

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

INPLASY2026100026

doi: 10.37766/inplasy2026.10.0026

Received: 6 October 2026

Published: 6 October 2026

Banc, R; Rusu, ME; Popa, DS.

Corresponding author:

Roxana Banc

broxxaro@yahoo.com

Author Affiliation:"Iuliu Hatieganu" University of
Medicine and Pharmacy.**ADMINISTRATIVE INFORMATION****Support** - This research received no external funding.**Review Stage at time of this submission** - Completed but not published.**Conflicts of interest** - None declared.**INPLASY registration number:** INPLASY2026100026**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 6 October 2026 and was last updated on 6 October 2026.**INTRODUCTION****Review question / Objective** Review questionHow do hazelnut (*Corylus avellana L.*) and its by-products interact with redox regulatory systems, and is the evidence consistent across in vitro, in vivo, and clinical studies?**Objective**

To critically evaluate and synthesize the evidence on the antioxidant and redox-regulatory mechanisms of hazelnut and its by-products (skin, leaf, shell, husk, green leafy covers, buds), using in vitro (including in silico), in vivo, and clinical studies.

Rationale Oxidative stress, the imbalance between reactive oxygen/nitrogen species and the antioxidant defence system, is involved in chronic metabolic, cardiovascular, hepatic, renal, and neurodegenerative diseases. Redox regulatory systems, such as the Nrf2/Keap1 pathway, antioxidant enzymes (SOD, CAT, GPx), and

glutathione, are therefore targets of interest for dietary antioxidants.

Hazelnut (*Corylus avellana L.*) is a source of phenolic compounds, including flavan-3-ols, flavonoids, phenolic acids, and diarylheptanoids. These are found not only in the edible kernel but also in by-products such as the skin, leaves, shells, husks, green leafy covers, and buds. Studies have reported antioxidant effects of hazelnut and its by-products in cell systems, animal models, and human interventions. However, the evidence on biomarkers of oxidative stress and inflammation and on the underlying redox mechanisms is scattered across different levels of evidence and is inconsistent. Studies differ in the plant material tested, extraction methods, models, stressors, outcomes, and reporting units.

To our knowledge, no systematic review has so far integrated the in vitro, in vivo, and clinical evidence on how hazelnut and its by-products interact with redox regulatory systems. Such a synthesis can show which mechanisms are supported at each level of evidence, how consistent they are across

models, and where gaps remain between mechanistic findings and human outcomes.

Condition being studied Oxidative stress and redox imbalance, and the antioxidant and redox-regulatory mechanisms of hazelnut (*Corylus avellana* L.) and its by-products (skin, leaf, shell, husk, green leafy covers, buds) in in vitro, in vivo, and clinical models.

METHODS

Search strategy Three databases were searched on 31 August 2026, with no restriction on publication date or language: PubMed/MEDLINE, Web of Science (Core Collection), and Scopus. The strategy combined five concept blocks with AND; within each block, synonyms were combined with OR. The reference lists of included studies were also screened.

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*)

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*))

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*)

Results: PubMed/MEDLINE, 22 records; Web of Science, 37 records; Scopus, 37 records (96 records in total, before removal of duplicates).

Participant or population The review includes three types of study populations or models:

In vitro and in silico: cell systems (cell lines, primary cells, isolated tissues or fractions) and in silico models (e.g., molecular docking).

In vivo: animal models (rodents or other species) of oxidative stress or organ injury, and animals receiving hazelnut-enriched diets.

Clinical: human participants of any age (children, adolescents, adults), sex, or health status (healthy individuals or patients with metabolic or lipid disorders), receiving hazelnut or hazelnut-based interventions.

Studies were excluded if hazelnut-specific effects could not be separated from those of other foods.

Intervention Intervention

Hazelnut (*Corylus avellana* L.) kernel and/or its by-products (skin, leaf, shell, husk, green leafy covers, buds), administered or tested as:

crude extracts or fractions (e.g., hydroalcoholic, methanolic, aqueous);

isolated compounds (e.g., diarylheptanoids, catechins);

formulated products (including nanocarrier-loaded extracts);

in in vivo and clinical studies, hazelnut-enriched diets or hazelnut consumption.

Any dose, concentration, duration, and route of administration were eligible.

Comparator In vitro and in vivo studies: untreated controls, vehicle controls, or stressor-alone controls (cells or animals exposed to the oxidative or toxic insult without hazelnut treatment); positive controls (e.g., a reference antioxidant) where used. Clinical studies: control diet, placebo, no-nut control group, or baseline (pre-intervention) values in crossover or sequential designs.

Study designs to be included In vitro and in silico studies: experimental studies in cell systems, isolated tissues or fractions, and computational studies (e.g., molecular docking). In vivo studies: controlled experimental studies in animal models. Clinical studies: randomized controlled trials and non-randomized clinical studies (e.g., sequential or single-arm intervention studies with a baseline or control comparison).

Eligibility criteria Inclusion criteria

Population/model: in vitro and in silico systems (cell lines, primary cells, isolated tissues or fractions); animal models; human participants of any age or health status.

Intervention/exposure: hazelnut (*Corylus avellana* L.) 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, antioxidant enzymes and glutathione, antioxidant capacity biomarkers, oxidative DNA damage, redox-sensitive signaling pathways, and expression of redox-related genes).

Study design: experimental in vitro and in silico studies; controlled in vivo animal studies; randomized and non-randomized clinical studies.

In vitro studies: eligible if they investigated interaction with cellular redox regulatory systems at the level of a signaling pathway or an explicitly characterized chemical or biochemical mechanism. Studies reporting only a functional antioxidant outcome were also included if redox-relevant cellular endpoints were assessed.

Language and date: articles in English; no restriction on publication date.

Exclusion criteria

Reviews, conference abstracts, editorials, and letters.

Studies without full text.

Studies not written in English (excluded at the screening stage).

Studies in which hazelnut-specific effects could not be separated from those of other foods.

Studies limited to chemical composition or to cell-free antioxidant assays without any redox-related biological outcome.

Information sources Three electronic bibliographic databases were searched: PubMed/MEDLINE, Web of Science (Core Collection), and Scopus. The searches were run on 31 August 2026, with no restriction on publication date. In addition, the reference lists of the included studies were screened to identify further eligible records.

Main outcome(s) The outcomes of interest are redox-related outcomes and the mechanisms underlying them, extracted at each level of evidence:

Oxidative damage and reactive species: reactive oxygen/nitrogen species (ROS/RNS), lipid peroxidation (e.g., MDA/TBARS), protein carbonylation, oxidized lipoproteins (ox-LDL), and oxidative DNA damage.

Endogenous antioxidant defences: activity or expression of antioxidant enzymes (e.g., SOD, CAT, GPx) and glutathione.

Redox regulatory mechanisms: modulation of redox-sensitive signaling pathways (e.g., Nrf2/Keap1, Hippo/Yap and ferroptosis-related proteins) and expression of redox-related genes.

Direct chemical mechanisms: radical scavenging and trapping of reactive carbonyl species.

Other outcomes reported alongside redox endpoints (markers of organ injury, inflammation, apoptosis, and fibrosis) were extracted as secondary information.

Timing. No restriction on timing or duration was applied. Outcomes were extracted at all reported time points, which range from short exposures in cell systems to longer administration periods in animal models, and from acute (postprandial) to longer-term interventions in humans.

Effect measures. Because of the heterogeneity of materials, models, assays, and reporting units, effect measures were extracted as reported by the authors (e.g., percentage change or fold change versus control, group means with measures of dispersion, enzyme activity or concentration, and the statistical significance reported). No pooled effect measure was calculated, and the evidence was synthesized narratively.

Quality assessment / Risk of bias analysis Risk of bias and methodological quality were assessed at the level of each primary study, using a tool adapted to its design.

In vitro studies. A custom nine-item checklist was applied, adapted from the SciRAP framework and the reliability principles of Klimisch et al. (1997), because no validated, field-standard tool exists for in vitro nutraceutical studies. The nine items were: (1) chemical characterization of the tested 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); (5) dose-response testing; (6) number of independent replicates; (7) appropriateness and reporting of the statistical analysis; (8) use of established, standard assays; and (9) funding and conflicts of interest. Each item was rated Yes (criterion fully met), Partial (met in part), or No (not met or not reported in the article). The rating criteria for each item were defined in advance (Supplementary Table S3). Ratings were based on the Methods, Results, figure legends, and supplementary material of each article.

In vivo studies. The SYRCLE risk-of-bias tool for animal studies was used.

Clinical studies. The Cochrane RoB 2 tool was used for randomized trials and ROBINS-I for non-randomized studies.

For studies combining in vitro and in vivo experiments, each component was assessed with the tool corresponding to its level of evidence. The assessment was performed by [two reviewers (R.B. and M.E.R.)], and disagreements were resolved by discussion, with a third reviewer (D.-S.P.) consulted when consensus could not be reached. 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 presented in tables and used to qualify the interpretation of the findings.

Strategy of data synthesis Because of the heterogeneity of the plant materials, extraction methods, models, assays, and reporting units, a meta-analysis was not considered feasible. The evidence was therefore synthesized narratively, following the PRISMA 2020 reporting guidance for synthesis without meta-analysis.

Grouping. Results were grouped by level of evidence (in vitro and in silico, in vivo, clinical) and, within each level, by mechanism or outcome. In the in vitro segment, the sections cover chemical composition and extraction, direct antioxidant activities, and mechanistic interactions with redox regulatory systems (modulation of endogenous antioxidant enzymes, signaling pathways beyond direct scavenging, and cellular protection against oxidative stress).

Data presentation. The main characteristics and findings of the included studies were summarized in structured tables for each level of evidence, together with a comparison across hazelnut matrices (kernel, skin, leaf, green leafy covers, buds).

Mechanistic depth. In the in vitro segment, each study was classified as demonstrating a signaling pathway-level mechanism, a direct chemical mechanism, or a functional outcome only, so that the strength of mechanistic evidence could be compared across studies.

Handling of data. Effect measures were extracted as reported by the authors. Values reported only graphically were estimated from the figures and flagged as such. Information not reported in the original articles was recorded as "not reported".

Risk of bias. The risk-of-bias ratings were presented alongside the findings and were used to qualify the interpretation of the results.

Subgroup and sensitivity analyses. None were planned or performed.

Subgroup analysis No formal subgroup analysis (statistical comparison between subgroups) was planned or performed, because a meta-analysis was not feasible. Results were instead compared descriptively across predefined strata: level of evidence (in vitro and in silico, in vivo, clinical) and, within the in vitro segment, hazelnut matrix (kernel, skin, leaf, green leafy covers, buds) and mechanistic depth (signaling pathway-level, direct chemical, functional only).

Sensitivity analysis Not applicable (narrative synthesis; no meta-analysis).

Language restriction No language limit on the searches; non-English articles excluded at screening.

Country(ies) involved Romania.

Keywords hazelnut; *Corylus avellana*; by-products; oxidative stress; redox regulation; Nrf2/Keap1; polyphenols; systematic review.

Contributions of each author

Author 1 - Roxana Banc - Conceptualization; Methodology; Writing—original draft preparation; Writing—review and editing.

Email: broxxaro@yahoo.com

Author 2 - Marius Emil Rusu - Conceptualization; Methodology; Writing—original draft preparation; Supervision.

Email: usu.marius@umfcluj.ro

Author 3 - Daniela-Saveta Popa - Conceptualization; Methodology; Writing—original draft preparation; Writing—review and editing; Supervision.

Email: dpopa@umfcluj.ro