antioxidants

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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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Supplementary Materials

S1. Tables

Table S1. Full search strategies used in each database (searches run on 31 August 2026).

Database	Search string	Fields searched and limits	Records retrieved
PubMed/MEDLINE	("Corylus"[Mesh] OR hazelnut* OR "hazel nut*") AND (Antioxidants[Mesh] OR antioxidant* OR polyphenol* OR flavonoid* OR tocopherol* OR catechin*) AND ("Oxidation-Reduction"[Mesh] OR "Oxidative Stress"[Mesh] OR redox OR "reactive oxygen species" OR ROS OR "oxidative stress" OR Nrf2 OR Keap1 OR "superoxide dismutase" OR catalase OR glutathione) AND (mechanism* OR pathway* OR signaling OR interact* OR modulat*) AND ("In Vitro Techniques"[Mesh] OR "In Vivo"[Filter] OR "in vitro" OR "in vivo" OR cell* OR animal* OR clinical* OR trial* OR human*)	MeSH terms and free-text (all fields); no language or date limits	22
Web of Science (Core Collection)	TS=((hazelnut* OR "hazel nut*" OR "Corylus avellana" OR filbert*) AND (antioxidant* OR polyphenol* OR phenol* OR flavonoid* OR tocopherol* OR catechin* OR proanthocyanidin*) AND (redox OR "redox homeostasis" OR "redox regulation" OR "reactive oxygen species" OR ROS OR "oxidative stress" OR Nrf2 OR Keap1 OR "superoxide dismutase" OR SOD OR catalase OR glutathione) AND (mechanism* OR pathway* OR signaling OR interact* OR modulat*) AND ("in vitro" OR "in vivo" OR cell* OR animal* OR rodent* OR mouse OR mice OR rat OR rats OR clinical OR trial* OR human*))	Topic (title, abstract, author keywords, Keywords Plus); no language or date limits	37
Scopus	TITLE-ABS-KEY(hazelnut* OR {hazel nut*} OR {Corylus avellana} OR filbert*) AND TITLE-ABS-KEY(antioxidant* OR polyphenol* OR phenol* OR flavonoid* OR tocopherol* OR catechin* OR proanthocyanidin*) AND TITLE-ABS-KEY(redox OR {reactive oxygen species} OR ROS OR {oxidative stress} OR Nrf2 OR Keap1 OR {superoxide dismutase} OR SOD OR catalase OR glutathione) AND TITLE-ABS-KEY(mechanism* OR pathway* OR signaling OR interact* OR modulat*) AND TITLE-ABS-KEY({in vitro} OR {in vivo} OR cell* OR animal* OR rodent* OR mouse OR mice OR rat OR rats OR clinical OR trial* OR human*)	Title, abstract, keywords; no language or date limits	37

Asterisks (*) denote truncation. MeSH—Medical Subject Headings; ROS—reactive oxygen species; SOD—superoxide dismutase; TS—Topic search.

Table S2. PICOS criteria for study eligibility.

Element	Inclusion criteria
Population/Model	In vitro: cell systems (cell lines, primary cells, isolated tissues or fractions) and in silico models. In vivo: animal models. Clinical: human participants of any age or health status.
Intervention/Exposure	Hazelnut kernel or by-products (skin, leaf, shell, husk, green leafy covers, buds), as crude extracts, fractions, isolated compounds, or formulated products (including nanocarriers); in in vivo and clinical studies, also hazelnut-enriched diets or hazelnut consumption.
Comparator	Untreated, vehicle, or stressor-alone controls (in vitro and in vivo); control diet, placebo, no-nut control, or baseline values (clinical).
Outcomes	Redox-related outcomes: reactive oxygen/nitrogen species, lipid peroxidation, protein carbonylation, oxidized lipoproteins (ox-LDL), antioxidant enzymes and glutathione, antioxidant capacity biomarkers, oxidative DNA damage, redox-sensitive signaling pathways (e.g., Nrf2/Keap1, Hippo/Yap), and expression of redox-related genes. Other outcomes reported alongside redox endpoints (e.g., markers of organ injury, inflammation, apoptosis, and fibrosis) were also extracted.
Study design	Experimental in vitro and in silico studies; controlled in vivo animal studies; randomized and non-randomized clinical studies.

ox-LDL—oxidized low-density lipoprotein; PICOS—Population, Intervention, Comparator, Outcomes, Study design.

Table S3. Criteria for the risk-of-bias assessment of in vitro studies.

Item	Yes	Partial	No
1. Chemical characterization	Phytochemical profile reported (HPLC/MS/NMR)	Only aggregate content (e.g., TPC), no profile	No characterization reported
2. Material identity	Species, plant part, origin and cultivar reported	Some of these elements missing	Not reported
3. Cell source	Commercial or named source reported	Partial source information	Not reported
4. Controls	Untreated and stressor-alone controls included	Only one of the two	Neither reported
5. Dose–response	≥3 concentrations tested for the main outcomes	Multiple concentrations for some assays only, or two concentrations	Single concentration, or concentrations not reported
6. Replicates	n ≥ 3 independent experiments reported	n unspecified or mixed (2–3)	n = 1 or not reported
7. Statistics	Test and multiple-comparison correction specified	Test or post hoc procedure not fully specified	Not specified
8. Assay validity	Standard, established assays	Modified assays without validation	Methods unclear
9. Funding/COI	Declared, with no commercial tie to the studied material	Declared but sponsor also supplied material, or incompletely declared	Not declared

COI—conflict of interest; HPLC—high-performance liquid chromatography; MS—mass spectrometry; n—number of independent experiments; NMR—nuclear magnetic resonance; TPC—total phenolic content.

Table S4. Support for judgement for the risk-of-bias assessment of the in vivo studies (SYRCLE).

Study	Support for judgement
Balta et al. [18]	Adult male CD1 mice (no numeric age, no weight); method of allocation to groups, randomization, allocation concealment and blinding not mentioned (histology "assessed by light microscopy"). Group size given only in one figure (n = 10); no exclusions reported. ALP announced in Methods but not reported in Results. Ethics approval and funding declared.
Liang et al. [24]	Male C57BL/6 mice, 6–8 weeks, 18–20 g, 1-week acclimatization; "randomly divided" into six groups (method not described), n per group not stated (36 mice); allocation concealment, blinding and exclusions not mentioned. Ethics approval and absence of funding declared.
Sun et al. [19]	Six-week-old male C57BL/6 mice, "randomly allocated" (method not described); weight not reported; allocation concealment and blinding not mentioned; n = 6 for four groups, not stated for the ZP + dihydrexidine group; Bax and Bcl-2 listed in Methods but not reported in the Results text.

	Ethics committee approval stated.
Wang et al. [30]	Seventy-five male C57BL/6J mice, 14–16 g, 1-week adaptation; "randomly divided" into five groups (method not described); allocation concealment and blinding not mentioned; five groups of n = 8 (40 animals) vs 75 mice supplied, the fate of the other animals is not explained (completeness of data Unclear). Ethics approval stated.
Öztürk et al. [20]	Ninety-six adult female Wistar-Albino rats, 250–300 g, 7-day adaptation; groups of six rats, but randomization or any other method of allocation, allocation concealment, blinding and exclusions are not mentioned. Two different ethics approval dates and numbers are given in the article (30/11/2020, no. 15,385; 08/12/2020, no. 2020/22) (other bias Unclear).
Olofinnade et al. [21]	Seventy aged (24 months) male Swiss mice, 35–39 g; "randomly divided" into seven groups of ten (method not described); allocation concealment not mentioned; behavioural scores by two observers blind to the groups, blinding of the biochemical assays not mentioned; exclusions not mentioned. Ethics approval stated.
Olofinnade et al. [22]	Eighty adult male Swiss mice, 18–20 g (age not reported); "randomly assigned" (method not described); no allocation concealment; behavioural tests scored by two observers blind to the groups, blinding of the biochemical assays not mentioned; exclusions not mentioned; ethics approval not mentioned; F(7,22) in the biochemical tables is inconsistent with 8 groups of 10, and two different blood collection routes are described.

Reference numbers correspond to the reference list of the main manuscript.