Systematic Review

A Systematic Review of the Beneficial Effects of Berry Extracts on Non-Alcoholic Fatty Liver Disease in Animal Models

Alejandro García-Beltrán [1], Aida Lozano Melero [1], Rosario Martínez Martínez [1], Jesús María Porres Foulquie [2], María López Jurado Romero de la Cruz [2], Garyfallia Kapravelou [3,*]

[1]Department of Physiology, Biomedical Research Center, Instituto mixto de Deporte y Salud, University of Granada, 18007 Granada, Spain; [2]Department of Physiology, Faculty of Pharmacy, University of Granada, 18011 Granada, Spain; [3]Department of Physiology, Faculty of Health Sciences, Campus of Melilla, University of Granada, 52005 Granada, Spain
*Correspondence: *G. Kapravelou*, Department of Physiology, Institute of Nutrition and Food Technology, Biomedical Research Center, University of Granada, Avda del Conocimiento s/n, 18100 Armilla, Spain. E-mail: kapravelou@ugr.es.
A.G.-B. and A.L.M. contributed equally to this article.

Context: *Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease in Western countries and is strongly associated with several metabolic disorders. Plant-derived bioactive extracts, such as berry extracts, with high antioxidant capacity have been used for the treatment and prevention of this pathology. Moreover, they promote circular economy and sustainability.* ***Objective:*** *To study the beneficial effects of extracts from different parts of berry plants in animal models of NAFLD.* ***Data Sources:*** *A systematic research of the MEDLINE (via PubMed), Cochrane, and Scopus databases was conducted to identify relevant studies published after January 2011. In vivo animal studies of NAFLD were included in which berry extracts of different parts of the plant were administered and significantly improved altered biomarkers related to the pathology, such as lipid metabolism and hepatic steatosis, glucose and glycogen metabolism, and antioxidant and anti-inflammatory biomarkers.* ***Data Extraction:*** *Of a total of 203 articles identified, 31 studies were included after implementation of the inclusion and exclusion criteria.* ***Data Analysis:*** *Most of the studies showed a decrease in steatosis and a stimulation of genes related to β-oxidation and downregulation of lipogenic genes, with administration of berry extracts. Berry extracts also attenuated inflammation and oxidative stress.* ***Conclusions:*** *Administration of berry extracts seems to have promising potential in the design of enriched foodstuffs or nutraceuticals for the treatment of NAFLD.*

Key words: *nonalcoholic fatty liver disease (NAFLD), berries, plant extract, lipid metabolism, antioxidants, inflammation.*

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a metabolic condition caused by a range of metabolic disorders, including excessive lipid accumulation, lipid oxidative stress, inflammation, and apoptosis.[1,2] It is the most common cause of chronic liver disease in Western countries, and the prevalence of this alteration in the general population ranges from 25% to -40%.[3,4] This disease has been considered as the hepatic manifestation of metabolic syndrome[5] and is strongly associated with obesity, dyslipidemia, insulin resistance, and hypertension.[3,6] Moreover, the prevalence of this pathology is increased in patients with type 2 diabetes.[7] The initial stage of NAFLD is hepatic steatosis, marked by an excessive triglyceride (TG) accumulation (>5% of liver

© The Author(s) 2024. Published by Oxford University Press on behalf of the International Life Sciences Institute.
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (https://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

https://doi.org/10.1093/nutrit/nuae132

Downloaded from https://academic.oup.com/nutritionreviews/advance-article/doi/10.1093/nutrit/nuae132/7811260 by Universidad de Granada - Biblioteca user on 23 October 2024

weight). In this pathology, lipid deposition is unrelated to alcohol consumption, hepatitis C, Wilson's disease, Reye's syndrome, or medication consumption,[8] and induces hepatic oxidative stress and inflammation in this organ, which can aggravate liver status, causing progression to fibrosis, cirrhosis, and hepatocarcinoma.[2,5,9] Due to the many risk factors of this pathology, especially metabolic dysregulation factors, an international panel of experts in 2020 led a consensus-driven process to develop a more appropriate term for the study of this disease. The term proposed was "metabolic dysfunction-associated fatty liver disease".[10]

Due to ineffectiveness of pharmacological approaches, lifestyle interventions are the main available strategies for the amelioration or prevention of NAFLD. Plant-derived bioactive substances, including phenolic compounds, flavonoids, and anthocyanins, act as antioxidants, anti-inflammatory compounds, lipid-lowering agents, and insulin sensitizers. Thus, they may contribute as an adjacent strategy to the treatment of metabolic diseases. In this regard, berries are considered high-nutritional foods because they have a high concentration of bioactive compounds, beyond basic nutrients, that provide several health benefits. They are rich in polyphenols, including anthocyanins, quercetin, proanthocyanidins, flavonoids, tannins, and phenolic acids, all of which contribute to the reduction of oxidative stress and inflammation and produce beneficial modifications to intestinal microbiota. Flavonoids, given their particular structure, are potent in vitro antioxidants. Their ability to scavenge reactive oxygen species (ROS) and reactive nitrogen species is mainly determined by the hydroxyl configuration of the flavonoid B-ring, because they can donate several electrons, thus reducing free radicals such as superoxide (O_2^-), hydroxyl (−OH), peroxyl (ROO^-), and peroxynitrite ($ONOO^-$) with highly oxidative potential.[11–13] Furthermore, certain flavonoids are associated specifically with a decrease in ROS production, exhibiting inhibitory action in mitochondrial complexes I and III. The decline in mitochondrial membrane potential due to an elevated flow of H^+ into the mitochondrial matrix leads to a reduction of ROS formation.[13] Moreover, most of the flavonoids, upon digestion, reach the colon unabsorbed and thus increase the abundance of beneficial bacteria and the production of short-chain fatty acids (FAs).[14–16] Interestingly, some of the resulting metabolites of these flavonoids after metabolization by the gut microbiome have shown anti-inflammatory and antitumor properties.[17]

Berries represent a variety of small fruits with different colors, such as red, purple and blue.[7] The most commonly consumed are blackberries (*Rubus* spp.), red raspberries (*R. idaeus*), black raspberries (*R. occidentalis*), blueberries (*Vaccinium* spp.), cranberries (*V. macrocarpon*), bilberries (*V. myrtillus*), blackcurrant (*Ribes nigrum*), and strawberries (*Fragaria* spp.). Less commonly consumed berries include chokeberries (*Aronia melanocarpa*), açai berries (*Euterpe oleraceae*), goji berries (*Lycium barbarum*), Indian gooseberry (*Phyllanthus emblica* L.), and mulberries (*Morus alba*).[18–22] Furthermore, another widely cultivated fruit with antioxidant properties, which could be considered a berry, is the grape (*Vitis vinifera* L.).[23] They are consumed both as fresh products as well as processed foods (eg, juices, beverages, jams, freeze-dried).[24] In general, berries exhibit a remarkable polyphenol content including flavonoids, condensed tannins, hydrolyzable tannins, phenolic acids, stilbenoids, and lignans,[18,25] although their concentration may vary according to species, genotype, and growing and post-harvesting conditions.[22] Nowadays, the development of dietary supplements based on concentrated extracts or nutraceuticals that combine different plant extracts to acquire optimal nutritional value is growing rapidly. Therefore, there is a need to identify plants that can fulfill this purpose. In this regard, the products of berry cultivation (fruits as well as different plant components like leaves, stem, or roots) are revealing increasing potential.

Considering the need to develop nutritional therapeutic strategies to combat NAFLD, our aim for this systematic review was to examine research in animal models, published in the academic literature, that studied the benefits that extracts from different parts of berry plants can offer to revert metabolic alterations caused by the onset of NAFLD. The inclusion of animal studies allows us to compare results not only in plasma but other tissues, and to analyze the key mechanisms responsible for the observed effects. Putting together these findings can help establish a wide base of knowledge that will guide and encourage the design of clinical studies including different extracts of berries, or even a combination of them, for the treatment of NAFLD.

METHODS

Information sources and search strategy

A literature search for the present systematic review was conducted in the following electronic databases: MedLars Online International Literature, via PubMed; SCOPUS, Web of Science, and Cochrane Library Plus. For the inclusion of the different genera of the berries, the following Medical Subject Headings were used: "Actaea," "Arctostaphylos," "Euterpe," "Fragaria," "Hippophae," "Lycium," "Mahonia," "Morus," "Photinia," "Phyllanthus," "Prunus," "Ribes," "Rubus," "Sambucus," "Ulmus," "Viburnum," "Vitis,"

Downloaded from https://academic.oup.com/nutritionreviews/advance-article/doi/10.1093/nutrit/nuae132/7811260 by Universidad de Granada - Biblioteca user on 23 October 2024

"Vaccinium," "non-alcoholic fatty liver disease," and "plant extracts."

The resulting algorithm was ((Plant Extracts[MeSH Terms]) AND ((((((((((((((((Actaea[MeSH Terms]) OR (Arctostaphylos[MeSH Terms])) OR (Euterpe[MeSH Terms])) OR (Fragaria[MeSH Terms])) OR (Hippophae [MeSH Terms])) OR (Mahonia[MeSH Terms])) OR (Morus[MeSH Terms])) OR (Photinia[MeSH Terms])) OR (Phyllanthus[MeSH Terms])) OR (Prunus[MeSH Terms])) OR (Ribes[MeSH Terms])) OR (Rubus[MeSH Terms])) OR (Sambucus[MeSH Terms])) OR (Ulmus [MeSH Terms])) OR (Viburnum[MeSH Terms])) OR (Vitis[MeSH Terms])) OR (Vaccinium[MeSH Terms])) OR (Lycium[MeSH Terms]))) AND ((((((((((((Non-alcoholic Fatty Liver Disease[MeSH Terms]) OR (Fatty Liver, Nonalcoholic[Title/Abstract])) OR (Fatty Livers, Nonalcoholic[Title/Abstract])) OR (Liver, Nonalcoholic Fatty[Title/Abstract])) OR (Livers, Nonalcoholic Fatty [Title/Abstract])) OR (NAFLD[Title/Abstract])) OR (Non alcoholic Fatty Liver Disease[Title/Abstract])) OR (Nonalcoholic Fatty Liver[Title/Abstract])) OR (Nonalcoholic Fatty Liver Disease[Title/Abstract])) OR (Nonalcoholic Fatty Livers[Title/Abstract])) OR (Nonalcoholic Steatohepatitides[Title/Abstract])) OR (Nonalcoholic Steatohepatitis[Title/Abstract])) OR (Steatohepatitides, Nonalcoholic[Title/Abstract])) OR (Steatohepatitis, Nonalcoholic[Title/Abstract])).

The same algorithm, with some adaptations when needed, was used in the different databases (Appendix S1). Next, a list of relevant studies was made, avoiding duplicated articles, and it was completed by searching the reference list of selected publications and implementing the inclusion and exclusion criteria.

The systematic review was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[20] (Table S1). The period of the search was set to the 10 years inclusive of January 2011 to December 2021, to include the most recent information on the subject. The use of high-nutritional foods and plant extracts in studies of metabolic diseases have increased in recent years. Therefore, the Burton-Kebler index was used for obsolescence to help us include the most current scientific texts published on this topic according to the median age or median production.[21] In addition, the term "NAFLD" was used in the search instead of "MAFLD" (for metabolic dysfunction-associated fatty liver disease), because the latter was proposed in 2020. Established PICOS criteria for the included studies are shown in Table 1.

Article selection

Two of this study's authors (A.G.-B. and A.L.M.) carried out the first screening of the literature separately, reviewed the abstracts of the retrieved articles, and selected the appropriate ones for further full-text examination. At this point, bibliographic reviews, epidemiological studies, editorials, case reports, and book chapters were excluded. There were no language restrictions so all relevant studies could be included. In the second stage of the selection process, the same 2 authors examined the full-text articles and decided which should be included in the review. Because the aim of this work was to review the existing data on animal intervention studies, in vitro studies as well as human clinical trials were manually excluded at this point. Figure 1 shows the flow diagram of the selection process for this systematic review.

Data extraction

After the study selection, the same 2 authors independently reviewed and extracted information from the selected articles. Risk-of-bias assessment was conducted in accordance with a tool developed for animal studies by the Systematic Review Centre for Laboratory Animal

Table 1. PICOS Criteria for Inclusion and Exclusion of Studies

	Inclusion criteria	Exclusion criteria
Population	In vivo animal models of diet-induced or genetic nonalcoholic fatty liver disease	Clinical studies, in vitro studies, bibliographic reviews, and meta-analyses
Intervention	Inclusion of berry extracts made from any part of the plant in the diet or otherwise administered orally or injected, added in the drinking water	Inclusion of a combination of several berries extracts or nutraceuticals Inclusion of berries but not as an extract
Comparators	Control group or group without berry intake, placebo group	No control group
Outcome	Significant improvements in lipid metabolism, hepatic steatosis, glucose and glycogen metabolism, antioxidant and inflammation biomarkers	No significant improvements
Study Design	Experimental, placebo-controlled studies	Bibliographic/systematic reviews and meta-analyses, clinical studies, theses, dissertations, book chapters

Downloaded from https://academic.oup.com/nutritionreviews/advance-article/doi/10.1093/nutrit/nuae132/7811260 by Universidad de Granada - Biblioteca user on 23 October 2024

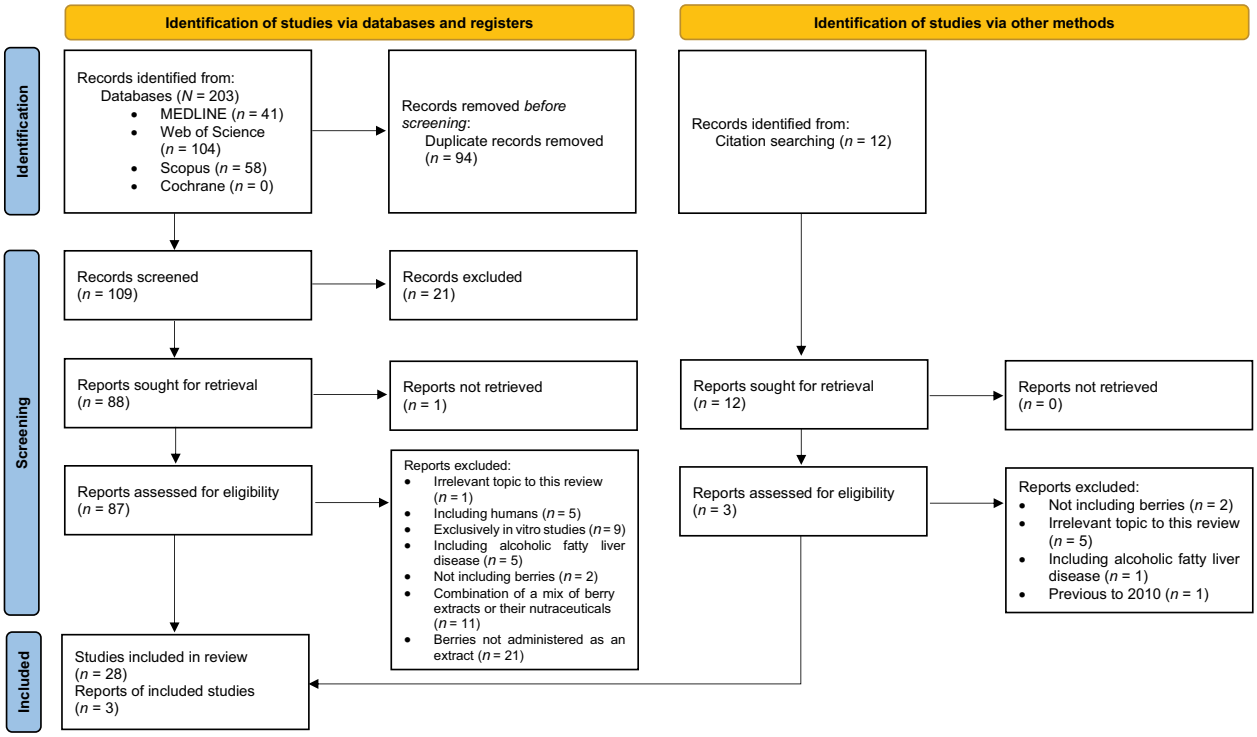

Figure 1. Flow Diagram for Systematic Reviews (Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020).

Experimentation.[22] Moreover, the ARRIVE 2.0 guidelines[26] for reporting animal research were used to evaluate the quality of the studies according to García-González et al.[27] Briefly, the evaluation of the 21 items (formed by different subitems) included the use of the following scale: "reported" (2 points) if the publication complied with all subitems; "not reported" (0 points) if it did not; and "unclear" (1 point) if the details were not provided for all the subitems. In this way, a predefined quality coefficient (excellent, 0.8-1; average, 0.5-0.8; poor, <0.5) was applied to each study, calculated as the sum of the points obtained and divided by 42 (the maximum possible points). Studies with a quality coefficient <0.5 were excluded. The agreement between the 2 reviewers was acceptable according to the Cohen κ statistical test[28] ($\kappa > 0.60$).[29] Any discrepancies were resolved in consensus between A.G.-B. and A.L.M. or between 2 other authors (R.M.M. and G.K.), if necessary.

RESULTS

As shown in Figure 1, 203 studies were identified in the initial systematic search of the different databases. After the exclusion of duplicated studies, 109 potentially eligible studies were found. The first screening resulted in the exclusion of other bibliographic reviews ($n = 19$) and book chapters ($n = 2$). The remaining eligible studies were then reduced to 88. The second screening, which was manually performed, resulted in the exclusion of articles without full-text access ($n = 1$), another topic irrelevant to this review ($n = 1$), and articles on studies including humans ($n = 5$), exclusively in vitro studies ($n = 9$), studies including alcoholic fatty liver disease ($n = 5$), studies that did not include berries in the intervention (n = 2), studies that combined a mix of several berries extracts or their nutraceuticals ($n = 11$), studies that included a berry consumption as an intervention but not administered as an extract ($n = 21$), and 5 articles that failed the quality scale. After the second screening, 28 eligible articles remained. Next, the reference lists of these 28 articles were checked for articles that met the inclusion criteria and did not appear in the initial search. Finally, 3 more articles were added, and the final number of eligible studies was 31. The interobserver raw agreement was calculated at 88.89% ($k = 0.647$).

A summary of the family and genus, and the part of the plant used for the development of the extracts, as well as the isolated compounds, is presented in Table 2. In Table 3, detailed information is presented on the animal models used, specific interventions, and their principal outcomes on altered biomarkers due to the development of NAFLD.

Upon examining these 31 articles, we found that over the past 10 years, most of the studies have focused

Downloaded from https://academic.oup.com/nutritionreviews/advance-article/doi/10.1093/nutrit/nuae132/7811260 by Universidad de Granada - Biblioteca user on 23 October 2024

Table 2. Description of the Characteristics of Berry Extracts in the Retrieved Studies

Reference	Family	Species	Plant portion	Extraction method	Chemistry composition
Al Zarzour et al[1]	Euphorbiaceae	*Phyllanthus niruri*	Whole plant	Water, 50% methanol and methanol	Ellagic acid, phyllantin
Tavares et al[2]	Arecaceae	*Euterpe oleracea* Mart.	Seeds	1. Water 2. Ethanol	Proanthocyanidins, catechin, epicatechin
De Oliveira et al[3]	Arecaceae	*Euterpe oleracea* Mart.	Seeds	1. Water 2. Ethanol	Proanthocyanidins, catechin, epicatechin
Morrison et al[4]	Ericaceae	*Vaccinium myrtillus L.*	Fruit	Commercial extract: Mirtoselect	Anthocyanins
Park et al[5]	Rosaceae	*Aronia melanocarpa*	–	Commercial ethanol extract (Daesan Co.)	Chlorogenic acid, neochlorogenic acid, flavanols, cyanidin 3-galactoside, cyanidin-3-glucoside, cyanidin-3-arabinoside, cyanidin-3-xyloside, procyanidins
Park et al[36]	Rosaceae	*Rubus fruticosus*	Fruit and leaves	50% ethanol	Cyanidin-3-glucoside (fruit extract), ellagic acid (leave extract)
Xu et al[30]	Moraceae	*Morus alba* L.	Leaves	1. Water 2. 70% ethanol 3. Ethyl acetate and petroleum ether	–
Ann et al[32]	Moraceae	*Morus alba* L.	Leaves	70% ethanol	Deoxynojirimycin (3.75%), resveratrol (0.015%)
Hu et al[33]	Moraceae	*Morus alba* L.	Leaves	Methanol	Quercetin (0.9%), rutin (2.6%)
Lee et al[34]	Moraceae	*Morus alba*	Leaves	Mulberry powder + 50% silkworm powder + 10% *Cordyceps militaris* (v/w) fermented for 4 wk; extraction with 95% ethanol	–
Ma et al[35]	Moraceae	*Morus alba*	Root bark	70% ethanol	–
Park et al[9]	Moraceae	*Morus alba* L.	Fruit	Water	Total polyphenols (35.1 ± 0.7), total flavonoids (24.8 ± 0.6), cyanidin-3-glucoside (6.51 ± 0.04), hydroxybenzoic acid (3.71 ± 0.14), rutin (8.82 ± 0.06).
Peng et al[6]	Moraceae	*Morus alba*	Leaves	Water	Neochlorogenic acid (35.5%), cryptochlorogenic acid (31.7%), chlorogenic acid (23.8%), rutin (9.2%), isoquercitrin (5.6%), astragalin acid (5.3%), nicotiflorin (3.5%), protocatechuic acid (1.3%)
Song et al[31]	Moraceae	*Morus nigra* L.	Fruit	80% ethanol and 0.1% trifluoroacetic acid	Cyanidin-3-*O*-glucoside (228.15 ± 15.42 mg g^{-1}), cyanidin-3-rutinoside (121.65 ± 7.13 mg g^{-1}), pelargonidin-3-glucoside (19.26 ± 0.97 mg g^{-1}), total polyphenols (29.02 ± 3.18 mg gallic acid g^{-1}), total flavonoids (36.94 ± 8.19 mg rutin g^{-1}), total sugar (40.29 ± 6.27 mg g^{-1})
Yang et al[37]	Moraceae	*Morus alba*	Fruit	70% ethanol	Cyanidin-3-glucoside (153.7 mg g^{-1}), cyanidin-3-rutin (53.6 mg g^{-1})

(continued)

Downloaded from https://academic.oup.com/nutritionreviews/advance-article/doi/10.1093/nutrit/nuae132/7811260 by Universidad de Granada - Biblioteca user on 23 October 2024

Table 2. Continued

Reference	Family	Species	Plant portion	Extraction method	Chemistry composition
Fotschki et al[38]	Rosaceae	*Rubus idaeus* L.	Pomace	30/70 (v/v) acetone/water	Lambertianin C, sanguiin h-6, ellagic acid, (+)-catechin, (−)-epicatechin, proanthocyanidins, cyanidin-3-*O*-spohoroside, cyanidin-3-*O*-glucosyl-rutinoside, cyanidin-3-*O*-glucoside, cyanidin-3-O-rutinoside, pelargonidin-3-*O*-glucoside
Li et al[39]	Rosaceae	*Rubus aleaefolius* Poir	Roots	Chloroform: methanol: ammonia solution (15:4:3)	Fructose, glucosamine, galactose, glucose, mannose
Nam et al[40]	Rosaceae	*Rubus coreanus*	Fruit	Commercial extract (Lee's Biotech Co., Ltd.)	–
Zhao et al[41]	Rosaceae	*Rubus aleaefolius* Poir.	Roots	Chloroform: methanol: ammonia solution (15:4:3)	Alkaloid (0.81 mg g^{-1})
Bae et al[42]	Solanaceae	*Lycium chinense*	Fruit	Water	Fructose, glucosamine, galactose, glucose, mannose
Glisan et al[43]	Ericaceae	*Vaccinium macrocarpon*	Fruit	Acetone: water: acetic acid (80:19.9:0.1, v:v:v)	A-type proanthocyanidin dimer (0.862 mg/g extract) B-type proanthocyanidin dimer (0.100 mg g^{-1} extract) B-type proanthocyanidin trimer (0.044 mg g^{-1} extract) Cyanidin-6-acetyl-3-glucoside (0.001 mg g^{-1} extract) Cyanidin galactoside or glucoside (0.659 mg g^{-1} extract) Delphinidin arabinoside (0.076 mg g^{-1} extract) Delphinidin-6-acetyl-3-glucoside (0.291 mg/g extract) Malvidin-6-acetyl-3 glucoside or galactoside 1 (0.188 mg g^{-1} extract), Malvidin-6-acetyl-3 glucoside or galactoside 2 (0.347 mg g^{-1} extract), Peonidin arabinoside 1 (0.118 mg g^{-1} extract), peonidin arabinoside 2 (0.955 mg g^{-1} extract), peonidin galactoside (3.97 mg g^{-1} extract), petunidin glycoside (0.638 mg g^{-1} extract)
Huang et al[44]	Euphorbiaceae	*Phyllantus emblica* L.	Fruit	Water	–
Tung et al[52]	Euphorbiaceae	*Phyllanthus emblica* L.	Fruit	Water (reverse osmosis)	–
Xiao et al[45]	Solanaceae	*Lycium barbarum* Lynn	Fruits	1. Ethanol 2. Water	–
Pak et al[23]	Vitaceae	*Vitis coignetiae* Pulliat	Leaves	Water	–
Al Zarzour et al[47]	Euphorbiaceae	*Phyllanthus niruri*	Whole plant	50% methanol	–

(continued)

Downloaded from https://academic.oup.com/nutritionreviews/advance-article/doi/10.1093/nutrit/nuae132/7811260 by Universidad de Granada - Biblioteca user on 23 October 2024

Table 2. Continued

Reference	Family	Species	Plant portion	Extraction method	Chemistry composition
Nanashima et al[50]	Grossulariaceae	*Ribes nigrum* L.	–	Commercial (Koyo Mercantile Co.)	Polyphenols (37.6 g 100 g^{-1} extract), Anthocyanins (38 g 100 g^{-1} extract)
Santos et al[48]	Vitaceae	*Vitis vinifera* L.	Skin	1. Water 2. Ion-exchange resin column washed with ethanol or water	Peonidin-3-*O*-glucoside, petunidin-3-*O*-glucoside, malvidin-3-*O*-glucoside, malvidin-3-(6-*O*-trans-*p*-coumaryl)-5-*O*-diglicoside
Charradi et al[51]	Vitaceae	*Vitis vinifera*	Seed and skin	10% ethanol	Catechin (1.31%), epicatechin (1.61%), procyanidin dimer (0.23%), quercetin (0.55%), resveratrol (0.07%), rutin (1.00%), vanillin (9.21%), gallic acid (41.53%), *p*-coumaric acid (0.19%), rosmarinic acid (0.37%), 2,5-dihydroxybenzoic acid (41.26%), caffeic acid (1.40%), chlorogenic acid (0.17%), ferulic acid (1.00%)
De Bem et al[46]	Arecaceae	*Euterpe oleracea* Mart.	Seeds	1. Water 2. Ethanol	Proanthocyanidins (88%), catechin, epicatechin
Freitas et al[49]	Arecaceae	*Euterpe edulis*	Pulp	Ethyl ether (Soxhlet extraction)	Polyphenols (mg GAE g^{-1}) 4.10 ± 0.13 (BE), 4.95 ± 0.07 (defatted BE); anthocyanins (mg GAE g^{-1}) 2130 ± 114 (BE), 3121 ± 139 (defatted BE); α-tocopherol 32.17 ± 0.61 (BE), 2.10 ± 0.30 (defatted BE), 140.45 ± 3.56 (BE oil); β-tocopherol 1.50 ± 0.01 (BE), 0.11 ± 0.01 (defatted BE), 7.10 ± 0.07 (BE oil); γ-tocopherol 1.71 ± 0.01 (BE), 0.10 ± 0.01 (defatted BE), 7.37 ± 0.03 (oil BE)

Abbreviations: BE, berry extract; GAE, gallic acid equivalents.

Downloaded from https://academic.oup.com/nutritionreviews/advance-article/doi/10.1093/nutrit/nuae132/7811260 by Universidad de Granada - Biblioteca user on 23 October 2024

Table 3. Effects of Functional Berry Extracts on Liver and Other Tissues of NAFLD Animal Models

Reference	Extract intervention	Animal model	Intervention and animal groups	Effects on liver of experimental groups that received berry extract vs NAFLDI group[1]	Effects on other tissues of experimental groups that received berry extract vs NAFLDI group[1]
Al Zarzour et al, 2017[1]	*Phyllanthus niruri,* MeOH-W extract	M: Male SD rats A/W: 10 wk	1. ND + DW (10 mL kg^{-1} BW) 2. HFD (ND + 10% margarine (wt/wt), 10% ghee fat (wt/wt), 1% CHOL and 0.5% cholic acid) + DW (10 mL kg^{-1} BW), OG 3. HFD + metformin 500 mg kg^{-1} BW (10 mL kg^{-1} BW), OG 4. HFD + BE (W): 10 mL kg^{-1} BW, OG 5. HFD + BE (50% MeOH, 50% W): 10 mL kg^{-1} BW, OG 6. HFD + BE (MeOH): 10 mL kg^{-1} BW, OG NAFLDI: 4 wk TP: 4 wk Dose-response assay: 1. ND + DW (10 mL kg^{-1} BW), OG 2. HFD + DW (10 mL kg^{-1} BW), OG 4. HFD + BE (50% MeOH -50% W) 1000 mg kg^{-1} (10 mL kg^{-1} BW), OG 5. HFD + BE (50% MeOH-50% W) 500 mg kg^{-1} (10 mL kg^{-1} BW) OG 6. HFD + BE (50% MeOH-50% W) 250 mg kg^{-1} (10 mL kg^{-1} BW) OG NAFLDI: 4 wk TP: 4 wk	Groups 4, 5, 6: ↓ steatosis, TC and MDA levels Group 5: ↓ LW Groups 5, 6: ↓ lobular inflammation, TG Dose response assay: HFD + BE (50% MeOH-50% W) ↓ LW, lobular inflammation and steatosis	Groups 4, 5, 6: ↓ visceral fat, Ins, HOMA-IR, TC, FFA, and LDL (serum) Groups 5, 6: ↓ ALT (serum) Group 5: ↓ ALP (serum) Dose response assay: Groups 4, 5, 6: ↓ TC, LDL, ALT and Ins, ↑AST to ALT ratio (serum) Groups 4, 5: ↓ ALP, Glu (serum) Group 4: ↓ visceral fat
Tavares et al, 2020[2]	*Euterpe oleracea* Mart. hydroalcoholic extract	M: Male C57BL/6 mice A/W: 4 wk	1. ND 2. HFD (60% kcal fat) + V, IG 3. HFD+ BE 300 mg kg^{-1} d^{-1}, IG NAFLDI: 8 wk TP: 4 wk	↓ LW and lipid accumulation ↓ MDA and carbonyl levels ↓ SOD, GPx, and CAT enzymatic activity	↓ BW ↓ TG, TC, LDL, VLDL, and ALT (serum)
De Oliveira et al,2015[3]	*Euterpe oleracea* Mart. hydroalcoholic extract	M: Male C57BL/6 mice A/W: 4 wk	1. ND 2. ND + 300 mg kg^{-1} d^{-1} BE, IG 3. HFD (60% fat) 4. HFD + 300 mg kg^{-1} d^{-1} BE, IG TP: 12 wk	↓ LW and steatosis ↓ TC, TG, MDA, and carbonyl protein levels ↑ pAMPK, pACACA to ACACA ratio, ABCG5 and ABCG8 ↓ HMGCR, and SREBP-1c ↑ SOD, CAT, and GPx enzymatic activity	↓ BW, epididymal and retroperitoneal adipose tissues weights ↓ TC, TG, LDL, VLDL (serum) ↓ Leptin (plasma) ↑ Adiponectin (plasma)

(continued)

Downloaded from https://academic.oup.com/nutritionreviews/advance-article/doi/10.1093/nutrit/nuae132/7811260 by Universidad de Granada - Biblioteca user on 23 October 2024

Table 3. Continued

Reference	Extract intervention	Animal model	Intervention and animal groups	Effects on liver of experimental groups that received berry extract vs NAFLDI group[1]	Effects on other tissues of experimental groups that received berry extract vs NAFLDI group[1]
Morrison et al, 2015[4]	*Vaccinium myrtillus* L. extract	M: Female E3L mice A/W: –	1. WTD (15% CCB, 1% CO, 40.5% SUC, 20% acid casein, 10% CS, and 6.2% CEL) + 1% CHOL 2. WTD 3. WTD+ 1% CHOL+ 0.1% BE NAFLDI: 4 wk TP: 16 wk	↓ Macro- and microvesicular steatosis ↓ Hepatocellular damage (CK-18) ↓ Inflammatory cell aggregates ↓ Intrahepatic CHOL crystal formation ↓ Collagen and TC, ↓ *Col1a1* and *Mpo,* ↓ p65-NF-κB activity	–
Park et al, 2017[5]	*Aronia melanocarpa* ethanolic extract	M: Male C57BL/6N mice A/W: 5 wk	1. ND 2. HFD (60% kcal fat) 3. HFD + BE 50 mg kg^{-1} d^{-1}, OG TP: 12 wk	↓ LW ↓ Lipid deposition, TG and FAS ↓ *Pparg2* ↓ *Fabp4* and *Lpl* (mRNA and protein) ↑ SOD and TEAC enzymatic activity	↓ BW ↓ AST, ALT, and leptin (serum)
Park et al, 2019[36]	Water extract of mulberry and silk amino acids	M: Male SD rats A/W: 11 wk; 306 ± 20 g	1. ND 2. HFD (51% fat) + CEL 0.6% 3. HFD + BE and SA (1:3) 200 mg kg^{-1} BW per day 4. HFD + BE and SA (1:3) 600 mg kg^{-1} BW per day 5. HFD + BE and SA (1:5) 200 mg kg^{-1} BW per day 6. HFD + BE and SA (1:5) 600 mg kg^{-1} BW per day TP: 12 wk	Groups 3, 4, 5, 6: ↓ LW, ballooning degeneration, macrophage infiltration, ↓ TNF-α, *Tnfa*, Groups 4 & 6: ↓ Liver cellular damage, liver size and fat accumulation, ↑ pAKT/AKT, pACACA/ACACA and ACACA, ↓ *Cyp2e1* Groups 4, 5, 6: ↓ TG and TC and MDA levels, *Il1b*, *Fasn and Srebf1*, ↑ glycogen levels, *Cpt1a* Groups 3, 4, 6: ↑ GSH-peroxidase enzymatic activity and GSH levels Group 4: ↑ SOD enzymatic activity	Groups 3, 4, 5, 6: ↓ AST and γ-GPT, HOMA-IR (serum), BW gain, ↓ AUC (Glu & Ins) Groups 3, 4, 6: ↑ HDL Groups 4, 5, 6: ↓ TNFa, ↓Glu and nonesterified FAs (serum) Groups 4, 6: ↓ LDL and Ins (serum) Groups 5, 6: ↓ BW, epididymal and retroperitoneal fat mass, TG Group 6: ↓ ALT (serum) Group 3, 4: ↑ Bacteroidales to Clostridiales ratio Group 4: ↑ gut bacterial species
Xu et al, 2017[30]	*Morus alba L.* hydroalcoholic extract	M: Male C57BL/6 mice A/W: 4 wk	1. ND 2. HFD (60% kcal fat) 3. HFD + β-glucan 200 mg kg^{-1} d^{-1}, OG 4. HFD + BE 200 mg kg^{-1} d^{-1}, OG 5. HFD + β-glucan 200 mg kg^{-1} d^{-1} + BE 200 mg kg^{-1} d^{-1}, OG TP: 12 wk	Groups 4, 5: ↓ LW Group 5: ↓ TG and TC, ↑ GST, GSSG, Cu/Zn-SOD enzymatic activity, GSH/GSSG and ROS content	Groups 4, 5: ↓ BW, ↓ TG, FFA, CHOL, LDL-c, leptin, AST, ALT, IL1b, IL4, and TNF-α (serum), ↓ perineal fat mass Group 5: ↓ AUC and fasting Glu and Ins

(continued)

Downloaded from https://academic.oup.com/nutritionreviews/advance-article/doi/10.1093/nutrit/nuae132/7811260 by Universidad de Granada - Biblioteca user on 23 October 2024

Table 3. Continued

Reference	Extract intervention	Animal model	Intervention and animal groups	Effects on liver of experimental groups that received berry extract vs NAFLDI group[1]	Effects on other tissues of experimental groups that received berry extract vs NAFLDI group[1]
Ann et al, 2015[32]	*Morus alba* L. ethanolic extract	M: C57BL/6 mice A/W: 4 wk	1. ND + DW 2. HFD (45% kcal fat) + DW 3. HFD + BE 133 mg kg^{-1} d^{-1} 5 times/wk OG 4. HFD + BE 666 mg kg^{-1} d^{-1} 5 times/wk OG TP: 12 wk	Groups 3, 4: ↓ fat accumulation, *Lpl*, *Srebf1*, *Fabp4*, *Ucp2*, *Ppara*, ↓ SREBP-1c and ACTA2 Group 4: ↓ *Nr1h3*, *Fasn*, *Cebpa*, *Col1a1*, ↓ LPL, 4-HNE, nuclear NRF2, HO-1, GPx enzymatic activity	Groups 3, 4: ↑ HDL, ↓TG, TC, LDL, AI, 4-HNE, ↓ GOT, GPT, GPx, and HO-1 plasma enzymatic activity Group 3: ↓ epididymal and retroperitoneal fat
Hu et al, 2020[33]	*Morus alba* L. methanolic extract	M: Male SD rats A/W: 100-120 g; 4 wk	1. ND 2. OAD (ND + 1% OA + 33% SUC) 3. OAD + fenofibrate 50 mg kg^{-1} d^{-1} OG 4. OAD + BE 50 mg kg^{-1} d^{-1} OG 5. OAD + BE 100 mg kg^{-1} d^{-1} OG 6. OAD + BE 200 mg kg^{-1} d^{-1} OG TP: Unknown	Groups 4, 5, 6: ↓ TC and TG, ↓ no. of lipid droplets and histological lesion, ↓ *Hmgcr* and miR-33a Groups 5, 6: ↓ *Srebf2* Groups 4, 5: ↑ *Cyp7a1*	–
Lee et al, 2020[34]	*Morus alba* fermented extract	M: Male C57BL/6N mice A/W: 8 wk	1. ND 2. HFD (60% kcal fat) + V 10 mg/kg (OO + 1% DMSO) 5 times wk^{-1}, OG 3. HFD+ orlistat 10 mg kg^{-1} 5 times wk^{-1}, OG 4. HFD + BE 50 mg kg^{-1} 5 times wk^{-1}, OG TP: 12 wk	↓ LW, ↓ no. and size of lipid droplets, and steatosis total score ↓ *Pparg*, *Fabp4*, *Fasn*, *Klf2*, *Nos2*, *Ptgs2*, *Il1b*, *Il6*, *Tnfa*, *Nfkb*, *Atg4b*, *Atg5*, *Atg7*, and *Atg12*; ↓ p-JNK, p-p38, p-mTOR, beclin, and LC3 levels; ↑ p-PI3K, p-AKT, and p-ERK levels	↓ BW
Ma et al, 2018[35]	*Morus alba* ethanolic extract	M: Male SD rats A/W: 8 wk; 275 ± 25 g	1. ND 2. ND + BE 3. HFD (60% kcal from fat) 4. HFD + BE prevention (10 g kg^{-1} d^{-1}) 4 mo + BE therapeutic (10 g kg^{-1} d^{-1}) 2 mo OG 5. HFD + BE therapeutic (10 g kg^{-1} d^{-1}) 3 mo OG NAFLDI: 3 mo HFD. Immediately after STZ/citrate buffer (CT) IP (40 mg kg^{-1}) TP: 6 mo	Groups 4, 5: ↓ *Srebf1* and *Mlxipl* Group 4: ↓ *Fasn*	Groups 4, 5: ↓ fasting Glu and HOMA-IR, ↑ Ins, ↓ TG, FFA, AST, ALT (serum) Group 4: ↓ TC (serum)

(continued)

Downloaded from https://academic.oup.com/nutritionreviews/advance-article/doi/10.1093/nutrit/nuae132/7811260 by Universidad de Granada - Biblioteca user on 23 October 2024

Table 3. Continued

Reference	Extract intervention	Animal model	Intervention and animal groups	Effects on liver of experimental groups that received berry extract vs NAFLDI group[1]	Effects on other tissues of experimental groups that received berry extract vs NAFLDI group[1]
Park et al, 2019[9]	*Rubus fruticosus* ethanolic extract	M: Male SD rats A/W: 11 wk; 195 ± 11 g	1. ND 2. HFD (51% kcal fat) + dextrin (450 mg kg^{-1} BW per day) 3. HFD + milk thistle extracts (150 mg kg^{-1} BW per day) 4. HFD + 50% BE leaf (450 mg kg^{-1} BW per day) 5. HFD + 50% BE fruit (450 mg kg^{-1} BW per day) 6. HFD + BE leaf and fruit (2:1) (150 mg kg^{-1} BW per day) TP: 12 wk	Groups 4, 5, 6: ↓ TG, MDA, and TNFa, *Acaca*, *Fasn*, *TNFa*; ↑glycogen levels, ↑ SOD enzymatic activity Groups 4, 6: ↓ enlargement of the nucleus and the cell size, macrophage infiltration, CHOL, *Srebf1* and *Il1b*, ↑ *Cpt1a* Group 6: ↑ GSH enzymatic activity	Groups 4, 5 & 6: ↓ epididymal and retroperitoneal fat, ↓Serum levels of AST, ALT, TC, LDL, nonesterified FFAs, AUC (Glu & Ins) Groups 4, 5: ↓ TG (serum) Groups 4, 6: ↓ Ins serum levels, HOMA-IR, ↑ % goblet cells, ↑ *Akkermansia* and *Lactobacillus* population in feces Group 6: ↑ intestinal surface area
Peng et al, 2017[6]	*Morus alba* aqueous extract	M: Male Wistar rats A/W: 220 ± 10 g	1. ND 2. HFD (ND + 20% fat + 2% CHOL) 3. HFD + BE 0.5% 4. HFD + BE 1% 5. HFD + BE 2% NAFLDI: 4 wk TP: 10 wk	Groups 3, 4, 5: ↓ FASN, HMGCR, and TBARS; ↑ CPT1 Groups 4, 5: ↓ TC, TG levels, and lipid accumulation; ↓ AGPAT; ↑ SOD enzymatic activity; ↑ PPARa	Groups 3, 4, 5: ↓ BW, ↓ total peripheral and total body fat, ↓ TNF-α and leptin serum levels Groups 4, 5: ↓ ALT, TG, TC, and LDL (serum) Group 5: ↓ perineal, mesenteric, subcutaneous, and groin fat; ↑ adiponectin (serum)
Song et al, 2016[31]	*Morus nigra* L. ethanolic extract	M: Male C57BL/6J mice A/W: 4 wk	1. LFD + saline 100 mg kg^{-1} d^{-1} OG 2. HFD (45% fat) + saline 100 mg kg^{-1} d^{-1} OG 3. HFD + BE 100 mg kg^{-1} d^{-1} OG TP: 14 wk	↓ Steatosis grade ↓ TG and TC levels, ↓ *Gk* and *Fads2*, ↑ *Adipor2* and *Insig1*	↓ BW, ↓ relative perineal and epididymal fat weight ↓ TC, LDL, AST, ALT, Glu, Ins (serum), HOMA-IR, HOMA-IS, adiponectin (serum); ↑ leptin (serum)
Yang et al, 2018[37]	*Morus alba* ethanolic extract	M: Male SD rats A/W: 240-260 g	1. SD + DW, OG 2. HFD + DW, OG 3. HFD + BE 100 mg kg^{-1} BW, OG 4. HFD + BE 200 mg kg^{-1} BW, OG TP: 10 wk	↓ LW, intracellular lipid accumulation, TG levels, *Srebf1*, *Fasn*, *Acaca*, and *Scd1* ↓ Mitochondrial ROS production and NADPH oxidase activity ↓ MDA, 4-HNE, and NOX4, ↑ SOD enzymatic activity, ↑ mitochondrial complex-I and complex-II activities, ↑ ATP content	↓ TG, TC, LDL, AST, and ALT, ↑ HDL (serum)

(continued)

Downloaded from https://academic.oup.com/nutritionreviews/advance-article/doi/10.1093/nutrit/nuae132/7811260 by Universidad de Granada - Biblioteca user on 23 October 2024

Table 3. Continued

Reference	Extract intervention	Animal model	Intervention and animal groups	Effects on liver of experimental groups that received berry extract vs NAFLDI group[1]	Effects on other tissues of experimental groups that received berry extract vs NAFLDI group[1]
Fotschki et al, 2021[38]	*Rubus idaeus* L. acetone-water extract	M: Male Wistar rats A/W: 8 wk; 165.3 ± 1.43 g	1. HFD (23% fat) 2. HFD + BE 0.64% 3. HFD + BE 0.64% + fructo-oligosaccharides 3% 4. HFD + BE 0.64% + pectins 3% TP: 12 wk	Groups 2, 3, 4: ↓ ballooning and portal inflammation, ↓ *Pparg* Groups 2, 3: ↓ lobular inflammation, ↓ MDA levels, ↓ *Il6* Groups 3, 4: ↓ steatosis, ↓ fat content Group 3: ↑ LW, ↓ TC and TG levels, ↓ *Ppara* and *Angplt4*	Groups 2, 3: ↓ AST (plasma) Groups 3, 4: ↑ cecum mass Group 3: ↓ TG (plasma) Group 4: ↓ cecum pH
Li et al, 2014[39]	*Rubus aleaefolius* Poir extract	M: Male Sprague-Dawley rats A/W: 8 wk; 180-200 g	1. ND + 10 mL kg^{-1} DW 2. mHFD (10% lard + 2 % CHOL) + DW 10 mL kg^{-1} OG 3. mHFD + BE 1.44 g kg^{-1} BW per day, OG 4. mHFD + BE 0.72 g kg^{-1} BW per day, OG NAFLDI: 8 wk TP: 28 d	↓ Fat accumulation, hepatocyte ballooning, scattered lobular inflammatory cell infiltration, and inflammatory foci, ↓ *Acaca*, *Fasn*, *Cpt1a*	↓ TG, TC, LDL; ↑ HDL (serum)
Nam et al, 2014[40]	*Rubus coreanus*	M: Male C57BL/6 mice A/W: –	1. ND 2. HFD (60% kcal fat) 3. HFD+ BE 100 mg kg^{-1} TP: 10 wk	↓ LW, TG, and TC, *Nr1h3*, *Srebf1*, *Acaca*, *Cd36*, *Fasn*, FASN, and HMGCR reductase activity; ↑CPT activity	↓ BW, ↓ epididymal fat mass ↓ AST, ALT, TC, TG, LDL, and leptin plasma levels
Zhao et al, 2013[41]	*Rubus aleaefolius* Poir. extract	M: Male SD A/W: 8 wk; 180-200 g	1. CT + DW, IG 2. HFD (10% lard + 2% CHOL) + DW, IG 3. HFD + polyene phosphatidylcholine 76 mg kg^{-1} BW per day IG 4. HFD + BE 1.44 g kg^{-1} BW per day IG 5. HFD + BE 0.72 g kg^{-1} BW per day IG NAFLDI: 8 wk TP: 7 d	Groups 4, 5: ↓ hepatocyte ballooning, scattered lobular inflammatory cell infiltration, and inflammatory foci ↓ Nfkb, Tnfa, Ptgs2, and Il6 protein and mRNA expression	Groups 4, 5: ↓ BW ↓ ALT, AST, GGT, ALP, TC, TG, and LDL serum levels
Bae et al, 2017[42]	*Lycium chinense* aqueous extract	M: Male C57BLS/J-m mice A/W: 7 wk	1. ND 2. MCD + PBS OG 3. MCD + betaine 10 mg kg^{-1} d^{-1}, OG 4. MCD + BE 100 mg kg^{-1} d^{-1}, OG 5. MCD + BE 200 mg kg^{-1} d^{-1}, OG 6. MCD + BE 400 mg kg^{-1} d^{-1}, OG TP: 4 wk	Group 6: ↓ LW Groups 5, 6: ↓ lipid accumulation, ↓ TG, GSH, and MDA levels, *F4/80*, *Itgax*, *Ccl2*, *Icam1*, *Tnfa*, *Il6*, *Il1b*, *Tgfb*, *Col1a1*, *Acta2*; ↑ SOD and CAT enzymatic activity, pERK; ↓ pJNK	↓ AST and ALT plasma levels

(continued)

Downloaded from https://academic.oup.com/nutritionreviews/advance-article/doi/10.1093/nutrit/nuae132/7811260 by Universidad de Granada - Biblioteca user on 23 October 2024

Table 3. Continued

Reference	Extract intervention	Animal model	Intervention and animal groups	Effects on liver of experimental groups that received berry extract vs NAFLDI group[1]	Effects on other tissues of experimental groups that received berry extract vs NAFLDI group[1]
Glisan et al, 2016[43]	*Vaccinium macrocarpon* acetone: water:acetic acid (80:19.9:0.1, v:v:v) extract	M: Male C57BL/6J mice A/W: 4 wk	1. HFD (60% kcal from fat) 2. HFD + BE 0.8% NAFLDI: 11 wk TP: 10 wk	↓ Degree of lipidosis and lipid droplets area, ↓ TNF-α, CCL2, and IL1b; ↓ *Tlr4*, *NFKB*, *Tnfa*, *Il1b*, *Ucp2*, *Ptgs2*, *Ccr2*, *Ccl3*, *Nlrp3*, *Casp1*, *Ppara*, *Txnip*	↓ FFA, IL-1b, ALT plasma levels
Huang et al, 2017[44]	*Phyllantus emblica* L. aqueous extract	M: Male SD rats A/W: 160 ± 10 g	1. ND 2. HFD (40% fat) 3. HFD + GA 100 mg kg^{-1}, OG 4. HFD + BE 125 mg kg^{-1} BW, OG 5. HFD + BE 250 mg kg^{-1} BW, OG 6. HFD + BE 500 mg kg^{-1} BW, OG TP: 20 wk	Groups 4, 5, 6: ↓ *Srebf1*, ↑ CAT and GST enzymatic activity Group 5: ↑ *Ppara* Group 6: ↓ lipid droplets and fat deposition, ↓ *Nr1h3*, ↑ GRd enzymatic activity	Groups 4, 5, 6: ↓ BW, ↓ AST (serum), ↑ adiponectin (peritoneal fat) Groups 5, 6: ↓ peritoneal and epididymal fat weight Group 6: ↓ ALT and LDL (serum)
Tung et al, 2018[52]	*Phyllanthus emblica* L. reverse osmosis aqueous extract	M: Male C57BL/6JNarl mice with specific pathogen-free conditions A/W: 5 wk; 20 ± 2 g	1. ND 2. MCD 3. MCD + GA 100 mg kg^{-1} BW per day OG 4. MCD + BE 125 mg kg^{-1} BW per day OG 5. MCD + BE 250 mg kg^{-1} BW per day OG 6. MCD + BE 500 mg kg^{-1} BW per day OG TP: 4 or 8 wk	Groups 4, 5, 6: ↑ GST, SOD, ↓CAT activity (wk 8), ↓*Cyp2e1*, *Tnfa* (weeks 4 and 8), ↓*Il1b* (week 8) Groups 4, 6: ↓ TBARs levels (week 4) Group 5: ↓ TBAR levels (week 8) Group 6: ↓ GPx enzymatic activity (weeks 4 and 8)	Group 4, 5, 6: ↓ AST and ALT (weeks 4 and 8), ↑ TG serum (week 8) Group 6: ↑ TG serum levels (week 4)
Xiao et al, 2018[45]	*Lycium barbarum* Lynn aqueous extract	M: Male and female C57BL/6N mice A/W: 20-25 g	1. ND 2. MCD 3. ND + BE 1 mg/kg/ OG 4. MCD + BE 1 mg kg^{-1} d^{-1} OG NAFLDI: 3 wk TP: 3 wk	↓ NAS score and apoptotic cells number ↓ ACTA2, SMAD2, TGFb1, p-SMAD2, MDA, TXNIP, TNF-α, IL10, NFKB p50, NFKBIA, BAX-1, cytochrome c, CYP2E1, cleaved CASP1, ASC, NLRP3, and NLRP6, ↑ CAT, GPx and BCL-2	↑ BW ↓ IL-18 and IL-1b
Pak et al,2012[23]	*Vitis coignetiae* Pulliat aqueous extract	M: Male Wistar rats A/W: 6 wk	1. ND 2. CD HFD 3. CD HFD + BE 100 mg kg^{-1} d^{-1} OG 4. CD HFD + BE 300 mg kg^{-1} d^{-1} OG NAFLDI: 13 wk (4 wk HFD+ 9 wk HFD and $NaNO_2$ 40 mg kg^{-1} d^{-1} IP) TP: weeks 10 to 13	Groups 3, 4: ↑ relative LW, ↓ mitochondria ROS derivation, ↓ MPO activity, ↓ NFKB p65 Group 4: ↓ % of fibrosis area	Group 3, 4: ↓ ALT plasma levels Group 4: ↑SOD enzymatic activity (serum)

(continued)

Downloaded from https://academic.oup.com/nutritionreviews/advance-article/doi/10.1093/nutrit/nuae132/7811260 by Universidad de Granada - Biblioteca user on 23 October 2024

Table 3. Continued

Reference	Extract intervention	Animal model	Intervention and animal groups	Effects on liver of experimental groups that received berry extract vs NAFLDI group[1]	Effects on other tissues of experimental groups that received berry extract vs NAFLDI group[1]
Al Zarzour et al, 2018[47]	*Phyllanthus niruri* methanolic extract	M: Male SD rats A/W: 10 wk	1. ND + DW (10 mL kg^{-1} BW) OG 2. HFD (8.23% margarine (wt/wt), 8.23% ghee fat (wt/wt), 0.82% CHOL, and 0.41% cholic acid) + DW (10 mL kg^{-1} BW) OG 3. HFD + metformin 500 mg kg^{-1} BW OG 4. HFD + BE 1000 mg kg^{-1} BW OG NAFLDI: 5 wk TP: 3 wk	↓ Micro- and macrovesicles and fibrosis ↓ *Pparg*, *Col1a1*, and *Slc10a2*	↑ Adiponectin serum levels ↓ TNF-α, RBP4, vaspin, and IL-6 (serum)
Nanashima et al, 2020[50]	*Ribes nigrum* L. commercial extract	M: ovariectomized and sham surgery female SD rats A/W: 12 wk; 249.7 ± 10.2 g	1. ND ovariectomized rats (AIN-93M) 2. ND sham surgery rats (AIN-93M) 3. Ovariectomized rats: ND (AIN-93M) + BE 3% TP: 12 wk	↓ Adipocyte diameter ↓ *Tnfa*, *Il6*, and *Il1b*	↓ BW ↓ Visceral fat weight ↓ TG, TC, LDL, adiponectin, and leptin (serum)
Santos et al, 2017[48]	*Vitis vinifera* L. hydroalcoholic extract	M: Male C57BL/6 mice A/W: 4 wk	1. ND + W, OG 2. HFD (60% fat) + W, OG 3. ND + BE 200 mg kg^{-1} d^{-1}, OG 4. HFD + BE 200 mg kg^{-1} d^{-1}, OG TP: 12 wk	↓ LW, ↓ liver fat density ↓ TC, TG, and glycogen levels ↓ MDA and carbonyl protein levels ↑ p-IRS-1, pAKT, PI3-1K, SLC2A2, pLKB1, pACACA, HMGCR, and pAMPK/AMPK ratio, ABCG5 and ABCG8, ↓ SREBP-1c,↑ CAT, GPx, and SOD enzymatic activity	↓ BW ↓ Epididymal and retroperitoneal fat mass ↓ Glu and Ins, HOMA-IR (serum)
Charradi et al, 2014[51]	*Vitis vinifera* ethanolic extract	M: Male Wistar rats A/W: 210-230 g	1. ND + 10% ethanol IP (daily) 2. HFD (39% kcal fat) + ethanol 10% IP (daily) 3. ND + BE 500 mg kg^{-1} d^{-1} BW IP 4. HFD + BE 500 mg kg^{-1} d^{-1} BW IP TP: 6 wk	↓ Relative LW, macrovesicular steatosis, dilatation, and fat accumulation within hepatocytes and sinusoids, ↓ TG, TC, LDL/HDL ratio, TPL, (LDL+VLDL) to HDL ratio, Apo B to Apo AI ratio, MDA, carbonyl protein, and GSSG levels; ↑ levels of ApoAI, GSH, and GSH to GSSG ratio, ↑ GPx and total-, Cu/Zn-, Mn-, and Fe-SOD enzymatic activity ↓ ALAT, ASAT, and lipase activity ↑ Liver alcohol dehydrogenase activity, ↓ Zn depletion	–

(continued)

Downloaded from https://academic.oup.com/nutritionreviews/advance-article/doi/10.1093/nutrit/nuae132/7811260 by Universidad de Granada - Biblioteca user on 23 October 2024

Table 3. Continued

Reference	Extract intervention	Animal model	Intervention and animal groups	Effects on liver of experimental groups that received berry extract vs NAFLDI group[1]	Effects on other tissues of experimental groups that received berry extract vs NAFLDI group[1]
De Bem et al, 2018[46]	*Euterpe oleracea* Mart. hydroalcoholic extract	M: Male Wistar rats A/W: 180-200 g	1. ND 2. ND + EXE (treadmill 30 min d^{-1}; 5 d wk^{-1}) 3. ND + BE 200 mg kg^{-1} d^{-1} IG 4. ND + EXE + BE 200 mg kg^{-1} d^{-1} IG 5. HFD (45% kcal fat) 6. HFD + EXE (treadmill 30 min d^{-1}; 5 d wk^{-1}) 7. HFD + BE 200 mg kg^{-1} d^{-1} IG 8. HFD + EXE + BE 200 mg kg^{-1} d^{-1} IG NAFLDI: 5 wk (streptozotocin/citrate buffer [CT] IP [35 mg kg^{-1}] once in wk 3) TP: 4 wk	Groups 7, 8: ↓ LW and steatosis, TC, TG, MDA, protein carbonyl and 8-isoprostane levels; ↑ ABCG5, pAMPK, pLKB1 to LKB1 ratio, pAMPK/AMPK, pACC/ACC; ↓ SREBP-1c, ACACA, HMGCR; ↑ SOD and GPx enzymatic activity Group 7: ↑ pACC Group 8: ↓ glycogen levels, AMPK	Groups 7, 8: ↓ TC, TG, VLDL, ALT, MDA, and protein carbonyl (serum) Group 8: ↓ AST (serum)
Freitas et al, 2016[49]	*Euterpe edulis* oil extract or defatted extract	M: Male Wistar rats A/W: 4 wk; 85 ± 5 g	1. ND 2. HFD (50% fat) 3. HFD + BE oil 4% 4. HFD + BE pulp 5% 5. HFD + BE pulp 10% 6. HFD + defatted BE 5% 7. HFD + defatted BE 10% NAFLDI: 4 wk TP: 4 wk	Groups 3, 4, 5, 6: ↓ CAT, SOD enzymatic activity Groups 3, 4, 6: ↓ TBARs Groups 4, 6: ↓ inflammatory infiltration and hepatocytes nucleus, GST enzymatic activity	Group 6: ↑ TC serum levels

[1]Outcomes refer to groups with berry extract administration vs groups after NAFLD induction, unless otherwise specified.

Abbreviations: A/W, age/weight; AI, atherogenic index (AI); AUC ROC, area under the receiver operating characteristic curve; BE, berry extract; BW, body weight; CCB, cocoa butter; CEL, cellulose; CHOL, cholesterol; CO, corn oil; CS, corn starch; DW, distilled water; FA, fatty acid; FFA, free fatty acid; Glu, glucose; HFD, high-fat diet; IG, intragastric; Ins, insulin; IP, intraperitoneal; LFD, low-fat diet; LW, liver weight; M, animal model; MCD, methionine-choline–deficient diet; MeOH, methanol; mHFD, modified high-fat diet; NAFLDI, nonalcoholic fatty liver disease induction; ND, normal diet; OA, orotic acid; OAD, orotic acid diet; OG, oral gavage; OO, olive oil; SA, silk amino acid; SD, Sprague-Dawley rats; STZ, streptozotocin; SUC, sucrose; TG, triglyceride; TEAC, trolox equivalent antioxidant capacity; TP, treatment period; V, vehicle; W, water; WTD, Western-type diet.

Biomarker abbreviations (genes and proteins): ABCG5, ABCG8: ATP binding cassette subfamily G member 5 and 8; ACC or ACACA: acetyl-CoA carboxylase; AdipoR2: adiponectin Receptor 2; AGPAT: 1-acylglycerol-3-phosphate-*O*-acyltransferase enzyme; ALAT: alanine transaminase; ALP, alkaline phosphatase; ANGPTL4: angiopoietin-like 4 gene; Apo: apolipoprotein; aP2 or FABP4: fatty acid binding protein 4; ASAT: aspartate aminotransferase; ASC or PYCARD: apoptosis-associated speck-like protein containing a CARD; α-SMA or Acta2: α smooth muscle actin; AST: aspartate aminotransferase; Atg4b, Atg5, Atg7, Atg12: autophagy-related cysteine peptidase 4, 5, 7, and 12; Bax-1: apoptosis regulator BAX; Bcl-2: B-cell lymphoma 2; CAT: catalase; CASP1: Casparian strip membrane protein 1; CCR2: C-C chemokine receptor type 2; CCL2 or 3: C-C motif chemokine ligand 2 or 3 protein; CD11c or Itgax: integrin α-X; CD36: platelet glycoprotein 4; C/EBPα or Cebpa: CCAAT-enhancer-binding proteins; CK-18: cytokeratin 18; CYP7A1: cholesterol 7-α-monooxygenase; CYP2E1: cytochrome P450 2E1; CPT1: carnitine palmitoyltransferase; Col1a1: collagen type I α 1 chain; COX2 or Ptgs2: cyclooxygenase-2; Mlxipl; ChREBP: carbohydrate-responsive element-binding protein; CYP2E1: *N*-nitrosodimethyl-amine demethylase; ERK: extracellular-signal-regulated kinase; Fabp4: fatty acid-binding protein 4; FASN: fatty acid synthase enzyme; Fads2: acyl-CoA 6-desaturase; F4/80: rat anti–mouse F4/80 antibody; GSH: glutathione reductase; GSSG: glutathione disulfide; GST: glutathione *S*-transferase; GPx: glutathione peroxide; GRd: glutathione reductase; Gk or GYK: glycerol kinase; SLC2A2 or Glut 2: glucose transporter 2; 4-HNE: 4-hydroxynonenal; HMGCR: 3-hydroxy-3-methy-glutaril-CoA reductase enzyme; HO-1: heme oxygenase-1; ICAM-1: intercellular adhesion molecule; IκB-α or Nfkbia: nuclear factor of κ light polypeptide gene enhancer in B-cells inhibitor, α; IL-6: interleukin 6 cytokine featuring pleiotropic activity; IL-1β: interleukin -1 β pro-inflammatory cytokine produced by cells of the innate immune system; Nos2 or iNOS: inducible nitric oxide synthase; INSIG1: insulin induced gene 1; JNK: Jun *N*-terminal kinase; Klf2: Krüppel-like factor 2; LC3: microtubule-associated protein light chain 3; LPL: lipoprotein lipase; LXRa or Nr1h3: liver X receptor α; MDA: malondialdehyde; MPO: myeloperoxidase; miR-33a: microRNA 33a; NADPH: nicotinamide adenine dinucleotide phosphate; NAS: NAFLD Activity Score; NF-κB: nuclear factor κ B; NLRP3: NACHT, LRR, and PYD domains-containing protein 3; NLRP6: NOD-like receptor family pyrin domain containing 6; Nrf2: nuclear factor erythroid 2-related factor 2; NOX4: NADPH oxidase 4; PPAR-γ: peroxisome proliferator-activated receptor γ; pAMPK: phosphorylated AMP-activated protein kinase; pAKT: phospho-AKT; p-ERK: extracellular signal-related kinase; p-IRS-1: phosphorylated insulin receptor substrate; PI3-1K: phosphatidylinositol 3-kinase 1; p-mTOR: phosphorylated serine/threonine-protein kinase mTOR; p-JNK: phosphorylated Jun N-terminal kinase; LKB1: serine/threonine protein kinase liver kinase B1; p-PI3K: phosphorylated phosphatidylinositol-3 kinase; PPARα: peroxisome proliferator-activated receptor α; ROS: reactive oxygen species; SCD-1: stearoyl-coenzyme A desaturase 1; SOD: superoxide dismutase; SLC10A2: ileal sodium/bile acid cotransporter; Smad2: Mothers Against Decantaplegic homolog 2; SREBP: sterol regulatory element-binding protein; Srebf1: sterol regulatory element binding transcription factor 1; TGF-β: transforming growth factor β; TXNIP: thioredoxin-interacting protein; TBARS: thiobarbituric acid reactive substances; TPL: protein TOPLESS; TNF-α: tumor necrosis factor α; Tlr4: Toll-like receptor 4; UCP2: mitochondrial uncoupling protein 2.

Downloaded from https://academic.oup.com/nutritionreviews/advance-article/doi/10.1093/nutrit/nuae132/7811260 by Universidad de Granada - Biblioteca user on 23 October 2024

on antioxidant activity of extracts from species of the genera *Morus* ($n = 9$)[6,30–37] and *Rubus* ($n = 5$).[9,38–41] The plant material mostly used to obtain the extracts was the fruit ($n = 10$),[4,31,36,37,40,42–45] followed by leaves ($n = 6$),[6,23,30,32–34] seeds ($n = 3$),[2,3,46] and roots ($n = 2$).[39,41] In contrast, the whole plant ($n = 2$),[1,47] skin ($n = 1$),[48] pulp or pomace ($n = 2$),[38,49] or root bark ($n = 1$)[35] have been seldom studied. Two of the retrieved articles did not mention the source of the plant material used for their intervention,[5,50] and 2 studies used a mixture of different parts from the plant fruits and leaves[9] or seed and skin.[51] The chemical composition of the extracts was reported in 22[1–6,9,31–33,36–39,41–43,46,48–51] of the 31 articles described in this review (Table 2).

The biological effects of the berry extracts in different animal models are summarized in Table 3. Male ($n = 27$)[1–3,5,6,9,23,30–32,34–44,46–49,51,52] and female ($n = 2$)[4,50] rodents were selected as animal models to study NAFLD. In 1 study, both male and female animals were included ($n = 1$)[45]; in 1 study, the sex was not mentioned.[32] Fourteen articles studied the effect of berry extract administration on mice.[2–5,30–32,34,40,42,43,45,52] In the remaining 17 articles, the animal model used was rat.[1,5,6,23,33,35–39,41,44,46,47,49–51] The induction of NAFLD was mainly carried out by the inclusion of a high-fat diet (HFD) in different fat percentages ($n = 15$)[2,3,5,9,30–32,34,36,38,40,43,44,48,51]; the combination of a high-fat and high-cholesterol diet (HFD-HCD) ($n = 6$)[1,6,37,39,41,47]; or a Western-type ($n = 1$)[4] or cafeteria diet ($n = 1$).[49] In 2 studies, hepatic steatosis was also induced by an HFD plus streptozotocin ($n = 2$)[35,46] or an orotic acid diet ($n = 1$).[33] Other strategies also included a methionine choline–deficient diet alone ($n = 3$)[42,45,52] to induce this pathology or in combination with sodium nitrite injection ($n = 1$).[18] Only 1 study did not develop a diet-induced NAFLD model ($n = 1$)[50] but instead used ovariectomized Sprague-Dawley rats to study the risk of NAFLD development due to estrogen deficit.

The most common form of berry extract administration was by oral gavage ($n = 17$)[1,5,23,30–35,37,39,42,44,45,47,48,52]; other studies mixed it with the rodent diet ($n = 9$)[4,6,9,36,38,40,43,49,50] or used intragastric administration ($n = 4$)[2,3,41,46] or intraperitoneal administration (n = 1).[51] After reviewing the collected studies, we found most of them used berry extract as the sole intervention. Nevertheless, in 1 article, the treatment with berry extract was combined with a protocol of physical activity,[46] and in others, berry extracts were co-administered with β-glucan,[30] silk amino acids,[36] and fructo-oligosaccharides or pectins[38] to enhance their activity.

The treatment period varied among articles, ranging from <4 weeks ($n = 4$),[23,41,45,47] to 4-8 weeks ($n = 8$),[1,2,39,42,46,49,51,52] 9-13 weeks ($n = 14$),[3,5,6,9,30,32,34,36–38,40,43,48,50] or 14-24 weeks ($n = 4$).[31,35,39,44] In 1 article, this period was not specified.[33] The most common duration of the treatment was 12 weeks ($n = 10$).[3,5,9,30,32,34,36,38,48,50] The obtained results of the different genera of the berries included in the retrieved studies are presented next.

Euterpe extract

As shown in Table 3, 4 of the retrieved studies assayed the antioxidant activity of berries belonging to the *Euterpe* genus on Wistar rats,[46,49] C57BL/6[2] and C57BL/6J[3] mice with NAFLD during 4[2,46,49] or 12 weeks.[3] These articles reported on studies of the seeds extracts of *E. oleracea* Mart.[2,3,46] and the pulp ethyl ether extract of *E. edulis*.[49] The intragastric administration of 2 doses (200 mg kg^{-1} d^{-1} [46] and 300 mg kg^{-1} d^{-1} [2,3]) of *E. oleracea* or the inclusion of *E. edulis* oil (4%), pulp, or defatted pulp (5% and 10%) in the diet resulted in a decrease in body weight (BW),[2,3] liver weight, and hepatic steatosis of the animals.[2,3,46,47] In addition, they reduced hepatic and serum[2,3,46] levels of total cholesterol (TC), TGs, and low-density lipoprotein (LDL) as well as hepatic lipogenic gene expression (*Srebf1*, *Hmgcr*, *Acaca*).[3,46] However, *E. edulis* extracts increased serum TC levels.[47] Different effects on antioxidant enzyme activities were reported in response to the inclusion of the extracts. In 1 case, superoxide dismutase (SOD), glutathione peroxide (GPx), and catalase (CAT) activities decreased,[2,49] whereas SOD, GPx, and CAT activities increased in the other 2 articles.[3,46] In addition, a decrease in glutathione *S*-transferase (GST) enzymatic activity and thiobarbituric acid reactive substances (TBARS) were also observed.[38] Furthermore, the AMP-activated protein kinase (AMPK) activity[3,46] and the expression of ABCG5 and ABCG8, transporters responsible for biliary and transintestinal secretion of cholesterol and dietary sterols,[3] were increased. de Bem et al[46] studied the combination of the administration of berry extract with physical activity, and they observed an improvement of the beneficial effects on lipid metabolism, reducing hepatic lipogenic proteins and cholesterol transporters.

Vaccinium extract

Fruit extracts were obtained from *Vaccinium myrtillus* L.[4] and *V. macrocarpon*.[43] One extract was commercially obtained[4] and the other was obtained by an extraction method using different solvents such as acetone, water, and acetic acid solutions.[43] These extracts

Downloaded from https://academic.oup.com/nutritionreviews/advance-article/doi/10.1093/nutrit/nuae132/7811260 by Universidad de Granada - Biblioteca user on 23 October 2024

were tested on E3L[4] and C57BL/6J[43] mice models for 10[43] or 16[4] weeks. Several effects were observed in the liver, such as a decrease in steatosis (measured by a reduction in the degree of lipidosis and lipid droplets area[43]), macrovesicular and microvesicular steatosis, hepatocellular damage, or inflammatory cell aggregates.[4] The administration of both extracts also decreased protein hepatic levels of TNF-α, CCL2, and IL-1β, and hepatic mRNA expression of inflammation markers.[4,43]

Phyllanthus extract

Two of the 4 studies of the genus *Phyllanthus* used the whole plant to produce a functional extract of *P. niruri*,[1,47] and the remaining 2 used extracts from *P. emblica* L. fruit.[44,52] These extracts were tested on Sprague-Dawley rats[1,44,47] and C57BL/6Narl mice,[52] using doses from 125 to 1000 mg kg^{-1} BW by oral gavage. *Phyllanthus* extracts reduced serum levels of alkaline phosphatase, alanine transaminase (ALT), aspartate transaminase (AST),[1,44,52] and visceral, peritoneal, and epididymal fat.[1,44] In addition, administration of the extracts increased the activity of antioxidant enzymes (CAT, GST, SOD, and GPx) in liver and plasma,[44,52] and downregulated hepatic gene expression of inflammatory (*Tnfa*, *Il1b*, *Nr1h3/Lxra*)[44,52] and lipogenic (*Srebf1*)[44] markers. Al Zarzour et al[1] observed that all doses of 50% methanol extract (1000, 500, and 250 mg kg^{-1} d^{-1}) of *P. niruri* significantly improved serum parameters, and the highest dose significantly improved the histological parameters. Together with these results, Al Zarzour et al[47] observed that the extract reduced micro- and macrovesicular steatosis and fibrosis in the liver; decreased serum levels of TNF-α, RBP4, vaspin, and IL-6; and increased adiponectin serum levels.

Ribes extract

The *Ribes* genus was studied in 1 article. A commercial extract of *R. nigrum* L. was used.[50] Different concentrations of berry extract (10, 100, and 200 mg kg^{-1}) were administered by oral gavage to C57BL/6 mice. Higher doses improved NAFLD status, decreased hepatic steatosis, and reduced body and visceral fat weight. In addition, it also reduced TC, TG, LDL, adiponectin, and leptin serum levels. The highest extract dose decreased hepatic *Tnfa*, *Il6*, and *Il1b* mRNA expression and increased serum levels of high-density lipoprotein.

Morus extract

Most of the articles ($n = 8$) reporting on research of this genus focused on *Morus alba* L. extracts from different plant parts, such as leaves ($n = 5$),[6,30,32–34] fruit ($n = 2$),[36,37] and root bark ($n = 1$)[35] and 1 on *M. nigra* L. fruit.[31] C57BL/6,[32,33] C57BL/6J,[48] and C57BL/6N mice,[34] and Wistar[6] and Sprague-Dawley[33,35–37] rats were used as animals models to test *Morus* extracts effects on NAFLD. In mice models, the doses used were between 100 and 600 mg kg^{-1}, whereas in rats, they ranged from 0.05 to 10 g kg^{-1}. *Morus* extracts decreased body and liver weight,[6,31,33,34,36] liver steatosis, TG levels,[30,31,36,37] lipogenic metabolism, and inflammatory status.[6,32–37] Moreover, extracts enhanced lipid β-oxidation via increased *Cpt1a* gene expression.[6,36] Regarding liver oxidative status, *Morus* extract decreased NADPH oxidase activity,[37] TBARS, and ROS levels[6,30] and increased SOD, GST, and glutathione disulfide antioxidant enzymatic activity.[6,30–34,36,37] Likewise, fat weight was also decreased.[6,30–32,36] Furthermore, the administration of the different extracts reduced serum levels of ALT, AST, TC, TG, LDL,[6,30–32,35] leptin,[6,31] and adiponectin,[6] and improved glucose metabolism decreasing glucose and insulin serum levels, area under the receiver operating characteristic curve (AUC) (after oral glucose tolerance test) and homeostatic model assessment for insulin resistance (HOMA)-IR and HOMA for insulin sensitivity (HOMA-IS).[31,35,36] Finally, the results observed by Xu et al[30] after the berry extract administration were enhanced with the inclusion of β-glucan (200 mg kg^{-1} d^{-1}).

Rubus extract

Five of the retrieved articles reported on studies of different species and plant portions belonging to the genus *Rubus*. Two of them evaluated the effects of root extracts from *Rubus aleaefolius* Poir,[39,41] 1 of them included raspberry pomace (*Rubus* spp.) extracted with 30% acetone,[38] and the other used fruits and leaves of blackberry (*Rubus* spp.), using 50% ethyl alcohol as solvent.[9] A commercial fruit extract of *R. coreanus* was also used.[40] *Rubus* extracts were assayed on different models, such as Wistar[38] and Sprague-Dawley rats,[9,39,41] and on C57BL/6 mice.[40] The extract was administered mostly by oral gavage,[38–40] in the diet,[9] or by intragastric injection,[41] using doses between 0.1 and 1.44 g kg^{-1} BW per day. *Rubus* extracts decreased body[40,41] and liver weight,[40] liver steatosis,[9,39,41] as well as epididymal and retroperitoneal fat.[9,40] Furthermore, *Rubus* extracts reduced plasma and/or serum levels of ALT, AST, alkaline phosphatase, GGT, TC, TG, and LDL,[9,38–41]and improved glucose metabolism, resulting in a decrease of insulin and AUC of serum glucose levels during either glucose or insulin tolerance testing.[9] In addition, lipogenic metabolism and inflammatory status in the liver was improved,[9,38–41] and lipid β-oxidation

Downloaded from https://academic.oup.com/nutritionreviews/advance-article/doi/10.1093/nutrit/nuae132/7811260 by Universidad de Granada - Biblioteca user on 23 October 2024

was favored by an increase in *Cpt1a* gene expression.[9,39,40] In addition, the hepatic antioxidant capacity was also increased by SOD and glutathione reductase (GSH) enzymatic activity after *Rubus* extract administration.[9] Fotschki et al[38] observed that benefits of *Rubus* spp. extracts were enhanced by the inclusion of fructo-oligosaccharides (3%) and pectins (3%).

Photinia extract

One of the retrieved studies[5] focused on *Aronia melanocarpa*, formerly *Photinia melanocarpa*. The effects of a 50 mg kg^{-1} d^{-1} dose (orally administered) of a commercial ethanolic extract (portion not specified) were tested on male C57BL/6N mice for 12 weeks. Results included a reduction in BW, liver weight, and serum levels of AST, ALT, and leptin. The extract also caused a reduction in hepatic lipid deposition, hepatic levels of TG and Fatty Acid Synthase (FAS), and in hepatic *Pparg2*, *Fabp4*, and *Lpl* mRNA and protein expression. On the other hand, SOD enzymatic activity and trolox equivalent antioxidant capacity increased after the consumption of this extract.

Lycium extract

Fruit aqueous extract from *Lycium chinense*[42] was studied in 1 study, and a second study used *L. barbarum* fruit extract that was prepared sequentially by decoloration, delipidation in alcohol, and boiling in distilled water.[45] *Lycium* extracts were tested in C57BL/6 and C57BLS/J-m mice by oral gavage, implementing 4 different doses (1, 100, 200, or 400 mg kg^{-1} d^{-1}).[42,45] A decrease in liver weight, as well as in plasma and serum levels of TG, AST, and ALT, was achieved after the administration of the extract.[42] Moreover, *Lycium* extracts improved liver steatosis,[42,45] which was related to a reduction in protein and gene expression of inflammatory markers in liver and an increase in antioxidant enzymes activities.[42,45]

Vitis extract

One of the 3 articles reporting on studies involving the genus *Vitis* focused on a *V. coignetiae* aqueous extract of leaves,[23] and the other 2 articles reported on studies of *V. vinifera* extracts of skin and a mixture of seed and skin, using water[48] and ethanol[51] as solvents, respectively. The doses administered (100, 300, 200, or 500 mg kg^{-1} d^{-1}) were tested in Wistar rats[23,51] and C57BL/6 mice.[48] Reductions in BW, epididymal and retroperitoneal fat mass, as well as hepatic steatosis[23,48,51] were observed. Liver weight was reduced in 2 studies,[48,51] although *V. coignetiae* increased this parameter.[23] In addition, hepatic levels of TG and TC[48,51] were decreased, whereas AMPK antioxidant enzymatic activity (GPx, SOD, CAT) were increased.[48,51] Furthermore, Santos et al[48] observed that *V. vinifera* aqueous extract improved insulin resistance via reduction of glucose and serum insulin levels, increased expression of hepatic insulin cascade proteins, and resulted in a decrease in hepatic lipogenic factors. *V. coignetiae*[23] treatment showed a beneficial effect on NAFLD by reducing the percentage of fibrosis area and NF-κB expression. Oxidative status was also improved, as seen by increased plasma antioxidant activity.

Therefore, *Vitis* genus treatments presented beneficial effects on the treatment of NAFLD. *V. vinifera* showed positive effects in lipid and glucose metabolism, whereas *V. coignetiae* contributed to modulate the interaction between inflammation and oxidative stress.

DISCUSSION

In the present systematic review, we aimed to provide a complete description of the benefits of berry extracts on NAFLD. Antioxidant properties of the berries and their therapeutic use to treat different metabolic pathologies are well known. Kowalska and Olejnik[53] reviewed the beneficial effects of berry fruits in the prevention and treatment of metabolic syndrome, showing their antioxidant effect and potential to treat obesity and diabetes, improve hepatic and plasma lipid profile, and protect against NAFLD through the modulation of lipogenic and inflammatory genes. Keeping in mind the importance of circular economy, in this review, the beneficial effects of berry extracts made from other parts of the plant in addition to fruit were gathered that have beneficial properties against metabolic diseases.

After performing an extensive screening, 31 articles were included, using extracts from numerous genera (*Euterpe*, *Vaccinium*, *Phyllanthus*, *Ribes*, *Morus*, *Rubus*, *Photinia*, *Lycium*, and *Vitis)* whose fruit are considered berries. These species are commonly used for nutritional purposes and most are consumed worldwide. Extracts were obtained using different methodologies and from different parts of the plants. This systematic review is a first attempt, to our knowledge, to collect information on the impact that extracts of different plant components of berries have on NAFLD and its associated metabolic outcomes. The available information was organized so that future studies could take it into account. According ARRIVE guidelines, the quality of the retrieved studies was good, although there was great heterogeneity among them.

Induction of NAFLD in animal models was mainly performed by the inclusion of an HFD with different fat percentages or modifications. In a few studies, the

Downloaded from https://academic.oup.com/nutritionreviews/advance-article/doi/10.1093/nutrit/nuae132/7811260 by Universidad de Granada - Biblioteca user on 23 October 2024

pathology was established by methionine choline–deficient diet or orotic acid addition. In this regard, diet-induced obesity models are similar to the onset of this pathology in humans.[54,55]

The plant materials most used to obtain the functional extracts were the fruit and leaves. The most common berry extract administration was by oral gavage, followed by its inclusion in the diet. Moreover, no toxicity effects of the administration of berries in any form were reported. The most common study treatment period was between 9 and 13 weeks, and doses ranged from 50 to 1000 mg kg^{-1}. The extraction process is critical for the isolation of bioactive compounds and depends on the intended use of the final products.[56] The most frequently used solvents in the studies in this systematic review were water and ethanol with different purity percentages (Table 2). In general, regardless of the type of plant portion, most of the compounds isolated were polyphenols, flavonoids, and anthocyanins. In the genus *Morus*, Peng et al[6] reported that, through water extraction, the main identified components were neochlorogenic, cryptochlorogenic, and chlorogenic acid, whereas Ann et al[32] using ethanol as the solvent and identified 1-deoxynojirimycin and resveratrol. Using another part of the plant and the same solvents, *M. alba*[36,37] and *M. nigra*[31] fruit extracts contained cyanidin-3-*O*-glucoside. It seemed that *M. alba*[36] water extract had a higher content of polyphenols, whereas *M. nigra*[31] ethanolic extract had more flavonoids. In *Rubus* spp., chloroform:methanol:ammonia extracts from roots[39,41] were mainly composed of carbohydrates and alkaloids, whereas the acetone:water extract of *Rubus* pomace[38] had a high polyphenol content. *Euterpe* spp.[2,3,46,49] presented remarkably high anthocyanidin and anthocyanin content in seeds and pulp when either hydroalcoholic or soxhlet extraction was carried out, respectively. Similar results were obtained in different members of *Vaccinium*.[4,43] Finally, bioactive compounds present in *Vitis vinifera* seeds and skin have been studied by Charradi et al[51] and Santos et al,[48] who found that seeds were mainly composed of polyphenols (gallic acid and 2,5-dihydroxybenzoic acid), whereas skin contained mostly anthocyanins.

The development of NAFLD by the theory of 2 "hits" or stages is widespread. The first hit is triggered by TG accumulation in hepatocytes, caused by exacerbated fat intake and insulin resistance. This condition increases the liver's vulnerability to other damaging factors, such as increased levels of oxidative stress, activation of inflammatory pathways, and the onset of fibrosis, collectively referred to as the second hit.[57] The most widely studied parameters related to NAFLD are liver weight, hepatic steatosis, hepatic and serum TG and TC levels, lipid metabolism, and inflammatory status. In this regard, a summary of the most representative effects of berry extracts on the alterations of NAFLD are summarized in Figure 2.

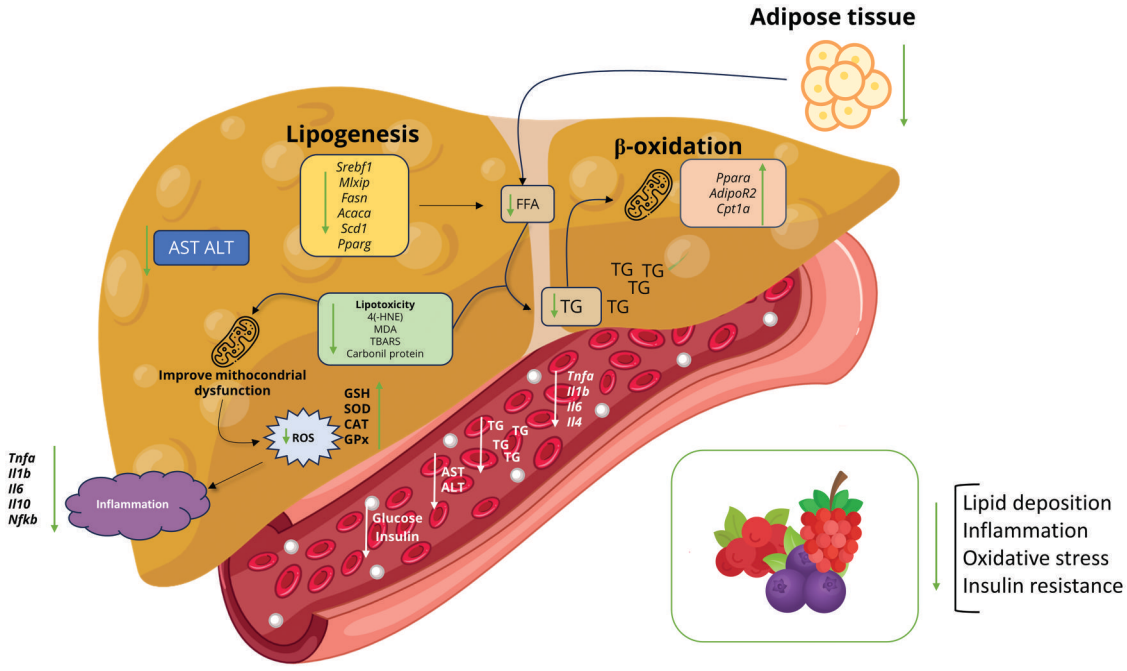

Figure 2. Representative Effects of Berry Extracts on the Alterations of Nonalcoholic Fatty Liver Disease. Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; CAT, catalase; GPx, glutathione peroxide; GSH, glutathione reductase; MDA, malondialdehyde; ROS, reactive oxygen species; SOD, superoxide dismutase; TBARS, thiobarbituric acid reactive substances.

Downloaded from https://academic.oup.com/nutritionreviews/advance-article/doi/10.1093/nutrit/nuae132/7811260 by Universidad de Granada - Biblioteca user on 23 October 2024

Lipid metabolism and hepatic steatosis

Hepatic fat deposition ensues as an unbalance among hepatic FA synthesis, de novo lipogenesis (DNL), hepatic availability of free fatty acids (FFAs) from hepatic lipolysis, and lipid exportation from the liver in the form of triglyceride-rich very-low-density lipoprotein. FFAs can be generated from several pathways, including increased hepatic DNL, delivery of FFAs from adipose tissue lipolysis, delivery of dietary fat, and reduced FA oxidation.[58] Regarding the effect of the functional plant extracts on the liver, a general decrease in liver weight and steatosis caused by a decrease in lipid deposition has been observed,[2,5,6,32,33,36–39,42,43,45,48,51] together with a reduction in macrovesicular and microvesicular steatosis,[1,3,4,9,31,33,34,36,39,41,43,45–47,51] and TG[1,3,6,9,30,31,33,36,37,40,42,46,48,51] and TC hepatic content.[1,3,4,6,30,31,33,36,38,39,46,48,51] In addition, administration of berry extracts led to a general decrease in plasma and serum TG,[2,6,30,32,35–41,46,50] TC,[1–3,6,30–32,35–37,39–41,46,50] LDL,[1–3,6,30–32,36,37,39–41,44,50] and very-low-density lipoprotein[2,3,46] content. Therefore, berry extracts could improve NAFLD by acting against the first hit hypothesis, decreasing plasma and serum leptin levels, preventing insulin resistance, and inhibiting lipogenesis.[3,5,6,30,40,50] Liver-weight reduction is a biomarker related to an improvement of NAFLD.[57] Berry extracts improved this biomarker with the exception of 2 studies in which liver weight was increased.[23,38] Although Pak et al[23] observed an increase in the relative liver weight, the *Vitis coignetiae* Pulliat. leaves extract alleviated liver fibrosis, improving nonalcoholic steatohepatitis by, theoretically, inhibition of the second hit.

One of the main actions of berry extracts was the hepatic DNL amelioration, in particular a decrease in the expression of genes such as *Srebf1*,[3,32,33,35–37,40,44,46,48] *Mlxipl* (ChREBP),[35] *Acaca*,[9,37,39,40,46] *Fasn*,[6,32,35–37,39,40] *Scd1*,[37] and *Pparg*,[5,34,38,47] which are genes that play a key role in this metabolic pathway.[59] Thus, lipid production and storage in NAFLD are attenuated after treatment with berry extract treatment, and there is a decrease in circulating FFAs levels.[1,30,35,43] Less FFA mobilization from adipose tissue is also related to decreased epididymal,[3,31,32,36,40,44,48] retroperitoneal,[3,31,32,36] perineal,[6,30,31,44] visceral,[1,50] peripheral, mesenteric, and subcutaneous repository levels, as well as groin and body crude fat levels.[6]

Another important mechanism of lipid metabolism in hepatocytes is the β-oxidation of FAs in mitochondria, with the upregulation of its major transcriptional peroxisome proliferator-activated receptor--α[60] by berry extracts.[6,32,44] In addition, AMPK phosphorylation was enhanced,[3,46] and this enzyme inactivated metabolic enzymes involved in FA and cholesterol synthesis, such as acetyl-coenzyme A (CoA) carboxylase (ACACA), and 3-hydroxy-3-methylglutaryl CoA reductase. In the first case, it was observed by an increase in the ratio of phosphorylated ACACA to ACACA,[3,36,46] leading as well to an increase in *Cpt1a* expression.[6,9,39,40] Cholesterol metabolism was also improved by a decrease in *Hmgcr*[3,6,33,40,46] and an increase in *Cyp7a1* gene expression.[33]

It is well known that the administration of an HFD also affects the expression of different genes regulated by transcription factors such as SREBP-1 and PPARG, which contribute to DNL. First, they reduce both hepatic and plasmatic lipid accumulation, correlated with liver weight reduction. In this sense, hepatic steatosis was ameliorated by an increase in enzymes involved in β-oxidation and a decrease in DNL. Liver function was also improved by berry extracts, as indicated by the reduction of AST[5,9,30,31,35,37,38,40–42,44,46,52] and ALT levels,[1,2,5,6,9,23,30,31,35,37,40–44,46,52] both linked to cellular damage and loss of functional integrity of the cell membranes.[46]

Glucose and glycogen metabolism

The most common risk factor for NAFLD development and progression is insulin resistance.[61] Systemic insulin resistance is characterized by the inability of insulin to reduce blood glucose levels appropriately, whereas hepatic insulin resistance is caused by interrupting hepatic glucose production but increasing lipogenesis stimulation. Insulin is also a key inhibitor of hepatic glucose production by suppression of glucose production through glycogenolysis and gluconeogenesis. Therefore, insulin resistance induces an elevation of glycogenolysis and an increase in hepatic glycolytic intermediates, which lead to raised glycolysis.[58] Despite its importance, only 2 studies included the effect of berry extracts on glycogen deposition.[9,36] In both articles, berry extracts increased glycogen content in NAFLD rats. In 1 study, blackberry leaf extract enhanced glycogen content more than the fruit extract, whereas in the second study, a high ratio or high dose of *Morus alba* extract in combination with silk amino acids increased glycogen content in NAFLD rats. Increased glycogen content may indicate decreased hepatic gluconeogenesis, favored by enhanced intrahepatic TG content. The reduction of TG content seems to explain the way that berries modulate glucose metabolism. The studies of Park et al[9,36] showed that both blackberry and mulberry extracts decreased serum glucose and insulin levels, as well as AUC of serum glucose levels during either glucose and insulin tolerance testing. Similarly, *M. nigra* L. and *M. alba* extracts,[30,31,35] *Phyllanthus niruri*,[1] and *Vitis vinifera* L.[48] decreased AUC after oral glucose tolerance

Downloaded from https://academic.oup.com/nutritionreviews/advance-article/doi/10.1093/nutrit/nuae132/7811260 by Universidad de Granada - Biblioteca user on 23 October 2024

testing, HOMA-IR, HOMA-IS, and glucose and insulin levels.

Anti-inflammatory and antioxidant properties

NAFLD is a pro-inflammatory condition, and inflammation and oxidative stress are critical for nonalcoholic steatohepatitis development and progression. Actually, inflammation and its main consequence, fibrosis, are key determinants of the long-term prognosis of the disease.[57] Therefore, a great variety of articles focused on the factors of the second hit hypothesis, such as effects on inflammatory markers and antioxidant enzymes. The inflammatory process was attenuated by berry extracts by decreasing inflammatory cell infiltration[9,36,39,41,49] and gene and protein expression of inflammatory markers such as *TNFa*,[9,34,36,41–43,45,50,52] *Il1b*,[9,34,36,42,43,50,52] *Il6*,[34,38,41,42,50] *Il10*,[45] *Nfkb*,[4,23,34,41,43,45] *Ppara*,[38,43] *Ptgs2* (COX-2),[34,41,43] *Ccl2*,[18,43] *Ccl3*,[43] *Ccr2*,[43] *Tgfb*,[42,45] *Nlrp3*,[43,45] *Nlrp6*,[45] *Casp1*,[43,45] *Nr1h3* (Lxra),[32,40,44] *Icam1*,[42] *Itgax* (CD11c),[42] *Fabp4*,[5,32,34] F4/80,[42] *Pycard* (ASC),[45] and *Tlr4*.[43] In the same way, inflammatory markers such as TNF-α,[6,30,36,47,52] IL-1β,[30,52] IL-4,[30] and IL-6[47,52] were decreased in serum. Even short periods of berry extracts (eg, 3-week administration of *Phyllanthus niruri*[47] and *Lycium barbarum* Lynn[45]) or 1-week administration of *Rubus aleaefolius* Poir. extract[41] resulted in a significant improvement in the anti-inflammatory status. Moreover, berry extracts enhanced the antioxidant capacity of the liver by increasing the activity of key role antioxidant enzymes (namely, SOD,[3,6,9,30,36,37,42,46,48,51,52] CAT,[3,42,44,45,48,52] GPX,[3,6,45,46,48,51,52] GRd,[44] UCP2,[32] and GSH[9,36,51]) and decreasing pro-oxidant markers (ie, Nrf2, malondialdehyde [MDA],[2,3,9,36–38,42,45,46,48] carbonyl protein,[2,3,46,48] TBARs,[6,49] 4-HNE,[32,37] 8-isoprostane,[46] and ROS[30]). In general, it has been observed that berries with the same extraction protocol and treatment period (aqueous extract; 4 weeks) but of different genera (*L. chinense*[42] and *P. emblica* L.[52]) had similar effects on the decrease of TBARS[52] and GSH and MDA levels.[42] Such beneficial actions could be explained by the presence of different compounds, such as flavonoids, anthocyanins, catechin, epicatechin, proanthocyanidins, gallic acid, and ellagic acid, which are well known for their antioxidant and anti-inflammatory properties.[3,37,42,44,52] In addition, berry extracts cause decrease of the secretion of various adipokines that contribute to hepatic inflammation.[32] The most representative effects of berry extracts against NAFLD and its associated alterations are summarized in Figure 2.

One of the principal limitations of this study is the difficulty in defining the term "berry" and the lack of a global Medical Subject Heading term for it. Therefore, this study included the most cultivated and commercialized berry genera. Another limitation was the difficulty of including clinical studies, due to the small number of studies that tested berry extracts in humans ($n = 5$). This corroborates the fundamental aspect of collecting the already existing results from animal studies for the encouragement of future clinical trials. Moreover, only 3 articles included female rodent models, which indicates lack of information for proving any sex inferences on the observed effects. The high variability of the treatment periods of the studies limits the value of the comparison of the observed effects of berry extracts. Therefore, there is a need for homogenization of the methodology. Also, the heterogeneity of extraction methodologies and solvents, as well as NAFLD induction protocols are a limitation to comparing the beneficial effects of the berry extracts. In addition, the chemical composition of the extracts is difficult to compare and unreliable because there is no established protocol for analysis of compounds, and each study used the standards and analyses the compounds the researchers deemed convenient.

CONCLUSIONS

In conclusion, all the studies in this systematic review reported beneficial effects of functional extracts of berries on altered biomarkers associated with NAFLD, although a wide discrepancy in the elaboration of the extracts was observed. Administration of berry extracts to genetically or diet-induced obese animal models demonstrates positive effects on lipid and glucose metabolism, ameliorating first-hit parameters such as body, liver, and fat weight. Additionally, they exhibit antioxidant and anti-inflammatory properties, counteracting the alterations involved in the 2-hit hypothesis. These results are encouraging for the inclusion of berry extracts in clinical trials as a complementary approach for the amelioration of certain disrupted biomarkers linked to NAFLD onset.

This systematic review primarily focuses on in vivo preclinical models that replicate some of the NAFLD-derived alterations to delve into the molecular mechanisms underlying these alterations and how they are influenced by the administration of the mentioned functional ingredients. Although these insights are promising, future research involving humans is necessary to fully understand the potential therapeutic benefits of berry extracts. Thus, these findings provide valuable groundwork for designing future clinical studies.

Downloaded from https://academic.oup.com/nutritionreviews/advance-article/doi/10.1093/nutrit/nuae132/7811260 by Universidad de Granada - Biblioteca user on 23 October 2024

Author Contributions

A.G.-B. and A.L.M. equally contributed to the data collection, analysis, and interpretation; and writing and revision of the original version of the manuscript. R.M.M. contributed to the conceptualization and design of the research, critical review of the manuscript, and to the funding acquisition, and served as an external reviewer when needed. J.M.P.F. and M.L.J.R.C. contributed to critical reviewing the manuscript, interpretation of the data, and funding acquisition. G.K. contributed to the conceptualization of the study, supervision of methodology, reviewing the retrieved studies when needed, critical review of the manuscript, and funding acquisition. All authors read and approved the submitted version of the manuscript.

Acknowledgments

The authors acknowledge the University of Granada, Junta de Andalucía, and the European Union for financing the FEDER program. Authors really appreciate the contribution of CBUA/University of Granada for covering the open access charges.

Supplementary Material

Supplementary Material is available at *Nutrition Reviews* online.

Funding

This work was supported by the Spanish Ministry of Science and Innovation (grants RTC2019-006870-1 and TED2021.131241A.I00), and the Regional Government of Andalusia (grants P21_00115 and B-AGR-662-UGR20). Moreover, funding for open access charges was supported by Universidad de Granada / CBUA.

Conflicts of Interest

The authors declare no conflict of interest.

REFERENCES

1. Al Zarzour RH, Ahmad M, Asmawi MZ, et al. *Phyllanthus niruri* standardized extract alleviates the progression of non-alcoholic fatty liver disease and decreases atherosclerotic risk in Sprague-Dawley rats. *Nutrients*. 2017;9(7):766. https://doi.org/10.3390/nu9070766
2. Tavares TB, Santos IB, de Bem GF, et al. Therapeutic effects of açaí seed extract on hepatic steatosis in high-fat diet-induced obesity in male mice: a comparative effect with rosuvastatin. *J Pharm Pharmacol*. 2020;72(12):1921-1932. https://doi.org/10.1111/jphp.13356
3. de Oliveira PRB, da Costa CA, de Bem GF, et al. *Euterpe oleracea* Mart.-derived polyphenols protect mice from diet-induced obesity and fatty liver by regulating hepatic lipogenesis and cholesterol excretion. *PLoS One*. 2015;10(12):e0143721. https://doi.org/10.1371/journal.pone.0143721
4. Morrison MC, Liang W, Mulder P, et al. Mirtoselect, an anthocyanin-rich bilberry extract, attenuates non-alcoholic steatohepatitis and associated fibrosis in ApoE(*)3Leiden mice. *J Hepatol*. 2015;62(5):1180-1186. https://doi.org/10.1016/j.jhep.2014.12.011
5. Park CH, Kim JH, Lee EB, et al. *Aronia melanocarpa* extract ameliorates hepatic lipid metabolism through PPARγ2 downregulation. *PLoS One*. 2017;12(1):e0169685. https://doi.org/10.1371/journal.pone.0169685
6. Peng CH, Lin HT, Chung DJ, Huang CN, Wang CJ. Mulberry leaf extracts prevent obesity-induced NAFLD with regulating adipocytokines, inflammation and oxidative stress. *J Food Drug Anal*. 2018;26(2):778-787. https://doi.org/10.1016/j.jfda.2017.10.008
7. Younossi ZM, Golabi P, de Avila L, et al. The global epidemiology of NAFLD and NASH in patients with type 2 diabetes: a systematic review and meta-analysis. *J Hepatol*. 2019;71(4):793-801. https://doi.org/10.1016/j.jhep.2019.06.021
8. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Hepatology*. 2012;55(6):2005-2023. https://doi.org/10.1002/hep.25762
9. Park S, Cho SM, Jin BR, Yang HJ, Yi QJ. Mixture of blackberry leaf and fruit extracts alleviates non-alcoholic steatosis, enhances intestinal integrity, and increases *Lactobacillus* and *Akkermansia* in rats. *Exp Biol Med (Maywood)*. 2019;244(18):1629-1641. https://doi.org/10.1177/1535370219889319
10. Gofton C, Upendran Y, Zheng MH, George J. MAFLD: how is it different from NAFLD? *Clin Mol Hepatol*. 2022;29(suppl):S17-S31. https://doi.org/10.3350/cmh.2022.0367
11. Pietta PG. Flavonoids as antioxidants. *J Nat Prod*. 2000;63(7):1035-1042. https://doi.org/10.1021/np9904509
12. Lotito SB, Frei B. Consumption of flavonoid-rich foods and increased plasma antioxidant capacity in humans: cause, consequence, or epiphenomenon? *Free Radic Biol Med*. 2006;41(12):1727-1746. https://doi.org/10.1016/j.freeradbiomed.2006.04.033
13. Kicinska A, Jarmuszkiewicz W. Flavonoids and mitochondria: activation of cytoprotective pathways? *Molecules*. 2020;25(13):3060. https://doi.org/10.3390/molecules25133060
14. Duda-Chodak A, Tarko T, Satora P, Sroka P. Interaction of dietary compounds, especially polyphenols, with the intestinal microbiota: a review. *Eur J Nutr*. 2015;54(3):325-341. https://doi.org/10.1007/s00394-015-0852-y
15. Sheng K, Zhang G, Sun M, et al. Grape seed proanthocyanidin extract ameliorates dextran sulfate sodium-induced colitis through intestinal barrier improvement, oxidative stress reduction, and inflammatory cytokines and gut microbiota modulation. *Food Funct*. 2020;11(9):7817-7829. https://doi.org/10.1039/D0FO01418D
16. Power KA, Lu JT, Monk JM, et al. Purified rutin and rutin-rich asparagus attenuates disease severity and tissue damage following dextran sodium sulfate-induced colitis. *Mol Nutr Food Res*. 2016;60(11):2396-2412. https://doi.org/10.1002/mnfr.201500890
17. Wang Z, Ma L, Su M, et al. Baicalin induces cellular senescence in human colon cancer cells via upregulation of DEPP and the activation of Ras/Raf/MEK/ERK signaling. *Cell Death Dis*. 2018;9(2):217-217. https://doi.org/10.1038/s41419-017-0223-0
18. Szajdek A, Borowska EJ. Bioactive compounds and health-promoting properties of berry fruits: a review. *Plant Foods Hum Nutr*. 2008;63(4):147-156. https://doi.org/10.1007/s11130-008-0097-5
19. Manganaris GA, Goulas V, Vicente AR, Terry LA. Berry antioxidants: small fruits providing large benefits. *J Sci Food Agric*. 2014;94(5):825-833. https://doi.org/10.1002/jsfa.6432
20. Muka T, Glisic M, Milic J, et al. A 24-step guide on how to design, conduct, and successfully publish a systematic review and meta-analysis in medical research. *Eur J Epidemiol*. 2020;35(1):49-60. https://doi.org/10.1007/s10654-019-00576-5
21. Száva-Kováts E. Unfounded attribution of the "half-life" index-number of literature obsolescence to Burton and Kebler: a literature science study. *J Am Soc Inf Sci*. 2002;53(13):1098-1105. https://doi.org/10.1002/asi.10105
22. Hooijmans CR, Rovers MM, de Vries RB, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. *BMC Med Res Methodol*. 2014;14(1):43. https://doi.org/10.1186/1471-2288-14-43
23. Pak W, Takayama F, Hasegawa A, et al. Water extract of *Vitis coignetiae* Pulliat leaves attenuates oxidative stress and inflammation in progressive NASH rats. *Acta Med Okayama*. 2012;66(4):317-327. https://doi.org/10.18926/AMO/48686
24. Vendrame S, Del Bo' C, Ciappellano S, Riso P, Klimis-Zacas D. Berry fruit consumption and metabolic syndrome. *Antioxidants (Basel)*. 2016;5(4):34. https://doi.org/10.3390/antiox5040034
25. Nile SH, Park SW. Edible berries: bioactive components and their effect on human health. *Nutrition*. 2014;30(2):134-144. https://doi.org/10.1016/j.nut.2013.04.007
26. du Sert NP, Ahluwalia A, Alam S, et al. Reporting animal research: explanation and elaboration for the ARRIVE guidelines 2.0. *PLoS Biol*. 2020;18(7):e3000411. https://doi.org/10.1371/journal.pbio.3000411
27. García-González M, Muñoz F, González-Cantalapiedra A, López-Peña M, Saulacic N. Systematic review and quality evaluation using ARRIVE 2.0 guidelines on

Downloaded from https://academic.oup.com/nutritionreviews/advance-article/doi/10.1093/nutrit/nuae132/7811260 by Universidad de Granada - Biblioteca user on 23 October 2024

animal models used for periosteal distraction osteogenesis. *Animals (Basel)*. 2021;11(5):1233. https://doi.org/10.3390/ani11051233
28. Cohen J. Weighted kappa: nominal scale agreement provision for scaled disagreement or partial credit. *Psychol Bull*. 1968;70(4):213-220. https://doi.org/10.1037/h0026256
29. Wanden-Berghe C, Sanz-Valero J. Systematic reviews in nutrition: standardized methodology. *Br J Nutr*. 2012;107 suppl 2(S2):S3-S7. https://doi.org/10.1017/S0007114512001432
30. Xu J, Wang X, Cao K, Dong Z, Feng Z, Liu J. Combination of β-glucan and *Morus alba* L. leaf extract promotes metabolic benefits in mice fed a high-fat diet. *Nutrients*. 2017;9(10):1110. https://doi.org/10.3390/nu9101110
31. Song H, Lai J, Tang Q, Zheng X. Mulberry ethanol extract attenuates hepatic steatosis and insulin resistance in high-fat diet-fed mice. *Nutr Res*. 2016;36(7):710-718. https://doi.org/10.1016/j.nutres.2016.01.011
32. Ann JY, Eo H, Lim Y. Mulberry leaves (*Morus alba* L.) ameliorate obesity-induced hepatic lipogenesis, fibrosis, and oxidative stress in high-fat diet-fed mice. *Genes Nutr*. 2015;10(6):46. https://doi.org/10.1007/s12263-015-0495-x
33. Hu Y, Xu J, Chen Q, et al. Regulation effects of total flavonoids in *Morus alba* L. on hepatic cholesterol disorders in orotic acid induced NAFLD rats. *BMC Complement Med Ther*. 2020;20(1):257. https://doi.org/10.1186/s12906-020-03052-w
34. Lee MR, Kim JE, Park JW, et al. Fermented mulberry (*Morus alba*) leaves suppress high fat diet-induced hepatic steatosis through amelioration of the inflammatory response and autophagy pathway. *BMC Complement Med Ther*. 2020;20(1):283. https://doi.org/10.1186/s12906-020-03076-2
35. Ma LL, Yuan YY, Zhao M, et al. Mori cortex extract ameliorates nonalcoholic fatty liver disease (NAFLD) and insulin resistance in high-fat-diet/streptozotocin-induced type 2 diabetes in rats. *Chin J Nat Med*. 2018;16(6):411-417. https://doi.org/10.1016/S1875-5364(18)30074-8
36. Park S, Zhang T, Qiu JY, Wu X. The combination of mulberry extracts and silk amino acids alleviated high fat diet-induced nonalcoholic hepatic steatosis by improving hepatic insulin signaling and normalizing gut microbiome dysbiosis in rats. *Evid Based Complement Alternat Med*. 2019;2019:8063121. https://doi.org/10.1155/2019/8063121
37. Yang DK, Jo DG. Mulberry fruit extract ameliorates nonalcoholic fatty liver disease (NAFLD) through inhibition of mitochondrial oxidative stress in rats. *Evid Based Complement Alternat Med*. 2018;2018:8165716. https://doi.org/10.1155/2018/8165716
38. Fotschki B, Juśkiewicz J, Jurgoński A, Sójka M. Fructo-oligosaccharides and pectins enhance beneficial effects of raspberry polyphenols in rats with nonalcoholic fatty liver. *Nutrients*. 2021;13(3):833. https://doi.org/10.3390/nu13030833
39. Li Y, Zhao J, Zheng H, Zhong X, Zhou J, Hong Z. Treatment of nonalcoholic fatty liver disease with total alkaloids in *Rubus aleaefolius* Poir through regulation of fat metabolism. *Evid Based Complement Alternat Med*. 2014;2014:768540. https://doi.org/10.1155/2014/768540
40. Nam MK, Choi HR, Cho JS, et al. Inhibitory effects of *Rubi fructus* extracts on hepatic steatosis development in high-fat diet-induced obese mice. *Mol Med Rep*. 2014;10(4):1821-1827. https://doi.org/10.3892/mmr.2014.2398
41. Zhao J, Zheng H, Liu Y, et al. Anti-inflammatory effects of total alkaloids from *Rubus alceifolius* Poir [corrected] on non-alcoholic fatty liver disease through regulation of the NF-κB pathway. *Int J Mol Med*. 2013;31(4):931-937. https://doi.org/10.3892/ijmm.2013.1281
42. Bae UJ, Oh MR, Park J, et al. Supplementation with *Lycium chinense* fruit extract attenuates methionine choline-deficient diet-induced steatohepatitis in mice. *J Funct Foods*. 2017;31:1-8. https://doi.org/10.1016/j.jff.2017.01.032
43. Glisan SL, Ryan C, Neilson AP, Lambert JD. Cranberry extract attenuates hepatic inflammation in high-fat-fed obese mice. *J Nutr Biochem*. 2016;37:60-66. https://doi.org/10.1016/j.jnutbio.2016.07.009
44. Huang CZ, Tung YT, Hsia SM, Wu CH, Yen GC. The hepatoprotective effect of *Phyllanthus emblica* L. fruit on high fat diet-induced non-alcoholic fatty liver disease (NAFLD) in SD rats. *Food Funct*. 2017;8(2):842-850. https://doi.org/10.1039/c6fo01585a
45. Xiao J, Wang F, Liong EC, So KF, Tipoe GL. *Lycium barbarum* polysaccharides improve hepatic injury through NFkappa-B and NLRP3/6 pathways in a methionine choline deficient diet steatohepatitis mouse model. *Int J Biol Macromol*. 2018;120(Pt B):1480-1489. https://doi.org/10.1016/j.ijbiomac.2018.09.151
46. de Bem GF, da Costa CA, da Silva Cristino Cordeiro V, et al. *Euterpe oleracea* Mart. (açaí) seed extract associated with exercise training reduces hepatic steatosis in type 2 diabetic male rats. *J Nutr Biochem*. 2018;52:70-81. https://doi.org/10.1016/j.jnutbio.2017.09.021
47. Al Zarzour RH, Alshawsh MA, Asif M, et al. Adipocytokine regulation and antiangiogenic activity underlie the molecular mechanisms of therapeutic effects of *Phyllanthus niruri* against non-alcoholic fatty liver disease. *Nutrients*. 2018;10(8):1057. https://doi.org/10.3390/nu10081057
48. Santos IB, de Bem GF, Cordeiro VSC, et al. Supplementation with *Vitis vinifera* L. skin extract improves insulin resistance and prevents hepatic lipid accumulation and steatosis in high-fat diet-fed mice. *Nutr Res*. 2017;43:69-81. https://doi.org/10.1016/j.nutres.2017.05.007
49. Freitas RB, Novaes RD, Gonçalves RV, et al. *Euterpe edulis* extract but not oil enhances antioxidant defenses and protects against nonalcoholic fatty liver disease induced by a high-fat diet in rats. *Oxid Med Cell Longev*. 2016;2016:8173876. https://doi.org/10.1155/2016/8173876
50. Nanashima N, Horie K, Yamanouchi K, et al. Blackcurrant (*Ribes nigrum*) extract prevents dyslipidemia and hepatic steatosis in ovariectomized rats. *Nutrients*. 2020;12(5):1541. https://doi.org/10.3390/nu12051541
51. Charradi K, Elkahoui S, Karkouch I, et al. Protective effect of grape seed and skin extract against high-fat diet-induced liver steatosis and zinc depletion in rat. *Dig Dis Sci*. 2014;59(8):1768-1778. https://doi.org/10.1007/s10620-014-3128-0
52. Tung YT, Huang CZ, Lin JH, Yen GC. Effect of *Phyllanthus emblica* L. fruit on methionine and choline-deficiency diet-induced nonalcoholic steatohepatitis. *J Food Drug Anal*. 2018;26(4):1245-1252. https://doi.org/10.1016/j.jfda.2017.12.005
53. Kowalska K, Olejnik A. Current evidence on the health-beneficial effects of berry fruits in the prevention and treatment of metabolic syndrome. *Curr Opin Clin Nutr Metab Care*. 2016;19(6):446-452. https://doi.org/10.1097/MCO.0000000000000322
54. Simoes ICM, Janikiewicz J, Bauer J, et al. Fat and sugar–a dangerous duet. A comparative review on metabolic remodeling in rodent models of nonalcoholic fatty liver disease. *Nutrients*. 2019;11(12):2871. https://doi.org/10.3390/nu11122871
55. Small L, Brandon AE, Turner N, Cooney GJ. Modeling insulin resistance in rodents by alterations in diet: what have high-fat and high-calorie diets revealed? *Am J Physiol Endocrinol Metab*. 2018;314(3):E251-E265. https://doi.org/10.1152/ajpendo.00337.2017
56. Abubakar AR, Haque M. Preparation of medicinal plants: basic extraction and fractionation procedures for experimental purposes. *J Pharm Bioallied Sci*. 2020;12(1):1-10. https://doi.org/10.4103/jpbs.JPBS_175_19
57. Bessone F, Razori MV, Roma MG. Molecular pathways of nonalcoholic fatty liver disease development and progression. *Cell Mol Life Sci*. 2019;76(1):99-128. https://doi.org/10.1007/s00018-018-2947-0
58. Chao HW, Chao SW, Lin H, Ku HC, Cheng CF. Homeostasis of glucose and lipid in non-alcoholic fatty liver disease. *Int J Mol Sci*. 2019;20(2):298. https://doi.org/10.3390/ijms20020298
59. García-Beltrán A, Martínez R, Porres JM, et al. Novel insights and mechanisms of diet-induced obesity: mid-term versus long-term effects on hepatic transcriptome and antioxidant capacity in Sprague-Dawley rats. *Life Sci*. 2023;324:121746. https://doi.org/10.1016/j.lfs.2023.121746
60. Ciapaite J, van den Broek NM, te Brinke H, et al. Differential effects of short- and long-term high-fat diet feeding on hepatic fatty acid metabolism in rats. *Biochim Biophys Acta*. 2011;1811(7-8):441-451. https://doi.org/10.1016/j.bbalip.2011.05.005
61. Bao L, Hao P, Jiang M, Chu W. Liquiritigenin regulates insulin sensitivity and ameliorates inflammatory responses in the nonalcoholic fatty liver by activation PI3K/AKT pathway. *Chem Biol Drug Des*. 2023;102(4):793-804. https://doi.org/10.1111/cbdd.14292

© The Author(s) 2024. Published by Oxford University Press on behalf of the International Life Sciences Institute.
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (https://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact journals.permissions@oup.com
Nutrition Reviews, 2024, 00, 1–23
https://doi.org/10.1093/nutrit/nuae132
Systematic Review

Downloaded from https://academic.oup.com/nutritionreviews/advance-article/doi/10.1093/nutrit/nuae132/7811260 by Universidad de Granada - Biblioteca user on 23 October 2024