Nutraceutical Properties of Polyphenols against Liver Diseases

Jorge Simón [1,2,*,†] , **María Casado-Andrés** [3,†] , **Naroa Goikoetxea-Usandizaga** [1,2] , **Marina Serrano-Maciá** [1,2] and **María Luz Martínez-Chantar** [1,2]

[1] Liver Disease Laboratory, Center for Cooperative Research in Biosciences (CIC bioGUNE), Basque Research and Technology Alliance (BRTA), Bizkaia Technology Park, Building 801A, 48160 Derio, Bizkaia, Spain; ngoikoetxea@cicbiogune.es (N.G.-U.); mserrano@cicbiogune.es (M.S.-M.); mlmartinez@cicbiogune.es (M.L.M.-C.)

[2] Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), 48160 Derio, Bizkaia, Spain

[3] Cell Biology and Histology Department, University of the Basque Country (UPV/EHU), Barrio Sarriena, S/N, 48940 Leioa, Spain; mdcasado002@gmail.com

* Correspondence: jsimon@cicbiogune.es; Tel.: +34-944-061304

† These authors contributed equally to this work.

Abstract: Current food tendencies, suboptimal dietary habits and a sedentary lifestyle are spreading metabolic disorders worldwide. Consequently, the prevalence of liver pathologies is increasing, as it is the main metabolic organ in the body. Chronic liver diseases, with non-alcoholic fatty liver disease (NAFLD) as the main cause, have an alarming prevalence of around 25% worldwide. Otherwise, the consumption of certain drugs leads to an acute liver failure (ALF), with drug-induced liver injury (DILI) as its main cause, or alcoholic liver disease (ALD). Although programs carried out by authorities are focused on improving dietary habits and lifestyle, the long-term compliance of the patient makes them difficult to follow. Thus, the supplementation with certain substances may represent a more easy-to-follow approach for patients. In this context, the consumption of polyphenol-rich food represents an attractive alternative as these compounds have been characterized to be effective in ameliorating liver pathologies. Despite of their structural diversity, certain similar characteristics allow to classify polyphenols in 5 groups: stilbenes, flavonoids, phenolic acids, lignans and curcuminoids. Herein, we have identified the most relevant compounds in each group and characterized their main sources. By this, authorities should encourage the consumption of polyphenol-rich products, as most of them are available in quotidian life, which might reduce the socioeconomical burden of liver diseases.

Keywords: polyphenols; liver; stilbenes; flavonoids; phenolic acids; lignans; curcuminoids; NAFLD; HCC; DILI; ALF; ALD

1. Introduction

Current food tendencies and suboptimal dietary habits, together with an unhealthy lifestyle, are leading to the development of metabolic pathologies and their spreading worldwide [1,2]. In this context, the prevalence of liver pathologies is increasing among population, as this organ is responsible for the metabolism of exogenous substances in the organism [3]. Chronic liver pathologies, one of the leading mortality causes in USA and Europe, have on nutritional imbalances and sedentary habits their main causative agent nowadays. Non-alcoholic fatty liver disease (NAFLD) has emerged as the most frequent form of chronic liver disease worldwide, with an estimated prevalence of around 25% of

general population [4,5]. Indeed, such elevated prevalence is expected to even increase within next years due to the rising of comorbidities from metabolic syndrome (MetS), making NAFLD a global health problem [6,7]. The term NAFLD is used to define a group of hepatic disorders that go from a simple lipid accumulation in the hepatocyte (steatosis) to its progression into more severe stages as non-alcoholic steatohepatitis (NASH), characterized by lipid-derived inflammation, hepatocellular ballooning and fibrosis. In case of a chronic fibrosis development, hepatocyte cell death and extracellular matrix (ECM) deposition, NASH may turn into cirrhosis. Moreover, the risk of developing NAFLD highly rises up the risk of developing hepatocellular carcinoma (HCC), the most frequent form of liver cancer [6,8–10].

Until date, the two-hit or multiple-hit hypothesis is the most extended explanation for the progression of NAFLD, in which a first hit induced steatosis and the aberrant lipid homeostasis leads to derived complications that contribute to its aggravation [11]. Related to the first hit, two imbalances have been reported to promote hepatic lipid accumulation, between: (i) fatty acid uptake and very-low-density lipoprotein (VLDL) export and (ii) de novo lipogenesis and fatty acid oxidation (FAO). Indeed, the metabolic triggering of the pathology has led to propose a new term MAFLD, metabolic-associated fatty liver disease, to define this group of pathologies [12]. Then, the appearance of second hits such as peroxidation, oxidative and reticulum stress development and mitochondrial dysfunction triggers an inflammatory response that may result in fibrosis development. In this process, the hepatocyte suffers from an antioxidant machinery depletion that finally leads to its death and, in the meantime, macrophage activation by pro-inflammatory cytokines such as tumor-necrosis factor (TNF) or several interleukine (IL) isoforms. Thus, hepatic stellate cells (HSC) are activate and proliferate by several signaling pathways such as transforming growth factor-beta (TGF-β)/SMAD, promoting collagen synthesis and ECM deposition, in which the matrix metalloproteinases (MMP)/tissue inhibitor of metalloproteinases (TIMP) is essential [13]. Regarding HCC development, the heterogeneity of the disease implies different molecular signaling pathways activated at the same time to deregulate hepatocyte growth, proliferation, differentiation and apoptosis. Several pro-proliferative pathways and signaling occur such as protein kinase B (AKT), nuclear factor-kappa B (NF-κB), mammalian target of rapamycin (mTOR) or c-MYC [14].

Furthermore, unhealthy lifestyle does not necessarily mean an inadequate food intake, but also into the excessive consumption of certain prescription and non-prescription medications or toxic compounds. As a consequence, liver can suffer from an acute liver failure (ALF) with drug-induced liver injury (DILI) as its main cause [15–17]. DILI is estimated to affect 14 of 100,000 inhabitants worldwide and it presents a real challenge to gastroenterologists when diagnosing the pathology [18]. The liver is the organ responsible of the metabolism of exogenous compounds. Under overdose conditions, compounds such as acetaminophen or carbon tetrachloride are converted by cytochrome P450 2E1 (CYP2E1) into toxic compounds by the hepatocyte [19]. These toxic compounds deplete the anti-oxidant machinery of the cell, mainly composed by reduced glutathione (GSH), catalase (CAT) and superoxide dismutase (SOD). The direct impact they have over mitochondrial integrity causes a damage that finally results on the necrosis of the hepatocyte [20,21]. During DILI, the release of mitochondrial pro-apoptotic proteins such as BAX or BCL-2 and the TNF- or NF-κB-mediated pro-inflammatory signaling are key hallmarks [22].

Additionally, the chronic and heavy consumption of alcohol leads to the development of steatosis in 90% of patients who drink over 60 g of alcohol per day and cirrhosis in 30% cases [23], making alcoholic liver disease (ALD) to follow a similar pattern of progression as NAFLD. Similarly to DILI, CYP2E1-mediated metabolism of ethanol leads to the production of acetaldehyde that leads to mitochondrial dysfunction [24] that impairs lipid homeostasis in the hepatocyte causing steatosis. The increased oxidative stress and depletion of anti-oxidant activity of the hepatocyte, together with aberrant lipid metabolism by peroxidation, induce a hepatocellular damage that promotes the progression of the disease from alcoholic steatosis to hepatitis and finally cirrhosis [24]. The molecular

basis of ALD progression from steatosis to cirrhosis follow similar molecular mechanisms to NAFLD, including an inflammatory environment and HSC proliferation and activation [24].

Considering the elevated prevalence of aforementioned liver pathologies and their expected increase, together with the lack of awareness of general population, authorities are focusing on reducing their prevalence and improving their prognosis [25]. Clinical and scientific studies point out lifestyle modifications as the mainstay and cornerstone in treating these pathologies, comprising adequate meal plans and physical activity [26,27]. Although behavioral interventions attempt to guarantee the adherence of the patients, in most of cases it is hard to achieve so they do not follow the designed plans.

Therefore, the supplementation with certain products may offer a more easy-to-adhere approach in order to prevent or improve liver pathologies. In this context, current evidence highlights the beneficial properties associated to polyphenols, a group of natural metabolites contained in plants that own a variety of beneficial effects for the liver and associated comorbidities. They play a role in the regulation of oxidative stress, the lipid metabolism, the development of insulin resistance, inflammation or body weight among others [28,29]. Moreover, they are capable of attenuate drug-induced toxicity by reducing apoptosis and enhancing the expression of antioxidant enzymes [30]. Thus, they offer an attractive nutraceutical approach not only for reducing the impact and prevalence of chronic liver diseases, but also for ameliorating the prognosis of acute liver alterations.

The aim of the present review is to highlight the benefits of polyphenols intake and identify the main polyphenol-rich sources. By this, we propose a change in dietary lifestyle pattern by presenting such polyphenol-rich foods, which can be easily introduced in the diet. Considering their nutraceutical value, they may represent a strategic approach in which future dietary guidelines and public health recommendations should be based on.

2. Polyphenols and Their Nutraceutical Value

Polyphenols are a large group of at least 10,000 different naturally occurring phytochemicals, with one or more aromatic rings and with one or more hydroxyl functional groups attached. They are secondary metabolites that represent a large and diverse group of substances abundantly present in vegetables, fruits, cereals, spices, teas, rizhomes, medical plants and flowers [29,31].

Although the diversity of their chemical structure makes their classification difficult, the number of phenol rings and the structural elements allows to distinguish between certain groups of polyphenols. So that, according to their structural similarities polyphenols can be grouped in stilbenes, flavonoids, phenolic acids, lignans and curcuminoids [31,32]. In the following work, the main polyphenolic compounds of each group, their beneficial properties for certain liver pathologies and their main food source will be deeply described.

2.1. Stilbenes

Stilbenes are phytochemicals, some of which are considered phytoalexins, mainly present in berries, grapes, peanuts and red wine. This group of polyphenols is composed by three main compounds: resveratrol and its derived compounds pterostilbene and piceatannol [32,33].

Resveratrol may be one of the most popular polyphenols in our society and it is found in coco, mulberries, peanuts, soy and grapes [34]. Preclinical studies have characterized its protective features at multiple levels, by modulating oxidative stress and hepatocellular damage in order to ameliorate NAFLD through the reduction of free radicals and pro-inflammatory cytokines and the increased response of anti-oxidant enzymes such as glutathione (GSH) and cytochrome P450 (CYP) 2E1 [35,36]. Moreover, resveratrol reduces hepatic lipid content by reducing sirtuin 1 (SIRT1)-mediated lipogenic activity through the modulation of acyl-coA carboxylase (ACC), peroxisome proliferation activity receptor γ (PPARγ) and sterol response element binding protein-1 (SREBP-1) [37].

As aforementioned, pterostilbene is a derivate from resveratrol which is mainly present in blueberries [38]. This compound is also reported to reduce steatosis and modify hepatic fatty acid profile stimulating carnitine-palmitoyltransferase-1 (CPT1)-mediated FAO, stimulating microsomal

triglyceride transfer protein (MTP)-mediated very-low-density lipoprotein (VLDL) export and reducing lipid uptake by CD36 [39]. Likewise, it enhances liver glucokinase and glucose-6-phosphatase activity to ameliorate insulin resistance and hepatic glycogen homeostasis and, therefore, lowering total cholesterol and triglyceride levels in serum [40].

Another derivate from the hydroxylation of resveratrol is piceatannol, present in grapes, passion fruit and peanut calluses [33]. Although this compound has been less studied than resveratrol due to its lower concentration in food, it has been reported to have a higher activity [41]. Thus, piceatannol also improves hepatic glycemic control by activating adenosine monophosphate-activated protein kinase (AMPK) through phosphorylation while ameliorating serum lipid profile in mice inhibiting the lipogenic flux mediated by ACC and fatty acid synthase (FAS) expression [42] Piceatannol-mediated AMPK phosphorylation also induces autophagy, a process reported to be dysregulated in NAFLD [43].

Regarding the effects of stilbenes among human population, clinical trials have been carried out only by evaluating the properties of resveratrol in NAFLD, liver cancer and hepatitis patients. Remarkably, the dietary supplementation with resveratrol has been shown to be effective in improving the inflammatory marker profile in NAFLD patients [44].

2.2. Flavonoids

Flavonoids comprise the larger group of polyphenols and the most abundant compounds in human diet. They are characterized by a C6-C3-C6 backbone structure and appear in almost all foods of vegetable origin and, particularly, in apples, berries, citrus fruits, onions, red wine, grapes, tea or olive oil [31]. Flavonoids are classified into six additional subgroups: anthocyanins, flavanols, flavanones, flavonols, flavones and isoflanoids. In the following section a detailed description of each subgroup and their main compounds is provided.

First, the subgroup of anthocyanins is composed by water-soluble flavonoid species as delphinidin, pelargonidin, cyanidin and malvidin. Delphinidin appears in flowers and berries as blueberry, Saskatoon berry, raspberry, strawberry or chokecherry, being its richest natural source the Maqui berry [45]. They have been reported to have anti-inflammatory properties targeting nuclear factor kappa-B (NF-κB), activator protein-1 (AP-1) and cyclooxygenase-2 (COX-2) [46]. Moreover, delphindin prevents triglyceride accumulation in in vitro NASH models modulating AMPK and FAS [47] or to downregulate fibrogenic stimuli to prevent fibrosis development in preclinical models [48]. Therein, fibrogenic response is attenuated by a decreased oxidative stress development, increasing matrix metalloproteinase (MMP)-9 and metallothionein (MT) I/II expression [48]. Although pelargonidins have been less studied, their protective properties against lipopolysaccharide (LPS)-induced liver injury have been characterized by modulating the inflammatory pathway mediated by toll-like receptor (TLR) [49]. This polyphenolic compound is mainly present in orange- or red-color fruits as raspberries, blackberries, strawberries or plums [50]. On another hand, cyanidin have been reported to promote lipid oxidative flux by increasing CPT1 and PPARα expression to enhance FAO and by decreasing FAS and SREBP-1 expression to downregulate lipogenesis [51]. Cyanidin prevents fibrosis development inhibiting collagen type I synthesis and downregulating extracellular-regulated kinase 1/2 (ERK1/2) [52], while promotes cAMP-mediated protein kinase A (PKA) activation to induce glutathione (GSH) synthesis and protect the hepatocyte [53]. Additionally, hepatocellular damage derived from alcoholic toxicity is also prevented by activating AMPK, that induces autophagy [54]. Cyanidins are present in red berries, grapes, bilberry, blackberry, blueberry, cherry, cranberry, elderberry, hawthorn, loganberry, açaai berry and raspberry [55]. Similar to cyanidin, malvidin is present in red grapes, cranberries, blueberries and black rice. They have been reported to increase FAO in the same way as cyanidins [51], and, remarkably, to attenuate tumor growth in HCC by regulating BAX and caspase-3 for apoptosis; several cyclin isoforms and phosphatase and tensin homolog (PTEN) for proliferation and metastasis derived from MMP-2/9 activity [56].

Secondly, flavanols share a general chemical structure of two rings linked by three carbons forming an oxygenated heterocyclic ring [57]. Among them epicatechin, epigallocatechin and its gallate derivate (EGCG) and procyanidins are the most popular compounds. Epicatechin is mainly present in dark chocolate and cocoa [58] and it has been reported to regulate lipid profile in serum and liver through regulating SREBP, FAS, liver X receptor (LXR) and SIRT [59]; as well as to attenuate oxidative stress and inflammatory injury via abrogation of NF-κB signaling pathway [60]. EGCGs, mainly present in green tea [61], may be another one of the most popular polyphenols in society normally sold as green tea extract. Their biological effects on NAFLD have been characterized in terms of lipid metabolism via pAMPK, SREBP-1, FAS and ACC; the oxidative response mediated by CYP2E1 or malonaldehyde production; TNF and IL-mediated inflammation and the fibrosis development induced by TGF-β/SMAD pathway [62]. EGCG also decreases body weight and reduces liver injury mediated by oxidative stress and inflammatory response, reducing the formation of collagen and alpha-smooth muscle actin (αSMA) in the liver and the expression of tissue inhibitor of metalloproteinase-2 (TIMP-2) in preclinical studies [63]. Moreover, EGCG has a protective effect on hepatotoxicity by decreasing bile acid and lipid absorption [60] and lowering cytochrome P450 (CYP)-mediated activation and toxicity of acetaminophen in DILI [64]. Related to HCC, EGCG has been also characterized to promote apoptosis in cancer cells in a multifactor way targeting genes involved in initiation (like NF-κB or BCL-2), proliferation (like cMyc, ERK1/2 or DDR mechanisms) and invasion (like MMPs or COX-2). [65]. The antioxidant properties of the last compound, procyanidins, have been also reported in fibrosis animal models via inhibition of CYP2E1-mediated metabolism of toxic compounds and improving antioxidant capacity through GSH or superoxide dismutase (SOD) [66]. Additionally, procyanidins exert a protective effect against ALD ameliorating SREBP-1-mediated steatosis and inflammation via IL-6 or TNF [67], with a possible involvement in preventing mitochondrial dysfunction and apoptosis [68]. Procyanidins are present in chocolate, apples, red grapes and cranberries [69].

The subgroup of flavanones is smaller than the previous one, as only hesperidin and naringenin compose it. Both compounds are characterized by a double bond between C2 and C3 and the lack of the oxygenation in C3 [70]. On one hand, hesperidin is mainly found in citrus fruits (grapefruit, lemon, lime or orange) and peppermint [71,72]. Similarly to other flavonoids, this compound has been found to protect against fibrosis enhancing GSH and decreasing catalase (CAT) and SOD levels [73]. Likewise, hesperidin reduced development of hepatic oxidative stress, dyslipidemia and histological changes via decreasing lipid peroxidation and recovering hepatocyte antioxidant properties [74]. On the other hand, naringenin is mainly found in Mexican oregano [75]. This flavanone's beneficial effects have been studied over DILI by downregulating caspase-3, BAX and BCL [76]. Hepatoxocity-induced fibrosis is also inhibited by naringenin, that inhibits the development of oxidative stress, the activation of HSC mediated TGF-β and the synthesis of ECM [77].

Flavonols present a large group of polyphenols in which quercetin is one of the most important flavonoids and, in addition, kaempferol, myricetin, isorhamnetin and galangin also compose this group. Quercetin is found in a variety of food that includes apples, berries, brassica vegetables, capers, grapes, onions, shallots, tea, tomatoes, many seeds and nuts [78,79]. This flavonol has been characterized to ameliorate fibrosis development by targeting NF-κB-mediated signal transduction, downregulating TNF, IL-6, IL-1β and IL-8 cytokines production [78], together with an increase of the antioxidant mechanisms mediated by GSH and IL-10 and decreasing lipid peroxidation in ALD [79]. Kampferol, present in tea, broccoli, apples, strawberries and beans [80] prevents tumor development by enhancing PTEN expression and inactivate PI3K/Akt/mTOR signaling in order to inhibit migration, proliferation and invasion [81]. Otherwise, CYP2E1 inhibition by kaempferol protects the hepatocyte against ALD development [82], whereas fibrosis development is attenuated by the inhibition of SMAD2/3 via the direct interaction between kaempferol and ATP-binding pocker of activing receptor-like kinase 5 (ALK5) [83]. Myricetin is found in berries, honey, vegetables, teas and wines [84]. This flavonolic compound has a regressive effect on steatosis development in preclinical NASH models by promoting NRF2-mediated mitochondrial functionality, which increases

antioxidative enzyme activities and PPAR-mediated fat decomposition [85]. Miricetin-mediated YAP downregulation also leads this polyphenol to exert anti-tumoral properties [86]. Isorhamnetin also alleviates steatosis decreasing FAS activity and fibrosis development via TGF-β-mediated HSC activation and proliferation [87], while decreasing the production of lipoperoxide compounds in serum and liver [88]. This compound is present in pears, onion, olive oil, grapes, tomato and the spice, Mexican Tarragon [80,89]. The last flavonol, galangin, is less abundant in nature as it is mainly present in galangal rizhome and propolis [90]. Similar to myricetin, galangin-mediated NRF2 activation attenuates oxidative damage, inflammation and apoptosis during hepatoxicity [91], while inhibiting the proliferation of HCC cells through the combined activation of NRF2 and hemooxygenase-1 (HO-1) [92].

The fifth flavonoid subgroup are flavones, distinguished by their double bond between C2 and C3, the lack of substitution at the C3 and the oxidation in C4 [93]. In this subgroup apigenin, chrysin and luteolin are the most relevant compounds. Apigenin is present in vegetables as parsley, broccoli, celery and onions; in fruits as oranges, olives, cherries and tomatoes; in herbs as chamomile, thyme, oregano, basil; and plant-based beverages as tea [93]. Between the beneficial properties of apigenin, it should be noted its anti-inflammatory properties against ALD by regulating CYP2E1-mediated oxidative stress and PPARα-mediated lipogenic gene expression [94] and the prospective effect for the damage induced by ischemia-reperfusion by suppressing inflammation, oxidative stress and apoptosis mediated by BAX and BCL-2 [95]. Additionally, this compound has been also characterized to ameliorate serum and hepatic lipid profile via metabolic and transcriptional modulations in the liver in genes involves in FAO, tricarboxylic acid cycle and oxidative phosphorylation among other [96]. Chrysin is specially present in honey and propolis [97] and this flavone has been reported to ameliorate NAFLD by modulating TNF- and IL-6-derived inflammatory response and SREBP-1-mediated lipogenesis in rats [98] and to reduce fibrosis development in a dose-dependent way via regulating MMP/TIMP imbalance [99]. Otherwise, luteolin is found in vegetables and fruits such as celery, parsley, broccoli, onion, carrots, peppers, cabbages or apple skins [100]. The protective properties of luteolin have been studied in DILI, where it restores the synthesis of antioxidant compounds as GSH while decreasing the inflammation signaling via TNF, NF-κB and IL-6 signaling and decreasing endoplasmic reticulum stress as well [101]. It also protects from developing liver pathologies derived from the chronic consumption of toxic substances as mercury, promoting mitochondrial functionality via NRF-2/NF-κB/P53 signaling [102] or alcoholic liver disease (ALD), where it downregulates the expression of SREBP-1 and recovers the AMPK activity [103].

The last subclass of flavonoids are isoflavonoids, where genistein and daidzein are the most common compounds. Genistein is found in soybeans and soy-based food and formulas, nuts and legumes as peas or lentils [104]. Its protective properties have been characterized on NAFLD by modulating PPARα-mediated lipid metabolism [105], while it also ameliorates hepatic inflammation by reducing TLR4 expression [106] and fibrosis development by decreasing lipid peroxidation and increasing GSH levels [107]. Similarly to genistein, daidzein is also found in the same food sources and the supplementation of daidzein, although it is less effective [108], has been reported to alleviate NAFLD by upregulating FAO and downregulating TNF expression [109].

Regarding the clinical trials carried out to determine the effect of flavonoids in human population, the effect of hesperidin supplementation has been studied in NASH development finding an improvement in steatosis, hepatic enzymes and several parameters as glycaemia [110]. A clinical study about naringenin has proposed this compound as an attractive approach for treating hepatitis C [111], while quercetin has been characterized to attenuate the secretion of the virus [112]. Additional clinical studies expected within next years will evaluate the effect of camu, a food rich in procyanidins, in obesity-related disorders as NAFLD and the effect of EGCG in cancer development from cirrhosis.

2.3. Phenolic Acids

This group of polyphenols is constituted by phenolic compounds, having one carboxylic group and typically in bound form as amides, esters or glycosides. They are found in a variety of plant-based

foods, seeds, skins or fruits and leaves of vegetables [113]. In the meantime, phenolic acids are divided into hydroxibenzoic acids, hydroxycinnamic acids and oleuropeunosides.

On one hand, hydroxibenzoic acids possess a common structure of C6-C1 derived from benzoic acid [113], being ellagic and gallic the most common compounds. Ellagic acid may be the most common compound in this subclass and it is present in nuts, walnuts, berries and fruits as pomegranates or berries [114]. This molecule has been reported to normalize the activity of antioxidative enzymes and to ameliorate histopathology by reducing inflammatory response via modulating oxidative stress [115], also reducing oxidative stress after ischemia-reperfusion liver injury [116] or impeding hepatotoxicity-derived fibrosis development in preclinical studies via downregulating caspase-3, BCL-2 and NF-κB expression while elevating NRF-2-mediated mitochondrial functionality [117]. Similarly to ellagic acid, gallic acid is found in berries as blueberries and strawberries, and fruits as mango [118]. This compound has been reported to exert protective properties in liver damage induced by drug abuse by reducing TNF-mediated inflammation and lipid peroxidation [119]. Moreover, gallic acid increases GSH and CAT antioxidative activities to protect the hepatocyte from ischemia-reperfusion [120] and decreases fibrosis development by restoring GSH and TGF-β levels while normalizing HSC activation and proliferation [121].

On the other hand, hydroxycinnamic acids derive from cinnamic acid and they are often present in food as simple esters with quinic acide or glucose [113], being ferulic and chlorogenic acids the most frequent compounds. Ferulic acid is found in commelinid plants as rice, wheat, oats or grains, and in vegetables, pineapple, beans, coffee, artichoke, peanut or nuts [122]. Similarly to hydroxybenzoic compounds, it upregulates NRF-2/HO-1 signaling to restore mitochondrial integrity and reduce the development of oxidative stress and inflammation in DILI [123], whereas it prevents fibrosis development by interfering in TGF-β/SMAD-mediated activation of HSCs [124]. Chlorogenic acid is particularly found in the coffee grain but it is also present in beans, potato tubers, fruits as apple and prunes [125]. This hydroxycinnamic compound also fibrosis development mediated by pro-inflammatory citokines such as TNF, IL-6 and IL-1β [126] and scavenges ROS production in alcohol consumption, reducing the steatosis, apoptosis and fibrosis development pathways mediated by TNF and TGF-β [127].

Oleuropein is mainly present in olive leaves, olives, virgin olive oil and olive mill waste [128]. Interestingly, this polyphenol has been shown to exert anti-inflammatory properties by scavenging ROS production under hepatotoxic conditions [129] and reduce lipid-derived inflammatory processes to prevent NASH progression such as TLR-mediated response [130].

Concerning the properties of phenolic acids in the human organism, clinical trials have been only developed by evaluating NAFLD development with a gallic acid-rich compound (Ajwa Date) and coffee supplementation, rich in chlorogenic acid. Although liver diseases were studied in the clinical trial evaluating Ajwa Date, outcomes have been focused on the prevention of atherosclerosis development. The results from the other clinical trial with coffee supplementation have not been published yet.

2.4. Lignans

Lignans are characterized by two phenylpropane units linked by a C6-C3 bond between the central atoms of the respective side chains. This group of polyphenols is present in a wide variety of plans in which latter, flaxseed and sesame seed represent the richest sources [131]. Moreover, lignans can be also found in fish, whole-grain cereals (as wheat or oats), meat, oilseed (as flax or soy) and beverages (as coffee, tea or wine) [131]. Although it can be distinguished among classical lignans, neolignans, flavonolignans and carbohydrate-conjugates, the main compounds present in nature are sesamin and diglucoside.

Sesamin is mainly present in sesame seeds and preclinical studies have reported metabolic properties in liver pathologies by preventing from ACC- [132] and SREBP-1-mediated fatty acid synthesis [133], while enhances FAO mediated by CPT1 or 3-hydroxyacyl-coA dehydrogenase [132].

Otherwise, diglucoside is found in flaxseed [134] and this compound has been also reported to downregulate hepatic lipid accumulation, while downregulating hepatic lipid peroxidation and decreasing cholesterol in serum [135].

Until date, no clinical trials for evaluating lignans have been carried out.

2.5. Curcuminoids

Regarding the group of curcuminoids, curcumin is the main compound as it gives the name to this group. This compound is the principal extract from the turmeric (Curcumula longa) herb [136] and preclinical approaches have characterized its anti-inflammatory and anti-oxidant properties derived from the intake of hepatotoxic compounds [137]. Curcumin alleviates hepatic dyslipidemia by inhibiting lipogenesis and promoting FAO, while enhancing cholesterol efflux and, in the meantime, reducing the lipid imbalance-derived oxidative stress [137]. By this, the expression of NRF-2 restores mitochondrial integrity in the hepatocyte, while GSH increase leads to an enhanced antioxidant capacity thus downregulating HSC activation [137].

There are currently three clinical trials under recruitment in order to evaluate the effects of different forms of curcumin, as dietary supplement or conjugated to phosphatidylcholine, in the development of NAFLD and insulin resistance. Another clinical trial has proven its effectivity in reducing steatosis, reducing body-mass index and improving serum profile in terms of cholesterol, triglycerides and transaminases [138].

3. Discussion

It is a fact that current unhealthy food tendencies, accompanied by a more sedentary lifestyle, have a direct impact over the health of global population [1]. Metabolic disorders are spreading worldwide and, among them, liver pathologies are on the most extended ones. Non-alcoholic fatty liver disease or NAFLD has an alarming prevalence of 25% worldwide and it is even expected to increase within next years due to such unhealthy lifestyle [5]. Otherwise, the excessive drug consumption that sometimes takes place can also lead to other liver pathologies, reaching an acute liver failure (ALF) in which drug-induced liver injury (DILI) is the main cause affecting [18] and chronic alcohol consumption leads to the development of alcoholic liver diseases (ALD) [23]. The management of liver pathologies presents a challenge to authorities and, although dietary and behavioral plans are currently being carried out, the long-term compliance of population sometimes presents the true challenge. Therefore, the supplementation or feeding with certain products can offer a more easy-to-adhere strategy in terms of preventing or ameliorating both chronic and acute liver diseases. Related to this, in the present work the role of different polyphenols has been described in detail as well as the most relevant clinical trials about them (Table 1). Overall, all polyphenols [26,31] described in the present review are reported to have beneficial properties towards either preventing or ameliorating NAFLD, DILI or ALD. Although some of them as resveratrol, EGCG, or curcumin are more popular in society, any of these compounds may offer healthy properties for the liver.

Thus, the consumption of polyphenol-rich food is a suitable option when planning a diet. As it can be observed in Table 2, most of them are present in foods that can be easily found in any supermarket so general population might not have problems when acquiring them. Therefore, it is an interesting point that authorities promote the consumption of these kind of foods when designing their programs for creating awareness, especially in such patients of liver diseases who are under treatment. Reducing their prize or promoting their inclusion in certain products or meals (e.g., strawberries in yogurts or coffee in some drinks) might be adequate options. Moreover, as it can be observed in Table 2, most part of the polyphenol-rich foods are not high-calorie so their inclusion should not have an impact over total daily calorie intake, another concern in the development of MetS and related metabolic disorders [139]. Furthermore, it must be always taken into account that not only polyphenols but also other micronutrients present beneficial properties, and the existence of variety in a diet is which makes it healthy.

Table 1. Clinical trials testing polyphenols against liver pathologies.

Polyphenol	Group/Subgroup	Pathology	Outcome
Resveratrol	Stilbenes	NAFLD, HCC, Hepatitis	Improved inflammatory profile in NAFLD [44].
Hesperidin	Flavonoids/Flavanones	NASH	Ameliorated steatosis, hepatic enzymes and glycaemia [110].
Naringenin	Flavonoids/Flavanones	Hepatitis C	Ameliorated phenotype [111].
Quercetin	Flavonoids/Flavonols	Hepatitis C	Attenuated secretion of the virus [112]
Procyanidins	Procyanidins/Flavanols	NAFLD	Not finished
EGCG	Flavonoids/Flavanols	Cirrhosis-derived HCC	Not finished
Gallic acid	Phenolic acids/Hydroxibenzoic acids	NAFLD	Atherosclerosis reduction.
Chlorogenic acid	Phenolic acids/Hydroxicinnamic acids	NAFLD	Not published
Curcumin	Curcuminoids	NAFLD	Reduction in steatosis and body-mass index and improved serum profile [138]

Table 2. List of most relevant polyphenols, their richest sources and pathologies with potential beneficial properties with each respective molecular target.

Polyphenol	Group/Subgroup	Source	Liver Pathology	Molecular Targets
Resveratrol	Stilbenes	Coco, mulberries, peanuts, soy and grapes [34]	Steatosis/NASH Steatosis	Glutathione, CYP2E1 [35,36] SIRT1, ACC, PPARγ, SREBP-1 [37]
Pterostilbene	Stilbenes	Blueberries [38]	Steatosis Steatosis	Glucokinase, Glucose-6-phosphatase [40] CPT1, MTP, CD36 [39]
Piceatannol	Stilbenes	Grapes, passion fruit and peanut calluses [33]	Steatosis	AMPK, ACC, FAS and autophagy [42]
Delphinidin	Flavonoids/anthocyanins	Flowers, blueberry, Saskatoon berry, raspberry, strawberry, chokecherry, Maqui berry [45]	NASH/ALD Steatosis Fibrosis	NF-κB, AP-1, COX-2 [46] AMPK, FAS [47] Oxidative stress, MMP-9 and MT [48]
Pelargonidin	Flavonoids/Anthocyanins	Raspberries, blackberries, strawberries or plums [50]	NASH/ALD	TLR [49]
Cyanidin	Flavonoids/Anthocyanins	Red berries, grapes, bilberry, blackberry, blueberry, cherry, cranberry, elderberry, hawthorn, loganberry, açaai berry and raspberry [55]	Steatosis Fibrosis NASH/Fibrosis ALD	CPT1, PPARα, FAS, SREBP-1 [51] Collagen I, ERK 1/2 [52] PKA, GSH [53] AMPK [54]
Malvidin	Flavonoids/Anthocyanins	Red grapes, cranberries, blueberries and black rice [80]	Steatosis HCC	CPT1, PPARα, FAS, SREBP-1 [51] BAX, Caspase-3, Cyclin, PTEN, MMP-2/9 [56]
Epicatechin	Flavonoids/Flavanols	Dark chocolate and cocoa [58]	Steatosis DILI/ALD NASH	SREBP-1, FAS, LXR, SIRT [59] Bile acid and lipid absorption [60] NF-κB [60]
Epigallocatechin/EGCG	Flavonoids/Flavanols	Green tea [61]	Steatosis/NASH Fibrosis DILI HCC	AMPK, SREBP-1, FAS, ACC; CYP2E1, malonaldehyde, TNF, IL; TGF/SMAD [62] Collagen, αSMA, TIMP-2 [63] CYP [64] NF-κB, BCL2; cMYC, ERK1/2, DDR; MMP, COX-2 [65]
Procyanidins	Flavonoids/Flavanols	Chocolate, apples, red grapes and cranberries [69]	NASH/Fibrosis ALD NASH/ALD/DILI	CYP2E1. GSH, SOD [66] SREBP-1, IL-6, TNF [67] Mitochondrial dysfunction and apoptosis [68]
Hesperidin	Flavonoids/Flavanones	Citrus fruits and peppermint [71,72]	NASH/Fibrosis Steatosis/NASH	GSH, CAT, SOD [73] Lipoperoxidation [74]
Naringenin	Flavonoids/Flavanones	Mexican oregano [75]	DILI Fibrosis	Caspase-3, BAX, BCL [76] TGF-β, ECM deposition [77]
Quercetin	Flavonoids/Flavonols	Apples, berries, brassica vegetables, capers, grapes, onions, shallots, tea, tomatoes, seeds and nuts [78,79]	Fibrosis ALD	NF-κB, TNF, IL-1β, IL-6, IL-8 [78] GSH, IL-10, lipid peroxidation [79]
Kaempferol	Flavonoids/Flavonols	Tea, broccoli, apples, strawberries and beans [80]	Fibrosis HCC ALD	ALK5, SMAD 2/3 PTEN, PI3K/AKT/mTOR [81] CYP2E1 [82]

Table 2. *Cont.*

Polyphenol	Group/Subgroup	Source	Liver Pathology	Molecular Targets
Myricetin	Flavonoids/Flavonols	Berries, honey, vegetables, teas and wines [84]	Steatosis/NASH	NRF-2, mitochondrial functionality, PPAR [85]
			HCC	YAP [86]
Isorhamnetin	Flavonoids/Flavonols	Pears, onion, olive oil, grapes, tomato, Mexican Tarragon [80,89]	Steatosis/NASH/Fibrosis	FAS, TGF.β, HSC activation [87]
			NASH	Lipoperoxidation [88]
Galangin	Flavonoids/Flavonols	Rizhome and propolis [90]	NASH/DILI	NRF-2, apoptosis [91]
			HCC	NRF-2, HO-1 [92]
Apigenin	Flavonoids/Flavones	Parsley, broccoli, celery, onions, oranges, olives, cherries, tomatoes, chamomile, thyme, oregano, basil, tea [93]	ALD	CYP2E1, PPARα [94]
			Steatosis	FAO, Tricarboxylic acid cycle, oxidative phosphorylation [96]
Chrysin	Flavonoids/Flavones	Honey and propolis [97]	Steatosis/NASH	TNF, IL-6, SREBP-1 [98]
			Fibrosis	MMP, TIMP [99]
Luteolin	Flavonoids/Flavones	Celery, parsley, broccoli, onion, carrots, peppers, cabbages and apple [100]	DILI	GSH, TNF, NF-κB, IL-6, ER stress [101]
			Fibrosis/DILI	NRF-2, NF-κB, P53 [102]
			ALD	SREBP-1, AMPK [103]
Genistein	Flavonoids/Isoflanoids	Soybeans, nuts and legumes [104]	Steatosis	PPARα [105]
			NASH	TLR4 [106]
			Fibrosis	Lipoperoxidation, GSH [107]
Daidzein	Flavonoids/Isoflanoids	Soybeans, nuts and legumes [104]	Steatosis/NASH	FAO, TNF [109]
Ellagic acid	Phenolic acids/Hydroxibenzoic acids	Nuts, walnuts, berries, pomegranades or berries [114]	NASH/DILI/ALD	Oxidative stress [115]
			IR	Oxidative stress [116]
			Fibrosis	Caspase-3, BCL-2, NF-kB, NRF-2 [117] aslan
Gallic acid	Phenolic acids/Hydroxibenzoic acids	Blueberries, strawberries and mango [118]	Fibrosis	GSH, TGF-β [121]
			DILI/ALD	TNF, lipoperoxidation [119]
			IR	GSH and CAT [120]
Ferulic acid	Phenolic acids/Hydroxycinnamic acids	Rice, wheat, oats, grains, vegetables, pineapple, beans, coffee, artichoke, peanut, nuts [122]	DILI	NRF-2/HO-1 [123]
			Fibrosis	TGF-β/SMAD [124]
Cholorogenic acid	Phenolic acids/Hydroxycinnamic acids	Coffee, beans, potato, apple and prunes [125]	Fibrosis	TNF, IL-6 and IL-1β [126]
			ALD	ROS, TNF, TGF-β [127]
Oleuropein	Phenolc acids/Oleuropeunosides	Olive leaves, olives, virgin olive oil and olive mill waste [128]	DILI/ALD	ROS [129]
			NASH	TLR [130]
Sesamin	Lignans	Flaxseed and sesame seeds [131]	Steatosis	ACC, CPT1, 3-hydroxyacyl-coA dehydrogenase [132]
			Steatosis	SREBP-1 [133]
Diglucoside	Lignans	Flaxseed [134]	Steatosis/NASH	Lipoperoxidation [135]
Curcumin	Curcuminoids	Curcuma longa [136]	Steatosis	FAO [137]
			Fibrosis/DILI/ALD	NRF-2, GSH, HSC activation [137]

4. Conclusions

The supplementation with polyphenols has an effect in treating liver pathologies: non-alcoholic fatty liver disease, drug-induced liver injury, hepatocellular carcinoma and alcoholic liver disease. The inclusion of polyphenol-rich foods is an attractive approach when developing a nutritional program. Authorities should encourage their consumption. Polyphenols and other micronutrients are essential for an equilibrated diet, where variety is an essential feature.

References

1. Yasutake, K.; Kohjima, M.; Kotoh, K.; Nakashima, M.; Nakamuta, M.; Enjoji, M. Dietary habits and behaviors associated with nonalcoholic fatty liver disease. *World J. Gastroenterol.* **2014**, *20*, 1756–1767. [CrossRef]

2. Micha, R.; Shulkin, M.L.; Peñalvo, J.L.; Khatibzadeh, S.; Singh, G.M.; Rao, M.; Fahimi, S.; Powles, J.; Mozaffarian, D. Etiologic effects and optimal intakes of foods and nutrients for risk of cardiovascular diseases and diabetes: Systematic reviews and meta-analyses from the Nutrition and Chronic Diseases Expert Group (NutriCoDE). *PLoS ONE* **2017**, *12*, e0175149. [CrossRef]

3. Tarasenko, T.N.; McGuire, P.J. The liver is a metabolic and immunologic organ: A reconsideration of metabolic decompensation due to infection in inborn errors of metabolism (IEM). *Mol. Genet. Metab.* **2017**, *121*, 283–288. [CrossRef]

4. Vernon, G.; Baranova, A.; Younossi, Z.M. Systematic review: The epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment. Pharmacol. Ther.* **2011**, *34*, 274–285. [CrossRef]

5. Younossi, Z.M.; Koenig, A.B.; Abdelatif, D.; Fazel, Y.; Henry, L.; Wymer, M. Global epidemiology of nonalcoholic fatty liver disease—Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* **2016**, *64*, 73–84. [CrossRef]

6. Loomba, R.; Sanyal, A.J. The global NAFLD epidemic. *Nat. Rev. Gastroenterol. Hepatol.* **2013**, *10*, 686–690. [CrossRef]

7. Mishra, A.; Younossi, Z.M. Epidemiology and Natural History of Non-alcoholic Fatty Liver Disease. *J. Clin. Exp. Hepatol.* **2012**, *2*, 135–144. [CrossRef]

8. Adams, L.A.; Lymp, J.F.; St. Sauver, J.; Sanderson, S.O.; Lindor, K.D.; Feldstein, A.; Angulo, P. The natural history of nonalcoholic fatty liver disease: A population-based cohort study. *Gastroenterology* **2005**, *129*, 113–121. [CrossRef]

9. Day, C.P. From fat to inflammation. *Gastroenterology* **2006**, *130*, 207–210. [CrossRef]

10. Noureddin, M.; Rinella, M.E. Nonalcoholic Fatty Liver Disease, Diabetes, Obesity, and Hepatocellular Carcinoma. *Clin. Liver Dis.* **2015**, *19*, 361–379. [CrossRef]

11. Neuschwander-Tetri, B.A. Hepatic lipotoxicity and the pathogenesis of nonalcoholic steatohepatitis: The central role of nontriglyceride fatty acid metabolites. *Hepatology* **2010**, *52*, 774–788. [CrossRef]

12. Eslam, M.; Sanyal, A.J.; George, J. MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease. *Gastroenterology* **2020**, *158*, 1999–2014. [CrossRef]

13. Friedman, S.L. Mechanisms of hepatic fibrogenesis. *Gastroenterology* **2008**, *134*, 1655–1669. [CrossRef]

14. Kim, E.; Lisby, A.; Ma, C.; Lo, N.; Ehmer, U.; Hayer, K.E.; Furth, E.E.; Viatour, P. Promotion of growth factor signaling as a critical function of β-catenin during HCC progression. *Nat. Commun.* **2019**, *10*. [CrossRef]

15. David, S.; Hamilton, J.P. Drug-induced Liver Injury. *US Gastroenterol. Hepatol.* **2010**, *6*, 73–80.

16. He, Y.; Jin, L.; Wang, J.; Yan, Z.; Chen, T.; Zhao, Y. Mechanisms of fibrosis in acute liver failure. *Liver Int.* **2015**, *35*, 1877–1885. [CrossRef]

17. Giordano, C.; Rivas, J.; Zervos, X. An Update on Treatment of Drug-Induced Liver Injury. *J. Clin. Transl. Hepatol.* **2014**, *2*, 74–79.

18. Bell, L.N.; Chalasani, N. Epidemiology of idiosyncratic drug-induced liver injury. *Semin. Liver Dis.* **2009**, *29*, 337–347. [CrossRef]

19. Ye, H.; Nelson, L.J.; Gómez Del Moral, M.; Martínez-Naves, E.; Cubero, F.J. Dissecting the molecular pathophysiology of drug-induced liver injury. *World J. Gastroenterol.* **2018**, *24*, 1373–1385. [CrossRef]

20. Bajt, M.L.; Ramachandran, A.; Yan, H.-M.; Lebofsky, M.; Farhood, A.; Lemasters, J.J.; Jaeschke, H. Apoptosis-Inducing Factor Modulates Mitochondrial Oxidant Stress in Acetaminophen Hepatotoxicity. *Toxicol. Sci.* **2011**, *122*, 598–605. [CrossRef]

21. Jaeschke, H.; Duan, L.; Akakpo, J.Y.; Farhood, A.; Ramachandran, A. The role of apoptosis in acetaminophen hepatotoxicity. *Food Chem. Toxicol.* **2018**, *118*, 709–718. [CrossRef] [PubMed]

22. Cao, L.; Quan, X.-B.; Zeng, W.-J.; Yang, X.-O.; Wang, M.-J. Mechanism of Hepatocyte Apoptosis. *J. Cell Death* **2016**, *9*, 19–29. [CrossRef] [PubMed]

23. Basra, S.; Anand, B.S. Definition, epidemiology and magnitude of alcoholic hepatitis. *World J. Hepatol.* **2011**, *3*, 108–113. [CrossRef] [PubMed]

24. Osna, N.A.; Donohue, T.M., Jr.; Kharbanda, K.K. Alcoholic Liver Disease: Pathogenesis and Current Management. *Alcohol Res.* **2017**, *38*, 147–161.

25. Asrani, S.K.; Devarbhavi, H.; Eaton, J.; Kamath, P.S. Burden of liver diseases in the world. *J. Hepatol.* **2019**, *70*, 151–171. [CrossRef]

26. Finicelli, M.; Squillaro, T.; Di Cristo, F.; Di Salle, A.; Melone, M.A.B.; Galderisi, U.; Peluso, G. Metabolic syndrome, Mediterranean diet, and polyphenols: Evidence and perspectives. *J. Cell. Physiol.* **2019**, *234*, 5807–5826. [CrossRef]

27. Petrides, J.; Collins, P.; Kowalski, A.; Sepede, J.; Vermeulen, M. Lifestyle Changes for Disease Prevention. *Prim. Care* **2019**, *46*, 1–12. [CrossRef]

28. Al-Dashti, Y.A.; Holt, R.R.; Stebbins, C.L.; Keen, C.L.; Hackman, R.M. Dietary Flavanols: A Review of Select Effects on Vascular Function, Blood Pressure, and Exercise Performance. *J. Am. Coll. Nutr.* **2018**, *37*, 553–567. [CrossRef]

29. Li, A.-N.; Li, S.; Zhang, Y.-J.; Xu, X.-R.; Chen, Y.-M.; Li, H.-B. Resources and biological activities of natural polyphenols. *Nutrients* **2014**, *6*, 6020–6047. [CrossRef]

30. Nguyen, N.U.; Stamper, B.D. Polyphenols reported to shift APAP-induced changes in MAPK signaling and toxicity outcomes. *Chem. Biol. Interact.* **2017**, *277*, 129–136. [CrossRef]

31. Manach, C.; Scalbert, A.; Morand, C.; Rémésy, C.; Jiménez, L. Polyphenols: Food sources and bioavailability. *Am. J. Clin. Nutr.* **2004**, *79*, 727–747. [CrossRef] [PubMed]

32. Li, S.; Tan, H.Y.; Wang, N.; Cheung, F.; Hong, M.; Feng, Y. The Potential and Action Mechanism of Polyphenols in the Treatment of Liver Diseases. *Oxid. Med. Cell. Longev.* **2018**, *2018*. [CrossRef] [PubMed]

33. Lee, H.J.; Kang, M.-G.; Cha, H.Y.; Kim, Y.M.; Lim, Y.; Yang, S.J. Effects of Piceatannol and Resveratrol on Sirtuins and Hepatic Inflammation in High-Fat Diet-Fed Mice. *J. Med. Food* **2019**, *22*, 833–840. [CrossRef] [PubMed]

34. Burns, J.; Yokota, T.; Ashihara, H.; Lean, M.E.J.; Crozier, A. Plant foods and herbal sources of resveratrol. *J. Agric. Food Chem.* **2002**, *50*, 3337–3340. [CrossRef]

35. Bishayee, A.; Darvesh, A.S.; Politis, T.; McGory, R. Resveratrol and liver disease: From bench to bedside and community. *Liver Int.* **2010**, *30*, 1103–1114. [CrossRef]

36. Peiyuan, H.; Zhiping, H.; Chengjun, S.; Chunqing, W.; Bingqing, L.; Imam, M.U. Resveratrol Ameliorates Experimental Alcoholic Liver Disease by Modulating Oxidative Stress. *Evidence-Based Complement. Altern. Med.* **2017**, *2017*. [CrossRef]

37. Andrade, J.M.O.; Paraíso, A.F.; de Oliveira, M.V.M.; Martins, A.M.E.; Neto, J.F.; Guimarães, A.L.S.; de Paula, A.M.; Qureshi, M.; Santos, S.H.S. Resveratrol attenuates hepatic steatosis in high-fat fed mice by decreasing lipogenesis and inflammation. *Nutrition* **2014**, *30*, 915–919. [CrossRef]

38. Paul, S.; DeCastro, A.J.; Lee, H.J.; Smolarek, A.K.; So, J.Y.; Simi, B.; Wang, C.X.; Zhou, R.; Rimando, A.M.; Suh, N. Dietary intake of pterostilbene, a constituent of blueberries, inhibits the beta-catenin/p65 downstream signaling pathway and colon carcinogenesis in rats. *Carcinogenesis* **2010**, *31*, 1272–1278. [CrossRef]

39. Aguirre, L.; Palacios-ortega, S.; Fernández-Quintela, A.; Hijona, E.; Bujanda, L.; Portillo, M.P. Pterostilbene reduces liver steatosis and modifies hepatic fatty acid profile in obese rats. *Nutrients* **2019**, *11*, 961. [CrossRef]

40. Gomez-Zorita, S.; Milton-Laskibar, I.; Aguirre, L.; Fernandez-Quintela, A.; Xiao, J.; Portillo, M.P. Effects of Pterostilbene on Diabetes, Liver Steatosis and Serum Lipids. *Curr. Med. Chem.* **2019**. [CrossRef]

41. Matsui, Y.; Sugiyama, K.; Kamei, M.; Takahashi, T.; Suzuki, T.; Katagata, Y.; Ito, T. Extract of passion fruit (Passiflora edulis) seed containing high amounts of piceatannol inhibits melanogenesis and promotes collagen synthesis. *J. Agric. Food Chem.* **2010**, *58*, 11112–11118. [CrossRef] [PubMed]

42. Tung, Y.-C.; Lin, Y.-H.; Chen, H.-J.; Chou, S.-C.; Cheng, A.-C.; Kalyanam, N.; Ho, C.-T.; Pan, M.-H. Piceatannol Exerts Anti-Obesity Effects in C57BL/6 Mice through Modulating Adipogenic Proteins and Gut Microbiota. *Molecules* **2016**, *21*, 1419. [CrossRef] [PubMed]

43. Zubiete-Franco, I.; Garcia-Rodriguez, J.L.; Martinez-Una, M.; Martinez-Lopez, N.; Woodhoo, A.; Juan, V.G.-D.; Beraza, N.; Lage-Medina, S.; Andrade, F.; Fernandez, M.L.; et al. Methionine and S-adenosylmethionine levels are critical regulators of PP2A activity modulating lipophagy during steatosis. *J. Hepatol.* **2016**, *64*, 409–418. [CrossRef] [PubMed]

44. Faghihzadeh, F.; Adibi, P.; Rafiei, R.; Hekmatdoost, A. Resveratrol supplementation improves inflammatory biomarkers in patients with nonalcoholic fatty liver disease. *Nutr. Res.* **2014**, *34*, 837–843. [CrossRef] [PubMed]

45. Hosseinian, F.S.; Beta, T. Saskatoon and wild blueberries have higher anthocyanin contents than other Manitoba berries. *J. Agric. Food Chem.* **2007**, *55*, 10832–10838. [CrossRef]

46. Watson, R.R.; Schönlau, F. Nutraceutical and antioxidant effects of a delphinidin-rich maqui berry extract Delphinol®: A review. *Minerva Cardioangiol.* **2015**, *63*, 1–12.

47. Parra-Vargas, M.; Sandoval-Rodriguez, A.; Rodriguez-Echevarria, R.; Dominguez-Rosales, J.A.; Santos-Garcia, A.; Armendariz-Borunda, J. Delphinidin ameliorates hepatic triglyceride accumulation in human HepG2 cells, but not in diet-induced obese mice. *Nutrients* **2018**, *10*, 1060. [CrossRef]

48. Domitrovic, R.; Jakovac, H. Antifibrotic activity of anthocyanidin delphinidin in carbon tetrachloride-induced hepatotoxicity in mice. *Toxicology* **2010**, *272*, 1–10. [CrossRef]

49. Lee, W.; Lee, Y.; Kim, J.; Bae, J.-S. Protective Effects of Pelargonidin on Lipopolysaccharide-induced Hepatic Failure. *Nat. Prod. Commun.* **2018**, *13*, 1934578X1801300114. [CrossRef]

50. Andersen, Ø; Jordheim, M. Basic Anthocyanin Chemistry and Dietary Source. In *Anthocyanins in Health and Disease*; CRC Press: Boca Raton, FL, USA, 2013; pp. 13–90. ISBN 9781439894712.

51. Park, S.; Kang, S.; Jeong, D.-Y.Y.; Jeong, S.-Y.Y.; Park, J.J.; Yun, H.S. Cyanidin and malvidin in aqueous extracts of black carrots fermented with Aspergillus oryzae prevent the impairment of energy, lipid and glucose metabolism in estrogen-deficient rats by AMPK activation. *Genes Nutr.* **2015**, *10*, 455. [CrossRef]

52. Bendia, E.; Benedetti, A.; Baroni, G.S.; Candelaresi, C.; Macarri, G.; Trozzi, L.; Di Sario, A. Effect of cyanidin 3-O-beta-glucopyranoside on hepatic stellate cell proliferation and collagen synthesis induced by oxidative stress. *Dig. Liver Dis.* **2005**, *37*, 342–348. [CrossRef] [PubMed]

53. Zhu, W.; Jia, Q.; Wang, Y.; Zhang, Y.; Xia, M. The anthocyanin cyanidin-3-O-beta-glucoside, a flavonoid, increases hepatic glutathione synthesis and protects hepatocytes against reactive oxygen species during hyperglycemia: Involvement of a cAMP-PKA-dependent signaling pathway. *Free Radic. Biol. Med.* **2012**, *52*, 314–327. [CrossRef] [PubMed]

54. Wan, T.; Wang, S.; Ye, M.; Ling, W.; Yang, L. Cyanidin-3-O-β-glucoside protects against liver fibrosis induced by alcohol via regulating energy homeostasis and AMPK/autophagy signaling pathway. *J. Funct. Foods* **2017**, *37*, 16–24. [CrossRef]

55. Tulio, A.Z.J.; Reese, R.N.; Wyzgoski, F.J.; Rinaldi, P.L.; Fu, R.; Scheerens, J.C.; Miller, A.R. Cyanidin 3-rutinoside and cyanidin 3-xylosylrutinoside as primary phenolic antioxidants in black raspberry. *J. Agric. Food Chem.* **2008**, *56*, 1880–1888. [CrossRef] [PubMed]

56. Wang, Y.; Lin, J.; Tian, J.; Si, X.; Jiao, X.; Zhang, W.; Gong, E.; Li, B. Blueberry Malvidin-3-galactoside Suppresses Hepatocellular Carcinoma by Regulating Apoptosis, Proliferation, and Metastasis Pathways In Vivo and In Vitro. *J. Agric. Food Chem.* **2019**, *67*, 625–636. [CrossRef]

57. Jaramillo Flores, M.E. Cocoa Flavanols: Natural Agents with Attenuating Effects on Metabolic Syndrome Risk Factors. *Nutrients* **2019**, *11*, 751. [CrossRef] [PubMed]

58.   Dower, J.I.; Geleijnse, J.M.; Kroon, P.A.; Philo, M.; Mensink, M.; Kromhout, D.; Hollman, P.C.H. Does epicatechin contribute to the acute vascular function effects of dark chocolate? A randomized, crossover study. *Mol. Nutr. Food Res.* **2016**, *60*, 2379–2386. [CrossRef] [PubMed]

59.   Cheng, H.; Xu, N.; Zhao, W.; Su, J.; Liang, M.; Xie, Z.; Wu, X.; Li, Q. (-)-Epicatechin regulates blood lipids and attenuates hepatic steatosis in rats fed high-fat diet. *Mol. Nutr. Food Res.* **2017**, *61*, 1700303. [CrossRef]

60.   Huang, Z.; Jing, X.; Sheng, Y.; Zhang, J.; Hao, Z.; Wang, Z.; Ji, L. (-)-Epicatechin attenuates hepatic sinusoidal obstruction syndrome by inhibiting liver oxidative and inflammatory injury. *Redox Biol.* **2019**, *22*, 101117. [CrossRef]

61.   Naumovski, N.; Blades, B.L.; Roach, P.D. Food Inhibits the Oral Bioavailability of the Major Green Tea Antioxidant Epigallocatechin Gallate in Humans. *Antioxidants* **2015**, *4*, 373–393. [CrossRef]

62.   Chen, C.; Liu, Q.; Liu, L.; Hu, Y.Y.; Feng, Q. Potential Biological Effects of (-)-Epigallocatechin-3-gallate on the Treatment of Nonalcoholic Fatty Liver Disease. *Mol. Nutr. Food Res.* **2018**, *62*, 1–11. [CrossRef] [PubMed]

63.   Tipoe, G.L.; Leung, T.M.; Liong, E.C.; Lau, T.Y.H.; Fung, M.L.; Nanji, A.A. Epigallocatechin-3-gallate (EGCG) reduces liver inflammation, oxidative stress and fibrosis in carbon tetrachloride (CCl4)-induced liver injury in mice. *Toxicology* **2010**, *273*, 45–52. [CrossRef] [PubMed]

64.   Yao, H.T.; Li, C.C.; Chang, C.H. Epigallocatechin-3-gallate reduces hepatic oxidative stress and lowers cyp-mediated bioactivation and toxicity of acetaminophen in rats. *Nutrients* **2019**, *11*, 1862. [CrossRef] [PubMed]

65.   Bimonte, S.; Albino, V.; Piccirillo, M.; Nasto, A.; Molino, C.; Palaia, R.; Cascella, M. Epigallocatechin-3-gallate in the prevention and treatment of hepatocellular carcinoma: Experimental findings and translational perspectives. *Drug Des. Devel. Ther.* **2019**, *13*, 611–621. [CrossRef]

66.   Dai, N.; Zou, Y.; Zhu, L.; Wang, H.F.; Dai, M.G. Antioxidant properties of proanthocyanidins attenuate carbon tetrachloride (CCl4)-induced steatosis and liver injury in rats via CYP2E1 regulation. *J. Med. Food* **2014**, *17*, 663–669. [CrossRef]

67.   Wang, Z.; Su, B.; Fan, S.; Fei, H.; Zhao, W. Protective effect of oligomeric proanthocyanidins against alcohol-induced liver steatosis and injury in mice. *Biochem. Biophys. Res. Commun.* **2015**, *458*, 757–762. [CrossRef]

68.   Miltonprabu, S.; Nazimabashir; Manoharan, V. Hepatoprotective effect of grape seed proanthocyanidins on Cadmium-induced hepatic injury in rats: Possible involvement of mitochondrial dysfunction, inflammation and apoptosis. *Toxicol. Rep.* **2016**, *3*, 63–77. [CrossRef]

69.   Hammerstone, J.F.; Lazarus, S.A.; Schmitz, H.H. Procyanidin content and variation in some commonly consumed foods. *J. Nutr.* **2000**, *130*, 2086S–2092S. [CrossRef]

70.   Habtemariam, S. The Nrf2/HO-1 Axis as Targets for Flavanones: Neuroprotection by Pinocembrin, Naringenin, and Eriodictyol. *Oxid. Med. Cell. Longev.* **2019**, *2019*, 4724920. [CrossRef]

71.   Guedon, D.J.; Pasquier, B.P. Analysis and Distribution of Flavonoid Glycosides and Rosmarinic Acid in 40 Mentha x piperita Clones. *J. Agric. Food Chem.* **1994**, *42*, 679–684. [CrossRef]

72.   Ooghe, W.C.; Detavernier, C.M. Detection of the Addition of Citrus reticulata and Hybrids to Citrus sinensis by Flavonoids. *J. Agric. Food Chem.* **1997**, *45*, 1633–1637. [CrossRef]

73.   Çetin, A.; Çiftçi, O.; Otlu, A. Protective effect of hesperidin on oxidative and histological liver damage following carbon tetrachloride administration in Wistar rats. *Arch. Med. Sci.* **2016**, *12*, 486–493. [CrossRef] [PubMed]

74.   Pari, L.; Karthikeyan, A.; Karthika, P.; Rathinam, A. Protective effects of hesperidin on oxidative stress, dyslipidaemia and histological changes in iron-induced hepatic and renal toxicity in rats. *Toxicol. Rep.* **2015**, *2*, 46–55. [CrossRef] [PubMed]

75.   Lin, L.-Z.; Mukhopadhyay, S.; Robbins, R.J.; Harnly, J.M. Identification and quantification of flavonoids of Mexican oregano (*Lippia graveolens*) by LC-DAD-ESI/MS analysis. *J. Food Compos. Anal. Off. Publ. United Nations Univ. Int. Netw. Food Data Syst.* **2007**, *20*, 361–369. [CrossRef] [PubMed]

76.   Ahmed, O.M.; Fahim, H.I.; Ahmed, H.Y.; Al-Muzafar, H.M.; Ahmed, R.R.; Amin, K.A.; El-Nahass, E.S.; Abdelazeem, W.H. The preventive effects and the mechanisms of action of navel orange peel hydroethanolic extract, naringin, and naringenin in N-Acetyl-p-aminophenol-induced liver injury in wistar rats. *Oxid. Med. Cell. Longev.* **2019**, *2019*. [CrossRef]

77.   Hernández-Aquino, E.; Muriel, P. Beneficial effects of naringenin in liver diseases: Molecular mechanisms. *World J. Gastroenterol.* **2018**, *24*, 1679–1707. [CrossRef]

78. Li, Y.; Yao, J.; Han, C.; Yang, J.; Chaudhry, M.T.; Wang, S.; Liu, H.; Yin, Y. Quercetin, Inflammation and Immunity. *Nutrients* **2016**, *8*, 167. [CrossRef]

79. Chen, X. Protective effects of quercetin on liver injury induced by ethanol. *Pharmacogn. Mag.* **2010**, *6*, 135–141. [CrossRef]

80. Somerset, S.M.; Johannot, L. Dietary flavonoid sources in Australian adults. *Nutr. Cancer* **2008**, *60*, 442–449. [CrossRef]

81. Zhu, G.; Liu, X.; Li, H.; Yan, Y.; Hong, X.; Lin, Z. Kaempferol inhibits proliferation, migration, and invasion of liver cancer HepG2 cells by down-regulation of microRNA-21. *Int. J. Immunopathol. Pharmacol.* **2018**, *32*. [CrossRef]

82. Wang, M.; Sun, J.; Jiang, Z.; Xie, W.; Zhang, X. Hepatoprotective effect of kaempferol against alcoholic liver injury in mice. *Am. J. Chin. Med.* **2015**, *43*, 241–254. [CrossRef] [PubMed]

83. Xu, T.; Huang, S.; Huang, Q.; Ming, Z.; Wang, M.; Li, R.; Zhao, Y. Kaempferol attenuates liver fibrosis by inhibiting activin receptor–like kinase 5. *J. Cell. Mol. Med.* **2019**, *23*, 6403–6410. [CrossRef] [PubMed]

84. Semwal, D.K.; Semwal, R.B.; Combrinck, S.; Viljoen, A. Myricetin: A Dietary Molecule with Diverse Biological Activities. *Nutrients* **2016**, *8*, 90. [CrossRef] [PubMed]

85. Xia, S.F.; Le, G.W.; Wang, P.; Qiu, Y.Y.; Jiang, Y.Y.; Tang, X. Regressive effect of myricetin on hepatic steatosis in mice fed a high-fat diet. *Nutrients* **2016**, *8*, 799. [CrossRef] [PubMed]

86. Li, M.; Chen, J.; Yu, X.; Xu, S.; Li, D.; Zheng, Q.; Yin, Y. Myricetin Suppresses the Propagation of Hepatocellular Carcinoma via Down-Regulating Expression of YAP. *Cells* **2019**, *8*, 358. [CrossRef] [PubMed]

87. Ganbold, M.; Owada, Y.; Ozawa, Y.; Shimamoto, Y.; Ferdousi, F.; Tominaga, K.; Zheng, Y.W.; Ohkohchi, N.; Isoda, H. Isorhamnetin Alleviates Steatosis and Fibrosis in Mice with Nonalcoholic Steatohepatitis. *Sci. Rep.* **2019**, *9*, 1–11. [CrossRef]

88. Igarashi, K.; Ohmuma, M. Effects of isorhamnetin, rhamnetin, and quercetin on the concentrations of cholesterol and lipoperoxide in the serum and liver and on the blood and liver antioxidative enzyme activities of rats. *Biosci. Biotechnol. Biochem.* **1995**, *59*, 595–601. [CrossRef]

89. Yang, J.H.; Kim, S.C.; Kim, K.M.; Jang, C.H.; Cho, S.S.; Kim, S.J.; Ku, S.K.; Cho, I.J.; Ki, S.H. Isorhamnetin attenuates liver fibrosis by inhibiting TGF-beta/Smad signaling and relieving oxidative stress. *Eur. J. Pharmacol.* **2016**, *783*, 92–102. [CrossRef]

90. Huang, H.; Chen, A.Y.; Ye, X.; Guan, R.; Rankin, G.O.; Chen, Y.C. Galangin, a Flavonoid from Lesser Galangal, Induced Apoptosis via p53-Dependent Pathway in Ovarian Cancer Cells. *Molecules* **2020**, *25*, 1579. [CrossRef]

91. Aladaileh, S.H.; Abukhalil, M.H.; Saghir, S.A.M.; Hanieh, H.; Alfwuaires, M.A.; Almaiman, A.A.; Bin-Jumah, M.; Mahmoud, A.M. Galangin activates Nrf2 signaling and attenuates oxidative damage, inflammation, and apoptosis in a rat model of cyclophosphamide-induced hepatotoxicity. *Biomolecules* **2019**, *9*, 346. [CrossRef]

92. Su, L.; Chen, X.; Wu, J.; Lin, B.; Zhang, H.; Lan, L.; Luo, H. Galangin inhibits proliferation of hepatocellular carcinoma cells by inducing endoplasmic reticulum stress. *Food Chem. Toxicol.* **2013**, *62*, 810–816. [CrossRef] [PubMed]

93. Hostetler, G.L.; Ralston, R.A.; Schwartz, S.J. Flavones: Food Sources, Bioavailability, Metabolism, and Bioactivity. *Adv. Nutr.* **2017**, *8*, 423–435. [CrossRef] [PubMed]

94. Wang, F.; Liu, J.-C.; Zhou, R.-J.; Zhao, X.; Liu, M.; Ye, H.; Xie, M.-L. Apigenin protects against alcohol-induced liver injury in mice by regulating hepatic CYP2E1-mediated oxidative stress and PPARalpha-mediated lipogenic gene expression. *Chem. Biol. Interact.* **2017**, *275*, 171–177. [CrossRef] [PubMed]

95. Tsaroucha, A.K.; Tsiaousidou, A.; Ouzounidis, N.; Tsalkidou, E.; Lambropoulou, M.; Giakoustidis, D.; Chatzaki, E.; Simopoulos, C. Intraperitoneal administration of apigenin in liver ischemia/reperfusion injury protective effects. *Saudi J. Gastroenterol.* **2016**, *22*, 415–422. [PubMed]

96. Jung, U.J.; Cho, Y.-Y.; Choi, M.-S. Apigenin Ameliorates Dyslipidemia, Hepatic Steatosis and Insulin Resistance by Modulating Metabolic and Transcriptional Profiles in the Liver of High-Fat Diet-Induced Obese Mice. *Nutrients* **2016**, *8*, 305. [CrossRef]

97. Balam, F.H.; Ahmadi, Z.S.; Ghorbani, A. Inhibitory effect of chrysin on estrogen biosynthesis by suppression of enzyme aromatase (CYP19): A systematic review. *Heliyon* **2020**, *6*, e03557. [CrossRef]

98. Pai, S.A.; Munshi, R.P.; Panchal, F.H.; Gaur, I.-S.; Juvekar, A.R. Chrysin ameliorates nonalcoholic fatty liver disease in rats. *Naunyn. Schmiedebergs. Arch. Pharmacol.* **2019**, *392*, 1617–1628. [CrossRef]

99. Balta, C.; Ciceu, A.; Herman, H.; Rosu, M.; Boldura, O.M.; Hermenean, A. Dose-dependent antifibrotic effect of chrysin on regression of liver fibrosis: The role in extracellular matrix remodeling. *Dose-Response* **2018**, *16*, 1–8. [CrossRef]

100. Lin, Y.; Shi, R.; Wang, X.; Shen, H.-M. Luteolin, a flavonoid with potential for cancer prevention and therapy. *Curr. Cancer Drug Targets* **2008**, *8*, 634–646. [CrossRef]

101. Tai, M.; Zhang, J.; Song, S.; Miao, R.; Liu, S.; Pang, Q.; Wu, Q.; Liu, C. Protective effects of luteolin against acetaminophen-induced acute liver failure in mouse. *Int. Immunopharmacol.* **2015**, *27*, 164–170. [CrossRef]

102. Zhang, H.; Tan, X.; Yang, D.; Lu, J.; Liu, B.; Baiyun, R.; Zhang, Z. Dietary luteolin attenuates chronic liver injury induced by mercuric chloride via the Nrf2/NF-κB/P53 signaling pathway in rats. *Oncotarget* **2017**, *8*, 40982–40993. [CrossRef] [PubMed]

103. Liu, G.; Zhang, Y.; Liu, C.; Xu, D.; Zhang, R.; Cheng, Y.; Pan, Y.; Huang, C.; Chen, Y. Luteolin alleviates alcoholic liver disease induced by chronic and binge ethanol feeding in mice. *J. Nutr.* **2014**, *144*, 1009–1015. [CrossRef] [PubMed]

104. Ritchie, M.R.; Cummings, J.H.; Morton, M.S.; Steel, C.M.; Bolton-Smith, C.; Riches, A.C. A newly constructed and validated isoflavone database for the assessment of total genistein and daidzein intake. *Br. J. Nutr.* **2006**, *95*, 204–213. [CrossRef] [PubMed]

105. Xin, X.; Chen, C.; Hu, Y.-Y.; Feng, Q. Protective effect of genistein on nonalcoholic fatty liver disease (NAFLD). *Biomed. Pharmacother.* **2019**, *117*, 109047. [CrossRef]

106. Yin, Y.; Liu, H.; Zheng, Z.; Lu, R.; Jiang, Z. Genistein can ameliorate hepatic inflammatory reaction in nonalcoholic steatohepatitis rats. *Biomed. Pharmacother.* **2019**, *111*, 1290–1296. [CrossRef]

107. Kuzu, N.; Metin, K.; Dagli, A.F.; Akdemir, F.; Orhan, C.; Yalniz, M.; Ozercan, I.H.; Sahin, K.; Bahcecioglu, I.H. Protective role of genistein in acute liver damage induced by carbon tetrachloride. *Mediators Inflamm.* **2007**, *2007*. [CrossRef]

108. Takahashi, Y.; Odbayar, T.O.; Ide, T. A comparative analysis of genistein and daidzein in affecting lipid metabolism in rat liver. *J. Clin. Biochem. Nutr.* **2009**, *44*, 223–230. [CrossRef]

109. Kim, M.-H.; Park, J.-S.; Jung, J.-W.; Byun, K.-W.; Kang, K.-S.; Lee, Y.-S. Daidzein supplementation prevents non-alcoholic fatty liver disease through alternation of hepatic gene expression profiles and adipocyte metabolism. *Int. J. Obes. (Lond.)* **2011**, *35*, 1019–1030. [CrossRef]

110. Cheraghpour, M.; Imani, H.; Ommi, S.; Alavian, S.M.; Karimi-Shahrbabak, E.; Hedayati, M.; Yari, Z.; Hekmatdoost, A. Hesperidin improves hepatic steatosis, hepatic enzymes, and metabolic and inflammatory parameters in patients with nonalcoholic fatty liver disease: A randomized, placebo-controlled, double-blind clinical trial. *Phytother. Res.* **2019**, *33*, 2118–2125. [CrossRef]

111. Nahmias, Y.; Goldwasser, J.; Casali, M.; van Poll, D.; Wakita, T.; Chung, R.T.; Yarmush, M.L. Apolipoprotein B-dependent hepatitis C virus secretion is inhibited by the grapefruit flavonoid naringenin. *Hepatology* **2008**, *47*, 1437–1445. [CrossRef]

112. Gonzalez, O.; Fontanes, V.; Raychaudhuri, S.; Loo, R.; Loo, J.; Arumugaswami, V.; Sun, R.; Dasgupta, A.; French, S.W. The heat shock protein inhibitor Quercetin attenuates hepatitis C virus production. *Hepatology* **2009**, *50*, 1756–1764. [CrossRef] [PubMed]

113. Kumar, N.; Goel, N. Phenolic acids: Natural versatile molecules with promising therapeutic applications. *Biotechnol. Rep. (Amsterdam, Netherlands)* **2019**, *24*, e00370. [CrossRef] [PubMed]

114. Kang, I.; Buckner, T.; Shay, N.F.; Gu, L.; Chung, S. Improvements in Metabolic Health with Consumption of Ellagic Acid and Subsequent Conversion into Urolithins: Evidence and Mechanisms. *Adv. Nutr.* **2016**, *7*, 961–972. [CrossRef] [PubMed]

115. Chen, P.; Chen, F.; Zhou, B. Antioxidative, anti-inflammatory and anti-apoptotic effects of ellagic acid in liver and brain of rats treated by D-galactose. *Sci. Rep.* **2018**, *8*, 2–11. [CrossRef]

116. Kapan, M.; Gumus, M.; Onder, A.; Firat, U.; Basarali, M.K.; Boyuk, A.; Aliosmanoglu, I.; Buyukbas, S. The effects of ellagic acid on the liver and remote organs' oxidative stress and structure after hepatic ischemia reperfusion injury caused by pringle maneuver in rats. *Bratisl. Lek. Listy* **2012**, *113*, 274–281. [CrossRef]

117. Aslan, A.; Gok, O.; Erman, O.; Kuloglu, T. Ellagic acid impedes carbontetrachloride-induced liver damage in rats through suppression of NF-kB, Bcl-2 and regulating Nrf-2 and caspase pathway. *Biomed. Pharmacother.* **2018**, *105*, 662–669. [CrossRef]

118. Setayesh, T.; Nersesyan, A.; Mišík, M.; Noorizadeh, R.; Haslinger, E.; Javaheri, T.; Lang, E.; Grusch, M.; Huber, W.; Haslberger, A.; et al. Gallic acid, a common dietary phenolic protects against high fat diet induced DNA damage. *Eur. J. Nutr.* **2019**, *58*, 2315–2326. [CrossRef]

119. Rasool, M.K.; Sabina, E.P.; Ramya, S.R.; Preety, P.; Patel, S.; Mandal, N.; Mishra, P.P.; Samuel, J. Hepatoprotective and antioxidant effects of gallic acid in paracetamol-induced liver damage in mice. *J. Pharm. Pharmacol.* **2010**, *62*, 638–643. [CrossRef]

120. Bayramoglu, G.; Kurt, H.; Bayramoglu, A.; Gunes, H.V.; Degirmenci, İ.; Colak, S. Preventive role of gallic acid on hepatic ischemia and reperfusion injury in rats. *Cytotechnology* **2015**, *67*, 845–849. [CrossRef]

121. El-Lakkany, N.M.; El-Maadawy, W.H.; Seif el-Din, S.H.; Saleh, S.; Safar, M.M.; Ezzat, S.M.; Mohamed, S.H.; Botros, S.S.; Demerdash, Z.; Hammam, O.A. Antifibrotic effects of gallic acid on hepatic stellate cells: In vitro and in vivo mechanistic study. *J. Tradit. Complement. Med.* **2019**, *9*, 45–53. [CrossRef]

122. Kumar, N.; Pruthi, V. Potential applications of ferulic acid from natural sources. *Biotechnol. Rep. (Amsterdam, Netherlands)* **2014**, *4*, 86–93. [CrossRef] [PubMed]

123. Mahmoud, A.M.; Hussein, O.E.; Hozayen, W.G.; Bin-Jumah, M.; Abd El-Twab, S.M. Ferulic acid prevents oxidative stress, inflammation, and liver injury via upregulation of Nrf2/HO-1 signaling in methotrexate-induced rats. *Environ. Sci. Pollut. Res.* **2020**, *27*, 7910–7921. [CrossRef] [PubMed]

124. Mu, M.; Zuo, S.; Wu, R.M.; Deng, K.S.; Lu, S.; Zhu, J.J.; Zou, G.L.; Yang, J.; Cheng, M.L.; Zhao, X.K. Ferulic acid attenuates liver fibrosis and hepatic stellate cell activation via inhibition of TGF-β/Smad signaling pathway. *Drug Des. Dev. Ther.* **2018**, *12*, 4107–4115. [CrossRef] [PubMed]

125. Nabavi, S.F.; Tejada, S.; Setzer, W.N.; Gortzi, O.; Sureda, A.; Braidy, N.; Daglia, M.; Manayi, A.; Nabavi, S.M. Chlorogenic Acid and Mental Diseases: From Chemistry to Medicine. *Curr. Neuropharmacol.* **2017**, *15*, 471–479. [CrossRef] [PubMed]

126. Shi, H.; Dong, L.; Jiang, J.; Zhao, J.; Zhao, G.; Dang, X.; Lu, X.; Jia, M. Chlorogenic acid reduces liver inflammation and fibrosis through inhibition of toll-like receptor 4 signaling pathway. *Toxicology* **2013**, *303*, 107–114. [CrossRef] [PubMed]

127. Kim, H.; Pan, J.H.; Kim, S.H.; Lee, J.H.; Park, J.-W. Chlorogenic acid ameliorates alcohol-induced liver injuries through scavenging reactive oxygen species. *Biochimie* **2018**, *150*, 131–138. [CrossRef]

128. Barbaro, B.; Toietta, G.; Maggio, R.; Arciello, M.; Tarocchi, M.; Galli, A.; Balsano, C. Effects of the olive-derived polyphenol oleuropein on human health. *Int. J. Mol. Sci.* **2014**, *15*, 18508–18524. [CrossRef]

129. Jemai, H.; Mahmoudi, A.; Feryeni, A.; Fki, I.; Bouallagui, Z.; Choura, S.; Chamkha, M.; Sayadi, S. Hepatoprotective Effect of Oleuropein-Rich Extract from Olive Leaves against Cadmium-Induced Toxicity in Mice. *BioMed Res. Int.* **2020**, *2020*, 4398924. [CrossRef]

130. Park, S.; Choi, Y.; Um, S.-J.; Yoon, S.K.; Park, T. Oleuropein attenuates hepatic steatosis induced by high-fat diet in mice. *J. Hepatol.* **2011**, *54*, 984–993. [CrossRef]

131. Durazzo, A.; Lucarini, M.; Camilli, E.; Marconi, S.; Gabrielli, P.; Lisciani, S.; Gambelli, L.; Aguzzi, A.; Novellino, E.; Santini, A.; et al. Dietary Lignans: Definition, Description and Research Trends in Databases Development. *Molecules* **2018**, *23*, 3251. [CrossRef]

132. Sirato-Yasumoto, S.; Katsuta, M.; Okuyama, Y.; Takahashi, Y.; Ide, T. Effect of Sesame Seeds Rich in Sesamin and Sesamolin on Fatty Acid Oxidation in Rat Liver. *J. Agric. Food Chem.* **2001**, *49*, 2647–2651. [CrossRef] [PubMed]

133. Ide, T.; Ashakumary, L.; Takahashi, Y.; Kushiro, M.; Fukuda, N.; Sugano, M. Sesamin, a sesame lignan, decreases fatty acid synthesis in rat liver accompanying the down-regulation of sterol regulatory element binding protein-1. *Biochim. Biophys. Acta* **2001**, *1534*, 1–13. [CrossRef]

134. Frank, J.; Eliasson, C.; Leroy-Nivard, D.; Budek, A.; Lundh, T.; Vessby, B.; Aman, P.; Kamal-Eldin, A. Dietary secoisolariciresinol diglucoside and its oligomers with 3-hydroxy-3-methyl glutaric acid decrease vitamin E levels in rats. *Br. J. Nutr.* **2004**, *92*, 169–176. [CrossRef] [PubMed]

135. Felmlee, M.A.; Woo, G.; Simko, E.; Krol, E.S.; Muir, A.D.; Alcorn, J. Effects of the flaxseed lignans secoisolariciresinol diglucoside and its aglycone on serum and hepatic lipids in hyperlipidaemic rats. *Br. J. Nutr.* **2009**, *102*, 361–369. [CrossRef] [PubMed]

136. Maiti, P.; Dunbar, G.L. Use of Curcumin, a Natural Polyphenol for Targeting Molecular Pathways in Treating Age-Related Neurodegenerative Diseases. *Int. J. Mol. Sci.* **2018**, *19*, 1637. [CrossRef] [PubMed]

137. Farzaei, M.H.; Zobeiri, M.; Parvizi, F.; El-Senduny, F.F.; Marmouzi, I.; Coy-Barrera, E.; Naseri, R.; Nabavi, S.M.; Rahimi, R.; Abdollahi, M. Curcumin in Liver Diseases: A Systematic Review of the Cellular Mechanisms of Oxidative Stress and Clinical Perspective. *Nutrients* **2018**, *10*, 855. [CrossRef]

138. Rahmani, S.; Asgary, S.; Askari, G.; Keshvari, M.; Hatamipour, M.; Feizi, A.; Sahebkar, A. Treatment of Non-alcoholic Fatty Liver Disease with Curcumin: A Randomized Placebo-controlled Trial. *Phytother. Res.* **2016**, *30*, 1540–1548. [CrossRef]

139. Saklayen, M.G. The Global Epidemic of the Metabolic Syndrome. *Curr. Hypertens. Rep.* **2018**, *20*, 12. [CrossRef]