Biomedicine & Healthcare Research

Biomedicine & Healthcare Research 2026 January;6:30-39

https://doi.org/10.71599/bhr.v6i1.178

Open Access

Review article

Olea europaea Leaves and Human Health: From Basic Research to Clinical Applications

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Abstract

Olive leaves (*Olea europaea* L.), once considered an agricultural by-product, are now recognized as a valuable source of bioactive polyphenols—mainly oleuropein and hydroxytyrosol—with high biomedical potential. Extensive experimental evidence demonstrates their strong antioxidant, anti-inflammatory, cardiometabolic, neuroprotective, and anticancer properties. These effects are mediated through key molecular pathways involved in oxidative stress regulation, inflammation control, apoptosis induction, and inhibition of tumor proliferation and angiogenesis. Notably, olive leaf compounds exhibit selective cytotoxicity toward cancer cells while preserving normal cell viability, supporting their potential role in integrative oncology. Although clinical investigations still limited in number, available trials have reported significant improvements in blood pressure, lipid metabolism, glucose tolerance, and cognitive performance, with a generally good safety profile in the available trials. Beyond their pharmacological promise, olive leaves offer an environmentally sustainable avenue for the valorization of olive cultivation by-products, aligning human health benefits with circular economy principles. This narrative review synthesizes mechanistic and clinical findings, while also discussing current limitations such as extract variability and the need for further clinical validation.

Keywords: olive leaf extract; oleuropein; anti-inflammatory; cardiometabolic diseases; neuroprotection; anticancer.

Received: November 9, 2025; Accepted: December 22, 2025

1. Introduction

The olive tree (*Olea europaea* L.), one of the oldest cultivated trees in human history, holds a central place in the Mediterranean diet, whose health benefits, particularly those of olive oil, are well documented. This dietary model is strongly associated with a reduced incidence of cardiovascular diseases, type 2 diabetes, and several cancers [1,2]. Beyond its fruits, olive leaves have a rich history in traditional Mediterranean medicine for treating ailments such as hypertension and infections [3].

In recent years, scientific interest has surged in plant-derived bioactive compounds due to their multi-target potential and ability to modulate interconnected biological pathways [4,5]. In this context, olive leaf extracts (OLEs) have emerged as a compelling subject of study. Their broad spectrum of pharmacological properties, including antioxidant, anti-inflammatory, antihyperglycemic, and anticancer activities, is primarily attributed to a high phenolic content, with the glycosylated secoiridoid oleuropein standing out as the major bioactive constituent [6-8].

This narrative review aims to provide a comprehensive and updated synthesis of the health-promoting properties of OLEs, with a dual focus on mechanistic insights and translational evidence.

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Special emphasis is placed on emblematic Tunisian cultivars (Chetoui and Chemlali), highlighting their unique phytochemistry and contribution to the literature.

To build this synthesis, we conducted a targeted literature search in PubMed and Scopus databases, prioritizing recent mechanistic studies (2020–2025), pivotal preclinical research, and available clinical trials, while also integrating foundational earlier work.

The review critically examines the molecular basis of OLE activities—spanning antimicrobial, antioxidant, anti-inflammatory, cardiometabolic, neuroprotective, and anticancer effects—and evaluates the current clinical evidence and nutritional applications. Finally, we discuss persistent challenges, such as extract standardization and bioavailability, and outline future research directions necessary to unlock the full therapeutic potential of this valuable agricultural by-product.

2. Phytochemical Profile of Olive Leaf Extracts

The therapeutic properties of olive leaves are mainly attributed to their richness in secondary metabolites, particularly polyphenols and secoiridoids [7]. These molecules play a crucial role in the plant's defense mechanisms against environmental (water and temperature) and biological (pathogens, herbivores) stresses [6,8]. Among the different plant organs, leaves contain the highest concentrations of bioactive compounds.

The total phenolic content can reach up to 1450 mg GAE 100 g^{-1} of fresh leaves—approximately 12 times higher than in fruits (110 mg GAE 100 g^{-1}) and 60 times higher than in virgin olive oil (23 mg 100 mL^{-1}) [8]. However, this composition varies according to olive variety, season, maturity stage, pedoclimatic conditions, and extraction method [7,9].

Secoiridoids represent the chemical signature of the species, followed by flavonoids. For instance, Edziri et al. (2019) demonstrated that methanolic extracts from the leaves of four Tunisian varieties (Chetoui, Meski, Oueslati, Jarboui) display distinct phytochemical profiles. The Chetoui variety exhibited the highest total polyphenol (47.47 mg GAE g^{-1}) and flavonoid (7.29 mg CE g^{-1}) contents, followed by Meski, Oueslati, and Jarboui. These elevated levels correlated with strong antioxidant activity and a notable inhibition of acetylcholinesterase (IC_{50} = 500 µg mL^{-1} for Chetoui and Meski, versus 750 µg mL^{-1} for Oueslati and Jarboui) [10]. The main bioactive compounds identified in these extracts can be classified into four families: Secoiridoids, characteristic of the olive tree, mainly include oleuropein, ligstroside, and oleacein; Flavonoids, such as luteolin-7-O-glucoside, apigenin-7-O-glucoside, diosmetin, rutin, and kaempferol; Simple phenols, including hydroxytyrosol, tyrosol, caffeic acid, vanillic acid, and oleanolic acid, and finally Phenylethanoid glycosides, represented primarily by verbascosides [10].

A complementary study conducted on eight olive groves in northern Tunisia (Chetoui variety) revealed high concentrations of macroelements (calcium, potassium, nitrogen, magnesium, phosphorus) and trace elements (manganese, iron, zinc, copper, boron), contributing to the elevated phenolic metabolism characteristic of this olive variety [9]. This influence of environmental factors is quantitatively illustrated in Table 1, which provides a detailed comparison of the phytochemical profile across a distinct altitudinal gradient. The study highlighted that oleuropein content increased from 19 mg g^{-1} DW in coastal growing regions (<300 m) to nearly 69 mg g^{-1} DW in high-altitude areas (>500 m), in parallel with an increase in hydroxytyrosol levels. Conversely, total flavonoids peaked at intermediate altitudes (300–500 m), while simple phenols varied more moderately [9]. This variability translates into higher antioxidant capacity in leaves rich in oleuropein, confirming its key role in the reducing activity of OLEs. It is important to note that the absolute values reported here and in the comparative literature can vary depending on extraction parameters and analytical techniques, highlighting a fundamental consideration for the reproducibility and standardization of future research and product development.

Table 1. Intra-regional variability of the Chetoui olive variety according to altitude (adapted from Zakraoui et al., 2023)

Growing region (altitude)	Oleuropein (mg g^{-1} DW)	Hydroxytyrosol* (mg g^{-1} DW)	Total flavonoids** (mg g^{-1} DW)	Simple phenols^{x} (mg g^{-1} DW)	Verbascoside (mg g^{-1} DW)
> 500 m	60 – 70	6 – 8	8 – 11	3 – 5	1.2 – 1.6
300 – 500 m	35 – 45	4 – 6	14 – 18	3 – 4	1.8 – 2.4
< 300 m	18 – 25	2 – 4	9 – 12	5 – 6	2.5 – 3.1

* Hydroxytyrosol + oleuropein aglycones. ** Sum of luteolin-7-O-glucoside + apigenin-7-O-glucoside + diosmetin + rutin. X Tyrosol + caffeic and vanillic acids.

3. Molecular and Cellular Basis of Olive Leaf Pharmacological Effects

In synergy with other bioactive compounds, oleuropein plays a central role in the numerous pharmacological properties reported for OLEs. This section outlines the main documented biological activities, emphasizing their underlying molecular mechanisms, the types of models used, and specific findings related to Tunisian olive varieties. An integrative overview of these mechanisms is presented in Fig. 1.

Antimicrobial and Antiparasitic Properties

OLEs have attracted growing interest as potential sources of natural antimicrobial agents in response to the increasing global issue of antibiotic resistance. Oleuropein inhibits Gram-positive and Gram-negative bacteria, including multidrug-resistant strains (E. coli, S. aureus, S. typhimurium, L. monocytogenes), and exhibits antifungal activity against C. albicans [11]. Other polyphenols, such as verbascoside and flavonoid glucosides, act synergistically by disrupting microbial membranes, inhibiting key metabolic enzymes, and reducing biofilm formation [12,13].

In Tunisia, extracts obtained from different local olive varieties have demonstrated broad-spectrum antibacterial activity, highlighting their potential as a valuable natural resource for developing antimicrobial agents [10,14]. Extracts from the Chemlali variety also exhibited significant antileishmanial effects against *Leishmania donovani*, *L. mexicana*, and *L. braziliensis*, with selectivity for human THP-1 cells [15,16].

Mechanistically, these extracts disrupt microbial membranes, inhibit bacterial ATPases, and alter redox balance [17]. In the case of leishmaniasis, triterpenes such as maslinic acid trigger mitochondrial dysfunction and programmed cell death [18].

Despite promising *in vitro* results, translating the antimicrobial potential of OLEs into therapies faces significant hurdles. Activity varies considerably with extraction methods, plant material processing, and pathogen strains, hindering direct comparisons and standardized evaluation. Crucially, robust evidence from *in vivo* infection models and clinical trials remains lacking. Thus, current findings primarily justify more rigorous, standardized preclinical and clinical research to determine true therapeutic utility

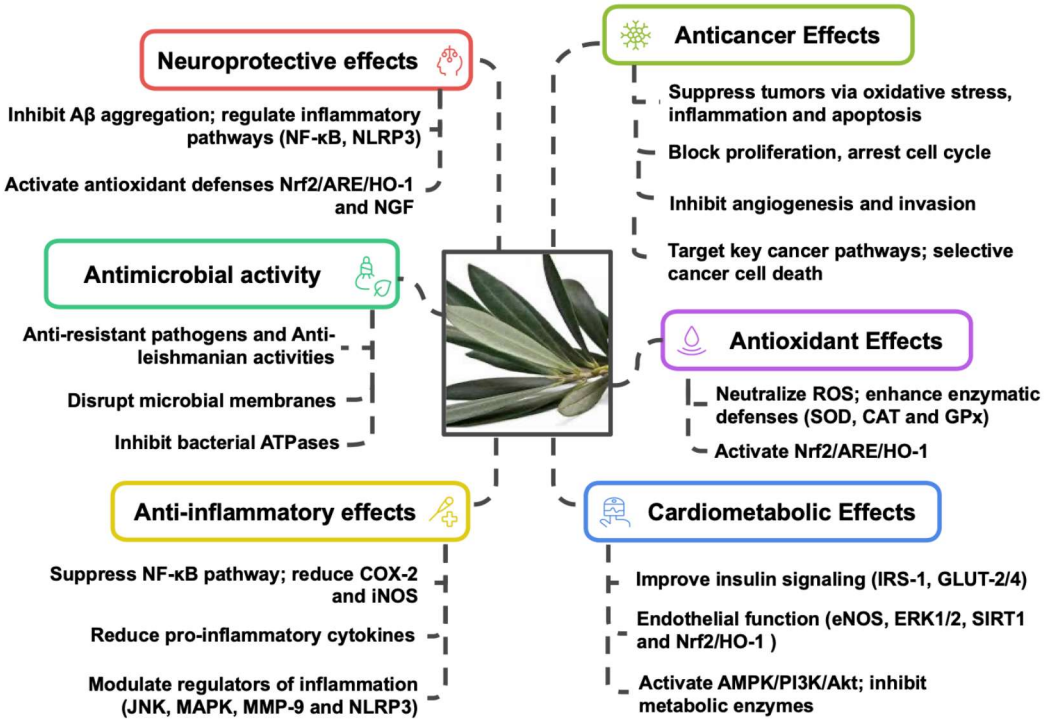

Fig 1. Schematic overview of the key molecular mechanisms and cellular targets modulated by olive leaf bioactives.

The figure summarizes the interconnected pathways underlying their pharmacological effects discussed in this section. Abbreviations: Aβ, β-amyloid; AMPK, AMP-activated protein kinase; ARE, antioxidant response element; ATPase, adenosine triphosphatase; CAT, catalase; COX-2, cyclooxygenase-2; eNOS, endothelial nitric oxide synthase; ERK1/2, extracellular signal-regulated kinases 1 and 2; GLUT, glucose transporter; GPx, glutathione peroxidase; HO-1, heme oxygenase-1; IL, interleukin; iNOS, inducible nitric oxide synthase; IRS-1, insulin receptor substrate 1; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; MMP-9, matrix metalloproteinase-9; NF-κB, nuclear factor kappa B; NGF, nerve growth factor; NLRP3, NOD-like receptor family pyrin domain-containing 3; Nrf2, nuclear factor erythroid 2-related factor 2; PI3K, phosphoinositide 3-kinase; Akt, protein kinase B; ROS, reactive oxygen species; SIRT1, sirtuin 1; SOD, superoxide dismutase; TNF-α, tumor necrosis factor-alpha; VEGF, vascular endothelial growth factor.

Antioxidant and redox-Regulating Mechanisms

Olive leaf polyphenols exhibit potent antioxidant activity *in vitro* and *in vivo*, neutralizing reactive oxygen species (ROS) and enhancing enzymatic defenses (superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx)) [19,20]. In Tunisian Chetoui leaves, antioxidant activity correlates with high oleuropein and flavonoid content, influenced by altitude and agroecological conditions [9]. At the molecular level, these polyphenols activate the nuclear factor erythroid 2-related factor 2 (Nrf2)/antioxidant response element (ARE)/heme oxygenase-1 (HO-1) pathway [1,21], modulating autophagy and oxidative stress responses [22,23].

These effects have been validated *in vivo*. In rats, OLEs enhance hepatic and pancreatic antioxidant defenses, reduce oxidative damage, and preserve β-cell function [20,24]. Collectively, these findings indicate that olive leaf polyphenols orchestrate redox and metabolic signaling networks, thereby enhancing cellular resilience and tissue homeostasis.

Anti-Inflammatory Activity and Immune Modulation

Chronic inflammation is a key driver in the pathogenesis of numerous non-communicable diseases, including cardiovascular, metabolic, and neurodegenerative disorders. OLEs exhibit well-documented anti-inflammatory activity.

Through their potent antioxidant properties, olive leaf compounds suppress the nuclear factor kappa B (NF-κB) pathway, leading to decreased expression of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS), as well as reduced production of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) and prostaglandin E_2 (PGE_2) [20,24]. Oleuropein further interferes with upstream regulators of inflammation, notably by modulating the c-Jun N-terminal kinase (JNK) and p38 mitogen-activated protein kinase (MAPK) pathways, inhibiting matrix metalloproteinase-9 (MMP-9) expression, and downregulating activation of the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome [25]. These combined actions contribute to the attenuation of leukocyte recruitment and tissue damage [26].

Such anti-inflammatory responses have been confirmed across multiple experimental models. *In vitro*, OLEs significantly reduce nitric oxide and cytokine release in lipopolysaccharide-stimulated macrophages [27]. In a murine model of paw edema, a high dose of OLE (150 mg kg^{-1}) reduced swelling by 88%, a result comparable to the effect of the reference anti-inflammatory drug diclofenac (97% reduction) in the same experimental setup [28]. This illustrates the potent anti-inflammatory activity achievable in this model, while the therapeutic dose-response and efficacy in human pathologies require separate clinical investigation.

Cardiometabolic Protection and Endothelial Function

Cardiometabolic disorders, including type 2 diabetes, dyslipidemia, and hypertension, represent a major global health burden. OLEs and their bioactive compounds display remarkable cardiometabolic potential in diverse models.

Regarding glycemic control, oleuropein improves glycemic and antioxidant status in diabetic models [29]. At the cellular level, extracts enhance insulin signaling (IRS-1, GLUT-2/4) and attenuate oxidative stress [30]. In diabetic rats, Chemlali leaf extract improved glucose tolerance and insulin sensitivity via phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) activation [31]. This is complemented by the α-glucosidase inhibitory activity observed in other extracts [32].

Concerning lipid regulation, triterpenoids like oleanolic acid exert vasoactive effects [33], while extracts demonstrate hypolipidemic actions. Studies on the Gerboui variety showed reductions in glucose, total cholesterol, triglycerides, and LDL, with an increase in HDL [34]. These benefits are linked to the inhibition of metabolic enzymes (e.g, HMG-CoA reductase), and PPAR-α modulation [20,31].

A key cardioprotective aspect is the improvement of endothelial function. Hydroxytyrosol exerts multifunctional vascular benefits by enhancing endothelial function via eNOS, AKT, and Nrf2/HO-1 pathways. It reduces oxidative and inflammatory markers, limits foam cell formation, promotes cholesterol efflux, and supports endothelial repair, thereby contributing to atherosclerosis prevention [1,25,35].

In summary, preclinical evidence outlines a compelling multi-target mechanism for cardiometabolic protection, involving insulin sensitization, lipid management, and endothelial improvement. Translational outcomes in humans, while promising, show variability likely influenced by extract composition and dosage, underscoring the need for standardized clinical trials to define therapeutic applications.

Neuroprotective Potential and Mechanistic Insights

Aging and neurodegenerative diseases, including Alzheimer's disease, pose an increasing public health challenge. OLEs display multi-target neuroprotective activity, acting concurrently on multiple pathological pathways [20]. At the molecular level, these compounds inhibit β-amyloid (Aβ) aggregation, reduce neuronal oxidative stress, regulate central inflammatory pathways (NF-κB, NLRP3), activate antioxidant defenses via Nrf2/HO-1, and induce neurotrophins such as nerve growth factor (NGF), promoting neuronal survival and plasticity [36,37].

In vitro studies demonstrate that oleuropein, hydroxytyrosol, and acetylated derivatives prevent amyloid aggregation, protect against hypoxia–reoxygenation-induced injury, and limit hydrogen peroxide-induced apoptosis, while decreasing ROS and modulating neuroinflammation [38]. Pharmacokinetic studies indicate efficient blood–brain barrier penetration for hydroxytyrosol (~70%), and passive diffusion of the more lipophilic oleuropein aglycone, enabling prolonged cerebral distribution [39].

In vivo, OLEs reduce lesion size, improve motor recovery, enhance spatial memory, and attenuate microglial activation and cerebral expression of TNF-α, IL-1β, and COX-2 in murine models of cerebral ischemia and neuroinflammation [40,41]. Furthermore, extracts inhibit acetylcholinesterase activity, supporting hippocampal cholinergic transmission and reinforcing their potential as adjuvants in Alzheimer's disease [37]. The translation of these effects requires caution due to inherent limitations of animal models in mimicking complex human neurodegenerative diseases.

Anticancer Effects and Molecular Mechanisms of Action

OLEs exhibit a broad-spectrum anticancer activity across numerous *in vitro* and *in vivo* models, affecting tumors of the brain, breast, lung, colon, prostate, and blood [2,5,42,43]. This activity stems from the polyphenols' ability to simultaneously modulate interconnected oncogenic processes.

Mechanistically, OLEs and their key constituents (oleuropein, hydroxytyrosol) inhibit cancer cell proliferation by inducing mitochondrial apoptosis (caspase-3/7 activation) and causing cell cycle arrest (G0/G1 or G2/M) [5]. They also restrict tumor progression by suppressing angiogenesis (via VEGF downregulation) and inhibiting invasion (via reduced MMP-2/9 expression) [44]. These effects are mediated through the modulation of central signaling hubs, including the p53, PI3K/Akt, NF-κB, and MAPK pathways [2,45].

A notable feature is their selective cytotoxicity towards malignant cells, sparing healthy counterparts. This selectivity may be attributed to the higher basal oxidative stress and elevated GLUT transporter expression in cancer cells, facilitating the uptake and pro-oxidant action of compounds like oleuropein [45]. Furthermore, OLEs show synergistic potential with conventional chemotherapy, enhancing efficacy while mitigating toxicity in preclinical models [45,46].

These multifaceted preclinical findings highlight a promising anticancer profile. The translational pathway for these effects, including challenges related to bioavailability and the current absence of clinical trial data, is discussed in Section 4.

4. Clinical Relevance and Nutritional Applications of Olive Leaf Extracts

Bioavailability, Metabolic Fate, and Pharmacokinetic Considerations

The bioavailability of the main polyphenols from OLE, particularly oleuropein and its metabolites remains moderate and strongly depends on the administration matrix, formulation, and individual metabolic profile. Following ingestion, hydroxytyrosol is rapidly absorbed and extensively metabolized to glucuronide and sulfate conjugates, reaching peak plasma concentrations (C_{max}) within 1-2 hours and exhibiting a short elimination half-life ($t_{1/2}$) of approximately 2-3 hours in humans [47]. Oleuropein, due to its glycosylated structure, is poorly absorbed intact; it is largely hydrolyzed by intestinal microbiota and esterases to hydroxytyrosol, which then enters systemic circulation [8].

This results in a significantly higher systemic exposure to hydroxytyrosol metabolites than to the parent oleuropein compound. The oral bioavailability of hydroxytyrosol from OLE is estimated to be relatively low (often <10%) but can be enhanced by lipid-based formulations [48]. These pharmacokinetic parameters underpin the rationale for fractionated daily dosing rather than single bolus administration to maintain stable bioactive levels.

Safety Profile, Tolerability, and Toxicological Insights

Preclinical toxicological studies indicate a wide safety margin for OLE, with no acute toxicity observed up to 2000 mg kg^{-1} and no significant hematological or histopathological alterations after 90-day oral administration at 1000 mg kg^{-1} per day in rodents [29]. Specific studies with standardized extracts like Bonolive™ have confirmed the absence of genotoxicity and good tolerance under repeated oral dosing [49].

In human trials, such as a randomized double-blind study (~51 mg oleuropein/day for 12 weeks), no serious adverse effects or significant alterations in standard biochemical markers were reported [50]. The most commonly reported effects are mild and gastrointestinal in nature. However, a critical consideration for clinical use is the potential for OLE-drug interactions. The established antihypertensive and hypoglycemic pharmacodynamic effects of OLEs suggest a possibility of additive effects with prescription antihypertensives (e.g., ACE inhibitors) and antidiabetic drugs (e.g., metformin, insulin), necessitating careful monitoring in patients on such therapies [51]. Furthermore, *in vitro* evidence indicates that olive leaf polyphenols may modulate drug-metabolizing enzymes (e.g., cytochrome P450) and transporters like P-glycoprotein, which could theoretically alter the pharmacokinetics of co-administered drugs [52]. While clinical reports of significant interactions remain scarce, this area requires further systematic investigation to ensure safe integration into therapeutic regimens.

Therapeutic and Clinical Application Potential

The pharmacological versatility of OLEs supports their investigation across a broad spectrum of chronic disorders. Available clinical data, while growing, originate largely from initial pilot studies and trials with modest sample sizes, underscoring the need for larger, confirmatory phase III trials. Table 2 summarizes these applications, the main effects observed, their clinical or preclinical status, and specific trial names or identifiers where available.

Table 2. Potential Clinical Applications of Olive Leaf Extract Across Major Health Domains

Health Area	Effect of Olive Leaf Extract	Clinical Status / Trial Name or ID	References
Cardiovascular	Lowers blood pressure, similar to captopril	RCTs; ongoing Phase 2/3 “Atherolive” (NCT05297110) in Tunisia	[53–55]
Metabolic	Improves glucose tolerance, insulin sensitivity, lipid profiles; supports bone health in postmenopausal women ↑ BMD, ↓ TGs	Pilot clinical studies; ESOLED	[56,57]
Neurological	Stabilizes or improves cognitive scores in mild Alzheimer’s; may reduce risk of Parkinson’s, stroke, depression, epilepsy	Clinical trials (GOLDEN; MICOIL; PREDIMED) and epidemiological studies	[21,58,59]
Oncology	May enhance chemotherapy efficacy and reduce drug-induced toxicity	Preclinical studies	[45]

RCT: Randomized Controlled Trial; BMD: Bone Mineral Density; TGs: Triglycerides

Cardiometabolic Applications: Supplementation with OLEs has demonstrated significant improvements in key cardiovascular parameters. A recent meta-analysis of randomized controlled trials confirmed the blood pressure-lowering efficacy of OLE in adults [53]. This is substantiated by specific clinical trials; for instance, in patients with stage-1 hypertension, OLE supplementation (e.g., 500 mg twice daily) elicited reductions in systolic and diastolic blood pressure (-11.5 ± 8.5 mmHg and -4.8 ± 5.3 mmHg, respectively) comparable to the ACE inhibitor captopril [54]. These findings are further supported by a recent double-blind Tunisian trial in hypertensive patients, which reported clinically relevant reductions in systolic and diastolic pressure [55]. The ongoing Tunisian "Atherolive" trial (NCT05297110) is further assessing this in a larger cohort. For metabolic health, pilot studies like ESOLED report improved glucose tolerance and insulin sensitivity in adults with type 2 diabetes [56]. A randomized trial in postmenopausal women also noted improvements in lipid profiles and bone mineral density, hinting at broader metabolic benefits [57].

Neurological Applications: The most direct clinical evidence in neurology comes from the "GOLDEN" trial in patients with mild Alzheimer's disease (n=55). After six months of supplementation with an OLE rich in oleuropein, participants showed stabilization or a modest mean improvement in cognitive scores (e.g., Mini-Mental State Examination (MMSE)), suggesting a potential for disease course modification [58]. Epidemiological data further associate higher intake of olive polyphenols with reduced risks of stroke, depression, and Parkinson's disease [21,59].

Oncological Potential: To date, the promising anticancer activity remains confined to preclinical models. While studies suggest oleuropein and hydroxytyrosol may potentiate chemotherapy and reduce its toxicity *in vitro* and in animal models [45], no clinical trials have yet been conducted to evaluate the efficacy or safety of OLEs in cancer patients. This represents a critical translational gap.

In summary, the clinical landscape for OLEs is promising but preliminary. Consistent signals in cardiometabolic and, to a lesser extent, cognitive health are evident, yet they require validation in larger, long-term studies. The translation of compelling preclinical anticancer findings into human oncology remains a key future challenge.

Nutritional Perspectives and Functional Food Integration:

Incorporating OLE into functional foods can enhance the health benefits of the Mediterranean diet. Its rich polyphenol content, along with micronutrients such as vitamins E, A, C and minerals including calcium, potassium, magnesium, and zinc, contributes to antioxidant defense and attenuation of chronic inflammation [9,60]. Adding OLE to food matrices—oils, cereals, or beverages—is promising, provided technologies like microencapsulation or lipid dispersion are used to preserve stability and bioactivity [60].

Emerging research highlights interactions with the gut microbiota: polyphenols metabolized into hydroxytyrosol promote beneficial bacterial strains (e.g., Lactobacillus, Bifidobacterium) and strengthen intestinal barrier integrity [61]. These effects may open new preventive strategies against metabolic, inflammatory, and oncological diseases.

5. Conclusion

Olive leaves (*Olea europaea* L.), long regarded as an agricultural by-product, have gained growing recognition as a rich source of bioactive molecules, particularly polyphenols such as oleuropein and hydroxytyrosol. An expanding body of preclinical evidence demonstrates their broad biological potential via the coordinated modulation of oxidative stress, inflammatory cascades, and apoptotic pathways, supporting their investigated roles in cardiometabolic, neurodegenerative, and oncological contexts. However, translating this promise into validated human applications faces defined challenges. The clinical evidence, while encouraging, remains preliminary, limited by small-scale trials, variability in extract composition, and generally moderate bioavailability of key compounds. Furthermore, the potential for herb-drug interactions requires further systematic study.

A strategic roadmap to bridge this translational gap is summarized in Fig. 2. To unlock the full therapeutic potential, future research must prioritize an integrated approach focusing on: (1) the standardization of extracts based on bioactive fingerprints; (2) the execution of large-scale, randomized controlled trials across target indications; (3) the development of advanced delivery systems to enhance bioavailability; and (4) the integration of omics-based approaches for biomarker discovery and personalized interventions.

Ultimately, OLEs exemplify how traditional phytochemicals can bridge nutrition and molecular medicine. Addressing the outlined challenges through rigorous science will be essential to define their specific place in preventive and adjunctive therapeutic strategies, reinforcing the health benefits of the Mediterranean diet paradigm.

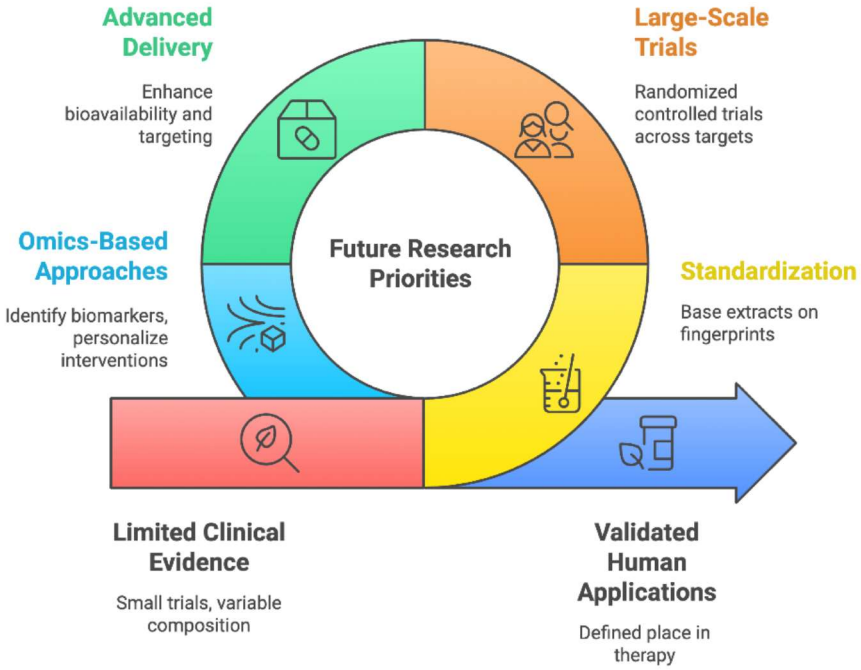

Fig 2. Strategic roadmap for translating olive leaf extract research into validated human applications.
The diagram outlines the key challenges in the current evidence base and prioritizes integrated future research avenues needed to unlock therapeutic potential

Competing Interests

None.

Funding

None.

Conflict of Interest Disclosures

All authors declare that they have no conflict of interest.

Authors' contribution

All authors listed have significantly contributed to the Data collection, development and writing of the review. All

authors have read and approved the final version of the manuscript.

Acknowledgements

AI tool (chatgpt) was used for linguistic correction.

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Cite this article as: Limam I, Abdelkarim M. Olea europaea leaves and human health: From basic research to clinical applications. Biomedicine Healthcare Res. 2026;6:30-39. https://doi.org/10.71599/bhr.v6i1.178