Review

Potential Roles and Key Mechanisms of Hawthorn Extract against Various Liver Diseases

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Abstract: The genus *Crataegus* (hawthorn), a flowering shrub or tree, is a member of the Rosaceae family and consists of approximately 280 species that have been primarily cultivated in East Asia, North America, and Europe. Consumption of hawthorn preparations has been chiefly associated with pharmacological benefits for cardiovascular diseases, including congestive heart failure and angina pectoris. Treatment with hawthorn extracts can be related to improvements in the complex pathogenesis of various hepatic and cardiovascular disorders. In this regard, the present review described that the presence of hawthorn extracts ameliorated hepatic injury, lipid accumulation, inflammation, fibrosis, and cancer in an abundance of experimental models. Hawthorn extracts might have these promising activities, largely by enhancing the hepatic antioxidant system. In addition, several mechanisms, including AMP-activated protein kinase (AMPK) signaling and apoptosis, are responsible for the role of hawthorn extracts in repairing the dysfunction of injured hepatocytes. Specifically, hawthorn possesses a wide range of biological actions relevant to the treatment of toxic hepatitis, alcoholic liver disease, non-alcoholic fatty liver disease, and hepatocellular carcinoma. Accordingly, hawthorn extracts can be developed as a major source of therapeutic agents for liver diseases.

Keywords: hawthorn; *Crataegus*; liver; antioxidant

1. Introduction

Liver disease is associated with high prevalence, increased mortality, and a substantial health care burden. By 2017, approximately 1.5 billion people were suffering from chronic liver disease (CLD), which, along with liver cirrhosis, accounts for 2 million annual deaths worldwide [1,2]. Non-alcoholic fatty liver disease (NAFLD) accounts for a major component (60%) of CLD, other components of which include hepatitis B and C viruses (38%) and alcohol consumption (2%) [1]. Acute liver failure is mainly a consequence of viral infection and drug-induced liver injury in the developing and developed worlds, respectively [3]. Although vaccination and novel antiviral agents have lowered the incidence of virus-induced liver diseases, including cirrhosis, considerable risk factors, including metabolic syndrome, obesity, and alcohol and drug misuse/overuse, still lead to various liver disorders [4,5]. However, there are no approved drugs currently available for managing various liver diseases, including NAFLD, non-alcoholic steatohepatitis (NASH), alcoholic liver disease (ALD), liver cirrhosis, and hepatocellular carcinoma (HCC).

A wide spectrum of risk factors affecting the liver, including obesity, drugs, alcohol, environmental pollutants, irradiation, and toxicants, can induce excessive oxidative stress in liver tissues and perturb the hepatic defense system against oxidative damage [6]. In this

Citation: Kim, E.; Jang, E.; Lee, J.-H. Potential Roles and Key Mechanisms of Hawthorn Extract against Various Liver Diseases. *Nutrients* 2022, 14, 867. https://doi.org/10.3390/nu14040867

Academic Editor: Pietro Vajro

Received: 24 January 2022
Accepted: 17 February 2022
Published: 18 February 2022

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context, multiple antioxidants, such as vitamin E, zinc, selenium, methionine, coenzyme Q10, silymarin, and N-acetylcysteine, have been hypothesized and used as main drugs or dietary supplements in treating liver diseases [6]. Specifically, most antioxidants possess remarkable hepatoprotective, antisteatotic, anti-inflammatory, and antifibrotic effects, as well as striking properties against oxidative damage. Hence, oxidative stress can be a key component of the molecular pathogenesis of liver damage, and altering the imbalance of production and removal of hepatic free radicals might be useful in preventing and treating various liver diseases. In addition, a variety of signaling pathways, including hepatic cholesterol maintenance, AMP-activated protein kinase (AMPK), and apoptosis, have been implicated in the pathogenesis of liver diseases [7–9].

Currently, approximately 50% of therapeutic drugs against liver diseases originate from natural plants [10]. This high predominance may be correlated with the abundance of multiple constituents with excellent pharmacological properties, including antioxidant action. Hawthorn (a common name indicating *Crataegus* species) is a promising medicinal plant, displaying substantial efficacy in interfering with the pathogenesis of liver diseases. In fact, although hawthorn has long been used as an alternative medicine to treat abdominal pain, dyspepsia, angina, and congestive heart failure, it also reportedly participates in NAFLD resolution [11,12]. Recently, available preclinical evidence investigating the counter-regulation and underlying signaling pathways of hawthorn species (*C. pinnatifida* in Korea and China; *C. cuneata* in Japan; and *C. monogyna*, *C. oxyacantha*, and *C. aronia* in Europe, the US, and the Middle East) is increasing [13].

Despite the accumulating data on the efficacy of hawthorn extract and its constituents in various liver diseases, a comprehensive review on the efficacy, mechanism, and safety for clinical use of the plant for liver disease treatment has not yet been performed. Thus, the present study summarized the preclinical evidence supporting the improvement of hawthorn extract against multiple pathologies of liver disease and demonstrated related mechanisms to further understand the role of hawthorn in this type of disorder.

2. Phytochemistry of Hawthorn

Hawthorn contains a variety of flavonoids, triterpenoids, monoterpenoids, lignans, and organic acids. To date, more than 150 chemical compounds have been identified from its leaves, flowers, and berries [14]. The Korean pharmacopoeia and pharmacopoeia of the People’s Republic of China allow *C. pinnatifida* to be the representative species of hawthorn and ursolic acid is used for the identification test of the fruits of *C. pinnatifida* [15,16]. According to the pharmacopoeia of the People’s Republic of China, *C. pinnatifida* fruits and leaves should contain more than 5.0% of citric acid, 7.0% of flavonoids, and 0.050% of hyperoside. In Europe and the US, *C. oxyacantha* and *C. monogyna* have mainly been used, and their fruits, leaves, and flowers must contain more than 1.0–1.5% flavonoids [17,18]. While South Korea, China, Europe, and the US emphasize the content of flavonoids in the genus *Crataegus*, which includes *C. pinnatifida*, *C. oxyacantha*, and *C. monogyna*, hyperoside has been the most frequently identified flavonoid. Other flavonoids, such as vitexin, rutin, and ferulic acid, have been recognized as common constituents of the above hawthorn extracts [19]. In addition, remarkable quantities of triterpenoids, including ursolic acid and corosolic acid, have been quantified in Chinese and European hawthorns [20,21]. Remarkably, the analysis of the quantification and profile of chemical compounds in hawthorn plants has reported considerable divergence between various medicinal parts, including fruits, leaves, and flowers of different *C. species*. A number of individual phenolics, including rutin, hyperoside, chlorogenic acid, vitexin, and isoquercetin, using high-performance liquid chromatography (HPLC) analysis, were selected for quality assessment of more than 50 samples (leaves and flowers) of different species of hawthorn plant [22]. Similarly, 11 available compounds, including hyperoside and chlorogenic acid, were separated and quantified using HPLC-electrospray ionization mass spectrometry in hawthorn fruits [23]. However, there is still an unmet need for sufficient data on the contents and profile of major constituents of all species of hawthorn owing to both lack of accurate quality measures
and insufficient sources of active compounds. Thus, further investigations need to be performed for data of chemical profiling, reference compounds, and reliable validation for quality assurance of hawthorn.

3. Pharmacological Properties of Hawthorn

3.1. Hepatoprotective Effect

The liver is an important solid organ that filters blood input from the gastrointestinal tract, decomposing toxicants and disposing of harmful materials from the body [24]. Lack of proper hepatic function due to oversupply of food, alcohol, medications, toxicants, and other harmful factors can lead to some degree of liver damage, suggesting abnormalities in the synthesis, processing, and secretory functions of hepatocytes. Hepatic injury is characterized by abnormal liver function due to increased activity of serum biochemical markers, and histological findings of damaged hepatocellular structures [25]. Reactive oxygen species (ROS) may be a key determinant in the development and aggravation of liver dysfunction because oxidative stress can primarily oxidize hepatocellular structure components, including DNA, proteins, and lipids [26]. In addition, pathological apoptosis excessively eliminates hepatocytes through the release of harmful cytokines and maximal immune responses [27].

Hawthorn extracts prevented liver damage induced by a high-fat/cholesterol/triglyceride/fructose diets, alcohol treatment, LPS, CCl4, cadmium, and partial hepatectomy in rodents and HepG2 cells, via inhibition of oxidative injury and apoptosis. Serum transaminase (AST and ALT) levels are frequently increased in liver injury because they leak into peripheral blood in cases of abnormal hepatocellular integrity [27]. Hence, regulating both serum markers within normal limits can represent liver protection and maintenance of liver function. The extracts of C. oxyacantha [28], C. aronia [29], C. monogyna [30], and C. pinnatifida [31–35] significantly decreased serum AST and ALT levels, which were markedly elevated by high-fat, high-cholesterol, high-triglyceride, and high-fructose feeding. In addition, these hawthorn species lowered the serum levels of ALP, GGT, total bilirubin, and direct bilirubin in the above animals [28,30,32,34,35]. Histological analysis of liver tissues using high fat/cholesterol/fructose diet-induced rodents revealed that hepatocytes highly express pyknotic nuclei, vacuolation, sinusoidal distension, necrosis, damaged endoplasmic reticuli, swollen and pleomorphic mitochondria, distorted intercellular spaces, irregular nuclear membranes, nuclear chromat condensation, and cellular degeneration, suggesting that these diets contribute to liver damage. Hawthorn extracts improved these hepatic tissue injuries through antioxidant mechanisms, including the regulation of Nrf2 and ARE expression [30,36,37]. Remarkably, polyphenols obtained from hawthorn peels and flesh exerted a potent hepatoprotective action by efficiently ameliorating biochemical markers, hepatic lipid peroxidation, and liver tissue injury via the regulation of apoptosis-related proteins and antioxidant enzymes dysregulated by a high-fructose diets [38].

C. pinnatifida and C. oxyacantha are involved in the protection of liver injury after alcohol exposure [10,31,39–42]. In HepG2 cells and Sprague Dawley rats, alcohol toxicity caused increased DNA damage in liver cells, and abnormal alcohol-metabolizing enzyme activity, biochemical marker levels, and histological findings. After co-treatment of these rats with an ethanol extract of C. pinnatifida, ALDH activity increased in the hepatic tissues [40], with decreased levels of serum AST, ALT, and GGT [31,42], and improved cell necrosis and sinusoidal distension [31]. In addition, the extract prevented alcoholic damage to HepG2 cells through the antioxidant defense system [10] and suppressed the catalytic activity of CYP2E1 [41], despite alcohol being a strong inducer of oxidative stress and CYP enzymes. Although the C. oxyacantha extract exhibited similarities against alcohol inducers, the hepatoprotective effects of the extract can be distinguished by the increase in liver glycogen levels, lack of which easily causes hepatic steatosis and insulin resistance [42]. In contrast to other causative factors, including lipopolysaccharides (LPSs), CCl4, cadmium, and hepatectomy, which are harmful to the liver, hawthorn extracts also reversed abnor-
mal serum markers and impaired liver tissue via the inhibition of PARP cleavage and TUNEL-positive hepatocytes, and activation of the hepatic antioxidant system [43–47]. Collectively, hawthorn extracts have hepatoprotective roles in the context of hepatic injury, probably due to the underlying anti-apoptosis and antioxidant defense mechanisms of the extracts (Figure 1, Table 1). This suggests that hawthorn extracts may maintain liver function and minimize the abrogation of hepatic damage caused by various factors.

Figure 1. Hepatoprotective roles of hawthorn extract against liver damage induced by diet, alcohol, toxicant, heavy metals, and partial hepatectomy. ARE, antioxidant response element; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma-2; DPPH, 2,2-diphenyl-1-picrylhydrazyl; GSH-Px, glutathione peroxidase; GST, glutathione S-transferase; HO-1, heme oxygenase-1; LDL, low-density lipoprotein; MPO, myeloperoxidase; Nrf-2, nuclear factor erythroid-2-related factor 2; PARP, poly-ADP ribose polymerase; P. Carbonyl, protein carbonyl; rGCS, r-glutamylcysteine synthetase; SOD, superoxide dismutase; TBARS, thiobarbituric acid reactive substances; and TUNEL, terminal deoxynucleotidyl transferase dUTP nick end labelling.

Table 1. Hepatoprotective effects and molecular mechanisms of hawthorn extract.

| Sources | Models | Doses | Results and Mechanisms | Reference |
|---------|--------|-------|-------------------------|-----------|
| Extract of C. pinnatifida (leaves) | In vivo, male Sprague Dawley rats fed with high-fat diets | 100 mg/kg | ↓Liver damage induced by high-fat diet ↓Serum ALP, LDH | [34] |
| Water extract of C. pinnatifida (fruits) | In vivo, male Sprague Dawley rats fed with high-fat diets | 10 mL/kg | ↓Liver damage induced by high-fat diet ↓Serum ALP, GGT ↓Liver pyknotic nuclei | [35] |
| Extract of hawthorn (leaves) | In vivo, male Sprague Dawley rats fed with high-fat diets | 160 mg/kg | ↓Liver damage induced by high-fat diet ↓Ballooning degeneration necrosis in liver tissue Antioxidant ↓Nrf2-positive stained hepatocytes ↑Hepatic Nrf2 mRNA ↓Hepatic GST, HO-1, rGCS mRNA and protein | [36] |
| Ethanolic extract of C. oxyacantha | In vivo, male Wistar rats fed with high-fat diets | 20 mg/kg | ↓Liver damage induced by high-fat diet ↓Serum AST, ALT, GGT, ALP, total bilirubin, direct bilirubin, LDH, and MDA | [28] |
| Sources                                      | Models                                                                 | Doses               | Results and Mechanisms                                                                                       | Reference |
|----------------------------------------------|------------------------------------------------------------------------|---------------------|----------------------------------------------------------------------------------------------------------------|-----------|
| 70% ethanol extract of C. aronia (leaves and flowers) | In vivo, male Wistar rats fed with high-fat diets                       | 200 mg/kg           | ↓Liver damage induced by high-fat diet                                                                     | [37]      |
|                                             |                                                                        |                     | ↓Highly vacuolated hepatocytes                                                                               |           |
|                                             |                                                                        |                     | ↓Damaged endoplasmic reticuli                                                                               |           |
|                                             |                                                                        |                     | ↓Distorted intercellular spaces                                                                            |           |
|                                             |                                                                        |                     | ↓Irregular nuclear membranes                                                                               |           |
|                                             |                                                                        |                     | **Antioxidant**                                                                                             |           |
|                                             |                                                                        |                     | ↑Hepatic GSH                                                                                               |           |
|                                             |                                                                        |                     | ↑Hepatic TBARS                                                                                              |           |
| Water extract of C. aronia                  | In vivo, male Wistar rats fed with high-fat diets                       | 200 mg/kg           | ↓Liver damage induced by high-fat diet                                                                     | [29]      |
|                                             |                                                                        |                     | ↓Serum AST, ALT, and GGT                                                                                   |           |
| 70% ethanol extract of C. monogyna           | In vivo, male Wistar rats fed with high-cholesterol diet                | 100 mg/kg           | ↓Liver damage induced by high-cholesterol diet                                                              | [30]      |
|                                             |                                                                        |                     | ↓Serum AST, ALT, and GGT                                                                                   |           |
|                                             |                                                                        |                     | ↓Hepatic MDA protein                                                                                        |           |
|                                             |                                                                        |                     | ↓Highly vacuolated hepatocytes and nuclear chromatin condensation in liver tissue                           |           |
|                                             |                                                                        |                     | **Antioxidant**                                                                                             |           |
|                                             |                                                                        |                     | ↑Hepatic total thiol molecules                                                                              |           |
|                                             |                                                                        |                     | ↑DPPH radical scavenging                                                                                   |           |
| 70% ethanol extract of C. pinnatifida31 (leaves) | In vivo, Sprague Dawley rats fed with high-cholesterol diet            | 5, 7.5, 10 mL/kg    | ↓Liver damage induced by high-cholesterol diet                                                              | [31]      |
|                                             |                                                                        |                     | ↓Serum AST, ALT, and GGT                                                                                   |           |
|                                             |                                                                        |                     | ↓Cell necrosis, sinusoidal distension in liver tissue                                                      |           |
| 80% ethanol extract of C. pinnatifida (fruits) | In vivo, male Sprague Dawley rats fed high-fat and high-cholesterol diets | 5, 10%             | ↓Liver damage induced by high fat and cholesterol diet                                                     | [32]      |
|                                             |                                                                        |                     | ↓Serum AST, ALT, ALP, and LDH                                                                               |           |
| Powder from dried C. pinnatifida (leaves)   | In vivo, Sprague Dawley rats fed with high-triglyceride diet            | 2%                  | ↓Liver damage induced by high triglyceride diet                                                             | [33]      |
|                                             |                                                                        |                     | ↓Serum ALT, ALP                                                                                            |           |
|                                             |                                                                        |                     | ↓Hepatocyte enlargement                                                                                   |           |
| Polyphenols from 80% ethanol extract of hawthorn peels and fleshes | In vivo, male Kunming mice fed with high-fructose diet                  | 400 mg/kg           | ↓Liver damage induced by high-fructose diet                                                                | [38]      |
|                                             |                                                                        |                     | ↓Serum AST, ALT, ALP                                                                                        |           |
|                                             |                                                                        |                     | ↓Hepatic MDA protein                                                                                        |           |
|                                             |                                                                        |                     | ↓Hepatic necrosis, cytoplasmic vacuolation, cellular degeneration, and the loss of cellular boundaries in liver tissue |           |
|                                             |                                                                        |                     | **Antioxidation**                                                                                           |           |
|                                             |                                                                        |                     | ↓Hepatic Bax, Bax/Bcl-2 protein                                                                             |           |
|                                             |                                                                        |                     | ↑Hepatic Bcl-2 protein (only in hawthorn peels)                                                             |           |
|                                             |                                                                        |                     | **Antioxidant**                                                                                             |           |
|                                             |                                                                        |                     | ↑Hepatic SOD, GSH-Px protein                                                                               |           |
|                                             |                                                                        |                     | ↑Hepatic Nrf-2, ARE protein                                                                                |           |
| Water extract of C. pinnatifida (fruits)    | In vivo, male Sprague Dawley rats fed 25% alcohol for 55 days          | 1 cc/100 g          | ↓Liver damage induced by alcohol                                                                            | [39]      |
|                                             |                                                                        |                     | ↓Serum AST, ALT, ALP, and LDH                                                                               |           |
| 95% ethanol extract of C. pinnatifida (fruits) | In vivo, male Sprague Dawley rats fed 50% alcohol for 6 weeks         | 100 mg/kg           | ↓Liver damage induced by alcohol                                                                            | [40]      |
|                                             |                                                                        |                     | ↑Hepatic ADH activity                                                                                        |           |
|                                             |                                                                        |                     | ↑Hepatic ALDH activity                                                                                     |           |
| 80% methanol extract of C. pinnatifida      | In vitro, human hepatoma HepG2 cells induced by 1.3% ethanol           | 0.4%                | ↓Liver damage induced by alcohol                                                                            | [10]      |
|                                             |                                                                        |                     | ↑Cell viability 152.5%                                                                                      |           |
|                                             |                                                                        |                     | **Antioxidant**                                                                                             |           |
|                                             |                                                                        |                     | ↑DPPH radical scavenging                                                                                   |           |
|                                             |                                                                        |                     | ↓LDL oxidation                                                                                             |           |
Table 1. Cont.

| Sources | Models | Doses | Results and Mechanisms | Reference |
|---------|--------|-------|------------------------|-----------|
| 70% ethanol extract of dried C. pinnatifida (branches) | In vitro, human hepatoma HepG2 cells induced by 1.3% ethanol | 0.4, 1% | ↓Liver damage induced by alcohol ↓Liver cell DNA damage ↓CYP2E1 enzyme expression ↓Catalytic activity of CYP2E1 | [41] |
| Methanol extract of C. oxyacantha (leaves) | In vivo, male Wistar rats administered with 3 g/kg/day of 35% ethanol | 50 mg/kg | ↓Liver damage induced by alcohol ↓Serum AST, ALT, GGT, ACP, and bilirubin ↑Liver glycogen ↓Hepatic MDA ↓Cell congestion, necrosis, and sinusoidal distension in liver tissue | [42] |
| 70% ethanol extract of the leaves of Crataegus pinnatifida from a local market in China | In vivo, Sprague Dawley rats fed 56% alcohol for 8 weeks | 5 mL/kg | ↓Liver damage induced by alcohol ↓Serum AST, ALT, and GGT ↓Cell necrosis, sinusoidal distension in liver tissue | [31] |
| Flavonoids from C. pinnatifida (fruits) | In vivo, male Sprague Dawley rats injected with LPS | 50, 100, 200 mg/kg | ↓Liver damage induced by LPS ↓Serum ALT ↓Extensive hepatocyte necrosis in liver tissue | [43] |
| Hawthorn capsule extracted from C. oxyacantha (leaves and flowers) | In vivo, male Wistar albino rats received an oral administration of CCl4 | 350 mg/kg | ↓Liver damage induced by toxic substances ↓Serum AST, ALT, GGT, and bilirubin ↑Serum albumin ↓Hepatic MDA, Antioxidant ↓Hepatic MPO activity ↓Hepatic P. Carbonyl activity ↓Hepatic SOD activity | [44] |
| Extract of hawthorn | In vivo, Sprague Dawley rats of both sexes received an oral administration of CCl4 | 40 mg/kg | ↓Liver damage induced by toxic substances ↓Serum AST, ALT, and ALP ↓Vacuolar degeneration in hepatocytes ↑Protein and mucopolysaccharide contents in hepatocytes ↓Liver damage induced by heavy metals ↑Cell viability ↓Hepatic degenerative regions and cells Hepatic centrolobular necrosis with peripheral hemorrhages/congestions | [45] |
| Water extract of C. pinnatifida (fruits) | In vitro, Rat hepatocytes H4IIE induced by cadmium | 0.1, 0.3 mg/mL | ↓Liver damage induced by heavy metals ↑Cell viability Antiaptoptosis ↓PARP cleavage | [46] |
| | In vivo, male Sprague Dawley rats intravenously injected with cadmium 4 mg/kg | 50, 100 mg/kg | ↓Liver damage induced by heavy metals ↓Serum AST, ALT, and LDH Hepatic degenerative regions and cells Hepatic centrolobular necrosis with peripheral hemorrhages/congestions | |
| 70% ethyl alcohol extract of C. aronia (flowers) | In vivo, male albino rats with partial hepatectomy | 0.5, 1% | ↓Liver damage induced by partial hepatectomy ↓Hepatic degenerative regions and cells Hepatic centrolobular necrosis with peripheral hemorrhages/congestions Antiaptoptosis ↓TUNEL-positive hepatocytes | [47] |

ACP, acid phosphatase; ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; ALP, alkaline phosphatase; ALT, alanine transaminase; ARE, antioxidant response element; AST, aspartate transaminase; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma-2; CCl4, carbon tetrachloride; CYP2E1, cytochrome P450 2E1; DPPH, 2,2-diphenyl-1-picrylhydrazyl; GGT, gamma glutamyl transpeptidase; GSH, glutathione; GSH-Px, glutathione peroxidase; GST, glutathione S-transferase; HO-1, heme oxygenase-1; LDL, lactate dehydrogenase; LDL, low-density lipoprotein; LPS, lipopolysaccharides; MDA, malondialdehyde; MPO, myeloperoxidase; Nrf-2, nuclear factor erythroid-2-related factor 2; PARP, poly-ADP ribose polymerase; P. Carbonyl, protein carbonyl; rGCS, r-glutamylcysteine synthetase; SOD, superoxide dismutase; TBARS, thiobarbituric acid reactive substances; and TUNEL, terminal deoxynucleotidyl transferase dUTP nick end labelling.
3.2. Antisteatotic Effect

Hepatocytes frequently become steatotic from several triggers, such as alcohol and metabolic or toxic stress. Steatosis is considered the most common and earliest stage of liver injury and is characterized by the accumulation of extra lipid droplets in the liver [48]. The presence of significant fatty infiltration in hepatic tissue is predominantly implicated in dysregulated lipid homeostasis, which is attributed to an imbalance between de novo lipogenesis and fatty acid oxidation [49]. Oxidative stress also possibly plays a pivotal role as an influential trigger for the initiation of hepatic steatosis and progression to inflammation or fibrosis [50]. Specifically, in NAFLD, the most common liver disease representing hepatic steatosis, oxidative stress, and impaired lipid metabolism may be two crucial mechanisms underlying the development of NAFLD in the progeny of obese mice [51]. Regarding these key triggers for the onset of hepatic steatosis, various transcriptional factors and hepatic enzymes have been implicated to regulate hepatic steatosis [52].

Hepatic steatosis is primarily characterized by histological findings of fatty infiltration and liver weight gain. As depicted in Figure 2, hawthorn extracts significantly reduced fat and cholesterol amounts in liver tissue, thereby decreasing the liver weight in rodents exposed to diet, ovariectomy, and alcohol-induced steatosis [28,29,31–36,38,39,53–73]. In particular, the fruits and leaves of C. pinnatifida have been frequently administered for their antisteatotic effects [31–35,57–66,72,73]. Studies in animal models induced by excess fat intake, MCD diet, alcohol consumption, and ovariectomy have demonstrated that the species extract reduced buildup of lipid droplets and liver weight via AMPK signaling, hepatic cholesterol homeostasis, and antioxidative defense mechanisms [31–35,57–66,72,73]. Specifically, haw pectin isolated from C. pinnatifida fruits markedly suppressed excessive lipid accumulation and weight gain induced by a high-fat diet, all of which are involved in the mechanisms underlying diet-associated hepatic steatosis. First, haw pectin improved hepatic steatosis by ameliorating hepatic oxidative stress injury by increasing the tissue reserves of superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), and total antioxidant capacity (TAC), which had been depleted by a high-fat diet in Kunming mice [74,75]. Second, haw pectin improved hepatic cholesterol catabolism to bile acids by increasing the levels of cholesterol 7α-hydroxylase (CYP7A1) mRNA and protein, thereby increasing hepatic bile acid levels in the gallbladder and feces [54–56]. In addition, haw pectin improved hepatic lipid metabolism by regulating the activity of lipogenesis-related enzymes (hepatic HMG-CoA reductase, Acyl-CoA: cholesterol acyltransferase (ACAT)), scavenger receptor class B type I (SR-BI, the HDL receptor), and hepatic ABC transporter A1 (ABCA1) expression, which promote lipid release [54,55]. Third, 5AMP-activated protein kinase (AMPK) signaling, a highly attractive target for glucolipid homeostasis to reduce hepatic steatosis, is involved in the benefits of haw pectin against fat overload in liver tissue, and PPARα, SIRT1, and NFXB may be closely associated with AMPK-dependent regulation of haw pectin in high-fat-diet-induced hepatic steatosis [34,53,76,77] (Figure 2, Table 2).

C. aronia, C. cuneata, and C. oxyacantha extracts also reduced the susceptibility of hepatocytes to steatosis induced by high-fat and high-atherogenic diets, mainly via mediating hepatic activity of HMG-CoA reductase, ACAT, and CYP7A1; hepatic cholesterol biosynthesis; and lipid excretion into bile acids [30,37,68–70]. C. aronia and C. monogyna attenuated hepatic fat content by regulating hepatic GSH and TBARS and hepatic total thiol molecules, respectively, in Wistar rats [30,37]. Specifically, the antioxidant activity of 200 mg/kg C. aronia was more potent than that of 4 mg/kg of simvastatin [37] (Figure 2, Table 2).

Oxidative stress and hepatic cholesterol metabolism dysfunction often cause fatty livers. Hawthorn reduces fat deposition in liver tissue by altering multiple intrahepatic factors associated with ROS generation, antioxidant defenses, lipogenesis, fatty acid oxidation, fatty acid uptake, and bile acid efflux. This review suggests that haw pectin obtained from Crataegus pinnatifida fruits may be effective in decreasing hepatic fat storage. Further animal and human studies investigating the additional efficacy and various genes that encode markers leading to hepatic steatosis are required. In addition, further studies regarding the role of C. pinnatifida on the interactions between the gut and liver in the management
of hepatic steatosis are needed as the extract decreases hepatic total cholesterol levels by impeding cholesterol absorption from the gut through the suppression of fibroblast growth factor receptor 4 (FGFR4) mRNA and protein.

Figure 2. Inducer, rodent, hawthorn species, experimental results, and underlying mechanism of preclinical studies on hawthorn extract exhibiting antisteatotic activities related to liver pathogenesis. ApoE, apolipoprotein E; AMPK, AMP-activated protein kinase; LDL, low-density lipoprotein; MCD, methionine choline deficient; TC, total cholesterol; and TG, triglyceride.

Table 2. Antisteatotic effects and molecular mechanisms of hawthorn extract.

| Sources                        | Models                                      | Doses   | Results and Mechanisms                                                                 | Reference |
|-------------------------------|---------------------------------------------|---------|----------------------------------------------------------------------------------------|-----------|
| Extract of hawthorn (leaves)  | In vivo, male Sprague Dawley rats fed with high-fat diets | 160 mg/kg | ↓Hepatic steatosis induced by high-fat diet  
Antioxidant  
↑Nrf2-positive stained hepatocytes  
†Hepatic Nrf2 mRNA  
↓Hepatic GST, HO-1, rGCS mRNA, and protein | [36]       |
| Extract of *C. pinnatifida* (leaves) | In vivo, male Sprague Dawley rats fed with high-fat diets | 100 mg/kg | ↓Hepatic steatosis induced by high-fat diet  
Adiponectin/AMPK signaling  
↑Serum adiponectin  
†Hepatic adiponectin receptor 2 mRNA and protein  
†Hepatic p-AMPKα protein  
↓Hepatic SREBP-1c mRNA and protein  
†Hepatic PPARα mRNA and protein  
↑Hepatic CD36, FAS, and SCD1 mRNA  
†Hepatic CPT1, ACO, and ACOX1 mRNA | [34]       |
| Haw pectin pentaoligosaccharide from *C. pinnatifida* (fruits) | In vivo, male Kunming mice fed with high-fat diets | 150 mg/kg | ↓Hepatic steatosis induced by high-fat diet  
AMPK signaling  
↑Hepatic CPT1, ACO mRNA  
†Hepatic PPARα mRNA and protein | [53]       |
| Sources | Models | Doses | Results and Mechanisms | Reference |
|---------|--------|-------|-------------------------|-----------|
| Haw pectin from C. pinnatifida (fruits) | In vivo, male Kunming mice fed with high-fat diets | 50, 150, 300 mg/kg | ↓Hepatic steatosis induced by high-fat diet  
↓Hepatic TC  
Hepatic cholesterol and bile acid metabolism  
↓Hepatic HMG-CoA reductase, ACAT mRNA, and protein  
↑Hepatic cholesterol 7α-hydroxylase mRNA and protein | [54] |
| Haw pectin from C. pinnatifida (fruits) | In vivo, male Kunming mice fed with high-fat diets | 300 mg/kg | ↓Hepatic steatosis induced by high-fat diet  
↓Liver weight  
↓Hepatic TC  
Hepatic cholesterol and bile acid metabolism  
↓Hepatic bile acids  
Gallbladder bile acids  
↑Hepatic cholesterol 7α-hydroxylase mRNA and protein  
↑Hepatic ABCA1, SR-BI, LXRα, BSEP mRNA, and protein | [55] |
| Haw pectin from C. pinnatifida (fruits) | In vivo, male Kunming mice fed with high-fat diets | 300 mg/kg | ↓Hepatic steatosis induced by high-fat diet  
↓Hepatic TC  
Hepatic cholesterol and bile acid metabolism  
↓Hepatic FGF4 mRNA and protein  
↑Hepatic cholesterol 7α-hydroxylase mRNA and protein  
↑Fecal bile acids  
↓Hepatic bile acids | [56] |
| Haw pectin from C. pinnatifida (fruits) | In vivo, male Kunming mice fed with high-fat diets | 50, 150, 300 mg/kg | ↓Hepatic steatosis induced by high-fat diet  
↓Liver weight  
Fat deposition in liver tissue  
Antioxidant  
↑Hepatic SOD activity | [74] |
| Haw pectin from C. pinnatifida (fruits) | In vivo, male Kunming mice fed with high-fat diets | 50, 150, 300 mg/kg | ↓Hepatic steatosis induced by high-fat diet  
↓Hepatic TG  
Antioxidant  
↑Hepatic SOD, CAT, and GSH-Px activity  
↑Hepatic TAC, GSH levels | [75] |
| Haw pectin from C. pinnatifida (fruits) | In vivo, male Kunming mice fed with high-fat diets | 150 mg/kg | ↓Hepatic steatosis induced by high-fat diet  
↓Liver weight  
Fat deposition in liver tissue  
Hepatic TG, total lipids  
AMPK/SIRT1/NFκB signaling  
↑Hepatic AMPKα, SIRT1 mRNA  
↓Hepatic NFκB mRNA and protein | [77] |
| 70% ethanol extract of C. aronia (leaves and flowers) | In vivo, male Wistar rats fed with high-fat diets | 200 mg/kg | ↓Hepatic steatosis induced by high-fat diet  
↓Liver weight  
Fat deposition in liver tissue  
Antioxidant  
↑Hepatic GSH  
↓Hepatic TBARS | [37] |
| 80% ethanol extract of C. pinnatifida (fruits) | In vivo, male Sprague Dawley rats fed high-cholesterol diet | 2% | ↓Hepatic steatosis induced by high-cholesterol diet  
↓Liver weight  
Fat deposition in liver tissue  
Antioxidant  
↑Hepatic SOD, CAT activity | [57] |
| Sources | Models | Doses | Results and Mechanisms | Reference |
|---------|--------|-------|-------------------------|-----------|
| 70% ethanol extract of *C. monogyna* | In vivo, male Wistar rats fed with high-cholesterol diet | 100 mg/kg | ↓Hepatic steatosis induced by high-cholesterol diet ↓Liver/body weight ↓Hepatic TC, TG, and LDL Antioxidant ↓Liver total thiol molecules ↑DPPH radical scavenging | [30] |
| Water extract of *C. pinnatifida* (fruits) | In vivo, male Sprague Dawley rats fed with high-fat diets | 397.3 mg/kg | ↓Hepatic steatosis induced by high-cholesterol diet ↓Liver weight | [58] |
| 80% ethanol extract of *C. pinnatifida* (fruits) | In vivo, male Sprague Dawley rats fed with high-fat and high-cholesterol diets | 5, 10% | ↓Hepatic steatosis induced by high-cholesterol diet ↓Fat deposition in liver tissue ↓Hepatic TC, TG | [32] |
| 80% ethanol extract of *C. pinnatifida* (fruits) | In vivo, male Sprague Dawley rats fed with high-cholesterol diet | 100 mg/kg | ↓Hepatic steatosis induced by high-cholesterol diet ↓Liver lipid contents Hepatic cholesterol metabolism ↑Hepatic cholesterol 7α-hydroxylase mRNA | [59] |
| 80% ethanol extract of *C. pinnatifida* (fruits) | In vivo, male Syrian golden hamsters fed with high-cholesterol diet | 0.5% | ↓Hepatic steatosis induced by high-cholesterol diet ↓Liver FFA contents Hepatic cholesterol metabolism ↑Hepatic cholesterol 7α-hydroxylase protein | [60] |
| Water extract of *C. pinnatifida* (fruits) | In vivo, male Sprague Dawley rats fed with high-cholesterol diet | 2% | ↓Hepatic steatosis induced by high-cholesterol diet ↓Liver TC, TG Hepatic cholesterol metabolism ↓Liver ACAT activity | [61] |
| Water extract of *C. pinnatifida* (fruits) | In vivo, male Sprague Dawley rats fed with high-cholesterol diet | 124 mg/kg | ↓Hepatic steatosis induced by high-cholesterol diet ↓Liver lipid contents | [62] |
| Water extract of *C. pinnatifida* (fruits) | In vivo, female ICR mice fed with high-cholesterol diet | 50, 100 mg/kg | ↓Hepatic steatosis induced by high-cholesterol diet ↓Liver weight ↓Hepatic TC, TG | [63] |
| 70% ethanol extract of *C. pinnatifida* (fruits) | In vivo, male Sprague Dawley rats fed with high-fat diets | 500, 1000 mg/kg | ↓Hepatic steatosis induced by high-fat diet ↓Hepatic TC, TG | [64] |
| Water extract of *C. pinnatifida* (fruits) | In vivo, male Sprague Dawley rats fed with high-fat diets | 10 mL/kg | ↓Hepatic steatosis induced by high-fat diet ↓Liver weight ↓Fat deposition in liver tissue ↓Hepatic TC, TG | [65] |
| Water extract of *C. pinnatifida* (fruits) | In vivo, male Sprague Dawley rats fed with high-fat diets | 10 mL/kg | ↓Hepatic steatosis induced by high-fat diet ↓Liver weight ↓Fat deposition in liver tissue | [35] |
| Methanol extract of *C. pinnatifida* (fruits) | In vivo, female ICR mice fed with high-fat diets | 100 μg | ↓Hepatic steatosis induced by high-fat diet ↓Liver weight | [66] |
| 95% ethanol extract of *C. cuneata* (fruits) | In vivo, male Kunming mice fed with high-fat diet | 90, 130 mg/kg | ↓Hepatic steatosis induced by high-cholesterol diet ↓Fat deposition in liver tissue | [67] |
| Sources | Models | Doses | Results and Mechanisms | Reference |
|---------|--------|-------|------------------------|-----------|
| Ethanol extract of *C. cuneata* (fruits) | In vivo, male mice fed with high-fat diet | 130 mg/kg | ↓Hepatic steatosis induced by high-fat diet | [68] |
| | | | ↓Hepatic TC Hepatic cholesterol metabolism ↓Hepatic HMG-CoA reductase mRNA ↓Hepatic HMG-CoA reductase promoter activity ↓Hepatic NFκB p65 mRNA | |
| Water extract of *C. aronia* (herba) | In vivo, male Wistar rats fed with high-fat diet | 200 mg/kg | ↓Hepatic steatosis induced by high-fat diet ↓Liver weight ↓Fat deposition in liver tissue | [29] |
| 70% ethanol extract of *C. pinnatifida* (leaves) | In vivo, Sprague Dawley rats fed with high-cholesterol diet | 5, 7.5, 10 mL/kg | ↓Hepatic steatosis induced by high-cholesterol diet ↓Liver weight ↓Fat deposition in liver tissue | [31] |
| Ethanol extract of *C. oxycantha* | In vivo, male Wistar rats fed high-fat diet | 20 mg/kg | ↓Hepatic steatosis induced by high-fat diet ↓Fat deposition in liver tissue | [28] |
| Water extract of *C. aronia* (fruits) | In vivo, New Zealand white rabbits fed high-fat diet | 10 mg/kg | ↓Hepatic steatosis induced by high-fat diet Hepatic cholesterol metabolism Hepatic cholesterol catabolism to bile acids ↑Hepatic LDL receptors ↑Hepatic cholesterol biosynthesis ↑Hepatic bile acids ↑Fecal bile acids | [69] |
| Polyphenols from 80% ethanol extracts of hawthorn peels and fleshes | In vivo, male Kunming mice fed with high-fructose diet | 400 mg/kg | ↓Hepatic steatosis induced by high-fructose diet ↓Liver weight ↓Fat deposition in liver tissue ↓Hepatic TC, TG Antioxidant ↑Hepatic SOD, GSH-Px protein ↑Hepatic Nrf-2, ARE protein AMPK signaling ↑Hepatic PPARα protein ↑Hepatic FAS protein | [38] |
| Ethanol extract of *C. oxycantha* (fruits) | In vivo, male Wistar rats fed atherogenic diet | 0.5 mL/100 g | ↓Hepatic steatosis induced by atherogenic diet ↓Hepatic TC Hepatic cholesterol catabolism to bile acids ↑Hepatic LDL receptors ↓Hepatic cholesterol biosynthesis ↑Hepatic bile acids ↑Fecal bile acids | [70] |
| 80% ethanol extract of hawthorn (fruits) | In vivo, ApoE−/− mice fed atherogenic diet | 2% | ↓Hepatic steatosis induced by atherogenic diet Hepatic fatty acids Antioxidant | [71] |
| 70% ethanol extract of *C. pinnatifida* (fruits) | In vivo, male C57BL/6J mice fed MCD diet | 300 mg/kg | ↓Hepatic steatosis induced by MCD diet ↓Fat deposition in liver tissue | [72] |
| | | | ↓Hepatic TG AMPK signaling ↑Hepatic p-AMPKα protein ↑Hepatic SREBP-1c, C/EBPα, and PPARγ protein ↓Hepatic ACC, FAS protein | |
Table 2. Cont.

| Sources | Models | Doses | Results and Mechanisms | Reference |
|---------|--------|-------|-------------------------|-----------|
| 70% ethanol extract of *C. pinnatifida* (fruits) | In vivo, female ovariectomized Sprague Dawley rats | 100, 200 mg/kg | ↓ Hepatic TG | ↑ Hepatic Nrf2 mRNA and protein | [73] |
| | | | Antioxidant | ↑ Hepatic HO-1 mRNA and protein | |
| | | | | ↑ Hepatic GSH-Px mRNA and protein | |
| | | | | ↑ Hepatic CAT mRNA and protein | |
| Water extract of *C. pinnatifida* (fruits) | In vivo, male Sprague Dawley rats fed 25% alcohol for 55 days | 1 cc/100 g | ↓ Hepatic steatosis induced by alcohol | ↓ Liver weight | [39] |
| 70% ethanol extract of *C. pinnatifida* (leaves) | In vivo, Sprague Dawley rats fed 56% alcohol for 8 weeks | 5 mL/kg | ↓ Hepatic steatosis induced by alcohol | ↓ Fat deposition in liver tissue | [31] |

ABCA1, ABC transporters A1; ACAT, acyl-CoA: cholesterol acyltransferase; ACC, acetyl-CoA carboxylase; ACO, acyl-CoA oxidase; ACOX1, acyl-CoA oxidase 1; AMPK, AMP-activated protein kinase; ARE, antioxidant response element; BSEP, bile salt export pump; CAT, catalase; C/EBP, CCAAT-enhancer-binding proteins; CPT1, carnitine palmitoyltransferase-1; FAS, fatty acid synthase; FFA, free fatty acids; FGFR4, fibroblast growth factor receptor 4; GSH, glutathione; GSH-Px, glutathione peroxidase; GST, glutathione S-transferase; HO-1, heme oxygenase-1; LXR, liver X receptor; MCD, methionine choline deficient; NFκB, nuclear factor kappa B; NrF2, nuclear factor erythroid-2-related factor 2; PPAR, peroxisome proliferator-activated receptor; rGCS, r-glutamylcysteine synthethase; SCD1, stearoyl CoA desaturase 1; SIRT, silent information regulator T; SOD, superoxide dismutase; SR-BI, scavenger receptor class B type I; SREBP, sterol regulatory element binding protein; TAC, total antioxidant capacity; TBARS, thiobarbituric acid reactive substances; TC, total cholesterol; and TG, triglyceride.

3.3. Anti-Inflammatory and Antifibrotic Effects

Hepatic injury and steatosis are commonly accompanied by inflammation and fibrosis. While hepatic inflammatory and fibrotic activation are essential for tissue repair and wound healing in response to injury, dysregulation and overexpression of inflammatory and fibrotic mediators in liver tissue can play a crucial role in accelerating liver damage [78]. Hepatic inflammation can be induced by oxidative stress, apoptosis, and inflammation-related signaling activation [79,80]. Initiation of inflammation is closely associated with macrophage infiltration and neutrophil recruitment to the liver, which elicit the secretion of various inflammatory cytokines. Overproduction of pro-inflammatory cytokines and chemokines in the liver generates and enhances hepatic fibrosis, mediated by active hepatic stellate cells (HSCs) and multiple extracellular matrix (ECM) deposition [81]. Hence, alteration in liver inflammation is regarded as an undoubtedly important target for improving liver disorders and preventing fibrogenic reactions.

Apoptotic liver cells frequently coexist with recruited neutrophils, suggesting that apoptosis can contribute to the pathogenesis of the inflammatory response. Additionally, lipids produced by apoptotic hepatocytes can act as chemotactic substances for recruiting inflammatory cells [27]. Hawthorn extracts reversed the hepatic production of apoptosis-related proteins (Bax and Bcl-2) dysregulated by a high-fructose diet in male Kunming mice, leading to the mitigation of inflammation, mediated by the decreased levels of hepatic IL-1, IL-6, and TNF-α [38]. In addition to targeting apoptosis, reducing oxidative stress, and activating AMPK, signaling by polyphenols from hawthorn extracts was involved in regulating hepatic inflammation induced by a high-fructose diet [38]. Specifically, oxidative stress is predominantly mediated by hawthorn extracts in ameliorating hepatic inflammation and fibrosis induced by metabolic triggers (high cholesterol [30,33,57,77], atherogenic [71], and high-fructose diet [38]) and toxic substances (LPS [43], CCl4 [44], and 35% ethanol [42]). Hawthorn fruit, *C. monogyna*, *C. oxyacantha*, and *C. pinnatifida* possess antioxidant action in both hepatic oxidative stress markers (MDA, total thiol molecules) and enzymatic antioxidant activity (SOD, CAT, GSH-Px, and T-AOC), thereby contributing to their anti-inflammatory activities by improving inflammatory cell (neutrophil leukocyte, mononuclear cell) infiltration and regulating the secretion of inflammatory cytokines, including TNF-α, IL-1β, IL-6, IL-10, and MCP-1, against hepatic inflammation induced by LPS, CCl4, and metabolic diets [30,43,44]. The antioxidant defense mechanism of hawthorn leaves and *C. oxyacantha* leaves and flowers in rats administered with CCl4 and ethanol led
to reduced hepatic fibrotic regions and collagen synthesis [44]. Specifically, *C. oxyacantha* leaves and flowers significantly reversed both CCl$_4$-induced inflammation and fibrosis via the antioxidant defense system, NFκB inhibition, and HSC inactivation [44], suggesting that this plant can play a key role in suppressing ECM production and improving liver inflammation. Among several species of hawthorn, haw pectin and polyphenols from *C. pinnatifida* regulate AMPK/SIRT1/NFκB and NIK/IKK/NFκB signaling against high-fat-diet-induced hepatic inflammation, confirming their applicability in NASH treatment [77,82] (Figure 3, Table 3).

**Figure 3.** Anti-inflammatory effects and antifibrotic effects of hawthorn extract through apoptosis suppression, AMPK and NIK activation, and antioxidant defense system. AMPK, AMP-activated protein kinase; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma-2; CAT, catalase; CCl$_4$, carbon tetrachloride; GSH-Px, glutathione peroxidase; HSC, hepatic stellate cell; IKK, IkB kinase; LPS, lipopolysaccharides; MDA, malondialdehyde; MPO, myeloperoxidase; NFκB, nuclear factor kappa B; NIK, NFκB inducing kinase; P. carbonyl, protein carbonyl; PPAR, peroxisome proliferator-activated receptor; SIRT, silent information regulator T; SOD, superoxide dismutase; SMA, smooth muscle actin; and TGF, transforming growth factor.

**Table 3.** Anti-inflammatory and antifibrotic effects and molecular mechanisms of hawthorn extract.

| Sources | Models | Doses | Results and Mechanisms | Reference |
|---------|--------|-------|-------------------------|-----------|
| Hawthorn capsule extracted from *C. oxyacantha* (leaves and flowers) | In vivo, male Wistar albino rats orally administered with CCl$_4$ | 350 mg/kg | ↓Hepatic inflammation induced by CCl$_4$ ↓Hepatic IL-1β, TNF-α mRNA ↓Hepatic COX-2 mRNA Antioxidant ↓Hepatic MPO activity ↓Hepatic P. carbonyl contents ↑Hepatic SOD activity NFκB signaling ↓Hepatic NFκB mRNA | [44] |
| Flavonoids from *C. pinnatifida* (fruits) | In vivo, male Sprague Dawley rats injected with LPS | 50, 100, 200 mg/kg | ↓Hepatic inflammation induced by LPS ↓Neutrophil leukocyte infiltration in liver tissue ↓Hepatic expression of iNOS and COX-2 | [43] |
| Sources | Models | Doses | Results and Mechanisms | Reference |
|---------|--------|-------|------------------------|-----------|
| 80% ethanol extract of C. pinnatifida (fruits) | In vivo, male Sprague Dawley rats fed with high-cholesterol diets | 2% | ↓Hepatic inflammation induced by high-cholesterol diet | [57] |
| 70% ethanol extract of C. pinnatifida (leaves) | In vivo, Sprague Dawley rats fed with high-cholesterol diets | 5, 7.5, 10 mL/kg | ↓Hepatic inflammation induced by high-cholesterol diet | [31] |
| Powder from dried C. pinnatifida (leaves) | In vivo, Sprague Dawley rats fed with high-triglyceride diets | 2% | ↓Hepatic inflammation induced by high triglyceride diet | [33] |
| Haw pectin from the water extract of C. pinnatifida | In vivo, male Kunming mice fed with high-fat diets | 150 mg/kg | ↓Hepatic inflammation induced by high-fat diet | [77] |
| Polyphenols from the ethanol extract of C. pinnatifida (fruits) | In vivo, male Wistar rats fed with high-fat diets and streptozotocin | 300 mg/kg | ↓Hepatic inflammation induced by high-fat diet and streptozotocin | [82] |
| Water extract of hawthorn fruits and leaves | In vivo, male Sprague Dawley rats fed with high-fat diets | 1 mg/100 g | ↓Hepatic inflammation induced by high-fat diet | [35] |
| 80% ethanol extract of hawthorn (fruits) | In vivo, ApoE−/- mice fed with atherogenic diets | 2% | ↓Hepatic inflammation induced by atherogenic diet | [71] |
Table 3. Cont.

| Sources | Models | Doses | Results and Mechanisms | Reference |
|---------|--------|-------|------------------------|-----------|
| Polyphenols from 80% ethanol extract of hawthorn peels and fleshes | In vivo, male Kunming mice fed with high-fructose diets | 400 mg/kg | ↓Hepatic inflammation induced by high-fructose diet ↓Hepatic expression of IL-1, IL-6, and TNF-α | [38] |
| | | | **Antioxidant** | | |
| | | | ↓Hepatic MDA protein ↑Hepatic SOD, GSH-Px protein ↓Hepatic Nrf-2, ARE protein | | |
| | | | **AMPK signaling** | | |
| | | | ↑Hepatic PPARG protein | | |
| 70% ethanol extract of C. pinnatifida (leaves) | In vivo, Sprague Dawley rats fed with 56% alcohol for 8 weeks | 5 mL/kg | ↓Hepatic inflammation induced by alcohol | [31] |
| | | | ↓Inflammatory cells infiltration in liver tissue | | |
| Extract of hawthorn | In vivo, Sprague Dawley rats orally administered with CCl₄ | 40 mg/kg | ↓Liver fibrosis induced by toxic substances ↓Marked fibrosis around the main blood vessels in liver tissue | [45] |
| Hawthorn capsule extracted from C. oxyacantha (leaves and flowers) | In vivo, male Wistar albino rats orally administered with CCl₄ | 350 mg/kg | ↓Liver fibrosis induced by toxic substances ↓Hepatic fibrotic septa ↓Severity score of Masson ↓Masson-positive area ↓Hepatic hydroxyproline protein ↓Hepatic collagen 1 and 3 protein and mRNA ↓Hepatic collagen 1 and 3 mRNA | [44] |
| | | | **HSC inactivation** | | |
| | | | ↓Hepatic α-SMA-positive cells ↓Hepatic α-SMA mRNA ↓Hepatic TGF-β mRNA | | |
| | | | **Antioxidant** | | |
| | | | ↓Liver MPO activity | | |
| | | | ↓Liver P. carbonyl contents | | |
| | | | ↑Liver SOD activity | | |
| Methanol extract of C. oxyacantha (leaves) | In vivo, male Wistar rats administered with 3 g/kg/day of 35% ethanol | 50 mg/kg | ↓Liver fibrosis induced by alcohol ↓Moderate fibrosis near lobule central veins in liver tissue | [42] |
| | | | **Antioxidant** | | |
| | | | ↓Hepatic MDA | | |

AMPK, AMP-activated protein kinase; ARE, antioxidant response element; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma-2; CAT, catalase; CCl₄, carbon tetrachloride; COX, Cyclooxygenase; DPPH, 2,2-diphenyl-1-picrylhydrazyl; GSH-Px, glutathione peroxidase; HSC, hepatic stellate cell; IKK, IκB kinase; IL, interleukin; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharides; MCP, monocyte chemoattractant protein; MDA, malondialdehyde; MPO, myeloperoxidase; NFκB, nuclear factor kappa B; NIK, NFκB inducing kinase; NOS, nitric oxide synthase; Nrf-2, nuclear factor erythroid-2-related factor 2; P. carbonyl, protein carbonyl; PPAR, peroxisome proliferator-activated receptor; RIP, receptor interacting protein kinase; SIRT, silent information regulator T; SOD, superoxide dismutase; SMA, smooth muscle actin; TAC, total antioxidant capacity; TGF, transforming growth factor; TNF, tumor necrosis factor; TNFR, TNF receptor; and TRAF, TNF receptor-associated factor.

Inflammation and fibrosis are major components that develop and aggravate liver injury, and hawthorn extracts can have promising pharmacological activities against both responses via the regulation of oxidative stress, apoptosis, AMPK and NIK signaling, and HSC activation.

### 3.4 Anticancer Effects

To fight against malignant cancer and discover novel anticancer drugs, the pharmacological effects of suppressing the viability and proliferation of fast-growing cancerous cells are of utmost importance. Specifically, chemotherapy efficiently eliminates uncontrolled
cancer cells by activating apoptotic pathways, cell cycle arrest, and inducing autophagic clearance. Indeed, various chemotherapeutic agents targeting these mechanisms are predominantly used because tumor cell survival often relies on aberrant function of the regulators of apoptosis, autophagy, and cell cycle progression [83,84]. In addition, elucidating the structure–activity relationship (SAR) of efficient candidates with anticancer activities might help determine their functional groups and assess their therapeutic potency to inhibit proliferation and mediate cell death pathways [85].

The antiproliferative property of hawthorn against liver cancer cells has been largely determined using a cell-based MTT assay in HepG2 and Hep3B cells. Among the various species of hawthorn, *C. pinnatifida*, *C. monogyna*, and *C. armena* have significantly suppressed the cell viability of human hepatoma cells, including HepG2 and Hep3B cells [20,86–90], while the water extract of *C. aronia* effectively increased the level of reduced intracellular antioxidant glutathione and glutathione disulfide in HepG2 cells, indicating no significant cytotoxicity against tumors. Interestingly, the 80% ethanol extract of *C. monogyna* exhibited dose-dependent cytotoxic activity toward HepG2 cells, although the extract had abundant polyphenolic compounds and zinc, possessing antioxidant properties [87]. In addition, the cytotoxic activity of *C. monogyna* extract was specific to HepG2 and showed no harmful effects in non-tumor normal human skin fibroblast BJ cells at the same concentration [87]. The selective cytotoxicity of HepG2 and protective effects on BJ cells of *C. monogyna* can be explained by the high amounts of bioactive antioxidant compounds and zinc present in its extract [87]. However, due to the abundant content of phenolic acid in 80% methanol extracts of *C. monogyna*, the extract might have displayed weaker cytotoxicity toward HepG2 cells, with IC\(_{50}\) values ranging from 88.45–318.72 µM, compared with those of the anticancer drug ellipticine (IC\(_{50}\), 1.21 µM) treatment [91].

Meanwhile, it should not be assumed that the potential anticancer activity of different hawthorn species is less effective than that of conventional chemotherapeutic drugs because of the high predominance of the antioxidant compounds found in their extracts. The stronger cytotoxicity of hydroxy-olean-12-en-28-oic acid triterpenoids obtained from the berries of *C. pinnatifida* (IC\(_{50}\) < 5 µM) was confirmed by comparing its IC\(_{50}\) with that of the positive control cisplatin (IC\(_{50}\) > 5 µM) using the MTT assay implemented in HepG2 cells [88]. In addition, lignans, a group of phenolic constituents found in the extract of the seeds of *C. pinnatifida* showed stronger growth inhibitory activities (IC\(_{50}\), 30.96–39.97 µM) than 5-fluorouracil (IC\(_{50}\) = 40.34 µM) against HepG2 cells [92,93]. Hence, the selective toxicity toward hepatoma cells and the potent effectiveness of hawthorn extract might be a therapeutic advantage compared to conventional anticancer drugs.

The cytotoxic properties of phenylpropanoids from *C. pinnatifida* fruits in HepG2 and Hep3B cells via proapoptotic signaling, autophagy induction, and cell cycle arrest are considered noteworthy [89,94]. Similarly, the ethanol extract of *C. pinnatifida* fruits exerted inhibitory activities against the viability of HepG2 cells, and the effects were supported by apoptosis induction by regulating caspase-3 activity and genetic expression of Bax and Bcl-2 [86]. Phenylpropanoids may have been partly responsible for the anticancer effects of the *C. pinnatifida* extract against HepG2 cells. Interestingly, some phytochemical results suggest a possible SAR that might help understand the pharmacological activities of phenylpropanoids in attacking hepatic cancer cells [94]. For example, the distinctive cytotoxicity of crapeugenosanoids A and B, which belong to phenylpropanoids, can be increased by the presence of the phenyl group at C-7" and (E)-2-styryl, respectively, against two hepatoma cell lines. In addition, SAR analysis of crapeugenoids C and D showed that two methoxy-substituted groups at the C-3′ position were associated with potent cytotoxic activities of both compounds against HepG2 cells [94].

In summary, *C. pinnatifida*, *C. monogyna*, and *C. armena* exhibited significant anticancer effects on human hepatoma cells, whose activity was comparable to that of conventional chemotherapy to treat HCC. In addition, because of the abundant amounts of antioxidant constituents found in the extract and chemical compound groups of these plants, hawthorn treatment could result in selective cytotoxicity in HepG2 cells. The antioxidant property
of hawthorn suggests its relative safety, even when prescribed for a long time or co-administered with anticancer drugs. The antitumor activity of hawthorn, triterpenoids, phenylpropanoids, and lignans isolated from *C. pinnatifida* might be potent candidates contributing to the cytotoxicity of hawthorn. Among the four pentacyclic triterpenoids, the IC\(_{50}\) of corosolic acid was the lowest in HepG2 cells (Figure 4, Table 4). Thus, further in-depth investigations of the molecular mechanisms, pharmacology against drug resistance, and SAR related to anticancer activities of various materials, including corosolic acid, are required.

**Figure 4.** Anticancer effects of hawthorn extract by inhibiting cell viability and cell proliferation in human hepatoma cell lines.

**Table 4.** Anticancer effects and molecular mechanisms of hawthorn extract and its compounds.

| Sources | Models | Doses | Results and Mechanisms | Reference |
|---------|--------|-------|------------------------|-----------|
| Ethanol extract of *C. pinnatifida* (fruits) | In vitro, human hepatoma HepG2 cells | 0.8 mg/mL | ↓Cell viability Apoptosis induction ↑Caspase-3 mRNA ↓Bcl-2 mRNA and protein ↑Bax mRNA and protein | [86] |
| 80% ethanol extract of *C. monogyna* (buds and fruits) | In vitro, human hepatoma HepG2 cells | 0.5, 1 mg/mL | ↓Cell viability | [87] |
| Triterpenoids from 80% acetone extract of *C. pinnatifida* (fruits) | In vitro, human hepatoma HepG2 cells | | ↓Cell viability (IC\(_{50}\) < 5 µM) | [88] |
| Phenylpropanoids from 70% ethanol extract of *C. pinnatifida* (fruits) | In vitro, human hepatoma HepG2 and Hep3B cells | 100 µM. | ↓Cell viability (IC\(_{50}\): 17.5–27.36 µM in HepG2 and 38.96–43.58 µM in Hep3B) Apoptosis induction | [89] |
Table 4. Cont.

| Sources | Models | Doses | Results and Mechanisms | Reference |
|---------|--------|-------|-------------------------|-----------|
| Phenypropanoids from 70% ethanol extract of C. pinnatifida (fruits) | In vitro, human hepatoma HepG2 and Hep3B cells | 50 µM | ↓Cell viability Apoptosis induction ↑Apoptotic cells Autophagy induction Monodansylcadaverine positive cells Cell cycle arrest G2/M arrest by (−)-crataegusyanoid A G0/G1 arrest by (−)-crataegusyanoid B | [94] |
| Lignans from 70% ethanol extract of C. pinnatifida (seeds) | In vitro, human hepatoma HepG2 cells | | ↓Cell viability (IC₅₀: 38.54–39.97 µM) | [92] |
| 80% methanol extract of C. monogyna (buds and fruits) | In vitro, human hepatoma HepG2 cells | | ↓Cell viability | [91] |
| 80% acetone extract of C. pinnatifida obtained from Shandong Institute of (fruits) | In vitro, human hepatoma HepG2 cells | 5–30 µg/ml | ↓Cell viability (IC₅₀: 11.58 µg/mL) ↓Cell proliferation IC₅₀ of ursolic acid 12.58 µM IC₅₀ of corosolic acid 9.44 µM IC₅₀ of maslinic acid 23.42 µM IC₅₀ of oleanolic acid 54.02 µM | [20] |
| Dihydrobenzofuran neolignan from 70% ethanol extract of C. pinnatifida (seeds) | In vitro, human hepatoma HepG2 cells | | ↓Cell viability (IC₅₀ = 30.96 µM) | [93] |
| 80% ethanol extract of C. armena (shoots, flowers, and fruits) | In vitro, human hepatoma HepG2 cells | | ↓Cell viability (IC₅₀ = 8.66 µg/mL) | [90] |

HepG2, hepatoma G2; Hep3B, hepatoma 3B; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma-2; and IC₅₀, half-maximal inhibitory concentration.

4. Safety of Hawthorn

It is necessary to evaluate and confirm the safety of hawthorn for its use as a therapeutic agent for various liver diseases. When the water extract of C. pinnatifida fruits (126 g/kg crude drugs) was administered to Kunming mice, none of the subjects died, and when the water extracts of C. cuneata and C. scabrifolia were administered to Kunming mice, only one subject died. The 50% lethal dose (LD₅₀) of crude drugs exceeded 126 g/kg; therefore, the toxicity of hawthorn fruit is expected to be very low [95]. The LD₅₀ of the water extract of C. oxyacantha leaves was measured as 13.5 g/kg, with no dead subjects and no behavioral changes from up to 10 g/kg [96]. The 70% ethanol extract of C. aronia leaves did not cause any behavioral changes, and there were no dead subjects up to 5000 mg/kg [97]. In addition, when the water extract of a whole plant of C. aronia (up to 2000 mg/kg, for 28 days) was administered orally to Wistar rats, there were no signs of acute toxicity or fatality [98]. Therefore, the LD₅₀ of C. aronia leaves and the whole plant may possibly exceed 5000 mg/kg and 2000 mg/kg, respectively. Although the LD₅₀ values vary depending on the hawthorn species, medicinal parts, and extraction methods, all the LD₅₀ values in rodent models exceeded 2000 mg/kg, which is considered relatively safe compared to aspirin (LD₅₀, 200 mg/kg) and metformin (LD₅₀, 1000 mg/kg).

A systematic review demonstrated that the adverse events of C. extract WS® 1442 (160–1800 mg/day for 3–24 weeks) include dizziness, gastrointestinal disturbance, headache, and palpitations [99], but another study emphasized that no significant adverse events and no specific drug interactions were observed after administration of WS® 1442 [100].

As demonstrated above, hawthorn extracts displayed significant hepatoprotective activities against various stimulants, including fat diet, alcohol, heavy metals, and heptectomy. Thus, considering animal studies and reviews of clinical trials on the safety of hawthorn, the plant can be regarded as a drug that can be prescribed with little toxicity in patients with liver diseases, despite further studies.
5. Discussion

Recently, herbal interventions have emerged as a therapeutic option for managing pathophysiologial changes in various liver diseases, including NAFLD, viral hepatitis, and HCC [11,101]. Hawthorn is efficacious and has high potential to be developed to treat liver diseases. Despite the availability of increasing preclinical evidence of hawthorn, there is still ambiguity in confirming the pharmacological benefits and mechanisms of hawthorn extracts against liver-related pathological conditions. This review, therefore, includes significant advances in the pharmacological and molecular understanding of hawthorn extracts in liver disease management.

As demonstrated above, treatment with hawthorn extracts significantly reversed abnormalities related to hepatic injury, steatosis, inflammation, fibrosis, and cancer. These pathological conditions have been suggested to be closely and intricately linked with the risk of various liver diseases. Hence, hawthorn can be used as a therapeutic target for various hepatic diseases. In addition, the potential mechanisms covering antioxidant, apoptosis regulation, AMPK signaling, cholesterol metabolism, HSC inactivation, cell cycle arrest, and autophagy induction account for the pharmacological actions of hawthorn. Presumably, antioxidant defense by hawthorn extract against hepatic disorders is likely to be of interest, as many studies have determined the regulation of oxidative stress in hawthorn extract in reducing liver injury, fat accumulation, inflammation, and fibrosis. In terms of apoptosis, hawthorn extracts had a flexible impact in mediating apoptosis, in that hawthorn exerted hepatoprotective, anti-inflammatory, and antifibrotic activities through antipapoptotic in hepatic tissue, while the plant-induced apoptotic signal suppressed the cell viability of HepG2 cells. Moreover, the additional involvement of hawthorn in AMPK signaling, HSC inactivation, and hepatic cholesterol metabolism make the herb a possible agent for developing drugs for the management of liver diseases (Tables 1–4, Figures 1–4).

Collectively, liver diseases are a leading cause of worldwide morbidity and mortality. Recently, cases of HCC, ALD, NAFLD, and viral hepatitis have been increasing [102]. First, hawthorn possesses marked hepatoprotective, antisteatotic, anti-inflammatory, and antifibrotic effects against alcohol-induced liver injury, liver weight gain, fat deposition, hepatic inflammatory cell aggregation, and hepatic fibrosis. The beneficial properties of C. pinnatifida and C. oxyacantha against alcohol may be mainly implicated in ALDH and CYP2E1 enzyme-modulating activities and antioxidant effects, suggesting that these species can inhibit the overaccumulation of acetaldehyde, efficiently scavenge ROS attack, and reduce oxidation induced by alcohol.

Second, hawthorn treats NAFLD and metabolic syndromes, including diabetes, obesity, and hyperlipidemia. Supported by a large number of available preclinical results, hawthorn extract antagonized the significant changes in a variety of NAFLD rodent models. Specifically, hawthorn extracts were potent in reducing lipid content, inflammatory cell infiltration, and the expression of cytokines in liver tissue, thereby improving simple steatosis and steatohepatitis, mainly through antioxidant and AMPK signaling. The coordinated regulation of hawthorn extract on steatosis and inflammation may effectively prevent NASH-related fibrosis. Unfortunately, there was no preclinical evidence relating to the antifibrotic activity of hawthorn extracts in experimental models induced by Western diets, but the extract reduced liver fibrosis induced by CCl4 and alcohol treatment. Hence, this field merits further research. Nevertheless, hawthorn extracts might be an effective regulator of metabolic changes that occur during NAFLD because an increasing amount of experimental data support that pharmacological effects of the herb are antidiabetic, antiobetic, and hypolipidemic, resulting in low risks of metabolic syndrome and cardiovascular diseases. Hence, it is conceivable that hawthorn extracts, specifically haw pectin and polyphenols from C. pinnatifida, act as potent anti-NAFLD drugs that orchestrate complex metabolic changes occurring in NAFLD, thereby treating hepatic steatosis and inflammation.

Third, hawthorn extracts may be involved in the treatment of HCC, which is the most common and aggressive form of liver cancer, with high morbidity and mortality.
Various curative therapies, including liver transplantation, surgical hepatectomy, and local ablation, are suitable for almost all early-stage cases. However, late diagnosis, inadequate hepatic reserves, and metastasis have lowered the therapeutic effects and 5-year survival rates of available treatment options [103]. Specifically, conventional chemotherapeutic agents often induce side effects by generating oxidative stress in non-targeted normal tissues. Similar to chemotherapy with cisplatin and 5-fluorouracil, hawthorn extracts also displayed anticancer effects against HepG2 cells. However, the abundance of antioxidant and hepatoprotective compounds constituting hawthorn extracts may reduce toxicity against normal cells. Although the effects of antioxidant and cytotoxic effects of hawthorn extract in HCC still need to be investigated, the triterpenoids, phenylpropanoids, and lignans obtained from *C. pinnatifida* might be crucial chemical groups for the control of HCC, as demonstrated above.

The present review also revealed the various species, parts, and compounds of hawthorn that were used to reduce hepatotoxicity, hepatic fat deposition, liver inflammation, fibrosis, and cancer in animal and cellular studies. The major species of hawthorn treated for alleviating hepatic pathological conditions are *C. pinnatifida*, *C. oxyacantha*, and *C. monogyna*. Among them, the fruits of *C. pinnatifida* can play a crucial role in improving hepatocytes overwhelmed by metabolic triggers leading to NAFLD by reducing oxidative stress and activating AMPK and NIK signaling. *C. oxyacantha* leaves and flowers may treat NASH-related fibrosis because the plant actively reduced hepatic fibrotic septa and collagen synthesis by CCl₄ via HSC inactivation and antioxidant processes. *C. monogyna* buds and fruits may have selective cytotoxicity against HCC, with no harmful effects on normal cells because of their abundant antioxidant substances. The specific groups of active ingredients of hawthorn have been shown to be responsible for the following beneficial actions: (1) polyphenols obtained from hawthorn extracts displayed hepatoprotective and anti-inflammatory actions by regulating apoptosis and oxidative stress. (2) Haw pectin isolated from hawthorn fruits enhanced the clearance of hepatic accumulation of lipids through AMPK-dependent regulation, reduced hepatic oxidative stress and hepatic cholesterol catabolism with the regulation of hepatic inflammation via NFκB inactivation. (3) Triterpenoids, phenylpropanoids, and lignans of hawthorn plant were shown to have anticancer effects against HCC cell lines. In particular, vitexin, hyperoside, and corosolic acid were found in hawthorn to be among the major active ingredients primarily contributing to the bioactive activities of hawthorn against various liver diseases [104–109], and these compounds need further investigation to evaluate their efficacy.

In summary, the efficacy of hawthorn extract can be linked to ameliorating pathological conditions, including liver toxicity, steatosis, inflammation, fibrosis, and cancer of various hepatic disorders. The antioxidant mechanism of hawthorn extract may be crucial for the control of hepatic injury, steatosis, inflammation, and fibrosis. In addition to reducing oxidative stress in hepatic tissue by hawthorn extract, AMPK activation and antiapoptotic signaling also account for the improvement of hepatic steatosis and inflammation. Thus, given the role of hawthorn extracts in the regulation of hepatic disorders, the plant can contribute to the treatment of ALD, NAFLD, and HCC, as well as improve liver injury. However, further in vivo and clinical studies need to be elaborately designed and performed to confirm the clinical application of hawthorn extract and its compounds.

6. Conclusions

In conclusion, the present review demonstrates that hawthorn extracts have benefits against hepatic toxicity, fat deposition, inflammation, fibrosis, and cancer. The pharmacological activities of hawthorn extracts may be mainly due to reduced hepatic oxidative stress, which prevents excessive ROS attack and induces consequent hepatocellular function recovery. In addition, the regulation of AMPK, NIK, apoptosis, cholesterol metabolism, HSC activation, cell cycle arrest, and autophagy by hawthorn extracts is involved in its modulatory role in hepatic pathologic conditions. Therefore, hawthorn extracts may be promising and safe in treating hepatic disorders, even though in-depth and elaborate
investigations on the efficacy, safety, and mechanism of action of the plant against liver diseases are needed.

**Author Contributions:** Conceptualization, E.K., E.J. and J.-H.L.; methodology, E.K. and E.J.; validation, E.J. and J.-H.L.; formal analysis, E.J. and J.-H.L.; investigation, E.K. and E.J.; data curation, E.K.; writing—original draft preparation, E.K. and E.J.; writing—review and editing, E.J. and J.-H.L.; visualization, E.J.; supervision, J.-H.L. All authors have read and agreed to the published version of the manuscript.

**Funding:** This research received no external funding.

**Institutional Review Board Statement:** Not applicable.

**Informed Consent Statement:** Not applicable.

**Data Availability Statement:** Not applicable.

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

**References**

1. James, S.L.; Abate, D.; Abate, K.H.; Abay, S.M.; Abbafati, C.; Abbasi, N.; Abbastabar, H.; Abd-Allah, F.; Abdela, J.; Abdelalim, A. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018, 392, 1789–1858. [CrossRef]

2. Tapper, E.B.; Parikh, N.D. Mortality due to cirrhosis and liver cancer in the United States, 1999–2016: Observational study. *BMJ* 2018, 362, k2817. [CrossRef] [PubMed]

3. Bernal, W.; Wendon, J. Acute Liver Failure. *N. Engl. J. Med.* 2013, 369, 2525–2534. [CrossRef] [PubMed]

4. Wong, M.C.; Huang, J.L.; George, J.; Huang, J.; Leung, C.; Eslam, M.; Chan, H.L.; Ng, S.C. The changing epidemiology of liver diseases in the Asia–Pacific region. *Nat. Rev. Gastroenterol. Hepatol.* 2019, 16, 57–73. [CrossRef] [PubMed]

5. Liangpunsakul, S.; Haber, P.; McCaughan, G.W. Alcoholic liver disease in Asia, Europe, and North America. *Gastroenterology* 2016, 150, 1786–1797. [CrossRef]

6. Li, S.; Tan, H.-Y.; Wang, N.; Zhang, Z.-J.; Lao, L.; Wong, C.-W.; Feng, Y. The role of oxidative stress and antioxidants in liver diseases. *Int. J. Mol. Sci.* 2015, 16, 26087–26124. [CrossRef]

7. Viollet, B.; Guigas, B.; Leclerc, J.; Hébrard, S.; Lantier, L.; Mounier, R.; Andreelli, F.; Foretz, M. AMP-activated protein kinase in the regulation of hepatic energy metabolism: From physiology to therapeutic perspectives. *Acta Physiol.* 2009, 196, 81–98. [CrossRef]

8. Malhotra, P.; Gill, R.K.; Saksena, S.; Alrefai, W.A. Disturbances in cholesterol homeostasis and non-alcoholic fatty liver diseases. *Front. Med.* 2020, 7, 467. [CrossRef]

9. Fingas, C.D.; Gerken, G.; Canbay, A. Apoptosis in selected liver diseases. *Turk. J. Gastroenterol.* 2009, 20, 171–179.

10. Song, E.J.; Kim, N.Y.; Heo, M.Y. Protective effect of korean medicinal plants on ethanol-induced cytotoxicity in HepG2 Cells. *Nat. Prod. Sci.* 2013, 19, 329–336.

11. Liu, Z.L.; Xie, L.Z.; Zhu, J.; Li, G.Q.; Grant, S.J.; Liu, J.P. Herbal medicines for fatty liver diseases. *Cochrane Database Syst. Rev.* 2013, 24, CD009059. [CrossRef] [PubMed]

12. Kumar, D.; Arya, V.; Bhat, Z.A.; Khan, N.A.; Prasad, D.N. The genus Crataegus: Chemical and pharmacological perspectives. *Rev. Bras.* 2012, 22, 1187–1200. [CrossRef]

13. Caliskan, O. *The Mediterranean Diet*, 1st ed.; Elsevier: San Diego, CA, USA, 2015; pp. 621–628.

14. Wu, J.; Feng, W.; Qin, R.; Zhou, H. Crataegus pinnatifida: Chemical constituents, pharmacology, and potential applications. *Molecules* 2014, 19, 1685–1712. [CrossRef] [PubMed]

15. Korea Ministry of Food and Drug Safety. *The Korean Pharmacopoeia*, 12th ed.; The KFDA Notification: Cheongju, Korea, 2020; p. 53.

16. National Pharmacopoeia Committee of China Ministry of Health. *Pharmacopoeia of the People’s Republic of China*, 11th ed.; The NMPA Notification: Beijing, China, 2020; pp. 33–34.

17. Council of Europe. *European Pharmacopoeia*, 4th ed.; European Directorate for the Quality of Medicines: Strasbourg, France, 2002; pp. 1292–1295.

18. The United States Pharmacopeial Convention. *The United States Pharmacopeia*, 38th ed.; United States Pharmacopeial Convention: Rockville, MD, USA, 2015; pp. 6102–6106.

19. Edwards, J.E.; Brown, P.N.; Talent, N.; Dickinson, T.A.; Shipley, P.R. A review of the chemistry of the genus Crataegus. *Phytochemistry* 2012, 79, 5–26. [CrossRef]

20. Wen, L.; Guo, R.; You, L.; Abbasi, A.M.; Li, T.; Fu, X.; Liu, R.H. Major triterpenoids in Chinese hawthorn “Crataegus pinnatifida” and their effects on cell proliferation and apoptosis induction in MDA-MB-231 cancer cells. *Food Chem. Toxicol.* 2017, 100, 149–160. [CrossRef]
21. Caligiani, A.; Malavasi, G.; Palla, G.; Marseglia, A.; Tognolini, M.; Bruni, R. A simple GC–MS method for the screening of betulinic, corosolic, maslinic, oleandric and ursolic acid contents in commercial botanicals used as food supplement ingredients. *Food Chem.* **2013**, *136*, 735–741. [CrossRef]

22. Alirezaal, A.; Salehi, P.; Ahmadi, N.; Sonbol, A.; Aceto, S.; Hatami Maleki, H.; Ayyari, M. Flavonoids profile and antioxidant activity in flowers and leaves of hawthorn species (*Crataegus* spp.) from different regions of Iran. *Int. J. Food Prop.* **2018**, *21*, 452–470. [CrossRef]

23. Liu, P.; Kallio, H.; Lü, D.; Zhou, C.; Yang, B. Quantitative analysis of phenolic compounds in Chinese hawthorn (*Crataegus* spp.) fruits by high performance liquid chromatography–electrospray ionisation mass spectrometry. *Food Chem.* **2011**, *127*, 1370–1377. [CrossRef][PubMed]

24. Bell, A. Lipid metabolism in liver and selected tissues in the whole body of ruminant animals. *Prog. Lipid Res.* **1979**, *18*, 117–164. [CrossRef]

25. Tahmasebi, M.; Sadeghi, H.; Nazem, H.; Kokhdan, E.P.; Omidifar, N. Hepatoprotective effects of *Crataegus* species on alcoholic fatty liver disease in rats. *Drug Res.* **2018**, *68*, 553–559. [CrossRef][PubMed]

26. Czaja, M.J. Cell signaling in oxidative stress-induced liver injury. *Semin. Liver Dis.* **2007**, *27*, 378–389. [CrossRef][PubMed]

27. Gucciardi, M.; Gores, G. Apoptosis: A mechanism of acute and chronic liver injury. *Gut* **2005**, *54*, 1024–1033. [CrossRef][PubMed]

28. Saeedi, G.; Jevid, F.; Goharbari, M.; Ghashlaghi, G.H.; Sabzevari, O. Ethanol extract of *Crataegus oxyacantha* L. ameliorates dietary non-alcoholic fatty liver disease in rats. *Bosn. J. Basic Med. Sci.* **2012**, *2*, 237–242. [CrossRef][PubMed]

29. Al Humayed, S. Protective and therapeutic effects of *Crataegus* fruit on non-alcoholic fatty liver disease. *Arch. Physiol. Biochem.* **2017**, *123*, 23–30. [CrossRef]

30. Rezaei-Golmisheh, A.; Malekinejad, H.; Asri-Rezaei, S.; Farshid, A.A.; Akbari, P. Hawthorn ethanolic extracts with triterpenoids and flavonoids exert hepatoprotective effects and suppress the hypercholesterolemia-induced oxidative stress in rats. *Iran. J. Basic Med. Sci.* **2015**, *18*, 691–699. [CrossRef]

31. Wang, S.Y.; Xu, Q.Y.; Zhang, W.J.; Liu, X.; Ying, X.X.; Kang, T.G. Study on effects of hawthorn leaves extract on fatty liver in rats. *China J. Tradit. Chin. Med. Pharm.* **2011**, *26*, 2955–2959.

32. Lee, J.-J.; Lee, H.-J.; Oh, S.-W. Antiobesity Effects of Sansa (*Crataegi fructus*) on 3T3-L1 Cells and on High-Fat–High-Cholesterol Diet-Induced Obese Rats. *J. Med. Food.* **2017**, *20*, 19–29. [CrossRef]

33. Housein, Z.M.I.; Othman, G.Q.; Mustafa, T.A. The liver protective role of hawthorn (*Crataegus sp.*) in hypertriglyceridemic induced rats. *Psychol. J.* **2017**, *7*, 111–118.

34. Li, Z.; Xu, J.; Zheng, P.; Xing, L.; Shen, H.; Yang, L.; Zhang, L.; Ji, G. Hawthorn leaf flavonoids alleviate nonalcoholic fatty liver disease by enhancing the adiponectin/AMPK pathway. *Int. J. Clin. Exp. Med.* **2015**, *8*, 17295–17307.

35. Gao, Z.Q.; Xie, M.J.; Chen, L.B. Effects of fruits and leaves of hawthorn on lipid metabolism and oxidative stress in fatty liver rats. *J. Tradit. Chin. Med.* **2016**, *34*, 50–53.

36. Wang, D.; Cai, Y.; Pan, S.; Zhang, L.; Chen, Y.; Chen, F.; Jin, M.; Yan, M.; Li, X.; Chen, Z. Effect of total flavone of haw Leaves on nuclear factor erythroid-2 related factor and other related factors in nonalcoholic steatohepatitis rats. *Chin. J. Integr. Med.* **2018**, *24*, 265–271. [CrossRef][PubMed]

37. Al Humayed, S.; Eid, R.A.; Shatoor, A.S.; Haidara, M.A.; Zaki, M.S.A.; Al-Ani, B. Differential Therapeutic Effects of *Crataegus aronia* and Simvastatin on the Hepatocyte Ultrastructure in Hepatic Steatosis. *J. Morphol.* **2017**, *35*, 578–583. [CrossRef]

38. Han, X.; Li, W.; Huang, D.; Yang, X. Polyphenols from hawthorn peels and fleshes differently mitigate dyslipidemia, inflammation and oxidative stress in association with modulation of liver injury in high fructose diet-fed mice. *Chem.-Biol. Interact.* **2016**, *257*, 132–140. [CrossRef][PubMed]

39. Seo, B. Preventive effects of water extracts from *Crataegi fructus* on hyperlipidemia and liver damage induced by alcohol. *Korea J. Herb.* **2005**, *20*, 35–43.

40. Kim, J.-S. Hypoglycemic Effect and Hepatic Detoxification Activity of Extracts from *Crataegus fructus* and *Morus alba* L. in Alcohol-treated Rats. *Biomed. Sci. Lett.* **2007**, *13*, 17–23.

41. Kim, N.Y.; Song, E.J.; Heo, M.Y. Protective Effect of *Crataegus pinnatifida* and *Cinnamomum cassia* on Ethanol-induced Cytotoxicity and DNA Damage in HepG2 Cells. *Nat. Prod. Sci.* **2014**, *20*, 237–242.

42. Martinez-Rodriguez, J.L.; Reyes-Estrada, C.A.; Gutierrez-Hernandez, R.; Adria, J. Antioxidant, hypolipidemic and preventive effect of Hawthorn (*Crataegus pinnatifida*) on alcoholic liver damage in rats. *J. Pharmacogn. Phytother.* **2016**, *8*, 193–202.

43. Kao, E.-S.; Wang, C.-J.; Lin, Y.-F.; Wang, C.-P.; Tseng, T.-H. Anti-inflammatory potential of flavonoid contents from dried fruit of *Crataegus pinnatifida* in vitro and in vivo. *J. Agric. Food Chem.* **2005**, *53*, 430–436. [CrossRef]

44. Hamza, A.A.; Lashin, F.M.; Hassanin, S.O.; Abdalla, Y.; Amin, A. Hawthorn herbal preparation from *Crataegus oxyacantha* attenuates in vivo carbon tetrachloride-induced hepatic fibrosis via modulating oxidative stress and inflammation. *Antioxidants* **2019**, *7*, 1107. [CrossRef]

45. Salam, O.M.A.; Sleem, A.A.; Shafee, N. Effect of *Crataegus* extract on carbon tetrachloride-induced hepatic damage. *Comp. Clin. Pathol.* **2012**, *21*, 1719–1726. [CrossRef]

46. Shin, J.-H.; Jo, M.-J.; Park, S.-M.; Park, S.-J.; Kim, S.-C. Hepatoprotective activity of *Crataegii fructus* water extract against cadmium-induced toxicity in rats. *J. Physiol. Pathol.* **2010**, *24*, 249–257.

47. Kesimal, N.; Mamadov, R.; Ili, P. The effects of *Crataegus aronia* var. dentata Browicz extract on biochemical indices and apoptosis in partially hepatomeitized liver in rats. *Bosn. J. Basic Med. Sci.* **2012**, *12*, 177–181. [CrossRef][PubMed]
48. Nassir, F.; Rector, R.S.; Hammoud, G.M.; Ibdah, J.A. Pathogenesis and prevention of hepatic steatosis. *Gastroenterol. Hepatol.* 2015, 11, 167–175.

49. Musso, G.; Gambino, R.; Cassader, M. Recent insights into hepatic lipid metabolism in non-alcoholic fatty liver disease (NAFLD). *Prog. Lipid Res.* 2009, 48, 1–26. [CrossRef] [PubMed]

50. Day, C.P.; James, O.F. Steatohepatitis: A tale of two “hits”? *Gastroenterology* 1998, 144, 842–845. [CrossRef]

51. Alfardhi, M.Z.; Fernandez-Twinn, D.S.; Martin-Gronert, M.S.; Musial, B.; Fowden, A.; Ozanne, S.E. Oxidative stress and altered lipid homeostasis in the programming of offspring fatty liver by maternal obesity. *Am. J. Physiol.-Regul. Integr. Comp. Physiol.* 2014, 307, R26–R34. [CrossRef]

52. Serviddio, G.; Bellanti, F.; Vendemiale, G. Free radical biology for medicine: Learning from nonalcoholic fatty liver disease. *Free Radic. Biol. Med.* 2013, 65, 952–968. [CrossRef]

53. Li, T.; Zhu, R.; Dong, Y.; Liu, Y.; Li, S.; Chen, G. Effects of pectin pentaoligosaccharide from Hawthorn (*Crataegus pinnatifida* Bunge. var. Major) on the activity and mRNA levels of enzymes involved in fatty acid oxidation in the liver of mice fed a high-fat diet. *J. Agric. Food Chem.* 2013, 61, 7599–7605. [CrossRef]

54. Zhu, R.; Li, T.; Dong, Y.; Liu, Y.; Li, S.; Chen, G.; Zhao, Z.; Jia, Y. Pectin pentaoligosaccharide from hawthorn (*Crataegus pinnatifida* Bunge. var. major) ameliorates disorders of cholesterol metabolism in high-fat diet fed mice. *Food Res. Int.* 2013, 54, 262–268. [CrossRef]

55. Zhu, R.-G.; Sun, Y.-D.; Hou, Y.; Fan, J.; Fan, J.; Chen, G.; Wei, J. Pectin pentaoligosaccharide reduces cholesterol accumulation by promoting bile acid biosynthesis and excretion in high-cholesterol-fed mice. *Chem.-Biol. Interact.* 2017, 272, 153–159. [CrossRef]

56. Kwon, S.H.; Kim, J.B. Effects of *Crataegus fructus* extract on the diet-induced hyperlipidemia in rats. *J. Funct. Foods.* 2010, 2, 179–186. [CrossRef]

57. Kwok, C.-Y.; Wong, C.N.-Y.; Yau, M.Y.-C.; Yu, P.H.-F.; Au, A.L.S.; Poon, C.C.-W.; Seto, S.-W.; Lam, T.-Y.; Kwan, Y.-W.; Chan, S.-W. Consumption of dried fruit of *Crataegus pinnatifida* (hawthorn) suppresses high-cholesterol diet-induced hypercholesterolemia in rats. *J. Funct. Foods.* 2010, 2, 179–186. [CrossRef]

58. Kwon, S.H.; Kim, J.B. Effects of *Crataegus fructus* extract on the diet-induced hyperlipidemia in rats. *J. Funct. Foods.* 2010, 2, 179–186. [CrossRef]

59. Zhu, R.; Li, T.; Dong, Y.; Liu, Y.; Li, S.; Chen, G.; Zhao, Z.; Jia, Y. Pectin pentaoligosaccharide from hawthorn (*Crataegus pinnatifida* Bunge. var. major) ameliorates disorders of cholesterol metabolism in high-fat diet fed mice. *Food Res. Int.* 2013, 54, 262–268. [CrossRef]

60. Zhang, Z.; Ho, W.K.; Huang, Y.; Chen, Z.-Y. Hypocholesterolemic activity of hawthorn fruit is mediated by regulation of cholesterol-7α-hydroxylase and acyl CoA: Cholesterol acyltransferase. *Food Res. Int.* 2002, 35, 885–891. [CrossRef]

61. Lee, H.-J.; Park, M.-S. Changes of Plasma and Hepatic Lipids, Hydroxy-Methyl-Glutarly CoA Reductase Activity and Acyl-CoA: Cholesterol Acyltransferase Activity by Supplementation of Hot Water Extracts from *Rosa rugosa*, *Crataegus pinnatifida* and *Polygonum cuspidatum* in High-Cholesterol Fed Rats. *Prev. Nutr. Food Sci.* 1998, 3, 344–350.

62. Kim, Y.-S.; Byun, S.-H.; Kim, S.-C.; Kuk, M.; Cho, E.-H. Effects on cure and prevention of an obesity (IV). *Korea J. Herbol.* 2000, 15, 37.

63. Go, K.J.; Song, Y.S. Influence of fructus *Crataegus* water extract on the obese mouse models. *J. Tradit. Korean Med.* 1998, 8, 1–8.

64. Gao, Y.; Xiao, Y. Effect of Hawthorn and hawthorn flavonoids extract on rats with hyperlipidemia. *Chin. J. Food Hyg.* 2002, 14, 14–16.

65. Ban, S.-S.; Yoon, H.-D.; Shin, O.-C.; Shin, Y.-J.; Park, C.-S.; Park, J.-H.; Seo, B.-I. The effects of *Artemisiae capillaris*, *Ponciri fructus* and *Cartaegi fructus* in obese rats induced by high fat diet. *Korea J. Herbol.* 2006, 21, 55–67.

66. Gal, S.-W.; Choi, Y.-J.; Cho, S.-J. Anti-obesity effect of *Crataegus fructus* extract from Chinese cultivation. *J. Life Sci.* 2011, 21, 1586–1591. [CrossRef]

67. Hu, H.; Dong, Q.; Wang, Q.; Pan, L.; Zhang, T.; Luo, X. Studies on protective effects of zhowntian hawthorn extract on hepatic steatosis. *J. Tianjin Univ. Sci. Technol.* 2018, 33, 14–19.

68. Hu, H.-J.; Luo, X.-G.; Dong, Q.-Q.; Mu, A.; Shi, G.-L.; Wang, Q.-T.; Chen, X.-Y.; Zhou, H.; Zhang, T.-C.; Pan, L.-W. Ethanol extract of Zhowntian hawthorn lowers serum cholesterol in mice by inhibiting transcription of 3-hydroxy-3-methylglutaryl-CoA reductase via diet-induced hypercholesterolemic rat model. *J. Funct. Foods.* 2013, 5, 1326–1335. [CrossRef]

69. Zhang, Z.; Ho, W.K.; Huang, Y.; Chen, Z.-Y. Hypocholesterolemic activity of hawthorn fruit is mediated by regulation of cholesterol-7α-hydroxylase and acyl CoA: Cholesterol acyltransferase. *Food Res. Int.* 2002, 35, 885–891. [CrossRef]

70. Khalil, R.; Abuharfeil, N.; Shabsoug, B. The effect of *Crataegus aronica* aqueous extract in rabbits fed with high cholesterol diet. *Eur. J. Sci. Res.* 2008, 22, 352–360. [CrossRef]

71. Rajendran, S.; Deepalakshmi, P.; Paraskathy, K.; Devaraj, H.; Devaraj, S.N. Effect of tincture of *Crataegus* on the LDL-receptor activity of hepatic plasma membrane of rat treated with anergic diet. *Atherosclerosis* 1996, 123, 235–241. [CrossRef]

72. He, Z.; Kwek, E.; Hao, W.; Zhu, H.; Liu, J.; Ma, K.Y.; Chen, Z.-Y. Hawthorn fruit extract reduced trimethylamine-N-oxide (TMAO)-exacerbated atherogenesis in mice via anti-inflammation and anti-oxidation. *Nutr. Metab.* 2021, 18, 1–15. [CrossRef]

73. Kim, M.-C.; Kong, R.; Han, H.-S.; Kang, D.-h.; Lee, S.-J.; Lee, C.-C.; Wang, S.; Kwon, D.-Y.; Kang, O.-H. Non-alcoholic fatty liver protective effects, and studies on the mechanism of action of *Crataegi fructus*. *Korea J. Herbol.* 2018, 33, 61–70.

74. Yoo, J.-H.; Liu, Y.; Kim, H.-S. Hawthorn Fruit Extract Elevates Expression of Nrfl2/HO-1 and Improves Lipid Profiles in Ovariectomized Rats. *Nutrients* 2016, 8, 283. [CrossRef]

75. Li, T.; Liu, Y.; Dong, Y.; Li, S.; Zhu, R. Anti-fat deposition and antioxidant effects of haw pectic oligosaccharide in the liver of high-fat-fed mice. *CYTAA-J. Food* 2014, 12, 27–31. [CrossRef]
75. Li, T.; Li, S.; Dong, Y.; Zhu, R.; Liu, Y. Antioxidant activity of penta-oligogalacturonide, isolated from haw pectin, suppresses triglyceride synthesis in mice fed with a high-fat diet. *Food Chem.*, 2014, 145, 335–341. [CrossRef]
76. Day, E.A.; Ford, R.J.; Steinberg, G.R. AMPK as a therapeutic target for treating metabolic diseases. *Trends Endocrinol. Metab.*, 2017, 28, 545–560. [CrossRef] [PubMed]
77. Li, T.; Chen, X.; Huang, Z.; Xie, W.; Tong, C.; Bao, R.; Sun, X.; Li, W.; Li, S. Pectin oligosaccharide from hawthorn fruit ameliorates hepatic inflammation via NF-κB inactivation in high-fat diet fed mice. *J. Funct. Foods*, 2019, 57, 345–350. [CrossRef]
78. Greuter, T.; Shah, V.H. Hepatic sinusoids in liver injury, inflammation, and fibrosis: New pathophysiological insights. *J. Gastroenterol.*, 2016, 51, 511–519. [CrossRef] [PubMed]
79. Wang, K. Molecular mechanisms of hepatic apoptosis. *Cell Death Dis.*, 2014, 5, e996. [CrossRef]
80. Somade, O.T.; Ajayi, B.O.; Olunaike, O.E.; Jimoh, L.A. Hepatic oxidative stress, up-regulation of pro-inflammatory cytokines, apoptotic and oncogenic markers following 2-methoxyethanol administrations in rats. *Biochem. Biophys. Rep.*, 2020, 24, 100806. [CrossRef]
81. Koyama, Y.; Brenner, D.A. Liver inflammation and fibrosis. *J. Clin. Investig.*, 2017, 127, 55–64. [CrossRef]
82. Liu, S.; Yu, J.; Fu, M.; Wang, X.; Chang, X. Regulatory effects of hawthorn polyphenols on hyperglycemic, inflammatory, insulin resistance responses, and alleviation of aortic injury in type 2 diabetic rats. *Food Res. Int.*, 2021, 142, 110239. [CrossRef]
83. Zheng, K.; He, Z.; Kitazato, K.; Wang, Y. Selective Autophagy Regulates Cell Cycle in Cancer Therapy. *Theranostics*, 2019, 9, 104–125. [CrossRef]
84. Pistritto, G.; Trisciuoglio, D.; Ceci, C.; Garufi, A.; D’Orazi, G. Apoptosis as anticancer mechanism: Function and dysfunction of its modulators and targeted therapeutic strategies. *Aging*, 2016, 8, 603–619. [CrossRef]
85. Lopez-Lazo, M. Flavonoids as Anticancer Agents: Structure-Activity Relationship Study. *Curr. Med. Chem. Anticancer Agents*, 2002, 2, 691–714. [CrossRef]
86. Peng, E.H.; Ma, X.; Hu, X.Y. Effect of hawthorn extract on apoptosis and related factors of HepG2 cells. *Zhongguo Shijian Fangjiuxue Zazhi*, 2016, 22, 169–172.
87. Nunes, R.; Pasko, P.; Tyszka-Czochara, M.; Szewczyk, A.; Szlosarczyk, M.; Carvalho, I.S. Antibacterial, antioxidant and anti-proliferative properties and zinc content of five south Portugal herbs. *Pharm. Biol.*, 2017, 55, 114–123. [CrossRef]
88. Qiao, A.; Wang, Y.; Xiang, L.; Zhang, Z.; He, X. Novel triterpenoids isolated from hawthorn berries functioned as antioxidant and anti-proliferative activities. *J. Funct. Foods*, 2015, 13, 308–313. [CrossRef]
89. Guo, R.; Lin, B.; Shang, X.Y.; Zhou, L.; Yao, G.D.; Huang, X.X.; Song, S.J. Phenylpropanoids from the fruit of *Crataegus pinnatifida* exhibit cytotoxicity on hepatic carcinoma cells through apoptosis induction. *Fitoterapia*, 2018, 127, 301–307. [CrossRef] [PubMed]
90. Manukyan, A.; Lumlerdkij, N.; Heinrich, M. Caucasian endemic medicinal and nutraceutical plants: In-vitro antioxidant and cytotoxic activities and bioactive compounds. *J. Pharm. Pharmacol.*, 2019, 71, 1152–1161. [CrossRef]
91. Rodrigues, S.; Calhelha, R.C.; Barreira, J.C.M.; Dueñas, M.; Abreu, R.M.V.; Santos-Buelga, C.; Ferreira, I.C.F.R. *Crataegus monogyna* buds and fruits phenolic extracts: Growth inhibitory activity on human tumor cell lines and chemical characterization by HPLC–DAD–ESI/MS. *Food Res. Int.*, 2013, 49, 516–523. [CrossRef]
92. Huang, X.X.; Zhou, C.C.; Li, L.Z.; Li, F.F.; Lou, L.L.; Li, D.M.; Ikejima, T.; Peng, Y.; Song, S.J. The cytotoxicity of 8-O-4′-neolignans from the seeds of *Crataegus pinnatifida*. *Bioorganic Med. Chem. Lett.*, 2013, 23, 5599–5604. [CrossRef]
93. Huang, X.-X.; Zhou, C.-C.; Li, L.-Z.; Peng, Y.; Lou, L.-L.; Liu, S.; Li, D.-M.; Ikejima, T.; Song, S.-J. Cytotoxic and antioxidant dihydrobenzo[α]neolignans from the seeds of *Crataegus pinnatifida*. *Fitoterapia*, 2013, 91, 217–223. [CrossRef] [PubMed]
94. Guo, R.; Shang, X.Y.; Lv, T.M.; Yao, G.D.; Lin, B.; Wang, X.B.; Huang, X.X.; Song, S.J. Phenylpropanoid derivatives from the fruit of *Crataegus pinnatifida* Bunge and their distinctive effects on human hepatoma cells. *Phytochemistry*, 2019, 164, 252–261. [CrossRef]
95. Chen, H.; Jiang, J.; Yu, L.; Gao, G. Comparisons of pharmacological effect and LD50 among four kinds of hawthorn fruit. *China J. Chin. Mater. Med.*, 1994, 19, 454–455, 510.
96. Jouad, H.; Lemhadri, A.; Maghrani, M.; Burcelin, R.; Eddouks, M. Hawthorn evokes a potent anti-hyperglycemic capacity in streptozotocin-induced diabetic rats. *J. Herb. Pharmacother.*, 2003, 3, 19–29. [CrossRef] [PubMed]
97. Abu-Gharbieh, E.; Shehab, N.G. Therapeutic potentials of *Crataegus azarolus* var. eu-azarolus Maire leaves and its isolated compounds. *BMC Complement. Altern. Med.*, 2017, 17, 218. [CrossRef] [PubMed]
98. Shattoor, A.S. Acute and sub-acute toxicity of *Crataegus aronia* syn. azarolus (L) whole plant aqueous extract in wistar rats. *Am. J. Pharmacomol. Toxicol.*, 2011, 6, 37–45. [CrossRef]
99. Daniele, C.; Mazanti, G.; Pittler, M.H.; Ernst, E. Adverse-Event Profile of Picroliv, a herbal medicine for liver disease. *BMC Complement. Altern. Med.*, 2008, 8, 55–64. [CrossRef]
100. Holubarsch, C.J.; Colucci, W.S.; Eha, J. Benefit-risk assessment of *Crataegus* extract WS 1442: An evidence-based review. *Drug Saf.*, 2006, 29, 523–535. [CrossRef]
101. Dhiman, R.K.; Chawla, Y.K. Herbal medicines for liver diseases. *Dig. Dis. Sci.*, 2005, 50, 1807–1812. [CrossRef]
102. Girish, C.; Pradhan, S.C. Drug development for liver diseases: Focus on picroliv, ellagic acid and curcumin. *Fundam. Clin. Pharmacol.*, 2008, 22, 623–632. [CrossRef]
103. Kumari, R.; Sahu, M.K.; Tripathy, A.; Uthansingh, K.; Behera, M. Hepatocellular carcinoma treatment: Hurdles, advances and prospects. *Hepatic Oncol.*, 2018, 5, HEP08. [CrossRef]
104. Sun, B.; Zhang, R.; Liang, Z.; Fan, A.; Kang, D. Hyperoside attenuates non-alcoholic fatty liver disease through targeting Nr4A1 in macrophages. *Int. Immunopharmacol.*, 2021, 94, 107438. [CrossRef]
105. Inamdar, S.; Joshi, A.; Malik, S.; Boppana, R.; Ghaskadbi, S. Vitexin alleviates non-alcoholic fatty liver disease by activating AMPK in high fat diet fed mice. *Biochem. Biophys. Res. Commun.* 2019, 519, 106–112. [CrossRef]

106. Li, C.; Chen, Y.; Yuan, X.; He, L.; Li, X.; Huang, S.; Hou, S.; Liang, J. Vitexin ameliorates chronic stress plus high fat diet-induced nonalcoholic fatty liver disease by inhibiting inflammation. *Eur. J. Pharmacol.* 2020, 882, 173264. [CrossRef] [PubMed]

107. Yuan, H.; Duan, S.; Guan, T.; Yuan, X.; Hou, S.; Lai, X.; Huang, S.; Du, X.; Chen, S. Vitexin protects against ethanol-induced liver injury through Sirt1/p53 signaling pathway. *Eur. J. Pharmacol.* 2020, 873, 173007. [CrossRef] [PubMed]

108. Zhang, J.-X.; Feng, W.-J.; Liu, G.-C.; Ma, Q.-Q.; Li, H.-L.; Gao, X.-Y.; Liu, H.-Z.; Piao, G.-C.; Yuan, H.-D. Corosolic acid attenuates hepatic lipid accumulation and inflammatory response via AMPK/SREBPs and NF-κB/MAPK signaling pathways. *Am. J. Chin. Med.* 2020, 48, 579–595. [CrossRef] [PubMed]

109. Liu, G.; Cui, Z.; Gao, X.; Liu, H.; Wang, L.; Gong, J.; Wang, A.; Zhang, J.; Ma, Q.; Huang, Y. Corosolic acid ameliorates non-alcoholic steatohepatitis induced by high-fat diet and carbon tetrachloride by regulating TGF-β1/Smad2, NF-κB, and AMPK signaling pathways. *Phytother. Res.* 2021, 35, 5214–5226. [CrossRef]