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Systematic Review

Redox-Regulatory Mechanisms of Hazelnut (*Corylus avellana* L.) and Its By-Products: A Systematic Review of In Vitro, In Vivo, and Clinical Studies

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Abstract

Oxidative stress and inflammation contribute to the pathology of chronic diseases, such as cardiometabolic diseases, neurological disorders, and cancer, and tree nuts have been associated with a wide array of health benefits. This systematic review (INPLASY2026100026) evaluated the antioxidant and redox-regulatory mechanisms of hazelnut (*Corylus avellana* L.) and its by-products (skin, leaf, green leafy cover). PubMed/MEDLINE, Web of Science and Scopus were searched up to 31 August 2026. In vitro (including in silico), in vivo, and clinical studies were eligible, risk of bias was assessed with study-specific tools, and results were narratively synthesized. Seventeen studies were included. In vitro, hazelnut extracts showed radical scavenging in cell-free assays, reduced intracellular ROS, carbonyl trapping and activation of the Nrf2 pathway, which is inversely related to NF-κB-mediated inflammation. In vivo studies reported enhanced antioxidant defenses and reduced lipid peroxidation, while clinical studies reported lower ox-LDL and DNA damage, although findings were heterogeneous. Limitations include the lack of dose–response testing in most in vitro studies and an unclear risk of bias in all in vivo studies, owing to incomplete reporting, and a high risk of bias in the non-randomized clinical studies. Hazelnuts and their by-products may be of interest for dietary and nutraceutical approaches to disease prevention, however, clinical evidence of efficacy and data on the safety of by-products are still lacking. No external funding was received.

Keywords: hazelnut; *Corylus avellana*; by-products; antioxidants; polyphenols; oxidative stress; redox regulation; Nrf2/Keap1; anti-inflammatory; systematic review

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1. Introduction

Oxidative stress and inflammation are the main contributors to the pathology of chronic diseases, including diabetes, cardiometabolic diseases, neurological disorders, and cancer [1,2], and dietary antioxidant and anti-inflammatory components have been proposed to protect against these processes [3]. Dietary patterns such as the Mediterranean diet, which includes nuts, have been associated with a wide array of health benefits [4,5]. Nut consumption has been linked to reduced cardiovascular risk [6] and to lower oxidative stress markers [7], an effect attributed to bioactive compounds that up-regulate the nuclear

factor erythroid 2-related factor 2 (Nrf2) pathway [7], and to polyphenols that prevent lipid peroxidation, support DNA repair and modulate mitogen-activated protein kinase signaling [8,9]. Animal studies have shown that dietary nuts improve oxidative stress biomarkers, whereas human studies have not been convincing regarding oxidative stress, inflammation or the prevention of cardiovascular disease [10]. Because each type of nut has its own bioactive profile, nut-specific evidence is needed. Hazelnuts (*Corylus avellana* L.) are a source of unsaturated fatty acids, tocopherols, minerals, flavonoids (e.g., catechin, quercetin) and phenolic acids (e.g., gallic and caffeic acids) [11], and the phenolic compounds of the kernel, mostly of the skin, and of by-products such as green leafy covers and leaves show antioxidant and radical-scavenging activities [12]. They are also among the most popular tree nuts worldwide, widely used by the confectionery industry, and their processing generates by-products (skin, hard shell, green leafy covers, and leaves) of low commercial value that are regarded as waste [11,12], which makes them a relevant model for studying redox-active nut constituents. However, the evidence on the modulation of oxidative stress and inflammation biomarkers by hazelnuts, as well as on the redox mechanisms involved, is inconsistent. Therefore, the aim of this systematic review was to critically investigate the antioxidant/redox mechanisms of hazelnuts and their by-products, which are relevant to cellular redox regulation, synthesizing the evidence from in vitro, in vivo, and clinical studies.

2. Materials and Methods

This systematic review aimed to comprehensively evaluate the antioxidant and redox-regulatory mechanisms of hazelnut and its by-products, integrating evidence from in vitro (including in silico), in vivo, and clinical studies. The study addressed how hazelnut-derived compounds interact with redox-regulatory systems across these levels of evidence.

The review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [13]. The review protocol was registered retrospectively on the INPLASY database, after the database searches had been conducted (registration number: INPLASY2026100026, with DOI 10.37766/inplasy2026.10.0026, https://inplasy.com/inplasy-2026-10-0026/ (accessed on 6 October 2026)). The registration was undertaken to improve the transparency of the review. A minor change was made to the title after registration (a single word); no other changes were made to the registered protocol, including the eligibility criteria and outcomes.

2.1. Search Strategy

A systematic search was conducted across three electronic databases: PubMed/MEDLINE, Web of Science, and Scopus without restriction on publication date. The investigations were concluded on 31 August 2026. The search strategy comprised five thematic groups of search terms linked by the Boolean operator AND, while synonymous terms within each group were joined by OR.

The first group identified the plant source: Corylus (MeSH term), hazelnut*, "hazel nut*", "Corylus avellana", and filbert*. The second group covered antioxidant compounds: Antioxidants (MeSH term), antioxidant*, polyphenol*, phenol*, flavonoid*, tocopherol*, catechin*, and proanthocyanidin*. The third group covered redox biology: "Oxidation-Reduction" and "Oxidative Stress" (MeSH terms), redox, "redox homeostasis", "redox regulation", "reactive oxygen species", ROS, "oxidative stress", Nrf2, Keap1, "superoxide dismutase", SOD, catalase, and glutathione. The fourth group targeted mechanistic evidence: mechanism*, pathway*, signaling, interact*, and modulat*. The fifth group covered study type and model system: "In Vitro Techniques" (MeSH term), "in vitro", "in vivo",

cell*, animal*, rodent*, mouse, mice, rat, rats, clinical, trial*, and human*. Truncation symbols (*) were used to capture word variants.

Two complementary approaches were used to identify eligible studies. First, direct searches were conducted in the electronic databases. In PubMed, controlled vocabulary (MeSH) and free-text terms were combined; in Web of Science, the search was applied to the Topic field; and in Scopus, it was applied to the title, abstract, and keywords (TITLE-ABS-KEY) fields. The strategy was adapted to the syntax of each database, and the full search strings are provided in Supplementary Table S1. Second, an indirect search was performed by examining the reference lists of the identified studies, in order to retrieve further eligible records not captured by the database searches.

2.2. Eligibility Criteria

Studies were selected according to the PICOS framework (Table S2). Eligible studies investigated the antioxidant and redox-regulatory effects of hazelnut and its by-products at one of three levels of evidence: in vitro (including in silico) studies, in vivo animal studies, and human clinical studies.

Reviews, conference abstracts, editorials, and letters were excluded, as were studies without full text, studies in which hazelnut-specific effects could not be separated from those of other foods, including other types of nuts, and studies limited to chemical composition or to cell-free antioxidant assays without any redox-related biological outcome. No language filter was applied in the database searches; articles not written in English were excluded at the screening stage.

For the in vitro segment, studies were eligible if they investigated the interaction between hazelnut-derived antioxidant compounds and cellular redox-regulatory systems at one of two mechanistic levels: (a) signaling pathway-level mechanisms confirmed by molecular, biochemical, or computational evidence (e.g., Western blot analysis of pathway proteins, molecular docking), or (b) direct chemical or biochemical mechanisms explicitly characterized (e.g., radical scavenging, trapping of reactive carbonyl species). Studies reporting only a functional antioxidant outcome were also included, provided that redox-relevant cellular endpoints were assessed; these are distinguished throughout the Results from studies demonstrating a defined pathway or chemical mechanism.

Studies combining in vitro and in vivo experiments were included only once and assigned to each level of evidence according to the experimental component reported, so that each component was assessed and synthesized in its own segment.

2.3. Study Screening and Inclusion

The records retrieved from the three databases (n = 96) were exported to Microsoft Excel, and duplicates were removed. Titles and abstracts were screened independently by two reviewers (R.B. and M.E.R.) against the eligibility criteria; articles not written in English were excluded at this stage. The full texts of potentially eligible records were then retrieved and assessed for eligibility in the same way, and the reasons for exclusion were recorded. Disagreements at either stage were resolved by discussion with a third reviewer (D.-S.P.) consulted when consensus could not be reached. Records identified by examining the reference lists of the included studies were screened using the same procedure. No automation tools were used to screen the records, apart from the removal of duplicates in Microsoft Excel. The selection process is summarized in the PRISMA 2020 flow diagram (Figure 1).

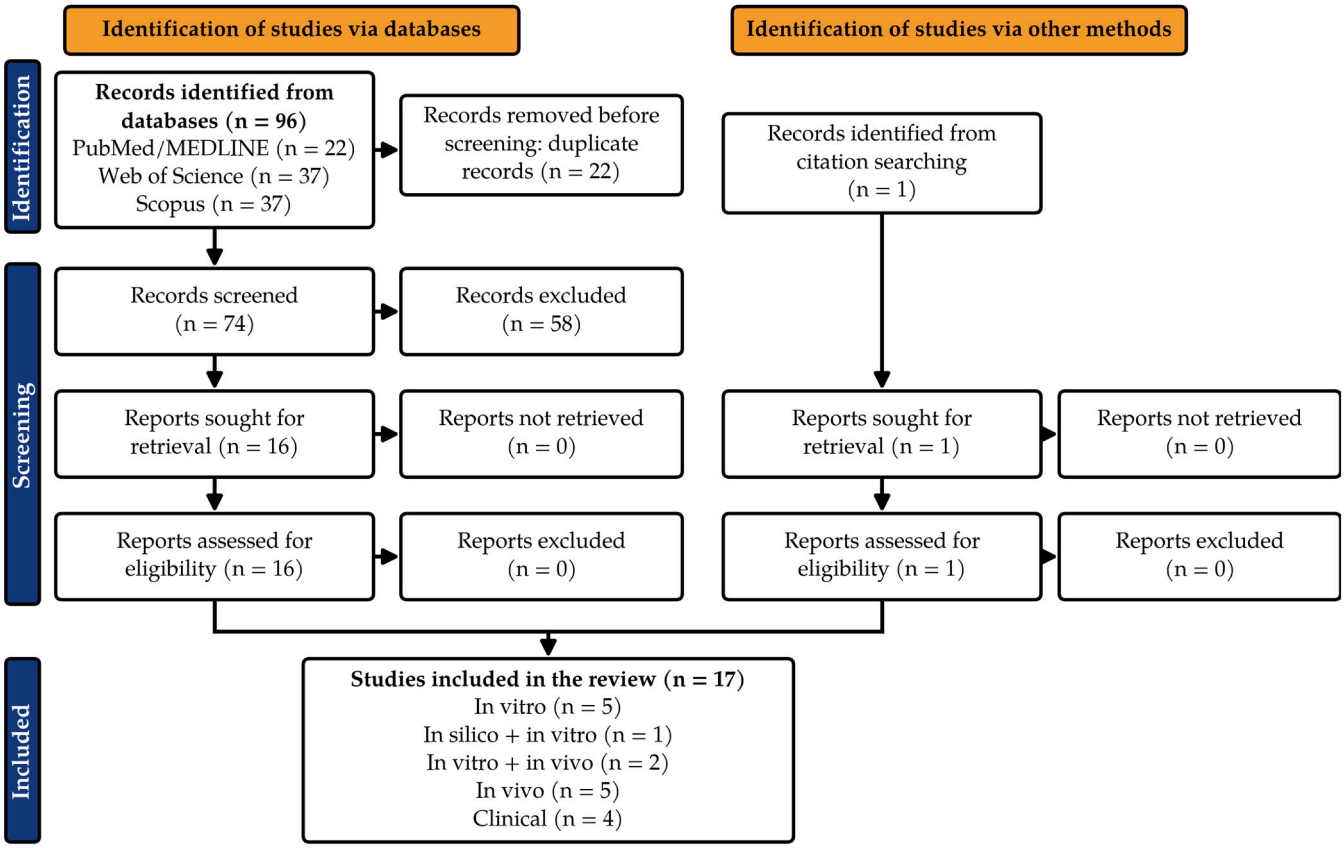


Figure 1. PRISMA 2020 flow diagram of the study selection process.

2.4. Data Extraction

Data were extracted by one researcher (R.B.) and verified by a second (M.E.R.), using a standardized form adapted to each level of evidence; disagreements were handled as described in Section 2.3. The authors of the included studies were not contacted to obtain or confirm data, and no automation tools were used for data extraction. For all studies, the following information was recorded: first author, year, country, study design, and funding source. For the tested material, the extracted data included the plant part, extraction procedure or formulation, chemical characterization, and dose or concentration. In the in vitro studies, the cell model, the stressors, the assays used, and the investigated mechanism were also extracted; in the in vivo studies, the animal species, the experimental model, and the duration and route of administration; and in the clinical studies, the participants' characteristics, the intervention, its duration, and the comparator. For all studies, the redox-related outcomes and the main findings were extracted, together with the statistical significance reported by the authors. In the in vitro segment, each study was additionally classified by mechanistic depth (pathway-level, direct chemical, or functional only).

Because of the heterogeneity of materials, models, assays, and reporting units, a meta-analysis was not feasible; the results were instead narratively synthesized, grouped by level of evidence (in vitro, in vivo, clinical) and by mechanism or outcome, respectively. Values only graphically reported were estimated from the figures and were identified as such in the tables. Information not reported in the original articles was recorded as "not reported".

Publication bias could not be assessed with statistical methods (e.g., funnel plots) for the same reason, although selective outcome reporting was evaluated within the risk-of-bias tools used for the in vivo and clinical studies. The certainty of the evidence was not formally graded because of the heterogeneity of study designs and the inclusion of in vitro studies.

2.5. Risk of Bias and Quality Assessment

2.5.1. In Vitro Studies

The methodological quality and risk of bias of the included in vitro studies were assessed using a custom nine-item checklist. No validated, field-standard tool exists for in vitro nutraceutical research, so the checklist was adapted from the Science in Risk Assessment and Policy (SciRAP) framework and the reliability principles of Klimisch et al. [14]. The items covered: (1) chemical characterization of the extract or compound; (2) identity and source of the plant material; (3) source of the cell line or primary cells; (4) controls (untreated and stressor-alone controls); (5) dose–response testing; (6) number of independent replicates; (7) appropriateness of statistical analysis; (8) use of established, standard assays; and (9) transparency of funding and conflicts of interest. Each item was rated as Yes (criterion fully met), Partial (met in part), or No (not met or not reported in the article). The rating criteria are given in Supplementary Table S3. Each rating was based on the Methods, Results, and figure legends of the original articles. For studies with a mixed in vitro/in vivo design, only the cellular component was assessed. Two reviewers (R.B. and M.E.R.) independently assessed each study, and disagreements were resolved by discussion. No summary score was calculated, to avoid assigning arbitrary weights to different items, and no study was excluded on the basis of its rating. The ratings were used to qualify the interpretation of the findings in Section 3.

2.5.2. In Vivo Studies

The SYRCLE's Risk of Bias tool was used to evaluate the risk of bias in the selected in vivo studies. This tool was developed based on the Cochrane Risk of Bias tool for randomized clinical trials, which was adapted to the specific aspects of in vivo experiments. The domains assessed included: sequence generation, baseline characteristics, allocation concealment, blinding of investigators, completeness of outcome data, selective outcome reporting, and other sources of bias. Each item was judged as "Low" (criterion clearly reported and adequate), "High" (explicit evidence of a problem) or "Unclear" (information missing or insufficient), in accordance with the SYRCLE methodology [15]. Missing information was not considered evidence of high risk, and detailed reporting of the results was not considered evidence of low risk. The overall risk of bias was classified as "Low", if all domains were rated Low, "Unclear" (some concerns), if at least one domain was rated Unclear and none High, and "High", if at least one domain was rated High. The rationale for each judgement is given in Supplementary Table S4.

2.5.3. Clinical Studies

The risk of bias for each study was assessed using the Cochrane Risk of Bias 2 (ROB 2) tool for randomized clinical trials [16] and the Risk Of Bias In Non-Randomized Studies—of Interventions, Version 2 (ROBINS-I V2) for non-randomized intervention studies [17].

The ROB 2 tool examines quality across five important domains: randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Studies were classified as having a low risk of bias if all domains were evaluated as "low-risk", moderate risk of bias if one or more domains presented "some concerns", or high risk of bias if any domain was valued to be "high-risk".

ROBINS-I V2 includes six domains of bias: risk of bias due to confounding, risk of bias in classification of interventions, risk of bias in selection of participants into the study (or into the analysis), risk of bias due to missing data, risk of bias arising from measurement of the outcome, and risk of bias in selection of the reported result. The ROBINS-I V2 overall risk of bias judgement is for the domain with the greatest risk of bias. Possible judgments

are "low risk of bias", "moderate risk of bias", "serious risk of bias", and "critical risk of bias". Two reviewers (M.E.R. and D.-S.P.) independently assessed each in vivo and clinical study, and disagreements were resolved by discussion.

3. Results and Discussion

3.1. Study Selection

The study selection process is summarized in the PRISMA flow diagram (Figure 1). Of the records excluded at screening, most were reviews or addressed topics outside the scope of this review, such as plant biotechnology, agricultural and animal-feed applications, other plant species or hazelnut-containing mixtures, and unrelated pharmacological topics; one article was excluded because it was not published in English.

All reports assessed in full text were eligible, and one additional eligible study was identified through the reference lists of the included studies. There were 17 studies included in our review (Figure 1), which originated from six countries: Italy (n = 8), China (n = 4), Nigeria (n = 2), Canada (n = 1), Romania (n = 1), and Turkey (n = 1).

3.2. Risk of Bias and Quality of Included Studies

3.2.1. In Vitro

The risk-of-bias ratings for the eight in vitro studies are presented in Table 1. Controls and assay validity were adequate in all studies, whereas the main weaknesses concerned chemical characterization of the tested material (absent in two studies using crude extracts), dose–response testing (absent or incomplete in six studies), and incomplete reporting of the cell source, replicates, or statistical analysis in some studies. Only one study fulfilled all nine criteria. One study was industry-funded, with the sponsor also supplying the hazelnut skin material.

3.2.2. In Vivo

The criteria used to evaluate the risk of bias in the selected in vivo studies and the results obtained are presented in Table 2.

The methods of randomization, allocation concealment and blinding were not reported in any of the seven studies, and the number of analyzed animals was incompletely reported in all of them (Table 2). Baseline characteristics of the animals were also incompletely reported in two studies [18,19], while Öztürk et al. [20] did not specify any method for assigning animals to groups. Olofinnade et al. [21,22] reported blinding for the behavioral tests only, and not for the biochemical measurements. These items were rated "Unclear", because missing information does not by itself indicate a high risk of bias. Consequently, all seven studies were rated as having an unclear overall risk of bias, and the findings of the in vivo studies should be interpreted with caution.

3.2.3. Clinical

The outcomes obtained after quality assessment for the studies are presented in Tables 3 and 4. The overall risk of bias was rated as moderate for the randomized trials and serious for the non-randomized trials.

3.3. In Silico/In Vitro Studies

3.3.1. Chemical Composition and Characterization of Hazelnut-Derived Antioxidants

The five studies summarized in Tables 5 and 6 demonstrate that hazelnut-derived antioxidant potential is determined jointly by the botanical matrix and the extraction strategy, and not merely by one of these factors in isolation.

Table 1. Risk of bias and methodological quality of the included in vitro studies.

Author, Year, Country, Ref.	1. Chemical Characterization	2. Material Identity	3. Cell Source	4. Controls	5. Dose–Response	6. Replicates	7. Statistics	8. Assay Validity	9. Funding/COI
Faraone et al., 2026 Italy [23]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Liang et al., 2025 China [24]	No	Partial	No	Yes	Yes	Partial	Partial	Yes	Yes
Cerulli et al., 2024 Italy [25]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes
Sun et al., 2024 China [19]	Yes	Partial	Yes	Yes	No	Yes	Partial	Yes	Yes
Spagnuolo et al., 2023 Italy [26]	Yes	Partial	Yes	Yes	Partial	Partial	Yes	Yes	Partial
Zhao et al., 2023 China [27]	Yes	Yes	Yes	Yes	Partial	Yes	Yes	Yes	Yes
Emanet et al., 2022 Italy [28]	Yes	Partial	No	Yes	Partial	Yes	No	Yes	Partial
Banach et al., 2009 Canada [29]	No	Partial	Yes	Yes	Partial	Yes	Yes	Yes	Yes

COI—conflict of interest; No—criterion not met or not reported; Partial—criterion partly met; Yes—criterion fully met. Rating criteria are detailed in Supplementary Table S3. For Liang et al. [24] and Sun et al. [19], only the cellular component was assessed.

Table 2. Risk of bias of the included in vivo studies (SYRCLE Risk of Bias tool).

Author, Year, Country, Ref.	Sequence Generation	Baseline Characteristics	Allocation Concealment	Blinding	Completeness of Outcome Data	Selective Outcome Reporting	Other Sources of Bias	Overall Risk of Bias
Balta et al., 2023 Romania [18]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Liang et al., 2025 China [24]	Unclear	Low	Unclear	Unclear	Unclear	Low	Low	Unclear
Sun et al., 2024 China [19]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Wang et al., 2024 China [30]	Unclear	Low	Unclear	Unclear	Unclear	Low	Low	Unclear
Öztürk et al., 2025 Turkey [20]	Unclear	Low	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Olofinnade et al., 2021 Nigeria [21]	Unclear	Low	Unclear	Unclear	Unclear	Low	Low	Unclear
Olofinnade et al., 2021 Nigeria [22]	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

Low—low risk of bias; Unclear—insufficient or missing information; High—high risk of bias. Missing information was rated "Unclear" and not as high risk. Overall: Low if all domains were Low; Unclear (some concerns) if at least one domain was Unclear and none were High; High if at least one domain was High.

Table 3. Risk of bias for randomized trials (n = 2).

Author, Year, Country, Ref.	Randomization Process	Deviations from Intended Interventions	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	Overall Risk of Bias
Di Renzo et al., 2017 Italy [31]	low	some concern	low	low	low	moderate
Guaraldi et al., 2018 Italy [32]	low	some concern	low	low	low	moderate

Table 4. Risk of bias for non-randomized trials (n = 2).

Author, Year, Country, Ref.	D1	D2	D3	D4	D5	D6	Overall Risk of Bias
Di Renzo et al., 2014 Italy [33]	serious	low	low	moderate	moderate	low	serious
Di Renzo et al., 2019 Italy [34]	serious	low	low	moderate	moderate	low	serious

D1—risk of bias due to confounding; D2—risk of bias in classification of interventions; D3—risk of bias in selection of participants into the study (or into the analysis); D4—risk of bias due to missing data; D5—risk of bias arising from measurement of the outcome; D6—risk of bias in selection of the reported result.

Across the four matrices represented—skin, green leafy covers, kernels, and leaf—phenolic composition differs not only quantitatively but qualitatively: flavan-3-ols and procyanidins dominate the skin, cyclic diarylheptanoids are essentially unique to the green leafy covers and kernels, and the leaf yields the broadest structural diversity, distributed across free, conjugated, and bound chemical forms. This matrix-dependent heterogeneity has direct methodological consequences, since none of the reporting conventions used across these studies (relative MS peak area, isolated pure-compound mass, colorimetric total phenolic content (TPC), or summed HPLC-quantified content) are mutually convertible, limiting direct quantitative comparison across sources.

Extraction strategy adds a second layer of variability. Only the study by Faraone et al. [23] addressed extraction as an optimization problem in itself, employing a full factorial experimental design to determine the conditions that maximize both phenolic compound yield and antioxidant capacity; the remaining studies applied established, non-optimized protocols suited to their specific downstream objective—chromatographic isolation of individual compounds [25], sequential recovery of polar and less polar phenolic subclasses from a food-industry by-product [26], fraction-resolved profiling of conjugation state [27], or nanoencapsulation for delivery purposes [28].

This distinction is methodologically important: it separates studies designed to answer "which extraction conditions yield the most bioactive extract" from studies designed to answer "what compounds are present" or "how can this extract be delivered," and this framing anticipates why direct potency comparisons across studies are not always meaningful.

Table 5. Phenolic profiles and major bioactive compounds in hazelnut matrices in selected in vitro studies.

Source/Matrix	Main Phenolic Classes Identified	Major Compounds (Quantified)	Total Phenolic Content	Method(s)	Ref.
Hazelnut skin	Phenolic acids Flavan-3-ols Flavonols Flavones Procyanidins Dihydrochalcones	3,5-dihydroxybenzoic acid: 2.71 mg/g +/−Catechin: 1.03 mg/g Kaempferol rhamnoside—nq Luteolin: 0.34 mg/g Procyanidin B2: 0.10 mg/g Phloridzin dihydrate: 0.16 mg/g	365.4 mg GAE/g dw	UHPLC-MS/MS Folin–Ciocalteu	[23]
Hazelnut green leafy covers Hazelnut kernels	Diarylheptanoids	Leafy covers: giffonin E (1.3 mg), giffonin H (2.1 mg), giffonin J (1.8 mg) Kernels: carpinontriol B (5.2 mg) *	TPC not assessed	NMR, HRMS	[25]
Hazelnut skin	Phenolic acids Flavan-3-ols Procyanidins Flavonols	Gallic acid: 15.7 mg/100 g (+)-catechin: 62.1 mg/100 g Procyanidin dimers: 92.7–100.5 mg/100 g Quercetin-3-rhamnoside: 39.6 mg/100 g	TPC: ~100 mg GAE/g Sum of 17 HPLC-quantified compounds: 445.9 mg/100 g **	HPLC-PDA/ESI-MS Folin–Ciocalteu	[26]
Hazel leaf	Phenolic acids Flavan-3-ols Flavonols Flavones Stilbenes	Gallic acid, chlorogenic acid, caffeic acid, p-coumaric acid Gallocatechin Myricetin, quercetin, kaempferol-3-*O*-rhamnoside Luteolin, pedalitin Resveratrol ***	24.5 mg GAE/g dw (sum of the phenolic fractions)	UPLC-MS/MS Folin–Ciocalteu	[27]

dw—dry weight; GAE—gallic acid equivalents; HPLC-PDA/ESI-MS—high-performance liquid chromatography-photodiode array/electrospray ionization-mass spectrometry; HRMS—high-resolution mass spectrometry; NMR—nuclear magnetic resonance; nq—non-quantified; TPC—total phenolic content; UHPLC-MS/MS—ultra-high-performance liquid chromatography–tandem mass spectrometry; UPLC-MS/MS—ultra-performance liquid chromatography–tandem mass spectrometry; * values for Cerulli et al. [25]—reporting isolated pure-compound mass from chromatographic purification, not native plant concentration; ** two non-comparable TPC values (colorimetric vs. summed HPLC); *** individual compound abundance—reported only as relative MS peak area ($\times 10^4$), not absolute concentration; comparable in kind only within this study.

Table 6. Extraction optimization strategies and technological outcomes for hazelnut phenolic compounds in selected in vitro studies.

Source/Matrix	Extraction Method/Parameters	Optimization Design/Key Steps	Key Technological Outcomes/Innovations	Ref.
Hazelnut skin	UAE; (0–100%) EtOH/H_2O, 30–70 °C, 1–3 h	3^3 full factorial design; multi-parametric optimization	Optimal: 21.1% EtOH, 30 °C, 70.9 min; mild/green extraction; high phenolic yield; 25 compounds identified (UHPLC-MS/MS)	[23]
Hazelnut green leafy covers/kernels	EtOH/H_2O (7:3) extraction; Sephadex LH-20 column and semipreparative HPLC fractionation	Chromatographic purification; structural characterization by NMR/HRMS	Isolation of rare cyclic diarylheptanoids; preparation of pure compounds for mechanistic and docking studies	[25]
Hazelnut skin	Sequential ultrasound-assisted + thermal extraction; 1% aqueous formic acid (30 min sonication + 70 °C, 1 h) followed by MeOH/H_2O (75:25)	Two-step sequential extraction; comparison of fraction yields and composition	Efficient recovery of both polar (acidic) and less polar phenolics from a food-industry by-product; supporting circular bioeconomy/waste valorization	[26]
Hazel leaf	70% MeOH/1% HCl extraction (lyophilized leaf powder); multi-step alkaline/acid hydrolysis for free/conjugated/bound fractions	Standardized multi-step protocol; sequential fraction separation	Detailed phenolic mapping of hazelnut leaf across three chemical forms (free, conjugated, bound); fraction-resolved antioxidant profiling	[27]
Hazelnut kernel loaded NLCs	Hydroethanolic extraction (EtOH:H_2O, 1:1 v/v) of freeze-dried kernel powder, 65 °C, 20 min; subsequently loaded into NLCs via hot homogenization and sonication	Two-stage process: (1) phytochemical extraction, (2) NLC formulation optimization (lipid/surfactant ratios, extract loading); physicochemical characterization (size, PDI, zeta potential, encapsulation efficiency); stability testing	Successful extract encapsulation (70% efficiency); high production yield (74.3%) and colloidal stability ($\zeta < -20$ mV) of extract-loaded NLCs vs. empty carriers	[28]

HPLC—high-performance liquid chromatography; HRMS—high-resolution mass spectrometry; NLCs—nanostructured lipid carriers; NMR—nuclear magnetic resonance; PDI—polydispersity index; UAE—ultrasound-assisted extraction; UHPLC-MS/MS—ultra-high-performance liquid chromatography–tandem mass spectrometry.

3.3.2. Direct Antioxidant Activities and Redox Homeostasis

In Vitro Chemical Antioxidant Assays

Among the selected studies, those that reported classical cell-free antioxidant capacity assays (Table 7) collectively demonstrated a marked radical scavenging and reducing capacity for hazelnut extracts, regardless of the plant matrix—skin, leaf, or kernel. At the same time, within the phenolic fractionation study [27], free phenolic compounds outperformed conjugated and bound phenolics, suggesting that chemical accessibility and structural form influence direct antioxidant reactivity. Finally, encapsulation of hazelnut extract in nanostructured lipid carriers significantly improved antioxidant capacity compared to unloaded carriers, highlighting the potential of delivery system engineering to preserve or potentiate extract bioactivity [28].

Reduction in Intracellular ROS and RNS in Cell-Based Systems

In addition to direct chemical assays, four studies (Table 8) reported a reduction in intracellular ROS/reactive nitrogen species (RNS) levels by hazelnut-derived compounds in cellular systems, using human, murine and neuronal/renal-relevant cell models challenged with different oxidative or glycation-related stressors (hydrogen peroxide (H_2O_2), tert-butyl hydroperoxide (TBHP), lipopolysaccharide (LPS), advanced glycation end-products (AGEs)). Across these models, hazelnut extracts and isolated diarylheptanoids consistently reduced intracellular ROS levels and where assessed, also attenuated nitric oxide (NO) production and downstream inflammatory cytokine release. Notably, the magnitude of the ROS reduction varied with both the phenolic fraction tested (free vs. conjugated/bound) [27] and the delivery format (nanoencapsulated vs. plain extract) [28], reinforcing the pattern already observed in the cell-free assays: bioavailability and structural accessibility, rather than phenolic content alone, shape antioxidant efficacy in a biological context. These cell-based findings are consistent with the cell-free evidence; however, reduced ROS-related fluorescence reflects the net intracellular redox state and does not by itself establish direct radical scavenging.

Prevention of Oxidative Damage

Beyond the reduction in ROS/RNS levels, two studies assessed protection against downstream oxidative damage—lipid peroxidation and protein carbonylation (Table 9). Cerulli et al. [25] showed this at the lipid-peroxidation level in neuronal and renal cells, with carpinontriol B most effective (mechanism detailed in Section "Pathways Beyond Direct Antioxidant Activity"). Banach et al. [29] offered more direct mechanistic insight: polar (methanolic/aqueous) hazelnut extracts and catechins (catechin, epicatechin and epigallocatechin gallate (EGCG)) reduced both lipid peroxidation and protein carbonylation, with catechin remaining protective even when added after the carbonylating stressor—consistent with a direct carbonyl-trapping mechanism distinct from radical scavenging. Together, these findings suggest hazelnut phenolics limit not only reactive species formation but also the structural damage that follows unresolved oxidative and carbonyl stress.

Statistical significance was consistently reported across these studies (typically $p < 0.05$ or stricter), though the specific comparisons and thresholds varied by study design (see Tables 7–9).

3.3.3. Mechanistic Interactions with Redox-Regulatory Systems

While the preceding sections established that hazelnut-derived extracts and compounds possess measurable antioxidant capacity—both as direct chemical reactivity and as functional protection in cellular systems—this section examines the underlying mechanisms by which these effects are achieved.

Table 7. Chemical antioxidant capacity assays of hazelnut extracts reported in selected in vitro studies.

Author, Year, Ref.	Extract/Compound	Assays Used	Quantitative Results	Key Qualitative Outcomes
Faraone et al., 2026 [23]	HS extracts	ABTS, DPPH, FRAP, BCB	* ABTS 1929.76 ± 117.38 mg TE/g; DPPH 3936.95 ± 143.94 mg TE/g; FRAP 2911.90 ± 165.32 mg TE/g; BCB 74.90 ± 2.25% AA	Strong radical scavenging and reducing activity of the optimized extract
Liang et al., 2025 [24]	HLP extract	DPPH, ABTS, OH scavenging, reducing power, total antioxidant capacity (FRAP)	Max scavenging at 2.0 mg/mL: DPPH 92.11%; $ABTS^+$ 98.41%; ·OH 81.89% ** Reducing power, total antioxidant capacity values ($p < 0.01$ vs. control for all, except ·OH with $p < 0.05$ vs. control)	Potent antioxidant activity: strong DPPH·, ABTS+, and ·OH radical scavenging; high reducing power and total antioxidant capacity
Zhao et al., 2023 [27]	Hazel leaf phenolic extracts	DPPH, FRAP	*** Free phenolics: DPPH: ≈5.2 µmol TE/g dw; FRAP: ≈50–51 µmol AAE/g dw ($p < 0.05$ free vs. conjugated/bound—for both assays)	Phenolics—the main substances with antioxidant activity in hazelnut leaf Free phenolics—highest radical scavenging and reducing power, followed by conjugated, and then bound phenolics
Emanet et al., 2022 [28]	HK extract-loaded NLCs	Total antioxidant capacity	Extract itself: 152.6 ± 8.3 ng TE/6 mg extract. At 1 mg/mL: Hazelnut extract-loaded NLCs 0.208 ± 0.003 ng/mL TE vs. plain nanostructured lipid carriers 0.054 ± 0.002 ng/mL TE ($p < 0.05$ vs. empty NLCs)	Enhanced antioxidant capacity of extract-loaded nanovectors compared to empty ones

%—AA percentage of antioxidant activity; AAEs—ascorbic acid equivalents; ABTS—2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid); BCB—β-carotene bleaching; DPPH—2,2-diphenyl-1-picrylhydrazyl; dw—dry weight; FRAP—ferric reducing antioxidant power; HK—hazelnut kernel; HLP—hazelnut leaf polyphenol; HS—hazelnut skin; NLCs—nanostructured lipid carriers; TE—Trolox Equivalents; * no treatment-*vs*-control significance value is reported for the optimized extract; ** reducing power and total antioxidant capacity values for Liang et al. [24]—reported graphically only (Figure 1D,E); not given as text values; *** values for Zhao et al. [27]—estimated from Figure 3; exact values not reported in text.

Table 8. Reduction in intracellular ROS/RNS levels by hazelnut extracts in cell-based systems.

Author, Year, Ref.	Extract/Compound	Cell Model	Stressor	ROS/RNS Assayed	Key Quantitative Results	Key Qualitative Findings
Cerulli et al., 2024 [25]	Giffonins E, H, J—isolated from a "green" extract of *C. avellana* green leafy covers Carpinontriol B—isolated from a "green" extract of *C. avellana* kernels	Human neuroblastoma cell line SH-SY5Y Human embryonic kidney cell line HEK293-Tau	H_2O_2 200 µM: SH-SY5Y H_2O_2 100 µM: HEK293-Tau	Intracellular ROS (DCFH-DA)	Giffonins H and J—most active: Giffonin H: ROS ↓ 48.7% at 15 min, 53.3% at 30 min vs. H_2O_2; Giffonin J: ROS ↓ 48.1% at 15 min, 33.2% at 30 min vs. H_2O_2 ($p < 0.05$–0.0001 vs. H_2O_2, varying by compound/time point)	Reduced H_2O_2-induced intracellular ROS by all four compounds Giffonins H and J—most potent
Spagnuolo et al., 2023 [26]	HSP extract	THP-1 macrophages	AGEs (BSA–MGO glycation model)	Intracellular ROS (DCFH-DA)	ROS ↓ by HSP extract (50 µg/mL) co-treatment vs. AGE alone ($p < 0.001$); TNF-α secretion and gene expression ↓ ($p < 0.01$); IL-1β secretion ↓ ($p < 0.05$), gene expression not significantly changed	AGE-induced ROS and pro-inflammatory cytokine production attenuated by HSP extract
Zhao et al., 2023 [27]	Hazel leaf phenolic extracts (free, conjugated, bound fractions)	HUVECs RAW264.7 mouse macrophages	TBHP: HUVECs LPS: RAW264.7	Intracellular ROS, MDA, SOD: HUVECs; NO, IL-1β, TNF-α, IL-6: RAW264.7	FP, ACP, BBP: ROS ↓, MDA ↓, SOD ↑ vs. TBHP ($p < 0.05$–0.01); BCP: weaker, partly non-significant effects (e.g., SOD not significant). NO and cytokines ↓ in RAW264.7 vs. LPS ($p < 0.01$) for FP/ACP/BBP/ABP; BCP significant only for IL-6	Free phenolics—strongest cellular antioxidant and anti-inflammatory activity, followed by conjugated, then bound fractions
Emanet et al., 2022 [28]	HK extract-loaded NLCs	HDFs	TBHP	Intracellular ROS	%ROS$^+$ cells: TBHP alone: 25.4 ± 0.3%; HK extract-loaded NLCs: 18.8 ± 1.1% ($p < 0.05$ vs. TBHP); plain extract: 17.6 ± 2.4% ($p < 0.05$ vs. TBHP); empty NLCs: no significant effect	Reduced TBHP-induced ROS by extract-loaded nano-vectors and plain extract

ABP—acid hydrolysis bound phenolics; ACP—acid hydrolyzed conjugated phenolics; AGE—advanced glycation end-product; BBP—base released bound phenolics; BCP—base-hydrolyzed conjugated phenolics; BSA—bovine serum albumin; DCFH–DA—2,7-dichlorofluorescein diacetate; FP—free phenolics; H_2O_2—hydrogen peroxide; HDFs—human dermal fibroblasts; HK—hazelnut kernel; HLP—hazelnut leaf polyphenol; HSP—hazelnut skin polyphenols; HUVECs—human umbilical vein endothelial cells; IL—interleukin; LPS—lipopolysaccharide; MDA—malondialdehyde; MGO—methylglyoxal; NLCs—nanostructured lipid carriers; NO—nitrogen monoxide; ROS—reactive oxygen species; SOD—superoxide dismutase; TBHP—tert-butyl hydroperoxide; TNF-α—tumor necrosis factor alpha; ↓—decreased, ↑—increased.

Table 10 summarizes the redox mechanism reported for each of the eight in vitro studies, together with an assessment of mechanistic depth: four studies [19,23–25] demonstrate modulation of a specific redox-regulatory signaling pathway, confirmed through molecular, biochemical, or computational evidence; two studies [26,29] characterize a direct chemical mechanism of action; and two other studies [27,28] report a functional antioxidant outcome without further mechanistic characterization.

The following subsections reflect this mechanistic evidence gradient: Section "Modulation of Endogenous Antioxidant Enzymes" addresses studies reporting modulation of endogenous antioxidant enzymes, Section "Pathways Beyond Direct Antioxidant Activity" examines pathway-level mechanisms extending beyond direct scavenging, and Section "Cellular Protection Against Oxidative Stress" discusses the resulting cellular protection against oxidative stress.

Modulation of Endogenous Antioxidant Enzymes

Three studies demonstrated that hazelnut-derived extracts counteract oxidative stress by restoring or enhancing the activity of endogenous antioxidant enzymes. In two of these, this enzymatic effect was specifically linked to activation of the Nrf2/kelch-like ECH-associated protein 1 (Keap1) signaling pathway, rather than to direct chemical scavenging alone.

Faraone et al. [23] showed that an optimized hazelnut skin extract reversed TBHP-induced suppression of superoxide dismutase (SOD)-2, catalase (CAT), and NAD(P)H:quinone acceptor oxidoreductase 1 (NQO-1) in HepG2 cells, restoring these antioxidant proteins, as well as Nrf2 itself, toward baseline levels. Likewise, Liang et al. [24] observed in ethanol-challenged LO2 hepatocytes that hazelnut leaf polyphenol extract restored SOD, CAT, and glutathione (GSH) levels, and decreased malondialdehyde (MDA) accumulation, which was again linked to Nrf2/Keap1 pathway modulation. Zhao et al. [27] reported a similar enzymatic effect (increase in SOD activity in TBHP-challenged human umbilical vein endothelial cells (HUVECs)), but without showing an upstream signaling pathway, indicating that enzymatic restoration can be documented without confirmation at the pathway level.

Taken together, these three studies—despite differing in plant matrix (skin, leaf), cell model, and oxidative stressor—converge on the same functional endpoint: restoration of the enzymatic antioxidant defense system, whether or not the upstream regulatory pathway was directly investigated. The Nrf2/Keap1 mechanism underlying the findings of Faraone et al. [23] and Liang et al. [24] is examined further in Section "Pathways Beyond Direct Antioxidant Activity", where upstream evidence for Keap1/Nrf2 interaction is provided, including molecular docking data.

These findings collectively suggest that hazelnut-derived antioxidants can reinforce cellular redox buffering both via direct upregulation of endogenous defense enzymes and, where shown, through activation of canonical redox signaling pathways.

Pathways Beyond Direct Antioxidant Activity

Two studies extended beyond the enzymatic outcomes to directly examine the upstream signaling mechanisms responsible for the redox regulation, targeting two different pathways, namely, Nrf2/Keap1 and Hippo signaling.

Table 9. Effects of hazelnut extracts on lipid peroxidation and protein carbonylation markers in vitro.

Author, Year, Ref.	Extract/Compound	Cell/Tissue Model	Stressor	Marker(s) Assayed	Key Quantitative Results	Key Qualitative Findings
Cerulli et al., 2024 [25]	Giffonins E, H, J—isolated from a "green" extract of *C. avellana* green leafy covers Carpinontriol B—isolated from a "green" extract of *C. avellana* kernels	Human neuroblastoma cell line SH-SY5Y Human embryonic kidney cell line HEK293-Tau	H_2O_2 200 µM: SH-SY5Y H_2O_2 100 µM: HEK293-Tau	Lipid peroxidation: TBARS	Carpinontriol B—most effective: SH-SY5Y: TBARS ↓ 54.8% ($p < 0.0001$); HEK293-Tau: TBARS ↓ 69.4% ($p < 0.01$) vs. H_2O_2 alone	Reduced H_2O_2-induced lipid peroxidation by all four compounds Carpinontriol B—most potent
Banach et al., 2009 [29]	Methanolic HK extract Ethyl acetate HK extract Aqueous HK extract Catechin, epicatechin, EGCG	Rat hepatocytes Rat liver microsomes	TBHP: lipid peroxidation model Glyoxal: carbonylation model	Lipid peroxidation: MDA/TBARS Protein carbonylation: DNPH	* Methanolic extract: Microsomes—lipid peroxidation ↓ up to 47% ($p < 0.05$) Methanolic extract: Rat hepatocytes—MDA ↓ up to 1.00 nmol/10^6 cells vs. 2.38 nmol/10^6 cells TBPH-only ($p < 0.05$) Catechin: MDA ↓ to 0.70 nmol/10^6 cells vs. 2.55 nmol/10^6 cells glyoxal-only ($p < 0.05$) Catechin: protein carbonylation ↓ up to ~55% ($p < 0.05$) Epicatechin and EGCG: protein carbonylation ↓ up to ~50% ($p < 0.05$)	Polar (methanolic/aqueous) extracts vs. lipophilic (ethyl acetate) extract—more protective against lipid peroxidation Catechins—direct glyoxal traping/early-stage carbonylation reversal, including when added after the stressor

DNPH—2,4-dinitrophenylhydrazine; EGCG—epigallocatechin gallate; H_2O_2—hydrogen peroxide; MDA—malondialdehyde; TBARS—thiobarbituric acid reactive substances; TBHP—tert-butyl hydroperoxide; * Statistical significance ($p < 0.05$)—varied by compound, time of assessment, and type of comparison (vs. control or stressor condition); not reported uniformly for each individual value in the original tables; ↓—decreased.

Table 10. Mechanisms of action and main findings from selected in silico and in vitro studies.

Author, Year, Country, Study Type, Ref.	Extract/Compound	Cell Model	Redox Mechanism	Key Findings	Mechanistic Depth	Primary Subsection
Faraone et al., 2026 Italy In vitro [23]	HS extracts	Human hepatocellular carcinoma (HepG2) cells	Nrf-2-mediated antioxidant defense pathway activation	Key antioxidant proteins restored: SOD-2, CAT, NQO-1, and Nrf-2 vs. TBHP-treated cells ($p < 0.05$–0.0001, varying by protein) *	Pathway-level	Section "Modulation of Endogenous Antioxidant Enzymes"
Liang et al., 2025 China In vitro [24]	HLP extract	LO2 liver cells	Nrf2/Keap1-mediated antioxidant defense pathway activation	Oxidative stress-related indicators restored: SOD, MDA, GSH, and CAT vs. NC group ($p < 0.05$–0.01) **	Pathway-level	Section "Modulation of Endogenous Antioxidant Enzymes"
Cerulli et al., 2024 Italy In silico/in vitro [25]	Giffonins E, H, J—isolated from a "green" extract of *C. avellana* green leafy covers Carpinontriol B—isolated from a "green" extract of *C. avellana* kernels	Human neuroblastoma cell line SH-SY5Y Human embryonic kidney cell line HEK293-Tau	Nrf-2-mediated antioxidant defense pathway activation (Keap1 binding predicted by docking; nuclear Nrf2 translocation shown by Western blot)	Reduced intracellular ROS—up to 53.3%: giffonin H Reduced lipid peroxidation—up to 69.4%: carpinontriol B Reduced LDH release—up to 71.2%: carpinontriol B Inhibited caspase-3 activation—up to 90.5%: giffonin E ($p < 0.05$–0.0001 across endpoints) *** Nuclear phosphorylated Nrf2 increased: +324.2% giffonin H, +224.7% carpinontriol B † Keap1 binding predicted by docking for all four compounds (direct binding not demonstrated)	Pathway-level	Section "Pathways Beyond Direct Antioxidant Activity"
Sun et al., 2024 China In vitro [19]	HLP extract	Human renal tubular epithelial cells HK-2	Inhibition of Hippo pathway activation	Reduced ROS levels and increased protein levels of GPX4, FSP1, and FTH1 vs. Model group ($p < 0.05$)	Pathway-level	Section "Pathways Beyond Direct Antioxidant Activity"
Spagnuolo et al., 2023 Italy In vitro [26]	HSP extract	THP-1 macrophages	Reduced intracellular ROS; direct ROS scavenging (electron or hydrogen-atom donation) and carbonyl trapping proposed by the authors	Improved cell viability under AGE-induced stress †† Decreased intracellular ROS levels ($p < 0.001$) Suppressed TNF-α ($p < 0.01$) and IL-1β ($p < 0.05$) secretion	Direct chemical (inferred)	Section "Cellular Protection Against Oxidative Stress"

Table 10. *Cont.*

Author, Year, Country, Study Type, Ref.	Extract/Compound	Cell Model	Redox Mechanism	Key Findings	Mechanistic Depth	Primary Subsection
Zhao et al., 2023 China In vitro [27]	Hazel leaf phenolic extracts	HUVECs RAW264.7 mouse macrophages	Reduced intracellular ROS, enzyme modulation, and lipid peroxidation reduction	Reduced intracellular ROS levels (significant vs. TBHP for all fractions) †† Increased SOD activity ($p < 0.05$–0.01; BCP not significant) Lower MDA levels ($p < 0.05$–0.01; BCP and ABP not significant) Attenuated inflammatory cytokines: NO, IL-1β, TNF-α, and IL-6 ($p < 0.01$ for FP/ACP/BBP/ABP) #	Functional only	Section "Modulation of Endogenous Antioxidant Enzymes"
Emanet et al., 2022 Italy In vitro [28]	HK extract-loaded NLCs	HDFs	Reduced intracellular ROS	Reduced ROS levels vs. TBHP alone ($p < 0.05$)	Functional only	Section "Cellular Protection Against Oxidative Stress"
Banach et al., 2009 Canada In vitro [29]	Methanolic HK extract Ethyl acetate HK extract Aqueous HK extract	Rat hepatocytes Rat liver microsomes	Reduced ROS formation, lipid peroxidation inhibition, and carbonyl trapping (as interpreted by the authors)	Reduced ROS formation in hepatocytes ($p < 0.05$ vs. hydroperoxide, all hazelnut extracts) Reduced MDA/TBARS in hepatocytes and liver microsomes ($p < 0.05$ vs. hydroperoxide) Reduced cytotoxicity in hepatocytes ##	Direct chemical	Section "Cellular Protection Against Oxidative Stress"

ABP—acid hydrolysis bound phenolics; ACP—acid hydrolyzed conjugated phenolics; AGE—advanced glycation end-product; BBP—base released bound phenolics; BCP—base-hydrolyzed conjugated phenolics; CAT—catalase; FP—free phenolics; FSP1—ferroptosis suppressor protein 1; FTH1—ferritin heavy chain 1; GPX4—glutathione peroxidase 4; GSH—glutathione; HDFs—human dermal fibroblasts; HK—hazelnut kernel; HLP—hazelnut leaf polyphenol; HS—hazelnut skin; HSP—hazelnut skin polyphenols; HUVECs—human umbilical vein endothelial cells; IL—interleukin; Keap 1—kelch-like ECH-associated protein 1; MDA—malondialdehyde; NC—negative controls; NLCs—nanostructured lipid carriers; NO—nitrogen monoxide; NQO1—NAD(P)H:quinone acceptor oxidoreductase 1; Nrf-2—nuclear factor erythroid 2-related factor 2; ROS—reactive oxygen species; SOD—superoxide dismutase; TBARS—thiobarbituric acid reactive substances; TBHP—tert-butyl hydroperoxide; TNF-α—tumor necrosis factor alpha; * significance thresholds vary by protein and comparison (vs. control or vs. TBHP-treated cells); ** significance thresholds—varied by marker; *** significance thresholds—varied by compound, endpoint, and time point; † significance level for Nrf2 quantification—not specified; †† exact *p* value—not specified; # dose–response pattern observed but not statistically tested per concentration step; ## significant only for methanolic extract at 120 min; aqueous extract not statistically significant.

The clearest indication that Nrf2/Keap1 is involved in this dataset is from Cerulli et al. [25] who used molecular docking combined with in vitro confirmation. Docking analysis showed that four diarylheptanoids isolated from green leafy covers and kernels, giffonins E, H, and J and carpinontriol B, could occupy amino acid subpockets within the Keap1 Kelch domain, which, according to the docking prediction, could allow them to compete with Nrf2 for binding. This computational prediction was complemented by Western blot data showing nuclear Nrf2 translocation following compound treatment, which supports the involvement of the Keap1/Nrf2 pathway but does not demonstrate direct Keap1 binding or disruption of the Keap1–Nrf2 complex (see Table 10 for quantitative values). Notably, the neuronal and Tau-overexpressing cell models used in this study were selected on the basis of a previously reported interrelation between Nrf2 signaling and Tau pathology, placing these findings within the framework of neurodegeneration. This is the first study to relate diarylheptanoid structure to predicted Keap1 binding, offering a structural hypothesis for the enzyme-level effects described for other Nrf2-activating extracts in Section "Modulation of Endogenous Antioxidant Enzymes".

Sun et al. [19] addressed a mechanistically distinct axis, centered on the Hippo signaling pathway in cisplatin-challenged HK-2 renal cells. Rather than activating a cytoprotective pathway directly, the compound acted by preventing the stressor-induced phosphorylation of the Hippo effector protein Yes-associated protein (Yap)—phosphorylation that would otherwise inactivate Yap and permit ferroptosis, an iron- and lipid peroxidation-dependent form of cell death. By maintaining Yap in its active, dephosphorylated state, the compound preserved expression of the anti-ferroptotic proteins—glutathione peroxidase 4 (GPX4), ferroptosis suppressor protein 1 (FSP1), and ferritin heavy chain 1 (FTH1)—in HK-2 cells. The causal role of this pathway, rather than of antioxidant activity alone, was confirmed pharmacologically: co-treatment with dihydrexidine, which forces Yap phosphorylation, abolished the compound's protective effect against ferroptosis despite its otherwise preserved antioxidant properties.

Together, these two studies indicate that hazelnut-derived compounds can engage redox homeostasis through mechanistically distinct upstream routes—predicted competitive interaction with Keap1 (docking) in the case of Nrf2/Keap1, and prevention of a pathological kinase cascade in the case of Hippo/Yap/ferroptosis—rather than through a single, uniform mode of action.

Cellular Protection Against Oxidative Stress

Unlike the pathway-level mechanisms discussed in Sections "Modulation of Endogenous Antioxidant Enzymes" and "Pathways Beyond Direct Antioxidant Activity", this section addresses studies reporting cellular protection against oxidative stress without demonstrating a defined upstream regulatory mechanism; where a chemical basis is proposed, it is either directly supported by kinetic evidence [29] or inferred from the known reactivity of individual constituents rather than tested directly within the biological system [26]. The protective effects can be explained by direct chemical antioxidant activity in models of macrophages, fibroblasts and hepatocytes challenged with glycation-, hydroperoxide- or carbonyl-based stressors.

Spagnuolo et al. [26] showed that hazelnut skin extract protected THP-1 macrophages from AGE-induced (bovine serum albumin (BSA)–methylglyoxal) damage in a concentration-dependent manner, restoring cell viability that had been reduced by AGE exposure alone. Notably, the extract was cytotoxic only at concentrations higher than 400–500 µg/mL, consistent with the dose-dependent shift from antioxidant to pro-oxidant activity often described for phenolic compounds at high doses. Beyond viability, the extract attenuated both the gene expression and secreted protein levels of tumor necrosis factor alpha (TNF-α) and, to a lesser

extent, interleukin (IL)-1β, indicating that its protective effect extended from redox status to downstream inflammatory signaling triggered by AGE–protein interactions. The authors attribute this combined anti-glycative, antioxidant, and anti-inflammatory activity to the extract's rich flavan-3-ol and flavonol content, several of which (e.g., quercetin, phloretin, protocatechuic acid, gallic acid) have documented carbonyl-trapping or AGE-inhibitory properties individually, suggesting a synergistic rather than single-compound mechanism.

Emanet et al. [28] reported comparable protection in a different cellular and formulation context: human dermal fibroblasts challenged with TBHP showed reduced ROS-positive cell counts following treatment with either free hazelnut extract or extract-loaded nanostructured lipid carriers, whereas unloaded carriers had no effect—indicating that the protective activity resided in the extract itself rather than the lipid vehicle, with encapsulation preserving rather than altering this bioactivity while additionally conferring high cytocompatibility and efficient cellular uptake.

Banach et al. [29] extended this pattern to primary rat hepatocytes and liver microsomes, testing both crude hazelnut extracts and purified catechins against two mechanistically distinct stressors: hydroperoxide-induced oxidative stress and glyoxal-induced carbonyl stress. Protection against hydroperoxide-induced cytotoxicity and ROS formation was consistently greater with polar (methanolic, aqueous) than with lipophilic (ethyl acetate) hazelnut extracts, pointing to polyphenolic rather than tocopherol-based compounds as the principal protective constituents—consistent with the broader shift in the literature away from tocopherols as the primary antioxidant class in nuts. Against glyoxal-induced carbonyl stress, catechin, epicatechin, and EGCG each protected hepatocytes from cytotoxicity, with protection evident even when the compounds were added after the stressor, and enhanced when premixed with glyoxal beforehand—a pattern the authors interpret as direct dicarbonyl trapping and reversal of early-stage Schiff base adducts, rather than classical radical scavenging.

Taken together, these three studies illustrate that hazelnut-derived compounds confer measurable cellular protection against structurally diverse forms of oxidative and carbonyl stress—AGE-driven, hydroperoxide-driven, and dicarbonyl-driven—through convergent, pathway-independent mechanisms: direct radical/carbonyl trapping, concentration-dependent efficacy, and preservation of activity following nanoencapsulation.

3.3.4. Comparative Insights: Matrix Effects and Source Variability

Kernel-Derived Extracts

Kernel-derived material spans compositionally diverse constituents—flavan-3-ols and catechins [29], phenolics [28], and one diarylheptanoid, carpinontriol B [25]—with mechanisms ranging from direct scavenging to Nrf2/Keap1 engagement. This diversity of compounds aligns with data from the literature on nut by-products, indicating that the levels of phenolic compounds—as well as the antioxidant potential—of the kernel are lower than those of fractions derived from the skin, shell, or outer husk of the same fruit [35,36]. These findings suggest that studies focusing exclusively on the kernel may have captured only a relatively modest portion of the total antioxidant potential of the nuts.

Interestingly, Emanet et al. [28] showed that bioactivity of kernel extracts was not reduced by nanoencapsulation, but rather preserved, which is consistent with an expanding body of the nanodelivery literature showing that encapsulation protects labile polyphenols from oxidative degradation and preserves or increases retention of antioxidants [37,38].

Skin-Derived Extracts

Hazelnut skin was the most extensively characterized matrix [23,26], consistent with its established status as the most phenolically concentrated hazelnut fraction: skin flavan-3-ol

content has been reported at levels giving total antioxidant capacity roughly three times that of whole walnuts and up to 25 times that of blackberries [39], with a comparative varietal study similarly reporting total antioxidant capacity of hazelnut skin approximately one hundred times higher than that of the kernel [40]. The two studies diverged mechanistically despite comparable phenolic richness—Faraone et al. [23] demonstrating Nrf2 pathway engagement following systematic extraction optimization, and Spagnuolo et al. [26] reporting reduced intracellular ROS using a standard sequential protocol—indicating that mechanistic depth in this dataset tracked cellular model and stressor choice rather than compositional differences alone.

Leaf-Derived Extracts

Leaf-derived material [19,24,27] yielded the broadest phenolic diversity of any matrix, distributed across free, conjugated, and bound chemical forms—consistent with earlier phytochemical surveys of hazel leaves identifying a comparably wide spread of caffeoylquinic acid derivatives, flavonol rhamnosides, and phenolic acids alongside concentration-dependent antioxidant activity [41]—and was the only matrix associated with two mechanistically distinct, pathway-confirmed outcomes: Nrf2/Keap1 activation in hepatocytes and Hippo/Yap-mediated ferroptosis suppression in renal cells. This mechanistic split suggests that the pathway engaged may reflect the pathological/cellular context under investigation (hepatic ethanol stress vs. renal ferroptosis) as well as the phytochemical source, although these factors cannot be separated in the available studies. Leaf material also features prominently among hazelnut by-products more broadly, with documented antioxidant properties comparable to skin, shell, and husk fractions [42].

Green Leafy Covers-Derived Extracts

Green leafy covers, examined exclusively by Cerulli et al. [25], yielded cyclic diarylheptanoids that are largely restricted to *Corylus* species [43]. This structural class has been independently shown—across several giffonin congeners—to inhibit H_2O_2-induced lipid peroxidation at levels comparable to, or even exceeding, the antioxidant potency of curcumin [44]. Furthermore, these compounds provided the dataset's most mechanistically resolved evidence chain: Keap1 binding predicted by docking, with nuclear Nrf2 translocation shown by Western blot. This distinct phytochemical profile is consistent with comparative phytochemical work showing that hazelnut by-products, including green leafy covers, can exhibit antioxidant activities exceeding those of the kernel itself [36]. Such findings suggest that by-product matrices—despite historically being treated as waste—may hold significant mechanistic and antioxidant value relative to the edible kernel, although their safety for human use has not been established.

3.3.5. Synthesis of Mechanistic Evidence

The Nrf2/Keap1 convergence across four hazelnut matrices (skin, leaf, green leafy covers and kernels) [23–25] (Table 10) mirrors a broader pattern in the polyphenol literature, where Nrf2 is now considered one of the most frequently engaged redox-regulatory targets of plant-derived antioxidants across metabolic, cardiovascular, hepatic, renal, neurodegenerative, and cancer-related contexts [45]. This is not hazelnut-specific: an unrelated polyphenolic fraction (*Cannabis sativa*) activated Nrf2 via Keap1 dissociation in H_2O_2-challenged SH-SY5Y cells using a docking-plus-Western-blot design [46] essentially identical to Cerulli et al.'s [25], and a screen of 29 structurally diverse flavonoids found that Keap1-binding affinity directly predicted antioxidant potency [47]. Cerulli et al.'s [25] docking findings therefore sit within an active line of natural-product Nrf2/Keap1 research, gaining increased plausibility through the analogy with curcumin—a related linear

diarylheptanoid—independently shown to modulate Keap1 through covalent cysteine modification at a structurally distinct site (Cys151, BTB domain), illustrating that diarylheptanoids as a class can engage Keap1 through multiple, mechanistically distinct routes [48].

Sun et al.'s [19] Hippo/Yap-ferroptosis mechanism is mechanistically distinct, and the distinction is informative against the recent literature on the same injury model. Ferroptosis in cisplatin-challenged HK-2 cells is currently an active research target: myricitrin [49], quercetin [50], and licochalcone A [51] have each been shown to protect against cisplatin-induced ferroptosis in this exact model, predominantly via the Nrf2/GPX4 axis, with a recent meta-analysis confirming this as the dominant route among natural polyphenols in cisplatin-induced acute kidney injury [52]. Against this backdrop, Sun et al.'s [19] upstream Hippo/Yap route represents a genuine mechanistic alternative rather than a restatement of the field's dominant pathway, supporting the inference that pathway engagement may depend as much on cellular context as on phytochemical source.

Spagnuolo et al. [26] proposed, without directly testing, an AGE-RAGE-NF-κB mechanism. The recent literature offers a useful external check on this hypothesis: polyphenols are reported to attenuate this cascade via dicarbonyl trapping, Nrf2-dependent glyoxalase-1 upregulation, and NF-κB suppression [53], though the same source cautions that cytokine suppression alone should not be read as evidence of direct RAGE repression absent receptor-level data—reinforcing why this mechanism remains classified as proposed rather than demonstrated.

Taken together, this literature supports two readings of Table 10: the Nrf2/Keap1 convergence reflects a mechanism documented repeatedly, with closely comparable designs, across unrelated polyphenol sources; and the Hippo/Yap divergence shows that even within one well-studied injury model, the specific pathway engaged is not fully predictable from source alone—underscoring the value of pathway-level confirmation over enzymatic readouts as the strongest form of mechanistic evidence in this field.

A tentative pattern emerges from Table 10: Nrf2/Keap1 activation was demonstrated in hepatic (HepG2, LO2) and neuronal (SH-SY5Y) cells, and Hippo/Yap-mediated ferroptosis suppression only in renal HK-2 cells, whereas macrophages (THP-1, RAW264.7) showed reduced intracellular ROS, carbonyl trapping and cytokine suppression; endothelial cells and fibroblasts yielded only functional readouts. However, each pathway was examined in a single cell type and study, with different matrices, stressors and doses, so cell-type specificity cannot be separated from these variables, and this pattern should be regarded as hypothesis-generating.

The pattern of outcomes across the included studies is compatible with the idea that the combined phytochemical profile of each hazelnut part, rather than a single constituent, shapes the redox response. The matrices rich in several phenolic classes, namely the skin [23,26] and the leaf [19,24,27], were associated with multiple concurrent effects in the same study or across studies: radical scavenging in cell-free assays, reduced intracellular ROS, carbonyl trapping [26,27], restoration of endogenous antioxidant enzymes [23,24,27], and pathway-level engagement [19,23,24]. By contrast, the green leafy covers and kernels, represented by a single compound class (cyclic diarylheptanoids) tested as isolated compounds, yielded one defined putative target, Keap1 (binding predicted by docking) [25]. This contrast suggests that in multi-class extracts, constituents with different chemical properties may act on complementary levels of the redox system, for instance scavenging species directly while others activate Nrf2-dependent defenses, so that their combined action is broader than that of any single compound [54,55]. In chemical models, for example, α-tocopherol can be regenerated by flavan-3-ols, which illustrates one route by which constituents may cooperate, although some combinations, such as those involving EGCG, reduced this effect [56]. Combinations of dietary phytochemicals can indeed be synergistic,

additive or antagonistic depending on the compounds and their ratios [54,55], so synergy cannot be assumed from the composition of an extract alone. The evidence for this interpretation is only correlative. No included study fractionated an extract and recombined its constituents, and only Banach et al. [29] compared crude extracts with purified compounds, finding that polar, polyphenol-rich extracts protected better than the lipophilic fraction and that purified catechins protected through direct carbonyl trapping. Therefore, whether the effects of each hazelnut part reflect additive or truly synergistic interactions among its constituents remains a hypothesis that was not tested in the included studies.

3.4. In Vivo Studies

Five in vivo studies were identified that evaluated the antioxidant effects and impact on cellular redox regulation of extracts prepared from hazelnut-derived products [18–20,24,30], as well as two studies that evaluated the effects of hazelnut-enriched diets on oxidative status in the brain of mice [21,22].

As a general remark, studies conducted with extracts prepared from hazelnut-derived products have investigated antioxidant mechanisms of action and their correlation with other cellular and redox-regulatory mechanisms involved in cytoprotection and the protection of certain organs in animal models with liver [18,24], renal [19,30], and gastric [20] induced pathologies, respectively. The characteristics of these studies, along with the main results obtained and the mechanisms investigated, are presented in Table 11.

Baltă et al. [18] tested a gemmotherapeutic extract obtained from fresh hazelnut buds. The extract was prepared in accordance with the European Pharmacopoeia, and phytochemical analysis performed by ultra-high-performance liquid chromatography coupled with electrospray ionization mass spectrometry revealed high levels of hyperoside, rutoside, and chlorogenic acid, regardless of the buds' stage of development or the season. The extract was tested on diabetic mice (diabetes induced by streptozotocin, intraperitoneal (i.p.)) with liver fibrosis (induced by carbon tetrachloride (CCl_4) injection, i.p.). CCl_4 is metabolized in the liver to form the trichloromethyl free radical ($\bullet CCl_3$), which attacks the unsaturated fatty acids in cell membranes and triggers a cascade of other free radicals and ROS. Thus, it induces lipid peroxidation and oxidative stress at the mitochondrial and endoplasmic reticulum levels, and triggers numerous biological processes, such as apoptosis, necrosis, ferroptosis, and autophagy [57]. Liver damage develops, progressing to steatosis, cirrhosis, and hepatoma [58].

Fibrotic diseases are of particular interest because, to the extent that they affect vital organs, they are associated with high mortality [59]. There is a particular focus on the development of new pharmaceutical agents with antifibrotic potential, including natural bioactive compounds. Fibrosis is a condition characterized by the excessive accumulation of collagen and other components of the extracellular matrix [59]. In the liver, fibrosis involves a complex interaction between different types of liver cells and various cellular signaling pathways. Oxidative stress is one of the etiological factors of liver fibrosis and is directly correlated with the activation of the transforming growth factor beta (TGF-β1)/Smad signaling pathway and the matrix metalloproteinase (MMP)/tissue inhibitor of metalloproteinases 1 (TIMP-1) imbalance [18].

In the liver, the activation of hepatic stellate cells (HSCs) is a key factor in liver fibrosis, characterized by proliferation, contractility, and chemotaxis. Viral hepatitis, alcohol, and nonalcoholic steatohepatitis are causes of HSC activation and are associated with hepatic fibrogenesis [60].

Table 11. The characteristics of the selected in vivo studies evaluating the impact of hazelnut-derived products on cellular redox regulation.

Author, Year, Country, Ref.	Study Purpose	Plant Materials/Extraction Procedures/Formulations	Animal Model/Investigations	Main Outcomes/Biological Activities	Investigated Mechanisms
Baltă et al., 2023 Romania [18]	Investigation of the hepatoprotective and antifibrotic effects of a gemmotherapy extract from hazelnut buds in diabetic mice with liver fibrosis.	An extract of hazelnut (*Corylus avellana* L.) fresh buds (CAE) was obtained in glycerin:96% ethyl alcohol (1:1, *v*/*v*) for an extraction ratio of 1:20 (g dw/mL) according to the European Pharmacopoeia (monograph 2.1.3).	Liver fibrosis model in diabetic mice: CD1 male adult mice; 4 groups: (1) control—saline solution; groups 2–4—diabetes induced with streptoxotocin (STZ, 102 mg/kg, i.p.), followed after 2 weeks of treatment with 20% CCl_4 in olive oil (2 mL/kg, i.p.), 2x/week, 7 weeks; (2) group DF—euthanatized after the last administration of CCl4; (3) group DFR—euthanatized 14 days after the last administration of CCl4; (4) group DCA—received CAE (6.71 µg flavonoids/kg bw) after the last administration of CCl4, daily, by gavage, 14 consecutive days. Samples collected: cardiac blood, liver tissue. Investigations: Serum transaminase levels (ALT and AST). Histopathological and immunohistochemical examination of liver tissue; TEM. qPCR analysis of ARNm expression of TGF-β1, Smad 2, 3, 7, Col 1, TIMP-1, α-SMA, MMP-1, MMP-2, MMP-3, and MMP-9. Antioxidant activity of tissue lysate: levels of MDA, GSH, and AOPP. Western blot analysis for Nrf2, HO-1, MMP-2, and MMP-9. Enzymatic activity of MMP-2 and MMP-9.	CAE treatment: Improved liver function and liver architecture in diabetic mice with liver fibrosis: ↓ serum levels of AST ($p < 0.05$ vs. DF) and ALT ($p < 0.001$ vs. DF) in diabetic mice with liver fibrosis after 2 weeks of administration; Significantly improved hepatic architecture and ultrastructural alterations compared to the fibrotic DF group and the self-regenerating DFR group. ↓ Col-1 expression ($p < 0.001$ vs. DF and DFR) previously induced by CCl_4 ($p < 0.001$ in DF vs. control); Significantly reduced the collagen deposits observed in the liver of the fibrotic group (DF), which persisted even after cessation of CCl_4 exposure (DFR). Modulated gene expression: ↓ α-SMA expression ($p < 0.001$ vs. DF and DFR) previously induced by CCl_4 ($p < 0.001$ in DF vs. control); Significantly reduced parenchymal lipid accumulation in the fibrotic liver (TEM) and restored HSC activity comparable to that of the control group; ↓ gene expression of TGF-β1, Smad2, and Smad3 ($p < 0.001$ vs. DF and DFR); ↑ Smad7 expression ($p < 0.001$ vs. control, DF, and DFR). ↓ ARNm expression of MMP-2, MMP-3, MMP-9, and TIMP-1 ($p < 0.001$ vs. DF), significantly increased in diabetic mice ($p < 0.001$ vs. control); ↑ ARNm expression of MMP-1 ($p < 0.001$ vs. control, DF, and DFR, respectively). Improved antioxidant status in the fibrotic livers of diabetic mice: ↓ insignificant lipid peroxidation; ↓ GSH and AOPP levels, and Ub-Nrf2 expression ($p < 0.05$ vs. DFR); ↑ HO-1 expression vs. DF ($p < 0.01$), but ↓ vs. DFR ($p < 0.05$).	CAE reduced oxidative stress and TGF-β1 activation and restored the antioxidant balance in fibrotic liver of diabetic mice; the mechanisms implicated: HSC inhibition, modulation of redox-sensitive signaling (TGF-β1/Smad) by oxidative stress reduction, and restoring balance of MMPs/TIMP-1.

Table 11. *Cont.*

Author, Year, Country, Ref.	Study Purpose	Plant Materials/Extraction Procedures/Formulations	Animal Model/Investigations	Main Outcomes/Biological Activities	Investigated Mechanisms
Liang et al., 2025 China [24]	Investigating the role of polyphenols from hazel leaves in regulating chronic alcohol-induced liver disease.	Hazelnut leaves were extracted with 65% ethanol (plant material to liquid ratio of 1:60) using UAE for 100 min, followed by centrifugation. The filtered supernatant constituted the crude polyphenol extract (HLP).	Chronic alcohol-induced liver disease (CALD) model in mice: Male C57BL/6 mice; 6 groups (n = 6): BC—control; NC (model); LH (50 mg HLP/kg); MH (100 mg HLP/kg); HH (200 mg HLP/kg); positive control (PC, 200 mg silymarin/kg). Except for the BC group, all others received 50% ethanol (0.1 mL/10 g bw) 2 h after extract/drug administration to induce CALD model. Administration by gavage for 28 days; 12 h post-intervention, the rats were sacrificed; blood and liver tissue were collected. Investigations: Serum liver transaminase (ALT and AST) levels. SOD, MDA, GSH, and CAT levels in the supernatant of the centrifuged liver homogenate. Histopathological examination of liver tissue—HE staining. Western Blot analysis of liver tissue.	HLP: ↓ ALT and AST levels in a dose-dependent manner, with statistical significance in the MH and HH groups ($p < 0.05$ vs. NC). In the HH group, the decrease was comparable to that induced by silymarin in the PC group (both $p < 0.01$ vs. NC). ↑ serum SOD and CAT activities and GSH level ($p < 0.05$ vs. NC); ↓ MDA level in a dose-dependent manner, with an effect comparable to that of PC at the highest tested dose (HH) (both $p < 0.01$ vs. NC). - significantly attenuated the severe ethanol-induced liver lesions observed histopathologically (presence of fat vacuoles, significant accumulation of lipid droplets, signs of hepatocellular destruction), more pronounced in the HH group. ↓ Keap1 expression ($p < 0.05$ for HH vs. NC); ↑ Nrf2, HO-1, and NQO1 expressions ($p < 0.01$ for HH vs. NC) in a dose-dependent manner, preventing or mitigating the hepatotoxic effects of ethanol.	HLP showed a hepatoprotective effect due to its powerful antioxidant action via modulation of Nrf2/HO-1 pathway, improving liver function, and correcting the body's redox imbalance caused by exposure to ethanol.

Table 11. *Cont.*

Author, Year, Country, Ref.	Study Purpose	Plant Materials/Extraction Procedures/Formulations	Animal Model/Investigations	Main Outcomes/Biological Activities	Investigated Mechanisms
Sun et al., 2024 China [19]	Investigation of the nephroprotective properties of polyphenols from hazel leaves through the modulation of oxidative stress, ferroptosis, and apoptosis.	Freeze-dried hazelnut leaves were extracted with 70% methanol: 1% HCl (1:1, v/v) by shaking and sonication (30 min). The methanol was removed using a vacuum rotary evaporator, and the supernatant was lyophilized, yielding hazelnut leaf polyphenol powder (ZP).	Acute kidney injury (AKI) model in mice: Male C57BL/6 mice; 5 groups (n = 6): (1) control; (2) model AKI; (3) ZPL (ZP, 250 mg/kg); (4) ZPH (ZP, 500 mg/kg); (5) ZP+D (9 mg dihydrexidine/kg, i.p.). The groups treated with ZP received the oral extract daily for 9 days. On day 7, all groups (except the control) received a single dose of 20 mg/kg cisplatin, i.p., one hour after ZP administration. The mice were euthanized under anesthesia, and serum and kidney tissue were collected Investigations: Serum levels of BUN, CRE, SOD, MDA, CAT și GSH. Histopathological examination of renal tissue (HE staining); TEM. Detection of apoptosis using the TUNEL assay. Immunohistochemistry (GPX4, FSP1, and FTH1) and immunofluorescence (YAP) on kidney tissues. Western blot analysis for caspase-3, caspase-9, GPX4, FSP1, FTH1, Yap, p-Yap, Lats, and p-Lats.	ZP attenuated cisplatin-induced AKI: ↓ cisplatin-induced serum BUN and CRE levels ($p < 0.05$ vs. model); - when administered prior to cisplatin treatment, it attenuated cisplatin-induced pathological changes in the kidneys of mice, including mitochondrial damage (TEM). ZP attenuated oxidative damage in the kidneys of mice: ↑ levels of endogenous antioxidants (GSH, SOD, and CAT) affected by cisplatin in the kidneys of mice ($p < 0.05$ vs. model); ↓ cisplatin-induced MDA level ($p < 0.05$ vs. model); ↓ the number of apoptotic cells ($p < 0.05$ vs. control) in mouse kidney tissue; ↓ cisplatin-induced caspase 3 level in kidneys of mice ($p < 0.05$ vs. model). ZP attenuated cisplatin-induced renal ferroptosis: - significantly increased levels of GPX4, FSP1, and FTH1 in the ZP-treated groups vs. model. ZP activated Hippo signaling in the kidneys of cisplatin-treated mice: ↑ Yap protein level in the ZP-treated groups vs. model; ↓ Yap level in the kidneys of mice in the ZP+D group vs. ZP group (dihydrexine enhances Yap phosphorylation) and exacerbated renal mitochondrial dysfunction; ↑ p-Yap/Yap in the kidneys of mice in the ZP+D group vs. ZP group ($p < 0.05$); ↓ GPX4 and FTH1 expressions in the ZP+D group vs. ZP groups ($p < 0.05$).	Polyphenols from hazelnut leaves prevented/mitigated oxidative damage and regulated antioxidant defense system (GSH, SOD, CAT) and anti-ferroptosis proteins (GPX4, FTH1, FSP1), and also modulated Hippo pathway signaling.

Table 11. *Cont.*

Author, Year, Country, Ref.	Study Purpose	Plant Materials/Extraction Procedures/Formulations	Animal Model/Investigations	Main Outcomes/Biological Activities	Investigated Mechanisms
Wang et al., 2024 China [30]	Investigation of the protective and redox-regulatory effects of polyphenols from hazel leaves in hyperuricemia-induced renal fibrosis in mice.	Hazel leaves extracted with 70% methanol: 1% HCl (1:1, *v*/*v*), stirred by eddy current (30 s). The methanol was removed using a vacuum rotary evaporator, and the supernatant was freeze-dried, yielding a powder of polyphenols from hazel leaves (HP).	Hyperuricemia-induced renal fibrosis model in mice: SPF male C57BL/6J mice; 5 groups (n = 8): (1) control; (2) model; (3) ALP (allopurinol, 25 mg/kg); (4) HPH (HP, 500 mg/kg); (5) HPL (HP, 250 mg/kg). After one week, hyperuricemia was induced in all groups except the control group (which received water) using 1 g/kg yeast extract + 100 mg/kg adenine + 250 mg/kg oteracil potassium. The solution was administered daily by gavage for 10 weeks. Investigations: Measurements: - renal blood flow; - serum levels of UA, XOD, BUN, CRE, total-SOD, MDA, GPX, CAT, IL-6, and TNF-α; - relative weight of the liver and kidneys. Histopathological examination of kidney tissue (HE and Masson stainings); (TEM). Western blot analysis for 15 proteins in kidney tissues of mice: urate transporters URAT1, ABCG2, SLC2A9; pro-fibrotic proteins TGF-β1 and α-SMA; Nrf2, HO-1, GAPDH, Histone-H3, p62 (sequestosome 1), Keap1, NQO-1, Nucleus-Nrf2, GPX4, and SLC7A11/xCT.	HP attenuated hyperuricemia induced in mice: - It slightly increased, though not statistically significantly, the reduced renal blood flow caused by induced hyperuricemia ($p < 0.01$ in the model group vs. control); ↓ serum UA level in the group treated with 250 mg/kg ($p < 0.05$ vs. model), but to a much lesser extent than allopurinol ($p < 0.05$ vs. model); It inhibited XOD in a dose-dependent manner ($p < 0.001$ vs. model), comparable to or even greater than allopurinol ($p < 0.001$ vs. model). HP attenuated hyperuricemia-induced fibrosis in mice: ↓ serum BUN and CRE levels (HPL $p < 0.05$ and HPH $p < 0.001$ vs. model) comparable to or greater than those of allopurinol; Histopathological examination confirmed a reduction in hyperuricemia-induced renal lesions in the HP-treated groups; It regulated the renal levels of URAT1, SLC2A9, ABCG2, and TGF-β1 (↑, $p < 0.001$ vs. model), as well as of α-SMA (↓, $p < 0.001$ vs. model); HP increased the antioxidant capacity of renal tissue by activating the Nrf2 signaling pathway: ↑ serum levels of SOD, GPX, and CAT (HPH, $p < 0.001$, vs. model); ↓ serum levels of MDA, IL-6, and TNF-α (HPH, $p < 0.05$, vs. model); ↑ Nrf2 expression ($p < 0.01$ vs. model) ↓ KEAP1 and p62 expressions ($p < 0.001$ vs. model), comparable to allopurinol. HP provided renal protection against ferroptosis: - mitochondrial damage was significantly reduced in the HP-treated groups (TEM analysis); ↓ Fe^{2+} in renal tissue in the HP groups (HPH, $p < 0.001$ vs. model); ↑ NQO-1, HO-1, GPX4, and SLC7A11/xCT ($p < 0.001$ vs. model), comparable to allopurinol	Direct evidence for Nrf2/HO-1 pathway modulation in vivo; renoprotection properties by attenuation of oxidative stress and ferroptosis via redox protein regulation and a better control of uric acid homeostasis.

Table 11. *Cont.*

Author, Year, Country, Ref.	Study Purpose	Plant Materials/Extraction Procedures/Formulations	Animal Model/Investigations	Main Outcomes/Biological Activities	Investigated Mechanisms
Öztürk et al., 2025 Turkey [20]	Investigation of the antioxidant and gastroprotective properties of certain hazelnut extracts in a rat model of indomethacin-induced gastric ulcer.	Hazelnuts from Giresun (GH) and Trabzon (TH) (Turkey)/Extractions in water (WE), ethanol:water (EWE), and methanol (ME), respectively, in a water bath at 50 °C for 2 days (100 g hazelnuts/500 mL solvent), followed by lyophilisation.	Indomethacin-induced gastric ulcer model in rats: Adult female Wistar-Albino rats; 12 groups (n = 6) treated with one extract each (two doses of each extract, in parallel: 100 and 250 mg/kg) by gavage, followed 10 min later by indomethacin (25 mg/kg, by gavage), in parallel with: (i) a control group (water, no intervention), (ii) a group treated with indomethacin (IND) alone, and (iii) a group treated with lansoprazole and indomethacin. 6 h after treatment, the rats were euthanized under anesthesia, and gastric tissue was collected. Investigations: The following levels were measured in the supernatant of the centrifuged gastric homogenate: CAT, LPO (lipid peroxidation—MDA), total GSH, and SOD.	All hazelnut extracts: ↓ ulcer index ($p < 0.05$); THME demonstrated similar efficacy (79.7% at 250 mg/kg) or even better efficacy (90.6% at 100 mg/kg) compared to lansoprazole (80% at 25 mg/kg). Hazelnut extracts: ↓ MDA in the gastric mucosa: from 89 nmol/g (IND model group) to ~54 nmol/g (THME, 250 mg/kg) or ~52 nmol/g (GHME, 250 mg/kg); ↑ SOD and GSH ($p < 0.05$ vs. IND) for most extracts	Hazelnut extracts restored glutathione, increased SOD activity, and reduced lipid peroxidation in rat gastric tissue—a direct investigation of antioxidant defense mechanisms against oxidative stress.

ABCG2—ATP-binding cassette transporter G2; AKI—acute kidney injury; ALP—allopurinol; ALT—alanine aminotransferase; AOPP—advanced oxidation products of proteins; AST—aspartate aminotransferase; BUN—blood urea nitrogen; bw—body weight; CAE—*Corylus avellana* L. extract; CALD—chronic alcohol-induced liver disease; CAT—catalase; CCl_4—carbon tetrachloride; Col 1—collagen I; CRE—serum creatinine; DF—diabetic fibrosis group; FSP1—ferroptosis suppressor protein 1; FTH1—ferritin heavy chain 1; GPX—glutathione peroxidase; GPX4—glutathione peroxidase 4; GSH—reduced glutathione; HE—hematoxylin–eosin staining; HO-1—heme oxygenase-1; HSC—hepatic stellate cells; IL-6—interleukin-6; Keap1—Kelch ECH associating protein 1; LPO—lipid peroxidation; MDA—malondialdehyde; MMP—matrix metalloproteinases; NQO-1—NADPH dehydrogenase quinone 1; Nrf2—nuclear factor erythroid 2-related factor 2; qPCR—real-time quantitative polymerase chain reaction; p62—sequestosome 1; SD—standard diet; SLC2A9 (Glut9)—glucose transporter 9; SLC7A11/xCT—cystine transporter solute carrier family 7 member 11; α-SMA—α-smooth muscle actin; SOD—superoxide dismutase; STZ—streptozotocin; TEM—transmission electron microscopy; TGF-β1—transforming growth factor-β1; TIMP-1—tissue inhibitor of metalloproteinases 1; TNF-α—tumor necrosis factor alpha; TUNEL—TdT-mediated dUTP nick-end labeling; UA—uric acid; UAE—ultrasound-assisted extraction; Ub-Nrf2—ubiquitinylated form of Nrf2; URAT1—urate transporter 1; XOD—xanthine oxidase; ↓—decreased, ↑—increased.

Oxidative stress and the production of proinflammatory and profibrogenic cytokines play an important role in HSC activation. ROS induce/activate TGF-β1, a cytokine ubiquitous in the body, which is considered to have the highest profibrogenic potential [61] and which is overexpressed in fibrotic tissues [59]. TGF-β1 is produced in the extracellular space, where it exists as a dimer bound to latency-associated protein (LAP). ROS and oxidants activate TGF-β1 directly by oxidizing LAP and indirectly by activating MMPs, such as MMP-2 and MMP-9, which degrade LAP and release TGF-β1. The TGF-β1 thus released triggers the activation of several cellular signaling pathways, including the Smad pathway, the MAPK pathways, the Wnt/β-catenin axis, and others [60,61]. At the same time, TGF-β1 increases ROS production at the mitochondrial level by inducing NADPH oxidases (Nox), primarily Nox4, and inhibits endogenous antioxidant systems—it decreases GSH synthesis and reduces the expression and activity of antioxidant enzymes (SOD, CAT, GPX, peroxiredoxins). Overall, TGF-β1 activation leads to a redox imbalance. In fact, a vicious cycle develops between ROS and TGF-β1, which contributes significantly to the development of fibrosis [61].

Normally, the TGF-β1/Smad pathway regulates various cellular functions, such as proliferation, differentiation, and apoptosis. It involves the phosphorylation of Smad 2/3 proteins, transcription factors that act as signal transducers for TGF-β1 and through which the expression of certain genes is modulated. Uncontrolled activation of this pathway induces the synthesis and accumulation of extracellular matrix (ECM) proteins, including collagen, while also inhibiting ECM degradation [59]. TGF-β1 induces the synthesis of alpha-smooth muscle actin (α-SMA) in HSCs, initiating the differentiation of these cells into type 1 collagen (Col-1)-producing myofibroblasts [18]. Furthermore, TGF-β1 stimulates apoptosis at the epithelial and endothelial levels and the epithelial–mesenchymal transition (EMT) [62].

Several studies have demonstrated that TGF-β activity and expression are regulated by the in vivo redox state. Thus, the TGF-β1/Smad axis represents an essential therapeutic target [62], and antioxidants, by reducing ROS, regulate cellular redox status, inhibit TGF-β1/Smad profibrotic signaling pathways, and represent effective therapeutic opportunities in the treatment of fibrotic pathologies [61].

Baltă et al. [18] demonstrated that the gemmotherapeutic extract of hazelnut (CAE), administered orally for 2 weeks to diabetic mice with liver fibrosis, improved liver function by reducing serum transaminase activity ($p < 0.05$ for AST and $p < 0.001$ for ALT, respectively, vs. the DF group, Table 11) and improved liver architecture by reducing collagen synthesis and deposits. Liver structure and ultrastructure were significantly improved compared to the diabetic fibrosis group (DF) and the self-regeneration group (spontaneous regeneration after discontinuation of CCl_4 administration, without gemmotherapy—the DFR group). Furthermore, CAE significantly reduced the activation of HSCs, as reflected by decreased α-SMA expression ($p < 0.001$ vs. DF and DFR) and brought lipid accumulation in the liver parenchyma to a level nearly identical to that of the control group, in contrast to liver self-regeneration (DFR group), which showed no significant difference compared to the DF group. One of the mechanisms through which CAE acted was the inhibition of the TGF-β1/Smad pathway and the regulation of tissue remodeling and ECM degradation via the modulation of MMPs and TIMP1 expressions (Table 11). Following the reduction in TGF-β1 expression ($p < 0.001$ vs. DF and DFR) and due to the remarkable antioxidant potential of the phytochemicals in CAE, particularly hyperoside, rutin, and chlorogenic acid, the hepatic antioxidant status improved: levels of advanced oxidation products of proteins (AOPP) and ubiquitinated Nrf2 (Ub-Nrf2, its inactive form) decreased (for both $p < 0.05$ vs. DFR), while heme oxygenase-1 (HO-1) expression increased ($p < 0.01$ vs. DF),

reflecting the activation of the Nrf2/HO-1 signaling pathway by the polyphenols in CAE and the restoration of cellular redox homeostasis.

An extract from hazel leaves, containing 20% flavones, 16% proanthocyanidins (represented by prodelfinine), and 56% tannic polyphenols, counteracted CCl_4 toxicity in a study conducted on rats exposed to CCl_4 for 7 days, when it was administered 30 min after the toxic agent. The extract reduced hepatocyte lysis and histopathological lesions and normalized liver enzyme levels compared to the positive control group, which was treated with CCl_4 alone ($p < 0.001$) [58].

Several studies conducted with various polyphenols have demonstrated that they can prevent or attenuate CCl_4-induced hepatic fibrosis in animal models through their antioxidant potential [60]. Baltă et al. [18] attributed the antioxidant and antifibrotic effects of CAE to its high polyphenol content, particularly hyperoside. Both hyperoside (quercetin-3-*O*-galactoside) and rutoside (quercetin-3-*O*-rutinoside), the two main components of CAE, are glycosylated forms of quercetin, a flavonoid known for its potent antioxidant properties. In fact, after ingestion, these glycosides undergo extensive metabolism, converting to quercetin in the digestive tract under the action of enzymes produced by the microbiota. Quercetin is the biologically active aglycone, bioaccessible in its conjugated form [63]. A study conducted on CCl_4-treated rats demonstrated that concomitant treatment with quercetin attenuated oxidative stress and inflammation and prevented the development of hepatic fibrosis, while maintaining low levels of serum transaminases. Among the identified mechanisms are: inhibition of NF-κB and inhibition of the expression of pro-inflammatory cytokines, prevention of HSC activation, decreased expression of TGF-β, Col-1a, and connective tissue growth factor, increased expression and activity of the antioxidant enzymes SOD and CAT, as well as activation of MMP2 and MMP9 [64]. A meta-analysis including 13 studies demonstrated that rutin (or rutoside) coordinately modulated the metabolic disturbances, oxidative stress, and fibrosis associated with renal fibrosis in a murine model of diabetic kidney disease [65].

Studies have shown that other components of CAE with antioxidant properties have also exhibited antifibrotic and hepatoprotective effects. Thus, Shi et al. [66] demonstrated that chlorogenic acid activates the Nrf2/ARE pathway and inhibits the inflammatory signaling pathway, thereby preventing the development of CCl_4-induced liver fibrosis in rats. Chlorogenic acid prevented lipid peroxidation and maintained the endogenous antioxidant system (GSH, SOD, and CAT), significantly attenuating the expression of α-SMA, collagen I, collagen III, and TIMP-1 in liver tissue [66]. Luteolin, the aglycone of luteolin-7-*O*-glucoside, another component of CAE, may exert antifibrotic effects, as demonstrated by studies on CCl_4-induced liver fibrosis in mice and rats. The mechanisms of action involve HSC apoptosis and inhibition of the TGF-β/Smad2 signaling pathway, as well as AKT activation [67]. Chrysin (5,7-dihydroxyflavone), another bioflavonoid quantified in CAE, attenuated CCl_4-induced liver fibrosis in mice in a dose-dependent manner, by reducing Col-1 production and ECM accumulation, as well as by regulating the imbalance between MMPs and TIMP-1 [68].

According to this evidence, all three major polyphenolic compounds quantified in the gemmotherapy extract from hazelnut buds, regardless of the harvest period (hyperoside, rutoside, and chlorogenic acid), as well as other identified components (e.g., luteolin, chrysin), are effective in preventing or alleviating experimental CCl_4-induced liver fibrosis. Furthermore, polyphenols in plant extracts have strong additive or synergistic effects with other bioactive compounds present in the matrix. In the gemmotherapeutic extracts, the biologically active phytocomplex depends on the plant product and the method of extraction; its profile of hydrophilic and lipophilic compounds determines its pharmacological action

and therapeutic indications. In these extracts, polyphenols synergistically act especially with plant hormones and growth factors that can stimulate the healing process [18].

The results reported by Baltă et al. suggest that the gemmotherapeutic extract from hazelnut buds has antioxidant, hepatoprotective, and antifibrogenic potential and warrants further study for its clinical use in the prevention and treatment of liver fibrosis.

Chronic alcohol consumption causes hepatotoxicity primarily through oxidative stress: in the initial phase, simple steatosis occurs, associated with increased ROS production, followed by the accumulation of proinflammatory and profibrogenic cytokines [60]. Liang et al. [24] tested a hydroalcoholic extract (65% ethanol) of polyphenols isolated from hazelnut leaves (HLP) in a murine model of chronic alcoholic liver disease (CALD). Treatment with HLP exerted dose-dependent hepatoprotective effects, keeping serum transaminase levels low in a manner comparable to silymarin ($p < 0.01$ compared to the negative control), used as a reference substance, at the highest dose of the tested extract (200 mg HLP/kg body weight (bw)). Furthermore, HLP prevented or attenuated alcohol-induced hepatic steatosis and hepatocellular damage. These hepatoprotective properties were based on the extract's antioxidant mechanism of action and its ability to modulate the Nrf2/HO-1 pathway, as evidenced by decreased Keap1 expression, which is associated with cytoprotection, detoxification, and stimulation of endogenous antioxidant systems: increased expressions of HO-1 and NQO1 and increased levels of GSH and activities of SOD and CAT enzymes, as well as the prevention/reduction in lipid peroxidation (Table 11). These results are consistent with those obtained from in vitro tests (Table 10). In fact, in the same study, HLP demonstrated potent, dose-dependent antioxidant activity under abiotic conditions—a high capacity to scavenge DPPH·, ABTS+, and ·OH radicals, as well as reducing power—and the ability to modulate ethanol-induced oxidative stress in LO2 cells [24].

The Nrf2/ARE (or Nrf2/HO-1) pathway is a key intracellular defense mechanism that regulates cellular responses to oxidative stress. Its activation is inversely correlated with NF-κB, a transcription factor involved in the inflammatory response.

In a recent review, Zhu et al. [69] summarized in vivo studies demonstrating the potential of certain Chinese herbal medicines in the treatment of alcoholic liver disease by modulating signaling pathways associated with oxidative stress, including quercetin, dihydromyricetin, resveratrol, curcumin, silymarin, etc. Quercetin, present in hazel polyphenol extracts, reduced levels of ROS, lipid peroxidation, and CYP2E1 expression (an isoenzyme involved in ethanol metabolism that leads to ROS formation) and induced endogenous antioxidant defense systems in Sprague–Dawley rats in alcohol subchronic toxicity studies [70,71]. A 14-day pretreatment with quercetin, followed by acute alcohol exposure, exerted hepatoprotective effects in both rats [69] and mice [72] by modulating oxidative stress (reducing ROS levels and lipid peroxidation, as well as stimulating endogenous antioxidant systems—GSH, SOD, CAT), decreasing inflammatory responses (TNF-α and certain proinflammatory interleukins), and modulating lipid metabolism (decreased serum triglycerides (TG)). In fact, there is ample evidence regarding the cytoprotective action of polyphenols, which is exerted through their antioxidant activity, their ability to directly donate hydrogen atoms to neutralize free radicals derived from lipid peroxidation, and their ability to inhibit peroxidase and thus prevent the formation of superoxide anions [24]. The hepatoprotective action of HLP results from the synergistic interaction of the polyphenolic complex. Their biological potential and therapeutic efficacy depend on the dose, as well as on the phytochemical profile, which is determined by the composition of the plant material and the extraction conditions.

Kidney disease is one of the leading noncommunicable diseases worldwide, with a prevalence exceeding 10%, and the kidney is an organ that is particularly sensitive to redox imbalance. Oxidative stress is the main etiological factor in acute kidney injury (AKI) and,

together with iron metabolism dysregulation, triggers ferroptosis—a form of non-apoptotic, iron-dependent cell death characterized by the accumulation of labile intracellular iron and lipid peroxides—which promotes the progression of AKI to chronic kidney disease [73].

Cisplatin is a nephrotoxic anticancer drug that accumulates intracellularly in the proximal tubules and triggers oxidative stress, mitochondrial dysfunction, inflammatory cascades, cellular necrosis, ferroptosis, and tubular epithelial apoptosis [74]. In clinical practice, cisplatin-induced nephrotoxicity limits the establishment of an optimal treatment regimen for cancer patients, making it imperative to discover safe and effective nephroprotective agents that can prevent cisplatin-induced kidney damage and ensure the drug's therapeutic efficacy.

In a model of cisplatin-induced AKI (i.p.) in mice, Sun et al. [19] demonstrated that polyphenols isolated from hazelnut leaves (ZP) exhibit renoprotective properties by improving cisplatin-impaired renal function (decreased serum levels of blood urea nitrogen (BUN) and creatinine (CRE)) and by attenuating structural and ultrastructural changes, particularly mitochondrial damage and the associated inflammatory process (Table 11). ZP attenuated cellular oxidative stress in the kidneys by stimulating antioxidant defense (GSH, SOD, and CAT), reducing lipid peroxidation (MDA), and prevented apoptosis (by reducing caspase-3 levels) ($p < 0.05$ compared to the control group) (Table 11).

The formation of lipid peroxides is regulated at the cellular level by two antioxidant systems: the GSH/GPX4 system and the coenzyme Q10/FSP1 system. The occurrence of ferroptosis depends on iron metabolism. Under physiological conditions, transferrin receptor 1 (TFR1) binds to transferrin, mediating cellular iron uptake via endocytosis. When TFR1 expression on the cell membrane is increased, excess absorbed Fe^{3+} is reduced to Fe^{2+}; this creates a labile iron pool (LIP). This iron can participate in the Fenton reaction, leading to the formation of hydroxyl radicals capable of inducing oxidative damage to cellular macromolecules. Another pathway through which LIP is formed is ferritinophagy—a process of selective autophagy through which ferritin releases the iron necessary for cellular and mitochondrial functions. The process is triggered by nuclear receptor coactivator 4, which, when overexpressed, binds to FTH1 and mitochondrial ferritin [73]. FTH1 possesses ferroxidase activity and converts Fe^{2+} to Fe^{3+}, which it stores in an inert form. Therefore, FTH1 plays an important role in regulating ferroptosis, and its absence or depletion is associated with the promotion of ferroptosis [75].

Sun et al. [19] identified via immunohistochemistry that ZP prevented or attenuated ferroptosis in the kidneys of cisplatin-treated mice by stimulating the GSH/GPX4 and FSP1 antioxidant systems, which control the formation of lipid peroxides, and by increasing FTH1 levels, which regulate iron metabolism (Table 11). Another mechanism through which ZP exerted nephroprotective effects is the modulation of the Hippo pathway, a signaling pathway involved in cell proliferation, differentiation, and apoptosis, which plays an essential role in the pathogenesis and repair of AKI. Transient activation of Yap, a downstream effector of this pathway, contributes to renal recovery and regeneration in AKI, whereas persistent activation of Yap can lead to inadequate repair and progression to chronic kidney disease [76]. ZP increased Yap levels in the kidneys of mice with cisplatin-induced AKI compared to the control group; however, co-administration of ZP with dihydrexine, a substance that induces Yap phosphorylation, abolished the nephroprotective effect of ZP: this exacerbated mitochondrial dysfunction associated with renal tubular damage and inflammation, as well as a decrease in the anti-ferroptosis proteins GPX4 and FTH1 ($p < 0.05$ for the ZP+dihydrexidine groups compared to the ZP groups) [19] (Table 11).

The ZP extract analyzed and tested by Sun et al. [19] contained nine key polyphenols, the main ones being kaempferol (221.99 mg/g) and chlorogenic acid (8.23 mg/g), along with myricetin, caffeic acid, *p*-coumaric acid, resveratrol, luteolin, gallic acid, and ellagic

acid [77]. Several phenolic compounds, including chlorogenic acid, flavonoids, and their glycosylated or methoxylated derivatives, have exerted nephroprotective effects in animal models of cisplatin-induced AKI as independent bioactive substances [50,78–82]. In the case of natural extracts (e.g., *Carthamus tinctorius* L.—safflower or *Arundina graminifolia* (D.Don) Hochr.—bamboo orchid), which are rich in such compounds, the preclinical nephroprotective efficacy has been attributed to the combined action of the compounds, which may act synergistically through related mechanisms: cellular redox regulation by enhancing antioxidant capacity, attenuation of inflammatory responses, and activation of anti-ferroptosis processes [74,83]. Similarly, ZP are of particular interest due to their complex phytochemical composition and their protective effect against cisplatin-induced nephrotoxicity in mice; these findings are preclinical and do not establish efficacy or safety as a complement for anticancer therapy. Wang et al. [30] investigated the nephroprotective role of polyphenols from hazelnut leaves in a murine model of hyperuricemia-induced renal fibrosis, comparing them with allopurinol (ALP) as a reference substance. They used the same ZP extract previously tested by Sun et al. [19], but in the form of a freeze-dried powder (designated HP), administered in parallel at two different doses (250 and 500 mg/kg bw) (Table 11).

Hyperuricemia is a consequence of purine metabolism dysfunction and represents an indicator of increased xanthine oxidase (XOD) activity or a consequence of reduced urinary excretion of uric acid. This causes urate deposits in tissues, leading to gout—a condition associated with oxidative stress, endothelial and mitochondrial dysfunctions, chronic local inflammation, as well as immune and microvascular damage, including in the kidneys—thereby contributing to the development of chronic kidney disease. HP significantly improved renal function impaired by hyperuricemia (decreased BUN and CRE levels, $p < 0.05$ vs. control) and reduced serum uric acid levels ($p < 0.05$ vs. control) and XOD activity ($p < 0.001$ vs. control) in a dose-dependent manner, proving to be as effective as or even more effective than ALP (Table 11). Furthermore, HP regulated the expression of certain uric acid transporters: URAT1 and SLC2A9, both involved in tubular reabsorption, and ABCG2, involved in tubular secretion, thereby improving renal excretion of uric acid, regulating serum uric acid levels, and reducing hyperuricemia-induced renal fibrosis (decreased α-SMA, $p < 0.001$ vs. control) [30] (Table 11). These results confirm data reported in a previous study, in which polyphenols from hazelnut leaves inhibited XOD and reduced uric acid levels in a zebrafish model of hyperuricemia [77].

Histopathological examinations revealed a significant improvement in the renal lesions observed in the hyperuricemia control group (degeneration of tubular epithelial cells, leukocyte infiltrate), while less mitochondrial damage (structural membrane lesions, ruptured cristae, and a cavernous, sagging matrix) was observed in the HP-treated groups by transmission electron microscopy (TEM). The HP-induced changes at the mitochondrial level suggested antioxidant and antiapoptotic effects. Indeed, biochemical tests and Western blot analysis confirmed HP's antioxidant activity, reflected by stimulation of the endogenous antioxidant system (increased levels of GSH, SOD, CAT, and GPX) and reduced lipid peroxidation (MDA); the identified mechanisms included activation of the Nrf2/HO-1 signaling pathway (increased expression of Nrf2 and HO-1, and decreased expression of KEAP1), associated with a decrease in pro-inflammatory biomarkers (TNF-α and IL-6) (Table 11). Regarding anti-apoptotic mechanisms, the authors highlighted increased expression of antioxidant molecules associated with Nrf2 activation (NQO-1, HO-1, GPX4, SLC7A11/xCT), which play a key role in antiapoptotic cytoprotection, as well as a significant reduction in labile iron ions, Fe^{2+}, in renal tissue ($p < 0.001$ vs. control at 500 mg HP/kg bw) [30] (Table 11).

Studies have demonstrated the beneficial nephroprotective effects of certain polyphenols found in hazelnut leaves, or their metabolites, in other animal models of kidney disease [77,84,85]. Thus, kaempferol demonstrated significant anti-inflammatory, anti-apoptotic, and anti-fibrotic effects in rats with diabetic kidney disease (DKD), attenuating renal fibrosis and restoring mitochondrial homeostasis [84]. Chlorogenic acid attenuated renal fibrosis and lipid deposition in the kidneys of mice with DKD by inhibiting the Notch1 and Stat3 signaling pathways [85]. Ellagic acid found in ZP [77] is metabolized by the microbiome into urolithins, bioactive metabolites with proven antioxidant properties [8]. In a murine model of folic acid-induced renal fibrosis, urolithin A attenuated renal dysfunction, reduced the inflammatory and profibrotic processes in the kidneys, inhibited ECM components, and blocked the EMT process, demonstrating antioxidant and antifibrotic properties mediated by the Nrf2/HO-1 and TGF-β1/Smad signaling pathways, respectively [86].

Therefore, the nephroprotective effect of the polyphenols isolated from hazelnut leaves is due to the phytochemical complex as a whole and to the synergistic or complementary action of the polyphenols present in the extract in exerting the antioxidant, anti-inflammatory, and antifibrogenic effects.

Öztürk et al. [20] studied the antioxidant and gastroprotective properties of methanolic, aqueous, and hydroalcoholic extracts obtained from hazelnuts sourced from two regions in Turkey, Giresun (GH) and Trabzon (TH), in an indomethacin-induced gastric ulcer model in rats. Indomethacin (IND) inhibits the synthesis of prostaglandins, which play a protective role for the gastric mucosa, and triggers the excessive formation of free radicals and ROS, which induce lipid peroxidation and oxidative stress. All hazelnut extracts tested by Öztürk et al. [20] reduced the ulcer index ($p < 0.05$) to varying degrees. The most effective extract was the TH methanol extract (100 mg/kg), which proved to be more effective than lansoprazole (25 mg/kg) used as a reference substance: 90.6% relative inhibition compared to IND vs. 80% for lansoprazole. Similarly, lipid peroxidation was most strongly inhibited by the two methanolic extracts: MDA levels were 39% lower (~54 nmol/g) in the TH methanol extract-treated group (250 mg/kg) and 41% (~53 nmol/g) in the GH methanol extract-treated group (250 mg/kg) compared to the control group (IND, 89 nmol/g) (Table 11). The hazelnut extracts enhanced endogenous antioxidant defense systems, significantly increasing SOD activity (the best result for TH water extract—a value 78% higher than that of IND; $p < 0.05$), as well as GSH levels (the best results for GH methanol extract and TH water extract—values 169% higher than that of IND; $p < 0.05$) [20].

A recent analysis has shown that the gastroprotective role of various fruit extracts in cases of gastric ulcers induced by nonsteroidal anti-inflammatory drugs is based on the antioxidant, cytoprotective, and anti-inflammatory properties of certain polyphenolic compounds or metabolites (the most abundant being flavonoids) present in the extracts, as well as on their antisecretory activity against gastric acid [87]. These extracts, similar to the hazelnut extracts studied by Öztürk et al. [20], reduced biomarkers of lipid peroxidation, increased the activity of antioxidant enzymes (SOD, CAT), and raised GSH levels, thereby supporting cellular antioxidant defense mechanisms. In addition, for certain extracts, increased prostaglandin levels and the formation of a protective film through protein precipitation in the ulcer area were observed [87]. One example is pomegranate (*Punica granatum* L.) extracts, which, due to the flavonoids and phenolic compounds they contain, possess superior antioxidant activity, the ability to neutralize ROS, and the capacity to stimulate the endogenous antioxidant system. Furthermore, pomegranate extracts have the ability to suppress pro-inflammatory cytokines (TNF-α, IL-1β), reduce gastric acidity, and enhance protection of the gastric mucosa [88].

Olofinnade et al. [21,22] conducted two studies evaluating the health benefits of hazelnut-enriched diets on cellular oxidative status in the brains of aged mice under condi-

tions of physiological aging [21], as well as in adult mice fed a high-fat diet (HFD) [22]. In both studies, two types of hazelnuts were used in parallel, sourced from Italy (ITA) and Turkey (TKY). The characteristics of these studies and the main results are presented in Table 12.

In some traditional medical texts, hazelnuts are mentioned alongside almonds and walnuts for their benefits in preventing cerebral atrophy and memory loss [21,89]. After 8 weeks of feeding a hazelnut-supplemented diet to aged mice (24 months), improvements in spatial memory and behavior were observed, including an increase in horizontal locomotion and grooming, as well as a significant anxiolytic effect at most of the concentrations tested (2%, 4%, and 8%). Biochemical analyses highlighted the antioxidant effects of the nut supplement through a statistically significant reduction in cerebral lipid peroxidation (MDA) and NO levels (both $p < 0.05$), which were more pronounced in the diet supplemented with Turkish hazelnuts (Table 12). A decrease in caspase-3 levels was also observed ($p < 0.05$)—caspase-3 plays a central role in the activation of caspases 6, 7, and 9 and in the induction of apoptosis [89], a decrease in acetylcholinesterase activity ($p < 0.05$), and an increase in dopamine levels ($p < 0.05$) at all hazelnut concentrations, generally more pronounced with Turkish hazelnuts. These results correlate with neurobehavioral effects related to improved working memory and reduced anxiety and reflect the neuroprotective effect of hazelnuts [21]. Bahaeddin et al. [89] also demonstrated that supplemental administration of Iranian hazelnut kernels (800 mg/kg) improved memory and reduced anxiety induced by intracerebral injection of beta-amyloid peptides into the hippocampal region in rats, central effects that correlated with a significant decrease in the levels of pro-apoptotic markers (caspase-3 and the Bax/Bcl-2 ratio) and neuroinflammatory markers (COX-2, IL-1β, and TNF-α). These findings are preclinical and do not establish efficacy for the prevention or treatment of Alzheimer's disease.

Hazelnuts may improve lipid metabolism and enhance antioxidant defense [90]. In a model of dyslipidemia induced in mice fed an HFD, Olofinnade et al. [22] demonstrated that including hazelnuts in the HFD maintained lipid (total cholesterol (TC), TG, LDL-C, HDL-C) and glycemic levels close to those of the control group, which was fed a standard diet (SD) ($p < 0.05$ vs. HFD). These effects were observed for all types of hazelnuts investigated (ITA and TKY) and at all concentrations (2%, 4%, and 8%), with the exception of Turkish hazelnuts, which reduced TC ($p < 0.05$ vs. HFD), but not to levels close to those of the control group (SD), and proved less effective compared to Italian hazelnuts ($p < 0.05$ vs. ITA). An HFD impairs brain function and induces neuroinflammation, affects learning and memory, and can exacerbate anxiety-like behavior [91]. Concurrent consumption of hazelnuts significantly improved memory, reduced anxiety, and increased locomotor activity and the ability to stand—all of which were significantly impaired by the HFD. These neurobehavioral effects correlated with improved antioxidant status (decreased MDA), increased dopamine levels, and reduced acetylcholinesterase activity, as well as decreased apoptosis (caspase-3)—changes observed for both hazelnut varieties (ITA and TKY) and at all tested concentrations ($p < 0.05$ vs. HFD) [22] (Table 12).

Overall, the analyzed in vivo studies demonstrate that hazelnuts and their derivatives could serve as a valuable adjunct in modulating key pathways involved in cellular redox regulation, such as oxidative stress and the inflammatory response, the regulation of mitochondrial apoptosis and ferroptosis, as well as the attenuation and rebalancing of metabolic processes. The redox-regulatory mechanisms supported by the included in vitro and in vivo studies are summarized in Figure 2.

Table 12. The characteristics of the in vivo studies evaluating the impact of diets supplemented with hazelnuts on antioxidant status and brain activity.

Author, Year, Country, Ref.	Study Purpose	Plant Materials/Extraction Procedures/Formulations	Animal Model/Investigations	Main Outcomes/Biological Activities	Investigated Mechanisms
Olofinnade et al., 2021 Nigeria [21]	Investigating the beneficial effects of a diet supplemented with Italian and Turkish hazelnuts, respectively, on the brain of aged mice.	Turkish hazelnuts (TKY—from Bartın, the Black Sea region) and Italian hazelnuts (ITA—from Piemonte, the province of Cuneo).	Male Swiss mice (24 months old); 7 groups (n = 10): (1) control (standard diet, SD); (2) SD + 2%ITA; (3) SD + 4%ITA; (4) SD + 8%ITA; (5) SD + 2%TKY; (6) SD + 4%TKY; (7) SD + 8%TKY. After 8 weeks, on the 56th day, the animals underwent testing and were euthanasied, and their brains were removed for analysis. Investigations: Changes in bw and food intake during the experiment. Behavioural tests: "elevated plus maze" and "open field". Memory tests: "radial arm maze" and "Y-maze". AChE and SOD activities; levels of MDA, NO, caspase-3, and dopamine.	The diet supplemented with hazelnuts: ↑ bw of aged mice ($p < 0.05$ vs. SD), with the exception of the 2% TKY group. ↑ spatial working memory in all groups ($p < 0.05$ vs. SD), with the exception of the 8% ITA group. For both hazelnut varieties, the best results were obtained with 4% hazelnuts. ↑ horizontal locomotor activity in all groups ($p < 0.05$ vs. SD). The best results were obtained in the 8% TKY group ($p < 0.05$ vs. 8% ITA). ↑ self-grooming behaviour in the 2% and 4% ITA, and in the 4% and 8% TKY groups, respectively ($p < 0.05$ vs. SD). The best result was obtained in the 4% ITA group. ↑ anxiolytic effect in the 2% and 4% ITA groups, and in the 4% and 8% TKY groups, respectively ($p < 0.05$ vs. SD). ↓ AChE activity in all groups ($p < 0.05$ vs. SD): ↓ SOD activity in all groups ($p < 0.05$ vs. SD); ↓ MDA level in all groups ($p < 0.05$ vs. SD), with the exception of the 8% ITA group; more pronounced in TKY groups ($p < 0.05$ vs. ITA); ↓ NO level in all groups ($p < 0.05$ vs. SD), more pronounced in the 2% and 4% TKY groups ($p < 0.05$ vs. ITA); ↓ caspase-3 level in all groups ($p < 0.05$ vs. SD); ↑ dopamine level in all groups ($p < 0.05$ vs. SD), more pronounced in the case of the 4% and 8% TKY groups ($p < 0.05$ vs. ITA).	Hazelnut-supplemented diet reduced MDA, NO, and caspase-3 levels, indicating modulation of redox and apoptosis pathways in brain tissue of aged mice.

Table 12. *Cont.*

Author, Year, Country, Ref.	Study Purpose	Plant Materials/Extraction Procedures/Formulations	Animal Model/Investigations	Main Outcomes/Biological Activities	Investigated Mechanisms
Olofinnade et al., 2021 Nigeria [22]	Investigating the beneficial effects of a diet supplemented with Italian and Turkish hazelnuts, respectively, on the brains of mice fed a high-fat diet.	Turkish hazelnuts (TKY—from Bartın, the Black Sea region) and Italian hazelnuts (ITA—from Piemonte, the province of Cuneo).	Male Swiss mice; 8 groups (n = 10): (1) control (standard diet, SD); (2) HFD (high-fat diet, model); (3) HFD + 2%ITA; (4) HFD + 4%ITA; (5) HFD + 8%ITA; (6) HFD + 2%TKY; (7) HFD + 4%TKY; (8) HFD + 8%TKY. After 8 weeks, the animals underwent testing and were euthanized. Blood and brain samples were collected for analysis. Investigations: Changes in bw and food intake during the experiment. Behavioural tests: "elevated plus maze" and "open field". Memory tests: "radial arm maze" and "Y-maze". Serum levels of glucose, TC, TG, HDL-C, and LDL-C. AChE and SOD activities; levels of MDA, NO, caspase-3, and dopamine.	The HFD supplemented with hazelnuts: ↓ bw of mice ($p < 0.05$ vs. HFD) in the TKY groups. ↑ spatial working memory in all groups ($p < 0.05$ vs. HFD), with the exception of the 8% TKY group. ↑ horizontal locomotor activity in all groups ($p < 0.05$ vs. HFD), with the exception of the 8% ITA group. The best results were obtained in the 2% ITA group. ↑ self-grooming behaviour in all groups ($p < 0.05$ vs. HFD), with the exception of the 4% ITA group. The best result was obtained in the 2% ITA group. ↑ anxiolytic effect in all groups ($p < 0.05$ vs. HFD). ↓ AChE activity in all groups ($p < 0.05$ vs. HFD); ↓ SOD activity in all groups ($p < 0.05$ vs. HFD); ↓ MDA level in all groups ($p < 0.05$ vs. HFD); more pronounced in TKY groups ($p < 0.05$ vs. ITA); ↓ NO level in all groups ($p < 0.05$ vs. HFD); ↓ caspase-3 level in all groups ($p < 0.05$ vs. HFD); ↑ dopamine level in all groups ($p < 0.05$ vs. HFD), more pronounced in 2% ITA and 8% TKY groups; ↓ glucose, TC, TG, LDL-C in all groups ($p < 0.05$ vs. HFD); ↑ HDL in all groups ($p < 0.05$ vs. HFD)	Hazelnuts prevented HFD-induced brain damage in mice by reducing lipid peroxidation, modulating redox and apoptotic pathways in the brain, as well as by regulating blood glucose levels and serum lipid profiles, thereby improving cognitive function and behavior impaired by the HFD.

AChE—acetylcholinesterase; bw—body weight; HDL-C—high-density lipoprotein cholesterol; HFD—high-fat diet; ITA—Italian; LDL-C—low-density lipoprotein cholesterol; MDA—malondialdehyde; NO—nitric oxide; SD—standard diet; SOD—superoxide dismutase; TKY—Turkish; TC—total cholesterol; TG—triglycerides; ↓—decreased, ↑—increased.

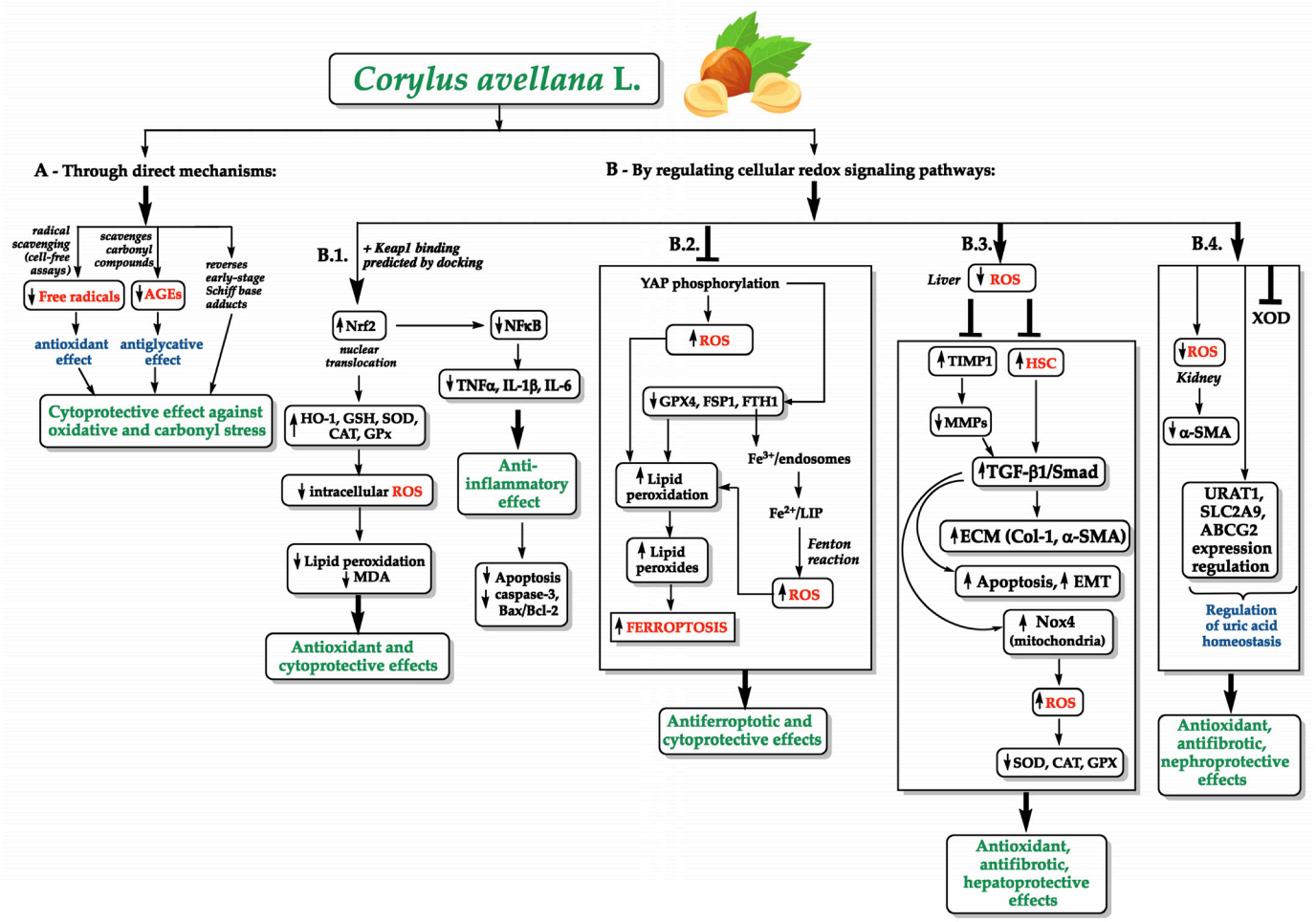


Figure 2. Redox-regulatory mechanisms of hazelnut (*Corylus avellana* L.) and its by-products supported by the included in vitro and in vivo studies. (**A**) Direct mechanisms: scavenging of free radicals in cell-free assays (↓ free radicals; antioxidant effect), scavenging of carbonyl compounds (↓ AGEs; antiglycative effect) and reversal of early-stage Schiff base adducts, resulting in cytoprotection against oxidative and carbonyl stress. (**B**) Regulation of cellular redox signaling pathways: (**B.1**) Keap1/Nrf2 pathway (Keap1 binding predicted by docking): ↑ Nrf2 (nuclear translocation), ↑ HO-1, GSH, SOD, CAT and GPx, ↓ intracellular ROS, ↓ lipid peroxidation and MDA, and ↓ NF-κB with ↓ TNF-α, IL-1β and IL-6, and ↓ apoptosis (caspase-3, Bax/Bcl-2); (**B.2**) YAP phosphorylation inhibition, ↑ GPX4, FSP1 and FTH1, and ↓ lipid peroxidation and ferroptosis; (**B.3**) liver: inhibition of the TGF-β1/Smad pathway, ↓ HSC activation, ↓ Nox4-derived ROS, ↓ ECM accumulation (Col-1, α-SMA) and EMT, and restored TIMP1/MMPs balance, with ↑ SOD, CAT and GPx; (**B.4**) kidney: regulation of uric acid homeostasis (XOD inhibition; URAT1, SLC2A9 and ABCG2 expression regulation), ↓ ROS and ↓ α-SMA. Pathways (**B.3**,**B.4**) were supported by in vivo studies only. ↑, increase; ↓, decrease; ⊣, inhibition. Abbreviations: ABCG2—ATP-binding cassette transporter G2; AGEs—advanced glycation end products; CAT—catalase; Col-1—type 1 collagen; ECM—extracellular matrix; EMT—epithelial–mesenchymal transition; FSP1—ferroptosis suppressor protein 1; FTH1—ferritin heavy chain 1; GPX4—glutathione peroxidase 4; GPx—glutathione peroxidase; GSH—glutathione; HO-1—heme oxygenase-1; HSC—hepatic stellate cells; IL—interleukin; Keap1—Kelch-like ECH-associated protein 1; LIP—labile iron pool; MDA—malondialdehyde; MMPs—matrix metalloproteinases; NF-κB—nuclear factor kappa B; Nox4—NADPH oxidase 4; Nrf2—nuclear factor erythroid 2-related factor 2; ROS—reactive oxygen species; SLC2A9—solute carrier family 2 member 9 (urate transporter GLUT9); SOD—superoxide dismutase; TGF-β1—transforming growth factor beta 1; TIMP1—tissue inhibitor of metalloproteinases 1; TNF-α—tumor necrosis factor alpha; URAT1—urate transporter 1; XOD—xanthine oxidase; YAP—Yes-associated protein; α-SMA—alpha-smooth muscle actin. Created with ChemDraw Professional v16.0.1.4 (PerkinElmer Informatics).

3.5. Clinical Studies

Four clinical studies assessed the antioxidant and oxidative stress status related to hazelnut consumption [31–34]. No other nut types were consumed in these trials. The characteristics and the key findings of the four selected studies are depicted in Table 13.

Two trials reported significant alterations in antioxidant and pro-oxidant gene expression between the dietary treatment with 40 g of hazelnuts and no treatment [33,34]. Antioxidant and anti-inflammatory genes, including glutathione peroxidase 2 (GPX2), GSR (glutathione reductase), thioredoxin reductase 1 (TXNRD1), SOD1, CAT, macrophage migration inhibitory factor (MIF), peroxisome proliferator-activated receptor gamma (PPARγ), vitamin D receptor (VDR), and methylenetetrahydrofolate reductase (MTHFR), were upregulated after hazelnuts were introduced into the diet, indicating a protective effect against oxidative stress, inflammation, and atherogenic processes. Indeed, plant foods like tree nuts rich in antioxidant phytochemicals exert a favorable effect on oxidative stress and inflammation, risk factors of cardiometabolic disease [92].

Previous studies revealed that phenolic compounds found in plant diets might contribute to human homeostasis through their potential to regulate gene expression, specifically mediated by epigenetic mechanisms [93]. A recent intervention trial [94] showed that replacing typical high-carbohydrate snacks with tree nuts modulated the expression of some genes, mostly those that act as nutrient sensors and regulators of energy homeostasis, including cytochrome P450 family 27 subfamily A member 1 (CYP27A1), fatty acid binding protein 5 (FABP5), adenylyl cyclase type 3 (ADCY3), chemokine (C-X-C motif) ligand 9 (CXCL9), protein kinase AMP-activated subunit gamma-1 (PRKAG1), and perilipin 1 (PLIN1). After 16 weeks, participants in the nut group showed an improvement in the unsaturated-to-saturated fat ratio of adipose tissue, based on the increased dietary monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids consumed, which could aid in preventing cardiometabolic diseases.

Lipid oxidation is a major factor in both food deterioration and biological processes. As mentioned before, oxidative stress contributes to the oxidation of lipoproteins and DNA damage, which increases the risk of mutagenesis and the development of many chronic diseases including cardiometabolic diseases, Alzheimer's disease, and cancer [95,96]. Hazelnut-enriched diets might have antiatherogenic outcomes by preventing the formation of ox-LDL, besides alteration of the lipid profile. These diets, where hazelnuts contributed 18–20% (49–86 g/day) to the total daily energy intake, significantly decreased ox-LDL levels [97]. After a high-fat meal, which represents a usual meal of a Western dietary pattern, the levels of ox-LDL were significantly higher compared to no dietary treatment ($p < 0.05$), but after adding 40 g of hazelnut after the high-fat meal, a significant decrease in ox-LDL levels was observed [31]. Moreover, Di Renzo et al. [33] found that the consumption of 40 g of hazelnuts daily added to a standard diet (Italian Mediterranean diet) for four weeks significantly lowered ($p \leq 0.005$) ox-LDL levels compared to a standard diet without hazelnuts. These findings are in agreement with a recent study which demonstrated that nut consumption could have cardioprotective properties [98].

Table 13. Effects of hazelnut intake on antioxidant and oxidative stress markers.

Author, Year, Country, Ref.	Study Design, Duration	Participant Characteristics	Treatments	Outcome
Di Renzo et al., 2014 Italy [33]	Sequential intervention periods 4 weeks	24 healthy adults (mean age 31.04 ± 5.88 y)	(i) 4-week standard diet (Italian Mediterranean diet) (ii) 4-week standard diet with hazelnuts 40 g/d	↓ ox-LDL in (ii) vs. (i) ($p < 0.05$) - after (ii): ↑ genes: BNIP3, GPX2, GSR, HSPAIA, TTN, TXNRDI ↓ genes: CCL5, KRTI, MBL2, PRDX6, SOD1
Di Renzo et al., 2017 Italy [31]	Randomized crossover, 3 h	22 healthy adults (mean age 31.23 ± 6.14 y)	(i) McDM (ii) McDM + 40 g of raw hazelnuts consumed as snacks once after the McDM (iii) no dietary treatment (NDT) −3 weeks washout period	↑ ox-LDL in (i) vs. (iii) (Δ% = 17.56%, $p < 0.05$) ↓ ox-LDL in (ii) vs. (i) (Δ% = −24.43%, $p < 0.05$) ↑ % expressed OS/IF genes in (ii) vs. (i)
Guaraldi et al., 2018 Italy [32]	Parallel intervention, 8 weeks	60 hyperlipidaemic children and adolescents (mean age 11.6 ± 2.6 y)	(i) Hazelnuts with skin (n = 22) (ii) Hazelnuts w/o skin (n = 20) (iii) control (no nuts) (n = 18) 15–30 g hazelnuts/day—(i) and (ii)	- DNA strand breaks: (a) ↓ 18.8% (95% CI: −36.8%, −2.71%, $p = 0.003$) in (i) (b) ↓ 13.9% (95% CI: −28.6%, 0.84%; $p = 0.001$) in (ii) (c) ↓ 21.2% (95% CI: −39.1%, −3.38%, $p = 0.015$) in (iii) - DNA damage (FPG-sensitive sites): (a) ↓ 18.9% (95% CI: −41.7%, +3.9%; $p = 0.002$) in (i) (b) ↓ 23.1% (95% CI: −45.5%, −0.66%; $p = 0.007$) in (ii) (c) ↑ 26.8% (96% CI: −0.84%, +54.5%; $p = 0.04$) in (iii) - no effect on ox-LDLs after treatments
Di Renzo et al., 2019 Italy [34]	Pilot study, 6 weeks	24 healthy adults (mean age 51.58 ± 9.37 y)	(i) Hazelnuts 40 g/d	↑ antioxidant and anti-inflammatory gene expression: SOD1 ($2^{-\Delta\Delta Ct} = 2.42$); CAT ($2^{-\Delta\Delta Ct} = 2.41$); MIF ($2^{-\Delta\Delta Ct} = 4.12$); PPARγ ($2^{-\Delta\Delta Ct} = 5.89$); VDR ($2^{-\Delta\Delta Ct} = 3.61$); MTHFR ($2^{-\Delta\Delta Ct} = 2.40$); ACE ($2^{-\Delta\Delta Ct} = 2.16$)

ACE—angiotensin converting enzyme; APOE—apolipoprotein E; BNIP3—BCL2/adenovirus E1B 19 kDa interacting protein; CAT—catalase; CCL5—chemokine (C-C motif) ligand 5; FPG—formamidopyrimidine DNA glycosylase; GPX2—glutathione peroxidase 2; GSR—glutathione reductase; HSPA1A—Heat shock 70 kDa protein 1A; IF—inflammasome; IFG2R—insulin-like growth factor 2 receptor; IL6R—interleukin 6 receptor; KRT1—keratin; MBL2—mannose-binding lectin (protein C) 2 soluble; McDM—McDonald's Meal; MIF—macrophage migration inhibitory factor; MTHFR—methylenetetrahydrofolate reductase; NDT—no dietary treatment; NF-κB—nuclear factor kappa-light-chain-enhancer of activated B cells; OS—oxidative stress; ox-LDL—oxidized low-density lipoprotein; PPARγ—peroxisome proliferator-activated receptor gamma; PRDX6—peroxiredoxine 6; SOD1—superoxide dismutase 1; TTN—titin; TXNRD1—thioredoxin reductase 1; UTF1—upstream transcription factor 1; VDR—vitamin D receptor. ↓—decreased, ↑—increased.

Additionally, a systematic review with clinical trials reported oxidative stress improvement after nut supplementation via pathways regulated by MUFAs and bioactive compounds in reducing ox-LDL and antioxidant activity, respectively, as action mechanisms [7]. MUFAs (mainly oleic acid) and other antioxidant components also changed the cholesterol profile in a group of young participants [99]. After hazelnut supplementation (1 g/day/kg bw) for 30 days, total cholesterol and LDL-C levels decreased, high-density lipoprotein cholesterol (HDL-C) and HDL-C/LDL-C ratio values increased, and, as plasma MDA levels were found to be significantly lower, the antioxidant potential value was higher, which pointed to reduced peroxidation reactions. Furthermore, Tey et al. [100] concluded that the consumption of three different forms of hazelnuts (ground, sliced, and whole) equally improved the α-tocopherol concentrations and lipid profile in individuals with mild hypercholesterolemia.

An 8-week trial conducted by Guaraldi et al. [32] randomized children and adolescents diagnosed with primary hyperlipidemia into three groups to receive hazelnuts with skin (HZN+S), hazelnuts without skin (HZN-S), at 15–30 g/day, depending on bw, and a no-nut control group. In addition, all groups received dietary guidelines. The outcomes showed that both types of hazelnuts significantly reduced the endogenous DNA damage levels, but only HZN+S lowered oxidatively induced DNA strand breaks, a suggested marker of antioxidant protection in cells. No significant differences in ox-LDL were noticed when hazelnut consumption was compared to a no-nut control. The study highlights the remarkable antioxidant potential and the antimutagenic/antitumor protective effects of hazelnuts with skin. A possible explanation for these results is that the kernels in both HZN+S and HZN-S provide similar amounts of MUFAs, phytosterols, α-tocopherol, and minerals, but the skin in HZN+S is rich in polyphenols with antioxidant activities [101]. The unchanged ox-LDL levels after hazelnut consumption could be due to the fact that the children followed a balanced diet and presented only mild LDL-C elevations.

As part of heart-healthy diets, besides raw hazelnuts, public health messages could include dry-roasted, lightly salted hazelnuts, as their consumption also improved HDL-C and apolipoprotein A1 concentrations, total-C/HDL-C ratio, and systolic blood pressure [102].

While the included human trials showed mixed results, the in vitro and in vivo experiments revealed that the extracts prepared from hazelnut-derived products could have beneficial effects in preclinical models, including effects relevant to neurodegenerative diseases and healthy aging. Based on these gaps between preclinical and clinical studies, we emphasize the importance of future human studies that may show whether hazelnuts and their by-products have a therapeutic effect in treating, preventing, or ameliorating diseases.

4. Strengths, Limitations and Future Directions

Strengths. This review followed the PRISMA 2020 guidelines [13] and covered four hazelnut matrices (kernel, skin, leaf and green leafy covers). It classified each study by mechanistic depth, which separates pathway-level evidence from purely functional readouts.

Limitations. The evidence is limited and heterogeneous in matrices, extraction methods, models, assays and reporting units, which precluded quantitative synthesis. In the in vitro studies, chemical characterization was absent in two studies and dose–response testing was absent or incomplete in six. One study was industry-funded, and the sponsor also supplied the hazelnut skin material. Only four of the eight in vitro studies provided pathway-level evidence. Synergistic effects among the constituents of each hazelnut part were not tested in any of the included studies, so the contribution of the combined phytochemical profile to the observed redox outcomes could not be separated from that of individual compounds. No validated risk-of-bias tool exists for in vitro studies, so a custom checklist was used. In the in vivo studies, the randomization method, allocation concealment and blinding were

not reported, and all seven studies were rated as having an unclear risk of bias because of incomplete reporting. The clinical trials differed in design, enrolled few participants, were short in duration and reported heterogeneous findings. Two of the four were non-randomized and had a serious risk of bias due to confounding. Regarding the review process, the protocol was registered after the searches, only three databases were searched (the grey literature was not included), and the search strategy, built around mechanistic and redox-related terms, may not have retrieved relevant studies that report oxidative stress markers only as secondary outcomes. Data extraction was performed by one reviewer and verified by a second, and only English-language articles were included.

Translational relevance. In vitro concentrations may not be achievable in tissues after dietary intake, and absorption and metabolism were generally not modeled. None of the in vivo studies addressed issues related to bioavailability, digestion, or the metabolism of polyphenols and bioactive compounds in hazelnuts or in the tested extracts, making it difficult to assess their actual therapeutic potential. In vitro and in vivo findings therefore support biological plausibility, whereas the clinical data are too limited to establish efficacy. Whole hazelnuts should not be equated with concentrated extracts or isolated compounds. All in vitro studies used extracts or isolated compounds, the in vivo evidence came from both extracts and hazelnut-enriched diets in rodent models, and all clinical studies tested whole hazelnuts. Findings obtained with concentrated extracts or isolated compounds therefore cannot be extrapolated to the consumption of whole hazelnuts. Clinical efficacy has not been established, including for the prevention or treatment of Alzheimer's disease and as a complement to anticancer therapy.

Safety and toxicity. Hazelnut allergy is a public health issue in developed countries [103]. Furthermore, hazelnuts are considered the leading cause of tree nut allergies in Europe [104]. Allergenic proteins in hazelnuts exhibit cross-reactivity with allergens from other tree nuts, including almonds, walnuts, and pistachios, as well as with birch, hazel, and alder pollen [103]. Of the clinical studies reviewed, only one [32] mentioned that a hazelnut allergy was an exclusion criterion for subjects selected for the trial. The other studies made no mention whatsoever of this potential toxic risk. The food safety of hazelnuts also raises concerns regarding mycotoxin contamination, which are known for their cytotoxic, mutagenic, and carcinogenic effects in humans and animals, resulting from fungal growth during fruit development or after harvest [105]. Public health and food control strategies are essential for limiting these potential adverse effects associated with the consumption of hazelnuts or products containing hazelnuts.

The safety of consuming or extracting bioactives from hazelnut by-products, particularly leaves, was not addressed in the included studies. Although safety assessments exist for some hazel-derived ingredients for use in cosmetic products [106], potential toxicity, anti-nutritional factors (e.g., tannins) [107], mycotoxins (especially aflatoxins) [105], and pesticide or environmental contaminant residues, including organochlorine pesticides and heavy metals that can accumulate in tree leaves [108,109], should be evaluated before any food or nutraceutical application.

Future directions. Priorities include:

- Chemically standardized extracts, characterized and reported according to consensus guidelines [110];
- Dose–response testing at physiologically relevant concentrations, since in vitro effects of dietary phenolics may not be reproduced in vivo, where concentrations are lower and effects may be indirect [111];
- Direct testing of the AGE–RAGE–NF-κB axis proposed by Spagnuolo et al. [26] through which polyphenols may act [112];

- Genetic validation of Keap1 and Yap involvement, for example by comparing wild-type with Nrf2-deficient models and by manipulating NF2–YAP/Hippo signaling in the same cells [113,114];
- Comparison of crude extracts, fractions and purified constituents, including recombined mixtures, within the same cellular model and stressor [54,55];
- Larger, longer, adequately controlled randomized trials, with oxidative stress biomarkers measured consistently [115].

5. Conclusions

This review indicates that hazelnut and its by-products, including skin, leaf and green leafy covers, exert redox-modulating effects across the three levels of evidence. In vitro, the effects involved radical scavenging in cell-free assays, reduced intracellular ROS, carbonyl trapping, activation of the Nrf2 pathway (with Keap1 binding predicted by docking) and Hippo/Yap-mediated suppression of ferroptosis. The pathway engaged may depend on the cellular context and experimental model. By-products, especially skin and leaf, were as bioactive as the kernel or more so in preclinical models, which makes them promising candidates for further investigation as sources of redox-active compounds. However, while skins are a food-grade by-product, leaves are generally considered agricultural residue; their use in food, supplements or extracts would require toxicological evaluation, assessment of anti-nutritional factors and testing for pesticide and heavy-metal residues, which the included studies did not address. In vivo, extracts and hazelnut-enriched diets enhanced endogenous antioxidant defenses and reduced lipid peroxidation, with effects on inflammation, apoptosis and ferroptosis in models of liver, kidney and brain injury, as well as metabolic disorders. In humans, hazelnut consumption was associated with lower ox-LDL after a high-fat meal, reduced DNA damage and increased expression of antioxidant genes, although the findings were not uniform across trials. Taken together, the evidence converges on a coherent redox-regulatory profile of hazelnut, with the strongest mechanistic support coming from preclinical models. The effects reported in the included studies were obtained mainly with extracts of whole hazelnut parts, which contain several classes of compounds, whereas isolated compounds were tested only in some of the in vitro studies; whether the effects result from the combined phytochemical profile or from individual constituents was not tested directly.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/antiox15121570/s1, Table S1: Full search strategies used in each database (searches run on 31 August 2026); Table S2: PICOS criteria for study eligibility; Table S3: Criteria for the risk-of-bias assessment of in vitro studies; Table S4: Support for judgement for the risk-of-bias assessment of the in vivo studies (SYRCLE).

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Abbreviations

The following abbreviations are used in this manuscript:

AGEs	advanced glycation end-products
AKI	acute kidney injury
ALP	allopurinol
AOPP	advanced oxidation products of proteins
α-SMA	alpha-smooth muscle actin
BSA	bovine serum albumin
BUN	blood urea nitrogen
bw	body weight
CAE	gemmotherapeutic extract of hazel (*Corylus avellana* L.)
CALD	chronic alcoholic liver disease
CAT	catalase
Col-1	type 1 collagen
CRE	creatinine
CVD	cardiovascular disease
DF	diabetic fibrosis group
DFR	self-regeneration group
DKD	diabetic kidney disease
ECM	extracellular matrix
EGCG	epigallocatechin gallate
EMT	epithelial–mesenchymal transition
FSP1	ferroptosis suppressor protein 1
FTH1	ferritin heavy chain 1
GH	Giresun hazelnut
GPX	glutathione peroxidase
GPX2	glutathione peroxidase 2
GPX4	glutathione peroxidase 4
GSH	glutathione
GSR	glutathione reductase
HDL-C	high-density lipoprotein cholesterol
HFD	high-fat diet
HLP	hazelnut leaf polyphenol
HO-1	heme oxygenase-1
HSCs	hepatic stellate cells
HUVECs	human umbilical vein endothelial cells
HZN+S	hazelnuts with skin
HZN-S	hazelnuts without skin
IL	interleukin
IND	indomethacin
i.p.	intraperitoneal
ITA	Italy
Keap1	kelch-like ECH-associated protein 1
LAP	latency-associated protein
LDL-C	low-density lipoprotein cholesterol
LIP	labile iron pool
LPS	lipopolysaccharide
MAPK	mitogen-activated protein kinases
MDA	malondialdehyde

MIF	macrophage migration inhibitory factor
MMP	matrix metalloproteinase
MTHFR	methylenetetrahydrofolate reductase
MUFA	monounsaturated fatty acid
NF-κB	nuclear factor kappa B
NO	nitric oxide
Nox	NADPH oxidases
NQO-1	NAD(P)H:quinone acceptor oxidoreductase 1
Nrf2	nuclear factor erythroid 2-related factor 2
ox-LDL	oxidized LDL
PPARγ	peroxisome proliferator-activated receptor gamma
RNS	reactive nitrogen species
ROS	reactive oxygen species
SD	standard diet
SOD	superoxide dismutase
TBHP	tert-butyl hydroperoxide
TC	total cholesterol
TEM	transmission electron microscopy
TFR1	transferrin receptor 1
TG	triglycerides
TGF-β1	transforming growth factor beta
TH	Trabzon hazelnut
TIMP-1	tissue inhibitor of metalloproteinases 1
TKY	Turkey
TNF-α	tumor necrosis factor alpha
TPC	total phenolic content
TXNRD1	thioredoxin reductase 1
Ub-Nrf2	ubiquitinated Nrf2
VDR	vitamin D receptor
XOD	xanthine oxidase
Yap	Yes-associated protein
ZP	hazel leaf polyphenol extract

References

1. Forman, H.J.; Zhang, H. Targeting Oxidative Stress in Disease: Promise and Limitations of Antioxidant Therapy. *Nat. Rev. Drug Discov.* **2021**, *20*, 689–709. Correction in *Nat. Rev. Drug Discov.* **2021**, *20*, 652. [CrossRef]
2. Furman, D.; Campisi, J.; Verdin, E.; Carrera-Bastos, P.; Targ, S.; Franceschi, C.; Ferrucci, L.; Gilroy, D.W.; Fasano, A.; Miller, G.W.; et al. Chronic Inflammation in the Etiology of Disease across the Life Span. *Nat. Med.* **2019**, *25*, 1822–1832. [CrossRef]
3. Bolling, B.W.; Chen, C.Y.O.; McKay, D.L.; Blumberg, J.B. Tree Nut Phytochemicals: Composition, Antioxidant Capacity, Bioactivity, Impact Factors. A Systematic Review of Almonds, Brazils, Cashews, Hazelnuts, Macadamias, Pecans, Pine Nuts, Pistachios and Walnuts. *Nutr. Res. Rev.* **2011**, *24*, 244–275. [CrossRef]
4. Branco-Rodrigues, I.; Costa-Rodrigues, J. Mediterranean Diet and Skeletal Health: Mechanistic Pathways and Implications for Osteoporosis. *Clin. Nutr. ESPEN* **2026**, *75*, 105057. [CrossRef]
5. Mitjavila, M.T.; Fandos, M.; Salas-Salvadó, J.; Covas, M.I.; Borrego, S.; Estruch, R.; Lamuela-Raventós, R.; Corella, D.; Martínez-Gonzalez, M.Á.; Sánchez, J.M.; et al. The Mediterranean Diet Improves the Systemic Lipid and DNA Oxidative Damage in Metabolic Syndrome Individuals. A Randomized, Controlled, Trial. *Clin. Nutr.* **2013**, *32*, 172–178. [CrossRef]
6. O'Neil, C.E.; Fulgoni, V.L.; Nicklas, T.A. Tree Nut Consumption Is Associated with Better Adiposity Measures and Cardiovascular and Metabolic Syndrome Health Risk Factors in U.S. Adults: NHANES 2005–2010. *Nutr. J.* **2015**, *14*, 64. [CrossRef]
7. Silveira, B.K.S.; da Silva, A.; Hermsdorff, H.H.M.; Bressan, J. Effect of Chronic Consumption of Nuts on Oxidative Stress: A Systematic Review of Clinical Trials. *Crit. Rev. Food Sci. Nutr.* **2022**, *62*, 726–737. [CrossRef]
8. Mateș, L.; Banc, R.; Zaharie, F.A.; Rusu, M.E.; Popa, D.S. Mechanistic Insights into the Biological Effects and Antioxidant Activity of Walnut (*Juglans regia* L.) Ellagitannins: A Systematic Review. *Antioxidants* **2024**, *13*, 974. [CrossRef]

9. Román, G.C.; Jackson, R.E.; Gadhia, R.; Román, A.N.; Reis, J. Mediterranean Diet: The Role of Long-Chain ω-3 Fatty Acids in Fish; Polyphenols in Fruits, Vegetables, Cereals, Coffee, Tea, Cacao and Wine; Probiotics and Vitamins in Prevention of Stroke, Age-Related Cognitive Decline, and Alzheimer Disease. *Rev. Neurol.* **2019**, *175*, 724–741. [CrossRef]
10. Dos Santos, J.L.; de Quadros, A.S.; Weschenfelder, C.; Garofallo, S.B.; Marcadenti, A. Oxidative Stress Biomarkers, Nut-Related Antioxidants, and Cardiovascular Disease. *Nutrients* **2020**, *12*, 682. [CrossRef]
11. Di Michele, A.; Pagano, C.; Allegrini, A.; Blasi, F.; Cossignani, L.; Di Raimo, E.; Faieta, M.; Oliva, E.; Pittia, P.; Primavilla, S.; et al. Hazelnut Shells as Source of Active Ingredients: Extracts Preparation and Characterization. *Molecules* **2021**, *26*, 6607. [CrossRef]
12. Bottone, A.; Cerulli, A.; Durso, G.; Masullo, M.; Montoro, P.; Napolitano, A.; Piacente, S. Plant Specialized Metabolites in Hazelnut (*Corylus avellana*) Kernel and Byproducts: An Update on Chemistry, Biological Activity, and Analytical Aspects. *Planta Med.* **2019**, *85*, 840–855. [CrossRef]
13. Page, M.J.; Moher, D.; Bossuyt, P.M.; Boutron, I.; Hoffmann, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.M.; Akl, E.A.; Brennan, S.E.; et al. PRISMA 2020 Explanation and Elaboration: Updated Guidance and Exemplars for Reporting Systematic Reviews. *BMJ* **2021**, *372*, n160. [CrossRef]
14. Klimisch, H.-J.; Andreae, M.; Tillmann, U. A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data 1. *Regul. Toxicol. Pharmacol.* **1997**, *25*, 1–5. [CrossRef]
15. Hooijmans, C.R.; Rovers, M.M.; De Vries, R.B.M.; Leenaars, M.; Ritskes-Hoitinga, M.; Langendam, M.W. SYRCLE's Risk of Bias Tool for Animal Studies. *BMC Med. Res. Methodol.* **2014**, *14*, 43. [CrossRef]
16. Sterne, J.A.C.; Savović, J.; Page, M.J.; Elbers, R.G.; Blencowe, N.S.; Boutron, I.; Cates, C.J.; Cheng, H.Y.; Corbett, M.S.; Eldridge, S.M.; et al. RoB 2: A Revised Tool for Assessing Risk of Bias in Randomised Trials. *BMJ* **2019**, *366*, l4898. [CrossRef]
17. Sterne, J.; Mathur, M.B.; Elbers, R.; Hróbjartsson, A.; Mcaleenan, A.; Reeves, B.; Shrier, I.; Tilling, K.; Armstrong, R.; Berkman, N.; et al. Risk of Bias in Non-Randomized Studies of Interventions, Version 2 (ROBINS-I V2): Assessment Tool for Follow-Up Studies. 2025. Available online: https://www.riskofbias.info/welcome/robins-i-v2 (accessed on 8 October 2026).
18. Balta, C.; Herman, H.; Ciceu, A.; Mladin, B.; Rosu, M.; Sasu, A.; Peteu, V.E.; Voicu, S.N.; Balas, M.; Gherghiceanu, M.; et al. Phytochemical Profiling and Anti-Fibrotic Activities of the Gemmotherapy Bud Extract of *Corylus avellana* in a Model of Liver Fibrosis on Diabetic Mice. *Biomedicines* **2023**, *11*, 1771. [CrossRef]
19. Sun, M.; Chang, H.; Jiang, F.; Zhang, W.; Yang, Q.; Wang, X.; Lv, G.; Lin, H.; Luo, H.; Lin, Z.; et al. Hazel Leaf Polyphenol Extract Alleviated Cisplatin-Induced Acute Kidney Injury by Reducing Ferroptosis through Inhibiting Hippo Signaling. *Molecules* **2024**, *29*, 1729. [CrossRef]
20. Öztürk, Y.; Atalay Dumlu, F.; Aydın Berktaş, Ö. Investigating the Effects of Hazelnut Extracts on Indomethacin-Induced Gastric Ulcers: Antioxidant and Gastroprotective Potential. *Plant Foods Hum. Nutr.* **2025**, *80*, 152. [CrossRef]
21. Olofinnade, A.T.; Onaolapo, A.Y.; Onaolapo, O.J.; Olowe, O.A. Hazelnut Modulates Neurobehaviour and Ameliorates Ageing-Induced Oxidative Stress, and Caspase-3-Mediated Apoptosis in Mice. *Curr. Aging Sci.* **2021**, *14*, 154–162. [CrossRef]
22. Olofinnade, A.T.; Onaolapo, A.Y.; Onaolapo, O.J.; Olowe, O.A.; Mollica, A.; Zengin, G.; Stefanucci, A. *Corylus avellana* L. Modulates Neurobehaviour and Brain Chemistry Following High-Fat Diet. *Front. Biosci.* **2021**, *26*, 537–551. [CrossRef]
23. Faraone, I.; Ponticelli, M.; Mangieri, C.; Nigro, I.; Lela, L.; Vassallo, A.; Cosentino, C.; Tzvetkov, N.T.; Carlucci, V.; Armentano, M.F.; et al. Technological Optimization and Antioxidant Efficacy via the NRF-2-Mediated Defense Pathway of *Corylus avellana* L. Skin Extracts: A Sustainable Approach for Developing Health-Promoting Natural Products. *Pharmaceuticals* **2026**, *19*, 539. [CrossRef]
24. Liang, B.M.; Wang, M.Y.; Ji, C.C.; Qi, X.; Cui, C.B. Regulation of Hazelnut Leaf Polyphenols on Oxidative Stress in Chronic Alcoholic Liver Injury. *eFood* **2025**, *6*, e70053. [CrossRef]
25. Cerulli, A.; De Vita, S.; Masullo, M.; Bove, C.; Bermejo Bescós, P.; Bifulco, G.; Piacente, S. *Corylus avellana* Cultivar "Tonda Di Giffoni", Source of Antioxidant Diarylheptanoids: Biological Evaluation and Molecular Docking Analysis. *J. Funct. Foods* **2024**, *119*, 106309. [CrossRef]
26. Spagnuolo, L.; Della Posta, S.; Fanali, C.; Dugo, L.; De Gara, L. Chemical Composition of Hazelnut Skin Food Waste and Protective Role against Advanced Glycation End-Products (AGEs) Damage in THP-1-Derived Macrophages. *Molecules* **2023**, *28*, 2680. [CrossRef]
27. Zhao, J.; Wang, X.; Wang, Y.; Lv, G.; Lin, H.; Lin, Z. UPLC-MS/MS Profiling, Antioxidant and Anti-Inflammatory Activities, and Potential Health Benefits Prediction of Phenolic Compounds in Hazel Leaf. *Front Nutr.* **2023**, *10*, 1092071. [CrossRef]
28. Emanet, M.; Şen, Ö.; Pignatelli, F.; Lavarello, C.; Petretto, A.; Ciofani, G. Hazelnut Extract-Loaded Nanostructured Lipid Carriers and Evaluation of Their Antioxidant Properties. *Front. Bioeng. Biotechnol.* **2022**, *10*, 953867. [CrossRef]
29. Banach, M.S.; Dong, Q.; O'Brien, P.J. Hepatocyte Cytotoxicity Induced by Hydroperoxide (Oxidative Stress Model) or Glyoxal (Carbonylation Model): Prevention by Bioactive Nut Extracts or Catechins. *Chem. Biol. Interact.* **2009**, *178*, 324–331. [CrossRef]
30. Wang, X.; Li, X.; Zhao, J.; Lin, Z.; Li, J.; Xu, X.; Zhou, X.; Wang, Y.; Lv, G.; Lin, H.; et al. Hazel Leaf Polyphenols Ameliorate Hyperuricemia-Induced Renal Fibrosis through Regulating Uric Acid Metabolism and Inhibiting Ferroptosis via the Nrf2/GPX4 Signaling Axis. *J. Funct. Foods* **2024**, *123*, 106579. [CrossRef]

31. Di Renzo, L.; Merra, G.; Botta, R.; Gualtieri, P.; Manzo, A.; Perrone, M.A.; Mazza, M.; Cascapera, S.; De Lorenzo, A.; De Lorenzo, A. Post-Prandial Effects of Hazelnut-Enriched High Fat Meal on LDL Oxidative Status, Oxidative and Inflammatory Gene Expression of Healthy Subjects: A Randomized Trial. *Eur. Rev. Med. Pharmacol. Sci.* **2017**, *21*, 1610–1626.
32. Guaraldi, F.; Deon, V.; Del Bo', C.; Vendrame, S.; Porrini, M.; Riso, P.; Guardamagna, O. Effect of Short-Term Hazelnut Consumption on DNA Damage and Oxidized LDL in Children and Adolescents with Primary Hyperlipidemia: A Randomized Controlled Trial. *J. Nutr. Biochem.* **2018**, *57*, 206–211. [CrossRef]
33. Di Renzo, L.; Carraro, A.; Minella, D.; Botta, R.; Contessa, C.; Sartor, C.; Iacopino, A.M.; De Lorenzo, A. Nutrient Analysis Critical Control Point (NACCP): Hazelnut as a Prototype of Nutrigenomic Study. *Food Nutr. Sci.* **2014**, *5*, 79–88. [CrossRef]
34. Di Renzo, L.; Cioccoloni, G.; Bernardini, S.; Abenavoli, L.; Aiello, V.; Marchetti, M.; Cammarano, A.; Alipourfard, I.; Ceravolo, I.; Gratteri, S. A Hazelnut-Enriched Diet Modulates Oxidative Stress and Inflammation Gene Expression without Weight Gain. *Oxid. Med. Cell. Longev.* **2019**, *2019*, 4683723. [CrossRef]
35. Okumus, E.; Temiz, M.A. Hazelnut By-Products as a Valuable Resource: Lipid Peroxidation Inhibition Effect, Bioaccessibility and Antidiabetic Properties. *Food Biosci.* **2025**, *65*, 106018. [CrossRef]
36. Shahidi, F.; Alasalvar, C.; Liyana-Pathirana, C.M. Antioxidant Phytochemicals in Hazelnut Kernel (*Corylus avellana* L.) and Hazelnut Byproducts. *J. Agric. Food Chem.* **2007**, *55*, 1212–1220. [CrossRef]
37. Hao, M.; Tan, X.; Liu, K.; Xin, N. Nanoencapsulation of Nutraceuticals: Enhancing Stability and Bioavailability in Functional Foods. *Front. Nutr.* **2026**, *12*, 1746176. [CrossRef]
38. Ozkan, G.; Ceyhan, T.; Çatalkaya, G.; Rajan, L.; Ullah, H.; Daglia, M.; Capanoglu, E. Encapsulated Phenolic Compounds: Clinical Efficacy of a Novel Delivery Method. *Phytochem. Rev.* **2024**, *23*, 781–819. [CrossRef]
39. Del Rio, D.; Calani, L.; Dall'Asta, M.; Brighenti, F. Polyphenolic Composition of Hazelnut Skin. *J. Agric. Food Chem.* **2011**, *59*, 9935–9941. [CrossRef]
40. Taş, N.G.; Gökmen, V. Bioactive Compounds in Different Hazelnut Varieties and Their Skins. *J. Food Compos. Anal.* **2015**, *43*, 203–208. [CrossRef]
41. Oliveira, I.; Sousa, A.; Valentão, P.; Andrade, P.B.; Ferreira, I.C.F.R.; Ferreres, F.; Bento, A.; Seabra, R.; Estevinho, L.; Pereira, J.A. Hazel (*Corylus avellana* L.) Leaves as Source of Antimicrobial and Antioxidative Compounds. *Food Chem.* **2007**, *105*, 1018–1025. [CrossRef]
42. Zhao, J.; Wang, X.; Lin, H.; Lin, Z. Hazelnut and Its By-Products: A Comprehensive Review of Nutrition, Phytochemical Profile, Extraction, Bioactivities and Applications. *Food Chem.* **2023**, *413*, 135576. [CrossRef]
43. Cerulli, A.; Lauro, G.; Masullo, M.; Cantone, V.; Olas, B.; Kontek, B.; Nazzaro, F.; Bifulco, G.; Piacente, S. Cyclic Diarylheptanoids from *Corylus avellana* Green Leafy Covers: Determination of Their Absolute Configurations and Evaluation of Their Antioxidant and Antimicrobial Activities. *J. Nat. Prod.* **2017**, *80*, 1703–1713. [CrossRef]
44. Masullo, M.; Lauro, G.; Cerulli, A.; Bifulco, G.; Piacente, S. *Corylus avellana*: A Source of Diarylheptanoids with α-Glucosidase Inhibitory Activity Evaluated by In Vitro and In Silico Studies. *Front. Plant Sci.* **2022**, *13*, 805660. [CrossRef]
45. Tkaczenko, H.; Kurhaluk, N. Antioxidant-Rich Functional Foods and Exercise: Unlocking Metabolic Health Through Nrf2 and Related Pathways. *Int. J. Mol. Sci.* **2025**, *26*, 1098. [CrossRef]
46. Cásedas, G.; Rojas-Márquez, H.; Ventura, L.; Moliner, C.; Maggi, F.; Rubio-Castellanos, A.; López, V. Involvement of Keap1/Nrf2 and the Antioxidant Defence in Cytoprotective Effects Induced by Cannabis Polyphenols in SH-SY5Y Neuronal Cells. *Biomed. Pharmacother.* **2026**, *196*, 119048. [CrossRef]
47. Roba, B.B.; Umar, A.B. Investigating the Potential of Novel Antioxidant Flavonoids: A Comprehensive Study of Drug-Likeness, Molecular Docking, Pharmacokinetics, and DFT Analysis. *Future J. Pharm. Sci.* **2025**, *11*, 84. [CrossRef]
48. Robledinos-Antón, N.; Fernández-Ginés, R.; Manda, G.; Cuadrado, A. Activators and Inhibitors of NRF2: A Review of Their Potential for Clinical Development. *Oxid. Med. Cell. Longev.* **2019**, *2019*, 9372182. [CrossRef]
49. Lin, J.; Zhang, Y.; Guan, H.; Li, S.; Sui, Y.; Hong, L.; Zheng, Z.; Huang, M. Myricitrin Inhibited Ferritinophagy-Mediated Ferroptosis in Cisplatin-Induced Human Renal Tubular Epithelial Cell Injury. *Front. Pharmacol.* **2024**, *15*, 1372094. [CrossRef]
50. Shi, M.; Mobet, Y.; Shen, H. Quercetin Attenuates Acute Kidney Injury Caused by Cisplatin by Inhibiting Ferroptosis and Cuproptosis. *Cell Biochem. Biophys.* **2024**, *82*, 2687–2699. [CrossRef]
51. Han, M.; Zhang, F.; Li, M.; Zhang, Q.; Shen, K.; Zhang, D.; Xu, H.; Zhou, F.; Wang, X. Licochalcone A Mitigates Cisplatin-Induced Nephrotoxicity by Inhibiting Ferroptosis and Mitochondrial Dysfunction via the Nrf2/GPX4 Axis. *Front. Pharmacol.* **2026**, *17*, 1759824. Correction in *Front. Pharmacol.* **2026**, *17*, 1876105. [CrossRef]
52. Yuksel, B.; Eryilmaz, N. Ferroptosis Inhibition as a Renoprotective Strategy in Cisplatin-Induced Acute Kidney Injury: Multilevel Meta-Analysis of Mechanistic Biomarkers. *Front. Med.* **2026**, *13*, 1801504. [CrossRef]
53. Amin, A.; Ávila-Quezada, G.D. Polyphenol-Based Modulation of the Glo1–Nrf2–RAGE Axis in Diabetes and Neurodegeneration: Mechanistic Evidence, Translational Constraints, and Critical Appraisal. *Front. Pharmacol.* **2026**, *17*, 1877182. [CrossRef]
54. Yu, J.; Xiao, X.; Chen, B.; Deng, Z.; Chen, X.; Fan, Y.; Li, H. Synergistic and Antagonistic Activity of Selected Dietary Phytochemicals against Oxidative Stress-Induced Injury in Cardiac H9c2 Cells via the Nrf2 Signaling Pathway. *Foods* **2024**, *13*, 2440. [CrossRef]

55. Chen, X.; Li, H.; Zhang, B.; Deng, Z. The Synergistic and Antagonistic Antioxidant Interactions of Dietary Phytochemical Combinations. *Crit. Rev. Food Sci. Nutr.* **2022**, *62*, 5658–5677. [CrossRef]
56. Fujisawa, S.; Ishihara, M.; Atsumi, T.; Kadoma, Y. A Quantitative Approach to the Free Radical Interaction Between Alpha-Tocopherol or Ascorbate and Flavonoids. *In Vivo* **2006**, *20*, 445–452.
57. Unsal, V.; Cicek, M.; Sabancilar, İ. Toxicity of Carbon Tetrachloride, Free Radicals and Role of Antioxidants. *Rev. Environ. Health* **2021**, *36*, 279–295. [CrossRef]
58. Rusu, M.A.; Bucur, N.; Puică, C.; Tămaş, M. Effects of *Corylus avellana* in Acetaminophen and CCl4 Induced Toxicosis. *Phyther. Res.* **1999**, *13*, 120–123. [CrossRef]
59. Ghafouri-Fard, S.; Askari, A.; Shoorei, H.; Seify, M.; Koohestanidehaghi, Y.; Hussen, B.M.; Taheri, M.; Samsami, M. Antioxidant Therapy against TGF-β/SMAD Pathway Involved in Organ Fibrosis. *J. Cell. Mol. Med.* **2024**, *28*, e18052. [CrossRef]
60. Niu, C.; Zhang, J.; Okolo, P.I. The Possible Pathogenesis of Liver Fibrosis: Therapeutic Potential of Natural Polyphenols. *Pharmacol. Rep.* **2024**, *76*, 944–961. [CrossRef]
61. Liu, R.M.; Desai, L.P. Reciprocal Regulation of TGF-β and Reactive Oxygen Species: A Perverse Cycle for Fibrosis. *Redox Biol.* **2015**, *6*, 565–577. [CrossRef]
62. Chen, F.; Lyu, L.; Xing, C.; Chen, Y.; Hu, S.; Wang, M.; Ai, Z. The Pivotal Role of TGF-β/Smad Pathway in Fibrosis Pathogenesis and Treatment. *Front. Oncol.* **2025**, *15*, 1649179. [CrossRef]
63. Murota, K.; Terao, J. Antioxidative Flavonoid Quercetin: Implication of Its Intestinal Absorption and Metabolism. *Arch. Biochem. Biophys.* **2003**, *417*, 12–17. [CrossRef]
64. Hernández-Ortega, L.D.; Alcántar-Díaz, B.E.; Ruiz-Corro, L.A.; Sandoval-Rodriguez, A.; Bueno-Topete, M.; Armendariz-Borunda, J.; Salazar-Montes, A.M. Quercetin Improves Hepatic Fibrosis Reducing Hepatic Stellate Cells and Regulating Pro-Fibrogenic/Anti-Fibrogenic Molecules Balance. *J. Gastroenterol. Hepatol.* **2012**, *27*, 1865–1872. [CrossRef]
65. Li, Z.; Wang, Y.; Fang, D.; Wang, Y.; Han, H.; Zhang, X.; Chen, Z. Effects of Rutin on Renal Function, Oxidative Stress and Fibrosis in Animal Models of Diabetic Nephropathy: A Systematic Review and Meta-Analysis. *Front. Pharmacol.* **2026**, *17*, 1771010. [CrossRef]
66. Shi, H.; Shi, A.; Dong, L.; Lu, X.; Wang, Y.; Zhao, J.; Dai, F.; Guo, X. Chlorogenic Acid Protects against Liver Fibrosis in Vivo and in Vitro through Inhibition of Oxidative Stress. *Clin. Nutr.* **2016**, *35*, 1366–1373. [CrossRef]
67. Li, J.; Li, X.; Xu, W.; Wang, S.; Hu, Z.; Zhang, Q.; Deng, X.; Wang, J.; Zhang, J.; Guo, C. Antifibrotic Effects of Luteolin on Hepatic Stellate Cells and Liver Fibrosis by Targeting AKT/mTOR/p70S6K and TGFβ/Smad Signalling Pathways. *Liver Int.* **2015**, *35*, 1222–1233. [CrossRef]
68. Balta, C.; Ciceu, A.; Herman, H.; Rosu, M.; Boldura, O.M.; Hermenean, A. Dose-Dependent Antifibrotic Effect of Chrysin on Regression of Liver Fibrosis: The Role in Extracellular Matrix Remodeling. *Dose-Response* **2018**, *16*, 1–8. [CrossRef]
69. Zhu, Y.; Jia, Y.; Zhang, E. Oxidative Stress Modulation in Alcohol-Related Liver Disease: From Chinese Botanical Drugs to Exercise-Based Interventions. *Front. Pharmacol.* **2025**, *16*, 1516603. [CrossRef]
70. Tang, Y.; Gao, C.; Xing, M.; Li, Y.; Zhu, L.; Wang, D.; Yang, X.; Liu, L.; Yao, P. Quercetin Prevents Ethanol-Induced Dyslipidemia and Mitochondrial Oxidative Damage. *Food Chem. Toxicol.* **2012**, *50*, 1194–1200. [CrossRef]
71. Tang, Y.; Tian, H.; Shi, Y.; Gao, C.; Xing, M.; Yang, W.; Bao, W.; Wang, D.; Liu, L.; Yao, P. Quercetin Suppressed CYP2E1-Dependent Ethanol Hepatotoxicity via Depleting Heme Pool and Releasing CO. *Phytomedicine* **2013**, *20*, 699–704. [CrossRef]
72. He, W.; Zhang, B.; Li, S.; Qian, Y. Quercetin Attenuates Acute Alcohol-Induced Liver Injury in Mice by Modulating Lipid Metabolism, Oxidative Stress, and Inflammation. *Front. Pharmacol.* **2026**, *17*, 1702639. [CrossRef]
73. Luo, Y.; Long, M.; Wu, X.; Zeng, L. Targeting Ferroptosis: Novel Therapeutic Approaches and Intervention Strategies for Kidney Diseases. *Front. Immunol.* **2025**, *16*, 1700004. Correction in *Front. Immunol.* **2025**, *16*, 1765613. [CrossRef]
74. Chang, Y.; Song, Y.; Ahmad, N.; Song, C.; Chu, Y.; Zhang, Y.; Feng, L.; Wei, W.; Zhang, M.; Liu, X. Safflower Extract Ameliorates Cisplatin-Induced Acute Kidney Injury by Regulating Microbiota-Metabolic-Redox Nexus and PI3K–Akt/Nrf2 Pathway. *Antioxidants* **2026**, *15*, 855. [CrossRef]
75. Deng, Y.; Zeng, L.; Liu, H.; Zuo, A.; Zhou, J.; Yang, Y.; You, Y.; Zhou, X.; Peng, B.; Lu, H.; et al. Silibinin Attenuates Ferroptosis in Acute Kidney Injury by Targeting FTH1. *Redox Biol.* **2024**, *77*, 103360. [CrossRef]
76. Zhang, C.; Li, C.L.; Xu, K.X.; Zheng, Z.H.; Cheng, G.Z.; Wu, H.J.; Liu, J. The Hippo Pathway and Its Correlation with Acute Kidney Injury. *Zool. Res.* **2022**, *43*, 897–910. [CrossRef]
77. Wang, X.; Zhao, J.; Lin, Z.; Li, J.; Li, X.; Xu, X.; Wang, Y.; Lv, G.; Lin, H.; Lin, Z. Analysis of Polyphenol Extract from Hazel Leaf and Ameliorative Efficacy and Mechanism against Hyperuricemia Zebrafish Model via Network Pharmacology and Molecular Docking. *Molecules* **2024**, *29*, 317. [CrossRef]
78. Hongya, Z.; Yichang, D.; Zheng, Z.; Yanzhu, Z.; Wei, N.; Caoxing, H.; Baishuang, Y. The Preventive Effect of Chlorogenic Acid on Cisplatin-Induced Acute Kidney Injury in Mice. *Front. Vet. Sci.* **2026**, *13*, 1763548. Correction in *Front. Vet. Sci.* **2026**, *13*, 1845799. [CrossRef]

79. Jian, J.; Yu-Qing, L.; Rang-Yue, H.; Xia, Z.; Ke-Huan, X.; Ying, Y.; Li, W.; Rui-zhi, T. Isorhamnetin Ameliorates Cisplatin-Induced Acute Kidney Injury in Mice by Activating SLPI-Mediated Anti-Inflammatory Effect in Macrophage. *Immunopharmacol. Immunotoxicol.* **2024**, *46*, 319–329. [CrossRef]
80. Yuan, W.; Kou, S.; Ma, Y.; Qian, Y.; Li, X.; Chai, Y.; Jiang, Z.; Zhang, L.; Sun, L.; Huang, X. Hyperoside Ameliorates Cisplatin-Induced Acute Kidney Injury by Regulating the Expression and Function of Oat1. *Xenobiotica* **2023**, *53*, 559–571. [CrossRef]
81. Shao, Y.F.; Tang, B.B.; Ding, Y.H.; Fang, C.Y.; Hong, L.; Shao, C.X.; Yang, Z.X.; Qiu, Y.P.; Wang, J.C.; Yang, B.; et al. Kaempferide Ameliorates Cisplatin-Induced Nephrotoxicity via Inhibiting Oxidative Stress and Inducing Autophagy. *Acta Pharmacol. Sin.* **2023**, *44*, 1442–1454. [CrossRef]
82. Chao, C.S.; Tsai, C.S.; Chang, Y.P.; Chen, J.M.; Chin, H.K.; Yang, S.C. Hyperin Inhibits Nuclear Factor Kappa B and Activates Nuclear Factor E2-Related Factor-2 Signaling Pathways in Cisplatin-Induced Acute Kidney Injury in Mice. *Int. Immunopharmacol.* **2016**, *40*, 517–523. [CrossRef]
83. Chen, M.; Zhu, Y.; Chen, J.; Zhou, R.; Li, G. Arundina Graminifolia Ameliorates Cisplatin-Induced Acute Kidney Injury via Pathological Targeted Recruitment of Flavonoid Aglycones: A Study Integrating Serum/Kidney Pharmacochemistry and Network Pharmacology. *Molecules* **2026**, *31*, 1951. [CrossRef]
84. Xia, C.; Zhang, J.; Chen, H.; Jiang, W.; Zhou, S.; Zheng, H.; Sun, W. Kaempferol Improves Mitochondrial Homeostasis via Mitochondrial Dynamics and Mitophagy in Diabetic Kidney Disease. *Int. Immunopharmacol.* **2025**, *162*, 115121. [CrossRef]
85. Yang, X.Y.; Jiang, D.; Wang, Y.Z.; Duan, M.Y.; Huang, Y.W.; Wang, X.J.; Xiang, Z.M.; Sheng, J.; Zhu, Q.Q. Chlorogenic Acid Alleviates Renal Fibrosis by Reducing Lipid Accumulation in Diabetic Kidney Disease through Suppressing the Notch1 and Stat3 Signaling Pathway. *Ren. Fail.* **2024**, *46*, 2371988. [CrossRef]
86. Wu, X.; Li, J.; Dong, Y.; Li, J.; Bian, J.; Liu, C.; Zhang, H.; Han, L.; Wang, M. Targeting the Nrf2/TGF-B1/Smad Signaling Pathway: A Novel Strategy for Urolithin A to Alleviate Renal Fibrosis. *Food Front.* **2026**, *7*, e70136. [CrossRef]
87. Garrido-Valdes, M.; Díaz-Velis, L.; Valdes-Gonzalez, M.; Garrido-Suárez, B.B.; Garrido, G. Gastroprotective Role of Fruit Extracts in Gastric Damage Induced by Non-Steroidal Anti-Inflammatory Drugs: A Systematic Review. *J. Med. Food* **2023**, *26*, 777–798. [CrossRef]
88. Zamanian, M.Y.; Gardanova, Z.R.; Hjazi, A.; Uthirapathy, S.; Jyothi, S.R.; Shit, D.; Pathak, P.K.; Saini, S.; Jahdari, A.; Golmohammadi, M. Pomegranate as a Natural Remedy for Gastric Ulcers Prevention: A Review of Its Gastroprotective Mechanisms and Pharmacological Benefits. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **2025**, *398*, 6675–6690. [CrossRef]
89. Bahaeddin, Z.; Yans, A.; Khodagholi, F.; Hajimehdipoor, H.; Sahranavard, S. Hazelnut and Neuroprotection: Improved Memory and Hindered Anxiety in Response to Intra-Hippocampal Aβ Injection. *Nutr. Neurosci.* **2017**, *20*, 317–326. [CrossRef]
90. Mazzola, G.; Rondanelli, M.; Buga, F.; Riso, P.; Perna, S. Bioactive Properties of Hazelnut-Derived Products in Colorectal Cancer Prevention: A Systematic Review of Preclinical and Epidemiological Studies. *Foods* **2025**, *14*, 2154. [CrossRef]
91. Evans, A.K.; Saw, N.L.; Woods, C.E.; Vidano, L.M.; Blumenfeld, S.E.; Lam, R.K.; Chu, E.K.; Reading, C.; Shamloo, M. Impact of High-Fat Diet on Cognitive Behavior and Central and Systemic Inflammation with Aging and Sex Differences in Mice. *Brain Behav. Immun.* **2024**, *118*, 334–354. [CrossRef]
92. Rajaram, S.; Damasceno, N.R.T.; Braga, R.A.M.; Martinez, R.; Kris-Etherton, P.; Sala-Vila, A. Effect of Nuts on Markers of Inflammation and Oxidative Stress: A Narrative Review. *Nutrients* **2023**, *15*, 1099. [CrossRef]
93. Lorente-Cebrián, S.; Costa, A.G.V.; Castillo-Rivas, J.A.; Castro, M.; Arbonés-Mainar, J.M.; Goñi, S.; Remón, S.; Aranaz, P.; López, V.; Martín-Burriel, I.; et al. Phenolic Compounds and Epigenetic Mechanisms Regulating Gene Expression: Effects on Human Health. *J. Physiol. Biochem.* **2025**, *81*, 1257–1274. [CrossRef]
94. Widmer, A.; Lillegard, K.; Wood, K.; Robles, M.; Fan, R.; Ye, F.; Koethe, J.R.; Silver, H.J. Consumption of Tree Nuts as Snacks Stimulates Changes in Plasma Fatty Acid Profiles and Adipose Tissue Gene Expression in Young Adults at Risk for Metabolic Syndrome. *Clin. Nutr.* **2025**, *48*, 25–34. [CrossRef]
95. Del Bo', C.; Marino, M.; Martini, D.; Tucci, M.; Ciappellano, S.; Riso, P.; Porrini, M. Overview of Human Intervention Studies Evaluating the Impact of the Mediterranean Diet on Markers of DNA Damage. *Nutrients* **2019**, *11*, 391. [CrossRef]
96. Perez-Robles, M.; Campos-Perez, W.; Godinez-Mora, S.; Lopez-Alvarez, V.; Ramos-Villalobos, L.E.; Corona-Ruiz, F.; Armendariz-Borunda, J.; Martinez-Lopez, E. Serum OxLDL Levels Are Positively Associated with the Number of Ischemic Events and Damaged Blood Vessels in Patients with Coronary Artery Disease. *Healthcare* **2025**, *13*, 1426. [CrossRef]
97. Orem, A.; Yucesan, F.B.; Orem, C.; Akcan, B.; Kural, B.V.; Alasalvar, C.; Shahidi, F. Hazelnut-Enriched Diet Improves Cardiovascular Risk Biomarkers beyond a Lipid-Lowering Effect in Hypercholesterolemic Subjects. *J. Clin. Lipidol.* **2013**, *7*, 123–131. [CrossRef]
98. Barbosa, A.R.; Pais, S.; Marreiros, A.; Correia, M. Impact of a Mediterranean-Inspired Diet on Cardiovascular Disease Risk Factors: A Randomized Clinical Trial. *Nutrients* **2024**, *16*, 2443. [CrossRef]
99. Durak, İ.; Köksal, İ.; Kaçmaz, M.; Büyükkoçak, S.; Çimen, B.M.Y.; Öztürk, H.S. Hazelnut Supplementation Enhances Plasma Antioxidant Potential and Lowers Plasma Cholesterol Levels. *Clin. Chim. Acta* **1999**, *284*, 113–115. [CrossRef]

100. Tey, S.L.; Brown, R.C.; Chisholm, A.W.; Delahunty, C.M.; Gray, A.R.; Williams, S.M. Effects of Different Forms of Hazelnuts on Blood Lipids and α-Tocopherol Concentrations in Mildly Hypercholesterolemic Individuals. *Eur. J. Clin. Nutr.* **2011**, *65*, 117–124. [CrossRef]
101. Pycia, K.; Kapusta, I.; Jaworska, G. Changes in Antioxidant Activity, Profile, and Content of Polyphenols and Tocopherols in Common Hazel Seed (*Corylus avellana* L.) Depending on Variety and Harvest Date. *Molecules* **2020**, *25*, 43. [CrossRef]
102. Tey, S.L.; Robinson, T.; Gray, A.R.; Chisholm, A.W.; Brown, R.C. Do Dry Roasting, Lightly Salting Nuts Affect Their Cardioprotective Properties and Acceptability? *Eur. J. Nutr.* **2017**, *56*, 1025–1036. [CrossRef]
103. Camus-Ela, M.; Wang, Y.; Rennie, G.H.; Raghavan, V.; Wang, J. Update on Hazelnut Allergy: Allergen Characterization, Epidemiology, Food Processing Technique and Detecting Strategy. *Compr. Rev. Food Sci. Food Saf.* **2025**, *24*, e70098. [CrossRef]
104. Calamelli, E.; Trozzo, A.; Di Blasi, E.; Serra, L.; Bottau, P. Hazelnut Allergy. *Medicina* **2021**, *57*, 67. [CrossRef]
105. Salvatore, M.M.; Andolfi, A.; Nicoletti, R. Mycotoxin Contamination in Hazelnut: Current Status, Analytical Strategies, and Future Prospects. *Toxins* **2023**, *15*, 99. [CrossRef]
106. Madhaven, N. Final Report on the Safety Assessment of *Corylus avellana* (Hazel) Seed Oil, *Corylus americana* (Hazel) Seed Oil, *Corylus avellana* (Hazel) Seed Extract, *Corylus americana* (Hazel) Seed Extract, *Corylus rostrata* (Hazel) Seed Extract, *Corylus avellana* (Hazel) Leaf Extract, *Corylus americana* (Hazel) Leaf Extract, and *Corylus rostrata* (Hazel) Leaf Extract. *Int. J. Toxicol.* **2001**, *20*, 15–20. [CrossRef]
107. Delimont, N.M.; Haub, M.D.; Lindshield, B.L. The Impact of Tannin Consumption on Iron Bioavailability and Status: A Narrative Review. *Curr. Dev. Nutr.* **2017**, *1*, 1–12. [CrossRef]
108. Barriada-Pereira, M.; González-Castro, M.J.; Muniategui-Lorenzo, S.; López-Mahía, P.; Prada-Rodríguez, D.; Fernández-Fernández, E. Determination of 21 Organochlorine Pesticides in Tree Leaves Using Solid-Phase Extraction Clean-up Cartridges. *J. Chromatogr. A* **2004**, *1061*, 133–139. [CrossRef]
109. Huseyinova, R.; Kutbay, H.G.; Býlgýn, A.; Kiliç, D.; Horuz, A.; Kirmanoglu, C. Sulphur and Some Heavy Metal Contents in Foliage of *Corylus avellana* and Some Roadside Native Plants in Ordu Province, Turkey. *Ekoloji Derg.* **2009**, *18*, 10–16. [CrossRef]
110. Heinrich, M.; Jalil, B.; Abdel-Tawab, M.; Echeverria, J.; Kulić, Ž.; McGaw, L.J.; Pezzuto, J.M.; Potterat, O.; Wang, J.B. Best Practice in the Chemical Characterisation of Extracts Used in Pharmacological and Toxicological Research—The ConPhyMP—Guidelines. *Front. Pharmacol.* **2022**, *13*, 953205. [CrossRef]
111. Halliwell, B.; Rafter, J.; Jenner, A. Health Promotion by Flavonoids, Tocopherols, Tocotrienols, and Other Phenols: Direct or Indirect Effects? Antioxidant or Not? *Am. J. Clin. Nutr.* **2005**, *81*, 268S–276S. [CrossRef]
112. González, I.; Morales, M.A.; Rojas, A. Polyphenols and AGEs/RAGE Axis. Trends and Challenges. *Food Res. Int.* **2020**, *129*, 108843. [CrossRef]
113. Cuadrado, A.; Rojo, A.I.; Wells, G.; Hayes, J.D.; Cousin, S.P.; Rumsey, W.L.; Attucks, O.C.; Franklin, S.; Levonen, A.L.; Kensler, T.W.; et al. Therapeutic Targeting of the NRF2 and KEAP1 Partnership in Chronic Diseases. *Nat. Rev. Drug Discov.* **2019**, *18*, 295–317. [CrossRef]
114. Wu, J.; Minikes, A.M.; Gao, M.; Bian, H.; Li, Y.; Stockwell, B.R.; Chen, Z.N.; Jiang, X. Intercellular Interaction Dictates Cancer Cell Ferroptosis via NF2–YAP Signalling. *Nature* **2019**, *572*, 402–406. Correction in *Nature* **2019**, *572*, E20. [CrossRef]
115. Frijhoff, J.; Winyard, P.G.; Zarkovic, N.; Davies, S.S.; Stocker, R.; Cheng, D.; Knight, A.R.; Taylor, E.L.; Oettrich, J.; Ruskovska, T.; et al. Clinical Relevance of Biomarkers of Oxidative Stress. *Antioxid. Redox Signal.* **2015**, *23*, 1144–1170. [CrossRef]

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