and acute liver failure (ALF). In fact, APAP-induced hepatotoxicity remains the most common cause of ALF in many countries [70]. Given the public concern caused by APAP hepatotoxicity, great efforts have been made to understand the mechanisms of its toxic effects. Generally, APAP-induced oxidative stress and mitochondrial dysfunction plays the central role in the pathogenesis of AILI [50]. As such, the United States Food and Drug Administration recommends N-acetyl cysteine (NAC), a known antioxidant, as the only therapeutic option for APAP-overdosed patients; however, this medication has its limitations including adverse effects and narrow therapeutic window [31]. If the early and/or the most treatable stage is missed, liver transplantation is the only choice to improve survival in patients with AILI [23]. Hence, the development of new drugs that are superior to NAC, in terms of effectiveness and therapeutic time frame, is clearly needed. In recent years, there have been intensive studies demonstrating the protective effects of natural products against APAP-induced hepatotoxicity, providing considerable drug candidates for AILI. It has been recognized that the APAP toxicity consists of multi-stages and multi-signaling pathways, including APAP metabolism, oxidative stress, endoplasmic reticulum (ER) stress, autophagy, sterile inflammation, microcirculatory dysfunction, and compensatory liver repair and regeneration. Many genes or molecules have been identified to play pivotal roles in the regulation of APAP hepatotoxicity, so they are suggested to be potential targets for therapeutic intervention against APAP-induced liver injury.

This review summarizes the generally accepted mechanisms of APAP hepatotoxicity and highlights the key signaling pathways as targets for AILI therapeutic interventions.

2. Targeting the metabolism phase for AILI intervention

When taken at therapeutic doses, most of APAP is metabolized by phase II conjugating enzymes, mainly UDP-glucuronosyltransferase (UGT) and sulfotransferase (SULT), converting it to nontoxic compounds which are then excreted with the urine. Only a very small portion is excreted unchanged in the urine. The remaining APAP,

* Corresponding author.
E-mail address: hongbo@cau.edu.cn (H. Hu).

https://doi.org/10.1016/j.redox.2018.04.019
Received 6 March 2018; Received in revised form 18 April 2018; Accepted 18 April 2018
Available online 22 April 2018

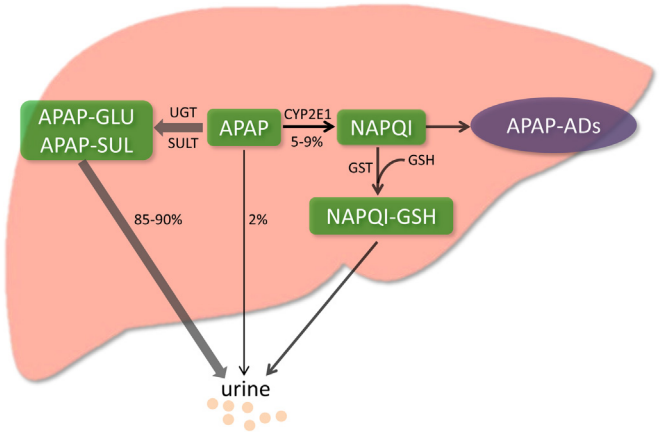

Fig. 1. Metabolic activation of acetaminophen. 85–90% of APAP is primarily metabolized by phase II conjugating enzymes (mainly UGT and SULT). Only 2% is excreted unchanged in the urine. And approximately 5–9% is metabolized mainly by CYP 2E1 into the highly reactive intermediate metabolite NAPQI. In general, NAPQI is detoxified by conjugating with GSH. However, excessive NAPQI depletes GSH following APAP overdose, leading to formation of APAP-ADs through covalent binding of sulfhydryl groups in cellular proteins. APAP, acetaminophen; UGT, UDP-glucuronosyltransferase; SULT, sulfotransferase; CYP 2E1, Cytochrome P450 2E1; NAPQI, N-acetyl-p-benzoquinone imine; GSH, glutathione; APAP-ADs, APAP protein adducts.

approximately 5–9% is metabolized by the cytochrome P450 enzymes (CYPs), mainly CYP 2E1 into the highly reactive intermediate metabolite N-acetyl-p-benzoquinone imine (NAPQI) [66]. Generally, NAPQI is rapidly detoxified by conjugating with glutathione (GSH). However, when phase II metabolizing enzymes are saturated after APAP overdose, excessive NAPQI deplete GSH, leading to covalent binding of sulfhydryl groups in cellular proteins, especially mitochondrial proteins [95]. This results in mitochondrial oxidative stress and dysfunction, ultimately hepatocytes necrosis [50] (Fig. 1).

Based on the pharmacokinetic studies of APAP, induction of antitoxic phase II enzymes may accelerate the metabolic inactivation of this drug, leading to a reduction of APAP metabolized by cytochrome P450 enzymes to NAPQI. In another word, the regulation of APAP detoxification at the phase II level is beneficial in alleviating APAP hepatotoxicity. This hypothesis is consistent with the observation that activation of liver X receptors (LXR) prevented APAP-induced liver injury through induction of phase II conjugating enzymes, as well as suppression of pro-toxic phase I P450 enzymes [103]. Multiple studies have shown that expressions and activities of cytochrome P450 enzymes were also positively regulated by some nuclear receptors and transcription factors, including pregnane X receptor (PXR), constitutive androstane receptor (CAR), and retinoid X receptor α (RXRα) [38,133,124]. Thus, any changes in the expression of these nuclear hormone receptors in response to lipids, cholesterols, bile acids, and xenobiotics could potentially alter APAP-induced toxicity through modulation of NAPQI generation. This assumption was verified in a follow-up study that activation of anti-viral responses by polyinosinic-polycytidylic acid attenuated APAP-induced hepatotoxicity through transcriptional down regulation of RXRα and PXR and their downstream CYPs [34]. Similarly, genetic deletion or pharmacological suppression of 5-lipoxygenase (5-LO) in mice led to induction of phase II detoxification enzyme SULT2A1 and inhibition of the pro-toxic phase I enzyme CYP 3A11, which subsequently reduced NAPQI formation and finally ameliorated AILI [94].

In addition to these genes and related proteins, pretreatment with some whole plant extracts or individual compounds would also alter APAP metabolic activation. It is, therefore, quite necessary and important to examine the expressions and activities of related cytochrome P450 enzymes, as well as the formation of NAPQI when natural products were tested in this model. In fact, many studies on natural products as potential therapy approaches against APAP hepatotoxicity were due to their enhancement effects on phase II metabolic enzymes and/or inhibitory effects on cytochrome P450 enzymes [17,125,130]. In some cases, neglect of the impact on the metabolism phase might lead to ambiguous, even opposite conclusions. A case in point is the green tea extract, which has been shown to protect mice from APAP toxicity through its antioxidant activity [89], whereas this protection was actually more relevant to the reduction of APAP protein adducts caused by suppression of CYP 2E1 and CYP 1A2 [18]. Moreover, when the extract was administered followed by APAP as a therapeutic approach, it could even potentiate APAP-induced hepatotoxicity [106]. Taken together, pretreatment of natural products may cause drug-drug interactions with APAP more easily to happen, and that could possibly lead to unconvincing conclusions on the therapeutic effects and molecular mechanisms. More importantly, patients of AILI often present too late for medical intervention in the course of disease, after the metabolism phase and after liver injury has already developed. Hence, therapeutic approaches, rather than prophylactic treatment, would be more clinically relevant.

3. Targeting mitochondrial oxidative stress and dysfunction for AILI treatment

In the injury process of APAP hepatotoxicity, mitochondrial proteins are the main targets of NAPQI, compared with total protein-binding in hepatocytes, including housekeeping protein, glutathione peroxidase (GPx) and adenosine triphosphate (ATP) synthase α-subunit [95]. NAPQI also interferes with complex I/II of mitochondrial electron transport chain (ETC), causing leakage of electrons from the ETC to oxygen and thus forms superoxide radicals [69,32]. Once formed, superoxide radicals are dismutated in mitochondria by manganese superoxide dismutase (MnSOD) to hydrogen peroxide (H_2O_2) and molecular oxygen (O_2), or react with endogenous nitric oxide (NO) to form peroxynitrite ($ONOO^-$) [50]. Then H_2O_2 is detoxified by GSH directly, or scavenged by a number of antioxidant enzymes in hepatocytes, such as catalase, glutathione peroxidase (GPx) and peroxiredoxin (Prx) [31]. $ONOO^-$ formed in mitochondria could also react with GSH to detoxify [61]. Consequently, GSH is depleted in response to these excessive free radicals, leading to accumulation of $ONOO^-$, which causes formation of nitrotyrosine protein adducts and damage to mitochondrial DNA [22,43]. Given the vital role of mitochondrial oxidative stress in the pathogenesis of AILI, NAC is used clinically as the only standard antidote to treat AILI, mainly via replenishing GSH to enhance detoxification of NAPQI. NAC also exerts protective effects when administered at the oxidative injury phase, when hepatocellular GSH is depleted, reactive oxygen species and peroxynitrite are generated in mitochondria [60,22]. Moreover, surplus NAC in the liver could supply energy substrates for the Krebs cycle, thereby support maintenance of hepatic ATP levels and improve mitochondrial function [105]. There is no doubt that NAC is the mainstay of treatment against hepatotoxicity following APAP overdose; however, this medication has some drawbacks in terms of side effects and narrow therapeutic window. Generally, adverse effects of NAC are not life threatening, including nausea, vomiting, and anaphylactoid reactions with initial infusion [10]. The main caveat of NAC is the decreased efficacy when the treatment is initiated more than 8 h after poisoning [120]. Therefore, medications that still have therapeutic potential beyond early stage would be of great help, especially for those patients presenting at late stage. A number of molecules have been found to be involved in the regulation of APAP-induced oxidative stress, including JNK, p53 and Nrf2 (Fig. 2), which may serve as potential therapeutic targets for AILI.

3.1. JNK

Depletion of GSH by NAPQI results in increased H_2O_2 release from

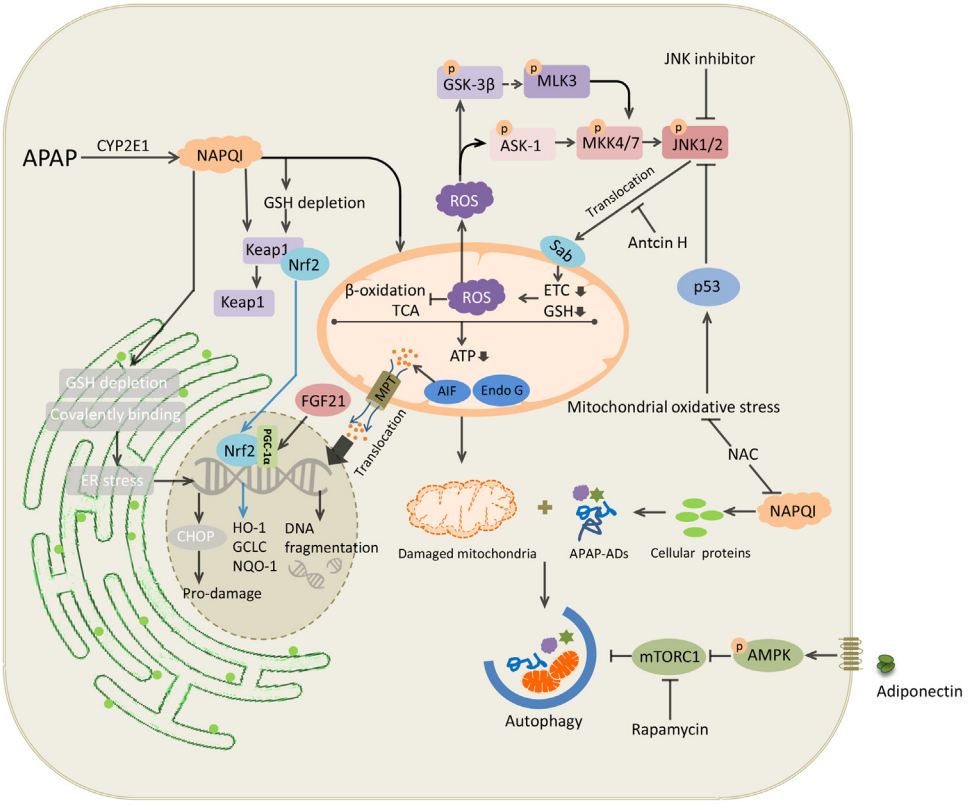

Fig. 2. Intracellular signaling events in acetaminophen hepatotoxicity. Excessive quantities of NAPQI generated by acetaminophen overdose deplete GSH in the cytoplasm, ER and mitochondria, leading to ER stress, mitochondrial oxidative stress and dysfunction. This induces TCA cycle and β-oxidation dysfunction, ATP depletion and the opening of the MPT pore, which, subsequently, leads to the translocation of mitochondrial proteins, such as AIF and Endo G, to the nucleus. This results in nuclear DNA fragmentation and ultimately necrotic cell death. ROS caused by NAPQI activates JNK signaling pathways. Sustained activation of JNK amplifies mitochondrial ROS and forms a self-sustaining activation loop. Nrf2, p53, adiponectin and FGF21 signaling pathways are activated to cope with cellular stress and injury. Similarly, autophagy alleviates AILI through removal of damaged mitochondria and detrimental APAP-ADs. NAPQI, N-acetyl-p-benzoquinone imine; ER, endoplasmic reticulum; TCA, tricarboxylic acid cycle; MPT, mitochondria permeability transition; AIF, apoptosis inducing factor; ROS, reactive oxygen species; JNK, c-Jun N-terminal kinase; AILI, acetaminophen-induced liver injury; APAP-ADs, acetaminophen protein adducts.

mitochondria to cytoplasm, which could oxidize thioredoxin and cause thioredoxin to disassociate from apoptosis signaling-regulating kinase 1 (ASK-1) [41]. This triggers self-activation of ASK-1, which phosphorylates mitogen-activated protein kinase kinase 4/7 (MKK4/7), then activates c-Jun N-terminal kinase (JNK) [104,84]. Once activated, p-JNK translocates to the mitochondria, where it binds to and phosphorylates SH3 homology-associated BTK-binding protein (Sab). This interaction leads to inactivation of intramitochondrial Src, which causes dysfunction of ETC and increase of ROS release. ROS continues to activate upstream mitogen-activated protein kinases, and then phosphorylates JNK. Sustained activation of JNK amplifies mitochondrial ROS and forms a self-sustaining activation loop [122]. p-JNK causes bax activation and translocation to mitochondria, which then triggers the opening of the mitochondrial permeability transition (MPT) pore in mitochondria with a collapse of the membrane potential and ATP depletion [37,58]. MPT facilitates the release of mitochondrial intermembrane proteins, including endonuclease G and apoptosis-inducing factor, both of which translocate to the nucleus. This then causes DNA fragmentation, and finally necrosis [9].

SP600125, a classical ATP-competitive inhibitor of JNK, has been reported to protect against APAP-induced liver injury in vivo and in vitro [67,42]. Importantly, its protection effect was even confirmed in primary human hepatocytes [126]. More importantly, 5 h delayed administration of SP600125 is more effective than NAC in AILI [42]. However, SP600125 was found to provide protection even in JNK-deleted hepatocytes, raising the possibility of off-target effects, e.g., on AMP-activated kinase (AMPK)-dependent survival signaling pathways [24]. Another type of JNK inhibitor that has been shown to protect against APAP hepatotoxicity is D-JNKI1 (JNK 1, D-stereoisomer), which is a peptide that inhibits the interaction of JNK with its substrates [42]. Considering JNK's function in liver regeneration and other possible protective effects (e.g., through activation of AP-1 transcription factor), strategies that inhibit JNK directly or indirectly may also inhibit the potential benefits of it, which may limit the therapeutic application of JNK inhibitors [107,99]. Recently, a terpenoid compound isolated from Antrodia Camphorate, Antcin H, was found to protect against APAP hepatotoxicity through inhibiting the interaction between p-JNK and mitochondria protein Sab [44]. This agent is very promising for future clinical use since it perturbs the self-sustaining activation loop of JNK, instead of inhibiting JNK directly, and therefore would not be expected to inhibit the possible protective/beneficial effects of transient JNK activation in AILI [5]. However, given the possible high research costs to develop these compounds specifically for AILI, existing drugs with therapeutic potential in this hepatotoxicity model may be better choices. A case in point is metformin, a commonly used drug to treat type 2 diabetes mellitus. Convincing evidence has demonstrated that the protective and therapeutic effects of metformin against AILI were dependent on the inhibition of p-JNK through up-regulation of Gadd45β [59]. Interestingly, a follow-up study found that neither prenor post-treatment of metformin against APAP hepatotoxicity inhibited JNK activation or its mitochondrial translocation [31,32]. Although AMPK dependent signaling pathway and autophagy were excluded from hepatoprotective mechanism of metformin [59], there are still many events probably being involved in the protective effects, including inhibition of hepatic gluconeogenesis, MPT and ROS production [55]. Taken together, further work will be needed to determine the exact mechanisms of metformin against APAP hepatotoxicity.

3.2. p53

The p53 tumor suppressor protein plays a crucial role in modulation of cell cycle, apoptosis, senescence and metabolism in response to diverse stimuli such as cellular stress and DNA damage [65]. Once activated, p53 promotes cell survival and repair of genetic damage (through target genes that mediate cell cycle arrest and facilitate DNA repair) in response to moderate cellular stress and damage; however, upon lethal levels of ROS and/or severe DNA damage, cells cannot be repaired and saved, then they would be eliminated permanently by high levels of p53-mediated cell death. This notion was confirmed in numerous conditions, under which the role of p53 was complicated and

dependent on the pathology of disease [65]. Hence, not surprisingly, p53 is also activated by oxidative stress in APAP hepatotoxicity [116], and its role in pathogenesis is stage specific [14]. Activated p53 plays a protective role during injury phase of APAP hepatotoxicity through inhibiting the activation of JNK [46], whereas it delays progression of liver repair in regeneration phase [14]. As such, p53 may not be a promising target for AILI due to the dual role of p53 in the pathogenesis of APAP-induced hepatotoxicity.

3.3. Nrf2

Apart from p53, many other compensatory pro-survival signaling pathways are activated in response to oxidative stress following hepatotoxic doses of APAP. The most well-established among them appears to be nuclear factor erythroid 2-related factor 2 (Nrf2), which is likely activated by redox status changes of the kelch-like ECH associated protein 1 (Keap1) induced by NAPQI. Mechanistically, Nrf2 activation leads to transcriptional activation of antioxidant enzymes, including microsomal epoxide hydrolase, heme oxygense-1 (HO-1), NADPH: quinone oxidoreductase 1 (NQO-1), and glutamate cysteine ligase (GCL), which catalyzes the initial and rate-limiting step in GSH synthesis. These antioxidant enzymes activated by Nrf2 act as cell defense system to detoxify NAPQI [35]. In addition to being activated by NAPQI directly, some other mechanisms are also involved in the activation and/or regulation of Nrf2 signaling pathway, including protein tyrosine phosphatase 1B (PTP1B) [79], fibroblast growth factor 21 (FGF21) [128] and M1 muscarinic receptors (M1R) [114]. In mice that lack PTP1B or M1R, APAP hepatotoxicity was attenuated through enhanced hepatic Nrf2 system, suggesting that PTP1B and M1R may serve as novel therapeutic targets against AILI. As for FGF21, remarkable elevation of this hormone by APAP overdose enhanced Nrf2-mediated antioxidant capacity through peroxisome proliferator-activated receptor coactivator protein-1α (PGC-1α), representing a compensatory mechanism to protect against APAP hepatotoxicity [128]. Given the positive role of Nrf2 in alleviating oxidative stress, many bioactive components that could further activate this adaptive, protective signaling pathway are reported to exert protective effects against APAP-induced hepatotoxicity (Table 1). Of note, the effects of these natural products on APAP hepatotoxicity were tested only by pretreatment method; however, therapeutic strategies would be more clinically relevant as APAP intoxication is unpredictable and patients with AILI often present late for medical treatment. Therefore, further study is needed to establish their efficacy in the clinically relevant therapeutic models. Another concern regarding these studies is the omission of specific assessment of their impact on APAP metabolism. Given the fact that APAP toxicity is initiated by metabolism through cytochrome P450 enzymes, any subtle interference with the formation of reactive metabolite NAPQI and accumulation of APAP protein adducts (APAP-ADs) can produce a profound impact on the outcome of APAP-induced liver injury. This omission challenges the causal relationships between Nrf2 activation induced by these natural products and their hepatoprotective effects on AILI.

3.4. Therapeutic approaches targeting other signaling pathways

In light of previous studies, mitochondrial oxidative stress is recognized as the critical event in APAP hepatotoxicity. Therefore, researches toward therapeutic approaches mainly focused on how to alleviate this event. Based on above, a large number of natural compounds have been studied and showed the potential to treat APAP-induced liver injury through antioxidant capacity (Table 2). Although it was claimed in these studies that the antioxidant capacity of these natural products were due to the enhanced levels of GSH, superoxide dismutase, catalase and other antioxidant enzymes, these could be also attributed to the APAP metabolism inhibition or a faster recovery from hepatotoxicity due to less injury. A tome-course instead of a single time point study to monitor the dynamic changes of NAPQI formation would be helpful to determine the contributions of these mechanisms. Moreover, when compared with the current standard antidote NAC, they could not offer more outstanding therapeutic effects. Hence, compounds with new mechanisms to protect mitochondrial beyond NAC may be better choices. More recently, a mitochondrial targeted antioxidant Mito-Tempo was reported to protect against AILI even at 3 h post-treatment of APAP compared with NAC alone, suggesting it as a potential therapeutic option for patients at late phase in APAP poisoning [29]. Another existing drug being proved to have hepatoprotective properties in APAP model is methylene blue, a clinically used antidote that can permeate through mitochondrial membranes. This medication effectively restores the ETC function and maintains mitochondrial bioenergy homeostasis by acting as an electron carrier substitute for impaired complex II, thus protecting mice from AILI [69].

4. Targeting autophagy for AILI treatment

Autophagy is a tightly regulated cellular process that renew cell through removing unwanted cytoplasmic contents, including misfolded or aggregated proteins, accumulated lipids, excessive or damaged organelles and harmful pathogens, via lysosomal degradation [80]. It is believed that APAP overdose can cause mitochondria damage and APAP-ADs accumulation in hepatocytes, resulting in hepatic necrosis and liver injury [75]. Therefore, it comes as no surprise that autophagy, serving as a protective mechanism to maintain cellular homeostasis, is activated in response to severe cellular stress caused by APAP. Moreover, pharmacological induction of autophagy by rapamycin alleviates APAP hepatotoxicity through removal of damaged mitochondria and detrimental APAP-ADs [86,87], indicating the induction of autophagy as a novel therapeutic approach for AILI.

However, the exact molecular mechanisms involved in APAP-induced autophagy remain unclear. Generally, the energy sensor AMPK can activate autophagy through inhibition of mammalian target of rapamycin complex 1 (mTORC1). Indeed, mTORC1 is inhibited following APAP overdose. Moreover, a recent study has described a role of adiponectin in promoting autophagy through activation of the AMPK signaling pathway [73]. Conversely, in other studies, p-AMPK was inhibited in responds to APAP intoxication [100,47]. Despite these contradictory observations, there is no doubt that activation of AMPK leads

Table 1
Protective effects of bioactive natural components in APAP-induced hepatotoxicity through Nrf2 activation.

Bioactive components	Effective dose	Pretreatment	Animal models/APAP dose	Mechanisms	Refs.
Withaferin A	7 mg/kg i.g.	24 h	C57BL/6J mice, 250 mg/kg i.p.	Pten/PI3k/Akt dependent activation of Nrf2	[90]
Tanshinone IIA	10–30 mg/kg p.o.	4 days	C57BL/6J, 300 mg/kg i.p.	Nrf2 activation	[118]
Quercitrin from *Toona sinensis* (Juss.) M.Roem.	10–50 mg/kg i.g.	7 days	Balb/c mice, 300 mg/kg i.p.	↓Oxidative stress, inflammation	[112]
Caffeic acid	10–30 mg/kg p.o.	7 days	ICR mice, 400 mg/kg p.o.	Keap1/Nrf2/HO-1, NQO1 activation	[91]
Esculentoside A	2.5 mg/kg i.p.	24 and 12 h	Balb/c mice, 400 mg/kg	Activation of Nrf2 through AMPK/Akt/GSK3β	[117]
Carnosic acid	100 mg/kg i.g.	3 days	C57BL/6J mice,400 mg/kg i.p.	↑Nrf2 nuclear translocation	[39]
Schisandrol B	200 mg/kg, i.g.	3 days	C57BL/6 mice, 400 mg/kg i.p.	Activation of Nrf2/ARE	[53]
Formononetin	50–100 mg/kg p.o.	7 days	Balb/c mice, 300 mg/kg i.p.	Nrf2 activation	[54]

Table 2
Antioxidant effects of bioactive natural components in APAP-induced hepatotoxicity.

Bioactive components	Effective dose	Animals models/APAP dose	Mechanisms	Refs.
Magnolol	0.01–1 μg/kg i.p.	Sprague-Dawley rat, 500 mg/kg i.p.	↓TBARS; ↑GSH	[19]
Gallic acid	100 mg/kg i.p.	Swiss albino mice, 900 mg/kg i.p.	↑SOD, CAT, GPx, GR, GST and GSH	[97]
6-Gingerol	30 mg/kg i.p.	Swiss albino mice, 900 mg/kg i.p.	↑SOD, CAT, GPx, GR, GST and GSH	[101]
Curcumin	10–20 mg/kg i.p.	BALB/c mice, 300 mg/kg i.p.	↑SOD; ↓MDA, apoptosis	[72]
Thearubigins	60 mg/kg i.p.	Swiss mice, 300 mg/kg i.p.	↓MDA,	[81]
Baicalin	30 mg/kg i.p.	C57BL/6 mice, 300 mg/kg i.p.	↓MDA, TNF-α, IL-17, IL-6	[71]
Paeonol	100 mg/kg i.g.	C57BL/6 mice, 400 mg/kg i.p.	↑SOD, GPx and GSH; ↓MDA, inflammation	[28]
Methanol extract of *Fagonia olivieri* DC.	200–400 mg/kg i.g. for 7 days	Sprague-Dawley rats, 700 mg/kg i.g.	↑SOD, CAT,GPx, GR and GSH	[96]
Lophirones B and C	20 mg/kg p.o. for 7 days	Swiss mice, 300 mg/kg	↑SOD, CAT, GPx;↓inflammation	[3]
Hydroglycol extract of red rice	128–512 mg/kg p.o. for 30 days	ICR mice, 60 mg/kg p.o. for 30 days	↑GSH; ↓GSSH	[109]
Methanol extract of *Adansonia digitata* L. (Malvaceae)	200 mg/kg p.o. for 7 days	Wistar rats,2 g/kg p.o. for 3 days	↑SOD, CAT and GSH; ↓MDA	[40]
Quercitrin from *Toona sinensis* (Juss.) M.Roem.	10–50 mg/kg i.g.	Balb/c mice, 300 mg/kg i.p.	↑SOD, CAT and GPx; ↓inflammation	[112]
Methanol extract of pomegranate peels	50 mg/kg p.o. for 14 days	Wistar rats, 750 mg/kg i.p.	↓Oxidative stress	[2]
Withanolide	50–200 mg/kg p.o. for 14 days	Wistar rats, 750 mg/kg p.o.	↑SOD and GSH; ↓MDA, NO	[27]
Acetone extract of *Passiflora subpeltata* leaves	200–400 mg/kg for 14 days	Wistar rats, 2 g/kg p.o. for 14 days	↑SOD, CAT, GPx, GST and GSH	[108]
Opuntia robusta	800 mg/kg p.o. for 5 days	Wistar rats, 500 mg/kg i.p.	↑GSH	[36]
Aqueous extract of *Zea mays* L. (Poaceae) *Stigma maydis*	200–400 mg/kg p.o. for 14 days	Wistar rats, 400 mg/kg p.o. for 14 days	↑SOD, CAT, GPx, GR and GSH; ↓MDA	[102]
Silymarin	25 mg/kg p.o. for 14 days	Wistar rats, 800 mg/kg i.p. for 3 days	↑SOD, GPx; ↓NO	[88]
n-Hexane extract of *Acrocarpus fraxinifolius* leaves	250–500 mg/kg p.o. for 14 days	Wistar rats, 400 mg/kg p.o. for 7 days	↓MDA	[1]
Tormentic acid	1.25–5 mg/kg i.p. for 6 days	ICR mice, 400 mg/kg i.p.	↑SOD, CAT and GPx;↓NO, TNF-α, IL-1β	[52]
Methanol extract of *Dicranopteris linearis* L. leaves	50–500 mg/kg p.o. for 7 days	Sprague-Dawley rats, 3 g/kg	↑SOD, CAT	[132]
Methanol extract of black ginseng	300–600 mg/kg i.g. for 7 days	ICR mice, 250 mg/kg i.p.	↑GSH; ↓3-nitrotyrosine and MDA	[44]
Ginsenosides	150–300 mg/kg i.g. for 7 days	ICR mice, 250 mg/kg i.p.	↑GSH, SOD; ↓3-nitrotyrosine, MDA, COX-2	[127]
Tannic acid	25–50 mg/kg p.o. for 3 days	Kunming mice, 400 mg/kg i.p.	↑SOD, CAT, GPx; ↓MDA, NO, TNF-α, IL-1β	[134]
Rice peptides	100–500 mg/kg p.o. for 7 days	ICR mice, 700 mg/kg i.p.	↑GSH	[57]
Cymbopogon citratus Essential Oil	125–500 mg/kg for 7 days	Swiss mice, 250 mg/kg p.o.	↓MPO, NO	[113]
Iridoid glycosides fraction of *Veronica ciliata* Fisch.	150–450 mg/kg p.o. for 14 days	Kunming mice, 180 mg/kg i.p.	↑SOD, GSH; ↓MDA, TNF-α	[111]
Rutin	20 mg/kg p.o. for 11 days	Wistar rats, 500 mg/kg p.o. for 3 days	↑SOD, CAT, GPx and GSH;↓MDA	[98]
Astaxanthin	30–60 mg/kg i.g. for 14 days	C57BL/6, 300 mg/kg i.p.	↑SOD and GSH;↓MDA	[135]

TBARS, thiobarbituric acid reactive substances; SOD, superoxide dismutase; CAT, catalase; GPx, glutathione peroxidase; GR, glutathione reductase; glutathione S-transferase; MDA, malonaldehyde; NO, nitric oxide; GSH, glutathione; GSSH, oxidized glutathione; IL-17, interleukin-17; IL-6, interleukin-6; TNF-α, tumor necrosis factor alpha; IL-1β, interleukin-1β; COX-2, cyclooxygenase 2.

to energy generation and promotion of survival signaling pathways, which finally protect against APAP-induced hepatotoxicity (Fig. 2).

5. Targeting endoplasmic reticulum stress for AILI treatment

ER stress can be observed in various hepatic injury models, including alcoholic liver disease, nonalcoholic fatty liver disease, ischemia-reperfusion injury and cholestatic liver disease [26]. Hence, it is not surprising that ER stress plays a role in APAP hepatotoxicity. This stress respond is initiated by impaired protein folding process, which is triggered by covalent binding of NAPQI to the ER proteins [119]. It is also conceivable that GSH depletion in the ER results in intraluminal redox imbalance, leading to phosphorylation of eIF2α and activation of ATF6 and CHOP [82,83]. Moreover, a recent study has found that CHOP plays a pro-damage role in response to APAP intoxication through inhibition of liver regeneration. This research, to some extent, clarified the role of unfolded protein response (UPR)/ER stress in mediating APAP-induced hepatotoxicity [115]. In light of these data, interventions to inhibit CHOP may be potential therapeutic strategies to treat APAP poisoning patients in whom liver damage has already been evident (Fig. 2).

6. Targeting glucose and lipid metabolism for AILI treatment

Mitochondria are key organelles that play an essential role in cell survival. One reason is that they are irreplaceable in control of many metabolic pathways, among which glucose metabolism and fatty acid β-oxidation are the most important. Hence, damaged mitochondria caused by APAP overdose inevitably lead to many metabolic changes in the liver. Metabolomics studies have shown that both the liver glucose and glycogen were depleted following APAP overdose [21]. There are two possible explanations for this observation: (1) both citric acid cycle and fatty acid β-oxidation are disrupted in response to mitochondria oxidative stress caused by APAP, resulting in ATP depletion. This mitochondrial malfunction then leads to compensatory increase of glycolysis [21]. (2) GSH depletion induced by APAP leads to decreased cellular NADPH/$NADP^+$ ratios, which is known to activate glucose-6-phosphate dehydrogenase allosterically to enhance oxidative pentose phosphate pathway flux. The increased flux is an attempt to maintain cellular NADPH level to reduce oxidized glutathione [131]. Consistent with this, fructose and fructose-1, 6-diphosphate were found to protect against cell injury in APAP-treated rat liver slices via maintaining high ATP levels [74]. However, sufficient dATP/ATP switched the hepatocytes injury from necrosis to caspase-dependent apoptosis [62]. This means supplementing ATP merely cannot rescue cell death in APAP hepatotoxicity.

As mentioned above, fatty acid β-oxidation is inhibited by APAP treatment, concomitant with compensatory increase of peroxisomal activity. Peroxisome proliferator-activated receptor α (PPARα) encodes peroxisomal and mitochondrial enzymes that promote fatty acid catabolism, and its protective effects against APAP toxicity were confirmed in several studies [16,85]. Although it was speculated that the

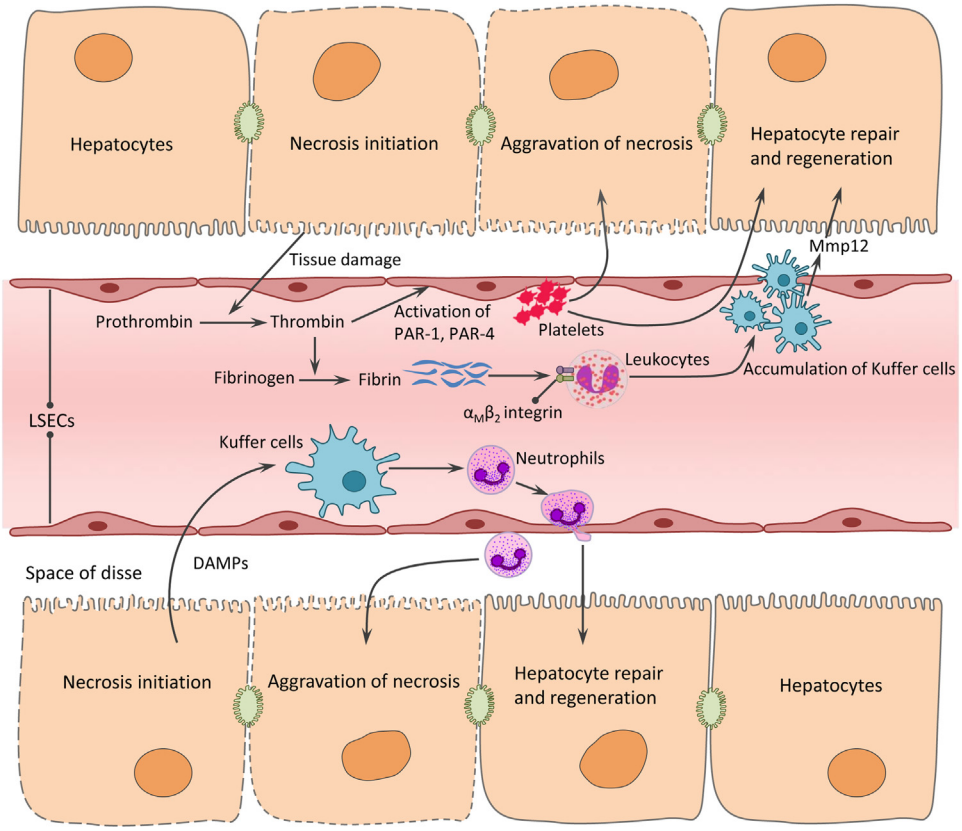

Fig. 3. Sterile inflammation and microcirculatory dysfunction induced by acetaminophen hepatotoxicity. DAMPs (including DNA fragments, HMGB1, uric acid and ATP) released from necrotic hepatocytes, transcriptional activate pro-inflammatory cytokines and chemokines in Kupffer cells. This causes neutrophils activation and recruited to the damage area of the liver, resulting in aggravation of hepatocytes necrosis at first, but contributing to liver repair and regeneration at a late stage. Tissue damage caused by APAP activate the coagulation system, concomitant with the generation of thrombin and formation of soluble and insoluble fibrin. Thrombin activates the platelets through downstream PAR-1 and PAR-4 signaling pathways, thereby exacerbates liver injury. During late stage, fibrin induced by thrombin contributes to liver repair through engagement of the leukocyte $\alpha_M\beta_2$ integrin and subsequent induction of Mmp12. DAMP, damage associated molecular pattern; HMGB1, high mobility group box-1 protein; LSEC, liver sinusoidal endothelial cell; PAR-1, proteinase-activated receptor 1; PAR-4, proteinase-activated receptor 4; Mmp12, matrix metalloproteinases 12.

protective effects of PPARα might depend on its role in facilitating fatty acid catabolism, a recent study showed that this protection is due in part to antioxidant function of the PPARα target gene mitochondrial uncoupling protein 2 (UCP2) [93].

7. Targeting sterile inflammation for AILI treatment

APAP-induced liver injury is characterized by hepatocyte necrosis, which causes release of cellular contents including nuclear DNA fragments [76], high mobility group box-1 protein [6], mitochondrial DNA [76], uric acid [63] and ATP [4]. These immune stimulatory factors function as damage-associated molecular patterns, which can transcriptionally activate pro-inflammatory cytokines (TNF-α, IL-1β, IL-6 and IL-10) and chemokines (MCP-1, MIP-2 and IL-8) [68,25,51]. As a result, neutrophils and later monocytes are activated and recruited to the damage area of the liver [68,7]. Unquestionably, APAP overdose provoke an acute inflammatory response (Fig. 3). However, the pathophysiological role of this response to APAP is still controversial-whether it contributes to the progression of liver injury or acts as cellular defense against toxicity [20,48,13,121]. Even though, there are still several studies targeting inflammation as therapeutic strategy. Benzyl alcohol (BA), often used as preservative when added to intravenous medication solutions, was shown to protect against AILI and reduce release of IL-1ß and IL-18 in a Toll-like receptor 4 (TLR4)-dependent manner [15]. However, mitochondrial toxic effect of this drug limits its clinical use for APAP overdose in patients [30]. Another case is resolvin, which was reported to attenuate APAP hepatotoxicity through inhibiting neutrophil migration into the liver. More importantly, resolvin given as late as 12 h after APAP was still protective, which means it extends the therapeutic window eight-fold compared to the standard antidote NAC [92].

Apart from its possible contributions to the progression of AILI, inflammation also helps to clear up dead cells and fragments and stimulates liver to repair and regenerate at a late stage [123]. That means inflammation may play a distinct role in different phases of the pathological process in APAP hepatotoxicity-e.g., a promoter in the injury phase and a helper in the regeneration phase. Hence, blockade of inflammation may protect at first, but actually be detrimental to the final outcomes. Hence, conclusions that BA and resolvin protect against AILI only relied on a single time point (24 h), making the results unconvincing. Therapeutic effects at late regeneration phase (24–72 h in mice) also need to be experimentally verified. The protective role of inflammation in APAP hepatotoxicity was confirmed by lactoferrin, a multifunctional protein presented in human colostrum and cow milk. This globular glycoprotein has been demonstrated to regulate inflammatory responses, as it is part of the innate immunity defense system and can modulate immune cell functions. Consistent with this, lactoferrin was found to inhibit APAP-induced liver sinusoidal endothelial cell damage and improved hepatic microcirculatory dysfunction through activation of Kupffer cells [129]. Taken together, the role of inflammation in AILI remains under considerable debate, and this makes it controversial to be as a therapeutic target (Fig. 3).

8. Targeting microcirculatory dysfunction for AILI treatment

In addition to direct hepatocellular damage caused by APAP, hepatic microcirculatory dysfunction also plays a vital role in the pathogenesis of AILI. Liver sinusoidal endothelial cells (LSECs) are sensitive and damaged earlier than hepatocytes in man and animal models following APAP overdose [49]. LSECs and hepatocyte injury then lead to activation of the coagulation cascade and thrombocytopenia. Subsequently, disturbances of the hemostatic system contribute to AILI, at least in part via downstream protease-activated receptor-1 (PAR-1) signaling pathway. Consistent with this, pharmacological inhibition of coagulation by heparin and genetic approaches (mice deficient in either tissue factor or PAR-1) attenuate APAP hepatotoxicity at an early stage (6 h) [33]. However, PAR-1 mediates activation of platelets by thrombin neither in mouse nor in human; therefore, studies by

Miyakawa et al. [78] defined the role of platelets in promoting AILI, depending on the action of PAR-4 on LSECs, as speculated by the authors (Fig. 3). In light of the previous studies, anticoagulation with thrombin inhibitor dabigatran etexilate (DABI) reduces the early hepatotoxicity in AILI, but significantly exacerbates liver injury at 24 h after APAP administration due to the attenuated hepatocyte proliferation [64]. Given the fact that anticoagulation can regulate AILI both positively and negatively, therapeutic strategies targeted on hemostatic system remain uncertain and need to be addressed in the future.

9. Targeting liver repair and regeneration for AILI treatment

Cellular stress and tissue injury induced by APAP overdose ultimately lead to compensatory liver repair and regeneration, which is a critical determinant of final outcome in patients of AILI. Though it is beneficial and important in recovery from AILI, specific details and mechanisms of this process have not been fully studied.

Epidermal growth factor receptor (EGFR) is a highly expressed tyrosine kinase receptor in the liver, and its ligands are direct mitogens for hepatocytes [77]. Therefore, it is not surprising that EGFR was found to promote liver regeneration after APAP overdose. However, it is worth noting that inhibition of EGFR activation at an early time remarkably attenuates AILI, suggesting a dual role of EGFR in both initiation of liver injury and subsequent regeneration in APAP hepatotoxicity [11]. Hence, it seems impossible to develop EGFR inhibitors as therapeutic medications for AILI, as undesirable outcomes may occur due to its opposite effects at late phase.

The Wnt family proteins are growth regulators acting as ligands of Frizzled receptors in the liver. They inhibit β-catenin ubiquitination in the cytoplasm, and then allow its translocation to the nucleus, where it initiates transcription of multiple genes related to cell proliferation (including EGFR, c-Myc and cyclin D1) [77]. Given the positive role of the Wnt/β-catenin signaling pathway in partial hepatectomy model, it was assumed that it might also contribute to liver regeneration in AILI, which was then confirmed in some previous studies [8,110,11,12]. Furthermore, with glycogen synthase kinase 3 (GSK3) defined as canonical upstream regulator of β-catenin [12], sympathetic nervous system (SNS) has been found to stimulate the Wnt/β-catenin signaling pathway in AILI, at least in part via expansion of hepatic progenitor/oval cells, which are both targets and sources of Wnt ligands [110]. As such, SNS agonist isoproterenol (β-adrenoceptor agonist) showed its therapeutic potential against APAP hepatotoxicity. Moreover, in contrast to NAC, isoproterenol was still therapeutically effective even being administered in a late phase [110].

Although liver regeneration is generally undertaken by hepatocytes, there are still several other factors contributing to liver recovery from APAP hepatotoxicity, including hepatic microvasculature reconstitution and interactions between different cell types. Hepatocytes produce mitogenic growth factors for endothelial cells, such as vascular endothelial growth factor (VEGF), which was found to facilitate liver repair by reconstituting the sinusoids in AILI [56]. A recent study identified a crosstalk between intrahepatic coagulation and inflammation after APAP overdose, through which liver repair was stimulated. It is believed that repair in this case requires fibrin (ogen) (one of coagulation factors)-leukocyte $\alpha_M\beta_2$ integrin engagement and subsequent induction of matrix metalloproteinase 12 (Mmp12) [64]. However, the precise mechanism by which Mmp12 functions in liver repair has not been well understood. These results suggest the activation of fibrin (ogen)-$\alpha_M\beta_2$ integrin engagement as a therapeutic approach against APAP hepatotoxicity by stimulating liver repair and regeneration.

In short, as mentioned above, liver regeneration is a compensatory beneficial process in response to hepatocyte death and tissue injury, thus stimulation of this process would be a potential therapeutic strategy to manage APAP hepatotoxicity. However, it should be noted that prolonged liver regeneration triggered by inflammation, pathogens or toxins may have adverse effects leading to cirrhosis and even liver cancer [77], a concern that may also be reflected in preclinical and clinical use of stimulating liver regeneration to treat AILI.

10. Concluding remarks

The mechanisms of APAP-induced liver injury are highly complex and many intracellular and extracellular events are involved in this pathophysiological process, including metabolism of APAP, mitochondrial oxidative stress, ER stress, autophagy, sterile inflammation, microcirculatory dysfunction and liver regeneration. These events regulate various aspects of AILI, such as initiating the injury, mediating hepatocyte death directly, limiting cellular stress response, helping liver to repair and regenerate. Consequently, not only mitochondrial oxidative stress (well defined), but many other processes can be potential therapeutic targets to treat AILI. However, it should be noted that some cellular events might play paradoxical roles in different phases of AILI, making them both positively and negatively in regulating APAP hepatotoxicity. As such, therapeutic strategies targeted on these events may not be beneficial at last, a concern that has been reflected in certain preclinical studies. Overall, more studies are needed to further clarify the precise role of these time-dependent events in AILI, thus making the late phase therapy become possible in clinical.

Conflicts of interest

The authors declare no conflicts of interest.

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