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Review Article

PHARMACOLOGICAL SIGNIFICANCE AND TOXICITY OVERVIEW OF OLEANOLIC ACID ISOLATED FROM *LANTANA CAMARA* ROOTS

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ABSTRACT

Preclinical Evidence on Oleanolic Acid from Lantana camara

Several therapeutic plants contain oleanolic acid (OA), a pentacyclic triterpenoid. Its drugs protect the liver, reduce inflammation, prevent diabetes, and fight cancer. *Lantana camara* roots are rich in OA, making them a promising medicine source. From 2000 to Up to present mid-2024, this study includes all published research on *L. camara* root OA, including phytochemical composition, pharmacological activity, toxicological evaluations, and mutagenicity assessments. We aggregated PubMed, Scopus, ScienceDirect, and Google Scholar data to find therapeutic relevance and safety margins. We thoroughly searched databases using relevant keywords. OA modulates oxidative stress pathways and detoxifying enzymes to protect the liver, and sub-chronic and acute toxicity studies in Wistar rats showed no mortality or adverse histopathological changes up to 2000 mg/kg. Ames tests showed its non-mutagenicity. However, insufficient clinical and chronic exposure investigations, poor water solubility, and bioavailability hinder translational applicability. The review finds that *L. camara* OA has promising lead phytotherapeutic potential, but more *in vivo* investigations and formulation improvements are needed to prove its efficacy and safety.

Keywords: Oleanolic acid, *Lantana camara*, Pentacyclic triterpenoid, Pharmacology, Toxicity, Mutagenicity.

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INTRODUCTION

Plant-based compounds have inspired or originated roughly 60% of clinically utilized medicines. Triterpenoids (triterpenes) [1-3], a structurally diverse family of secondary metabolites, have several therapeutic effects [4]. Their anti-inflammatory [5], anticancer, antiviral, hepatoprotective [6] antitumor-promotion effect [7], and antidiabetic [8] properties have been extensively studied [9-11]. This stresses the importance of cautious and informed medical use and their significant therapeutic potential.

Oleanolic acid (OA), a pentacyclic triterpenoid, has several therapeutic uses and is found in various plants. Fruit and leaf waxes include it to protect plants from dangerous microorganisms and other environmental pressures [12]. Over the past 30 years, OA has gained popularity because to its wide plant source availability, low toxicity, and broad therapeutic range [13-15].

A widely widespread tropical and subtropical plant, *Lantana camara* L. [16] (family: Verbenaceae) (Fig. 1), has been intensively investigated and remains a pharmacologically promising source. Ethnomedicine has utilized *L. camara* parts to treat wounds (wound healing) [17,18], fever, asthma, and gastrointestinal issues [19]. The roots of *L. camara* are rich in pentacyclic triterpenoids (Fig. 2), including OA, a significant bioactive [20-23] ingredient discovered by chromatographic and spectroscopic techniques [24,25]. Even though *L. camara* has many traditional medical uses; its leaves can be poisonous [26-29] to grazing animals and cause hepatotoxicity [30,31]. Due to its dual nature, long-term toxicity studies, bioavailability assessments, and safety evaluations [32] are needed to distinguish the toxicity of the crude plant from that of its isolated constituents, particularly OA [33,34].

When determining if bioactive substances [35] are safe to use, toxicological studies are crucial. Research on the oral toxicity of both single and multiple doses in rats is necessary to develop [36]. No-Observed-Adverse-Effect Levels (NOAELs) and Maximum Tolerated Doses (MTDs), as per OECD recommendations [37]. Investigations into the long-term exposure of OA extracted [38] from *L. camara* roots have revealed that acute and sub-chronic toxicity studies in Wistar rats resulted in no mortality at doses up to 2000 mg/kg in a single administration, suggesting a wide safety margin[39,40]. Furthermore, sub-chronic exploratory studies showed safety at doses of 1000 mg/kg body weight, with hematological and biochemical parameters remaining within normal ranges. Histopathological examinations of vital organs, such as the liver, kidneys, and spleen revealed no treatment-related abnormalities or adverse changes.

In addition to systemic toxicity, the mutagenic potential of new therapeutic candidates must also be thoroughly assessed. Genotoxic and mutagenic compounds pose a potential risk of mutagenic compound, or heritable genetic damage [41]. For assessing mutagenicity, the Ames test, which uses TA98 and TA100, two strains of *Salmonella* typhimurium that are histidine-dependent, is still considered the gold standard [42]. S9 metabolic activity or not, the Ames test on *L. camara* root OA did not show a statistically significant increase in revertant colonies. Thus, OA is non-mutagenic under test circumstances [43]. These findings support research showing that triterpenoids, including OA, are seldom genotoxic or mutagenic.

OA has been extensively researched in chemically induced liver damage [45] models for its hepatoprotective effects [44]. Its therapeutic effectiveness comes from modulating oxidative stress, detoxifying enzymes, and pro-inflammatory signaling pathways. Recently, OA has been shown to induce apoptosis, prevent metastasis, and decrease angiogenesis in numerous cancer cell lines [46]. OA has been approved

Fig. 1: *Lantana camara* plant

Fig. 2: Roots of *Lantana camara*

in China as an over-the-counter oral liver problem therapy for over two decades, proving its therapeutic relevance and safety.

OA drug development confronts several obstacles despite its medicinal potential [47-50]. No long-term exposure, pharmacokinetic data, limited water solubility, or oral bioavailability hinder clinical translation. Overcoming these limits requires pharmacological, biochemical, toxicological, formulation [51], and bioavailability investigations.

The efficient extraction of OA from *L. camara* roots makes this neglected botanical source useful. Systematic toxicological and pharmacological studies of OA can elucidate *L. camara*'s toxicity and its phytoconstituents' safety. This study wants all phytochemical [52], pharmacological [53], and toxicological data [54,55] on *L. camara* foliage-extracted OA. This paper evaluates scientific facts, stresses OA's therapeutic potential, safety profile, information gaps, and future research to establish it as a safe and effective lead chemical for drug discovery and development.

METHODS

The literature was evaluated using Google Scholar, Scopus, and PubMed. The search terms were "oleanolic acid," "*Lantana camara*," "pentacyclic triterpenoid," "toxicity," and "pharmacology." The study examined the medicinal, pharmacological, and toxicological effects of OA, primarily from *L. camara* roots.

The phytochemical composition, biological activity [56], and safety of OA, along with the Comparative Toxicological Profile: *L. camara* (whole plant) vs. OA were summarized from peer-reviewed studies and reports. Comparative evaluation of OA: Potency, Pharmacological Efficacy, and Inter-Study Variability Across Experimental Models were done summarized from peer-reviewed studies and reports. We discussed study gaps, future directions, and *L. camara*'s ecological value as a natural OA source based on the data.

Traditional uses

L. camara is traditionally used as a decorative plant, while it is also known as an invasive [57] plant in many tropical and invasive in many tropical/subtropical regions [58-60] it forms dense thickets that displace native flora and alters ecosystem. A wholesome work is done in India on the extract of plants and roots, leaves are used as an antimicrobial [61-64], nematicidal. Oil is used as a wound healing activity. The plant is used to cure a lot of respiratory order. The fruits are used in rheumatism, fistula, tumours, and pustules. The roots are used in rheumatism, malarial [65-70]

Phytochemistry of OA

A pentacyclic triterpenoid (3β-hydroxyolean-12-en-28-oic acid) called oleanolic acid (OA) (Fig. 3) is a member of the oleanane class of secondary metabolites [71]. It possesses a hydroxyl group at C-3 and a carboxylic group at C-28, which contribute to its amphiphilic and bioactive nature [72,73]. OA is widely distributed in plants, such as olive (*Olea europaea*), ginseng (*Panax ginseng*), apples, plums, and the roots [41,42] of *L. camara*, which serve as a major source for extraction. Traditional medicine considers OA hepatoprotective and anti-inflammatory. Ethanol or methanol extraction and chromatographic purification are normal for *L. camara* roots [74,75]. Advanced methods include ultrasound-assisted and supercritical carbon dioxide extraction yield more and are more environmentally friendly. Fourier transform infrared (FTIR), mass spectrometry (MS), and nuclear magnetic resonance (NMR) verify structural purity, whereas high-performance liquid chromatography (HPLC) and gas chromatography–mass spectrometry (GC-MS) quantify it. OA biosynthesis involves the mevalonate (MVA) route, including acetyl-CoA, squalene, and β-amyrin intermediates catalyzed by cytochrome P450 oxidases. Reported yields of 0.5–1.2% in *L. camara* roots suggest its potential as a renewable pharmaceutical and phytochemical source [76].

Natural occurrence

OA occurs extensively in higher plants, including fruits, vegetables, and medicinal herbs. High amounts are present in olive leaves (*O. europaea*), ginseng (*P. ginseng*), apples, and plums [19]. In ethnomedicine, OA is usually linked to hepatoprotective and anti-inflammatory activities in Indian and traditional Chinese medicine systems [76-78]. The *L. camara* roots have been found to be a rich and renewable source of OA, and hence they can be considered viable raw material for industrial extraction [79].

Extraction methods

The extraction of OA from *L. camara* roots and other plants typically involves solvent extraction techniques. The process typically begins with an active extraction using methanol or ethanol and continues with partitioning using increasingly polar solvents commonly employed in chromatography, such as hexane and ethyl acetate or dichloromethane and methanol. After drying, the root is crushed into a powder. The triturated material is mixed with a solvent in a 1:5 or 1:10 ratio (Fig. 4), which undergoes a solid extraction process using a reflux apparatus for 4–6 h at a moderate temperature of 50–60°C. After extraction, the mixture is filtered to remove solid residues or dirt. Then, under reduced pressure, the solvent is evaporated using a rotary evaporator, leaving behind a crude extract. This raw extract is then purified using column chromatography, with silica gel as the stationary phase. A solvent gradient, with hexane and ethyl acetate or dichloromethane and methanol, is employed to differentially separate OA from the other substances. Subsequent evaporation produces a final formulation

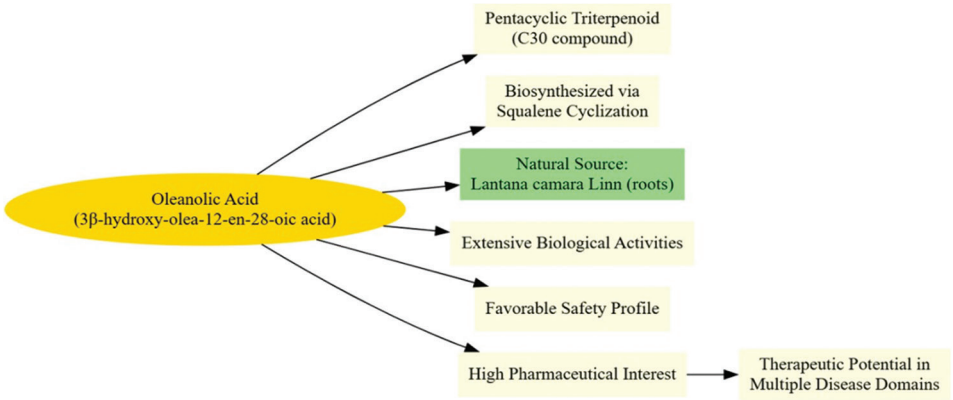

Fig. 3: Overview of oleanolicacid: Structure, origin and pharmaceutical significance

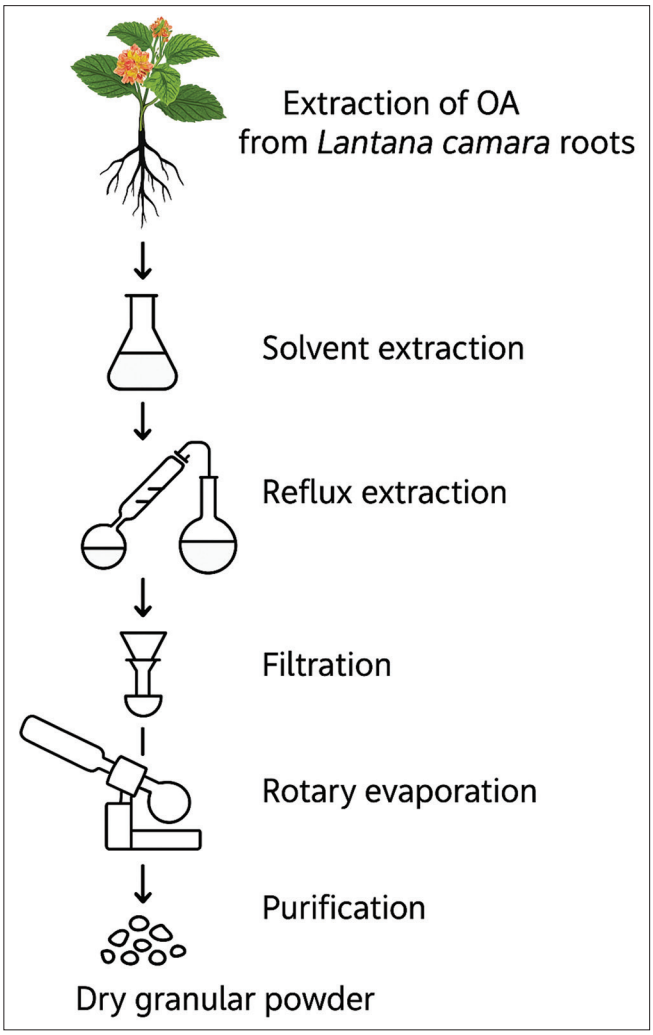

Fig. 4: Extraction process of oleanolic acid

of dry granular powder [80]. Better yields and less environmentally harmful chemistry are the results of these and other documented approaches, such as ultrasonic-assisted extraction and supercritical CO_2 extraction [81]. Recent research on *L. camara* roots identified ethanolic extraction with subsequent chromatographic fractionation to give a purified OA fraction, as identified by analytical characterization [82,83]. Efficiency of extraction varies with solvent polarity, part of the plant, and condition of drying.

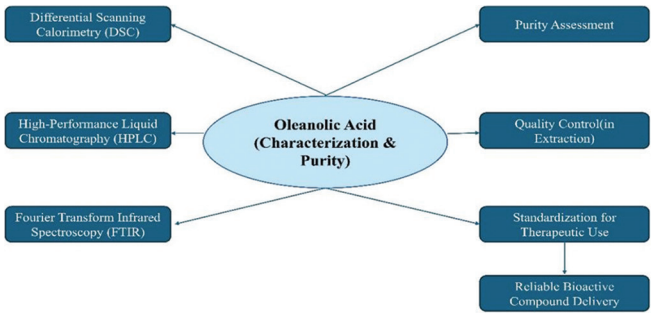

Fig. 5: Analytical characterization of oleanolic acid

Isolation and purification

Isolating OA is accomplished via column chromatography, which uses silica gel, or high-performance liquid chromatography, which uses HPLC. The use of crystallization methods allows for the last stage of purification.

Structural purity is critical since triterpenoids are usually found in association with ursolic acid, which shares similar pharmacological activity [84]. Today, cutting-edge analytical characterization techniques, including differential scanning calorimetry, HPLC [85,86] (Fig. 5), and FTIR spectroscopy allow for the precise identification and determination of OA's purity. These innovations improve extraction quality control and therapeutic preparation standardization, ensuring bioactive constituent delivery [87-95].

Analytical characterization

Several powerful analytical tools verify OA's authenticity and purity:

- Fourier transform infrared spectroscopy can identify functional groups, such as hydroxyl (-OH) and carboxyl (-COOH) vibrations
- MS determines molecular weight (m/z = 456 for OA)
- NMR (^{1}H-NMR, ^{13}C-NMR) reveals OA structure. Quantitative plant extract analysis uses HPLC and GC-MS.

Biosynthetic pathway

Plants produce OA from MVA (Fig. 6). The process begins with acetyl-CoA and continues to squalene and β-amyrin. Oxidative alteration of β-amyrin leads to OA. These procedures need cytochrome P450 oxidases. The routes allow metabolic engineering in microbial OA production. OA levels vary by species and plant component, such as olive leaves (0.2–0.6% dry weight) and apple peels (0.4%). The yield of *L. camara* roots varies from ~0.5% to 1.7% dry weight, depending on extraction conditions [96,97].

Genetic and biotechnological developments

Recent molecular biology research has characterized key genes for β-amyrin synthase and some CYP450 enzymes responsible for OA

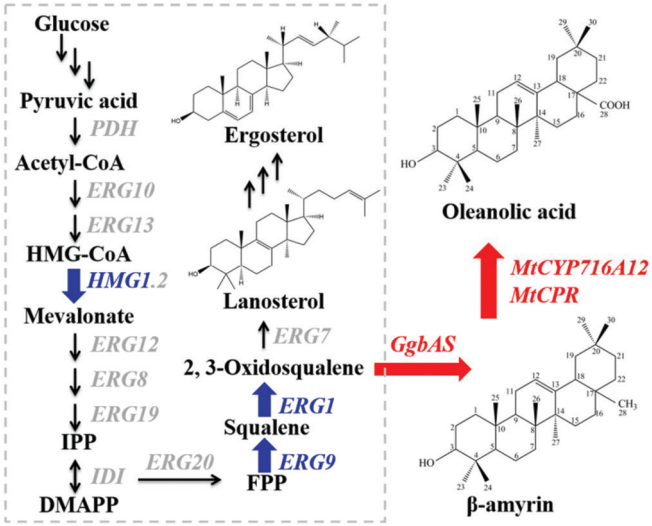

Fig. 6: Mevalonate pathway

biosynthesis. Gene engineering of these genes into microbial systems, such as Saccharomyces cerevisiae and Yarrowia lipolytica, has made it possible to produce OA within these organisms [98,99]. These findings demonstrate the potential of synthetic biology in the large-scale production of OA without recourse to plant extraction.

Ecological and plant defense functions

OA is a phytoalexin that assists plants in defending themselves against infection by pathogens [100,101], insects, and other forms of environmental stress. Its amphiphilic configuration destabilizes microbial membranes, leading to antifungal [102-105] and antibacterial resistance. This ecological function explains its ubiquity within different plant families.

Pharmacological and therapeutic potential of OA

The antioxidant, anti-inflammatory, hepatoprotective, antidiabetic, antibacterial, and anticancer [106,107] effects of OA are the main reasons for its broad pharmacological range. Its potency and efficacy vary with species, cell type, dose, and administration route. *In vitro* studies [108] often show stronger effects than *in vivo*, and differences in extraction, purity, and protocols contribute to inter-study variability. Overall, OA demonstrates consistent beneficial effects, but their magnitude is study-dependent, highlighting the need for standardized models and dosing.

The chemical modulates nuclear factor-kappa B (NF-κB), nuclear factor erythroid 2-related factor 2 (Nrf2), and mitogen-activated protein kinase pathways, suppressing pro-inflammatory cytokines and enhancing cellular defense against oxidative stress. OA improves antioxidant enzyme [109] activity and lowers lipid peroxidation in chemically induced liver damage models, protecting the liver. In tumor cell lines, it activates caspase-3, inhibits metastasis, and stops angiogenesis. OA reduces blood glucose and enhances insulin sensitivity by modulating peroxisome proliferator-activated receptor gamma and metabolic enzymes, demonstrating antidiabetic effects. OA protects the heart and kidneys from oxidative and chemical damage. Multi-target activity and low toxicity make the molecule a promising phytopharmaceutical, but poor solubility and bioavailability hinder clinical translation. OA has significantly advanced over the past half a decade. Synthetic OA derivatives, such as bardoxolone methyl (CDDO-Me/RTA-402) also succeeded in reaching through large clinical programs of Phase-III trials, indicating a marked progress in translational interest, indicating safety/tolerability lessons from earlier studies (link to the survey: https://clinicaltrials.gov/study/NCT03918447); however, failed to proceed due to adverse cardiovascular outcomes. More recently done medicinal chemistry and SAR studies have produced numerous OA derivatives and analogs with improved potency and drug-like properties. Several up-to-date scholarly articles have summarized these structure activity developments [110,111]. A significant thrust has been formulation science, lipid-based nanoparticles, nanosuspensions, peptide-assisted carriers and other nanoformulations have been developed to overcome OA's poor solubility and low oral bioavailability [112,113], with pre-clinical studies and formulation reviews reporting improved pharmacokinetics and enhanced *in vivo* efficacy.Early human pharmacokinetic and bioavailability data are now appearing (for example, the BIO-OLTRAD human study). OA is already described in the Chinese pharmacopeia/regulatory context as a liver-protective agent, illustrating both clinical testing and regional therapeutic use [114,115].

OA consistently shows strong pharmacological activity across anti-inflammatory, antioxidant, and other experimental models, though reported potency varies due to differences in extraction, purity, and study design. Despite this inter-study variability, its overall efficacy remains well supported, highlighting the need for more standardized protocols (Table 1).

Toxicological evaluation of OA

Acute toxicity

The toxicological safety of OA for therapeutic application is crucial. Oral toxic studies upon oral administration to rat models have confirmed that no mortality or behavioral issues appear, indicating a significant safety margin. Further validation came upon hematological [122] biochemical and organ-weight evaluations, which did not display any signs of changes even after 90 days of the OA administration in half dosages. Histopathology demonstrated standard vital organ architecture, ruling out systemic toxicity in the heart, liver, kidneys, and spleen.

An evaluation has also been made from the literature about *S.* Typhimurium strains TA98 and TA100 with and without S9 metabolic activation. Revertant colonies did not increase at any dose in this experiment, indicating OA is not mutagenic. These results are consistent with previous findings on pentacyclic triterpenoids, which generally exhibit low genotoxic potential. Overall, available evidence demonstrates that OA might possess a favorable toxicological and genetic-safety profile at an acceptable level, supporting its development as a safe phytochemical for long-term pharmacological and nutraceutical applications.

However, a broader reading of recent (2022–2025) literature reveals both supporting and contradictory toxicology signals that must be acknowledged. Multiple genotoxicity and mutagenicity-based studies report no clear mutagenic potential for OA in standard bacterial assays (TA98/TA100 ± S9) and conclude low genotoxic risk for isolated OA preparations [123].

Several well-conducted pre-clinical reports and reviews find minimal acute/sub-chronic toxicity at typical pharmacological doses and even at relatively high single doses in rodents, supporting a wide therapeutic index in short-term studies [124]. At the same time, multiple studies also document dose- and duration-dependent hepatotoxicity/cholestasis in rodents after repeated high-dose OA exposure, with FXR/BSEP-related bile-acid handling implicated as a mechanistic mediator, i.e., low doses are often hepatoprotective while long-term or very high dosing can impair bile acid transport and produce cholestatic injury [125]. Species, formulation, and route greatly modify outcomes. Targeted delivery and inhalation studies report favorable acute safety profiles for lung delivery in rats, while dietary or chronic oral exposures show more variable results across species (rodent vs. livestock/poultry models [126,127]. Nanoparticle or derivatization strategies that increase OA systemic exposure improve pharmacodynamics, but can also alter the toxicology profile, so formulation-driven pharmacokinetic changes must be accompanied by repeat-dose and chronic toxicology (including liver/biliary endpoints)

Table 1: Comparative evaluation of oleanolic acid: Potency, pharmacological efficacy, and inter-study variability across experimental models [116-121]

S. No.	Effect area	Model	Dose/Potency	Main outcome	Consistency across studies	References
1.	Hepatotoxicity (high dose only)	Mice	300–500 mg/kg	Cholestatic injury, ↑ bile acids	Seen only at very high doses	Lu *et al*. (2013)
2.	Hepatoprotective effect	CCl_4, APAP, α-amanitin models	25–100 mg/kg	Strong liver protection	Highly consistent across toxins	Feng *et al*. (2020)
3.	Anti-inflammatory effect	LPS-stimulated macrophages	1–20 μM	↓ TNF-α, IL-6, NO	Moderate variability by cell type	Iqbal *et al*. (2023)
4.	Anti-diabetic activity	STZ-diabetic rats	20–50 mg/kg	↓ Glucose, ↑ insulin sensitivity	Mild to moderate variability	Fan *et al*. (2015)
5.	Anti-oxidant/metal toxicity protection	$HgCl_2$ injury model	25–100 mg/kg	↓ Oxidative stress	Limited but consistent evidence	Martín *et al*. (2007)
6.	Cholestasis protection	Bile-duct ligated rats	100 mg/kg	↓ Bile acids, ↓ inflammation	Strong consistency	Alqahtani *et al*. (2013)
7.	Anti-cancer activity	Cancer cell lines	5–50 μM	Anti-proliferative, apoptosis	High variability across cell types	Ouyang *et al*. (2022)

Keys:↑: Increase , ↓: Decrease. CCl_4: Carbon tetrachloride, TNF-α: Tumor necrosis factor-alpha, IL-6: Interleukin-6, NO: Nitric oxide, STZ: Streptozotocin, APAP: Acetaminophen/Paracetamol, LPS: Lipopolysaccharide

rather than PD-only cases [128,129]. Translational caution is supported by clinical-stage lessons from related oleanane triterpenoid programs (e.g., bardoxolone methyl), where large trials revealed unexpected cardiovascular safety signals emphasizing the need for rigorous human pharmacokinetics, thorough dose-finding, and targeted organ safety monitoring in any OA development program [130].

Sub-acute/sub-chronic toxicity

Repeated-dose studies with OA and related pentacyclic triterpenoids generally show low toxicity at therapeutic doses. Some studies report mild, reversible changes only at high doses. Ninety-day studies on related triterpenes (e.g., UA) suggest acceptable safety but emphasize the need for long-term studies specifically on OA. No treatment-related side effects were seen at limited dosages up to a certain level in the *L. camara* OA research. Thissupports a favorable NOAEL region for short-term use. However, long-term studies (chronic, reproductive, and developmental) remain limited. While some limited data are available on the study of *L. camara* on Rat fertility [131].

L. camara is known to be toxic due to lantadenes that cause hepatotoxicity and photosensitization, leading to illness and mortality in animals. In contrast, isolated OA shows a much safer profile, with studies reporting low acute toxicity, hepatoprotective effects, and no mutagenicity. Thus, the plant's toxicity is linked to lantadenes, while OA itself is considered non-toxicunder typical pre-clinical conditions (Table 2).

Mutagenicity and genotoxicity

Ames test and bacterial reverse mutation assay

Analyzing bacterial ames testing and reverse mutation, one of the most used methods for determining mutagenicity is the Ames test, which is also known as the bacterial reverse mutation assay. *S.* Typhimurium strains TA98, TA100, TA102, TA1535, and TA1537, as well as metabolic activation (S9), are utilized as needed. No mutagenic effects were seen in any of the strains tested for by OA. It failed to elicit point mutations regardless of the dosage studied and regardless of the presence or absence of metabolic activity. Therefore, it was determined that OA was non-mutagenic up to 5000 μg/plate based on the circumstances of this investigation.

Evidence for OA

Multiple studies indicate OA and many oleanane triterpenoids exhibit low or no mutagenic potential in the Ames assay and related genotoxicity screens. Specifically, OA isolated from *L. camara* roots was non-mutagenic across standard Salmonella strains (including tests with S9 activation) in the author's characterization/mutagenicity study

Interpretation and limitations

While negative Ames results reduce concern for direct bacterial mutagenicity, they do not exclude other genotoxic mechanisms (chromosomal aberrations, *in vivo* genotoxicity); therefore, a battery of genotoxicity tests (*in vitro* mammalian cell genotoxicity and *in vivo* tests) is recommended for regulatory completeness facilitate better interpretation of results and establish appropriate safety margins. Evidence from pharmacology and toxicology suggests that OA is a promising therapeutic candidate with broad bioactivity and a favorable short-term safety profile. The OA isolated from *L. camara* roots, characterized chemically and shown to be non-mutagenic in Ames' testing, strengthens confidence for further development. Nevertheless, essential data gaps persist: (1) Chronic toxicity and carcinogenicity studies; (2) Reproductive and developmental toxicity; (3) Robust ADME/PK and human safety data; and (4) Improved formulations to overcome OA's bioavailability limitations. Clinical translation under GLP necessitates resolving these gaps, notably long-term safety and human research. Pharmacology and toxicology show OA has extensive bioactivity and short-term safety. *L. camara* root OA was chemically identified and non-mutagenic in Ames experiments, improving study confidence. OA's bioavailability issues need novel formulations, chronic toxicity and carcinogenicity studies, reproductive and developmental toxicity, ADME/PK, and human safety data. GLP clinical translation must address long-term safety and human research limitations. We would also like to highlight that the purification studies of OA from *L. camara* are scarce in number, due to which the topic is not covered in depth within this review. Due to this limitation, no chronic (>6 months), reproductive, or carcinogenicity studies are covered in depth, and future studies should focus on this topic.

DISCUSSION AND FUTURE PROSPECTS

L. camara roots are a practical OA source because the plant is widespread, low-cost, and often removed as invasive biomass, and metabolomic analyses confirm OA among its abundant triterpenoids, making root valorization an attractive, sustainable feedstock for local extraction/lead-finding [141,142]. Without any doubt, olive-leaf/pomace and apple-peel supply chains are already industrialized, better standardized (and nutraceuticals exploited), and have clearer GRAS/nutritional pathways for near-term commercialization; however, all sources share the same translational constraints of low oral bioavailability and variable yields unless paired with improved formulation or derivatization [143]. OA is a potential treatment due to its efficacy and safety. Its anticancer [144], antioxidant, anti-inflammatory, antimicrobial, and hepatoprotective properties

Table 2: Comparative toxicological profile: *L. camara* vs. Oleanolic acid [132-140]

Parameter	*L. camara* (Whole plant/ crude extract)	Oleanolic acid (isolated compound)	Key references
Primary toxic constituents	Lantadene A, Lantadene B (pentacyclic triterpenoids known for hepatotoxicity)	No known hepatotoxic constituents; shows hepatoprotective properties	Seawright and Hrdlicka (1977)
Toxicological profile	Highly toxic; induces cholestatic hepatotoxicity, photosensitization, GI disturbances, and mortality in livestock and rodents	Low toxicity; high LD_{50} (>5 g/kg in rodents); protective against CCl_4- and paracetamol-induced liver injury	Chen *et al*. (2015)
Mechanism of toxicity/safety	Lantadenes inhibit bile flow, cause hepatocellular necrosis, and oxidative stress	OA enhances antioxidant defenses, stabilizes liver membranes, and reduces oxidative stress	Kaya *et al*. (2010); Santos *et al*. (2012)
Dose range associated with toxicity/safety	Toxicity observed at 50–200 mg/kg of lantadenes in animal models	OA shows no significant toxicity up to 2,000–5,000 mg/kg oral dosing	Ghisalberti (2000); Nyarko and Addy (1990)
Pharmacological relevance	Limited due to toxicity; crude plant preparations are unsafe	Broad pharmacological actions: Anti-inflammatory, hepatoprotective, antidiabetic, anticancer	Pollier and Goossens (2012); Huang *et al*. (2006)
Outcome in pre-clinical models	Liver damage, increased ALT/AST, jaundice, and mortality	Reduction in ALT/AST, improved histopathology, and strong protective effects	Liu *et al*. (1995); Zhang *et al*., (2011)
Safety recommendation	Not recommended for therapeutic use due to unstable and toxic profile	Considered safe; widely explored as a lead compound in drug development	ESCOP Monographs; WHO phytochemical safety review

L. camara: *Lantana camara*, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, WHO: World Health Organization, CCl_4: Carbon tetrachloride, GI: Gastrointestinal, LD_{50}: Lethal dose 50%

result from NF-κB and Nrf2 pathway modulation. Several recent studies and reviews temper enthusiasm and point to clear limitations that must be acknowledged. Quantitative pharmacokinetic work in rodents and recent reviews report very low oral bioavailability (for example, measured oral bioavailability as low as ~0.7% in rat studies), which helps explain inconsistent efficacy between models and motivates formulation research; thus, its clinical use is hindered. Human pharmacokinetic data are still sparse, and the controlled BIO-OLTRAD study (single-dose PK in healthy volunteers) illustrates detectable systemic exposure after an oral/food formulation but emphasizes that human exposure data remains limited and variable, so direct translation of many animal dosing regimens is uncertain. Several recent pre-clinical reports also document variable or absent effects at commonly used 'reasonable' doses in animal models or agricultural studies (for example, dietary OA showed limited impact on growth/performance end points in broiler studies and mixed results across other species), indicating that efficacy is not universal and depends strongly on dose, formulation, and model. Some studies flag safety and dose-related concerns (including cholestasis or liver index changes at high or long-term dosing in animals and the well-documented safety lessons from related synthetic oleanane triterpenoids), underscoring that "safe" in pre-clinical short-term studies does not guarantee safety in chronic human use [145]. Because of these contradictions, a major recent thrust in the literature has been on delivery and formulation strategies (nanoparticles, peptide carriers, lipid formulations, and other approaches) that demonstrably increase systemic exposure and tissue delivery in pre-clinical work, but these improved PK/PD profiles still require careful dose-finding and long-term toxicology before clinical claims can be solidified.

A focused comparison with structurally related pentacyclic triterpenoids (most commonly UA, but also betulinic and other lupane-type triterpenes) clarifies both shared opportunities and important differences [146]- OA and UA are constitutional isomers with highly similar pharmacology, both modulate NF-κB, Nrf2, and other redox/inflammatory nodes, and show overlapping therapeutic activities in pre-clinical work. But recent comparative scholarly articles emphasize that outcome, potency, and translational readiness differ by molecule, preparation, and indication [147,148]. Mechanistic and *in vivo* data indicate areas where UA currently has stronger or more consistent evidence. Several recent animal studies (and a 2023 gut-microbiome/metabolomics mouse study) identify UA as having reproducible anti-obesity and metabolic effects (reduced adiposity, improved insulin sensitivity, altered gut microbiota) that are less consistently reported for OA under comparable models and doses [149,150]. OA retains a comparative clinical advantage in hepatoprotection because of its long history of human use and productization in China and the emergence of human pharmacokinetics data, which provide at least preliminary human exposure and regulatory context that UA lacks at the same level. A major unifying limitation for both OA and UA is pharmacokinetics. Pharmacokinetics studies have shown low oral bioavailability for both triterpenoids in standard formulations (OA reported as low as ~0.7% in rodent work), which helps explain discordant preclinical results and argues that apparent inter-molecule differences sometimes reflect delivery/pharmacokinetics rather than intrinsic potency. Accordingly, 2022 to 2024 medicinal-chemistry and formulation studies have emphasized three parallel routes to translation: (1) Structural derivatization to improve potency and drug-like properties, (2) Nano/lipid/solubilizing delivery systems to raise systemic and tissue exposure, and (3) Head-to-head preclinical comparisons using standardized PK-matched dosing. Continuous efforts are still active with programs for both OA and UA derivatives and multiple nanoformulation approaches that improve exposure and PD readouts *in vivo*, but none yet provide definitive evidence that improved exposure uniformly translates to safe, reproducible clinical benefit. These comparative data between OA and UA suggests three practical recommendations for the field, (i) Where possible, perform head-to-head preclinical studies that match systemic exposure (dosing) when comparing to each other or other triterpenoids, (ii) Prioritize derivatization + formulation pipelines that report both pharmacokinetics and -dynamics endpoints (not anyone alone), and (iii) When moving to humans, choose indications and formulations guided by the molecule's strongest translational signal. It should also accompany early trials with intensive pharmacokinetics and liver/biliary safety monitoring. These steps will make comparative claims evidence-based instead of anecdotal and

will help determine whether scaffold choice (oleanane vs. ursane vs. lupane) materially changes clinical potential. Compiling all these facts, we can reach to the conclusion that future studies should therefore prioritize dose finding, validated human pharmacokinetic studies, standardized efficacy endpoints across models, and in-depth sub-chronic/chronic toxicology (including liver/biliary markers) alongside advanced formulation strategies to determine whether improved exposure translates into reproducible therapeutic benefit. Comparative analysis with comparable triterpenoids and well-structured clinical trials are also needed for safe OA usage, with the incorporation of new data to take a lesson from the failures. OA may be a safe, multi-targeted phytotherapeutic compound with better transport and pharmacology.

CONCLUSION

OA derived from *L. camara* roots presents a compelling profile as a lead phytotherapeutic compound, characterized by a range of promising pharmacological activities and a favorable short-term preclinical safety profile. Existing evidence, including acute and sub-chronic toxicity studies in rodent models and negative Ames test results, suggests a wide therapeutic index and low mutagenic potential under the conditions tested. However, significant data gaps that currently preclude a definitive declaration of its safety and efficacy for human use still remain unanswered. The promising preliminary findings are tempered by the absence of chronic toxicity, carcinogenicity, and clinical data. OA's well-documented challenges with poor aqueous solubility and low oral bioavailability represent a major translational hurdle that limits its therapeutic application. Therefore, the future trajectory for establishing OA as a viable therapeutic agent must prioritize rigorous, targeted research. Key priorities include conducting comprehensive chronic toxicity and carcinogenicity studies, advancing formulation strategies, such as nano-delivery systems to overcome bioavailability limitations, and validating its efficacy and safety in well-designed clinical trials. Only through such systematic efforts can the translational promise of OA be fully and reliably evaluated.

AUTHOR'S CONTRIBUTIONS

Navika Gupta: Conceptualization, writing, proofreading, funding acquisition, reviewing, and editing. Sumer Singh: Proofreading, reviewing, editing original draft, Anu T. Singh: Proofreading, reviewing, editing original draft, Manu Jaggi: Proofreading, reviewing, editing original draft.

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CONFLICT OF INTERESTS

Authors declare that we have no conflict of interest.

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