The Regulatory Roles of Polysaccharides and Ferroptosis-Related Phytochemicals in Liver Diseases

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Abstract: Liver disease is a global health burden with high morbidity and mortality worldwide. Liver injuries can develop into severe end-stage diseases, such as cirrhosis or hepatocellular carcinoma, without valid treatment. Therefore, identifying novel drugs may promote liver disease treatment. Phytochemicals, including polysaccharides, flavonoids, alkaloids, and terpenes, are abundant in foods and medicinal plants and have various bioactivities, such as antioxidation, immunoregulation, and tumor killing. Recent studies have shown that many natural polysaccharides play protective roles in liver disease models in vitro and in vivo, such as fatty liver disease, alcoholic liver disease, drug-induced liver injury, and liver cancer. The mechanisms of liver disease are complex. Notably, ferroptosis, a new type of cell death driven by iron and lipid peroxidation, is considered to be the key mechanism in many hepatic pathologies. Therefore, polysaccharides and other types of phytochemicals with activities in ferroptosis regulation provide novel therapeutic strategies for ferroptosis-related liver diseases. This review summarizes our current understanding of the mechanisms of ferroptosis and liver injury and compelling preclinical evidence of natural bioactive polysaccharides and phytochemicals in treating liver disease.

Keywords: polysaccharide; phytochemical; ferroptosis; liver injury

1. Overview of Liver Diseases and Polysaccharides

Chronic liver disease (CLD) is an important public health problem in the world, which is a major cause of morbidity and mortality worldwide. There are many types of CLDs, mainly including alcoholic liver disease (ALD), nonalcoholic fatty liver disease (NAFLD), viral hepatitis, cirrhosis, and hepatocellular carcinoma (HCC), etc. [1]. The causes of CLDs are complex, including hepatic viruses, excessive alcohol consumption, metabolic syndrome, and drug toxicity, which are the major risk factors resulting in chronic liver injury [2]. CLD patients always have persistent inflammation, massive cell death (such as apoptosis and ferroptosis), and abnormal hepatocyte regeneration in the liver, which develop to end-stage liver pathologies, such as cirrhosis and HCC [3]. Due to the increase in hospitalized CLD patients, the economic and social burden has significantly increased, especially in developing countries [4].

Phytochemicals refer to active substances derived from plants, such as polysaccharides, polyphenols, and alkaloids. Many studies have shown that many phytochemicals, such as baicalin and curcumin, have remarkable anti-tumor efficacies with lower side effects compared to other chemotherapeutic drugs [5]. Some phytochemicals have advantageous effects on obesity, cardiovascular diseases, neurological diseases, and cancer by alleviating oxidative stress due to their antioxidative activity [6]. Meanwhile, various natural antioxidants protect against the hepatotoxicity induced by the chemotherapeutic drug cisplatin via antioxidant, anti-inflammatory, and anti-apoptosis activities [7].

The natural sources of polysaccharides are abundant, including plants, fungi, and algae. Polysaccharides have a variety of biological and pharmacological activities, especially...
in treating diseases, which have been summarized in several recent reviews. For example, polysaccharides have been reported to play protective roles in metabolic syndrome, cardiovascular diseases, and neurodegenerative diseases due to their activities in glucose and lipid metabolism regulation and antioxidant and anti-inflammation activities [8–12]. Other studies revealed algal polysaccharides killing tumor cells via apoptosis while reducing the adverse effect of chemotherapy [13]. Besides, non-starch polysaccharides may improve health by regulating gut microbiota [14]. Moreover, polysaccharides deriving from traditional Chinese medicinal herbs have anti-hypertensive and cardioprotective activities and they also could be used as drug delivery systems to improve therapeutic effects by promoting bioavailability and reducing toxicity [15,16]. Two or three years ago, Yuan et al. summarized the protective effects of polysaccharides in several types of liver injuries [11], and Qu et al. reviewed the signaling pathways by which the plant polysaccharides regulate apoptosis and inflammation [12]. These previous reviews provided insights into the use of polysaccharides in treating liver diseases.

Due to the rapidly increasing number of bioactive phytochemicals, the functions and mechanisms of polysaccharides with hepaprotective effects identified in the latest two years have not been systematically summarized. In this review, we summarize the regulatory functions and mechanisms of various polysaccharides in different liver diseases, including NAFLD, ALD, fibrosis, drug-induced liver injury, and HCC, mainly involving research from the last five years. Moreover, we also summarize the polysaccharides and other types of phytochemicals with activities in regulating ferroptosis, which is the novel mechanism in many types of liver diseases. The progress of studies on polysaccharides and ferroptosis-related phytochemicals will provide novel therapeutic strategies in treating CLDs.

2. Polysaccharides in Different Liver Diseases

2.1. Nonalcoholic Fatty Liver Disease and Ethanol-induced Liver Disease

Superfluous fatty-acid-induced oxidative stress and inflammation during metabolism are central to the pathogenesis of NAFLD [17]. NAFLD includes simple steatosis and nonalcoholic steatohepatitis (NASH), which is the most common cause of liver dysfunction and is associated with an increased risk of cardiovascular diseases [18,19]. NAFLD is the most universal liver disease in obesity, metabolic syndrome, and diabetes [20]. Generally, without valid treatment, all kinds of chronic hepatitis will finally progress into end-stage liver diseases, such as cirrhosis or HCC [20]. NAFLD is the fastest increasing cause of HCC in many parts of the world, including the USA and parts of Europe [21]. The underlying mechanisms in the development and progression of NAFLD are complex, including insulin resistance, hormones secreted from the adipose tissue, nutrients, and gut microbiota [22].

Alcohol has wide-ranging effects on the gut and liver, resulting in liver inflammation, oxidative damage, fibrosis, and cirrhosis [23]. Alcohol is considered to be a risk factor for liver cirrhosis and has a significant impact on the mortality of liver cirrhosis [24]. The oxidative damage remains a crucial pathology involved in ethanol-induced liver disease (ALD) [25]. Ethanol-induced liver disease is a negative outcome of excessive drinking of ethanol, with increased reactive oxygen species (ROS) during ethanol metabolism in the liver. ROS promote hepatocyte apoptosis by inducing mitochondrial alterations or necrosis by initiating lipid peroxidation on cell membranes [26,27]. A lot of polysaccharides could be used as therapeutics for ameliorating NAFLD or ALD by modulating macronutrient metabolism and reducing cell apoptosis, inflammation, and oxidative stress (Table 1). Adiponectin reduces hepatic lipid accumulation via AMPK (AMP-activated protein kinase) signaling, which activates lipid oxidation and inhibits fatty acid synthesis [42,43]. YZW-A, MDG-1, CP, MP-A, and CSP could inhibit lipid accumulation in the liver by activating...
the AMPK pathway [28,35–37,40]. CP could significantly reduce hepatic lipid accumulation via increasing the lipid-oxidation-related gene Pparab’s expression and reducing lipid-synthesis-related gene (i.e., Fasn and Srebf1) expression in rats [30,39]. LBP and CVMP could activate the AMPK signaling pathway to reduce steatosis in alcohol-induced fatty liver [33,34].

Many polysaccharides could play hepatoprotective roles in NAFLD via moderating glucose metabolism, such as Angelica sinensis polysaccharide (ASP), SCP, and FFM. The PI3K/Akt pathway mediates glucose metabolism to decrease lipid accumulation in the liver [44]. ASP reduced blood glucose levels and ameliorated insulin resistance by activating the PI3K/Akt pathway in high-fat-diet-fed mice [45]. SCP alleviated insulin resistance by regulating the metabolism of ascorbic acid and uronic acid as well as the transformation pathway of pentose and glucuronic acid [29]. FFIM has the potential to reduce insulin resistance in patients with NAFLD in a clinical trial [32].

Acidic polysaccharides from carrot (CPS), polysaccharide from the residue of Panax notoginseng (PNPS), and modified polysaccharides from Coprinus comatus (MPCC) could regulate alcohol metabolism in the liver to reduce hepatic steatosis with the upregulation of hepatic alcohol dehydrogenase and aldehyde dehydrogenase [46–48]. Dendrobium huoshanense polysaccharide also protected liver function from alcoholic injury via correcting the hepatic methionine disorder [49]. LBP, Dendrobium officinale polysaccharide (DOP), Echinacea purpurea polysaccharide (EPP), CPS, polysaccharide from Pleurotus geesteranus (PPF-1), Pinus koraiensis pine nut polysaccharide (PNP80b-2), PNPS, CVMP, MPCC, alkalic-extractable polysaccharides from Coprinus comatus (APCC), garlic polysaccharide (GP), Triticum aestivum sprout-derived polysaccharide (TASP), and polysaccharide from maca (Lepidium meyenii) (MP) were reported to ameliorate alcohol-induced hepatic oxidative stress and inflammatory damage [33,34,46,48,50–59]. DOP, EPP, PPF-1, PNP80b-2, and TASP could ameliorate alcohol-induced hepatic oxidative stress via promoting the transcription of antioxidant genes mediated by nuclear factor E2-related factor 2 (Nrf2) [50–52,54,56]. Polysaccharides from Pleurotus geesteranus mycelium, LBP, DOP, and EPP could ameliorate alcohol-induced hepatic inflammatory damage by inhibiting nuclear factor kappa-B (NF-κB) signaling pathways [50,56,60] or by reducing-thioredoxin interacting protein (TXNIP)-induced NLRP3 inflammasome formation [55,56]. Besides, EPP, CPS, PPF-1, MPCC, APCC, Pleurotus geesteranus mycelium polysaccharide, GP, TASP, and MP could reverse ethanol-induced lipid disorder, i.e., decreasing serum triglycerides, total cholesterol, and low-density lipoprotein cholesterol (LDL-C) and increasing serum high-density lipoprotein cholesterol (HDL-C) [46,48,50,51,53–55,57–59].

2.2. Hepatic Fibrosis

Hepatic fibrosis is an outcome of wound healing in response to chronic liver injury. Without timely and valid treatment, liver fibrosis might finally develop into end-stage cirrhosis. The mechanisms of liver fibrosis are complex, consisting of inflammation, hepatic stellate cell (HSC) activation, extracellular matrix (ECM) production, and the deposit of collagen in liver [61,62]. Therefore, liver fibrosis can be reversed via ceasing chronic liver damage, blocking inflammation, deactivating HSCs, and degrading ECM [63]. The progression of hepatic fibrosis could be blocked by polysaccharides (Table 1) via these anti-fibrosis pathways.

O. lanpingensis polysaccharides (OLP) and Dictyophora polysaccharides could significantly decrease the accumulation of ECM and collagen by upregulating MMPs and collagenase expression, which are essential for collagenolysis [64,65]. Quiescent HSCs play important roles in the progression of liver fibrosis because active HSC can transdifferentiate into myofibroblasts, which produce ECM [62]. ASP could alleviate liver fibrosis by activating the IL-22/STAT3 pathway in HSCs to inhibit the HSC–myofibroblast switch [66,67].

In chronic liver damage, the persistent activation of NF-κB signaling and inflammatory cytokines always results in fibrosis [68]. OLP could alleviate liver fibrosis by decreasing
inflammatory cytokines and oxidative stress [64], and *Pleurotus citrinipileatus* polysaccharide could inhibit the progression of liver fibrosis via targeting the NF-κB pathway [69].

Intestinal dysbiosis from alcohol or a high-fat diet might result in liver inflammation and fibrosis and eventually develop to liver cirrhosis [70]. Polysaccharides could affect the development of liver fibrosis by improving gut health. LBP, *Miltiorrhiza bunge* polysaccharides, walnut green husk polysaccharides (WGHP), and MDG-1 were reported to alleviate hepatic steatosis via modulating gut microbiota in a high-fat-diet-induced NAFLD model [35,71–73]. In a randomized controlled trial, LBP could alleviate the hepatic injury and intestinal dysbiosis in NAFLD patients [74]. WGHP and MDG-1 could moderate the intestinal microecology in mice to reduce liver lipid accumulation [35,72]. Moreover, EPP could attenuate intestinal inflammation and improve barrier integrity to protect against alcohol-induced liver damage [50]. Similarly, DOP also protected against CCl₄-induced liver fibrosis by improving the intestinal barrier [75].

### 2.3. Hepatocellular Carcinoma (HCC)

Liver cancer is one of the top 10 cancer types, with the mortality of 8.2%, and it ranks fifth in terms of global cases and second in terms of deaths for males. Hepatitis viruses (such as HBV and HCV), alcohol, metabolic syndrome, diabetes, obesity, NAFLD, tobacco, aflatoxins, and other dietary factors have been consistently associated with the affected risk of liver cancer. The prevalence of NAFLD/NASH is increasing and may soon overtake viral factors as the major cause of HCC globally [76]. Several polysaccharides were reported to have therapeutic effects on HCC (Table 1).

Polysaccharides could inhibit the progression of tumors by reducing immunosuppression. The liver has a complex immune microenvironment, and immunosuppressive cells in the tumor tissue can promote HCC tolerance. Tumor-associated macrophages (TAMs), which are one of the key components maintaining the immunosuppressive microenvironment of HCC, can facilitate tumor growth [77]. Therefore, remodeling the microenvironment of tumors could be a therapeutic strategy for anti-tumor immune responses [76]. *Astragalus* polysaccharides (APS) and polysaccharide from *Pleurotus ostreatus* could inhibit HCC growth via immunoregulation with the enhanced secretion of immune-stimulating cytokines (IL-2, TNF-α, IFN-γ, etc.) [78,79]. *Ganoderma lucidum* spore polysaccharide (GLSP) promoted the polarization of primary macrophages into M1 type and cytokine expression (such as TNF-α, IL-1β, IL-6, and TGF-β1) [80].

HCC is highly vascularized. Polysaccharides could inhibit the invasion of HCC cells by reducing tumor angiogenesis. The initiation of angiogenesis is driven by the metabolic demands of tumor cells, such as hypoxia or nutrients. Many factors stimulate this process, including hypoxia-inducible factors (HIFs), mammalian target of rapamycin (mTOR), and PI3K/AKT signaling [81]. Several polysaccharides could block HCC angiogenesis by downregulating hypoxia-inducible factor 1α (HIF-1α) and vascular endothelial growth factors (VEGFs). Moreover, asparagus and dandelion polysaccharides could inhibit MAPK and PI3K signaling pathways to block tumor angiogenesis [82–84].

APS, GLSP, fucoidan, *Pleurotus ostreatus* polysaccharide, ginger polysaccharide, *Aconitum coreanum* polysaccharide, pumpkin polysaccharide (PPPF), *Rhizopus Nigru*m polysaccharide, and an acid-soluble polysaccharide from *Grifola frondose* could inhibit hepatocellular carcinoma growth by apoptosis [78–80,85–90]. The JAK/STAT, PI3K/AKT, and RAS/ERKs pathways are enhanced in many HCC cells, conferring on them resistance to apoptotic stimuli [91]. GLSP triggers HCC cell apoptosis via regulating the PI3K/AKT pathway, with increased Bax/caspases and decreased Bcl-2 [80]. PPPF treatment induces apoptosis in HepG2 cells by increasing the protein tyrosine phosphatase SHP-1 to inhibit JAK2/STAT3 signaling [88].

Many polysaccharides could enhance the effect of chemotherapeutics or simultaneously reduce the negative effects or toxicities of these drugs. Mannan conjugation could enhance the effect of adenovirus-mediated phosphatase and tensin homologue (*PTEN*) gene therapy in a murine HCC model [92]. Polysaccharides from *Lachnum* sp. (LSP) com-
bined with 5-fluorouracil or cyclophosphamide (CTX) and polysaccharides from *Lentinus edodes* combined with oxaliplatin were reported to inhibit the migration and invasion of HCC in a synergistic manner in vitro or in vivo [93–95]. Neutral polysaccharide from *Panax notoginseng* combined with CTX and aconitine combined with crude monkshood polysaccharide enhanced the tumor-killing effect by immunoregulation [96,97]. Moreover, nanoparticles made by polysaccharides are also applied in chemotherapeutic drug delivery. ASP, a plant polysaccharide with good biocompatibility, aqueous solubility, and intrinsic liver-targeted capability has been developed into targeted drug delivery nanoparticles for HCC therapy [98,99].

### 2.4. Drug-Induced Liver Injury (DILI)

Due to the first-pass effect of the liver in gastrointestinal nutrition metabolism, the liver is more susceptible to drug toxicity during clinical treatment. The incidence of DILI was estimated to be higher in Asia than that in Western countries [100]. Polysaccharides have significant protective roles in drug-induced liver damage (Table 1). ASP, *Schisandra chinensis* acidic polysaccharide, *Phellinus linteus* mycelia polysaccharide, PNP80b-2, fucoidan, and Seabuckthorn berry polysaccharide could protect against acetaminophen (APAP)-induced acute liver injury and cell death by suppressing oxidative stress [52,101–105]. *Sagittaria sagittifolia* L. polysaccharide and Yulangsan polysaccharide exert protective effects against isoniazid- or rifampicin-induced liver injury via Nrf2 activation and downstream antioxidant gene transcription [106,107]. Meanwhile, the administration of GLP reversed *Bacillus Calmette Guérin*-induced hepatic injury in vivo via inhibiting nitric oxide production and inflammation [108].

### Table 1. Polysaccharides in liver diseases.

| Polysaccharide                          | Source                          | Types of Liver Disease Treated | Cell/Animal Models | Effects and Mechanisms                                      | References |
|----------------------------------------|---------------------------------|--------------------------------|--------------------|-------------------------------------------------------------|------------|
| Acidic polysaccharides from carrot (CPS) | Carrot                          | ALD                            | Mice               | Reducing lipid droplets                                      | [46]       |
| *Aconitum coreanum* polysaccharide     | *Aconitum coreanum*             | HCC                            | H22 cells/mice     | Inducing apoptosis by suppressing P13K/Akt and activating p38 | [86]       |
| Alkallic-extractable polysaccharides from *Coprinus comatus* (APCC) | *Coprinus comatus*              | ALD                            | Mice               | Inhibiting inflammation and ROS. Improving alcohol metabolism. | [58]       |
| *Angelica sinensis* polysaccharide (ASP) | The dry roots of *Angelica sinensis* | NAFLD                          | Mice               | Inhibiting ROS. Increasing PPARγ and SIRT1-AMPK signaling.   | [45]       |
|                                        |                                 | Hepatic fibrosis                | Mice               | Inhibiting inflammation. Decreasing ECM accumulation         | [66]       |
|                                        |                                 | HCC                            | Mice               | Drug delivery nanoparticles                                   | [98,99]   |
|                                        |                                 | DILI                           | Hepatocytes/rats   | Inhibiting ROS and apoptosis                                  | [101]     |
| *Asparagus* polysaccharide             | *Asparagus*                     | HCC                            | SK-Hep1 and Hep-3B cells | Suppressing MAPK/P13K and HIF-1α/VEGF signaling pathway     | [83,84]   |
| Polysaccharide                          | Source                  | Types of Liver Disease Treated | Cell/Animal Models | Effects and Mechanisms                                                                                     | References |
|----------------------------------------|-------------------------|--------------------------------|--------------------|------------------------------------------------------------------------------------------------------------|------------|
| *Astragalus* polysaccharides (APS)     | *Astragalus*             | HCC                            | Mice               | Inducing apoptosis by increasing Bax and decreasing Bcl-2                                               | [79]       |
| *Bletilla striata* polysaccharide      | *Bletilla striata*       | NAFLD                          | Mice               | Regulating fatty acids and arachidonic acid metabolism                                                  | [41]       |
| Chicory polysaccharide (CP)            | Chicory                 | NAFLD                          | Zebrafish and rats | Inhibiting ROS and lipogenesis. Promoting lipolysis and AMPK.                                            | [30,37,39] |
| *Cordyceps sinensis* polysaccharide   | *Cordyceps Sinensis*    | NAFLD                          | Mice               | Modulating lipid metabolism and gut microbiota                                                           | [28]       |
| *Coriolus versicolor* mycelia polysaccharide (CVMP) | *Coriolus versicolor* mycelia | ALD                            | Mice               | Inhibiting inflammation and ROS. Regulating lipid metabolism                                            | [34]       |
| Crude monkshood polysaccharide        | Monkshood               | HCC                            | Hepa1-6 cells/mice | Enhancing the immunocyte to kill the tumor                                                               | [97]       |
| Dandelion polysaccharide              | Dandelion               | HCC                            | HepG2, Hepa1-6, H22 cells/mice | Suppressing the HIF-1α/VEGF signaling                                                                   | [82]       |
| *Dendrobium huoshanense* polysaccharide (DHP) | *Dendrobium huoshanense* | ALD                            | Mice               | Correcting the abnormal hepatic methionine metabolism pathway and decreasing the hepatic methylglyoxal level | [49]       |
| *Dendrobium officinale* polysaccharide (DOP) | *Dendrobium officinale* | ALD                            | L02 cells/rats     | Inhibiting TLR4/NF-κB signaling                                                                         | [56]       |
| *Doritaenopsis unilatilis* polysaccharides | *Doritaenopsis unilatilis* | ALD                            | Hepatic fibrosis   | Inhibiting the TLR4-NF-κB pathway                                                                        | [75]       |
| *Dictyophora* polysaccharides         | *Dictyophora*           | Hepatic fibrosis                | Rats               | Decreasing ECM accumulation                                                                             | [65]       |
| *Echinacea purpurea* polysaccharide   | *Echinacea purpurea*    | ALD                            | Mice               | Activation of the Nrf2/HO-1 pathway                                                                      | [50]       |
| Enteromorpha prolifera polysaccharide | Enteromorpha prolifera  | NAFLD                          | Rats               | Reducing serum lipid levels by increasing H2S production                                                 | [31]       |
| *Fucoidan*                            | Brown algae             | HCC                            | MHCC97H, Hep3B cells/mice | Inducing apoptosis by increasing lncRNA LINC0261 expression                                             | [87]       |
|                                       |                         |                                | DILI               | Inhibiting ROS by Nrf2 signaling                                                                        | [105]      |
| *Fucoidan–fucoxanthin mix* (FFM)      | *Sargassum hemiphyllum* | NAFLD                          | HepaRG cells/mice/patients | Inhibiting inflammation. Modulating the leptin–adiponectin axis                                         | [32]       |
| Polysaccharide                        | Source                        | Types of Liver Disease Treated | Cell/Animal Models | Effects and Mechanisms                                                                 | References |
|--------------------------------------|-------------------------------|-------------------------------|--------------------|----------------------------------------------------------------------------------------|------------|
| *Ganoderma lucidum* polysaccharide   | *Ganoderma lucidum*           | NAFLD                         | HepG2 cells/mice   | Modulating bile acid synthesis through the FXR-SHP/FGF pathway                          | [38]       |
| (GLP)                                |                               | DILI                          | Mice               | Inhibiting nitric oxide production and inflammation                                     | [108]      |
| *Ganoderma lucidum* spore polysaccharide | The spores of *Ganoderma lucidum* | HCC                           | Mice               | Promoting the polarization of primary macrophages to the M1 type                         | [80]       |
| Garlic polysaccharide (GP)           | Garlic                        | ALD                           | Mice               | Regulating gut microbiota                                                                | [59]       |
| Ginger polysaccharide                | Ginger                        | HCC                           | HepG2 cells        | Inducing apoptosis                                                                       | [89]       |
| *Grifola frondosa* polysaccharide    | *Grifola frondosa*            | HCC                           | H22 and HepG2 cells| Inducing the mitochondrial apoptotic pathway                                              | [90]       |
| *Lycium barbarum* polysaccharide (LBP)| *Lycii Fructus*              | NAFLD                         | Rats/humans        | Inhibiting inflammation and regulating host gut microbiota                              | [71,74]    |
|                                      |                               | ALD                           | BRL-3A cells/mice  | Inhibiting TXNIP and activating AMPK. Inhibiting inflammation, ROS, and apoptosis.      | [33,55]    |
| *Miltiorrhiza bunge* polysaccharide  | *Salvia miltiorrhiza*         | NAFLD                         | Mice               | Modulating gut microbiota and improving insulin resistance                               | [73]       |
| Modified polysaccharides from *Coprinus comatus* (MPCC) | *Coprinus comatus* | ALD                           | Mice               | Inhibiting inflammation and ROS. Reducing serum lipid levels. Promoting alcohol metabolism. | [48]       |
| Mussel polysaccharide α-D-glucan (MP-A) | *Mytilus coruscus*           | NAFLD                         | Rats               | Inhibiting inflammation. Increasing short-chain fatty acids. Inhibiting PPAR signaling. | [36]       |
| Neutral polysaccharide from *Panax notoginseng* | *Panax notoginseng* | HCC                           | Mice               | Enhancing the anti-tumor effect of cyclophosphamide                                      | [96]       |
| *Ophiocordyceps lanpingensis* polysaccharides (OLP) | *Ophiocordyceps lanpingensis* | Hepatic fibrosis               | Mice               | Inhibiting inflammation, ROS, and apoptosis                                              | [64]       |
| *Ophiopogon japonicus* polysaccharide (MDG-1) | *Ophiopogon* | NAFLD                         | Mice               | Inhibiting inflammation. Modulating the gut-liver axis and hepatic lipid metabolism.    | [35]       |
| *Phellinus linteus* mycelia polysaccharide (PL-N1) | *Phellinus linteus* mycelia | DILI                          | Mice               | Decreasing cytochrome P450 2E1 expression and hepatic release of cytokines                | [103]      |
Table 1. Cont.

| Polysaccharide | Source | Types of Liver Disease Treated | Cell/Animal Models | Effects and Mechanisms | References |
|----------------|--------|--------------------------------|-------------------|------------------------|------------|
| *Pinus koraiensis* pine nut polysaccharide (PNP80b) | Pine nut | ALDDILI | Mice | Inhibiting inflammation and ROS by Nrf2 signaling | [52] |
| *Pleurotus citrinipileatus* polysaccharide | *Pleurotus citrinipileatus* | Hepatic fibrosis | Mice | Reducing the level of cytokine TGF-β1 | [69] |
| Polysaccharide from *Lachnum* sp. (LSP) | *Lachnum* sp. | HCC | HepG2, SMMC7721, H22 and L02 cells/mice | Inducing apoptosis by inhibiting the MEK and PI3K pathways | [94,95] |
| Polysaccharide from *Lentinus* | *Lentinus edodes* | HCC | HepG2 and H22 cells/mice | Inducing the mitochondrial apoptotic pathway and inhibiting NF-κB, Stat3, and survivin signaling | [93] |
| Polysaccharide from Maca (MP) | Maca (*Lepidium meyenii*) | ALD | HepG2 cells/mice | Reducing ROS and serum lipid levels | [57] |
| Polysaccharide from *Pleurotus geesteranus* mycelium | The mycelium of *Pleurotus geesteranus* | ALD | Mice | Inhibiting inflammation and ROS. Regulating alcohol metabolism. Reducing serum lipid levels. | [53,60] |
| Polysaccharide from *Pleurotus geesteranus* (PP-1) | The fruiting body of *Pleurotus geesteranus* | ALD | Mice | Activating Nrf2 signaling and inhibiting the TLR4-mediated NF-κB signal pathways | [54] |
| Polysaccharide from *Pleurotus ostreatus* | *Pleurotus ostreatus* | HCC | HepG2 and HCCLM3 cells/mice | Inducing apoptosis. Downregulation of regenerative genes and secretion of immunological factors. | [78] |
| Polysaccharide from the residue of *Panax notoginseng* (PNPS) | the residue of *Panax notoginseng* | ALD | Mice | Inhibiting inflammation and ROS by Nrf2 signaling. Reducing serum lipid levels. | [47] |
| Pomelo fruitlet polysaccharide (YZW-A) | Pomelo fruitlet | NAFLD | Mice | Promoting hepatic AMPK and Nrf2 signaling. | [40] |
| Pumpkin polysaccharide (PPPF) | Pumpkin | HCC | HepG2 cells | Inducing apoptosis by inhibiting the JAK2/STAT3 pathway | [88] |
| *Rhizopus Nigrum* polysaccharide | *Rhizopus Nigrum* | HCC | HepG2 and Huh7 cells/mice | Inducing apoptosis | [85] |
| *Sagittaria sagittifolia* L. polysaccharide | The root tubers of *S. sagittifolia* | DILI | Mice | Inhibiting ROS by Nrf2 | [107] |
| *Schisandra chinensis* caulis polysaccharide (SCP) | *Schisandra chinensis* Caulis | DILI | Mice | Inhibiting inflammation, ROS, and apoptosis | [102] |
| | | NAFLD | Rats | Inhibiting ROS. Regulating glucose and lipid metabolism. | [29] |
### Table 1. Cont.

| Polysaccharide                        | Source                                           | Types of Liver Disease Treated | Cell/Animal Models | Effects and Mechanisms                                                                 | References |
|---------------------------------------|--------------------------------------------------|-------------------------------|--------------------|----------------------------------------------------------------------------------------|------------|
| Seabuckthorn berry polysaccharide (SP)| The berries of seabuckthorn (Hippophae rhamnoides L.) | DILI                          | Mice               | Inhibiting ROS and apoptosis by Nrf2/HO1/SOD signaling                                  | [104]      |
| *Triticum aestivum* sprout-derived polysaccharide (TASP) | *Triticum aestivum* | ALD                           | Mice               | Inhibiting inflammation, ROS, and apoptosis by Nrf2 signaling. Reducing serum lipid levels. | [51]      |
| Walnut green husk polysaccharides (WGHP) | Walnut green husk | NAFLD                         | Rats               | Improving gut microbiota and short-chain fatty acids                                   | [72]      |
| Yulangsan polysaccharide             | The root of *Millettia pulchra*                   | DILI                          | Mice               | Inhibiting ROS                                                                          | [106]      |

3. Cell Death in Liver Diseases

Cell death is a critical event for liver injury, often persisting over decades. Long-term or massive dysregulated cell death may develop into severe clinical outcomes. For example, massive hepatocellular death always results in liver failure, while hepatocyte immortalization may cause HCC. Different types of cell death (such as apoptosis, necrosis, autophagy, and ferroptosis) trigger specific pathological responses and promote the progression of liver disease through distinct mechanisms [109]. The discovery of novel modes of cell death has greatly improved our understanding of the development of liver disease.

3.1. Polysaccharides Regulating Apoptosis

Apoptosis is classic cell death, and hepatocyte apoptosis is often considered to be the major mechanism of liver injury over decades. At the molecular level, apoptosis is divided into two major branches, the intrinsic and extrinsic pathways. The extrinsic apoptosis of hepatocytes can be initiated by inflammatory cytokines, which then trigger Fas-dependent death-inducing signaling complex and downstream caspase-8/9 activation [110]. The caspase-9-induced pro-death protein BID–BAX axis is the major link between the intrinsic and extrinsic pathways. In the intrinsic apoptotic pathway, the mitochondrial outer membrane permeabilization by BAX and BAK results in the release of mitochondrial pro-death effectors, such as the hemoprotein cytochrome c, which triggers the formation of the apoptosome and caspase-3/7 activation [110,111]. Cytochrome c is normally bound to cardiolipin, and therefore the oxidation of cardiolipin by ROS also triggers cytochrome c release and downstream apoptotic signaling, including caspase activation and death execution [112].

Many polysaccharides have been identified as apoptosis regulators (Table 1). Polysaccharides with activities to suppress apoptosis can protect against NASH, ALD, and APAP-induced acute liver injury. On the other hand, polysaccharides such as apoptosis agonists can inhibit HCC development by promoting tumor cells apoptosis.

3.2. Polysaccharides and Other Phytochemicals Regulating Ferroptosis

Ferroptosis is a new type of cell death that was identified in 2012 [113]. Ferroptosis was observed in RAS-mutated tumor cells treated with the lethal compound erastin or RSL3. RAS mutations always result in apoptosis resistance, indicating ferroptosis is morphologically, biochemically, and genetically distinct from other forms of cell death. In the discovery of ferroptosis, either lipid peroxidation scavengers (i.e., ferrostatin-1) or iron chelators (i.e., defereroxamine) could specifically inhibit ferroptosis agonist (erastin or RSL3)-induced cell death, and therefore ferroptosis was characterized as a lipid-peroxidation-induced and...
Iron-dependent cell death [113–115]. Ferroptosis serves as a major pathological mechanism in a wide range of organs, including the liver, heart, brain, and kidney [115–117]. In the past decade, the regulatory mechanisms of ferroptosis have been revealed (Figure 1) but not fully elucidated. Iron homeostasis is tightly maintained in the body, including iron absorption, storage, and utilization. Dysregulated iron metabolism is the key trigger of ferroptosis. In previous studies, an iron overload resulting from a high-iron diet or hereditary hemochromatosis was shown to cause hepatic ferroptosis, and an iron-deficient diet challenge or ferrostatin-1 treatment could rescue iron-overload-induced ferroptosis and liver damage [118,119]. Moreover, in normal cells, excessive iron is stored in ferritin, and the deletion of ferritin H in cardiomyocytes could increase the liable iron pool and result in ferroptotic heart injury [120]. Lipid peroxidation, the oxygenation of polyunsaturated phosphatidylethanolamines (PEs) in the cytoplasm membrane or mitochondrial membrane, is considered to be the executor of ferroptosis by decreasing the membrane integrity [117,121]. Lipid peroxidation is mediated by PE-binding protein 1 (PEBP1), a scaffolding protein that binds with both PEs and lipoxigenases and allows them to generate lipid peroxides [115]. The antioxidant glutathione (GSH)–glutathione peroxidases (GPXs) axis is a major mechanism for cleaning lipid peroxidation. The cystine/glutamate antiporter xc− is essential for cellular GSH, and its subunit SLC7A11 mediates cystine uptake, which is then reduced into cysteine for GSH synthesis [115]. The genetic deletion or mutation of SLC7A11 inhibited GSH synthesis and resulted in increased tissue lipid peroxidation and ferroptotic injury [118], while overexpressing SLC7A11 could increase the GSH content and rescue ferritin H knockout-induced ferroptotic heart damage [120]. GPX4, an enzyme that catalyzes GSH reacting with lipid peroxidation, plays critical roles in blocking ferroptosis. Therefore, inducing ferroptosis by the pharmacological inhibition of SLC7A11 and GPX4 provides novel strategies for tumor chemotherapy [113,122–124]. Nrf2 is the key transcription factor of many antioxidant genes involved in ferroptosis, including SLC7A11 and GPXs. Besides GSH, other antioxidants, including NADPH and reduced thioredoxin (Trx), can also inhibit ferroptosis by reducing lipid peroxidation [125–127]. Recently, the FDA-approved anti-rheumatoid arthritis drug auranofin was identified as a novel ferroptosis agonist by pan-inhibiting thioredoxin reductases (TXNRDs), which could refresh reduced Trx after reacting with lipid peroxidation. Therefore, auranofin and ferroptosis inhibitor (i.e., ferrostatin-1) combined treatment was suggested to be a safer strategy in the clinic to avoid ferroptotic toxicity from high-dose auranofin [127]. Moreover, polyunsaturated fatty acids (PUFAs) are essential for ferroptosis due to their sensitivity to lipid peroxidation [128,129]. ACSL4, an enzyme that catalyzes arachidonic acids synthesizing into PUFAs, could drive ferroptosis via oxidized phospholipids accumulating in the cell membrane [130–133].

Several polysaccharides have been identified as ferroptosis regulators to date, consisting of ferroptosis agonists and inhibitors (Table 2). Red ginseng polysaccharide and LBP exhibited anti-tumor efficacy by triggering ferroptosis [134–136]. Fucoidans, APS, and polysaccharide of *atractyloides macrocephala Koidz* could alleviate tissue injuries by inhibiting ferroptosis [137–139].

The liver is one of the most important organs for iron storage. The hepatic iron and ROS burden are greater in the diseased liver than in the normal liver, suggesting that ferroptosis may be associated with chronic liver diseases [116]. Currently, ferroptosis has been identified as the key mechanism in NASH, ALD, ischemia/reperfusion, and iron overload (hemochromatosis)-related liver injury [118,140–143]. However, polysaccharides have not been reported to regulate ferroptosis in liver diseases, while many phytochemicals of other types, such as terpene, alkaloid, and flavonoid, can alleviate the pathogenesis of liver diseases via regulating ferroptosis (Table 2). For one thing, phytochemicals could induce ferroptosis to suppress the progression of liver fibrosis and HCC. For instance, magnesium isoglycyrrhizinate, derivatives of artemisinin (such as artemether, artemunate, and dihydroartemisinin (DHA)), wild bitter melon extracts, chrysophanol, and zalkaloid berberine could block the development of liver fibrosis by triggering HSC ferroptosis [144–152]. Be-
sides, several studies revealed that DHA could trigger ferroptosis to block HCC growth by promoting PEBP1/15LO formation or an unfolded protein response [153,154]. Moreover, DHA and artesunate could enhance the anti-tumor efficacy of sorafenib on HCC by inducing ferroptosis [155,156]. In addition, alkaloid solasonine promotes the ferroptosis of HCC cells via inhibiting GPX4 and GSH synthetase [157]. Meanwhile, heteronemin, a natural marine product isolated from *Hippospongia sp.*, was reported to trigger HCC cell ferroptosis and apoptosis by increasing intracellular ROS and inhibiting MAPK signaling [158].

**Figure 1.** Regulatory pathways of ferroptosis. Iron metabolism is tightly regulated in transport and storage. Cellular iron overload can trigger ferroptosis. Cellular iron uptake is mediated by TfR1, which imports transferrin-binding iron, and by DMT1 and SLC39A14, which import non-transferrin-binding iron. Ferroportin1 (Fpn1) is the only known iron exporter to date. Heme can be degraded by HO-1 to release free iron. Cellular excess iron is stored in ferritin, while ferritin can be degraded by NCOA4-mediated ferritinophagy in an iron-deficiency condition. **System xc**−, a heterodimer composed of SLC7A11 and SLC3A2, is a cystine/glutamate antiporter that mediates the efflux of glutamate and the influx of cystine at a 1:1 ratio. After entering the cell, cystine is reduced to cysteine and then synthesized into GSH. GPX4 scavenges lipid ROS via GSH. Lipid ROS derives from PUFAs-PE oxidation by lipoxygenases. The scaffolding protein PEBP1 can bind PE on the cell membrane and then recruit the lipoxygenase 15LO to generate lipid ROS. ACSL4 can increase lipid ROS by producing PUFAs-PE. Moreover, TCA cycle disorder or iron overload in mitochondria can also increase ROS, which results in ferroptosis. The CoQ/FSP1 and Trx/TXNRD axes inhibit ferroptosis in a GSH-independent manner. The Keap1/NRF2, p53, and YAP/TAZ signaling are necessary for the transcription of ferroptosis regulators, such as *SLC7A11* and *ACSL4*. Erastin, RSL3, and auranofin are ferroptosis agonists by targeting *SLC7A11*, GPX4, and TXNRD, respectively. Ferroptosis inhibitors include iron chelators and lipid ROS scavengers (ferrostatin-1, liproxstatin-1, vitamin E, etc.).
For another thing, some phytochemicals also inhibit hepatic ferroptosis to protect against NASH, drug-induced liver injury, and acute liver failure (Table 2). For example, some investigations discovered that some natural products, such as ginkgolide B and dehydroabietic acid, could alleviate NASH pathology by activating Nrf2 signaling to inhibit ferroptosis [159,160]. Clausenamide could prevent drug-induced hepatocyte ferroptosis via the activation of the Keap1-Nrf2 pathway [161]. Glycyrrhizin significantly reduced the degree of ferroptosis in acute liver failure by enhancing glutathione synthesis [162]. Holly (Ilex latifolia Thunb.) polyphenol extracts are able to relieve hepatic ferroptosis by inhibiting iron transport and enhancing GPX4 expression [163]. Moreover, baicalein supplementation ameliorates CCl4-induced acute liver injury in mice by inhibiting ferroptosis and inflammation, which involves the activation of Nrf2 and the inhibition of lipoxygenases and the NF-kB pathway [164].

Table 2. Phytochemicals in ferroptotic diseases.

| Agonist/Inhibitor | Phytochemicals | Types of Phytochemicals | Types of Diseases Treated | Cell/Animal Models | Mechanisms | References |
|-------------------|----------------|-------------------------|---------------------------|-------------------|------------|------------|
| Agonist           | Artemether     | Terpene                 | Liver fibrosis            | LX2 cells/mice    | Activating p53 signaling; Accumulating IRP2 | [148,151] |
| Agonist           | Artemether     | Terpene                 | Liver fibrosis            | Mice              | Promoting ferritinophagy                   |           |
| Agonist           | Artesunate     | Terpene                 | Liver fibrosis            | Huh7, SNU-449, SNU-182 HCC cells | Promoting ferritin degradation and decreasing GSH | [156] |
| Agonist           | Chrysophanol   | Quinone                 | Liver fibrosis            | Mice              | Promoting ER stress                        | [146] |
| Agonist           | Dihydroartemisinin (DHA) | Terpene | Liver fibrosis | Rats, mice | Promoting ferritinophagy | [150,152] |
|                   |                |                         |                           | HCC               | Promoting ER stress and PEP1/15-LO formation | [153–155] |
| Agonist           | Heteronemin    | Terpene                 | HCC                        | HA22T, HA59T cells | Increasing ROS                              | [158] |
| Agonist           | Lycium barbarum polysaccharide (LBP) | Polysaccharide | Breast cancer | MCF-7 and MDA-MB-231 cells | Triggering ferroptosis by downregulating SLC7A11 and GPX4 | [134] |
| Agonist           | Magnesium isoglycyrrhizinate | Terpene | Liver fibrosis | Rats | Increasing HO-1 expression | [147] |
| Agonist           | Red ginseng polysaccharide | Polysaccharide | Lung and breast cancer | A549 and MDA-MB-231 cells | Triggering ferroptosis by inhibiting GPX4 | [136] |
| Agonist           | Solasonine     | Alkaloid                | HCC                        | HepG2, HepRG cells | Inhibiting GPX4 and GSH synthetase           | [157] |
| Agonist           | Wild bitter melon extract | Alkaloid | Liver fibrosis | Mice | Inhibiting GPX4 and SLC7A11 | [144] |
| Agonist           | Alkaloid berberine | Alkaloid | Liver fibrosis | Mice | Blocking the autophagy–lysosome pathway and increasing ROS | [149] |
| Inhibitor         | Astragalus polysaccharide (APS) | Polysaccharide | Colitis | Caco-2 cells/DSS-challenged mice | Decreasing lipid ROS | [137] |
| Inhibitor         | Baicalein      | Flavonoid               | Acute liver injury         | HepG2 cells/mice | Inhibiting the NF-kB pathway and ALOX12     | [164] |
| Inhibitor         | Clausenamide   | Pyrrolidone             | DILI                       | Hepa RG and HepG2 cells/mice | Activating the Keap1-Nrf2 pathway | [161] |
Table 2. Cont.

| Agonist/Inhibitor | Phytochemicals | Types of Phytochemicals | Types of Diseases Treated | Cell/Animal Models | Mechanisms | References |
|-------------------|----------------|-------------------------|---------------------------|--------------------|------------|------------|
| Inhibitor         | Dehydroabietic acid | Terpene | NAFLD | HEK293T and HL7702 cells/mice | Activating the Nrf2-ARE pathway | [159] |
| Inhibitor         | Fucoidans | Polysaccharide | Retinal disease | ARPE-19 and OMM-1 cells | Inhibiting ferroptosis by increasing GPX4 | [138] |
| Inhibitor         | Ginkgolide B | Terpene | NAFLD | HepG2 cells/mice | Activating Nrf2 signaling | [160] |
| Inhibitor         | Glycyrrhizin | Terpene | Acute liver injury | L02 cells/mice | Promoting the Nrf2/HO-1/HMGB1 pathway | [162] |
| Inhibitor         | Holly (Ilex latifolia Thunb.) polyphenols | Polyphenol | Acute liver injury | Piglet | Decreasing lipid ROS | [163] |
| Inhibitor         | Polysaccharide of atracylodis macrocephala Koidz | Polysaccharide | Spleen injury in infections | Goslings | Inhibiting ferroptosis by restoring the expression and distribution of GPX4 | [139] |

4. Conclusions and Future Directions

Liver disease is a global health burden that has complex mechanisms and needs effective therapeutics in the early stage of liver injury. Given a growing number of polysaccharides with bioactivities (such as antioxidant, immunoregulation, and tumor killing activities) have been identified, the polysaccharide may provide a promising therapeutic strategy for liver diseases. Recently, various natural polysaccharides have been reported to possess protective roles in several liver diseases resulting from fatty liver, alcohol, drug toxicity, or HCC. Moreover, angelica polysaccharides can be developed into a hypoxia-responsive nano-drug delivery system that facilitated HCC chemotherapy. However, studies about polysaccharides on virus hepatitis have been reported less than other liver diseases, suggesting polysaccharides with anti-virus bioactivity need to be identified. Currently, the majority of data are collected from in vitro and animal experiments. Therefore, further studies in humans are needed in order to evaluate the efficacy of these polysaccharides in the clinic.

Cell death, including apoptosis or ferroptosis, is a double-edged sword for health. Therefore, phytochemicals, such as cell death agonists or inhibitors, may play different roles in treating liver diseases. For example, some phytochemicals that inhibit cell death could alleviate ALD, DILI, or chemotherapeutic toxicity in the liver, while lethal phytochemicals may serve as chemotherapeutics in HCC. Ferroptosis is a new type of cell death with features of iron and lipid ROS accumulation that is different from other types of cell death. The discovery of ferroptosis has greatly improved the understanding and therapeutic strategies of liver disease. Several compounds and phytochemicals could alleviate liver injury by targeting ferroptosis, while inhibitors of other cell death (such as apoptosis) could not. Moreover, phytochemicals with ferroptosis-inducing activities might be effective and promising drugs for HCC because ferroptosis agonists can evade the drug resistance of classic chemotherapeutics (e.g., cisplatin, which kills tumors by apoptosis). Therefore, elucidating the mechanisms of ferroptosis and identifying more ferroptosis-regulatory phytochemicals may provide novel therapeutic strategies for liver diseases in the future.

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**Abbreviations**

- ALD: alcoholic liver disease
- AMPK: AMP-activated protein kinase
- APAP: acetaminophen
- APCC: alkaline-extractable polysaccharides from *Coprinus comatus*
- APS: *Astragalus* polysaccharides
- ASP: *Angelica sinensis* polysaccharide
- CLD: chronic liver disease
- CP: chicory polysaccharide
- CPS: carrot polysaccharide
- CSP: *Cordyceps sinensis* polysaccharide
- CTX: cyclophosphamide
- CVMP: polysaccharide from *Coriolus versicolor* mycelia
- DHA: dihydroartemisinin
- DILI: drug-induced liver injury
- DOP: *Dendrobium officinale* polysaccharide
- ECM: extracellular matrix
- EPP: *Echinacea purpurea* polysaccharide
- FFM: fucoidan and fucoxanthin mix
- GLP: *Ganoderma lucidum* polysaccharide
- GLSP: *Ganoderma lucidum* spore polysaccharide
- GP: garlic polysaccharide
- GPX: glutathione-glutathione peroxidases
- GSH: glutathione
- HCC: hepatocellular carcinoma
- HDL-C: high-density lipoprotein cholesterol
- HIF: hypoxia-inducible factor
- HIF-1α: hypoxia-inducible factor 1α
- HSC: hepatic stellate cells
- LBP: *Lycium barbarum* polysaccharide
- LDL-C: low-density lipoprotein cholesterol
- LSP: polysaccharide from *Lachnum* sp.
- MDG-1: *Ophiopogon japonicus* polysaccharide
- MP: *maca* (*Lepidium meyenii*) polysaccharide
- MP-A: mussel polysaccharide α-D-glucan
- MPCC: modified polysaccharides from *Coprinus comatus*
- mTOR: mammalian target of rapamycin
- NAFLD: nonalcoholic fatty liver disease
- NASH: nonalcoholic steatohepatitis
- NF-κB: nuclear factor kappa-B
- Nrf2: nuclear factor E2-related factor 2
- OLP: *O. lanpingensis* polysaccharides
- PE: phosphatidylethanolamine
- PEBP1: PE-binding protein 1
- PFP-1: *Pleurotus geesteranus* polysaccharide
- PNP80b-2: *Pinus koraiensis* pine nut polysaccharide
- PNPS: polysaccharide from the residue of *Panax notoginseng*
- PPPF: polysaccharide from pumpkin fruit
PUFAs  polyunsaturated fatty acids
ROS  reactive oxygen species
SCP  *Schisandra chinensis* caulis polysaccharide
TAMs  tumor-associated macrophages
TASP  *Triticum aestivum* sprout-derived polysaccharide
Trx  thioredoxin
TXNIP  thioredoxin-interacting protein
TXNRD  thioredoxin reductase
VEGFs  vascular endothelial growth factors
WGHPS  walnut green husk polysaccharides
YZW-A  polysaccharide extract from pomelo fruitlet

References

1. Marcellin, P.; Kutala, B.K. Liver diseases: A major, neglected global public health problem requiring urgent actions and large-scale screening. *Liver. Int.* 2018, 38 (Suppl. 1), 2–6. [CrossRef] [PubMed]
2. Wong, M.C.S.; Huang, J.L.W.; George, J.; Huang, J.; Leung, C.; Esram, M.; Chan, H.L.Y.; Ng, S.C. The changing epidemiology of liver diseases in the Asia-Pacific region. *Nat. Rev. Gastroenterol. Hepatol.* 2019, 16, 57–73. [CrossRef]
3. Asrani, S.K.; Hall, L.; Hagan, M.; Sharma, S.; Yeramaneni, S.; Trotter, J.; Talwalkar, J.; Kanwal, F. Trends in Chronic Liver Disease-Related Hospitalizations: A Population-Based Study. *Am. J. Gastroenterol.* 2019, 114, 98–106. [CrossRef] [PubMed]
4. Udompap, P.; Kim, D.; Kim, W.R. Current and Future Burden of Chronic Nonmalignant Liver Disease. *Clin. Gastroenterol. Hepatol.* 2015, 13, 2031–2041. [CrossRef] [PubMed]
5. Dong, X.; Zhou, M.; Xiong, Z.; Lu, G.; Ma, W.; Lv, Q.; Wang, L.; Jia, X.; Feng, L. A review on the applications of Traditional Chinese medicine polysaccharides in drug delivery systems. *Biomed. Pharmacother.* 2021, 144, 112328. [CrossRef] [PubMed]
6. Guan, R.; van Le, Q.; Yang, H.; Zhang, D.; Gu, H.; Yang, Y.; Sonne, C.; Chan, H.L.Y.; Ng, S.C. The role of natural phytocompounds and their relation to oxidative stress and human diseases. *Chemosphere* 2021, 271, 129499. [CrossRef]
7. Abd Rashid, N.; Abd Halim, S.A.S.; Teoh, S.L.; Budin, S.B.; Hussan, F.; Adib Ridzuan, N.R.; Abdul Jalil, N.A. The role of natural antioxidants in cisplatin-induced hepatotoxicity. *Biomed. Pharmacother.* 2021, 144, 112328. [CrossRef] [PubMed]
8. Ouyang, Y.; Qiu, Y.; Liu, Y.; Zhu, R.; Chen, Y.; El-Seedi, H.R.; Chen, X.; Zhao, C. Cancer-fighting potentials of algal polysaccharides and their relation to oxidative stress and human diseases. *Chemosphere* 2021, 271, 129499. [CrossRef]
9. Li, Y.; Qin, J.; Cheng, Y.; Lv, D.; Li, M.; Qi, Y.; Lan, J.; Zhao, Q.; Li, Z. Marine Sulfated Polysaccharides: Preventive and Therapeutic Effects on Metabolic Syndrome: A Review. *Mar. Drugs* 2021, 19, 608. [CrossRef] [PubMed]
10. Yuan, Y.; Che, L.; Qi, C.; Meng, Z. Protective effects of polysaccharides on hepatic injury: A review. *Int. J. Mol. Macromol.* 2019, 141, 822–830. [CrossRef] [PubMed]
11. Qu, J.; Huang, P.; Zhang, L.; Qiu, Y.; Qi, H.; Leng, A.; Shang, D. Hepatoprotective effect of plant polysaccharides from natural resources: A review of the mechanisms and structure-activity relationship. *Int. J. Mol. Macromol.* 2020, 161, 24–34. [CrossRef] [PubMed]
12. Ouyang, Y.; Qiu, Y.; Liu, Y.; Zhu, R.; Chen, Y.; El-Seedi, H.R.; Chen, X.; Zhao, C. Cancer-fighting potentials of algal polysaccharides as nutraceuticals. *Food Res. Int.* 2021, 147, 110522. [CrossRef] [PubMed]
13. Zhang, H.; Jiang, F.; Zhang, J.; Wang, W.; Li, L.; Yan, J. Modulatory effects of polysaccharides from plants, marine algae and edible mushrooms on gut microbiota and related health benefits: A review. *Int. J. Biol. Macromol.* 2022, 204, 169–192. [CrossRef] [PubMed]
14. Wang, B.; Wang, X.; Xiong, Z.; Lu, G.; Ma, W.; Lv, Q.; Wang, L.; Jia, X.; Feng, L. A review on the applications of Traditional Chinese medicine polysaccharides in drug delivery systems. *Chin. Med.* 2022, 17, 12. [CrossRef] [PubMed]
15. Xie, M.; Tao, W.; Wu, F.; Wu, K.; Huang, X.; Ling, G.; Zhao, C.; Lv, Q.; Wang, Q.; Zhou, X.; et al. Anti-hypertensive and cardioprotective activities of traditional Chinese medicine-derived polysaccharides: A review. *Int. J. Biol. Macromol.* 2021, 185, 917–934. [CrossRef]
16. Friedman, S.L.; Neuschwander-Tetri, B.A.; Rinella, M.; Sanyal, A.J. Mechanisms of NAFLD development and therapeutic strategies. *Nat. Med.* 2018, 24, 908–922. [CrossRef] [PubMed]
17. Brutn, E.M.; Wong, V.W.; Nobili, V.; Day, C.P.; Sookian, S.; Maher, J.J.; Bugianses, E.; Sirlin, C.B.; Neuschwander-Tetri, B.A.; Rinella, M.E. Nonalcoholic fatty liver disease. *Nat. Rev. Dis. Primers* 2015, 1, 15080. [CrossRef]
18. Nabi, O.; Boursier, J.; Lacombe, K.; Mathurin, P.; de Ledinghen, V.; Goldberg, M.; Zins, M.; Serfaty, L. Comorbidities Are Associated with Fibrosis in NAFLD Subjects: A Nationwide Study (NASH-CO Study). *Dig. Dis. Sci.* 2021. [CrossRef]
19. Wang, F.S.; Fan, J.G.; Zhang, Z.; Gao, B.; Wang, H.Y. The global burden of liver disease: The major impact of China. *Hepatology* 2014, 60, 2099–2108. [CrossRef] [PubMed]
20. Huang, D.Q.; El-Serag, H.B.; Loomba, R. Global epidemiology of NAFLD-related HCC: Trends, predictions, risk factors and prevention. *Nat. Rev. Gastroenterol. Hepatol.* 2021, 18, 223–238. [CrossRef] [PubMed]
22. Buzzetti, E.; Pinzani, M.; Tsochatzis, E.A. The multiple-hit pathogenesis of non-alcoholic fatty liver disease (NAFLD). *Metabolism* **2016**, *65*, 1038–1048. [CrossRef] [PubMed]
23. Pohl, K.; Moodley, P.; Dhandha, A.D. Alcohol’s Impact on the Gut and Liver. *Nutrients* **2021**, *13*, 3170. [CrossRef] [PubMed]
24. Rehm, J.; Taylor, B.; Mohapatra, S.; Irving, H.; Baliunas, D.; Patra, J.; Roerecke, M. Alcohol as a risk factor for liver cirrhosis: A systematic review and meta-analysis. *Drug Alcohol Rev.* **2010**, *29*, 437–445. [CrossRef]
25. Michalak, A.; Lach, T.; Cicchoz-Lach, H. Oxidative Stress-A Key Player in the Course of Alcohol-Related Liver Disease. *J. Clin. Med.* **2021**, *10*, 3011. [CrossRef]
26. Albano, E. Oxidative mechanisms in the pathogenesis of alcoholic liver disease. *Mol. Aspects Med.* **2008**, *29*, 9–16. [CrossRef]
27. Tilg, H.; Moschen, A.R.; Kaneider, N.C. Pathways of liver injury in alcoholic liver disease. *J. Hepatol.* **2011**, *55*, 1159–1161. [CrossRef]
28. Chen, L.; Zhang, L.; Wang, W.; Qiu, W.; Liu, L.; Ning, A.; Cao, J.; Huang, M.; Zhong, M. Polysaccharides isolated from Cordyceps Sinensis contribute to the progression of NASH by modifying the gut microbiota in mice fed a high-fat diet. *PLoS ONE* **2020**, *15*, e0232972. [CrossRef]
29. Feng, Y.; Li, H.; Chen, C.; Lin, H.; Xu, G.; Li, H.; Wang, C.; Chen, J.; Sun, J. Study on the Hepatoprotection of Schisandra chinensis Caulis Polysaccharides in Nonalcoholic Fatty Liver Disease in Rats Based on Metabolomics. *Front. Pharmacol.* **2021**, *12*, 727636. [CrossRef]
30. Li, M.; Ma, J.; Ahmad, O.; Cao, Y.; Wang, B.; He, Q.; Li, J.; Yin, H.; Zhang, Y.; He, J.; et al. Lipid-modulate activity of Cichorium endivia L. et Huet polysaccharide in nonalcoholic fatty liver disease larval zebrafish model. *J. Pharmacol. Sci.* **2018**, *138*, 257–262. [CrossRef]
31. Ren, R.; Yang, Z.; Zhao, A.; Huang, Y.; Lin, S.; Gong, J.; Chen, J.; Zhu, P.; Huang, F.; Lin, W. Sulfated polysaccharide from Enteromorpha prolifera increases hydrogen sulfide production and attenuates non-alcoholic fatty liver disease in high-fat diet rats. *Food Funct.* **2018**, *9*, 4376–4383. [CrossRef] [PubMed]
32. Shih, P.H.; Shiu, S.J.; Chen, C.N.; Cheng, S.W.; Lin, H.Y.; Wu, L.W.; Wu, M.S. Fucoidan and Fucoxanthin Attenuate Hepatic Steatosis and Inflammation of NAFLD through Modulation of Leptin/Adiponectin Axis. *Mar. Drugs* **2021**, *19*, 148. [CrossRef] [PubMed]
33. Wang, F.; Tipoe, G.L.; Yang, C.; Nanji, A.A.; Hao, X.; So, K.F.; Xiao, J. *Lycium barbarum* Polysaccharide Supplementation Improves Liver Function in Rats with Non-Alcoholic Fatty Liver Disease. *Chem. Biodivers* **2021**, *18*, 1163–1179. [CrossRef]
34. Huang, X.; Liu, G.; Guo, J.; Su, Z. The PI3K/AKT pathway in obesity and type 2 diabetes. *Int. J. Biol. Sci.* **2013**, *9*, 152–162. [CrossRef] [PubMed]
35. Wang, X.; Shi, L.; Wang, X.; Feng, Y.; Wang, Y. MDG-1, an Ophiopogon polysaccharide, restrains process of non-alcoholic fatty liver disease via modulating the gut-liver axis signaling pathways. *Int. J. Biol. Macromol.* **2019**, *129*, 1102–1111. [CrossRef] [PubMed]
36. Wang, F.; Tipoe, G.L.; Yang, C.; Nanji, A.A.; Hao, X.; So, K.F.; Xiao, J. Lycium barbarum Polysaccharide Supplementation Improves Alcoholic Liver Injury in Female Mice by Inhibiting Stearoyl-CoA Desaturase 1. *Mol. Nutr. Food Res.* **2018**, *62*, e1800144. [CrossRef]
37. Wang, K.L.; Lu, Z.M.; Mao, X.; Chen, L.; Gong, J.S.; Ren, Y.; Geng, Y.; Li, H.; Xu, H.Y.; Xu, G.H.; et al. Structural characterization and preventive effect on alcoholic liver injury activity of a polysaccharide from *Coriolus versicolor* mycelia. *Int. J. Biol. Macromol.* **2019**, *137*, 1102–1111. [CrossRef] [PubMed]
38. Wang, F.; Tipoe, G.L.; Yang, C.; Nanji, A.A.; Hao, X.; So, K.F.; Xiao, J. Lycium barbarum Polysaccharide Supplementation Improves Alcoholic Liver Injury in Female Mice by Inhibiting Stearoyl-CoA Desaturase 1. *Mol. Nutr. Food Res.* **2018**, *62*, e1800144. [CrossRef]
39. Wang, X.; Shi, L.; Wang, X.; Feng, Y.; Wang, Y. MDG-1, an Ophiopogon polysaccharide, restrains process of non-alcoholic fatty liver disease via modulating the gut-liver axis. *Int. J. Biol. Macromol.* **2019**, *141*, 1013–1021. [CrossRef] [PubMed]
40. Wu, J.; Shao, H.; Zhang, J.; Ying, Y.; Cheng, Y.; Zhao, D.; Dou, X.; Lv, H.; Li, S.; Liu, F.; et al. Muscle polysaccharide alpha-D-glucan (MP-A) protects against non-alcoholic fatty liver disease via maintaining the homeostasis of gut microbiota and regulating related gut-liver axis signaling pathways. *Int. J. Biol. Macromol.* **2019**, *130*, 68–78. [CrossRef]
41. Wu, Y.; Zhou, F.; Jiang, H.; Wang, Z.; Hua, C.; Zhang, Y. Chycory (*Cichorium intybus* L.) polysaccharides attenuate high-fat diet induced non-alcoholic fatty liver disease via AMPK activation. *Int. J. Biol. Macromol.* **2018**, *118*, 886–895. [CrossRef]
42. Zhong, D.; Xie, Z.; Huang, B.; Zhu, S.; Wang, G.; Zhou, H.; Lin, S.; Lin, Z.; Yang, B. Ganoderma Lucidum Polysaccharide Peptide Alleviates Hepatotasisation via Modulating Bile Acid Metabolism Dependent on FXR-SHP/FGF. *Cell Physiol. Biochem.* **2018**, *49*, 1163–1179. [CrossRef]
43. Zhu, H.; Wang, Z.; Wu, Y.; Jiang, H.; Zhou, F.; Xie, X.; Wang, R.; Hua, C. Untargeted metabonomics reveals intervention effects of chycory polysaccharide in a rat model of non-alcoholic fatty liver disease. *Int. J. Biol. Macromol.* **2019**, *128*, 363–375. [CrossRef]
44. Zhou, C.; Fang, Y.; Lin, N.; Liu, H. Polysaccharide extract from pomelo fruitlet ameliorates diet-induced nonalcoholic fatty liver disease in hybrid grouper (Epinephalus lanceolatusmale symbol x Epinephalus fuscoguttatusfemale symbol). *Fish Shellfish Immunol.* **2021**, *119*, 114–127. [CrossRef]
45. Hu, B.; Yang, H.; Chen, G.; Sun, X.; Zou, X.; Ma, J.; Yeo, X.; Liang, Q.; Liu, H. Structural characterization and preventive effect on non-alcoholic fatty liver disease of oligosaccharides from Bletilla striata. *Food Funct.* **2022**, *13*, 4757–4769. [CrossRef] [PubMed]
46. Hasenour, C.M.; Berglund, E.D.; Wasserman, D.H. Emerging role of AMP-activated protein kinase in endocrine control of metabolism in the liver. *Mol. Cell Endocrinol.* **2013**, *366*, 152–162. [CrossRef] [PubMed]
47. Ruderman, N.B.; Xu, X.J.; Nelson, L.; Cacicedo, J.M.; Saha, A.K.; Lan, F.; Ido, Y. AMPK and SIRT1: A long-standing partnership? *Am. J. Physiol. Endocrinol. Metab.* **2010**, *298*, E751–E760. [CrossRef] [PubMed]
48. Huang, X.; Liu, G.; Guo, J.; Su, Z. The PI3K/AKT pathway in obesity and type 2 diabetes. *Int. J. Biol. Sci.* **2018**, *14*, 1483–1496. [CrossRef]
49. Wang, K.; Cao, P.; Wang, H.; Tang, Z.; Wang, N.; Wang, J.; Zhang, Y. Chronic administration of Angelica sinensis polysaccharide effectively improves fatty liver and glucose homeostasis in high-fat diet-fed mice. *Sci. Rep.* **2016**, *6*, 26229. [CrossRef]
50. Kong, X.; Liang, W.; Li, X.; Qiu, M.; Xu, W.; Chen, H. Characterization of an Acidic Polysaccharides from Carrot and Its Hepatoprotective Effect on Alcoholic Liver Injury in Mice. *Chem. Biodivers* **2021**, *18*, e2100359. [CrossRef]
47. Wang, C.; Zheng, L.; Liu, S.; Guo, X.; Qu, Y.; Gao, M.; Cui, X.; Yang, Y. A novel acidic polysaccharide from the residue of Panax notoginseng and its hepatoprotective effect on alcoholic liver damage in mice. *Int. J. Biol. Macromol.* 2020, 149, 1084–1097. [CrossRef]

48. Zhao, H.; Li, H.; Lai, Q.; Yang, Q.; Dong, Y.; Liu, X.; Wang, W.; Zhang, J.; Jia, L. Antioxidant and hepatoprotective activities of modified polysaccharides from Coprinus comatus in mice with alcohol-induced liver injury. *Int. J. Biol. Macromol.* 2019, 127, 476–485. [CrossRef]

49. Wang, X.Y.; Luo, J.P.; Chen, R.; Zha, X.Q.; Wang, H. The effects of daily supplementation of Dendrobium huoshanense polysaccharide on ethanol-induced subacute liver injury in mice by proteomic analysis. *Food Funct.* 2014, 5, 2020–2035. [CrossRef]

50. Jiang, W.; Zhu, H.; Xu, W.; Liu, C.; Hu, B.; Guo, Y.; Cheng, Y.; Qian, H. Echinacea purpurea polysaccharide prepared by fractional precipitation prevents alcoholic liver injury in mice by protecting the intestinal barrier and regulating liver-related pathways. *Int. J. Biol. Macromol.* 2021, 187, 143–156. [CrossRef]

51. Nepali, S.; Ki, H.H.; Lee, J.H.; Cha, J.Y.; Lee, Y.M.; Kim, D.K. Triticum aestivum sprout-derived polysaccharide exerts hepatoprotective effects against ethanol-induced liver damage by enhancing the antioxidant system in mice. *Int. J. Mol. Med.* 2017, 40, 1243–1252. [CrossRef] [PubMed]

52. Qu, H.; Gao, X.; Wang, Z.Y.; Yi, J.J. Comparative study on hepatoprotection of pine nut (*Pinus koraiensis* Sieb. et Zucc.) polysaccharide against different types of chemical-induced liver injury models in vivo. *Int. J. Biol. Macromol.* 2020, 155, 1050–1059. [CrossRef] [PubMed]

53. Song, X.; Liu, Z.; Zhang, J.; Zhang, C.; Dong, Y.; Ren, Z.; Gao, Z.; Liu, M.; Zhao, H.; Jia, L. Antioxidative and hepatoprotective effects of enzymatic and acidic-hydrolysis of Pleurotus geesteranus mycelium polysaccharides on alcoholic liver diseases. *Carbohydr. Polym.* 2018, 201, 75–86. [CrossRef] [PubMed]

54. Song, X.; Sun, W.; Cui, W.; Jia, L.; Zhang, J. A polysaccharide of PFP-1 from Pleurotus geesteranus attenuates alcoholic liver diseases via Nrf2 and NF-kappaB signalling pathways. *Food Funct.* 2021, 12, 4591–4605. [CrossRef] [PubMed]

55. Xiao, J.; Zhu, Y.; Liu, Y.; Tipoe, G.L.; Xing, F.; So, K.F. Lycium barbarum polysaccharide attenuates alcoholic cellular injury through TXNIP-NLRP3 inflammasome pathway. *Int. J. Biol. Macromol.* 2014, 69, 73–78. [CrossRef] [PubMed]

56. Yang, K.; Zhan, L.; Lu, T.; Zhou, C.; Chen, X.; Dong, Y.; Lv, G.; Chen, S. Dendrobium officinale polysaccharides protected against ethanol-induced acute liver injury in vivo and in vitro via the TLR4/NF-kappaB signalling pathway. *Cytokine* 2020, 130, 150586. [CrossRef] [PubMed]

57. Zhang, L.; Zhao, Q.; Wang, L.; Zhao, M.; Zhao, B. Protective effect of polysaccharide from maca (*Lepidium meyenii*) on Hep-G2 cells and alcoholic liver oxidative injury in mice. *Int. J. Biol. Macromol.* 2017, 99, 63–70. [CrossRef]

58. Zhao, H.; Zhang, J.; Liu, X.; Yang, Q.; Dong, Y.; Jia, L. The antioxidant activities of alkalic-extractable polysaccharides from Coprinus comatus on alcohol-induced liver injury in mice. *Sci. Rep.* 2018, 8, 11695. [CrossRef]

59. Wang, Y.; Guan, M.; Zhao, X.; Li, X. Effects of garlic polysaccharide on alcoholic liver fibrosis and intestinal microflora in mice. *Pharm. Biol.* 2018, 56, 325–332. [CrossRef]

60. Song, X.; Cui, W.; Meng, F.; Xia, Q.; Li, X.; Hou, M.; Jia, L.; Zhang, J. Glucopyranose from Pleurotus geesteranus prevent alcoholic liver diseases by regulating Nrf2/HO-1-TLR4/NF-kappaB signalling pathways and gut microbiota. *Food Funct.* 2022, 13, 2441–2455. [CrossRef]

61. Kisseleva, T.; Brenner, D. Molecular and cellular mechanisms of liver fibrosis and its regression. *Nat. Rev. Gastroenterol. Hepatol.* 2021, 18, 151–166. [CrossRef] [PubMed]

62. Meurer, S.K.; Karsdal, M.A.; Weiskirchen, R. Advances in the clinical use of collagen as biomarker of liver fibrosis. *Expert Rev. Mol. Diagn.* 2020, 20, 947–969. [CrossRef] [PubMed]

63. Tao, C.; Trautwein, C. Mechanisms of liver fibrosis resolution. *J. Hepatol.* 2015, 63, 1038–1039. [CrossRef] [PubMed]

64. Ying-Mei, K.E.; Min, J.; Shu-Bo, Z.; Hong, Y.U.; Juan, W.; Feng, G.E. Component analysis of Ophiocordyceps lanpingensis polysaccharide on alleviation of hepatic fibrosis in mice by polysaccharides. *Zhongguo Zhong Yao Za Zhi* 2019, 40, 5256–5264. [CrossRef]

65. Wang, G.; Zuo, P.; Ding, K.; Zeng, Q.; Hu, T.; Wei, S.; Luo, P. Intervention Study of Dictyophora Polysaccharides on Arsenic-Induced Liver Fibrosis in SD Rats. *Biomed. Res. Int.* 2022, 2022, 7509620. [CrossRef]

66. Wang, K.; Wang, J.; Song, M.; Wang, H.; Xia, N.; Zhang, Y. Angelica sinensis polysaccharide attenuates CCl4-induced liver fibrosis via the IL-22/STAT3 pathway. *Int. J. Biol. Macromol.* 2020, 155, 273–283. [CrossRef]

67. Zhangdi, H.J.; Su, S.B.; Wang, F.; Liang, Z.Y.; Yan, Y.D.; Qin, S.Y.; Jiang, H.X. Crosstalk network among multiple inflammatory mediators in liver fibrosis. *World J. Gastroenterol.* 2019, 25, 4835–4849. [CrossRef]

68. Luedde, T.; Schwabe, R.F. NF-kappaB in the liver—Linking injury, fibrosis and hepatocellular carcinoma. *Nat. Rev. Gastroenterol. Hepatol.* 2011, 8, 108–118. [CrossRef]

69. Liu, X.; Pang, H.; Gao, Z.; Zhao, H.; Zhang, J.; Jia, L. Antioxidant and hepatoprotective activities of residue polysaccharides by Pleurotus citrinipileatus. *Int. J. Mol. Sci.* 2019, 131, 315–322. [CrossRef]
71. Gao, L.L.; Ma, J.M.; Fan, Y.N.; Zhang, Y.N.; Ge, R.; Tao, X.J.; Zhang, M.W.; Gao, Q.H.; Yang, J.J. Lycium barbarum polysaccharide combined with aerobic exercise ameliorated non-alcoholic fatty liver disease through restoring gut microbiota, intestinal barrier and inhibiting hepatic inflammation. *Int. J. Biol. Macromol.* 2021, 183, 1379–1392. [CrossRef] [PubMed]

72. Wang, G.; Yang, X.; Wang, J.; Zhong, D.; Zhang, R.; Zhang, Y.; Feng, L.; Zhang, Y. Walnut green husk polysaccharides prevent obesity, chronic inflammatory responses, non-alcoholic fatty liver disease and colonic tissue damage in high-fat diet fed rats. *Int. J. Biol. Macromol.* 2021, 182, 879–898. [CrossRef] [PubMed]

73. Wang, W.; Xu, A.L.; Li, Z.C.; Li, Y.; Xu, S.F.; Sang, H.C.; Zhi, F. Combination of Probiotics and Salvia miltiorrhiza Polysaccharide Alleviates Hepatic Steatosis via Gut Microbiota Modulation and Insulin Resistance Improvement in High Fat-Induced NAFLD Mice. *Diabetes Metab. J.* 2020, 44, 336–348. [CrossRef]

74. Gao, L.L.; Li, Y.X.; Ma, J.M.; Guo, Y.Q.; Li, L.; Gao, Q.H.; Fan, Y.N.; Zhang, M.W.; Tao, X.J.; Yu, J.Q.; et al. Effect of Lycium barbarum polysaccharide supplementation in non-alcoholic fatty liver disease patients: Study protocol for a randomized controlled trial. *Trials* 2021, 22, 566. [CrossRef] [PubMed]

75. Wang, K.; Yang, X.; Wu, Z.; Wang, H.; Li, Q.; Mei, H.; You, R.; Zhang, Y. Dendrobium officinale Polysaccharide Protected Oxaliplatin possesses the synergy and attenuation effect in hepatocellular carcinoma. *Cancer Lett.* 2016, 377, 117–125. [CrossRef] [PubMed]

76. Parmar, D.; Apte, M. Angiopoietin inhibitors: A review on targeting tumor angiogenesis. *Eur. J. Pharmacol.* 2021, 899, 174021. [CrossRef] [PubMed]

77. Khinsar, K.H.; Abdul, S.; Hussain, A.; Ud Din, R.; Lei, L.; Cao, J.; Abbasi, M.; Ur Rehman, A.; Farooqui, N.; Yi, X.; et al. Anti-tumor effect of polysaccharide from Pleurotus ostreatus. *AMB Express* 2021, 11, 160. [CrossRef]

78. Lai, X.; Xia, W.; Wei, J.; Ding, X. Therapeutic Effect of Astragalus Polysaccharides on Hepatocellular Carcinoma H22-Bearing Mice. *Dose Response* 2017, 15, 159392816685182. [CrossRef]

79. Song, M.; Li, Z.H.; Gu, H.S.; Tang, R.Y.; Zhang, R.; Zhu, Y.L.; Liu, J.L.; Zhang, J.J.; Wang, L.Y. Ganoderma lucidum Spore Polysaccharide Inhibits the Growth of Hepatocellular Carcinoma Cells by Altering Macrophage Polarity and Induction of Apoptosis. *J. Immunol. Res.* 2021, 2021, 6696606. [CrossRef]

80. Shen, W.; Chen, C.; Guan, Y.; Song, X.; Jin, Y.; Wang, J.; Hu, Y.; Xin, T.; Jiang, Q.; Zhong, L. A pumpkin polysaccharide induces apoptosis of hepatocellular carcinoma (HCC) cells via pituitary tumor transforming gene 1 (PTTG1)-mediated suppression of the PI3K/Akt and activation of p38 MAPK signaling pathway in vitro. *Evid Based Complement. Alternat. Med.* 2019, 2019, 3769879. [CrossRef] [PubMed]

81. Cheng, W.; Cheng, Z.; Xing, D.; Zhang, M. Asparagus Polysaccharide Suppresses the Migration, Invasion, and angiogenesis of Hepatocellular Carcinoma Cells partly through regulating HIF1alpha/VEGF expression via MAPK and PI3K signaling pathway. *J. Cancer* 2021, 12, 3920–3929. [CrossRef] [PubMed]

82. Cheng, W.; Cheng, Z.; Xing, D.; Zhang, M. Asparagus Polysaccharide Suppresses the Migration, Invasion, and Angiogenesis of Hepatocellular Carcinoma Cells partly by Targeting the HIF-1alpha/VEGF Signalling Pathway In Vitro. *Eur. J. Pharmacol.* 2020, 879–898. [CrossRef] [PubMed]

83. Chu, G.; Miao, Y.; Huang, K.; Song, H.; Liu, L. Role and Mechanism of Rhizopus Nigrum Polysaccharide EPS1-1 as Pharmaceutical and Immunotheapeutics on Hepatocellular Carcinoma. *Front. Oncol.* 2021, 11, 699060. [CrossRef]

84. Khinsar, K.H.; Abdul, S.; Hussain, A.; Ud Din, R.; Lei, L.; Cao, J.; Abbasi, M.; Ur Rehman, A.; Farooqui, N.; Yi, X.; et al. Anti-tumor effect of polysaccharide from Pleurotus ostreatus. *AMB Express* 2021, 11, 160. [CrossRef]

85. Khinsar, K.H.; Abdul, S.; Hussain, A.; Ud Din, R.; Lei, L.; Cao, J.; Abbasi, M.; Ur Rehman, A.; Farooqui, N.; Yi, X.; et al. Anti-tumor effect of polysaccharide from Pleurotus ostreatus on H22 mouse Hepatoma ascites in-vivo and hepatocellular carcinoma in-vitro model. *AMB Express* 2021, 11, 160. [CrossRef]

86. Parmar, D.; Apte, M. Angiopoietin inhibitors: A review on targeting tumor angiogenesis. *Eur. J. Pharmacol.* 2021, 899, 174021. [CrossRef] [PubMed]

87. Gao, L.L.; Fan, Y.N.; Zhang, Y.N.; Ge, R.; Tao, X.J.; Zhang, M.W.; Gao, Q.H.; Yang, J.J. Lycium barbarum polysaccharide combined with aerobic exercise ameliorated non-alcoholic fatty liver disease through restoring gut microbiota, intestinal barrier and inhibiting hepatic inflammation. *Int. J. Biol. Macromol.* 2021, 183, 1379–1392. [CrossRef] [PubMed]

88. Gao, L.L.; Ma, J.M.; Fan, Y.N.; Zhang, Y.N.; Ge, R.; Tao, X.J.; Zhang, M.W.; Gao, Q.H.; Yang, J.J. Lycium barbarum polysaccharide combined with aerobic exercise ameliorated non-alcoholic fatty liver disease through restoring gut microbiota, intestinal barrier and inhibiting hepatic inflammation. *Int. J. Biol. Macromol.* 2021, 183, 1379–1392. [CrossRef] [PubMed]

89. Wang, W.; Xu, A.L.; Li, Z.C.; Li, Y.; Xu, S.F.; Sang, H.C.; Zhi, F. Combination of Probiotics and Salvia miltiorrhiza Polysaccharide Alleviates Hepatic Steatosis via Gut Microbiota Modulation and Insulin Resistance Improvement in High Fat-Induced NAFLD Mice. *Diabetes Metab. J.* 2020, 44, 336–348. [CrossRef]

90. Yu, J.; Liu, C.; Ji, H.Y.; Liu, A.J. The caspases-dependent apoptosis of hepatoma cells induced by an acid-soluble polysaccharide from Grifola frondosa. *Int. J. Biol. Macromol.* 2020, 159, 364–372. [CrossRef]

91. Fabregat, I. Dysregulation of apoptosis in hepatocellular carcinoma cells. *World J. Gastroenterol.* 2009, 15, 513–520. [CrossRef] [PubMed]

92. Liu, Z.; Ke, F.; Duan, C.; Lan, H.; Li, J.; Gao, C.; Li, J.; Zhong, Z. Mannan-conjugated adenovirus enhanced gene therapy effects on murine hepatocellular carcinoma cells in vitro and in vivo. *Biconjuga. Chem.* 2013, 24, 1387–1397. [CrossRef] [PubMed]

93. Zhang, Y.; Li, Q.; Wang, J.; Cheng, F.; Huang, X.; Cheng, Y.; Wang, K. Polysaccharide from Lentinus edodes combined with oxaiplatin possesses the synergy and attenuation effect in hepatocellular carcinoma. *Cancer Lett.* 2016, 377, 117–125. [CrossRef] [PubMed]
94. Zong, S.; Li, J.; Yang, L.; Huang, Q.; Hou, G.; Ye, Z.; Ye, M. Mechanism of bioactive polysaccharide from Lachnum sp. acts synergistically with 5-flourouracil against human hepatocellular carcinoma. J. Cell Physiol. 2019, 234, 15548–15562. [CrossRef]

95. Zong, S.; Li, J.; Yang, L.; Huang, Q.; Ye, Z.; Hou, G.; Ye, M. Synergistic antitumor effect of polysaccharide from Lachnum sp. in combination with cyclophosphamide in hepatocellular carcinoma. Carbohydr. Polym. 2018, 196, 33–46. [CrossRef]

96. Liu, Y.H.; Qin, H.Y.; Zhong, Y.Y.; Li, S.; Wang, H.J.; Wang, H.; Chen, LL.; Tang, X.; Li, Y.L.; Qian, Z.Y.; et al. Neutral polysaccharide from Panax notoginseng enhanced cyclophosphamide antitumor efficacy in hepatoma H22-bearing mice. BMC Cancer 2021, 21, 37. [CrossRef]

97. Yoo, F.; Jiang, G.R.; Liang, G.Q.; Yuan, Q.; Zhu, Y.; Liu, M.; Zhang, L.R. The antitumor effect of the combination of aconitine and crude monkshood polysaccharide on hepatocellular carcinoma. Pak. J. Pharm. Sci. 2021, 34, 971–979.

98. Zhang, Y.; Cui, Z.; Mei, H.; Xu, J.; Zhou, T.; Cheng, F.; Wang, K. Angelica sinensis polysaccharide nanoparticles as a targeted drug delivery system for enhanced therapy of liver cancer. Carbohydr. Polym. 2019, 219, 143–154. [CrossRef]

99. Liu, X.; Wu, Z.; Guo, C.; Guo, H.; Su, Y.; Chen, Q.; Sun, C.; Liu, Q.; Chen, D.; Mu, H. Hypoxia responsive nano-drug delivery system based on angelica polysaccharide for liver cancer therapy. Drug Deliv. 2022, 29, 138–148. [CrossRef]

100. Andrade, R.J.; Chalasani, N.; Bjornsson, E.S.; Suzuki, A.; Kullak-UBlick, G.A.; Watkins, P.B.; Devarthavi, H.; Merz, M.; Lucena, M.I.; Kaplowitz, N.; et al. Drug-induced liver injury. Nat. Rev. Dis. Primers 2019, 5, 58. [CrossRef]

101. Cao, P.; Sun, J.; Sullivan, M.A.; Huang, X.; Wang, H.; Zhang, Y.; Wang, N.; Wang, K. Angelica sinensis polysaccharide protects against acetaminophen-induced acute liver injury and cell death by suppressing oxidative stress and hepatic apoptosis in vivo and in vitro. Int. J. Mol. Biol. Macromol. 2018, 111, 1133–1139. [CrossRef] [PubMed]

102. Che, J.; Yang, S.; Qiao, Z.; Li, H.; Sun, J.; Zhuang, W.; Chen, J.; Wang, C. Schisandra chinensis acidic polysaccharide partially reverses acetaminophen-induced liver injury in mice. J. Pharmocol. Sci. 2019, 140, 248–254. [CrossRef] [PubMed]

103. Chen, C.; Liu, X.; Qi, S.; A, C.P.; Yan, J.; Zhang, X. Hepatoprotective effect of Phellinus linteus mycelia polysaccharide (PL-N1) against acetaminophen-induced liver injury in mice. Int. J. Biol. Macromol. 2020, 154, 1276–1284. [CrossRef] [PubMed]

104. Dong, Y.; Huang, J.; Lin, X.; Zhang, S.; Jiao, Y.; Liang, T.; Chen, Z.; Huang, R. Hepatoprotective effects of Yulangsan polysaccharide extracts protect against acetaminophen induced hepatotoxicity in mice via activating the Nrf-2/HO-1-SOD-2 signaling pathway. Phytomedicine 2018, 38, 90–97. [CrossRef] [PubMed]

105. Wang, Y.Q.; Wei, J.G.; Tu, M.J.; Gu, J.G.; Zhang, W. Fucoidan Alleviates Acetaminophen-Induced Hepatotoxicity via Oxidative Stress Inhibition and Nrf2 Translocation. Int. J. Mol. Sci. 2018, 19, 4050. [CrossRef] [PubMed]

106. Dong, Y.; Huang, J.; Lin, X.; Zhang, S.; Jiao, Y.; Liang, T.; Chen, Z.; Huang, R. Hepatoprotective effects of Yulangsan polysaccharide against isoniazid and rifampicin-induced liver injury in mice. J. Ethnopharmacol. 2014, 152, 201–206. [CrossRef] [PubMed]

107. Wang, J.; Luo, W.; Li, B.; Lv, J.; Ke, X.; Ge, D.; Dong, R.; Wang, C.; Han, Y.; Zhang, C.; et al. Sagittaria sagittifolia polysaccharide protects against isoniazid and rifampicin-induced hepatic injury via activation of nuclear factor E2-related factor 2 signaling in mice. J. Ethnopharmacol. 2018, 227, 237–245. [CrossRef]

108. Zhang, G.L.; Wang, Y.H.; Ni, W.; Teng, H.L.; Lin, Z.B. Hepatoprotective role of Ganoderma lucidum polysaccharide against isoniazid and rifampicin-induced liver injury in mice. J. Ethnopharmacol. 2018, 205, 765–783.e764. [CrossRef]

109. Luedde, T.; Kaplowitz, N.; Schwabe, R.F. Cell death and cell death responses in liver disease: Mechanisms and clinical relevance. Gastroenterology 2014, 147, 765–785.e764. [CrossRef]

110. Singh, R.; Letai, A.; Sarosiek, K. Regulation of apoptosis in health and disease: The balancing act of BCL-2 family proteins. Nat. Rev. Mol. Cell Biol. 2019, 20, 175–193. [CrossRef]

111. Bock, F.J.; Tait, S.W.G. Mitochondria as multifaceted regulators of cell death. Nat. Rev. Mol. Cell Biol. 2020, 21, 85–100. [CrossRef] [PubMed]

112. Bonora, M.; Giorgi, C.; Pinton, P. Molecular mechanisms and consequences of mitochondrial permeability transition. Nat. Rev. Mol. Cell Biol. 2021, 23, 266–285. [CrossRef] [PubMed]

113. Dixon, S.J.; Lemberg, K.M.; Lamprecht, M.R.; Skouta, R.; Zaitsev, E.M.; Gleason, C.E.; Patel, D.N.; Bauer, A.J.; Cantley, A.M.; Yang, W.S.; et al. Ferroptosis: An iron-dependent form of nonapoptotic cell death. Cell 2012, 149, 1060–1072. [CrossRef] [PubMed]

114. Jiang, X.; Stockwell, B.R.; Conrad, M. Ferroptosis: Mechanisms, biology and role in disease. Nat. Rev. Mol. Cell Biol. 2021, 22, 266–282. [CrossRef]

115. Wenzel, S.E.; Tyurina, Y.Y.; Zhao, J.; St Croix, C.M.; Dar, H.H.; Mao, G.; Tyurin, V.A.; Anthonymuthu, T.S.; Kapralov, A.A.; Amoscato, A.A.; et al. PEBP1 Wardens Ferroptosis by Enabling Lipoxygenase Generation of Lipid Death Signals. Cell 2017, 171, 628–641.e626. [CrossRef]

116. Chen, J.; Li, X.; Ge, C.; Min, J.; Wang, F. The multifaceted role of ferroptosis in liver disease. Cell Death Differ. 2022, 29, 467–480. [CrossRef]

117. Fang, X.; Wang, H.; Han, D.; Xie, E.; Yang, X.; Wei, J.; Gu, S.; Gao, F.; Zhu, N.; Yin, X.; et al. Ferroptosis as a target for protection against cardiomypathy. Proc. Natl. Acad. Sci. USA 2019, 116, 2672–2680. [CrossRef]

118. Wang, H.; An, P.; Xie, E.; Wu, Q.; Fang, X.; Gao, H.; Zhang, Z.; Li, Y.; Wang, X.; Zhang, J.; et al. Characterization of ferroptosis in murine models of hemochromatosis. Hepatology 2017, 66, 449–465. [CrossRef]

119. Yu, Y.; Jiang, L.; Wang, H.; Shen, Z.; Cheng, Q.; Zhang, P.; Wang, J.; Wu, Q.; Fang, X.; Duan, L.; et al. Hepatic transferrin plays a role in systemic iron homeostasis and liver ferroptosis. Blood 2020, 136, 726–739. [CrossRef]

120. Fang, X.; Cai, Z.; Wang, H.; Han, D.; Cheng, Q.; Zhang, P.; Gao, F.; Yu, Y.; Song, Z.; Wu, Q.; et al. Loss of Cardiac Ferritin H Facilitates Cardiomyopathy via Slc7a11-Mediated Ferroptosis. Circ. Res. 2020, 127, 486–501. [CrossRef]
121. Gao, M.; Yi, J.; Zhu, J.; Minikes, A.M.; Monian, P.; Thompson, C.B.; Jiang, X. Role of Mitochondria in Ferroptosis. *Mol. Cell* **2019**, *73*, 354–363.e353. [CrossRef] [PubMed]

122. Ingold, I.; Berndt, C.; Schmitt, S.; Doll, S.; Poschmann, G.; Buday, K.; Roveri, A.; Peng, X.; Porto Freitas, F.; Seibt, T.; et al. Selenium Utilization by GPX4 Is Required to Prevent Hydroperoxide-Induced Ferroptosis. *Cell* **2018**, *172*, 409–422.e421. [CrossRef] [PubMed]

123. Mao, C.; Liu, X.; Zhang, Y.; Lei, G.; Yan, Y.; Lee, H.; Koppula, P.; Wu, S.; Zhuang, L.; Fang, B.; et al. DHODH-mediated ferroptosis defence is a targetable vulnerability in cancer. *Nature* **2021**, *593*, 586–590. [CrossRef] [PubMed]

124. Yang, W.S.; SriRamaratnam, R.; Welsch, M.E.; Shimada, K.; Skouta, R.; Viswanathan, V.S.; Cheah, J.H.; Clemens, P.A.; Shchepinov, M.S.; Clish, C.B.; et al. Regulation of ferroptotic cancer cell death by GPX4. *Cell* **2014**, *156*, 317–331. [CrossRef]

125. Doll, S.; Freites, F.P.; Shah, R.; Aldrovandi, M.; da Silva, M.C.; Ingold, I.; Goya Grocin, A.; Xavier da Silva, T.N.; Panzilius, E.; Scheel, C.H.; et al. FSP1 is a glutathione-independent ferroptosis suppressor. *Nature* **2019**, *575*, 693–698. [CrossRef]

126. Shimada, K.; Hayano, M.; Paganò, N.C.; Stockwell, B.R. Cell-Line Selectivity Improves the Predictive Power of Pharmacogenomic Analyses and Helps Identify NADPH as Biomarker for Ferroptosis Sensitivity. *Cell Chem. Biol.* **2016**, *23*, 225–235. [CrossRef]

127. Yang, W.S.; Kim, K.J.; Gaschler, M.M.; Patel, M.; Shchepinov, M.S.; Stockwell, B.R. Peroxidation of polyunsaturated fatty acids by lipoxigenases drives ferroptosis. *Proc. Natl. Acad. Sci. USA* **2016**, *113*, E4966–E4975. [CrossRef]

128. Lo, A.C.Y.; Yang, M.L. *Lycium barbarum* polysaccharides and ferroptosis: Jumping into the era of novel regulated cell death. *Regen. Res.* **2022**, *17*, 1473–1474. [CrossRef] [PubMed]

129. Duc, X.; Fang, B.; Henry, W.S.; Ricq, E.L.; Graham, E.T.; Phadnis, V.V.; Maretich, P.; Paradkar, S.; Boehnke, N.; Deik, A.A.; Reinhardt, F.; et al. Auranofin mitigates systemic iron overload and induces ferroptosis via distinct mechanisms. *Signal. Transduct. Target. Ther.* **2020**, *5*, 138. [CrossRef]

130. Doll, S.; Proneth, B.; Tyurina, Y.Y.; Panzilius, E.; Kobayashi, S.; Ingold, I.; Clemens, P.A.; Samjhi, A.F.; Li, W.; Zhou, X.; Xu, S.; Cao, N.; Li, B.; Chen, W.; Yang, B.; Yuan, M.; Xu, D. Lipopolysaccharide-induced splenic ferroptosis in chickens was alleviated by polysaccharide of *Atractylodes macrocephala* Koidz associated with proinflammatory factors. *Mar. Drugs* **2021**, *19*, 68–81. [CrossRef]

131. Zhai, F.G.; Liang, Q.C.; Wu, Y.Y.; Liu, J.Q.; Liu, J.W. Red ginseng polysaccharide exhibits anticancer activity through GPX4 downregulation-induced ferroptosis. *Pharm. Biol.* **2020**, *58*, 909–914. [CrossRef]

132. Zou, Y.; Henry, W.S.; Ricq, E.L.; Graham, E.T.; Phadnis, V.V.; Mareteich, P.; Paradažek, S.; Boehnke, N.; Deik, A.A.; Reinhardt, F.; et al. Plasticity of ether lipids promotes ferroptosis susceptibility and evasion. *Nature* **2020**, *585*, 603–608. [CrossRef]

133. Du, X.; Zhang, J.; Li, L.; Yu, B.; Han, H.; Bai, W.; Pei, X.; Fu, X.; Hou, S. A novel anticancer property of *Lycium barbarum* polysaccharide in triggering ferroptosis of breast cancer cells. *J. Zhejiang Univ. Sci. B* **2022**, *23*, 286–299. [CrossRef] [PubMed]

134. He, S.; Li, R.; Peng, Y.; Wang, Z.; Huang, J.; Meng, H.; Min, J.; Wang, F.; Ma, Q. ACSL4 contributes to ferroptosis-mediated rhabdomyolysis in exertional heat stroke. *J. Cachexia Sarcopenia Muscle* **2022**, *13*, 1473–1474. [CrossRef] [PubMed]

135. Lo, A.C.Y.; Yang, M. *Lycium barbarum* polysaccharides and ferroptosis: Jumping into the era of novel regulated cell death. *Neural Regen. Res.* **2022**, *17*, 1473–1474. [CrossRef] [PubMed]

136. Zhai, F.G.; Liang, Q.C.; Wu, Y.Y.; Liu, J.Q.; Liu, J.W. Red ginseng polysaccharide exhibits anticancer activity through GPX4 downregulation-induced ferroptosis. *Pharm. Biol.* **2020**, *58*, 909–914. [CrossRef] [PubMed]

137. Chen, Y.; Ding, C.; Chen, Y.; Hu, W.; Yu, C.; Peng, C.; Peng, X.; Cheng, Q.; Wu, W.; Lu, Y.; et al. ACSL4 reprograms fatty acid metabolism in hematopoietic stem cells via c-Myc/SREBP1 pathway. *Cancer Lett.* **2021**, *502*, 154–165. [CrossRef] [PubMed]

138. Chen, Y.; Wang, J.; Li, J.; Zhu, J.; Wang, R.; Xi, Q.; Wu, H.; Shi, T.; Chen, W. Astragalus polysaccharide prevents ferroptosis in a murine model of experimental colitis and human Caco-2 cells via inhibiting NFR2/FOX-1 pathway. *Eur. J. Pharmocol.* **2021**, *911*, 174518. [CrossRef]

139. Dorschmann, P.; Apitz, S.; Hellige, I.; Neupane, S.; Alban, S.; Kopplin, G.; Ptak, S.; Frette, X.; Roeder, J.; Zille, M.; et al. Evaluation of the Effects of Eucoidans from Fucus Species and Laminaria hyperborea against Oxidative Stress and Iron-Dependent Cell Death. *Mar. Drugs* **2021**, *19*, 557. [CrossRef] [PubMed]

140. Liu, W.; Zhou, X.; Xu, S.; Cao, N.; Li, B.; Chen, W.; Yang, B.; Yuan, M.; Xu, D. Lipopolysaccharide-induced splenic ferroptosis in goslings was alleviated by polysaccharide of *Atractylodes macrocephala* koidz associated with proinflammatory factors. *Poult. Sci.* **2022**, *101*, 101725. [CrossRef]

141. Friedmann Angeli, J.P.; Schneider, M.; Proneth, B.; Tyurina, Y.Y.; Tyurin, V.A.; Hammond, V.J.; Herbach, N.; Aichler, M.; Walch, A.; Eggenhofer, E.; et al. Inactivation of the ferroptosis regulator Gpx4 triggers acute renal failure in mice. *Nat. Cell Biol.* **2014**, *16*, 1180–1191. [CrossRef]

142. Liu, C.Y.; Wang, M.; Hu, Y.M.; Han, F.X.; Wu, Q.S.; Cai, X.J.; Kurihara, H.; Chen, Y.X.; Li, Y.F.; He, R.R. Ferroptosis is involved in alcohol-induced cell death in vivo and in vitro. *Biosci. Biotechnol. Biochem.* **2020**, *84*, 1621–1628. [CrossRef] [PubMed]

143. Qi, J.; Kim, J.W.; Zhou, Z.; Lim, C.W.; Kim, B. Ferroptosis Affects the Progression of Nonalcoholic Steatohepatitis via the Modulation of Lipid Peroxidation-Mediated Cell Death in Mice. *Am. J. Pathol.* **2020**, *190*, 68–81. [CrossRef] [PubMed]

144. Tsurusaki, S.; Tsuchiya, Y.; Koumura, T.; Nakasone, M.; Sakamoto, T.; Matsuoka, M.; Imai, H.; Yuet-Yin Kok, C.; Okochi, H.; Nakano, H.; et al. Hepatic ferroptosis plays an important role as the trigger for initiating inflammation in nonalcoholic steatohepatitis. *Cell Death Dis.* **2019**, *10*, 449. [CrossRef] [PubMed]

145. Kong, Z.; Liu, R.; Cheng, Y. Artesunate alleviates liver fibrosis by regulating ferroptosis signaling pathway. *Biomed. Pharmacother.* **2019**, *109*, 2043–2053. [CrossRef]
146. Kuo, C.Y.; Chiu, V.; Hsieh, P.C.; Huang, C.Y.; Huang, S.J.; Tseng, I.S.; Tsai, F.M.; Chen, M.L.; Liu, C.T.; Chen, Y.R. Chrysophanol attenuates hepatitis B virus X protein-induced hepatic stellate cell fibrosis by regulating endoplasmic reticulum stress and ferroptosis. J. Pharmacol. Sci. 2020, 144, 172–182. [CrossRef]

147. Sui, M.; Jiang, X.; Chen, J.; Yang, H.; Zhu, Y. Magnesium isoglycyrrhizinate ameliorates liver fibrosis and hepatic stellate cell activation by regulating ferroptosis signaling pathway. Biomed. Pharmacother. 2018, 106, 125–133. [CrossRef]

148. Wang, L.; Zhang, Z.; Li, M.; Wang, F.; Jia, Y.; Zhang, F.; Shao, J.; Chen, A.; Zheng, S. P53-dependent induction of ferroptosis is required for artemether to alleviate carbon tetrachloride-induced liver fibrosis and hepatic stellate cell activation. IUBMB Life 2019, 71, 45–56. [CrossRef]

149. Yi, J.; Wu, S.; Tan, S.; Qin, Y.; Wang, X.; Jiang, J.; Liu, H.; Wu, B. Berberine alleviates liver fibrosis through inducing ferrous redox to activate ROS-mediated hepatic stellate cells ferroptosis. Cell Death Discov. 2021, 7, 374. [CrossRef]

150. Zhang, Z.; Wang, X.; Wang, Z.; Zhang, Z.; Cao, Y.; Wei, Y.; Shao, J.; Chen, A.; Zhang, F.; Zheng, S. Dihydroartemisinin alleviates hepatic fibrosis through inducing ferroptosis in hepatic stellate cells. Biofactors 2021, 47, 801–818. [CrossRef]

151. Li, Y.; Jin, C.; Shen, M.; Wang, Z.; Tan, S.; Chen, A.; Wang, S.; Shao, J.; Zhang, F.; Zhang, Z.; et al. Iron regulatory protein 2 is required for artemether-mediated anti-hepati fibrosis through ferroptosis pathway. Free Radic. Biol. Med. 2020, 160, 845–859. [CrossRef] [PubMed]

152. Shen, M.; Guo, M.; Li, Y.; Wang, Y.; Qiu, Y.; Shao, J.; Zhang, F.; Xu, X.; Yin, G.; Wang, S.; et al. m(6)A methylation is required for dihydroartemisinin to alleviate liver fibrosis by inducing ferroptosis in hepatic stellate cells. Free Radic. Biol. Med. 2022, 182, 246–259. [CrossRef] [PubMed]

153. Su, Y.; Zhao, D.; Jin, C.; Li, Z.; Sun, S.; Xia, S.; Zhang, Y.; Zhang, Z.; Zhang, F.; Xu, X.; et al. Dihydroartemisinin Induces Ferroptosis in HCC by Promoting the Formation of PEBP1/15-LO. Oxid. Cell Longev. 2021, 2021, 3456725. [CrossRef] [PubMed]

154. Wang, Z.; Li, M.; Liu, Y.; Qiao, Z.; Bai, T.; Yang, L.; Liu, B. Dihydroartemisinin triggers ferroptosis in primary liver cancer cells by promoting and unfolded protein responseinduced upregulation of CHAC1 expression. Oncol. Rep. 2021, 46, 240. [CrossRef] [PubMed]

155. Cui, Z.; Wang, H.; Li, S.; Qin, T.; Shi, H.; Ma, J.; Li, L.; Yu, G.; Jiang, T.; Li, C. Dihydroartemisinin enhances the inhibitory effect of sorafenib on HepG2 cells by inducing ferroptosis and inhibiting energy metabolism. J. Pharmacol. Sci. 2022, 148, 73–85. [CrossRef] [PubMed]

156. Li, Z.; Dai, H.Q.; Huang, X.W.; Feng, J.; Deng, J.H.; Wang, Z.X.; Yang, X.M.; Liu, Y.J.; Wu, Y.; Chen, P.H.; et al. Artesunate synergizes with sorafenib to induce ferroptosis in hepatocellular carcinoma. Acta Pharmacol. Sin. 2021, 42, 301–310. [CrossRef] [PubMed]

157. Jin, M.; Shi, C.; Li, T.; Wu, Y.; Hu, C.; Huang, G. Solasonine promotes ferroptosis of hepatoma carcinoma cells via glutathione peroxidase 4-induced destruction of the glutathione redox system. Biomed. Pharmacother. 2020, 129, 110282. [CrossRef]

158. Chang, W.T.; Bow, Y.D.; Fu, P.J.; Li, C.Y.; Wu, C.Y.; Chang, Y.H.; Teng, Y.N.; Li, R.N.; Lu, M.C.; Liu, Y.C.; et al. A Marine Terpenoid, Heteronemin, Induces Both the Apoptosis and Ferroptosis of Hepatocellular Carcinoma Cells and Involves the ROS and MAPK Pathways. Oxid. Med. Cell Longev. 2021, 2021, 7689045. [CrossRef]

159. Gao, G.; Xie, Z.; Li, E.W.; Yuan, Y.; Fu, Y.; Wang, P.; Zhang, X.; Qiao, Y.; Xu, J.; Holscher, C.; et al. Dehydroabietic acid improves nonalcoholic fatty liver disease through activating the Keap1/Nrf2-ARE signaling pathway to reduce ferroptosis. J. Pharmacol. Sci. 2020, 152599. [CrossRef]

160. Yang, Y.; Chen, J.; Gao, Q.; Shan, X.; Wang, J.; Lv, Z. Study on the attenuated effect of Ginkgolide B on ferroptosis in high fat diet induced nonalcoholic fatty liver disease. Toxicology 2020, 445, 152599. [CrossRef]

161. Wang, M.; Liu, C.Y.; Wang, T.; Yu, H.M.; Ouyang, S.H.; Wu, Y.P.; Gong, H.B.; Ma, X.H.; Jiao, G.L.; Fu, L.L.; et al. (+)-Clausenamide protects against drug-induced liver injury by inhibiting hepatocyte ferroptosis. Cell Death Dis. 2020, 11, 781. [CrossRef]

162. Wang, Y.; Chen, Q.; Shi, C.; Jiao, F.; Gong, Z. Mechanism of glycyrrhizin on ferroptosis during acute liver failure by inhibiting oxidative stress. Mol. Med. Rep. 2019, 20, 4081–4090. [CrossRef] [PubMed]

163. He, P.; Hua, H.; Tian, W.; Zhu, H.; Liu, Y.; Xu, X. Holly (Ilex latifolia Thunb.) Polyphenols Extracts Alleviate Hepatic Damage by Regulating Ferroptosis Following Diquat Challenge in a Piglet Model. Front. Nutr. 2020, 7, 604328. [CrossRef] [PubMed]

164. Dai, C.; Li, H.; Wang, Y.; Tang, S.; Velkov, T.; Shen, J. Inhibition of Oxidative Stress and ALOX12 and NF-kappaB Pathways Contribute to the Protective Effect of Baicalein on Carbon Tetrachloride-Induced Acute Liver Injury. Antioxidants 2021, 10, 976. [CrossRef] [PubMed]