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Cholestatic liver injury induced by food additives, dietary supplements and parenteral nutrition

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ABSTRACT

Cholestasis refers to the accumulation of toxic levels of bile acids in the liver due to defective bile secretion. This pathological situation can be triggered by drugs, but also by ingredients contained in food, food supplements and parenteral nutrition. This paper provides an overview of the current knowledge on cholestatic injury associated with such ingredients, with particular emphasis on the underlying mechanisms of toxicity.

1. Introduction

Cholestasis describes any situation of impaired bile flow within the liver as such (intrahepatic cholestasis) or in the biliary tree (extrahepatic cholestasis) leading to the accumulation of toxic levels of bile acids (BAs) (Tanaka et al., 2017). In adult patients it is usually depicted as an increase in serum levels of alkaline phosphatase (ALP) to more than twice the upper limit of normal and an alanine aminotransferase (ALT) to ALP ratio (ALT/ALP) below 2 (Bjornsson and Jonasson, 2013). Additionally, although hyperbilirubinemia is not a synonym of cholestasis, cholestatic injury usually leads to impaired conjugated bilirubin excretion. Therefore, recent guidelines for establishing cholestatic jaundice in infants suggest considering serum levels of direct bilirubin, mainly conjugated, above 1 mg/dL as a surrogate marker (Fawaz et al., 2017), but most clinical reports actually refer to values above 2 mg/dL (Calkins et al., 2014; Fortenberry et al., 2017; Gao et al., 2018; Jenniskens et al., 2018).

Cholestasis may be triggered by drugs, which constitutes a subtype of drug-induced liver injury (DILI). This is one of the main reasons for drug withdrawal in pre-marketing and post-marketing phases of drug development, therefore implying a considerable economic burden for pharmaceutical industry (Kullak-Ublick et al., 2017; Lee, 2003). In this particular case, interspecies differences restrict its detection in regular preclinical animal testing. These include differences in BA composition, particularly the toxic lithocholic acid, differences in substrate specificity of BA transporters, along with differences in metabolic, detoxification and hepatocellular excretion pathways concerning drugs and BAs (Yang et al., 2015). Additionally, the knowledge gaps on the mechanistic implementation and development of cholestasis have also been hampering the characterization of this hazard for new drugs and chemicals in general. Furthermore, the frequently delayed onset of cholestasis limits its detection in *in vitro* models, which in most cases can only be used for short-term studies. A significant effort has been made in recent years to develop *in vitro* models that can better mimic the *in vivo* human scenario for longer periods of time (Gijbels et al., 2019; Vilas-Boas et al., 2019a). Spheroid cultures of primary human hepatocytes provide reliable and versatile tools for studying drug-induced cholestasis due to their similarity to the clinical situation and to the possibility of performing long-term studies (Baze et al., 2018; Bell et al., 2016; Hendriks et al., 2016).

The main mechanisms so far implicated in the onset of drug-induced cholestasis are summarized in Fig. 1. These include altered bile

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AMA, anti-mitochondrial antibodies; AOP, adverse outcome pathway; AST, aspartate aminotransferase; BA(s), bile acid(s); BSEP, bile salt export pump; CYP, cytochrome P450; DILI, drug-induced liver injury; EFSA, European Food Safety Authority; ERα, Estrogen receptor alpha; FDA, Food and Drug Administration; FGF19, fibroblast growth factor 19; FGFR4, FGF receptor 4; FXR, Farnesoid X receptor; GPBAR1, G protein-coupled bile acid receptor 1; IL-1β, interleukin 1 beta; LXR, liver X receptor; MRP, multidrug resistance-associated protein; Nrf2, nuclear factor erythroid 2-related factor 2; NTCP, sodium-taurocholate cotransporting polypeptide; PN, parenteral nutrition; PN-AC, PN-associated cholestasis; ROS, reactive oxygen species; RXR, retinoid X receptor; TGR5, Takeda G protein-coupled receptor 5; TNFα, tumor necrosis factor alpha

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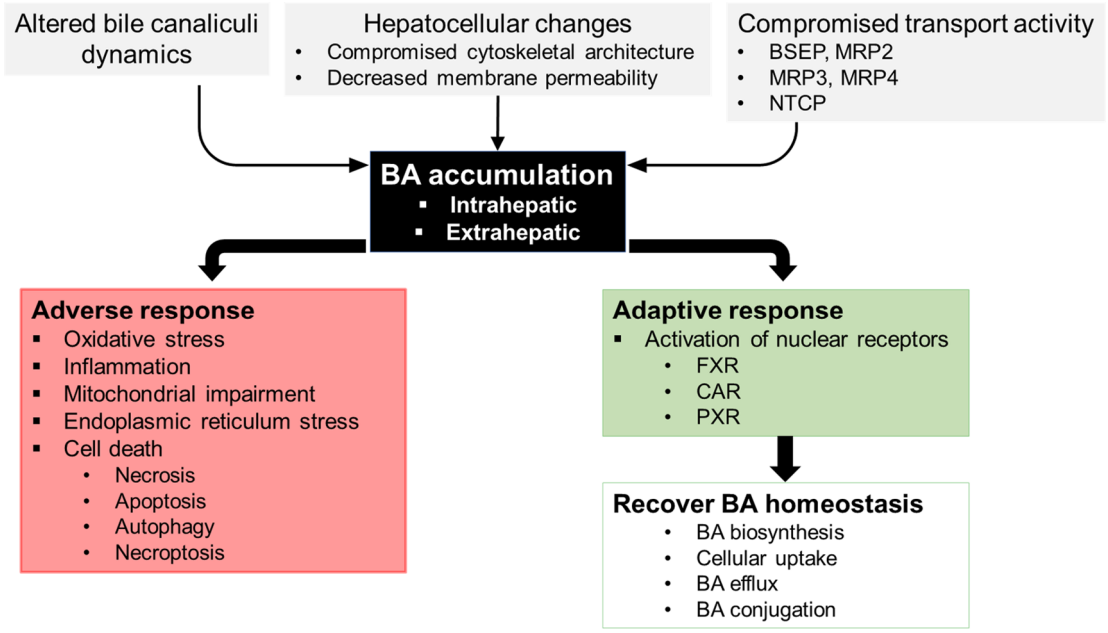

Fig. 1. Mechanisms of bile acid accumulation and subsequent deteriorative and compensatory responses. The accumulation of BAs triggers an adverse response that may ultimately lead to cell death. An adaptive response is simultaneously activated to counteract the observed unbalance in the BA levels. BA – Bile acid; BSEP – Bile salt export pump; MRP – Multidrug resistance-associated protein; NTCP – Sodium-taurocholate cotransporting polypeptide; FXR – Farnesoid X receptor; CAR – Constitutive androstane receptor; PXR – Pregnane X receptor.

canaliculi dynamics, *i.e.* the constriction/dilation of the bile canaliculi due to activation/inhibition of the Rho kinase/myosin light chain kinase pathway (Burbank et al., 2016), and hepatocellular changes, such as cytoskeletal alterations and decreased membrane fluidity (Gijbels et al., 2019). Apart from these, the best described mechanism of drug-induced cholestasis relies on compromised activity of BA transporters. The most relevant BA transporters in this context are the bile salt export pump (BSEP) and the multidrug resistance-associated protein (MRP) 2, both exporters of BAs to the bile canaliculi, the MRP3 and MRP4 that export BAs to the sinusoidal blood, and the sodium-taurocholate co-transporting polypeptide (NTCP) involved in the uptake of BAs from the enterohepatic circulation (Yang et al., 2013).

The subsequent bile accumulation events evoke 2 types of cellular responses, namely an adverse response and an adaptive response. The adverse response is accompanied by the onset of processes, such as oxidative stress, inflammation and different cell death modes. The adaptive response, aimed at decreasing the uptake and increasing the export of BAs into and from hepatocytes, respectively, depends on the activation of several nuclear receptors (Gijbels et al., 2019).

Many chemical agents other than drugs, including industrial chemicals, cosmetic ingredients and biocides, have been related to cholestasis (Vilas-Boas et al., 2019b). This equally holds true for a number of chemical mixtures regularly used as food additives or common dietary supplements, such as herbal extracts. Amidst the main factors known to predispose individuals to dietary supplement-induced cholestatic liver injury are genetics, the concomitant use of drugs or other supplements and the existence of underlying disease (Brown, 2017; Elinav et al., 2007). Furthermore, the intravenous administration of nutrition known as parenteral nutrition (PN) has been linked to induction of cholestasis (Beath and Kelly, 2016; Guglielmi et al., 2008), although the specific mechanism(s) and the exact culprit(s) have not yet been fully identified (Kumar and Teckman, 2015).

The present manuscript provides an overview of the most documented and relevant chemicals used in food industry that may represent a cholestatic hazard. Among the dietary supplements, a number of herbal-based products and bodybuilding formulas have been related to cholestatic episodes. In some cases, the observed hepatotoxicity has been attributed to contamination with anabolic steroids, known to promote cholestasis (Stolz et al., 2019). Although this represents a major problem, considering the lack of governmental responsibility in the assessment of these products' safety, these cases fall out of the scope of this review paper. On the other hand, given the increased use of parenteral nutrition, especially in a long-term home setting (Bond et al., 2019; Cotogni et al., 2019), the involvement of PN in the onset of cholestasis will be discussed in this manuscript.

2. Food additives

A number of chemicals have been approved as food additives to improve the appearance, taste and the stability of food products. This approval is part of the responsibilities of regulatory bodies, such as the European Food Safety Authority (EFSA) in Europe and the Food and Drug Administration (FDA) in the US. Those chemicals include food colorings, preservatives, acidity regulators and antioxidants, emulsifiers and stabilizers, anti-caking agents, flavor enhancers, glazing agents and others (Kramer et al., 2019). Many of the scientific opinions released by EFSA rely on data collected from animal studies and in most cases those studies evaluate each chemical individually. Therefore, the continuous widespread use of these chemicals provides a source of essential data for the permanent evaluation of the actual safety of food additives for human consumption. In particular, the long-term use of some food additives has been correlated with the development of cholestatic events in laboratory animals (Table 1). Among those are tartrazine and sunset yellow, which are used as colorants in food and cosmetics industry (Vilas-Boas et al., 2019b). EFSA has established an acceptable daily intake up to 7.5 mg/kg body weight (bw)/day for tartrazine and 4 mg/kg bw/day for sunset yellow (EFSA, 2009; 2014). *In vitro* studies have demonstrated that these compounds significantly activate human estrogen receptor alpha (ERα) transcriptional activity (Axon et al., 2012), which warrants their classification as xenoestrogens or, more broadly, endocrine disrupting chemicals. (Xeno)estrogens have been described to cause cholestasis through ERα-dependent decrease of transporter expression (Yamamoto et al., 2006) or ERα-stimulated transporter internalization (Barosso et al., 2012). More recently, the

Table 1
Food additives associated with cholestatic liver injury and proposed mechanisms of hepatotoxicity.

Additive name	Mechanisms of hepatotoxicity	Reference
Tartrazine	– ERα induction possibly leading to decreased transporter expression or increased internalization – Sulphotransferase inhibition	(Axon et al., 2012) (Meyer et al., 2017)
Sunset yellow	ERα induction possibly leading to decreased transporter expression or increased internalization	(Axon et al., 2012)
2-Octynoic acid	Induced modifications on pyruvate dehydrogenase complex leading to production of AMA	(Amano et al., 2005)
Polysorbate 80	Increased membrane permeability	(Ellis et al., 1996)
Brilliant blue FCF Carmoisine Trans-anethole Propylene glycol	Not described	(El-Wahab and Moram, 2013)
Iron tartrate Oxidized polyethylene wax Neotame	Not described	(Kramer et al., 2019)

ERα – Estrogen receptor alpha; AMA - anti-mitochondrial antibodies.

potential of tartrazine to promote cholestasis was confirmed in mice, but seemingly through a distinct mechanism related to the inhibition of sulphotransferase, an enzyme involved in BA sulphation and subsequent excretion (Meyer et al., 2017). The use of tartrazine in rats, either alone or in combination with the flavoring agent vanillin, also resulted in increased serum ALP levels, along with elevated ALT, aspartate aminotransferase (AST) and total bilirubin amounts (El-Wahab and Moram, 2013). The same study also suggested that other colorants, in particular brilliant blue FCF and carmoisine, and other flavoring agents, including trans-anethole and propylene glycol, may cause similar effects. Importantly, with the exception of trans-anethole, for which the test concentration was 20–100 fold above the acceptable daily intake (EFSA, 2011), all other compounds were tested in concentrations approximate to that established threshold (EFSA, 2010; 2015a; 2018b). This highlights the need to further assess the effects of such widespread chemicals in human-based models. Those results confirmed previous *in vivo* data on the effects of tartrazine and carmoisine (Aboel-Zahab et al., 1997; Amin et al., 2010), and of sunset yellow and brilliant blue FCF (Aboel-Zahab et al., 1997). A more recent study denoted increased ALP, ALT, AST and bilirubin serum levels in mice treated with 50–100 fold the acceptable daily intake of carmoisine, but no changes were observed at the acceptable daily intake concentration (4 mg/kg bw/day) (Reza et al., 2019). While biochemical parameters were suggestive of cholestatic events, histopathological evidence of cholestasis was not observed (Reza et al., 2019).

Primary biliary cholangitis is a rare auto-immune disease of the liver that mainly targets cholangiocytes and leads to the destruction of the intrahepatic bile ducts (Poupon, 2010). It is a chronic inflammatory condition characterized by the presence of anti-mitochondrial antibodies (AMA) against the lipoyl domain of the mitochondrial pyruvate dehydrogenase complex and by elevated serum levels of liver enzymes (Kouroumalis and Notas, 2015). Primary biliary cholangitis has a delayed onset that initially displays a cholestatic pattern, subsequently progressing to fibrosis, cirrhosis and eventually liver failure. Although the precise etiology of the disease is still unclear, both genetic and environmental factors, namely exposure to xenobiotics, seem to play a role in its development (Tanaka et al., 2017). 2-Octynoic acid, approved by the FDA for human consumption as an artificial flavoring additive under the designation methyl-2-octynoate, is amongst those xenobiotics (Amano et al., 2005). It is suspected that this compound has the potential to modify the pyruvate dehydrogenase complex in a similar manner to lipoic acid, thereby initiating AMA production and the onset of the disease (Amano et al., 2005). This chemical is also widely used in the cosmetic industry (Vilas-Boas et al., 2019b).

Polysorbate 80, also known as tween 80, has been approved, along with other polysorbates, as an emulsifier for foods and parenteral nutrition formulations, and as a solubilizing and dispersing agent for drug formulations and cosmetics. The acceptable daily intake was set at 10 mg/kg bw/day (EFSA, 2015b). Polysorbate 80 has been implicated in hepatic toxicity originating from the intake of vitamin E formulations, in which it was used as an emulsifier (Bhat et al., 1985). A subsequent study suggested its cholestatic potential in an isolated perfused rat liver model as evidenced by decreased bile flow, possibly due to increased membrane permeability (Ellis et al., 1996).

A recent study describes the systematic screening of EFSA safety evaluation reports to characterize different types of toxicity induced by food additives (Kramer et al., 2019). Clinical indicators of cholestasis were identified for iron tartrate, oxidized polyethylene wax and neotame, used as anti-caking agent, glazing agent and sweetener, respectively. These additives increased serum BAs and/or ALP levels in animal studies (Kramer et al., 2019).

3. Herbs and dietary supplements

Dietary supplements are considered a subset of foods that includes not only vitamins, minerals, amino acids and essential fatty acids, but also herbal extracts, usually in concentrated forms (EFSA, 2018a; FDA, 2018). They are popular agents that are perceived as natural and harmless, and do not require a prescription, which makes them easily accessible to the general public in an uncontrolled manner. The labeling legislation requires that the category or nature of the substances is described, along with some other predefined statements. However, the establishment of the product's safety is the responsibility of the manufacturer, importer, supplier or distributor (EFSA, 2018a; FDA, 2018) and not of a public authority.

The intake of dietary supplements has been implicated as a causal factor in 2–15.5% of all reported cases of hepatotoxicity (Navarro et al., 2017; Stickel et al., 2011; Stickel and Shouval, 2015). These numbers may be slightly higher when considering the underreported events and the difficult diagnosis which, like for DILI cases, relies on the exclusion of every other possible cause(s) for the observed adverse effects (Tajiri and Shimizu, 2008). In most situations, withdrawal of the insult leads to recovery. The gold standard to establish causality is the rechallenge test, which is ethically debatable and clinically not recommended (Tajiri and Shimizu, 2008). Hepatotoxic herbs and dietary supplements are various in nature (Table 2). The complex composition of such supplements offers an additional challenge for the identification of the real causative agent. In general, genetic polymorphisms in cytochrome P450 (CYP) enzymes or in the immune response, the presence of underlying disease and the concomitant intake of other supplements or medication may predispose certain people to such type of hepatotoxicity (Elinav et al., 2007; Stolz et al., 2019).

3.1. Herbal supplements

In the long list of plants known as germanders, the species *Teucrium polium* and *Teucrium chamaedrys* have been associated with liver injury, frequently with a cholestatic signature. They have been used as

Table 2
Dietary supplements related to cholestatic events and suggested mechanisms of hepatotoxicity.

Herbal/dietary supplement (*Scientific name*)	Mechanism of hepatotoxicity	Reference
Germander (*Teucrium polium; Teucrium chamaedrys*)	Metabolic activation of furano neoclerodane diterpenoids teucrin A and teuchmaedryn A	(Kotsiou and Christine, 2017)
Kava extract (*Piper methysticum*)	– Kava lactones-mediated CYP1A2 and CYP2D6 inhibition and glutathione depletion – Inflammatory cholestasis, including Kupffer cell activation, release of pro-inflammatory mediators and ROS formation	(Brown, 2017; Rowe et al., 2011)
Polygonum multiflorum	Idiosyncratic	(Jung et al., 2011)
Hydroxycut®	Oxidative stress prompted by catechin (−)-epigallocatechin gallate	(Stickel et al., 2011)
– Green tea extract (*Camellia sinensis*)		
Herbalife™	– Immune-mediated – Oxidative stress prompted by catechin (−)-epigallocatechin gallate	(Elinav et al., 2007)
– Green tea extract (*Camellia sinensis*)		
– Vitamin A	RXR activation by vitamin A metabolites resulting in co-regulation of BSEP and FGF19 expression	(Saeed et al., 2017)
– *Bacillus subtillis*	Contamination	(Stickel et al., 2009)
Celandine (*Chelidonium majus*)	– Idiosyncratic – Auto-immunity	(Stickel et al., 2003)
Oleanolic acid	Nrf2 activation resulting in decreased CYP7A1, BSEP, NTCP, among others Immune-mediated TGR5 activation leads to increased levels of IL-1β and TNFα	(Lu et al., 2013; Lou et al., 2014)
Fructus Psoraleae (*Psoralea corylifolia*, mature seeds)	Decreased FXR levels, increased CYP7A1 BSEP, MRP2 and MRP3 levels	(Wang et al., 2012)
Artemisinin (*Artemisia annua*)	Immunological reaction to hepatic metabolite	(NIH, 2012)

CYP – cytochrome P450; ROS – Reactive oxygen species; RXR – Retinoid X receptor; BSEP – Bile salt export pump; FGF19 – Fibroblast growth factor 19; Nrf2 – Nuclear factor erythroid 2-related factor 2; NTCP – Sodium-taurocholate cotransporting polypeptide; TGR5 – Takeda G protein-coupled receptor 5; IL-1β – Interleukin 1 beta; TNFα – Tumor necrosis factor alpha; FXR – Farnesoid X receptor; MRP – Multidrug resistance-associated protein

supplements for the control and management of weight, diabetes and hyperlipidemia (NIH, 2012). The mechanism of liver toxicity described so far relies on metabolic activation of the furano neoclerodane diterpenoids teucrin A and teuchmaedryn A to highly reactive epoxides inducers of hepatocyte apoptosis (Kotsiou and Christine, 2017).

Kava extract (*Piper methysticum*) has been used as part of herbal remedies to treat anxiety and insomnia, as the kavapyrones in the extract act as agonists of the gamma-aminobutyric acid receptor (Garcia-Cortes et al., 2008). Despite its traditional use in Polynesia as a beverage, kava has been withdrawn from many consumer markets in European countries (EMA, 2017) and has not been accepted in the US Pharmacopeia (NIH, 2012) due to liver injury concerns. The lactones composing the kava extract seem to be responsible for the inhibition of certain CYP enzymes as well as for glutathione depletion (Brown, 2017), though the results from preclinical and human studies are conflicting (NIH, 2012). The direct or indirect activation of Kupffer cells, and consequent release of inflammatory mediators and reactive oxygen species results in cholestatic inflammation (Rowe et al., 2011). The aqueous kava extracts, however, seem to be less hepatotoxic than the organic ones (Stickel and Shouval, 2015), although hepatotoxicity has been observed in both circumstances (Sarris et al., 2011). Both germander and kava stand out in the midst of the herbs with more related publications, though not case reports (Brown, 2017). These herbs are no longer sold in some countries but may still be available *via* the internet.

Polygonum multiflorum, re-classified as *Reynoutria multiflora,* is also known as Sho-Wu-Pian in China and as Fo-Ti in the US. It has for a long time been used in traditional medicine for its anti-aging properties, but other biological activities have been described, such as anti-inflammatory and anti-hyperlipidemic, among others. Stilbenes and anthraquinones are recognized as major characteristic constituents of this herb, but the real composition depends on whether it is used raw or processed, as this generates changes in the chemical composition (Bounda and Feng, 2015). Even though the most commonly observed hepatic injury follows a hepatocellular pattern (NIH, 2012), it has been implicated in a case of cholestatic hepatitis, which resolved after discontinuation (Park et al., 2001). Additionally, it was identified as possible cause of 25 incidents of toxin-induced acute hepatitis, 7 of which displayed a mixed hepatocellular and cholestatic pattern (Jung et al., 2011). In that report, the causality was probable because the herb was consumed in its natural form and most patients recovered after conservative measures and discontinuation of the insult. There was one positive rechallenge, which established the cause as definite. The mechanism of Fo-Ti-induced cholestasis is not known, yet it has been described as idiosyncratic (Jung et al., 2011). Increased levels of CYP7A1, the main enzyme involved in BA synthesis, were found in mice treated with 2,3,5,4′-tetrahydroxystilbene-2-O-β-D-glucoside, another constituent of Fo-Ti (Chen et al., 2018), an effect that, in the authors' opinion, could underlie the development of cholestasis after Fo-Ti ingestion. Interestingly, it was recently pointed out that the geographical origin of the herb can significantly impact the observed toxicity, possibly due to different composition of the analyzed preparations (Lin et al., 2017). This work also highlighted that even though emodin might be the most toxic component of Fo-Ti, it is not one of the main constituents and, therefore, most likely not the source of the hepatotoxicity. The same study identified tetrahydroxystilbene-O-(galloyl)-hex and emodin-O-hex-sulfate as the possible toxic ingredients (Lin et al., 2017).

3.2. Bodybuilding and weight loss supplements

Hydroxycut® is a brand marketing products for weight loss and bodybuilding, which complex composition has been updated with time following records of cardiotoxicity and hepatotoxicity, including one fatal casualty (Fong et al., 2010). Hepatocellular injury is more frequently described, but a cholestatic pattern has been observed in some cases (Dara et al., 2008; Fong et al., 2010; Stevens et al., 2005). The initial formulation contained Ephedra, which was banned in 2004 (NIH, 2012). More recently, green tea (*Camellia sinensis*) extract, *Garcinia cambogia* and chromium have all been identified as possible contributors to the hepatotoxic effects (Dara et al., 2008). Hepatotoxicity has been noted after prolonged consumption of green tea extract, presenting a cholestatic or mixed hepatocellular and cholestatic signature in more than one third of the cases (Mazzanti et al., 2009). Considering the positive dechallenge and the positive rechallenge in 85% and in 20% of them, respectively, the causality was considered certain or definite (Mazzanti et al., 2009). Green tea has been widely consumed due to its alledged anti-cancer, anti-obesity, anti-diabetes, anti-inflammatory and neuroprotective effects (Miyoshi et al., 2015). Amidst

the distinct components, the catechin (−)-epigallocatechin gallate has the strongest bioactivity, but is also one of the main suspects, along with its metabolites, for the observed oxidative stress that results in hepatotoxicity (Stickel et al., 2011).

Other bodybuilding supplements have been associated with cholestatic manifestations, yet in many instances, a combination of dietary supplements was used, which makes it impractical to determine the causative agent. In this respect, Avelar and co-workers outlined the simultaneous use of NO-Xplode®, Growth Factor ATN® and SimiCarnitina® by a 17-year old male presenting an acute mixed hepatocellular and cholestatic pattern of hepatotoxicity and acute renal failure (Avelar-Escobar et al., 2012). These supplements are all based on amino acids, resulting in excessive dosing when taken simultaneously. After treatment with cholestyramine, ursodeoxycholic acid and discontinuation of the supplements, biochemical parameters returned to normal within a month (Avelar-Escobar et al., 2012). A cholestatic type of liver injury has also been depicted in a 28-year old male following the combined use of NO-Xplode® and Hydroxycut® for 4 weeks (Peterson et al., 2013). The situation was normalized 4 months after the discontinuation of the supplements, and causality was determined as possible. A combination of creatine and whey protein supplements has been related to an occurrence of acute cholestatic liver injury with elevated bilirubin and ALP levels and a liver biopsy showing marked cholestasis (Whitt et al., 2008). The administration of intravenous fluids along with the discontinuation of the supplements led to recovery which, considering that other possible causes were excluded, correlates the episode with the intake of the supplements (Whitt et al., 2008). The weight loss supplement OxyElite Pro® has been associated with a number of cases of hepatotoxicity (Heidemann et al., 2016). One of the reported cases, concerns a 31-year old woman who took the supplement for 11 weeks before she was hospitalized. Liver biopsy revealed acute hepatitis with cholestasis. The absence of auto-antibodies reactivity excluded the possibility of an auto-immune hepatitis and OxyElite Pro® was described as the probable cause of the hepatotoxicity.

There have been many reports associating the intake of Herbalife™ supplements with the occurrence of acute liver injury, namely in Israel (Elinav et al., 2007), Switzerland (Schoepfer et al., 2007) and Spain (Manso et al., 2011). On the basis of the biochemical parameters, most of the cases were classified as hepatocellular injury, but liver biopsies revealed cholestatic insults in a considerable number of them (Stickel and Shouval, 2015). Herbalife™ products are complex mixtures composed of plants and herbs supplemented with nutrients, commonly with an undisclosed composition, and consumers typically use multiple formulations simultaneously (Schoepfer et al., 2007). Clearly, this hinders the identification of the exact ingredient(s) causing the hepatotoxic effects. In this regard, hepatotoxicity caused by green tea extract cannot be ruled out as well as the hepatotoxic effects likely due to Aloe vera (*Aloe barbadensis*) (NIH, 2012). To date, the mechanism by which Herbalife™ products cause hepatotoxic injury, particularly with a cholestatic pattern, has not been elucidated, but the abundant immune cell infiltrates and the presence of auto-antibodies in some patients suggests an immune-mediated response (Elinav et al., 2007). Another ingredient that may be to blame for the cholestatic type of hepatotoxicity in Herbalife™ products is vitamin A, a regulator of BA homeostasis. Although vitamin A has been described to relieve extrahepatic cholestasis through the activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) in a bile-duct ligation mouse model of cholestasis (Wang et al., 2014), its consumption in high doses has conversely resulted in cholestatic liver injury in a few case reports (Becker et al., 2007; Ramanathan et al., 2010). The authors advance no mechanistic explanation for such observation. However, it is known that vitamin A metabolites activate retinoid X receptor (RXR), which forms heterodimers with farnesoid X receptor (FXR), therefore co-regulating the expression of various FXR target genes, such as BSEP and fibroblast growth factor (FGF) 19 (Saeed et al., 2017). Others found that some Herbalife™ products were contaminated with *Bacillus subtilis*, and these proved to be directly hepatotoxic in *in vitro* tests (Stickel et al., 2009).

3.3. Hepatoprotective supplements

Some of the dietary supplements with the potential to promote liver injury are paradoxically marketed as hepatoprotective agents, namely celandine (*Chelidonium majus*), freshwater clam extracts and oleanolic acid. In particular, celandine has been used for treating gallstone disease, dyspepsia and irritable bowel syndrome (Benninger et al., 1999; Brown, 2017; Kotsiou and Christine, 2017). Its consumption underlies a number of cases of acute cholestatic hepatitis and, although not yet mechanistically understood, induced auto-immunity might play a role (Stickel et al., 2003). Causality has been confirmed by herbal withdrawal and rechallenge (Benninger et al., 1999; Stickel et al., 2003). Despite the well-established hepatotoxic episodes, the exact culprit(s) has(have) not been identified within the 20 possible molecules, including various biologically active isoquinoline alkaloids (Kotsiou and Christine, 2017). The hepatoprotective properties of freshwater clam extract have been mentioned in ancient books and have been confirmed in rats (Hsu et al., 2010; Laurent et al., 2013). However, a recent study has correlated its consumption with cholestatic liver damage in humans, which was confirmed by the strongly positive results of the drug-induced lymphocyte stimulation test (Yokomori et al., 2016). Oleanolic acid is a natural pentacyclic triterpenoid found in many fruits, vegetables and herbs. Low concentrations of oleanolic acid have been found to protect the liver against lithocholic acid-induced toxicity in mice, likely due to its ability to activate Nrf2, which leads to increased expression of MRP2, MRP3 and MRP4 (Chen et al., 2014). However, prolonged exposure to increased doses of oleanolic acid resulted in cholestasis (Lu et al., 2013). Interestingly, this correlated with increased basal levels of Nrf2 and decreased levels of transcripts involved in BA biosynthesis, such as CYP7A1, and BA transport, such as BSEP and NTCP *in vivo* (Lu et al., 2013). Additionally, oleanolic acid is an activator of the G protein-coupled BA receptor 1 (GPBAR1), also known as Takeda G protein-coupled receptor 5 (TGR5), which is a BA sensor involved in the maintenance of BA homeostasis. However, activation of TGR5 has shown to increase the expression of interleukin 1 beta (IL-1β) and tumor necrosis factor alpha (TNF-α) in immune cells *in vitro* (Lou et al., 2014), creating a pro-inflammatory environment that contributes to the disturbance of BA homeostasis resulting in cholestasis (Woolbright and Jaeschke, 2019).

3.4. Other herbal and dietary supplements

Other dietary supplements have only limited data on their cholestatic potential. Thus, *Fructus psoraleae*, the dried mature seeds of *Psoralea corylifolia* used to alleviate bone disorders and skin conditions, such as osteoporosis and psoriasis, respectively, has been implicated in a case of acute cholestatic hepatitis, albeit most likely due to an excessive intake (Nam et al., 2005). The chemical components of the seeds include psoralen, psoralidin, isobavachalcone, bakuchiol among others. Increased levels of CYP7A1, BSEP, MRP2 and MRP3 and decreased quantities of FXR have been found in female rats exposed to an ethanolic extract of the seeds for 28 days (Wang et al., 2012). The cholestatic effect was believed to involve the destruction of the biosynthesis and transportation of BAs, yet the specific causative component has not been identified. While a correlation between the increased CYP7A1 levels and the decreased FXR levels has been established (Wang et al., 2012), the increased levels of BA transporters could be a compensatory reaction, considering the prolonged exposure time. Of note, male rats displayed a distinct response, namely decreased amounts of FXR and CYP7A1 with no changes in BA transporter levels (Wang et al., 2012). This suggests gender-specific differences in sensitivity to the hepatotoxic effects of the extract. Venoplant® is composed of flavonoids extracted from *Aesculus hippocastanum*, used for the

treatment of peripheral circulatory disorder, which has been related to cholestasis and liver cell damage (Takegoshi et al., 1986). Despite the delay between the administration and the appearance of the cholestatic symptoms, a link could be established based on the positive results of the lymphocyte stimulation test (Takegoshi et al., 1986). Likewise, the supplement Lipodrene® with Ephedra has been related to cholestasis in a military servant who presented elevated serum bilirubin and ALP levels and cholestatic injury upon liver biopsy (Peterson et al., 2013). Biochemical parameters returned to normal 4 months after supplement withdrawal and the causality was established as probable. Similarly, the supplement C4® Extreme has been considered the likely cause of acute cholestatic liver injury confirmed by liver biopsy and biochemical parameters (Peterson et al., 2013). Although it is not possible to pinpoint a particular ingredient, it has been hypothesized that synephrine-containing *Citrus aurantium* extract could play a role in the observed toxicity due to the chemical similarity between synephrine and Ephedra (Stickel et al., 2011). A report described cholestatic liver injury caused by the supplement Move Free® Advanced used for the treatment of arthritis (Yang et al., 2012). Besides glucosamine and chondroitin, this formulation contained 2 herbal ingredients, namely black catechu (*Senegalia catechu*) and Chinese skullcap (*Scutellaria baicalensis*). Several other episodes, including some with cholestatic hallmarks, have been listed following the intake of Flavocoxid, a mix of purified bioflavonoids derived from black catechu and Chinese skullcap (Chalasani et al., 2012). This supplement is available under prescription as a medical food used for the therapy of arthritis, but the FDA advices not to take it due to the possibility of instigating liver injury (FDA, 2017). Artemisinin, extracted from the leaves of *Artemisia annua*, is a widely used Chinese herbal supplement with acknowledged antimalarial and anti-helminthic activities, particularly in patients with established resistance to drugs. A case of cholestatic hepatitis has been published following a 6-week intake of a supplement containing artemisinin for general well-being reasons (Kumar, 2015), but there are several other records of hepatocellular injury patterns (NIH, 2012). The mechanism of hepatotoxicity, though not exhaustively described, could rely on an immunological reaction to a metabolite (NIH, 2012). Valerian (*Valeriana officinalis*) is a herbal remedy widely known for its anxiolytic and sedative effects. Even though in most situations it has been consumed simultaneously with other herbal supplements, it has been implicated in a few cases of hepatotoxicity (NIH, 2012), including cholestasis (Garcia-Cortes et al., 2008). Other herbs linked to the development of cholestatic hepatitis include *Cimicifuga racemosa*, also known as cohosh, *Atractylis gummifera*, used in traditional medicine for its antipyretic, diuretic, purgative and emetic properties, and *Larrea tridentata*, commonly known as chaparral (Kotsiou and Christine, 2017).

4. Parenteral nutrition-associated cholestasis

The intravenous administration of nutrients, named parenteral nutrition (PN), is a beneficial way to provide nutrients whenever the enteric route is compromised or is insufficient to cover caloric and protein needs. Parenteral nutrition can be classified as total or partial, when patients only get nutrition through this route, or when nutrients are also provided *via* enteric route, respectively (Heidegger et al., 2013). However, parenteral nutrition is not without flaws. It may lead to many complications, including liver disorders, in particular, cholestasis (Beath and Kelly, 2016; Guglielmi et al., 2008). This is especially frequent during prolonged and/or total PN and in children (Fawaz et al., 2017; Jolin-Dahel et al., 2013), varying between 40 and 60% in infants and up to 85% in neonates under total PN (Lauriti et al., 2014).

PN-associated cholestasis (PN-AC) can be related to the amount, quality and duration of the nutrient infusion, enteral fasting and prematurity (Table 3). Premature children's impaired immunity and immaturity of the enterohepatic circulation seem to prompt them more prone to developing cholestasis, particularly following total PN (Guglielmi et al., 2008). Those factors favor intestinal bacterial overgrowth, consequently increasing the deconjugation of chenodeoxycholic acid to the toxic lithocholic acid, as well as enteral fasting-induced enterocyte hypoplasia that facilitates bacterial translocation and the release of endotoxins (Kumar and Teckman, 2015). Endotoxins, such as lipopolysaccharides, and certain inflammatory mediators, such as TNF-α and cytokines, including IL-1β, are known downregulators of BA transporters, namely NTCP, BSEP and MRP2, contributing to the development of cholestasis (Kumar and Teckman, 2014). Furthermore, human fetal liver expresses lower levels of BA transporters than the adult liver (Chen et al., 2005), contributing for increased incidence of PN-AC in premature infants.

In the intestine, BAs act as natural activators of FXR, which in turn stimulates the production of FGF19. This growth factor is subsequently carried *via* portal circulation to the liver, where it binds the FGF receptor 4 (FGFR4), suppressing the expression of CYP7A1, also known as cholesterol 7α-hydroxylase, a major enzyme in BA synthesis from cholesterol (Fig. 2).

In the absence of BA release in the intestine due to enteral fasting, the FXR pathway is repressed, culminating in increased BA synthesis (Reihner et al., 1989). The reduced levels of cholecystokinin observed during enteral starvation (Mashako et al., 1991) could also contribute for the onset of cholestasis, as this hormone stimulates the emptying of the gallbladder and reduces biliary sludge (Sitzmann et al., 1990). Controversially, animal studies revealed that the administration of cholecystokinin does not have an impact on the incidence of total PN-AC (Moss and Amii, 1999).

Table 3
Main factors and suspected mechanisms of parenteral nutrition-associated cholestasis.

Factors	Mechanisms of hepatotoxicity	References
Prematurity: – Overgrowth of intestinal bacteria	– Overproduction/ accumulation of toxic BAs – Endotoxin-induced transporter inhibition	Guglielmi et al., 2008; Kumar and Teckman, 2014)
Enteral fasting: – Enterocyte hypoplasia – Absence of BA release	– Facilitated bacterial translocation – Endotoxin-induced transporter inhibition – Intestinal FXR repression – Reduced cholecystokinin levels	(Kumar and Teckman, 2015)
Nutrients: – Protein, glucose	Unknown	(Gupta et al., 2016; Vileisis et al., 1980)
– Omega-6 fatty acids	Pro-inflammatory activity	(Carter et al., 2007; El Kasmi et al., 2013)
– Phytosterols	FXR and LXR antagonism: – Decreased BSEP and MRP2 levels – Increased BA synthesis	(Carter et al., 2007)
– Manganese	Unknown	(Livingstone, 2018)
– Aluminum	Unknown	(Arnold et al., 2003; Klein et al., 1988)

BA – Bile acid; FXR – Farnesoid X receptor; LXR – Liver X receptor; BSEP – Bile salt export pump; MRP2 – Multidrug resistance-associated protein 2.

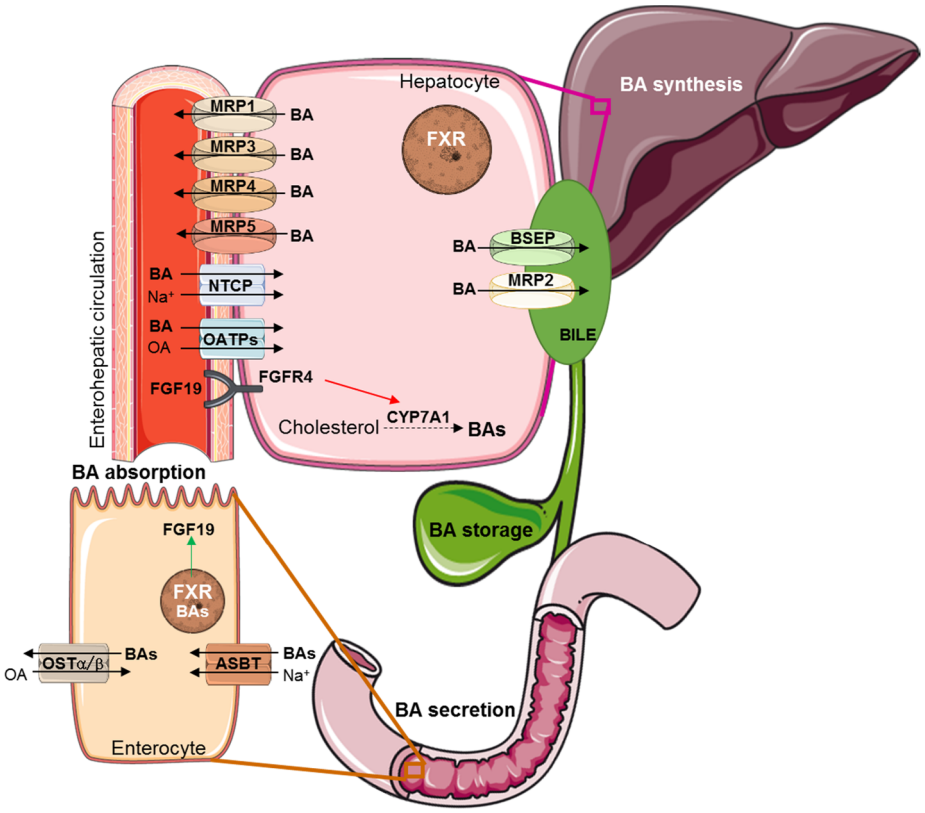

Fig. 2. Simplified representation of the bile acid cycle and negative feedback regulation of bile acid synthesis. In hepatocytes, BAs are synthesized from cholesterol in a series of reactions mainly mediated by CYP7A1. They are excreted to the sinusoids *via* MRP1, MRP3, MRP4 and MRP5 located in the basolateral membrane of the hepatocytes, and to the bile canaliculi *via* BSEP and MRP2 in the canalicular membrane. Bile is collected in the gallbladder and released in the duodenum upon a stimulus. The BAs are taken up through the ASBT into the enterocytes, where they activate FXR and upregulate (green arrow) the expression of FGF19. BAs are then excreted (BA absorption) *via* the heterodimer OSTα/β to the portal circulation, that brings them back to the hepatocytes where they are taken up by the NTCP and the OATPs. After being released from the enterocytes, FGF19 will interact with FGFR4 in the hepatocytes to downregulate (red arrow) CYP7A1. BA – Bile acid; CYP7A1 – Cytochrome P450 isoform 7A1; MRP – Multidrug resistance-associated protein; BSEP – Bile salt export pump; ASBT – Apical sodium bile salt transporter; OSTα/β – Organic solute transporter alpha/ beta; NTCP – Sodium-taurocholate cotransporting polypeptide; OA – Organic anion; OATP – OA transporting polypeptide; FXR – Farnesoid X receptor; FGF19 – Fibroblast growth factor 19; FGFR4 – Fibroblast growth factor receptor 4.

The occurrence of PN-AC also seems to correlate with the amount and the quality of the infused nutrients, although the exact culprit and mechanisms have not yet been unveiled. Early reports have linked increased protein intake with a faster onset and increased magnitude of cholestatic jaundice, and increased dextrose uptake with increased frequency of cholestatic jaundice (Vileisis et al., 1980). When comparing similar caloric intake, a glucose-rich regime seemed to disturb liver functions more than a high fat counterpart (Smirniotis et al., 1990). Subsequent retrospective studies assessing the role of each individual PN macronutrient, *in casu* dextrose *versus* protein *versus* lipids, correlated the daily intake of parenteral dextrose with a higher incidence of PN-AC (Gupta et al., 2016). The administration of a PN solution based on the amino acid composition of the umbilical cord was recently published not to differ from the breast milk-based one in what concerns the incidence of PN-AC (Anaya-Florez et al., 2019). In the past few years, focus has been put on the involvement of lipid emulsions in the induction of cholestasis (El Kasmi et al., 2013; Xu et al., 2012). The lipid component of PN may be either from vegetable or from animal origin. Soy oil-based lipid emulsions, the only FDA-approved lipid emulsions for children in the US, are rich in phytosterols, such as stigmasterol, and omega-6 fatty acids, like arachidonic acid (Amusquivar et al., 2008), known to act in a pro-inflammatory way. In particular, phytosterols antagonize FXR and the liver X receptor (LXR) therefore leading to activation of macrophages, downregulation of BA and bilirubin transporters, and interference with the synthesis and metabolism of BAs. These events ultimately result in cholestasis *in vitro* (Carter et al., 2007) and *in vivo* (El Kasmi et al., 2013). On the other hand, fish oil-based lipid emulsions, such as Omegaven™, are mostly used in European countries. They have lower levels of omega-6 fatty acids and phytosterols, and increased amounts of essential omega-3 fatty acids, namely eicosapentaenoic acid and docasahexaenoic acid (Amusquivar et al., 2008). The anti-inflammatory activity of omega-3 fatty acids contributes to decreased triglyceride synthesis, decreased production of reactive oxygen species and other pro-inflammatory molecules *in vitro*, in animals and in humans (Kalish et al., 2013; Ventro et al., 2016). Ultimately, the inclusion of fish oil-based lipid emulsions, either alone or in combination with soy and olive oil-based ones, seems to exert a hepatoprotective effect, correlating with lower incidence or faster resolution of PN-AC, shorter hospitalization period, and reversal of intestinal failure-associated liver disease in infants (Calkins et al., 2014; Kasirer et al., 2019; Lee et al., 2016). Nowadays, most commercially available ready-to-use PN products contain a mixture of different fatty acids including soy bean, olive oil, medium chain triglycerides and fish oils to benefit from different characteristics and spread risks (Cai et al., 2018). Recently, it has been published that enteral fish oil supplementation, whenever possible, is an alternative to the more expensive intravenous administration, showing beneficial results, such as decreased duration of cholestasis and increased weight gain in infants (Thavamani et al., 2019). This and other studies support a beneficial role for the enteral administration of nutrients (Manzanares et al., 2015).

Micronutrients present in PN formulations, in particular manganese, have also been implicated in the development of cholestasis. High levels of manganese have been found in the blood of patients with PN-AC (Fell et al., 1996; Hambidge et al., 1989). Recommended intake levels for children ranged from 2 to 10 μg/kg/day in 1979, and decreased to 1 μg/kg/day as a consequence of such studies (Fell et al., 1996; Livingstone, 2018). In adults, this change was even more drastic, namely from 150 to 800 μg/day to 55 μg/day since 2014 (Livingstone, 2018). However, it is still not clear whether hypermanganesaemia causes liver disease or *vice versa*, as manganese is almost totally excreted *via* the bile (Livingstone, 2018). In many instances, manganese is only present as a trace contaminant of PN, which potentiates its accumulation and consequent toxicity, particularly in long-term schemes and patients with impaired biliary secretion (Livingstone, 2018). PN-AC has also been related to increased exposure to aluminum, also commonly found as contaminant. Most studies detected increased amounts of aluminum in infants under PN (Arnold et al., 2003; Fortenberry et al., 2017; Kumar and Teckman, 2015). Similarly, *in vivo* studies have shown that increased aluminum intake coexists with increased serum

BAs and decreased bile flow. These findings positively correlate with the duration of exposure (Klein et al., 1988) and the aluminum concentration exposure (Arnold et al., 2003; Klein et al., 1988), but causality has not been fully established yet.

5. Concluding remarks and future perspectives

The present paper reviewed the current knowledge and evidence regarding the induction of cholestatic injury by food-related products, including food additives, dietary supplements and PN.

Food additives fall under the oversight of national and international agencies, which assure their general safety. The effectiveness of this strategy is supported by the shortage of case reports involving this class of substances. Nevertheless, some food additives are hepatotoxic in animal studies at concentrations around the acceptable daily intake established by EFSA (El-Wahab and Moram, 2013). This suggests that more toxicological studies are warranted to determine if similar effects are observed in humans.

Concerning herbal and dietary supplements, the incidence of hepatotoxic damage is low, up to 15.5% of all DILI cases (Stickel and Shouval, 2015), and mostly reversible. However, their increasing consumption worldwide might elevate this number in the future. Moreover, the combination of insufficient awareness among both consumers and clinicians about their potential hazards, with the usual latency for hepatotoxicity to become manifested, impedes the collection of epidemiological data. As herbal and dietary supplements are exempt from preclinical and clinical testing, the communication of post-marketing pharmacological vigilance is imperative. The issue of illegal substance contamination is an additional critical point that significantly impacts the field (Stolz et al., 2019). A multidisciplinary approach is required to tackle these problems, first by recognizing possible injurious products at a clinical level, and subsequently isolating and testing the ingredients for their toxicological profile at a research level. These types of collaborative efforts are necessary to improve the prevailing legislation, assuring the development of safer products, adequate quality control during manufacture, and the timely removal of the harmful products from the market.

With respect to PN, which is mostly used in the clinical context and, therefore, closely monitored by health practitioners, there is a frequent and unequivocal correlation with the incidence of cholestatic events (Guglielmi et al., 2008). The detailed understanding of what triggers this response is critical to advance the management and prevention of PN-AC.

In all the above cases, the current diagnosis, treatment, management and prevention of cholestatic liver injury due to the intake of food-related products poses a complex challenge. The difficulty in identifying the responsible ingredient(s) is a major obstacle to understand the mechanisms by which these substances and products trigger cholestatic liver damage (Navarro et al., 2017). Such knowledge will be invaluable to determine predisposing factors, such as metabolic polymorphisms and other idiosyncrasies, and for the discovery of new biomarkers, thus contributing to improved prediction of chemical-induced cholestasis. Therefore, more basic and applied research is necessary to decipher the role of ingredients, both individually and in relevant mixtures, in the triggering of cholestatic insults.

Considering species differences known to occur between rodent models and humans (Yang et al., 2015), and the present ethical constraints and limitations, future research will fully rely on human liver-based *in vitro* models that appropriately mimic the *in vivo* situation. In this context, spheroid cultures of primary human hepatocytes offer an excellent tool for long-term mechanistic studies of the cholestatic potential of drugs (Hendriks et al., 2016) and other chemicals.

In summary, recognizing potentially harmful food-based products and identifying the responsible ingredient(s) is one of the greatest challenges for correctly diagnosing and appropriately managing cholestatic liver injury due to the intake of food ingredients. The complex nature of most products, along with the simultaneous intake of interacting supplements or drugs, and the delayed onset of cholestatic damage, hampers the determination of causality. Therefore, the mechanisms by which cholestasis is triggered by these chemicals remain mostly unexplored. This knowledge is crucial for the improvement of the currently low clinical predictability of this type of chemical-induced liver injury, with potential impact on the actual regulation and, consequently, in overall human safety.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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