

EXPLORING THE ANTI-ULCER POTENTIAL OF OLEUROPEIN GRANULES FROM WILD OLIVE LEAVES: A PHYTOPHARMACEUTICAL REVIEW

Original Research

Tahmina Maqbool^{1*}, Zufi Shad¹, Abdul Wahab Siddiqui¹, Syed Muzammil Ali¹, Jalal Bin Junaid¹, Ikram-Ul-Hassan¹, Abdul Malik¹

¹Department of Pharmaceutics, Faculty of Pharmacy, Hamdard University Karachi, Pakistan.

Corresponding Author: Department of Pharmaceutics, Faculty of Pharmacy, Hamdard University, Madinat al-Hikmah, Hakim Mohammed Said Road, Karachi, Pakistan,

Tahmina.adnan@hamdard.edu.pk

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ABSTRACT

Background: Gastric ulcers continue to pose a major global health challenge, with millions affected annually. Conventional therapies, such as proton pump inhibitors and antibiotics, though effective, are increasingly limited by adverse effects, drug resistance, and recurrence. Oleuropein, a polyphenolic compound from *Olea europaea* (olive leaves), has attracted attention for its antioxidant and anti-inflammatory actions. Its granule formulation has been proposed to enhance bioavailability, stability, and patient compliance in ulcer prevention and management.

Objective: This review aimed to evaluate the therapeutic efficacy, mechanisms, and safety of oleuropein-based granule formulations in preventing and treating gastric ulcers, and to identify current knowledge gaps for future clinical application.

Methods: A systematic search of Google Scholar identified 50 studies published between 1998 and 2025 using keywords “oleuropein,” “olive leaf,” “granules,” and “ulcer.” Of these, 30 met inclusion criteria focusing on experimental and preclinical models of ethanol-, NSAID-, or acetic acid-induced gastric ulcers. Studies reporting quantifiable data on ulcer index, inflammatory markers (TNF- α , IL-1 β), and antioxidant enzymes (SOD, catalase) were analyzed.

Results: Oleuropein granules significantly reduced ulcer area by 40–70%, decreased gastric acid output, and improved mucus production. Anti-inflammatory effects included a 45–60% reduction in TNF- α and IL-1 β levels, while antioxidant enzyme activity (SOD, catalase) increased by 50–65%. Doses of 300–450 mg/kg produced optimal outcomes. In preclinical comparisons, efficacy was comparable to omeprazole (20 mg/kg). Granule and nanoparticle formulations improved oleuropein stability (up to 99.8% purity) and bioavailability without toxicity.

Conclusion: Oleuropein granules demonstrate strong gastroprotective potential through anti-inflammatory, antioxidant, and mucosal defense-enhancing mechanisms. Their favorable safety profile and natural origin support further exploration as an alternative to conventional ulcer therapies. However, large-scale human trials remain essential to validate efficacy and determine safe, standardized dosing.

Key Words: Antioxidants; Gastroprotection; Gastric Ulcer; Nanoparticles; *Olea europaea*; Oleuropein; Polyphenols.

INTRODUCTION

Gastric ulcers, also referred to as peptic ulcers, remain a prevalent gastrointestinal disorder worldwide, representing a major cause of morbidity and reduced quality of life (1). Characterized by mucosal erosions in the stomach lining, these lesions often manifest through epigastric pain, indigestion, and in severe cases, gastrointestinal bleeding. Untreated or recurrent ulcers can lead to life-threatening complications such as perforation, peritonitis, or even malignant transformation in chronic cases. Conventional therapeutic regimens—including proton pump inhibitors and antibiotics for *Helicobacter pylori*-associated ulcers—have proven effective; however, their prolonged use poses substantial risks. These include dysbiosis, micronutrient malabsorption, increased susceptibility to infections, and the escalating global threat of antibiotic resistance (2-4). Consequently, there is growing clinical interest in exploring natural, plant-derived compounds that offer gastroprotective benefits with minimal adverse effects. Among the promising bioactive agents, oleuropein—a phenolic compound primarily extracted from olive leaves (*Olea europaea*)—has gained significant scientific attention for its potential role in gastric mucosal protection (5,6). Preclinical evidence suggests that oleuropein exerts anti-inflammatory, antioxidant, and cytoprotective actions by modulating gastric acid secretion, suppressing pro-inflammatory cytokines such as TNF- α and IL-1 β , and promoting mucosal healing. Experimental studies report that doses ranging from 300 to 450 mg/kg effectively reduce gastric acidity and ulcer index by 40–70%, underscoring its potential as a natural anti-ulcer agent (7,8). Despite these encouraging outcomes, variability in effective dosing and lack of human trials remain key limitations that hinder its clinical translation.

A major challenge limiting oleuropein's therapeutic application lies in its poor oral bioavailability and low stability under physiological conditions, which reduce its systemic absorption and efficacy (9). To overcome these pharmacokinetic barriers, researchers have explored advanced delivery systems such as granule formulations and chitosan-based nanoencapsulation, both aimed at enhancing its stability, controlled release, and mucosal targeting. Preliminary studies indicate that granule formulations may improve the compound's pharmacodynamic properties and patient compliance, while nanoparticle encapsulation significantly augments its anti-ulcer effects even at reduced doses (10,11). However, comparative analyses of these novel formulations remain limited, and their long-term safety and efficacy in humans have yet to be established. This review systematically compiles and evaluates available literature published between 2004 and 2025 on the gastroprotective potential of oleuropein, particularly in granulated formulations (12,13). It critically examines experimental evidence on its efficacy in preventing or healing acid- and drug-induced ulcers, highlights the current gaps in translational research, and identifies the pharmacological and formulation-related challenges that need to be addressed. The central research question guiding this review is whether oleuropein granules offer a clinically viable, plant-based therapeutic alternative for ulcer prevention and treatment. The objective is to assess existing evidence to rationalize its future development as a safe, effective, and sustainable approach for managing gastric ulcer disease (14).

METHODS

The present review followed a structured methodological framework to ensure a comprehensive and unbiased assessment of the anti-ulcer potential of oleuropein-based granule formulations. A systematic search strategy was implemented using Google Scholar to identify relevant studies published between 1998 and 2025 that investigated the gastroprotective or ulcer-healing effects of oleuropein in granulated form (10). The search employed a combination of specific keywords and Boolean operators, including “oleuropein,” “olive leaf,” “granules,” and “ulcer,” to maximize retrieval of relevant literature. Duplicate entries were removed manually before screening. Titles and abstracts were initially evaluated to determine relevance, and full-text articles were subsequently reviewed to confirm eligibility. Studies were included if they met the following criteria: (1) original investigations employing granule formulations primarily composed of oleuropein derived from *Olea europaea*; (2) experimental models of gastric ulcers—whether chemically induced (e.g., ethanol-, acetic acid-, or NSAID-induced) or clinically studied—designed to assess ulcer formation, prevention, or healing; and (3) measurable outcomes such as ulcer index reduction, histopathological improvement, or biochemical markers including pro-inflammatory cytokines (TNF- α , IL-1 β) and antioxidant enzymes like superoxide dismutase (SOD) and catalase. Both *in vivo* and *in vitro* studies were eligible for inclusion if they presented quantifiable and reproducible results supported by appropriate statistical analyses.

Exclusion criteria included studies lacking original experimental data, such as review articles or conference abstracts; publications not available in English; and investigations that referred broadly to olive extracts or derivatives without specifying the concentration or standardization of oleuropein content. Such exclusions were necessary to ensure consistency and precision in evaluating the compound's isolated therapeutic effects. Data from included studies were extracted systematically, focusing on the formulation type, dosage, model of ulcer induction, biochemical outcomes, and percentage reduction in ulcer area. Where applicable, statistical measures such as mean differences, p-values, and confidence intervals were recorded to assess the reliability of findings. Although the review synthesized secondary data and did not involve direct human or animal experimentation, ethical standards were upheld by adhering to established principles of scientific integrity, proper citation, and data transparency. All included studies were assumed to have obtained prior institutional review board (IRB), as is customary for animal or clinical experimental research. No new ethical approval was required for this review since it relied exclusively on previously published data in the public domain.

RESULTS

1. Oleuropein Granules ability to Heal Ulcers:

Findings from multiple experimental studies demonstrated that granule formulations enriched with oleuropein produced significant gastroprotective and ulcer-healing effects across diverse gastric ulcer models (11). Administration of oleuropein granules in doses ranging from 300 mg/kg to 450 mg/kg consistently reduced ulcer index and mucosal lesions by 40–70%, while improving mucus secretion and reducing gastric acidity (12). When directly compared with omeprazole (20 mg/kg), oleuropein granules (300 mg/kg) achieved a 100% prevention rate of ethanol-induced mucosal damage, indicating a therapeutic equivalence in preclinical rat models (13). Further, the bioefficacy of oleuropein varied according to its botanical origin and extraction process. Studies showed that oleuropein concentration and activity depended on *Olea europaea* genotype, leaf maturity, and environmental factors, all of which affected its stability and antioxidant potency (14). Despite heterogeneity in formulations, all included studies demonstrated consistent mucosal protection, suppression of acid output, and enhanced epithelial recovery. However, no completed human trials were identified, indicating that existing evidence remains confined to preclinical investigations (15).

2. Anti-Inflammatory and Antioxidant Effects:

Oleuropein-enriched granules exhibited robust anti-inflammatory and antioxidant effects that contributed significantly to their gastroprotective efficacy. Experimental studies reported substantial upregulation of endogenous antioxidant enzymes, particularly superoxide dismutase (SOD) and catalase, following oral administration of oleuropein granules (16). These biochemical changes corresponded with a marked decrease in reactive oxygen species (ROS) and lipid peroxidation markers, contributing to a 50–65% improvement in mucosal integrity across different models. Additionally, oleuropein treatment consistently reduced the expression of inflammatory mediators such as TNF- α and IL-1 β by approximately 45–60%, suggesting suppression of cytokine-driven inflammation (17). Chronic administration produced more pronounced effects than short-term dosing, implying that duration of treatment may influence therapeutic efficacy. Comparative evidence from olive-derived compounds, including sodium oleate and oleuropein aglycone, demonstrated similar reductions in TNF- α , IL-6, and IL-1 β , supporting the compound's systemic anti-inflammatory potential (18–20).

3. Benefits of Formulation and Safety Accords:

Oleuropein extraction and stabilization studies revealed environmentally friendly processes using Tween 80 and salting-out methods, achieving up to 99.8% recovery and enhanced thermal stability without compromising antioxidant capacity (21). Oleuropein demonstrated no cytotoxicity toward normal cells and inhibited proliferation in several human cancer cell lines (22). Evidence further supported the compound's safety and additional health benefits, including improved lipid oxidation resistance, bone metabolism enhancement, and cardiovascular protection (23). The compound's stability was identified as a critical determinant of its pharmacological efficacy. Experimental data showed that oleuropein degraded under high pH, elevated temperature, or prolonged storage, generating hydroxytyrosol as a degradation product (24). Formulation strategies such as granulation and encapsulation significantly improved its shelf life and bioavailability, enabling more consistent pharmacodynamic responses. Collectively, the reviewed studies confirmed that oleuropein granules were non-toxic, biocompatible, and safe for long-term therapeutic use in preclinical models.

Table 1: Oleuropein in managing Gastric Ulcer

Study Model	Route of Administration	compound	Outcome	Reference
NSAID-induced ulcers (e.g., indomethacin)	Oral	Ole and Thym	Attenuation of mucosal damage, decreased pro-inflammatory cytokines (TNF- α , IL-1 β)	[15]
Ethanol-induced ulcers	Oral (gavage)	Oleaster leaf extract (OLE) and purified oleuropein (OLR)	Significant reduction in ulcer index, increased antioxidant enzyme levels (SOD, catalase), and reduced lipid peroxidation	[16]
Acetic acid-induced ulcers	Oral	malondialdehyde (MDA), superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX), myeloperoxidase (MPO), and nitric oxide (NO)	Promoted ulcer healing, enhanced mucus production and antioxidant defense	[17]
Stress-induced ulcers (e.g., cold restraint stress)	Oral	Olive leaf extract (OLE) malondialdehyde (MDA)	Reduced gastric lesions, modulated oxidative stress and inflammation	[18]
Anti-inflammatory cyclooxygenase/lipoxygenase inhibitors	Oral	Hydroxytyrosol	Potent anti-oxidant	[19]
Anti-inflammatory, arachidonic acid-dependent inflammatory cascades	Oral	Oleacein	Anti-inflammatory	[20]
Anti-inflammatory and antioxidant effects on healing burn injury	Topical	Caffeic acid	Anti-oxidant and anti-inflammatory	[21]
Anti-inflammatory coupled with their capacity to modulate key cellular functions	In Vitro Application	Luteolin-7-O glucoside	Anti-oxidant	[22].
Antioxidant capacity and inhibition of α -amylase and tyrosinase	In Vitro Application, Oral	Apigenin-O-glucoside	Anti-oxidant	[23]
Antioxidant property treatment of diabetes, cancers and some cardiovascular diseases.	Oral, Topical	Quercitin	Anti-inflammatory	[24]

DISCUSSION

The current findings highlighted the therapeutic potential of oleuropein-based granule formulations in the prevention and management of gastric ulcers, confirming and expanding upon prior preclinical research that has emphasized the compound's potent antioxidant and anti-inflammatory activities (7). Evidence from animal models of ethanol-, acetic acid-, and NSAID-induced ulcers indicated that oleuropein granules exerted dose-dependent effects, with 300–450 mg/kg doses reducing ulcer area by 40–70% and demonstrating comparable efficacy to standard proton pump inhibitors such as omeprazole (11,13). These findings suggested that oleuropein could represent a viable, natural, and safe alternative for managing gastric ulcer disease, particularly in individuals who experience adverse effects from conventional anti-ulcer medications (14). However, translation to clinical practice remains limited due to the absence of human trials and the compound's unfavorable pharmacokinetic characteristics. The primary challenge restricting oleuropein's clinical use lies in its low stability under physiological conditions and poor oral bioavailability (7). These pharmacokinetic limitations hinder systemic absorption and reduce therapeutic efficiency. Advances in formulation science—particularly the use of chitosan-based nanoparticles and salting-out assisted cloud-point extraction methods with Tween 80—have shown significant promise in overcoming these challenges, achieving up to 99.8% purity and improved thermal stability while preserving antioxidant capacity (8,15). Such innovations mark critical progress toward developing pharmaceutically viable oleuropein preparations that maintain bioactivity and achieve effective concentrations at the gastric mucosa. Moreover, standardization of raw material and extraction protocols has emerged as an essential factor in ensuring consistent pharmacological outcomes across experimental studies and manufacturing batches (16).

The strong preclinical evidence for oleuropein's gastroprotective efficacy has yet to be supported by clinical validation. Animal data cannot be directly extrapolated to human physiology due to species differences in metabolism, enzyme systems, and drug absorption pathways (17). The lack of clinical pharmacokinetic data, such as absorption rates, plasma concentration-time profiles, and metabolic fate in humans, represents a significant gap in translational research. Furthermore, long-term toxicity, safety thresholds, and optimal therapeutic doses remain undefined. These limitations must be addressed through controlled human trials to confirm efficacy, safety, and appropriate dosing strategies before oleuropein can be integrated into evidence-based medical practice. Beyond its anti-ulcer potential, oleuropein and its derivatives—including hydroxytyrosol, oleacein, and quercetin—exhibit wide-ranging biological activities relevant to cardiovascular, metabolic, and inflammatory diseases (18-20). These compounds possess synergistic antioxidant and anti-inflammatory effects that may collectively contribute to the observed health benefits of the Mediterranean diet (21). Hydroxytyrosol and oleuropein are full-spectrum active molecules with excellent safety profiles but remain constrained by limited bioavailability and insufficient human clinical evidence (22). Similar limitations have been observed in other therapeutic contexts, such as oleuropein's proposed benefits in osteoarthritis, where promising *in vitro* anti-inflammatory and cartilage-protective effects have yet to be substantiated *in vivo* (23). From a pharmacological perspective, the ability of oleuropein to modulate immune responses has also been explored in autoimmune disorders such as rheumatoid arthritis. Experimental findings suggest that oleuropein may facilitate immune reprogramming by promoting the conversion of CD4⁺ T cells into regulatory T cell lineages, thereby reducing chronic inflammation (24,25). This immunomodulatory property may extend its therapeutic potential beyond gastroenterology into broader inflammatory pathologies. However, most evidence remains preliminary and mechanistic, underscoring the necessity for molecular-level investigations and well-designed clinical trials to delineate these effects in humans.

The safety profile of oleuropein is one of its strongest attributes. Its long-standing presence in the Mediterranean diet and extensive use in animal models have not revealed any significant toxicological concerns (26). Formulations stabilized through advanced extraction and encapsulation methods have demonstrated consistent bioactivity with minimal degradation. Nevertheless, potential instability due to pH variation, temperature, and storage duration requires careful formulation control to preserve pharmacological integrity (27). The pharmaceutical industry thus plays a pivotal role in optimizing oleuropein's delivery systems to enhance stability, absorption, and sustained therapeutic release. Despite its promise, several research gaps persist. While experimental data confirm oleuropein's efficacy in gastric ulcer prevention, antioxidant enhancement, and mucosal healing, its long-term safety, bioavailability in humans, and drug interaction profiles remain undefined. Future studies should focus on multi-phase clinical trials exploring the pharmacokinetics, dose–response relationships, and comparative efficacy of oleuropein granules versus established ulcer therapies. Moreover, investigations into its metabolic pathways and systemic effects will be essential for understanding its broader therapeutic potential. In summary, oleuropein granules represent a scientifically credible and biocompatible natural therapy with strong preclinical backing for anti-ulcer, antioxidant, and anti-inflammatory properties. The strengths of current evidence lie in consistent preclinical efficacy, proven safety, and innovative formulation technologies that enhance stability and purity. However, limitations include the absence of clinical validation, inadequate pharmacokinetic characterization, and variability in oleuropein content among formulations. Advancing this compound from bench to

bedside will depend on rigorous clinical research, optimized delivery systems, and industry collaboration to transform oleuropein's laboratory promise into a clinically established therapy for gastric ulcer management and beyond.

CONCLUSION

In conclusion, the evidence gathered from this review supports oleuropein granules as a promising natural gastroprotective agent with significant anti-inflammatory and antioxidant potential. The compound demonstrated notable efficacy in reducing ulcer severity and enhancing mucosal defense in preclinical settings, suggesting its possible therapeutic role in gastric ulcer management. However, translating these findings into clinical practice requires well-designed human trials to confirm its safety, determine optimal dosing, and validate its long-term benefits. The integration of oleuropein into clinical use could provide a safer, plant-based alternative to conventional ulcer therapies, aligning with the growing demand for natural, effective, and well-tolerated treatments in modern medicine.

AUTHOR CONTRIBUTION

Author	Contribution
Tahmina Maqbool*	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Zufi Shad	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Abdul Wahab Siddiqui	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Syed Muzammil Ali	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Jalal Bin Junaid	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Ikram-Ul-Hassan	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published
Abdul Malik	Contributed to study concept and Data collection Has given Final Approval of the version to be published

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