



HAL
open science

Acetaminophen-Induced Hepatotoxicity in Obesity and Nonalcoholic Fatty Liver Disease: A Critical Review

Karima Begriche, Clémence Penhoat, Pénélope Bernabeu-Gentey, Julie Massart, Bernard Fromenty

► **To cite this version:**

Karima Begriche, Clémence Penhoat, Pénélope Bernabeu-Gentey, Julie Massart, Bernard Fromenty. Acetaminophen-Induced Hepatotoxicity in Obesity and Nonalcoholic Fatty Liver Disease: A Critical Review. *Livers*, 2023, 3 (1), pp.33-53. 10.3390/livers3010003 . hal-03972013

HAL Id: hal-03972013

<https://hal.science/hal-03972013>

Submitted on 3 Feb 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.


L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons Attribution 4.0 International License

Review

Acetaminophen-Induced Hepatotoxicity in Obesity and Nonalcoholic Fatty Liver Disease: A Critical Review

Karima Begriche, Clémence Penhoat, Pénélope Bernabeu-Gentey, Julie Massart  and Bernard Fromenty *

INSERM, Univ Rennes, INRAE, Institut NUMECAN (Nutrition Metabolisms and Cancer) UMR_A 1341, UMR_S 1241, F-35000 Rennes, France

* Correspondence: bernard.fromenty@inserm.fr; Tel.: +33-2-23-23-30-44

Abstract: The epidemic of obesity, type 2 diabetes and nonalcoholic liver disease (NAFLD) favors drug consumption, which augments the risk of adverse events including liver injury. For more than 30 years, a series of experimental and clinical investigations reported or suggested that the common pain reliever acetaminophen (APAP) could be more hepatotoxic in obesity and related metabolic diseases, at least after an overdose. Nonetheless, several investigations did not reproduce these data. This discrepancy might come from the extent of obesity and steatosis, accumulation of specific lipid species, mitochondrial dysfunction and diabetes-related parameters such as ketonemia and hyperglycemia. Among these factors, some of them seem pivotal for the induction of cytochrome P450 2E1 (CYP2E1), which favors the conversion of APAP to the toxic metabolite N-acetyl-*p*-benzoquinone imine (NAPQI). In contrast, other factors might explain why obesity and NAFLD are not always associated with more frequent or more severe APAP-induced acute hepatotoxicity, such as increased volume of distribution in the body, higher hepatic glucuronidation and reduced CYP3A4 activity. Accordingly, the occurrence and outcome of APAP-induced liver injury in an obese individual with NAFLD would depend on a delicate balance between metabolic factors that augment the generation of NAPQI and others that can mitigate hepatotoxicity.

Keywords: acetaminophen; drug-induced liver injury; obesity; nonalcoholic fatty liver disease; steatosis; nonalcoholic steatohepatitis; diabetes; cytochrome P450 2E1; fatty acids; mitochondria



Citation: Begriche, K.; Penhoat, C.; Bernabeu-Gentey, P.; Massart, J.; Fromenty, B.

Acetaminophen-Induced Hepatotoxicity in Obesity and Nonalcoholic Fatty Liver Disease: A Critical Review. *Livers* **2023**, *3*, 33–53. <https://doi.org/10.3390/livers3010003>

Academic Editor: James Luyendyk

Received: 12 December 2022

Revised: 22 December 2022

Accepted: 9 January 2023

Published: 12 January 2023



Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

The epidemic of obesity is associated with a steady rise in drug consumption in order to treat several associated diseases such as type 2 diabetes mellitus (T2DM), hypertension, atherosclerosis, dyslipidemia and osteoarthritis [1,2]. In addition, numerous drugs are currently being developed in order to specifically treat nonalcoholic fatty liver disease (NAFLD), which is frequently associated with obesity and overweight [3,4]. This implies increased polypharmacy among obese patients, which can augment the risk of adverse events including drug-induced liver injury (DILI) [5,6]. In line with this, recent investigations reported a higher frequency of DILI in patients with NAFLD [7,8]. More specifically, the common pain reliever acetaminophen (APAP) is one of the identified drugs that could be more hepatotoxic in obesity and NAFLD, at least after an overdose [9]. The present article reviews the clinical and experimental investigations published on APAP-induced liver injury in the context of these metabolic diseases and also discusses the possible reasons that might explain why some studies are discrepant from others. Because our previous review on this matter was published in 2014 [9], many recent investigations are now discussed in this updated review.

2. APAP Hepatotoxicity

2.1. General Overview

APAP, also referred to as paracetamol, is one of the most widely prescribed drugs for the management of pain and hyperthermia. The current maximum recommended

dosage of APAP is 4 g/day in adults even though the Food and Drug Administration (FDA) advises doses below 3.25 g/day for chronic use [10]. Although therapeutic doses of APAP can induce hepatic cytolysis in some patients [11,12], most cases of severe APAP-induced acute liver injury occur after accidental or intentional overdoses [13,14]. Actually, APAP is deemed to have a narrow therapeutic margin since as little as 7.5 g/day might be hazardous [15]. Currently, administration of N-acetylcysteine (NAC) is the only approved therapy to treat APAP overdose-induced liver injury in patients [10,14]. The rationale of NAC administration is to restore hepatic levels of glutathione (GSH), a major endogenous antioxidant limiting the noxious effects of the APAP toxic metabolite N-acetyl-*p*-benzoquinone imine (NAPQI) (Figure 1) [16,17]. Notably, repeated or long-term intake of APAP at therapeutic doses can occasionally cause acute hepatic cytolysis of different severities [11,12] but also chronic liver injury such as granulomatous hepatitis and cirrhosis [18–20].

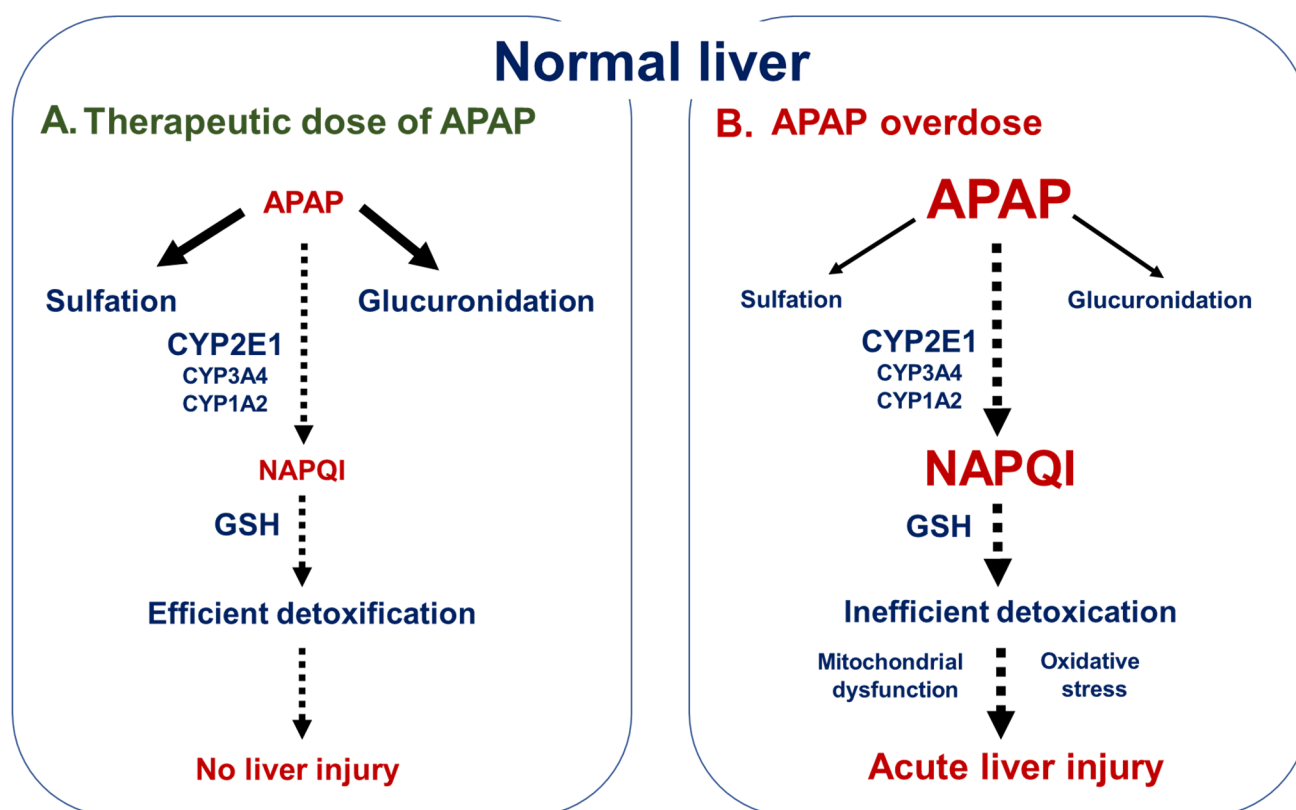


Figure 1. Biotransformation and toxicity of APAP in normal liver. **(A).** For therapeutic dose, APAP is mainly detoxified through sulfation and glucuronidation, while a small proportion is metabolized to N-acetyl-*p*-benzoquinone imine (NAPQI) via the cytochrome P450 2E1 (CYP2E1) and to a lesser extent CYP3A4 and CYP1A2. In normal liver, the low amounts of NAPQI are efficiently detoxified by glutathione (GSH), a major antioxidant molecule present in different cellular compartments including mitochondria. **(B).** After APAP overdoses, the sulfation and glucuronidation pathways are overwhelmed and more APAP undergoes CYP-dependent oxidation to NAPQI. However, GSH concentrations in hepatocytes are not sufficient to allow the efficient detoxification of NAPQI, which then induces major mitochondrial dysfunction, oxidative stress and acute liver injury. More information is provided in the text.

A key player in APAP liver injury is cytochrome P450 2E1 (CYP2E1), an enzyme that catalyzes the oxidation of APAP to NAPQI (Figure 1) [10,21,22]. Indeed, NAPQI is a highly reactive metabolite inducing severe mitochondrial dysfunction, overproduction of reactive oxygen species (ROS), and c-jun N-terminal kinase (JNK) activation, eventually leading to ATP depletion and massive hepatocellular necrosis [17,22,23]. Importantly, mitochondrial CYP2E1 could play a major role in APAP-induced cytotoxicity [24,25]. Finally, CYP3A4

(referred to as CYP3A2 in rats and CYP3A11 in mice) and CYP1A2 might also play a role in the conversion of APAP to NAPQI (Figure 1), although to a lesser extent than CYP2E1 in normal physiological conditions [26,27].

2.2. Predisposing Factors

Except for APAP ingested dose, APAP-induced hepatotoxicity could be favored by different factors such as chronic alcohol abuse, severe or chronic liver diseases, prolonged fasting and malnutrition, older age, and some comedications such as antituberculosis and antiepileptic drugs [12,16,28,29]. Importantly, increased activity of hepatic CYP2E1 (and possibly other CYPs) seems to be a common mechanism whereby chronic alcohol abuse, prolonged fasting and some comedications favor APAP-induced liver injury [16,30]. As discussed in this review, obesity, NAFLD and both types 1 and 2 diabetes could also predispose to APAP liver injury, at least in part, due to higher hepatic CYP2E1 activity [9,10,13]. Finally, the risk of APAP hepatotoxicity could be modulated by polymorphisms in different genes [16], such as *UGT1A* encoding UDP-glucuronosyltransferase (UGT) 1A, which plays a pivotal role in APAP glucuronidation and detoxification (Figure 1) [28,31].

3. APAP Hepatotoxicity in NAFLD

3.1. Main Features of NAFLD

Because of the epidemic of obesity and T2DM, NAFLD is now the most frequent chronic liver disease worldwide with a global prevalence of 25% [32]. NAFLD comprises a large spectrum of histologic changes including simple fatty liver, nonalcoholic steatohepatitis (NASH), advanced fibrosis and cirrhosis [33], which can evolve into hepatocellular carcinoma (HCC) [34]. It is estimated that simple fatty liver progresses to NASH in about 10 to 20% of the patients [35]. NASH itself is defined by the presence of steatosis (mostly macrovacuolar), some necrosis and apoptosis, hepatocellular ballooning and lobular inflammation [33]. Of note, the presence of microvesicular steatosis has been associated with histological markers of NASH severity [36]. Although the mechanisms of progression of fatty liver to NASH in some patients are not fully understood, mitochondrial dysfunction, oxidative stress and lipid peroxidation are deemed to play a primary role in the occurrence of cell death and inflammation [37–39].

3.2. Clinical Investigations on Acute APAP Hepatotoxicity in Obesity and NAFLD

There is some clinical evidence that obesity and NAFLD can predispose to APAP hepatotoxicity in the setting of APAP overdose (Table 1). Two large retrospective studies reported that APAP-induced acute liver injury was more frequent in NAFLD patients [40,41]. In these studies, patients with pre-existing NAFLD hospitalized for APAP overdose had a four- to sevenfold higher prevalence of acute liver injury as compared to those without NAFLD [40,41]. In another study, APAP-induced acute liver injury was more frequent in overweight or obese patients, but NAFLD presence was not investigated [42]. Obesity might also favor APAP hepatotoxicity when this analgesic and antipyretic drug is taken at therapeutic doses. Indeed, mild to moderate hepatic cytolysis, as evidenced by increased plasma transaminases (ALT and AST), was reported in some morbidly obese patients but not in nonobese individuals after receiving 4–5 g of intravenous APAP [43].

In contrast to these studies, the occurrence of APAP-induced acute liver injury was reported to be similar, or even lower, in obese patients compared to nonobese individuals (Table 1) [44,45]. However, one of these studies showed that obese patients had significantly poorer clinical outcomes after acute liver failure [44]. The discrepancies between the aforementioned studies might arise from several factors including the degree of obesity, the existence of NASH and advanced fibrosis and the presence of insulin resistance and T2DM. Indeed, these factors could alter APAP absorption, distribution, metabolism and excretion (ADME) but also basal antioxidant defenses and mitochondrial function, as discussed in Section 4.

Table 1. Summary of the clinical studies (ordered by increasing year) carried out on APAP-induced acute liver injury in obesity and NAFLD.

Authors, Year [References]	Design of the Study	Presence of NAFLD	Hepatic CYP2E1 Activity	APAP Overdose	APAP-Induced Acute Liver Injury
Rutherford et al., 2006 [44]	Prospective	Not reported in this study ¹	Not reported in this study	Yes	Lower incidence (but poorer outcomes) in obese patients
Nguyen et al., 2008 [40]	Retrospective	Yes	Not reported in this study	Yes	Higher prevalence in patients with NAFLD
Myers and Shaheen, 2009 [41]	Retrospective	Yes	Not reported in this study	Yes	Higher prevalence in patients with NAFLD
Radosevich et al., 2016 [45]	Retrospective	Not reported in this study ¹	Not reported in this study	Yes	Equal prevalence between obese and nonobese patients
Van Rongen et al., 2016 [43]	Prospective	Not reported in this study ¹	Increased	No (4 to 5 g)	Increased plasma ALT and AST in morbidly obese patients but not in nonobese individuals
Chomchai and Chomchai, 2018 [42]	Retrospective	Not reported in this study ¹	Not reported in this study	Yes	Higher prevalence in overweight and obese patients

¹ There is now ample evidence that obesity is strongly associated with NAFLD (reviewed in [32,35]).

3.3. Rodent Studies on Acute APAP Hepatotoxicity in Obesity and NAFLD

APAP-induced acute hepatotoxicity has also been investigated in different rodent models of obesity and NAFLD (Table 2). However, while several investigations reported greater APAP hepatotoxicity in obese rodents [9,46–53], others showed no difference or even lower APAP-induced liver injury compared to lean rodents [9,46,54–57]. In addition to some factors mentioned in the previous section, discrepancies between these experimental investigations might be due to differences in the rodent model (rats vs. mice), the origin of obesity (genetic vs. diet-induced) and the composition of the hypercaloric diet, as discussed in Section 4.

In some aforementioned investigations, APAP not only caused more severe hepatic cytolysis in obese mice (as evidenced by increased ALT and AST) but also worsened liver fat accumulation through a mechanism that might involve inhibition of autophagy and exacerbation of oxidative stress [52,53]. Interestingly, aggravation of steatosis was also observed in ob/ob mice acutely intoxicated with APAP although this was not associated with higher plasma transaminases and more severe hepatic necrosis [49]. In NAFLD, distinct mechanisms might thus be involved in APAP-induced hepatic cytolysis and worsening of steatosis, respectively.

Table 2. Summary of the rodent studies (ordered by increasing year) carried out on APAP-induced hepatotoxicity in obesity and NAFLD.

Authors, Year [References]	Rodent Models of Obesity and NAFLD	Presence of NAFLD	Hepatic CYP2E1 Activity	Dose of APAP	APAP-Induced Hepatotoxicity
Corcoran and Wong, 1987 [47]	Male Sprague–Dawley rats fed a high-fat diet for 24 weeks	Not reported in this study ¹	Not reported in this study	710 mg/kg (i.p.)	Higher hepatotoxicity after 48 h, compared to rats fed a standard diet
Blouin et al., 1987 [58]	Male obese Zucker fa/fa rats	Not reported in this study ²	Not reported in this study ²	1300 mg (p.o.)	Similar hepatotoxicity after 48 h, compared to lean rats

Table 2. Cont.

Authors, Year [References]	Rodent Models of Obesity and NAFLD	Presence of NAFLD	Hepatic CYP2E1 Activity	Dose of APAP	APAP-Induced Hepatotoxicity
Tuntaterdtum et al., 1993 [54].	Male obese Zucker fa/fa rats	Not reported in this study ²	Not reported in this study ²	3000 mg/kg (p.o.)	Lower hepatotoxicity after 48 h, compared to lean rats
Ito et al., 2006 [55]	Male C57Bl/6 mice fed a Western-style diet for 16 weeks	Yes	Not reported in this study	300 mg/kg (p.o.)	Lower hepatotoxicity after 6 h, compared to mice fed a standard diet
	Male ob/ob mice	Not reported in this study ³	Not reported in this study ³	300 mg/kg (p.o.)	Lower hepatotoxicity after 6 h, compared to wild-type mice
Donthamsetty et al., 2008 [59]	Male Swiss Webster mice fed a MCD diet for 1 month ⁴	Yes	Unchanged	360 mg/kg (i.p.)	Higher hepatotoxicity from 6 to 48 h after overdose, compared to mice fed a standard diet
Kon et al., 2010 [48]	Male KK-A ^y mice	Yes	Not reported in this study ⁵	300 or 600 mg/kg (p.o.)	Higher hepatotoxicity after 6 h, compared to wild-type mice
Kucera et al., 2012 [50]	Male Sprague-Dawley rats fed a high-fat diet for 6 weeks	Yes	Not reported in this study	1 g/kg (p.o.)	Higher hepatotoxicity after 24 and 48 h, compared to rats fed a standard diet
Aubert et al., 2012 [49]	Female db/db mice	Yes	Increased	500 mg/kg (p.o.)	Higher hepatotoxicity after 8 h, compared to wild-type mice
	Female ob/ob mice	Yes	Unchanged	500 mg/kg (p.o.)	Similar hepatotoxicity after 8 h, compared to wild-type mice
Kim et al., 2017 [56]	Male C57Bl/6 mice fed a fast food diet for 14 weeks	Yes	Not reported in this study (but higher CYP2E1 protein levels)	200 mg/kg (i.p.)	Lower hepatotoxicity compared to wild-type mice (timing not specified)
Piccinin et al., 2019 [51]	Male FVB/N mice fed a high-fat diet for 1 month	Yes	Not reported in this study	300 mg/kg (i.p.)	Higher hepatotoxicity after 6 h, compared to wild-type mice
Shi et al., 2019 [52]	Male C57Bl/6 mice fed a high-fat diet for 8 weeks	Yes	Not reported in this study	50, 100 or 200 mg/kg (p.o.)	Significant hepatotoxicity after 24 h but no comparison with wild-type mice
Wang et al., 2021 [53]	Male C57Bl/6J mice fed a high-fat diet for 8 weeks	Yes	Not reported in this study	100 mg/kg (p.o.)	Significant hepatotoxicity after 24 h but no comparison with wild-type mice
Ghallab et al., 2021 [57]	Male C57Bl/6N mice fed a Western diet for 48 to 50 weeks	Yes	Not reported in this study (but lower CYP2E1 immunostaining)	300 mg/kg (i.p.)	Lower hepatotoxicity compared to wild-type mice (timing not specified)

¹ Numerous investigations in rodents including rats showed that long-term feeding of high-fat diets consistently induces NAFLD (reviewed in [60–62]). ² Other studies showed that male obese and insulin resistant Zucker fa/fa rats present moderate fatty liver [63,64] but reduced CYP2E1 activity [63,65]. ³ Other investigations showed that male obese and diabetic ob/ob mice present major fatty liver [66,67], with unchanged [49] or reduced [68] CYP2E1 activity. ⁴ Methionine and choline-deficient (MCD) diet is known to induce NASH, which is however associated with reduced body weight and blood glycemia [9,60]. ⁵ Previous studies showed that hepatic CYP2E1 mRNA expression [69] and activity [70] are unchanged in KK-A^y mice.

3.4. *In Vitro* Studies on Acute APAP Hepatotoxicity in Models of Fatty Acid Exposure and NAFLD

Several *in vitro* studies investigated APAP acute cytotoxicity in different models of fatty acid exposure and NAFLD. Two studies were carried out in hepatocytes isolated from rats fed different types of lipids. The first study reported that liver slices from rats fed a diet rich in butter (which mainly contains saturated fatty acids) were significantly more sensitive to APAP cytotoxicity than those from rats fed a diet enriched in polyunsaturated fatty acids (PUFAs) [71]. Unfortunately, lipid accumulation was not evaluated in this study nor were included liver slices from rats fed a standard diet. Nevertheless, this study suggests that exposure to long-chain saturated fatty acids could be more detrimental than to polyunsaturated linoleic acid (C18:2) and arachidonic acid (C20:4) [71]. In the second study, steatotic primary hepatocytes isolated from rats fed a diet enriched in corn oil (which mainly contains PUFAs) were more sensitive to APAP cytotoxicity than those from rats fed a standard diet [72]. The role of n-3 PUFAs (also referred to as ω -3 PUFAs) in APAP hepatotoxicity is discussed in Section 4.2.5.

Two other studies were performed in hepatocyte cell lines incubated with different fatty acids. In the first study, carried out in L02 liver cells, the investigations showed that a 24 h exposure to the monounsaturated oleic acid (C18:1) exacerbated APAP cytotoxicity whereas different medium chain fatty acids did not cause this effect [73]. Unfortunately, this study did not determine whether these different fatty acids induced steatosis in L02 liver cells. Other investigations performed in differentiated HepaRG cells incubated 7 days with stearic acid (C18:0) or oleic acid (which both induced steatosis) showed that only stearate supplementation induced greater APAP-induced cytotoxicity, which was blunted by the CYP2E1 inhibitor chlormethiazole [74]. The apparent discrepancy between these two studies could be due to the cell lines and the duration of oleic acid exposure. Nonetheless, these *in vitro* investigations clearly indicate that exposure to some fatty acids could favor APAP hepatotoxicity. Although this might be due to their propensity to induce CYP2E1, other possible mechanisms cannot be excluded, as briefly discussed in Section 4.1.3.

Finally, *in vitro* investigations also reported that APAP worsened lipid deposition in steatotic L02 cells [52,53], thus confirming *in vivo* results in diet-induced and genetically obese mice [49,52,53]. However, steatosis in L02 cells was induced by cotreating the cells with oleic acid and ethanol, which does not reflect pure NAFLD. Nevertheless, these investigations suggest that acute APAP could aggravate steatosis through a direct effect on hepatocytes and not via extrahepatic pathways such as fat mobilization from adipose tissue [75,76].

3.5. *Investigations on Chronic APAP Hepatotoxicity in Obesity and NAFLD*

Repeated or chronic intake of therapeutic doses of APAP can sporadically cause different types of liver injury, as previously mentioned [18–20]. Unfortunately, there are no clinical studies investigating the occurrence of repeated or chronic APAP hepatotoxicity in obesity and NAFLD. In rodents, a 13-week treatment with APAP was less hepatotoxic in leptin receptor-deficient obese (fa/fa) Zucker rats than in lean rats [77]. According to the authors, this might be explained by lower hepatic CYP2E1 expression in obese Zucker rats [77]. This is in line with previous studies showing downregulation of hepatic CYP2E1 in obese Zucker rats [63,68] and lower acute APAP hepatotoxicity in obese Zucker rats compared with their lean littermates [54]. The role of the adipokine leptin in CYP2E1 expression is briefly discussed in Section 4.2.2. In another study, a 35-day treatment with APAP caused more severe hepatic cytolysis in spontaneously diabetic torii (SDT) rats as compared to nondiabetic rats [78]. While SDT rats are not obese, this study did not investigate fatty liver [78]. APAP hepatotoxicity in type 1 diabetes is discussed in Section 6.

4. Factors Modulating APAP Hepatotoxicity in Obesity and NAFLD

From the abovementioned studies carried out in humans and rodents, it appears that obesity and NAFLD do not always increase the risk or the severity of APAP-induced liver

injury. Hence, while several factors would favor APAP hepatotoxicity in these metabolic diseases, others might limit APAP toxicity.

4.1. Factors That Could Favor APAP Hepatotoxicity in Obesity and NAFLD

4.1.1. CYP2E1 Induction

Hepatic CYP2E1 induction could be a major mechanism associated with greater APAP hepatotoxicity observed in most clinical and experimental studies (Figure 2A), although other explanations can be considered as discussed below. Indeed, higher CYP2E1 activity is expected to cause an overproduction of NAPQI and deeper GSH depletion, thus leading to more severe mitochondrial dysfunction and oxidative stress [9,13,79]. In line with this hypothesis, the study by van Rongen et al. reported higher CYP2E1 activity in morbidly obese patients, which was associated with mild to moderate hepatic cytolysis after administration of 4–5 g of APAP [43]. However, CYP2E1 activity was not determined in the other investigations reporting a higher risk of APAP-induced liver injury in patients with obesity and NAFLD [40–42]. Experimentally, investigations in ob/ob and db/db obese mice showed that APAP hepatotoxicity correlated with hepatic CYP2E1 activity but not with liver fat accumulation [49]. Unfortunately, most other rodent studies showing higher APAP hepatotoxicity in obese animals did not investigate CYP2E1 expression, or activity [47,48,50–53].

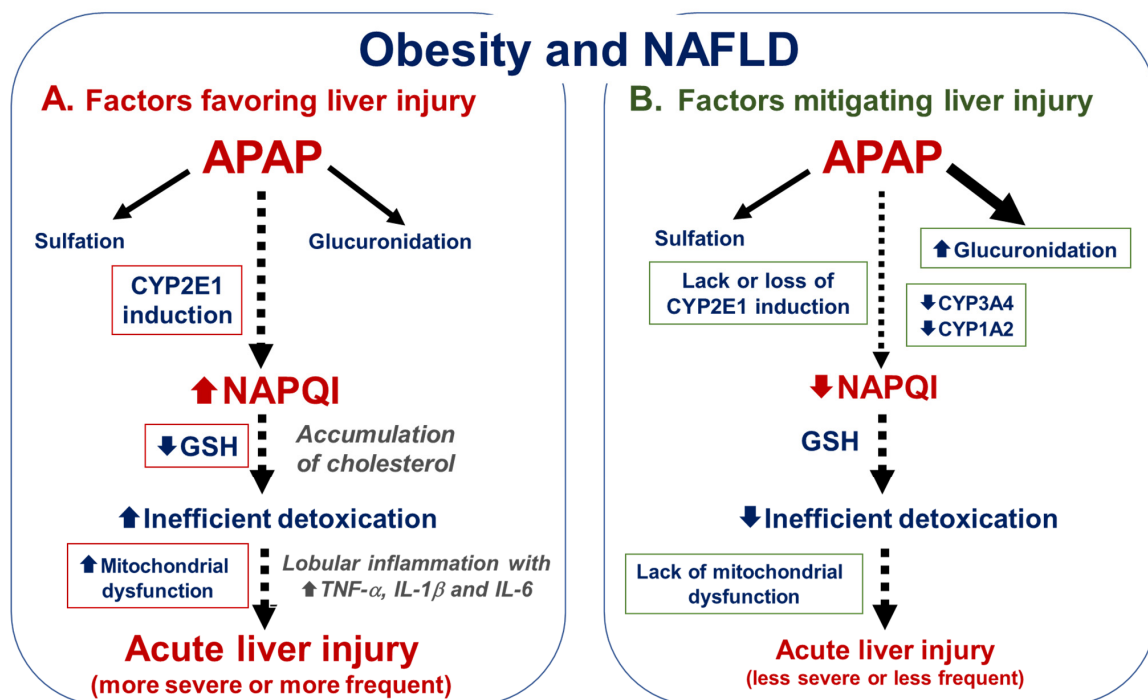


Figure 2. Hepatotoxicity of APAP in obesity and NAFLD. **(A).** Different factors in obesity and NAFLD could favor liver injury induced by APAP overdose, for instance by increasing cytochrome P450 2E1 (CYP2E1) activity, reducing basal concentrations of glutathione (GSH) and promoting preexisting mitochondrial dysfunction. In addition, the accumulation of cholesterol could sensitize the liver to APAP-induced hepatotoxicity by favoring mitochondrial GSH depletion. Lobular inflammation might also favor APAP hepatotoxicity via several cytokines such as tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β) and IL-6. **(B).** On the contrary, some factors in obesity and NAFLD could mitigate APAP-induced liver injury, for instance by increasing APAP glucuronidation and reducing CYP3A4 and CYP1A2 activity. Moreover, CYP2E1 induction could be absent or lost in some metabolic and pathological conditions. The absence of preexisting mitochondrial dysfunction in some patients might also mitigate APAP-induced hepatotoxicity. Consequently, obese people with one or several of these mitigating factors might not have a higher risk of severe APAP-induced liver injury. More information is provided in the text.

In a study carried out in mice fed a fast food diet enriched in saturated fatty acids, cholesterol and fructose, less severe APAP liver injury was observed despite enhanced hepatic CYP2E1 protein expression but CYP2E1 activity was not measured [56]. Adaptive responses in different antioxidant and anti-inflammatory pathways might explain this protective effect in this mouse model of obesity [56]. Conversely, higher APAP hepatotoxicity was observed in a mouse model of NASH despite unchanged CYP2E1 activity [59]. Although the reasons for the lack of CYP2E1 induction are unclear, it should be underlined that NASH was induced in this work with a methionine and choline-deficient (MCD) diet [59], which significantly reduces body weight and blood glycemia and does not cause systemic insulin resistance [9,60]. Hence, this peculiar metabolic profile might have removed some cues that otherwise might have led to CYP2E1 induction, as discussed in Section 4.2.2.

Hepatic CYP2E1 induction is a salient feature of obesity and NAFLD. Indeed, many clinical investigations consistently reported higher hepatic CYP2E1 expression and activity in patients with these metabolic diseases [9,43,80–85]. Hepatic CYP2E1 induction has also been found in many studies performed in different rodent models of obesity and NAFLD [49,57,82,86–91], although there are some exceptions as mentioned in Section 4.2.2.

Hepatic CYP2E1 induction in obese patients would not only cause more frequent or more severe APAP hepatotoxicity but may also favor the transition of fatty liver to NASH [82,89,92–94]. In steatotic hepatocytes, ROS overproduction secondary to CYP2E1 induction is indeed deemed to cause lipid peroxidation and the generation of noxious reactive aldehydes such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), which then promote necroinflammation and fibrosis [82,92–95]. Accordingly, the key role of CYP2E1 in NASH pathophysiology makes CYP2E1 inhibition or downregulation a promising therapeutic strategy in NAFLD [92,96,97].

The mechanisms of CYP2E1 induction in NAFLD are poorly understood. Accumulation of some fatty acids such as palmitic acid (C16:0) and stearic acid (C18:0) might play a role [74,98,99]. In keeping with the role of some fatty acids or lipids, a recent interventional study in healthy individuals showed that a short-term regular diet supplemented with whipped cream induced hepatic steatosis and significantly enhanced CYP2E1 activity [100]. Other mechanisms might involve hyperleptinemia, hyperglucagonemia and insulin resistance [10,25,82]. The exact downstream signaling pathways involved in CYP2E1 induction in NAFLD are still unknown.

4.1.2. Low Basal Levels of GSH

Low basal levels of liver GSH might also favor APAP hepatotoxicity in NAFLD as this is expected to hasten and even promote the profound GSH depletion taking place after APAP overdose (Figure 2A). Consequently, less NAPQI can be detoxified by hepatic GSH thus allowing the APAP reactive metabolite to covalently bind to different proteins and other cellular components, especially in mitochondria [16,17,23]. Significant reduction of basal levels of liver GSH has been reported in NAFLD, either in patients [101,102] or in some rodent models [103,104]. However, other animal investigations did not find any significant decrease in hepatic GSH content [49,50,105,106], although this was sometimes associated with higher levels of oxidized GSH (GSSG) [105].

The mechanisms that can cause low basal levels of liver GSH in NAFLD might be complex. Several factors might be involved including the extent of ROS overproduction via mitochondrial dysfunction, reduced synthesis of GSH and impairment of other antioxidant defenses, which can occur during the progression of NAFLD [37,105,107,108].

4.1.3. Extent of Steatosis and Accumulation of Deleterious Fatty Acids and Lipid Species

Investigations in genetically obese mice intoxicated with APAP showed that higher basal levels of hepatic triglycerides did not cause more severe APAP-induced hepatic cytolysis [49]. Hence, the extent of steatosis per se does not seem to favor APAP hepatotoxicity in NAFLD. In contrast, the accumulation of some fatty acids might specifically

favor liver injury. For instance, palmitic and stearic acids could be particularly harmful by promoting hepatic CYP2E1 induction [74,98,99], as previously mentioned. Furthermore, studies carried out in transgenic fat-1 mice, which endogenously convert n-6 PUFAs to n-3 PUFAs, showed that male animals were more susceptible to APAP-induced acute liver injury, possibly via a JNK-dependent mechanism and downregulation of signal transducer and activator of transcription 3 (STAT3) [109,110].

Cholesterol accumulation might also favor APAP hepatotoxicity in NAFLD (Figure 2A). Indeed, investigations in mice fed a high-cholesterol diet for 4 weeks showed more severe APAP-induced acute liver injury, possibly through the Toll-like receptor 9 (TLR9)/inflammasome pathway [111]. Interestingly, mitochondrial free cholesterol loading leads to mitochondrial GSH depletion in hepatocytes [112], which could promote mitochondrial dysfunction and cell death [113]. In contrast, CYP2E1 might not be involved because hepatic CYP2E1 expression and activity were reduced in rats fed a high-cholesterol diet for 11 weeks [114].

4.1.4. Mitochondrial Dysfunction

NAFLD is associated with complex mitochondrial alterations. In simple fatty liver, mitochondrial oxidative metabolism is stimulated, most probably as an adaptation to the increased levels of different substrates including fatty acids [37,38,108,115]. However, this adaptation can be lost in NASH, which is associated with reduced expression and activity of different mitochondrial respiratory complexes [37,38,108,115–117]. Accordingly, NASH-associated mitochondrial dysfunction might favor APAP hepatotoxicity (Figure 2A) since respiratory chain impairment is pivotal in APAP-induced liver injury [118–120]. However, there are currently no available data to confirm this hypothesis but different rodent models reproducing NAFLD progression can be useful for this [60,61,121].

4.1.5. Presence of Lobular Inflammation

Simple fatty liver can progress in some patients to NASH which is characterized by lobular inflammation, hepatocellular ballooning and the presence of some necrotic hepatocytes and apoptotic bodies, as previously mentioned. These pathological lesions are due at least in part to the overproduction of several proinflammatory cytokines such as tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β) and IL-6 [122,123], which could sensitize the liver to APAP-induced hepatotoxicity (Figure 2A). Interestingly, APAP-induced acute liver injury is exacerbated in Nlrp6^{-/-} mice [124], a well-established mouse model of intestinal dysbiosis associated with enhanced gut–liver inflammatory responses [125]. However, it remains to be determined whether obesity- and NAFLD-associated gut dysbiosis [126,127] could play a role in higher APAP hepatotoxicity in these metabolic diseases. Other investigations showed that hepatic inflammation favors liver injury induced by different drugs and chemicals [128–130].

4.2. Factors That Could Mitigate APAP Hepatotoxicity in Obesity and NAFLD

4.2.1. Alteration in APAP Absorption and Distribution

Only a few clinical studies dealt with the impact of obesity on gastrointestinal absorption of APAP and its whole-body distribution. To our knowledge, only one study reported a lower absorption rate of APAP in obese subjects, which was associated with a decrease in the maximum plasma concentrations of the pain reliever [131]. Regarding whole-body distribution, two studies reported higher APAP volume of distribution (Vd) in obese subjects [43,132]. However, all these investigations were carried out in morbidly obese persons and further investigations would be needed to confirm these data for body mass index (BMI) below 40 kg/m². Nevertheless, decreased APAP gastrointestinal absorption and higher Vd could favor lower APAP plasma and liver concentrations, at least in some obese patients [9].

4.2.2. Lack of CYP2E1 Induction or CYP2E1 Downregulation

Although hepatic CYP2E1 activity is frequently increased in NAFLD (see Section 4.1.1), some investigations reported a lack of CYP2E1 induction, which might not allow NAPQI overproduction (Figure 2B). Indeed, several clinical studies showed that some obese patients had CYP2E1 activity in the range of nonobese individuals [43,46,85,133]. Experimentally, hepatic CYP2E1 expression and activity are not increased in obese leptin-deficient ob/ob mice and leptin receptor-deficient fa/fa Zucker rats [49,68,134]. Although this might suggest that the leptin signaling pathway is needed for CYP2E1 induction in obesity and NAFLD, hepatic CYP2E1 activity is enhanced in leptin receptor-deficient db/db mice, especially in females [49]. The very high glycemia and ketonemia in these mice [49,66] might play a role in CYP2E1 induction in this context of severe diabetes [10]. Because many endogenous molecules, hormones and cytokines are deemed to regulate hepatic CYP2E1 expression and activity, sometimes with opposite effects [10,82,135–137], it is possible that CYP2E1 induction might not always occur in obesity and NAFLD.

Another possibility could be the loss of CYP2E1 induction during NAFLD progression (Figure 2B). Indeed, recent investigations suggested that CYP2E1 induction seems to wane when NASH progresses toward advanced fibrosis [57], in line with clinical data reporting a significant reduction of CYP2E1 expression with the progression of liver fibrosis [138,139]. Increased production of proinflammatory cytokines including TNF- α might play a role in this progressive decline of CYP2E1 expression [135,139]. In contrast, the profibrotic cytokine transforming growth factor-beta (TGF- β) does not seem to be involved in fibrosis-associated CYP2E1 downregulation [140,141].

4.2.3. Reduced CYP3A4 and CYP1A2 Activity

CYP3A4 (also referred to as CYP3A) and CYP1A2 are also involved in APAP bio-transformation to NAPQI, although to a lesser extent than CYP2E1 [26,27]. Many clinical and experimental studies consistently reported lower hepatic expression and activity of CYP3A4 in obesity and NAFLD [83,142–150]. Hence, lower CYP3A4 activity in obesity and NAFLD might reduce the generation of NAPQI after an APAP overdose (Figure 2B).

Several clinical studies on CYP1A2 activity reported little or no change in obesity [83,147,149]. Interestingly, investigations in patients with NAFLD reported that CYP1A2 expression and activity were unaltered in fatty liver but significantly reduced in NASH [151,152]. These data seem to be in line with the investigations carried out in obese patients since NASH occurs only in a minority of those people [35]. In rodent models of NAFLD, CYP1A2 expression and activity were significantly decreased in most investigations [153–158], but increased or unchanged in some others [143,159]. Like CYP3A4, lower CYP1A2 activity in NAFLD might also reduce the generation of NAPQI after an APAP overdose (Figure 2B).

4.2.4. Increased APAP Glucuronidation

Clinical and experimental investigations consistently reported increased APAP glucuronidation in obesity and NAFLD [9,43,49,83,160,161], which is expected to reduce the extent of APAP bioactivation to NAPQI (Figure 2B). Of note, UGT1A6 and UGT1A9 are the main UGT isoforms involved in APAP glucuronidation in humans [162] but only UGT1A9 protein expression tended to be increased in patients with obesity-related fatty liver [163].

4.2.5. Exposure and Accumulation of Protective Fatty Acids

Two studies carried out in female transgenic fat-1 mice (which endogenously convert n-6 PUFAs to n-3 PUFAs) showed significant protection against APAP-induced acute liver injury [109,164]. In the study by Liu et al., the opposite effect was observed in male mice and this gender difference was attributed to estrogens [109]. Of note, the expression of hepatic CYP2E1 in female mice was unchanged in one study [164], whereas CYP2E1 was not investigated in the second one [109]. Other investigations in rats showed that dietary supplementation with the n-3 polyunsaturated eicosapentaenoic and docosahex-

aeonic acids (EPA and DHA) protected against acute APAP liver injury [165]. According to the authors, the hepatoprotective effect of n-3 PUFAs against APAP liver injury might be mediated via their anti-inflammatory and antioxidant properties [164,165]. Another study in rats fed a diet with 20% fish oil (i.e., rich in n-3 PUFAs) also reported protection against APAP-induced acute liver injury, which was deemed to be related to higher APAP glucuronidation [166]. Interestingly, n-3 PUFAs reduced hepatic CYP2E1 activity in insulinopenic diabetic rats [167] but their protective effect against APAP hepatotoxicity was not investigated in this study.

5. APAP-Induced Liver Injury after Bariatric Surgery

Roux-en-Y gastric bypass and sleeve gastrectomy are surgical procedures increasingly used for the treatment of morbid obesity and comorbidities including NAFLD [168,169]. A retrospective study suggested that weight loss surgery may predispose to acute liver failure after APAP overdose and this was independent of alcohol abuse and the use of APAP–narcotic combination drugs [170]. More recently, a case of fulminant hepatitis was observed after laparoscopic sleeve gastrectomy in a young woman who received therapeutic doses of APAP [171]. In addition to malnutrition and vitamin deficiency, the authors pointed to other possible risk factors including rapid weight loss, which might have aggravated preexisting fatty liver [171]. Notably, although CYP2E1 activity in obese patients decreases after bariatric surgery it remains higher than in healthy volunteers [133,172]. Thus, increased CYP2E1 activity might favor APAP-induced liver injury in obese patients even after such surgery. However, beyond CYP2E1 activity, other metabolic parameters most probably explain the profound alterations of APAP bioavailability observed after weight loss surgery [173,174]. Hence, further investigations would be needed to determine the mechanisms whereby bariatric surgery might predispose to APAP hepatotoxicity.

6. APAP-Hepatotoxicity in Type 1 Diabetes Mellitus

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disease caused by insulin deficiency and leading to severe hyperglycemia [175]. Importantly, the pathogenesis of T1DM significantly differs from that of obesity-related T2DM [176,177]. Nonetheless, T1DM seems to be frequently associated with fatty liver, which can progress to steatohepatitis and cirrhosis in some patients [178,179]. Some clinical investigations disclosed that diabetes increases the risk and the severity of DILI but these studies did not specify whether there was a difference between T1DM and T2DM [180–182]. Moreover, these investigations did not provide specific information on APAP.

T1DM can be induced in rats and mice by single or repeated injections of streptozotocin, a pancreatic β -cell poison [10,183]. Using this experimental model, a recent study reported that APAP-induced acute liver injury was exacerbated in diabetic mice possibly via a hyperglycemia-induced proinflammatory response in liver Kupffer cells [184]. Although not investigated in this study, it is possible that CYP2E1 induction might also have played a role in liver injury aggravation [10]. Indeed, numerous studies (but not all—see below) showed that streptozotocin-induced diabetes is associated with higher hepatic CYP2E1 protein expression and activity [10,167,185–188].

Contrasting with the study by Wang et al. [184], several investigations in streptozotocin-treated rodents showed that T1DM protected against APAP-induced acute hepatotoxicity [189–191]. The exact reasons for these discrepancies are unknown although higher APAP glucuronidation and improved liver repair in diabetic animals might play a role [189–191]. However, it is worth mentioning that hepatic CYP2E1 activity was not increased in these studies, thus contrasting with many other investigations reporting CYP2E1 induction in streptozotocin-treated rodents [10,167,185–188]. Further studies would be needed in order to determine why hepatic CYP2E1 induction is not always observed in streptozotocin-induced experimental diabetes. The extent of insulinopenia, ketonemia and hyperglycemia might be pivotal [10], in addition to other metabolic factors already discussed in this review.

7. Conclusions

Although obesity and NAFLD appear to increase the risk or the severity of APAP-induced acute liver injury, this relationship has not always been reported. As discussed in previous reviews [9,13,46] and this one, we propose that the occurrence and outcome of APAP-induced liver injury in these metabolic diseases might depend on a subtle balance between metabolic factors that can be protective for the liver and others that favor the generation of NAPQI (Figure 2). Hence, further investigations are needed in order to understand why some obese individuals could be at risk for APAP-induced hepatotoxicity and why some others are not. Although the absence of hepatic CYP2E1 induction might explain the lack of increased risk, other mechanisms might be involved including reduced APAP gastrointestinal absorption, enhanced Vd, higher hepatic glucuronidation and lower hepatic CYP3A4 activity (Figure 2B). In contrast, robust CYP2E1 induction, lobular inflammation, low basal concentrations of hepatic GSH and NASH-associated mitochondrial dysfunction might favor APAP hepatotoxicity in obesity and NAFLD (Figure 2A). While some of these factors are difficult to investigate in patients, many rodent models can be useful for mechanistic purposes [60,61,121]. Of note, these rodent models of obesity and NAFLD could also be valuable in order to determine whether repeated or chronic administration of APAP at therapeutic doses can cause more severe liver injury.

From a clinical viewpoint, physicians are encouraged to carry out regular monitoring of liver function in obese patients treated with chronic APAP administration, in particular in patients with pre-existing NAFLD. Finally, it should be underlined that chronic ethanol consumption constantly causes hepatic CYP2E1 induction while recent investigations reported that alcohol consumption and obesity (or metabolic syndrome) can synergistically augment the risk and severity of steatohepatitis, cirrhosis and HCC [192–194]. Hence, further investigations would be required to determine whether obese people who regularly consume alcohol have an even higher risk of APAP-induced hepatotoxicity.

Finally, a major issue for the future is to better prevent liver failure and mortality after APAP overdose, irrespective of the patient's body weight. Although NAC is the only approved antidote to treat APAP-induced liver injury [10,14], other therapeutic compounds are currently being developed to inhibit CYP2E1 activity (fomepizole), or to prevent mitochondrial oxidative stress (MitoTEMPO) and peroxynitrite formation (calmangafodipir) [195]. Numerous phytochemicals with efficient antioxidant properties might also be promising antidotes [196]. As for NAC, these compounds might be able to protect against APAP-induced necrosis [17,197] and other possible types of cell death including necroptosis and apoptosis [198,199]. Furthermore, targeting autophagy, mitophagy and mitochondrial biogenesis could also be promising therapeutic strategies [22,195,200].

Author Contributions: Conceptualization, K.B., J.M. and B.F.; writing—original draft preparation, B.F.; writing—review and editing, K.B., C.P., P.B.-G. and J.M.; visualization, K.B., J.M. and B.F.; supervision, B.F.; project administration, B.F. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: We are grateful to the Institut National de la Santé et de la Recherche Médicale (INSERM) for its constant support.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Barrett, L.A.; Xing, A.; Sheffler, J.; Steidley, E.; Adam, T.J.; Zhang, R.; He, Z. Assessing the Use of Prescription Drugs and Dietary Supplements in Obese Respondents in the National Health and Nutrition Examination Survey. *PLoS ONE* **2022**, *17*, e0269241. [[CrossRef](#)] [[PubMed](#)]
2. Pulipati, V.P.; Pannain, S. Pharmacotherapy of Obesity in Complex Diseases. *Clin. Obes.* **2022**, *12*, e12497. [[CrossRef](#)] [[PubMed](#)]
3. Chew, N.W.S.; Ng, C.H.; Truong, E.; Noureddin, M.; Kowdley, K.V. Nonalcoholic Steatohepatitis Drug Development Pipeline: An Update. *Semin. Liver Dis.* **2022**, *42*, 379–400. [[CrossRef](#)]
4. Negi, C.K.; Babica, P.; Bajard, L.; Bienertova-Vasku, J.; Tarantino, G. Insights into the Molecular Targets and Emerging Pharmacotherapeutic Interventions for Nonalcoholic Fatty Liver Disease. *Metabolism* **2022**, *126*, 154925. [[CrossRef](#)] [[PubMed](#)]
5. Scott, I.A.; Hilmer, S.N.; Reeve, E.; Potter, K.; Le Couteur, D.; Rigby, D.; Gnjdic, D.; Del Mar, C.B.; Roughead, E.E.; Page, A.; et al. Reducing Inappropriate Polypharmacy: The Process of Deprescribing. *JAMA Intern. Med.* **2015**, *175*, 827–834. [[CrossRef](#)]
6. Suzuki, A.; Yuen, N.A.; Ilic, K.; Miller, R.T.; Reese, M.J.; Brown, H.R.; Ambroso, J.I.; Falls, J.G.; Hunt, C.M. Comedications Alter Drug-Induced Liver Injury Reporting Frequency: Data Mining in the WHO Vigibase™. *Regul. Toxicol. Pharm.* **2015**, *72*, 481–490. [[CrossRef](#)]
7. Lammert, C.; Imler, T.; Teal, E.; Chalasani, N. Patients With Chronic Liver Disease Suggestive of Nonalcoholic Fatty Liver Disease May Be at Higher Risk for Drug-Induced Liver Injury. *Clin. Gastroenterol. Hepatol.* **2019**, *17*, 2814–2815. [[CrossRef](#)]
8. Hwang, S.; Won, S.; Lee, S. Nonalcoholic Fatty Liver Disease for the Incidence of Drug-Induced Liver Injury. *Clin. Gastroenterol. Hepatol.* **2022**, *20*, 964–965. [[CrossRef](#)]
9. Michaut, A.; Moreau, C.; Robin, M.-A.; Fromenty, B. Acetaminophen-Induced Liver Injury in Obesity and Nonalcoholic Fatty Liver Disease. *Liver Int.* **2014**, *34*, e171–e179. [[CrossRef](#)]
10. Massart, J.; Begriche, K.; Fromenty, B. Cytochrome P450 2E1 Should Not Be Neglected for Acetaminophen-Induced Liver Injury in Metabolic Diseases with Altered Insulin Levels or Glucose Homeostasis. *Clin. Res. Hepatol. Gastroenterol.* **2021**, *45*, 101470. [[CrossRef](#)]
11. Borlak, J.; Chatterji, B.; Londhe, K.B.; Watkins, P.B. Serum Acute Phase Reactants Hallmark Healthy Individuals at Risk for Acetaminophen-Induced Liver Injury. *Genome Med.* **2013**, *5*, 86. [[CrossRef](#)] [[PubMed](#)]
12. Louvet, A.; Ntandja Wandji, L.C.; Lemaître, E.; Khaldi, M.; Lafforgue, C.; Artru, F.; Quesnel, B.; Lassailly, G.; Dharancy, S.; Mathurin, P. Acute Liver Injury With Therapeutic Doses of Acetaminophen: A Prospective Study. *Hepatology* **2021**, *73*, 1945–1955. [[CrossRef](#)] [[PubMed](#)]
13. Massart, J.; Begriche, K.; Moreau, C.; Fromenty, B. Role of Nonalcoholic Fatty Liver Disease as Risk Factor for Drug-Induced Hepatotoxicity. *J. Clin. Transl. Res.* **2017**, *3*, 212–232. [[CrossRef](#)] [[PubMed](#)]
14. Licata, M.; Minisalle, M.G.; Stankeviciute, S.; Sanabria-Cabrera, J.; Lucena, M.M.; Andrade, R.J.; Almasio, P.L. N-Acetylcysteine for Preventing Acetaminophen-Induced Liver Injury: A Comprehensive Review. *Front. Pharm.* **2022**, *13*, 828565. [[CrossRef](#)] [[PubMed](#)]
15. Larson, A.M.; Polson, J.; Fontana, R.J.; Davern, T.J.; Lalani, E.; Hynan, L.S.; Reisch, J.S.; Schiodt, F.V.; Ostapowicz, G.; Shakil, A.O.; et al. Acetaminophen-Induced Acute Liver Failure: Results of a United States Multicenter, Prospective Study. *Hepatology* **2005**, *42*, 1364–1372. [[CrossRef](#)]
16. Yoon, E.; Babar, A.; Choudhary, M.; Kutner, M.; Pyrsopoulos, N. Acetaminophen-Induced Hepatotoxicity: A Comprehensive Update. *J. Clin. Transl. Hepatol.* **2016**, *4*, 131–142. [[CrossRef](#)]
17. Ramachandran, A.; Jaeschke, H. A Mitochondrial Journey through Acetaminophen Hepatotoxicity. *Food Chem. Toxicol.* **2020**, *140*, 111282. [[CrossRef](#)]
18. Biour, M.; Ben Salem, C.; Chazouillères, O.; Grangé, J.-D.; Serfaty, L.; Poupon, R. Drug-induced liver injury; fourteenth updated edition of the bibliographic database of liver injuries and related drugs. *Gastroenterol. Clin. Biol.* **2004**, *28*, 720–759. [[CrossRef](#)]
19. Watelet, J.; Laurent, V.; Bressenot, A.; Bronowicki, J.-P.; Larrey, D.; Peyrin-Biroulet, L. Toxicity of Chronic Paracetamol Ingestion. *Aliment. Pharm.* **2007**, *26*, 1543–1544. [[CrossRef](#)]
20. Yaghi, C.; Assaf, A. Acetaminophen Toxicity at Therapeutic Doses. *Intern. Med. Rev.* **2017**, *3*, 1–13.
21. McGill, M.R.; Hinson, J.A. The Development and Hepatotoxicity of Acetaminophen: Reviewing over a Century of Progress. *Drug Metab. Rev.* **2020**, *52*, 472–500. [[CrossRef](#)] [[PubMed](#)]
22. Jaeschke, H. Acetaminophen Hepatotoxicity: Not as Simple as One Might Think! Introductory Comments on the Special Issue—Recent Advances in Acetaminophen Hepatotoxicity. *Livers* **2022**, *2*, 105–107. [[CrossRef](#)] [[PubMed](#)]
23. Fernandez-Checa, J.C.; Bagnaninchi, P.; Ye, H.; Sancho-Bru, P.; Falcon-Perez, J.M.; Royo, F.; Garcia-Ruiz, C.; Konu, O.; Miranda, J.; Lunov, O.; et al. Advanced Preclinical Models for Evaluation of Drug-Induced Liver Injury—Consensus Statement by the European Drug-Induced Liver Injury Network [PRO-EURO-DILI-NET]. *J. Hepatol.* **2021**, *75*, 935–959. [[CrossRef](#)] [[PubMed](#)]
24. Knockaert, L.; Descatoire, V.; Vadrot, N.; Fromenty, B.; Robin, M.-A. Mitochondrial CYP2E1 Is Sufficient to Mediate Oxidative Stress and Cytotoxicity Induced by Ethanol and Acetaminophen. *Toxicol. Vitro.* **2011**, *25*, 475–484. [[CrossRef](#)] [[PubMed](#)]
25. Massart, J.; Begriche, K.; Hartman, J.H.; Fromenty, B. Role of Mitochondrial Cytochrome P450 2E1 in Healthy and Diseased Liver. *Cells* **2022**, *11*, 288. [[CrossRef](#)]

26. Brackett, C.C.; Bloch, J.D. Phenytoin as a Possible Cause of Acetaminophen Hepatotoxicity: Case Report and Review of the Literature. *Pharmacotherapy* **2000**, *20*, 229–233. [[CrossRef](#)]
27. McGill, M.R.; Jaeschke, H. Metabolism and Disposition of Acetaminophen: Recent Advances in Relation to Hepatotoxicity and Diagnosis. *Pharm. Res.* **2013**, *30*, 2174–2187. [[CrossRef](#)]
28. Caparrotta, T.M.; Antoine, D.J.; Dear, J.W. Are Some People at Increased Risk of Paracetamol-Induced Liver Injury? A Critical Review of the Literature. *Eur. J. Clin. Pharm.* **2018**, *74*, 147–160. [[CrossRef](#)]
29. Hidaka, N.; Kaji, Y.; Takatori, S.; Tanaka, A.; Matsuoaka, I.; Tanaka, M. Risk Factors for Acetaminophen-Induced Liver Injury: A Single-Center Study from Japan. *Clin. Ther.* **2020**, *42*, 704–710. [[CrossRef](#)]
30. Tsuchiya, Y.; Sakai, H.; Hirata, A.; Yanai, T. Effects of Food Restriction on the Expression of Genes Related to Acetaminophen-Induced Liver Toxicity in Rats. *J. Toxicol. Pathol.* **2018**, *31*, 267–274. [[CrossRef](#)]
31. Court, M.H.; Freytsis, M.; Wang, X.; Peter, I.; Guillemette, C.; Hazarika, S.; Duan, S.X.; Greenblatt, D.J.; Lee, W.M. Acute Liver Failure Study Group The UDP-Glucuronosyltransferase (UGT) 1A Polymorphism c.2042C>G (Rs8330) Is Associated with Increased Human Liver Acetaminophen Glucuronidation, Increased UGT1A Exon 5a/5b Splice Variant mRNA Ratio, and Decreased Risk of Unintentional Acetaminophen-Induced Acute Liver Failure. *J. Pharm. Exp.* **2013**, *345*, 297–307. [[CrossRef](#)]
32. Henry, L.; Paik, J.; Younossi, Z.M. Review Article: The Epidemiologic Burden of Non-Alcoholic Fatty Liver Disease across the World. *Aliment. Pharm.* **2022**, *56*, 942–956. [[CrossRef](#)] [[PubMed](#)]
33. Brunt, E.M.; Kleiner, D.E.; Carpenter, D.H.; Rinella, M.; Harrison, S.A.; Loomba, R.; Younossi, Z.; Neuschwander-Tetri, B.A.; Sanyal, A.J. American Association for the Study of Liver Diseases NASH Task Force NAFLD: Reporting Histologic Findings in Clinical Practice. *Hepatology* **2021**, *73*, 2028–2038. [[CrossRef](#)] [[PubMed](#)]
34. Ahmad, M.I.; Khan, M.U.; Kodali, S.; Shetty, A.; Bell, S.M.; Victor, D. Hepatocellular Carcinoma Due to Nonalcoholic Fatty Liver Disease: Current Concepts and Future Challenges. *J. Hepatocell. Carcinoma* **2022**, *9*, 477–496. [[CrossRef](#)]
35. Koch, L.K.; Yeh, M.M. Nonalcoholic Fatty Liver Disease (NAFLD): Diagnosis, Pitfalls, and Staging. *Ann. Diagn. Pathol.* **2018**, *37*, 83–90. [[CrossRef](#)] [[PubMed](#)]
36. Tandra, S.; Yeh, M.M.; Brunt, E.M.; Vuppalanchi, R.; Cummings, O.W.; Ünalp-Arida, A.; Wilson, L.A.; Chalasani, N. Presence and Significance of Microvesicular Steatosis in Nonalcoholic Fatty Liver Disease. *J. Hepatol.* **2011**, *55*, 654–659. [[CrossRef](#)] [[PubMed](#)]
37. Begriche, K.; Massart, J.; Robin, M.-A.; Bonnet, F.; Fromenty, B. Mitochondrial Adaptations and Dysfunctions in Nonalcoholic Fatty Liver Disease. *Hepatology* **2013**, *58*, 1497–1507. [[CrossRef](#)]
38. Sunny, N.E.; Bril, F.; Cusi, K. Mitochondrial Adaptation in Nonalcoholic Fatty Liver Disease: Novel Mechanisms and Treatment Strategies. *Trends Endocrinol. Metab.* **2017**, *28*, 250–260. [[CrossRef](#)]
39. Pafili, K.; Roden, M. Nonalcoholic Fatty Liver Disease (NAFLD) from Pathogenesis to Treatment Concepts in Humans. *Mol. Metab.* **2021**, *50*, 101122. [[CrossRef](#)]
40. Nguyen, G.C.; Sam, J.; Thuluvath, P.J. Hepatitis C Is a Predictor of Acute Liver Injury among Hospitalizations for Acetaminophen Overdose in the United States: A Nationwide Analysis. *Hepatology* **2008**, *48*, 1336–1341. [[CrossRef](#)]
41. Myers, R.P.; Shaheen, A.A.M. Hepatitis C, Alcohol Abuse, and Unintentional Overdoses Are Risk Factors for Acetaminophen-Related Hepatotoxicity. *Hepatology* **2009**, *49*, 1399–1400. [[CrossRef](#)] [[PubMed](#)]
42. Chomchai, S.; Chomchai, C. Being Overweight or Obese as a Risk Factor for Acute Liver Injury Secondary to Acute Acetaminophen Overdose. *Pharm. Drug Saf.* **2018**, *27*, 19–24. [[CrossRef](#)] [[PubMed](#)]
43. van Rongen, A.; Väliälto, P.A.J.; Peeters, M.Y.M.; Boerma, D.; Huisman, F.W.; van Ramshorst, B.; van Dongen, E.P.A.; van den Anker, J.N.; Knibbe, C.A.J. Morbidly Obese Patients Exhibit Increased CYP2E1-Mediated Oxidation of Acetaminophen. *Clin. Pharm.* **2016**, *55*, 833–847. [[CrossRef](#)]
44. Rutherford, A.; Davern, T.; Hay, J.E.; Murray, N.G.; Hassanein, T.; Lee, W.M.; Chung, R.T. Acute Liver Failure Study Group Influence of High Body Mass Index on Outcome in Acute Liver Failure. *Clin. Gastroenterol. Hepatol.* **2006**, *4*, 1544–1549. [[CrossRef](#)] [[PubMed](#)]
45. Radosevich, J.J.; Patanwala, A.E.; Erstad, B.L. Hepatotoxicity in Obese Versus Nonobese Patients With Acetaminophen Poisoning Who Are Treated With Intravenous N-Acetylcysteine. *Am. J. Ther.* **2016**, *23*, e714–e719. [[CrossRef](#)]
46. Allard, J.; Le Guillou, D.; Begriche, K.; Fromenty, B. Drug-Induced Liver Injury in Obesity and Nonalcoholic Fatty Liver Disease. *Adv. Pharm.* **2019**, *85*, 75–107. [[CrossRef](#)]
47. Corcoran, G.B.; Wong, B.K. Obesity as a Risk Factor in Drug-Induced Organ Injury: Increased Liver and Kidney Damage by Acetaminophen in the Obese Overfed Rat. *J. Pharm. Exp. Ther.* **1987**, *241*, 921–927.
48. Kon, K.; Ikejima, K.; Okumura, K.; Arai, K.; Aoyama, T.; Watanabe, S. Diabetic KK-A(y) Mice Are Highly Susceptible to Oxidative Hepatocellular Damage Induced by Acetaminophen. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2010**, *299*, G329–G337. [[CrossRef](#)] [[PubMed](#)]
49. Aubert, J.; Begriche, K.; Delannoy, M.; Morel, I.; Pajaud, J.; Ribault, C.; Lepage, S.; McGill, M.R.; Lucas-Clerc, C.; Turlin, B.; et al. Differences in Early Acetaminophen Hepatotoxicity between Obese Ob/Ob and Db/Db Mice. *J. Pharm. Exp. Ther.* **2012**, *342*, 676–687. [[CrossRef](#)]
50. Kučera, O.; Roušar, T.; Staňková, P.; Haňáčková, L.; Lotková, H.; Podhola, M.; Cervinková, Z. Susceptibility of Rat Non-Alcoholic Fatty Liver to the Acute Toxic Effect of Acetaminophen. *J. Gastroenterol. Hepatol.* **2012**, *27*, 323–330. [[CrossRef](#)]

51. Piccinin, E.; Ducheix, S.; Peres, C.; Arconzo, M.; Vegliante, M.C.; Ferretta, A.; Bellafante, E.; Villani, G.; Moschetta, A. PGC-1 β Induces Susceptibility To Acetaminophen-Driven Acute Liver Failure. *Sci. Rep.* **2019**, *9*, 16821. [[CrossRef](#)]
52. Shi, C.; Xue, W.; Han, B.; Yang, F.; Yin, Y.; Hu, C. Acetaminophen Aggravates Fat Accumulation in NAFLD by Inhibiting Autophagy via the AMPK/MTOR Pathway. *Eur. J. Pharm.* **2019**, *850*, 15–22. [[CrossRef](#)]
53. Wang, J.; Jiang, W.; Xin, J.; Xue, W.; Shi, C.; Wen, J.; Huang, Y.; Hu, C. Caveolin-1 Alleviates Acetaminophen-Induced Fat Accumulation in Non-Alcoholic Fatty Liver Disease by Enhancing Hepatic Antioxidant Ability via Activating AMPK Pathway. *Front. Pharm.* **2021**, *12*, 717276. [[CrossRef](#)]
54. Tuntaterdtum, S.; Chaudhary, I.P.; Cibull, M.; Robertson, L.W.; Blouin, R.A. Acetaminophen Hepatotoxicity: Influence of Phenobarbital and Beta-Naphthoflavone Treatment in Obese and Lean Zucker Rats. *Toxicol. Appl. Pharm.* **1993**, *123*, 219–225. [[CrossRef](#)]
55. Ito, Y.; Abril, E.R.; Bethea, N.W.; McCuskey, M.K.; McCuskey, R.S. Dietary Steatotic Liver Attenuates Acetaminophen Hepatotoxicity in Mice. *Microcirculation* **2006**, *13*, 19–27. [[CrossRef](#)]
56. Kim, T.H.; Choi, D.; Kim, J.Y.; Lee, J.H.; Koo, S.-H. Fast Food Diet-Induced Non-Alcoholic Fatty Liver Disease Exerts Early Protective Effect against Acetaminophen Intoxication in Mice. *BMC Gastroenterol.* **2017**, *17*, 124. [[CrossRef](#)]
57. Ghallab, A.; Myllys, M.; Friebel, A.; Duda, J.; Edlund, K.; Halilbasic, E.; Vucur, M.; Hobloss, Z.; Brackhagen, L.; Begher-Tibbe, B.; et al. Spatio-Temporal Multiscale Analysis of Western Diet-Fed Mice Reveals a Translationally Relevant Sequence of Events during NAFLD Progression. *Cells* **2021**, *10*, 2516. [[CrossRef](#)]
58. Blouin, R.A.; Dickson, P.; McNamara, P.J.; Cibull, M.; McClain, C. Phenobarbital induction and acetaminophen hepatotoxicity: Resistance in the obese Zucker rodent. *J. Pharm. Exp. Ther.* **1987**, *243*, 270–565.
59. Donthamsetty, S.; Bhave, V.S.; Mitra, M.S.; Latendresse, J.R.; Mehendale, H.M. Nonalcoholic Steatohepatitic (NASH) Mice Are Protected from Higher Hepatotoxicity of Acetaminophen upon Induction of PPAR α with Clofibrate. *Toxicol. Appl. Pharm.* **2008**, *230*, 327–337. [[CrossRef](#)]
60. Jahn, D.; Kircher, S.; Hermanns, H.M.; Geier, A. Animal Models of NAFLD from a Hepatologist's Point of View. *Biochim. Biophys. Acta Mol. Basis Dis.* **2019**, *1865*, 943–953. [[CrossRef](#)]
61. Radhakrishnan, S.; Yeung, S.F.; Ke, J.-Y.; Antunes, M.M.; Pellizzon, M.A. Considerations When Choosing High-Fat, High-Fructose, and High-Cholesterol Diets to Induce Experimental Nonalcoholic Fatty Liver Disease in Laboratory Animal Models. *Curr. Dev. Nutr.* **2021**, *5*, nzab138. [[CrossRef](#)]
62. Carreres, L.; Jilkova, Z.M.; Vial, G.; Marche, P.N.; Decaens, T.; Lerat, H. Modeling Diet-Induced NAFLD and NASH in Rats: A Comprehensive Review. *Biomedicines* **2021**, *9*, 378. [[CrossRef](#)]
63. Carmiel-Haggai, M.; Cederbaum, A.I.; Nieto, N. Binge Ethanol Exposure Increases Liver Injury in Obese Rats. *Gastroenterology* **2003**, *125*, 1818–1833. [[CrossRef](#)]
64. Cipriani, S.; Mencarelli, A.; Palladino, G.; Fiorucci, S. FXR activation reverses insulin resistance and lipid abnormalities and protects against liver steatosis in Zucker (fa/fa) obese rats. *J. Lipid Res.* **2010**, *51*, 771–784. [[CrossRef](#)]
65. Zaluzny, L.; Farrell, G.C.; Murray, M. Effect of genetic obesity and experimental diabetes on hepatic microsomal mixed function oxidase activities. *J. Gastroenterol. Hepatol.* **1990**, *5*, 256–263. [[CrossRef](#)]
66. Trak-Smayra, V.; Paradis, V.; Massart, J.; Nasser, S.; Jebara, V.; Fromenty, B. Pathology of the Liver in Obese and Diabetic Ob/Ob and Db/Db Mice Fed a Standard or High-Calorie Diet. *Int. J. Exp. Pathol.* **2011**, *92*, 413–421. [[CrossRef](#)]
67. Robin, M.A.; Demeilliers, C.; Sutton, A.; Paradis, V.; Maisonneuve, C.; Dubois, S.; Poirel, O.; Lettéron, P.; Pessayre, D.; Fromenty, B. Alcohol increases tumor necrosis factor α and decreases nuclear factor- κ B to activate hepatic apoptosis in genetically obese mice. *Hepatology* **2005**, *42*, 1280–1290. [[CrossRef](#)]
68. Enriquez, A.; Leclercq, I.; Farrell, G.C.; Robertson, G. Altered Expression of Hepatic CYP2E1 and CYP4A in Obese, Diabetic Ob/Ob Mice, and Fa/Fa Zucker Rats. *Biochem. Biophys. Res. Commun.* **1999**, *255*, 300–306. [[CrossRef](#)]
69. Okumura, K.; Ikejima, K.; Kon, K.; Abe, W.; Yamashina, S.; Enomoto, N.; Takei, Y.; Sato, N. Exacerbation of dietary steatohepatitis and fibrosis in obese, diabetic KK-A(y) mice. *Hepatol. Res.* **2006**, *36*, 217–228. [[CrossRef](#)]
70. Teraoka, N.; Mutoh, M.; Takasu, S.; Ueno, T.; Nakano, K.; Takahashi, M.; Imai, T.; Masuda, S.; Sugimura, T.; Wakabayashi, K. High susceptibility to azoxymethane-induced colorectal carcinogenesis in obese KK-Ay mice. *Int. J. Cancer* **2011**, *129*, 528–535. [[CrossRef](#)]
71. McDanell, R.E.; Beales, D.; Henderson, L.; Sethi, J.K. Effect of Dietary Fat on the in Vitro Hepatotoxicity of Paracetamol. *Biochem. Pharm.* **1992**, *44*, 1303–1306. [[CrossRef](#)]
72. Kučera, O.; Al-Dury, S.; Lotková, H.; Roušar, T.; Rychtrmoc, D.; Červinková, Z. Steatotic Rat Hepatocytes in Primary Culture Are More Susceptible to the Acute Toxic Effect of Acetaminophen. *Physiol. Res.* **2012**, *61*, S93–S101. [[CrossRef](#)]
73. Yang, J.; Peng, T.; Huang, J.; Zhang, G.; Xia, J.; Ma, M.; Deng, D.; Gong, D.; Zeng, Z. Effects of Medium- and Long-Chain Fatty Acids on Acetaminophen- or Rifampicin-Induced Hepatocellular Injury. *Food Sci. Nutr.* **2020**, *8*, 3590–3601. [[CrossRef](#)]
74. Michaut, A.; Le Guillou, D.; Moreau, C.; Bucher, S.; McGill, M.R.; Martinais, S.; Gicquel, T.; Morel, I.; Robin, M.-A.; Jaeschke, H.; et al. A Cellular Model to Study Drug-Induced Liver Injury in Nonalcoholic Fatty Liver Disease: Application to Acetaminophen. *Toxicol. Appl. Pharm.* **2016**, *292*, 40–55. [[CrossRef](#)]
75. Hubel, E.; Fishman, S.; Holopainen, M.; Käkälä, R.; Shaffer, O.; Houry, I.; Zvibel, I.; Shibolet, O. Repetitive Amiodarone Administration Causes Liver Damage via Adipose Tissue ER Stress-Dependent Lipolysis, Leading to Hepatotoxic Free Fatty Acid Accumulation. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2021**, *321*, G298–G307. [[CrossRef](#)]

76. Mathur, M.; Yeh, Y.-T.; Arya, R.K.; Jiang, L.; Pornour, M.; Chen, W.; Ma, Y.; Gao, B.; He, L.; Ying, Z.; et al. Adipose Lipolysis Is Important for Ethanol to Induce Fatty Liver in the National Institute on Alcohol Abuse and Alcoholism Murine Model of Chronic and Binge Ethanol Feeding. *Hepatology* **2022**. [[CrossRef](#)]
77. Toyoda, T.; Cho, Y.-M.; Akagi, J.-I.; Mizuta, Y.; Matsushita, K.; Nishikawa, A.; Imaida, K.; Ogawa, K. A 13-Week Subchronic Toxicity Study of Acetaminophen Using an Obese Rat Model. *J. Toxicol. Sci.* **2018**, *43*, 423–433. [[CrossRef](#)]
78. Kondo, K.; Yamada, N.; Suzuki, Y.; Hashimoto, T.; Toyoda, K.; Takahashi, T.; Kobayashi, A.; Sugai, S.; Yoshinari, K. Enhancement of Acetaminophen-Induced Chronic Hepatotoxicity in Spontaneously Diabetic Torii (SDT) Rats. *J. Toxicol. Sci.* **2020**, *45*, 245–260. [[CrossRef](#)]
79. Arconzo, M.; Piccinin, E.; Moschetta, A. Increased Risk of Acute Liver Failure by Pain Killer Drugs in NAFLD: Focus on Nuclear Receptors and Their Coactivators. *Dig. Liver Dis.* **2021**, *53*, 26–34. [[CrossRef](#)]
80. Chalasani, N.; Gorski, J.C.; Asghar, M.S.; Asghar, A.; Foresman, B.; Hall, S.D.; Crabb, D.W. Hepatic Cytochrome P450 2E1 Activity in Nondiabetic Patients with Nonalcoholic Steatohepatitis. *Hepatology* **2003**, *37*, 544–550. [[CrossRef](#)]
81. Chtioui, H.; Semela, D.; Ledermann, M.; Zimmermann, A.; Dufour, J.-F. Expression and Activity of the Cytochrome P450 2E1 in Patients with Nonalcoholic Steatosis and Steatohepatitis. *Liver Int.* **2007**, *27*, 764–771. [[CrossRef](#)]
82. Aubert, J.; Begriche, K.; Knockaert, L.; Robin, M.A.; Fromenty, B. Increased Expression of Cytochrome P450 2E1 in Nonalcoholic Fatty Liver Disease: Mechanisms and Pathophysiological Role. *Clin. Res. Hepatol. Gastroenterol.* **2011**, *35*, 630–637. [[CrossRef](#)]
83. Brill, M.J.E.; Diepstraten, J.; van Rongen, A.; van Kralingen, S.; van den Anker, J.N.; Knibbe, C.A.J. Impact of Obesity on Drug Metabolism and Elimination in Adults and Children. *Clin. Pharm.* **2012**, *51*, 277–304. [[CrossRef](#)]
84. Aljomah, G.; Baker, S.S.; Liu, W.; Kozielski, R.; Oluwole, J.; Lupu, B.; Baker, R.D.; Zhu, L. Induction of CYP2E1 in Non-Alcoholic Fatty Liver Diseases. *Exp. Mol. Pathol.* **2015**, *99*, 677–681. [[CrossRef](#)]
85. Gade, C.; Dalhoff, K.; Petersen, T.S.; Riis, T.; Schmeltz, C.; Chabanova, E.; Christensen, H.R.; Mikus, G.; Burhenne, J.; Holm, J.C.; et al. Higher Chlorzoxazone Clearance in Obese Children Compared with Nonobese Peers. *Br. J. Clin. Pharm.* **2018**, *84*, 1738–1747. [[CrossRef](#)]
86. Raucy, J.L.; Lasker, J.M.; Kraner, J.C.; Salazar, D.E.; Lieber, C.S.; Corcoran, G.B. Induction of Cytochrome P450IIE1 in the Obese Overfed Rat. *Mol. Pharm.* **1991**, *39*, 275–280.
87. Baumgardner, J.N.; Shankar, K.; Hennings, L.; Badger, T.M.; Ronis, M.J.J. A New Model for Nonalcoholic Steatohepatitis in the Rat Utilizing Total Enteral Nutrition to Overfeed a High-Polyunsaturated Fat Diet. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2008**, *294*, G27–G38. [[CrossRef](#)]
88. Begriche, K.; Lettéron, P.; Abbey-Toby, A.; Vadrot, N.; Robin, M.-A.; Bado, A.; Pessayre, D.; Fromenty, B. Partial Leptin Deficiency Favors Diet-Induced Obesity and Related Metabolic Disorders in Mice. *Am. J. Physiol. Endocrinol. Metab.* **2008**, *294*, E939–E951. [[CrossRef](#)]
89. Abdelmegeed, M.A.; Banerjee, A.; Yoo, S.-H.; Jang, S.; Gonzalez, F.J.; Song, B.-J. Critical Role of Cytochrome P450 2E1 (CYP2E1) in the Development of High Fat-Induced Non-Alcoholic Steatohepatitis. *J. Hepatol.* **2012**, *57*, 860–866. [[CrossRef](#)]
90. Lai, Y.-S.; Lee, W.-C.; Lin, Y.-E.; Ho, C.-T.; Lu, K.-H.; Lin, S.-H.; Panyod, S.; Chu, Y.-L.; Sheen, L.-Y. Ginger Essential Oil Ameliorates Hepatic Injury and Lipid Accumulation in High Fat Diet-Induced Nonalcoholic Fatty Liver Disease. *J. Agric. Food Chem.* **2016**, *64*, 2062–2071. [[CrossRef](#)]
91. Liu, W.; Shang, J.; Deng, Y.; Han, X.; Chen, Y.; Wang, S.; Yang, R.; Dong, F.; Shang, H. Network Pharmacology Analysis on Mechanism of Jian Pi Qing Gan Yin Decoction Ameliorating High Fat Diet-Induced Non-Alcoholic Fatty Liver Disease and Validated in Vivo. *J. Ethnopharmacol.* **2022**, *295*, 115382. [[CrossRef](#)]
92. Seth, R.K.; Das, S.; Pourhoseini, S.; Dattaroy, D.; Igwe, S.; Ray, J.B.; Fan, D.; Michelotti, G.A.; Diehl, A.M.; Chatterjee, S. M1 Polarization Bias and Subsequent Nonalcoholic Steatohepatitis Progression Is Attenuated by Nitric Oxide Donor DETA NONOate via Inhibition of CYP2E1-Induced Oxidative Stress in Obese Mice. *J. Pharm. Exp. Ther.* **2015**, *352*, 77–89. [[CrossRef](#)]
93. Correia, M.A.; Kwon, D. Why Hepatic CYP2E1-Elevation by Itself Is Insufficient for Inciting NAFLD/NASH: Inferences from Two Genetic Knockout Mouse Models. *Biology* **2020**, *9*, 419. [[CrossRef](#)]
94. Leclercq, I.A.; Farrell, G.C.; Field, J.; Bell, D.R.; Gonzalez, F.J.; Robertson, G.R. CYP2E1 and CYP4A as Microsomal Catalysts of Lipid Peroxides in Murine Nonalcoholic Steatohepatitis. *J. Clin. Investig.* **2000**, *105*, 1067–1075. [[CrossRef](#)]
95. Abdelmegeed, M.A.; Choi, Y.; Godlewski, G.; Ha, S.-K.; Banerjee, A.; Jang, S.; Song, B.-J. Cytochrome P450-2E1 Promotes Fast Food-Mediated Hepatic Fibrosis. *Sci. Rep.* **2017**, *7*, 39764. [[CrossRef](#)]
96. Leung, T.-M.; Nieto, N. CYP2E1 and Oxidant Stress in Alcoholic and Non-Alcoholic Fatty Liver Disease. *J. Hepatol.* **2013**, *58*, 395–398. [[CrossRef](#)]
97. Wang, K.; Tan, W.; Liu, X.; Deng, L.; Huang, L.; Wang, X.; Gao, X. New Insight and Potential Therapy for NAFLD: CYP2E1 and Flavonoids. *Biomed. Pharm.* **2021**, *137*, 111326. [[CrossRef](#)]
98. Raucy, J.L.; Lasker, J.; Ozaki, K.; Zoleta, V. Regulation of CYP2E1 by Ethanol and Palmitic Acid and CYP4A11 by Clofibrate in Primary Cultures of Human Hepatocytes. *Toxicol. Sci.* **2004**, *79*, 233–241. [[CrossRef](#)]
99. Zhou, Z.; Qi, J.; Lim, C.W.; Kim, J.-W.; Kim, B. Dual TBK1/IKK ϵ Inhibitor Amlexanox Mitigates Palmitic Acid-Induced Hepatotoxicity and Lipopoptosis in Vitro. *Toxicology* **2020**, *444*, 152579. [[CrossRef](#)]

100. Achterbergh, R.; Lammers, L.A.; Klumpen, H.-J.; Mathôt, R.A.A.; Romijn, J.A. Short-Term High-Fat Diet Alters Acetaminophen Metabolism in Healthy Individuals. *Ther. Drug Monit.* **2022**, *44*, 797–804. [[CrossRef](#)]
101. Videla, L.A.; Rodrigo, R.; Orellana, M.; Fernandez, V.; Tapia, G.; Quiñones, L.; Varela, N.; Contreras, J.; Lazarte, R.; Csendes, A.; et al. Oxidative Stress-Related Parameters in the Liver of Non-Alcoholic Fatty Liver Disease Patients. *Clin. Sci.* **2004**, *106*, 261–268. [[CrossRef](#)]
102. Hardwick, R.N.; Fisher, C.D.; Canet, M.J.; Lake, A.D.; Cherrington, N.J. Diversity in Antioxidant Response Enzymes in Progressive Stages of Human Nonalcoholic Fatty Liver Disease. *Drug Metab. Dispos.* **2010**, *38*, 2293–2301. [[CrossRef](#)]
103. Lin, Z.; Cai, F.; Lin, N.; Ye, J.; Zheng, Q.; Ding, G. Effects of Glutamine on Oxidative Stress and Nuclear Factor-KB Expression in the Livers of Rats with Nonalcoholic Fatty Liver Disease. *Exp. Ther. Med.* **2014**, *7*, 365–370. [[CrossRef](#)]
104. Wang, G.; Wu, B.; Zhang, L.; Jin, X.; Wang, K.; Xu, W.; Zhang, B.; Wang, H. The Protective Effects of Trelagliptin on High-Fat Diet-Induced Nonalcoholic Fatty Liver Disease in Mice. *J. Biochem. Mol. Toxicol.* **2021**, *35*, e22696. [[CrossRef](#)]
105. Li, L.; Zhang, G.-F.; Lee, K.; Lopez, R.; Previs, S.F.; Willard, B.; McCullough, A.; Kasumov, T. A Western Diet Induced NAFLD in LDLR(-/-) Mice Is Associated with Reduced Hepatic Glutathione Synthesis. *Free Radic. Biol. Med.* **2016**, *96*, 13–21. [[CrossRef](#)]
106. Staňková, P.; Kučera, O.; Peterová, E.; Lotková, H.; Maseko, T.E.; Nožičková, K.; Červinková, Z. Adaptation of Mitochondrial Substrate Flux in a Mouse Model of Nonalcoholic Fatty Liver Disease. *Int. J. Mol. Sci.* **2020**, *21*, 1101. [[CrossRef](#)]
107. Smirne, C.; Croce, E.; Di Benedetto, D.; Cantaluppi, V.; Comi, C.; Sainaghi, P.P.; Minisini, R.; Grossini, E.; Pirisi, M. Oxidative Stress in Non-Alcoholic Fatty Liver Disease. *Livers* **2022**, *2*, 30–76. [[CrossRef](#)]
108. Fromenty, B.; Roden, M. Mitochondrial Alterations in Fatty Liver Diseases. *J. Hepatol.* **2022**, Oct 7. 22, S0168–S8278. [[CrossRef](#)]
109. Liu, Y.; Chen, Y.; Xie, X.; Yin, A.; Yin, Y.; Liu, Y.; Dong, L.; Zhu, Z.; Zhou, J.; Zeng, Q.; et al. Gender Difference on the Effect of Omega-3 Polyunsaturated Fatty Acids on Acetaminophen-Induced Acute Liver Failure. *Oxid. Med. Cell Longev.* **2020**, *2020*, 8096847. [[CrossRef](#)]
110. Liu, Y.; Lin, J.; Chen, Y.; Li, Z.; Zhou, J.; Lu, X.; Chen, Z.; Zuo, D. Omega-3 Polyunsaturated Fatty Acids Inhibit IL-11/STAT3 Signaling in Hepatocytes during Acetaminophen Hepatotoxicity. *Int. J. Mol. Med.* **2021**, *48*, 190. [[CrossRef](#)]
111. Teratani, T.; Tomita, K.; Suzuki, T.; Furuhashi, H.; Irie, R.; Hida, S.; Okada, Y.; Kurihara, C.; Ebinuma, H.; Nakamoto, N.; et al. Free Cholesterol Accumulation in Liver Sinusoidal Endothelial Cells Exacerbates Acetaminophen Hepatotoxicity via TLR9 Signaling. *J. Hepatol.* **2017**, *67*, 780–790. [[CrossRef](#)]
112. Marí, M.; Caballero, F.; Colell, A.; Morales, A.; Caballeria, J.; Fernandez, A.; Enrich, C.; Fernandez-Checa, J.C.; García-Ruiz, C. Mitochondrial Free Cholesterol Loading Sensitizes to TNF- and Fas-Mediated Steatohepatitis. *Cell Metab.* **2006**, *4*, 185–198. [[CrossRef](#)]
113. Ribas, V.; García-Ruiz, C.; Fernández-Checa, J.C. Glutathione and Mitochondria. *Front Pharm.* **2014**, *5*, 151. [[CrossRef](#)]
114. Xu, Y.; Lu, J.; Guo, Y.; Zhang, Y.; Liu, J.; Huang, S.; Zhang, Y.; Gao, L.; Wang, X. Hypercholesterolemia Reduces the Expression and Function of Hepatic Drug Metabolizing Enzymes and Transporters in Rats. *Toxicol. Lett.* **2022**, *364*, 1–11. [[CrossRef](#)]
115. Karkucinska-Wieckowska, A.; Simoes, I.C.M.; Kalinowski, P.; Lebidzinska-Arciszewska, M.; Zieniewicz, K.; Milkiewicz, P.; Górska-Ponikowska, M.; Pinton, P.; Malik, A.N.; Krawczyk, M.; et al. Mitochondria, Oxidative Stress and Nonalcoholic Fatty Liver Disease: A Complex Relationship. *Eur. J. Clin. Investig.* **2022**, *52*, e13622. [[CrossRef](#)]
116. Pérez-Carreras, M.; Del Hoyo, P.; Martín, M.A.; Rubio, J.C.; Martín, A.; Castellano, G.; Colina, F.; Arenas, J.; Solis-Herruzo, J.A. Defective Hepatic Mitochondrial Respiratory Chain in Patients with Nonalcoholic Steatohepatitis. *Hepatology* **2003**, *38*, 999–1007. [[CrossRef](#)]
117. Koliaki, C.; Szendroedi, J.; Kaul, K.; Jelenik, T.; Nowotny, P.; Jankowiak, F.; Herder, C.; Carstensen, M.; Krausch, M.; Knoefel, W.T.; et al. Adaptation of Hepatic Mitochondrial Function in Humans with Non-Alcoholic Fatty Liver Is Lost in Steatohepatitis. *Cell Metab.* **2015**, *21*, 739–746. [[CrossRef](#)]
118. Ramsay, R.R.; Rashed, M.S.; Nelson, S.D. In Vitro Effects of Acetaminophen Metabolites and Analogs on the Respiration of Mouse Liver Mitochondria. *Arch. Biochem. Biophys.* **1989**, *273*, 449–457. [[CrossRef](#)]
119. Chrøis, K.M.; Larsen, S.; Pedersen, J.S.; Rygg, M.O.; Boilsen, A.E.B.; Bendtsen, F.; Dela, F. Acetaminophen Toxicity Induces Mitochondrial Complex I Inhibition in Human Liver Tissue. *Basic Clin. Pharm. Toxicol.* **2020**, *126*, 86–91. [[CrossRef](#)]
120. Fromenty, B. Alteration of Mitochondrial DNA Homeostasis in Drug-Induced Liver Injury. *Food Chem. Toxicol.* **2020**, *135*, 110916. [[CrossRef](#)]
121. Farrell, G.; Schattenberg, J.M.; Leclercq, I.; Yeh, M.M.; Goldin, R.; Teoh, N.; Schuppan, D. Mouse Models of Nonalcoholic Steatohepatitis: Toward Optimization of Their Relevance to Human Nonalcoholic Steatohepatitis. *Hepatology* **2019**, *69*, 2241–2257. [[CrossRef](#)]
122. Schuster, S.; Cabrera, D.; Arrese, M.; Feldstein, A.E. Triggering and Resolution of Inflammation in NASH. *Nat. Rev. Gastroenterol. Hepatol.* **2018**, *15*, 349–364. [[CrossRef](#)]
123. Kazankov, K.; Jørgensen, S.M.D.; Thomsen, K.L.; Møller, H.J.; Vilstrup, H.; George, J.; Schuppan, D.; Grønbaek, H. The Role of Macrophages in Nonalcoholic Fatty Liver Disease and Nonalcoholic Steatohepatitis. *Nat. Rev. Gastroenterol. Hepatol.* **2019**, *16*, 145–159. [[CrossRef](#)]
124. Schneider, K.M.; Elfers, C.; Ghallab, A.; Schneider, C.V.; Galvez, E.J.C.; Mohs, A.; Gui, W.; Candels, L.S.; Wirtz, T.H.; Zuehlke, S.; et al. Intestinal Dysbiosis Amplifies Acetaminophen-Induced Acute Liver Injury. *Cell Mol. Gastroenterol. Hepatol.* **2021**, *11*, 909–933. [[CrossRef](#)]

125. Levy, M.; Shapiro, H.; Thaiss, C.A.; Elinav, E. NLRP6: A Multifaceted Innate Immune Sensor. *Trends Immunol.* **2017**, *38*, 248–260. [[CrossRef](#)]
126. Aron-Wisniewsky, J.; Vigliotti, C.; Witjes, J.; Le, P.; Holleboom, A.G.; Verheij, J.; Nieuwdorp, M.; Clément, K. Gut Microbiota and Human NAFLD: Disentangling Microbial Signatures from Metabolic Disorders. *Nat. Rev. Gastroenterol. Hepatol.* **2020**, *17*, 279–297. [[CrossRef](#)]
127. Breton, J.; Galmiche, M.; Déchelotte, P. Dysbiotic Gut Bacteria in Obesity: An Overview of the Metabolic Mechanisms and Therapeutic Perspectives of Next-Generation Probiotics. *Microorganisms* **2022**, *10*, 452. [[CrossRef](#)]
128. Sneed, R.A.; Grimes, S.D.; Schultze, A.E.; Brown, A.P.; Ganey, P.E. Bacterial Endotoxin Enhances the Hepatotoxicity of Allyl Alcohol. *Toxicol. Appl. Pharm.* **1997**, *144*, 77–87. [[CrossRef](#)]
129. Shaw, P.J.; Ganey, P.E.; Roth, R.A. Idiosyncratic Drug-Induced Liver Injury and the Role of Inflammatory Stress with an Emphasis on an Animal Model of Trovafloxacin Hepatotoxicity. *Toxicol. Sci.* **2010**, *118*, 7–18. [[CrossRef](#)]
130. Wu, W.; Zhao, L.; Yang, P.; Zhou, W.; Li, B.; Moorhead, J.F.; Varghese, Z.; Ruan, X.Z.; Chen, Y. Inflammatory Stress Sensitizes the Liver to Atorvastatin-Induced Injury in ApoE^{-/-} Mice. *PLoS ONE* **2016**, *11*, e0159512. [[CrossRef](#)]
131. Lee, W.H.; Kramer, W.G.; Granville, G.E. The Effect of Obesity on Acetaminophen Pharmacokinetics in Man. *J. Clin. Pharm.* **1981**, *21*, 284–287. [[CrossRef](#)]
132. Abernethy, D.R.; Divoll, M.; Greenblatt, D.J.; Ameer, B. Obesity, Sex, and Acetaminophen Disposition. *Clin. Pharm. Ther.* **1982**, *31*, 783–790. [[CrossRef](#)]
133. Emery, M.G.; Fisher, J.M.; Chien, J.Y.; Kharasch, E.D.; Dellinger, E.P.; Kowdley, K.V.; Thummel, K.E. CYP2E1 Activity before and after Weight Loss in Morbidly Obese Subjects with Nonalcoholic Fatty Liver Disease. *Hepatology* **2003**, *38*, 428–435. [[CrossRef](#)]
134. Leclercq, I.A.; Field, J.; Enriquez, A.; Farrell, G.C.; Robertson, G.R. Constitutive and Inducible Expression of Hepatic CYP2E1 in Leptin-Deficient Ob/Ob Mice. *Biochem. Biophys. Res. Commun.* **2000**, *268*, 337–344. [[CrossRef](#)]
135. Abdel-Razzak, Z.; Loyer, P.; Fautrel, A.; Gautier, J.C.; Corcos, L.; Turlin, B.; Beaune, P.; Guillouzo, A. Cytokines Down-Regulate Expression of Major Cytochrome P-450 Enzymes in Adult Human Hepatocytes in Primary Culture. *Mol. Pharm.* **1993**, *44*, 707–715.
136. Wang, J.; Hu, Y.; Nekvindova, J.; Ingelman-Sundberg, M.; Neve, E.P.A. IL-4-Mediated Transcriptional Regulation of Human CYP2E1 by Two Independent Signaling Pathways. *Biochem. Pharm.* **2010**, *80*, 1592–1600. [[CrossRef](#)]
137. Lin, Q.; Kang, X.; Li, X.; Wang, T.; Liu, F.; Jia, J.; Jin, Z.; Xue, Y. NF- κ B-Mediated Regulation of Rat CYP2E1 by Two Independent Signaling Pathways. *PLoS ONE* **2019**, *14*, e0225531. [[CrossRef](#)]
138. Drozdziak, M.; Lapczuk-Romanska, J.; Wenzel, C.; Szelag-Pieniek, S.; Post, M.; Skalski, Ł.; Kurzawski, M.; Oswald, S. Gene Expression and Protein Abundance of Hepatic Drug Metabolizing Enzymes in Liver Pathology. *Pharmaceutics* **2021**, *13*, 1334. [[CrossRef](#)]
139. Nakai, K.; Tanaka, H.; Hanada, K.; Ogata, H.; Suzuki, F.; Kumada, H.; Miyajima, A.; Ishida, S.; Sunouchi, M.; Habano, W.; et al. Decreased Expression of Cytochromes P450 1A2, 2E1, and 3A4 and Drug Transporters Na⁺-Taurocholate-Cotransporting Polypeptide, Organic Cation Transporter 1, and Organic Anion-Transporting Peptide-C Correlates with the Progression of Liver Fibrosis in Chronic Hepatitis C Patients. *Drug Metab. Dispos.* **2008**, *36*, 1786–1793. [[CrossRef](#)]
140. Müller, G.F.; Döhr, O.; El-Bahay, C.; Kahl, R.; Abel, J. Effect of Transforming Growth Factor-Beta1 on Cytochrome P450 Expression: Inhibition of CYP1 mRNA and Protein Expression in Primary Rat Hepatocytes. *Arch. Toxicol.* **2000**, *74*, 145–152. [[CrossRef](#)]
141. Ciuculan, L.; Ehnert, S.; Ilkavets, I.; Weng, H.-L.; Gaitantzi, H.; Tsukamoto, H.; Ueberham, E.; Meindl-Beinker, N.M.; Singer, M.V.; Breitkopf, K.; et al. TGF-Beta Enhances Alcohol Dependent Hepatocyte Damage via down-Regulation of Alcohol Dehydrogenase I. *J. Hepatol.* **2010**, *52*, 407–416. [[CrossRef](#)]
142. Kolwankar, D.; Vuppalanchi, R.; Ethell, B.; Jones, D.R.; Wrighton, S.A.; Hall, S.D.; Chalasani, N. Association between Nonalcoholic Hepatic Steatosis and Hepatic Cytochrome P-450 3A Activity. *Clin. Gastroenterol. Hepatol.* **2007**, *5*, 388–393. [[CrossRef](#)]
143. Chiba, T.; Noji, K.; Shinozaki, S.; Suzuki, S.; Umegaki, K.; Shimokado, K. Diet-Induced Non-Alcoholic Fatty Liver Disease Affects Expression of Major Cytochrome P450 Genes in a Mouse Model. *J. Pharm. Pharm.* **2016**, *68*, 1567–1576. [[CrossRef](#)]
144. Woolsey, S.J.; Mansell, S.E.; Kim, R.B.; Tirona, R.G.; Beaton, M.D. CYP3A Activity and Expression in Nonalcoholic Fatty Liver Disease. *Drug Metab. Dispos.* **2015**, *43*, 1484–1490. [[CrossRef](#)]
145. Cobbina, E.; Akhlaghi, F. Non-Alcoholic Fatty Liver Disease (NAFLD)—Pathogenesis, Classification, and Effect on Drug Metabolizing Enzymes and Transporters. *Drug Metab. Rev.* **2017**, *49*, 197–211. [[CrossRef](#)]
146. Jamwal, R.; de la Monte, S.M.; Ogasawara, K.; Adusumalli, S.; Barlock, B.B.; Akhlaghi, F. Nonalcoholic Fatty Liver Disease and Diabetes Are Associated with Decreased CYP3A4 Protein Expression and Activity in Human Liver. *Mol. Pharm.* **2018**, *15*, 2621–2632. [[CrossRef](#)]
147. Smit, C.; De Hoogd, S.; Brüggemann, R.J.M.; Knibbe, C.A.J. Obesity and Drug Pharmacology: A Review of the Influence of Obesity on Pharmacokinetic and Pharmacodynamic Parameters. *Expert. Opin. Drug Metab. Toxicol.* **2018**, *14*, 275–285. [[CrossRef](#)]
148. Zeng, H.; Lin, Y.; Gong, J.; Lin, S.; Gao, J.; Li, C.; Feng, Z.; Zhang, H.; Zhang, J.; Li, Y.; et al. CYP3A Suppression during Diet-Induced Nonalcoholic Fatty Liver Disease Is Independent of PXR Regulation. *Chem. Biol. Interact.* **2019**, *308*, 185–193. [[CrossRef](#)]
149. Krogstad, V.; Peric, A.; Robertsen, I.; Kringen, M.K.; Vistnes, M.; Hjelmæsæth, J.; Sandbu, R.; Johnson, L.K.; Angeles, P.C.; Jansson-Löfmark, R.; et al. Correlation of Body Weight and Composition With Hepatic Activities of Cytochrome P450 Enzymes. *J. Pharm. Sci.* **2021**, *110*, 432–437. [[CrossRef](#)]

150. Wiese, M.D.; Meakin, A.S.; Varcoe, T.J.; Darby, J.R.T.; Sarr, O.; Kiser, P.; Bradshaw, E.L.; Regnault, T.R.H.; Morrison, J.L. Hepatic Cytochrome P450 Function Is Reduced by Life-Long Western Diet Consumption in Guinea Pig Independent of Birth Weight. *Life Sci.* **2021**, *287*, 120133. [CrossRef]
151. Fisher, C.D.; Lickteig, A.J.; Augustine, L.M.; Ranger-Moore, J.; Jackson, J.P.; Ferguson, S.S.; Cherrington, N.J. Hepatic Cytochrome P450 Enzyme Alterations in Humans with Progressive Stages of Nonalcoholic Fatty Liver Disease. *Drug Metab. Dispos.* **2009**, *37*, 2087–2094. [CrossRef]
152. Lake, A.D.; Novak, P.; Fisher, C.D.; Jackson, J.P.; Hardwick, R.N.; Billheimer, D.D.; Klimecki, W.T.; Cherrington, N.J. Analysis of Global and Absorption, Distribution, Metabolism, and Elimination Gene Expression in the Progressive Stages of Human Nonalcoholic Fatty Liver Disease. *Drug Metab. Dispos.* **2011**, *39*, 1954–1960. [CrossRef]
153. Li, H.; Clarke, J.D.; Dzierlenga, A.L.; Bear, J.; Goedken, M.J.; Cherrington, N.J. In Vivo Cytochrome P450 Activity Alterations in Diabetic Nonalcoholic Steatohepatitis Mice. *J. Biochem. Mol. Toxicol.* **2017**, *31*, e21840. [CrossRef]
154. Hou, C.; Feng, W.; Wei, S.; Wang, Y.; Xu, X.; Wei, J.; Ma, Z.; Du, Y.; Guo, J.; He, Y.; et al. Bioinformatics Analysis of Key Differentially Expressed Genes in Nonalcoholic Fatty Liver Disease Mice Models. *Gene Expr.* **2018**, *19*, 25–35. [CrossRef]
155. Gabbia, D.; Roverso, M.; Guido, M.; Sacchi, D.; Scaffidi, M.; Carrara, M.; Orso, G.; Russo, F.P.; Floreani, A.; Bogialli, S.; et al. Western Diet-Induced Metabolic Alterations Affect Circulating Markers of Liver Function before the Development of Steatosis. *Nutrients* **2019**, *11*, 1602. [CrossRef]
156. Al Nebaihi, H.M.; Al Batran, R.; Ussher, J.R.; Maayah, Z.H.; El-Kadi, A.O.S.; Brocks, D.R. Dietary-Induced Obesity, Hepatic Cytochrome P450, and Lidocaine Metabolism: Comparative Effects of High-Fat Diets in Mice and Rats and Reversibility of Effects With Normalization of Diet. *J. Pharm. Sci.* **2020**, *109*, 1199–1210. [CrossRef]
157. Wu, J.; Lou, Y.-G.; Yang, X.; Wang, R.; Zhang, R.; Aa, J.-Y.; Wang, G.-J.; Xie, Y. Silybin Regulates P450s Activity by Attenuating Endoplasmic Reticulum Stress in Mouse Nonalcoholic Fatty Liver Disease. *Acta Pharm. Sin.* **2022**, *44*, 133–144. [CrossRef]
158. Xiang, L.; Jiao, Y.; Qian, Y.; Li, Y.; Mao, F.; Lu, Y. Comparison of Hepatic Gene Expression Profiles between Three Mouse Models of Nonalcoholic Fatty Liver Disease. *Genes Dis.* **2022**, *9*, 201–215. [CrossRef]
159. Wahlang, B.; Song, M.; Beier, J.I.; Cameron Falkner, K.; Al-Eryani, L.; Clair, H.B.; Prough, R.A.; Osborne, T.S.; Malarkey, D.E.; States, J.C.; et al. Evaluation of Aroclor 1260 Exposure in a Mouse Model of Diet-Induced Obesity and Non-Alcoholic Fatty Liver Disease. *Toxicol. Appl. Pharm.* **2014**, *279*, 380–390. [CrossRef]
160. Abernethy, D.R.; Greenblatt, D.J.; Divoll, M.; Shader, R.I. Enhanced Glucuronide Conjugation of Drugs in Obesity: Studies of Lorazepam, Oxazepam, and Acetaminophen. *J. Lab. Clin. Med.* **1983**, *101*, 873–880.
161. Barshop, N.J.; Capparelli, E.V.; Sirlin, C.B.; Schwimmer, J.B.; Lavine, J.E. Acetaminophen Pharmacokinetics in Children with Nonalcoholic Fatty Liver Disease. *J. Pediatr. Gastroenterol. Nutr.* **2011**, *52*, 198–202. [CrossRef]
162. Mazaleuskaya, L.L.; Sangkuhl, K.; Thorn, C.F.; FitzGerald, G.A.; Altman, R.B.; Klein, T.E. PharmGKB Summary: Pathways of Acetaminophen Metabolism at the Therapeutic versus Toxic Doses. *Pharm. Genom.* **2015**, *25*, 416–426. [CrossRef]
163. Hardwick, R.N.; Ferreira, D.W.; More, V.R.; Lake, A.D.; Lu, Z.; Manautou, J.E.; Slitt, A.L.; Cherrington, N.J. Altered UDP-Glucuronosyltransferase and Sulfotransferase Expression and Function during Progressive Stages of Human Nonalcoholic Fatty Liver Disease. *Drug Metab. Dispos.* **2013**, *41*, 554–561. [CrossRef]
164. Feng, R.; Wang, Y.; Liu, C.; Yan, C.; Zhang, H.; Su, H.; Kang, J.X.; Shang, C.-Z.; Wan, J.-B. Acetaminophen-Induced Liver Injury Is Attenuated in Transgenic Fat-1 Mice Endogenously Synthesizing Long-Chain n-3 Fatty Acids. *Biochem. Pharm.* **2018**, *154*, 75–88. [CrossRef]
165. Eraky, S.M.; Abo El-Magd, N.F. Omega-3 Fatty Acids Protect against Acetaminophen-Induced Hepatic and Renal Toxicity in Rats through HO-1-Nrf2-BACH1 Pathway. *Arch. Biochem. Biophys.* **2020**, *687*, 108387. [CrossRef]
166. Speck, R.F.; Lauterburg, B.H. Fish Oil Protects Mice against Acetaminophen Hepatotoxicity in Vivo. *Hepatology* **1991**, *13*, 557–561. [CrossRef]
167. Maksymchuk, O.; Shysh, A.; Stroy, D. Treatment with Omega-3 PUFAs Does Not Increase the Risk of CYP2E1-Dependent Oxidative Stress and Diabetic Liver Pathology. *Front. Endocrinol.* **2022**, *13*, 1004564. [CrossRef]
168. Jain, P.; Hejjaji, V.; Thomas, M.B.; Garcia, R.A.; Kennedy, K.F.; Goyal, A.; Sperling, L.; Das, S.R.; Hafida, S.; Enriquez, J.R.; et al. Use of Primary Bariatric Surgery among Patients with Obesity and Diabetes. Insights from the Diabetes Collaborative Registry. *Int. J. Obes.* **2022**, *46*, 2163–2167. [CrossRef]
169. Zhou, H.; Luo, P.; Li, P.; Wang, G.; Yi, X.; Fu, Z.; Sun, X.; Cui, B.; Zhu, L.; Zhu, S. Bariatric Surgery Improves Nonalcoholic Fatty Liver Disease: Systematic Review and Meta-Analysis. *Obes. Surg.* **2022**, *32*, 1872–1883. [CrossRef]
170. Holt, E.W.; DeMartini, S.; Davern, T.J. Acute Liver Failure Due to Acetaminophen Poisoning in Patients With Prior Weight Loss Surgery: A Case Series. *J. Clin. Gastroenterol.* **2015**, *49*, 790–793. [CrossRef]
171. Abusabeib, A.; El Ansari, W.; Alobaidan, J.; Elhag, W. First Case Report of Fulminant Hepatitis After Laparoscopic Sleeve Gastrectomy Associated with Concomitant Maximal Therapeutic Dose of Acetaminophen Use, Protein Calorie Malnutrition, and Vitamins A and D, Selenium, and Glutathione Deficiencies. *Obes. Surg.* **2021**, *31*, 899–903. [CrossRef]
172. Puris, E.; Pasanen, M.; Ranta, V.-P.; Gynther, M.; Petsalo, A.; Käkälä, P.; Männistö, V.; Pihlajamäki, J. Laparoscopic Roux-En-Y Gastric Bypass Surgery Influenced Pharmacokinetics of Several Drugs given as a Cocktail with the Highest Impact Observed for CYP1A2, CYP2C8 and CYP2E1 Substrates. *Basic. Clin. Pharm. Toxicol.* **2019**, *125*, 123–132. [CrossRef]

173. Porat, D.; Markovic, M.; Zur, M.; Fine-Shamir, N.; Azran, C.; Shaked, G.; Czeiger, D.; Vaynshtein, J.; Replyanski, I.; Sebbag, G.; et al. Increased Paracetamol Bioavailability after Sleeve Gastrectomy: A Crossover Pre- vs. Post-Operative Clinical Trial. *J. Clin. Med.* **2019**, *8*, 1949. [[CrossRef](#)]
174. Chen, K.-F.; Chan, L.-N.; Senn, T.D.; Oelschlager, B.K.; Flum, D.R.; Shen, D.D.; Horn, J.R.; Lin, Y.S. The Impact of Proximal Roux-En-Y Gastric Bypass Surgery on Acetaminophen Absorption and Metabolism. *Pharmacotherapy* **2020**, *40*, 191–203. [[CrossRef](#)]
175. Katsarou, A.; Gudbjörnsdóttir, S.; Rawshani, A.; Dabelea, D.; Bonifacio, E.; Anderson, B.J.; Jacobsen, L.M.; Schatz, D.A.; Lernmark, Å. Type 1 Diabetes Mellitus. *Nat. Rev. Dis. Prim.* **2017**, *3*, 17016. [[CrossRef](#)]
176. Zaccardi, F.; Webb, D.R.; Yates, T.; Davies, M.J. Pathophysiology of Type 1 and Type 2 Diabetes Mellitus: A 90-Year Perspective. *Postgrad. Med. J.* **2016**, *92*, 63–69. [[CrossRef](#)]
177. Eizirik, D.L.; Pasquali, L.; Cnop, M. Pancreatic β -Cells in Type 1 and Type 2 Diabetes Mellitus: Different Pathways to Failure. *Nat. Rev. Endocrinol.* **2020**, *16*, 349–362. [[CrossRef](#)]
178. de Vries, M.; Westerink, J.; Kaasjager, K.H.A.H.; de Valk, H.W. Prevalence of Nonalcoholic Fatty Liver Disease (NAFLD) in Patients With Type 1 Diabetes Mellitus: A Systematic Review and Meta-Analysis. *J. Clin. Endocrinol. Metab.* **2020**, *105*, 3842–3853. [[CrossRef](#)]
179. Mertens, J.; De Block, C.; Spinhoven, M.; Driessen, A.; Francque, S.M.; Kwanten, W.J. Hepatopathy Associated With Type 1 Diabetes: Distinguishing Non-Alcoholic Fatty Liver Disease From Glycogenic Hepatopathy. *Front. Pharm.* **2021**, *12*, 768576. [[CrossRef](#)]
180. El-Serag, H.B.; Everhart, J.E. Diabetes Increases the Risk of Acute Hepatic Failure. *Gastroenterology* **2002**, *122*, 1822–1828. [[CrossRef](#)]
181. Chalasani, N.; Fontana, R.J.; Bonkovsky, H.L.; Watkins, P.B.; Davern, T.; Serrano, J.; Yang, H.; Rochon, J. Drug Induced Liver Injury Network (DILIN) Causes, Clinical Features, and Outcomes from a Prospective Study of Drug-Induced Liver Injury in the United States. *Gastroenterology* **2008**, *135*, 1924–1934, 1934.e1-4. [[CrossRef](#)]
182. Lu, R.-J.; Zhang, Y.; Tang, F.-L.; Zheng, Z.-W.; Fan, Z.-D.; Zhu, S.-M.; Qian, X.-F.; Liu, N.-N. Clinical Characteristics of Drug-Induced Liver Injury and Related Risk Factors. *Exp. Ther. Med.* **2016**, *12*, 2606–2616. [[CrossRef](#)]
183. Deeds, M.C.; Anderson, J.M.; Armstrong, A.S.; Gastineau, D.A.; Hiddinga, H.J.; Jahangir, A.; Eberhardt, N.L.; Kudva, Y.C. Single Dose Streptozotocin-Induced Diabetes: Considerations for Study Design in Islet Transplantation Models. *Lab. Anim.* **2011**, *45*, 131–140. [[CrossRef](#)]
184. Wang, Q.; Wei, S.; Zhou, H.; Shen, G.; Gan, X.; Zhou, S.; Qiu, J.; Shi, C.; Lu, L. Hyperglycemia Exacerbates Acetaminophen-Induced Acute Liver Injury by Promoting Liver-Resident Macrophage Proinflammatory Response via AMPK/PI3K/AKT-Mediated Oxidative Stress. *Cell Death Discov.* **2019**, *5*, 119. [[CrossRef](#)]
185. Wu, D.; Cederbaum, A.I. Combined Effects of Streptozotocin-Induced Diabetes plus 4-Methylpyrazole Treatment on Rat Liver Cytochrome P450E1. *Arch. Biochem. Biophys.* **1993**, *302*, 175–182. [[CrossRef](#)]
186. Raza, H.; Prabu, S.K.; Robin, M.-A.; Avadhani, N.G. Elevated Mitochondrial Cytochrome P450 2E1 and Glutathione S-Transferase A4-4 in Streptozotocin-Induced Diabetic Rats: Tissue-Specific Variations and Roles in Oxidative Stress. *Diabetes* **2004**, *53*, 185–194. [[CrossRef](#)]
187. Sindhu, R.K.; Koo, J.R.; Sindhu, K.K.; Ehdaie, A.; Farmand, F.; Roberts, C.K. Differential Regulation of Hepatic Cytochrome P450 Monooxygenases in Streptozotocin-Induced Diabetic Rats. *Free Radic. Res.* **2006**, *40*, 921–928. [[CrossRef](#)]
188. Maksymchuk, O.; Shysh, A.; Rosohatska, I.; Chashchyn, M. Quercetin Prevents Type 1 Diabetic Liver Damage through Inhibition of CYP2E1. *Pharmacol. Rep.* **2017**, *69*, 1386–1392. [[CrossRef](#)]
189. Price, V.F.; Jollow, D.J. Increased Resistance of Diabetic Rats to Acetaminophen-Induced Hepatotoxicity. *J. Pharm. Exp. Ther.* **1982**, *220*, 504–513.
190. Shankar, K.; Vaidya, V.S.; Apte, U.M.; Manautou, J.E.; Ronis, M.J.J.; Bucci, T.J.; Mehendale, H.M. Type 1 Diabetic Mice Are Protected from Acetaminophen Hepatotoxicity. *Toxicol. Sci.* **2003**, *73*, 220–234. [[CrossRef](#)]
191. Shankar, K.; Vaidya, V.S.; Corton, J.C.; Bucci, T.J.; Liu, J.; Waalkes, M.P.; Mehendale, H.M. Activation of PPAR-Alpha in Streptozotocin-Induced Diabetes Is Essential for Resistance against Acetaminophen Toxicity. *FASEB J.* **2003**, *17*, 1748–1750. [[CrossRef](#)]
192. Boyle, M.; Masson, S.; Anstee, Q.M. The Bidirectional Impacts of Alcohol Consumption and the Metabolic Syndrome: Cofactors for Progressive Fatty Liver Disease. *J. Hepatol.* **2018**, *68*, 251–267. [[CrossRef](#)]
193. Di Ciaula, A.; Bonfrate, L.; Krawczyk, M.; Frühbeck, G.; Portincasa, P. Synergistic and Detrimental Effects of Alcohol Intake on Progression of Liver Steatosis. *Int. J. Mol. Sci.* **2022**, *23*, 2636. [[CrossRef](#)]
194. Massart, J.; Begriche, K.; Corlu, A.; Fromenty, B. Xenobiotic-Induced Aggravation of Metabolic-Associated Fatty Liver Disease. *Int. J. Mol. Sci.* **2022**, *23*, 1062. [[CrossRef](#)]
195. Akakpo, J.Y.; Ramachandran, A.; Jaeschke, H. Novel strategies for the treatment of acetaminophen hepatotoxicity. *Expert. Opin. Drug Metab. Toxicol.* **2020**, *16*, 1039–1050. [[CrossRef](#)]
196. Subramanya, S.B.; Venkataraman, B.; Meeran, M.F.N.; Goyal, S.N.; Patil, C.R.; Ojha, S. Therapeutic Potential of Plants and Plant Derived Phytochemicals against Acetaminophen-Induced Liver Injury. *Int. J. Mol. Sci.* **2018**, *19*, 3776. [[CrossRef](#)]
197. Jaeschke, H.; Adelusi, O.B.; Ramachandran, A. Ferroptosis and Acetaminophen Hepatotoxicity: Are We Going Down Another Rabbit Hole? *Gene Expr.* **2021**, *20*, 169–178. [[CrossRef](#)]
198. Liao, Y.; Yang, Y.; Wang, X.; Wei, M.; Guo, Q.; Zhao, L. Oroxyloside ameliorates acetaminophen-induced hepatotoxicity by inhibiting JNK related apoptosis and necroptosis. *J. Ethnopharmacol.* **2020**, *258*, 112917. [[CrossRef](#)]

199. Hwang, K.A.; Hwang, Y.; Hwang, H.J.; Park, N. Hepatoprotective Effects of Radish (*Raphanus sativus* L.) on Acetaminophen-Induced Liver Damage via Inhibiting Oxidative Stress and Apoptosis. *Nutrients* **2022**, *14*, 5082. [[CrossRef](#)]
200. Du, K.; Ramachandran, A.; McGill, M.R.; Mansouri, A.; Asselah, T.; Farhood, A.; Woolbright, B.L.; Ding, W.X.; Jaeschke, H. Induction of mitochondrial biogenesis protects against acetaminophen hepatotoxicity. *Food Chem. Toxicol.* **2017**, *108*, 339–350.

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.