INPLASY

Antioxidant Activity and Mechanistic Insight into the Therapeutic Potential of Ellagitannins and Their Metabolites from Walnuts (Juglans regia L.): A Systematic Review

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ADMINISTRATIVE INFORMATION

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 22 July 2024 and was last updated on 22 July 2024.

INTRODUCTION

Review question / Objective This systematic review aims to comprehensively analyze (1) the antioxidant activity and preventive or therapeutic potential of ellagitannins and their metabolites from walnuts and assess the possible mechanisms of action; (2) the evidence found in preclinical and clinical studies emphasizes that dietary ETs and their metabolites from walnuts could prevent or reduce the impact of chronic and age-related diseases.

Rationale Human life and health are constantly impacted by various physical, emotional, or environmental stress-generating conditions, which can increase the levels of reactive oxygen species (ROS) and reactive nitrogen species (RNS). At higher concentrations, these components may cause oxidative stress and are risk factors for pathophysiologi-cal conditions including lipid oxidation, cardiometabolic diseases (CVD), neurodegen-erative disorders, and cancer. Nevertheless, the harmful effects can be alleviated by the presence of antioxidants, compounds that, at low concentrations, can delay or prevent oxidative stress produced by ROS or RNS. Antioxidants, part of the antioxidant defense system, include endogenous antioxidants, such as superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), or glutathione peroxidase (GPx), and exogenous antioxidants, vitamins, minerals, or polyphenols. Endogenous and exogenous antioxidants play significant roles in the oxidation and antioxidation equilibrium in living systems and act synergistically to maintain redox homeostasis. Exogenous antioxidants, such as vitamins, minerals, and polyphenols, have the function to annihilate excess reactive species. Polyphenols, secondary plant metabolites, have emerged as important preventive and therapeutic bioactive compounds capable of modulating diverse physiological pathways, combat oxidative stress and associated health conditions. Tannins, naturally occurring polyphenols found mostly in nuts (walnuts, hazelnuts, almonds, pistachios) and fruits (pomegranate, berries, grapes, apples), have shown significant antioxidant activity. Ellagitannins

(ETs), a class of hydrolysable tannins, have previously shown antioxidant capacity, explained by the strong potential to donate hydrogen atoms from hydroxyl groups, and cancer prevention ability, mechanistically justified by suppressing TNF alpha-induced COX-2 protein expression and NF-kB or through inhibiting Wnt signaling pathway.
ETs are esters of hexahydroxydiphenic acid (HHDP) with a polyol, usually glucose or quinic acid. The HHDP group, a characteristic unit of all ETs, is released by hydrolysis of ETs with acids or bases and is subsequently spontaneously lactonized to EA. EA is a dimeric derivative of gallic acid, from which numerous ETs deriva-tives are formed in plants, as a result of glycosylation, methylation or methoxylation of its hydroxyl groups.
The use of ETs is restricted by their limited bioavailability, despite their presence in numerous natural products. In general, they are large molecules, for exam-ple, the molecular weight of Lambertianin D, an ellagitannin naturally found in Rubus species, can reach 3740 Da. In addition to their polar nature, the presence of the HHDP moiety(ies) in their structure, which is formed by a C-C bond connection be-tween adjacent galloyl residues, results in components with low bioavailability. Most ETs undergo hydrolysis in the gastrointestinal tract resulting EA that is fur-ther converted to urolithins under physiological conditions by the gut microbiota. Urolithin A, also known as Uro-A, is one of the main metabolites of EA and has demonstrated a variety of bioactivities, including antioxidant, anti-inflammatory, neuroprotective, antidiabetic, and anticancer effects. Additionally, urolithin B (Uro-B) and its isomeric forms, isoUro-A and isoUro-B, can be identified as final me-tabolites of ETs and EA.
Among dietary plant foods, walnuts (Juglans regia L.) are classified as having one of the highest antioxidant activities, most of it can be attributed to the polyphenolic constituents, including the ETs, present mainly in the pellicle.
Clinical trials have demonstrated that long term walnut consumption may contribute to a cardio-protective effect by lowering oxidative stress and inflammation, without concern for adverse effects on body weight or body composition. To the best of our knowledge, there are no reviews in the scientific literature that evaluate the antioxidant activity of walnut ellagitannins and their metabolites. Consequently, this is the first systematic review to comprehensively analyze the antioxidant activity and preventive or therapeutic potential of ellagitannins and their metabolites from walnuts and assess the possible mechanisms of actions. The evidence found in preclinical and clinical studies and revealed in our systematic review emphasize that dietary ETs and their metabolites from walnuts could prevent or reduce the impact of chronic and age-related diseases.

Condition being studied Antioxidant, anti-inflammatory, cardioprotective, neuroprotective, anticarcinogenic, and antiaging activities.

METHODS

Search strategy To search the databases, we used a combination of free-text words, along with their synonyms, singular and plural forms, thesaurus words (Medical Subject Headings for PubMed: ((Juglans[MeSH Terms]) OR (juglans[Title/Abstract]) OR (walnut[MeSH Terms]) OR (walnut[Title/Abstract]) OR (walnuts[Title/Abstract]) OR (juglans regia[MeSH Terms]) OR (juglans regia[Title/Abstract])) AND ((ellagic acid[MeSH Terms]) OR (ellagic acid[Title/Abstract]) OR (ellagitannin[Title/Abstract]) OR (ellag-itannins[Title/Abstract]) OR (urolithin[Title/Abstract]) OR (urolithins[Title/Abstract])), Emtree for EMBASE: ('juglans'/exp OR 'juglans' OR 'walnut'/exp OR 'walnut' OR 'wal-nuts' OR 'juglans regia'/exp OR 'juglans regia') AND ('ellagic acid' OR 'ellagitannin' OR 'ellagitannins' OR 'urolithin'/exp OR 'urolithin' OR 'urolithins') and Scopus: (TI-TLE-ABS-KEY (juglans) OR TITLE-ABS-KEY (walnut) OR TITLE-ABS-KEY (walnuts) OR TITLE-ABS-KEY (juglans AND regia) AND TITLE-ABS-KEY (ellagic acid) OR TI-TLE-ABS-KEY (ellagitannin) OR TITLE-ABS-KEY (ellagitannins) OR TITLE-ABS-KEY (urolithin) AND TITLE-ABS-KEY (urolithin)).

Participant or population In vivo and in vitro studies. Clinical studies: healthy paticipants and/or patients with different patologies.

Intervention Walnut (Juglans regia L.) kernels.

Comparator Diets or teatments without walnut kernels or walnut extracts, respectively.

Study designs to be included Our systematic review included analytical, in vitro, in vivo, and clinical studies.

Eligibility criteria We included: (1) studies performed on both peeled and unpeeled walnut kernels, as well as walnut pellicle plant material; (2) identification and/or quantification of ellagic acid, ellagitannins and their active metabolites/urolithins; and (3) examination of the biological activity of identified compounds via (4) in vivo, (5) in vitro testing, and (6) in clinical studies.
We excluded: (1) abstracts, narrative reviews, comments, opinions, methodological papers,

editorials, conference abstracts, or any other publications lacking primary data and/or explicit method explanations; (2) publications with full text not available; (3) duplicate studies or databases; and (4) publications in languages that were not known.

Information sources We performed a systematic literature search in PubMed, EMBASE, Scopus, and ClinicalTrials.gov databases for studies describing the identification and/or quantification and biological activity of ellagic acid, ellagitannins from walnut (Juglans regia L.) and their active metabolites from the inception of each database through May 31, 2024. The literature search had no language constraints. We also screened the bibliographies of the included studies and current reviews to ensure thorough research.

Main outcome(s) ETs, EA, and urolithins have been shown to have a variety of beneficial effects, including antiinflammatory, antioxidant, anticarcinogenic, antibacterial, cardioprotec-tive, and neuroprotective properties, both in vitro and in vivo studies. Although recent research has described the enhancement of mitochondrial and cellular health in elderly adults with urolithin ingestion, the data in human studies are still lacking. The variations in health outcomes found in living organisms following the consumption of foods high in ETs can be largely attributed to the significant differences between individuals in the production of urolithins resulting from GM variations. The beneficial effects are associated with the urolithins biosynthesis and the type of urolithins that are produced. The primary metabolite detected in the plasma and urine of urolithin producers (UM-A and UM-B) is uro-A. It has been linked to several health advantages, primary the ability to reduce intestinal inflammation. Other bioactive metabolites with comparable effects to Uro-A include Uro-B and IsoUro-A, albeit these have received less research.

Quality assessment / Risk of bias analysis We did not perform quality assessments or risk of bias for the selected studies.

Strategy of data synthesis Three investigators (L.M., F.A.Z., and R.B.) conducted a comprehensive examina-tion of the titles and abstracts to identify the relevant articles for the study. Subse-quently, the whole texts of the documents that appeared to meet the selection criteria were obtained for further evaluation. Each whole text was independently checked by the same investigators. In the event of a disagreement, the studies were debated until a consensus was achieved. Only the most recent or useful article was chosen where there were multiple publications from the same trial.
Data regarding the outcomes were extracted in a spreadsheet Microsoft (Mi-crosoft Office 365, MS, Redmond, WA, USA) Excel file containing the following data: materials/type of extract/biological samples, phytochemical composition studies, in vitro studies/ biological systems analysis methods, in vivo studies/animal models, and clinical trials/ metabolites profile and their biological effects. Furthermore, data re-garding study characteristics were extracted in a spreadsheet file: country, study de-sign, study purpose, and study outcomes.
Other investigators than those who extracted the initial full-text articles re-checked the extracted data (D.-S.P. and M.E.R.).

Subgroup analysis No subgrup analysis.

Sensitivity analysis No sensitivity analysis.

Language restriction The literature search had no language constraints.

Country(ies) involved Romania.

Keywords oxidative stress, anti-inflammatory, ellagic acid, urolithins, cardiometabolic health, anti-cancer, biological activity, in vitro, in vivo, clinical studies.

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