JOURNAL OF NATURAL REMEDIES
DOI: 10.18311/jnr/2025/49431
REVIEW ARTICLE

Therapeutic Applications of Oleanolic Acid: Molecular Mechanisms and Clinical Perspectives

Aarti S. Zanwar[1*], Kirti V. Patel[2], Dhanya B. Sen[1], Ashim Kumar Sen[1], Krupa Joshi[1], Rajesh A. Maheshwari[1], Sushil S. Burle[3] and Sachin B. Zanwar[2]

[1]Department of Pharmacy, Sumandeep Vidyapeeth Deemed to be University, Piparia, Waghodia, Vadodara – 391760, Gujarat, India; aarti.zanwar@gmail.com

[2]Department of Pharmacology, Faculty of Pharmacy, Kalabhavan Campus, The Maharaja Sayajirao University of Baroda, Vadodara – 390001, Gujarat, India

[3]Department of Chemistry, Smt. Kishoritai Bhoyar College of Pharmacy, Kamptee – 441002, Maharashtra, India

Abstract

People in developing nations have long used plants as an adjunct or alternative treatment for chronic illnesses. Researchers are concentrating their efforts on finding the bioactive chemicals in plants and their products because of their obvious therapeutic. Human health benefits from an increase in the consumption of plant-based diets. A pentacyclic triterpene, Oleanolic Acid (OA), is present in a variety of plants and serves as an aglycone precursor or free acid for a number of triterpenoid saponins. With strong antibacterial, antioxidant, antitumor, anti-inflammatory, anti-diabetic, and neuroprotective qualities, OA and its derivatives are thought to be promising compounds. Since OA is hydrophobic in nature, it has historically been regarded as a low-bioavailable biomolecule. More recent research, however, has demonstrated that delivering it in lipophilic matrices can greatly increase its bioavailability. Oleanolic acid has been quantified using a variety of analytical techniques to ensure its efficacy, safety, and quality. It provides a framework for both industry and regulatory bodies to establish and maintain high standards in the production and its medicinal value. The goal of this review is to give an overview of the therapeutic potential of oleanolic acid against various diseases based on preclinical and clinical research.

Major Findings: This review shows strong preclinical efficacy in diabetes, cancer, liver injury, and neurodegeneration, with early clinical evidence supporting metabolic and anti-inflammatory benefits. Its market uptake is growing through clean-label functional foods and cosmeceuticals, while advances in semi-synthetic derivatives are enhancing bioavailability and driving clinical development.

Keywords: Anticancer, Angiogenesis, Apoptosis, Cell Cycle Inhibitors, Neuroprotective, Oleanolic Acid

1. Introduction

The quest for health and wellness has led humanity to explore a myriad of treatment options, among which natural medicine stands out for its time-honoured roots and holistic approach. For the treatment of numerous ailments, nature has provided medicine in the form of plants or herbs. Increased obesity brought on by a more sedentary lifestyle has led to oxidative stress, changes in insulin signalling pathways, and inflammation, all of which pave the way for a number of metabolic illnesses. Researchers are focusing their efforts on finding the bioactive chemicals found in plants and their products because of the apparent therapeutic benefits of the plants. Abundant research findings have shown the pharmacological effects of phytochemicals from plants that protect against long-term illnesses. Numerous culinary and therapeutic plants contain OA, a naturally occurring chemical substance[1]. OA, a pentacyclic triterpenoid abundant in Oleaceae family plants like olives, primarily resides in epicuticular waxes, acting as a

*Author for correspondence

Article Received on: 14.04.2025 Revised on: 22.07.2025 Accepted on: 29.07.2025

protective barrier against pathogens and water loss. In addition to its ecological roles, OA has a variety of medicinal effects. In different types of illness models, it exhibits antibacterial, anti-inflammatory, anti-tumour, antioxidant, and anti-diabetic activities. In China, oleanolic acid has been used as an over-the-counter medication for liver disorders such as viral hepatitis[2].

Analysing the additional biological activities of OA and its derivatives has shown that they are effective medications for treating human ailments. Many foods and natural herbs contain oleanolic acid, which is crucial for healthy diets[3]. Over 2000 plant species contain oleanolic acid, along with numerous food and medicinal plants[4,5]. Various fruits and vegetables like apples, grapes, pears, strawberries, rosemary, fennel, and ginseng contain OA. OA is one of the active components in a number of therapeutic herbs, including ginseng, dark plums, papaya fruit, olive fruit, and apple peel, which contain up to 1% of OA[6].

OA is a low-bioactive biomolecule, but when it has been delivered in lipophilic matrices, its bioavailability increases. When given as a pure compound, the natural OA's bioavailability varies since it is a complex compound with phytochemicals. The occurrence of fat appears as key importance for solubilisation and micellisation prior to its absorption. After hepatic metabolism, oleanolic acid undergoes widespread distribution throughout the tissues and associates with plasma proteins for transportation in the bloodstream, as evidenced by research findings. Additionally, it has no discernible adverse effects on humans or animals when used therapeutically[7,8].

2. Pharmacological Activity of Oleanolic Acid

2.1 Anti-tumour Effect

Numerous research works have documented the tumour-inhibiting properties of OA in various preclinical models. OA affected the proliferation of several cancer cell types, such as colorectal cancer (HCT-116), hepatocellular carcinoma (HepG2), astrocytoma (1321N1), and breast cancer (MCF-7).

As illustrated in Figure 1, OA inhibits the growth of tumour cells by blocking the migration and invasion of cancer cells, reducing angiogenesis, triggering apoptosis, triggering autophagy, and blocking the cell cycle[9,10]. The anticancer activity of OA is induced through various pathways. The body's primary defence mechanism against cancerous and virally infected cells is apoptosis. In several cancer cell lines, including SMMC-7721 (hepatocellular carcinoma), SW-579 (thyroid), and PC-3 (prostate cancer), OA increases the apoptosis-related protein Bax and lowers the Bcl-2 protein[11,12]. Another study showed that OA suppresses the expression of Bcl-2 in different tumour cell lines, such as MCF-7, HepG2, MDA-MB-231, and lung adenocarcinoma cells, which results in apoptosis. OA induces cell death by increasing the Bax/Bcl-2 ratio and promoting the release of mitochondrial cytochrome c into the cytoplasm, thereby triggering a caspase-dependent apoptotic cascade[13].

The PI3K/AKT and MAPK pathways control a number of cellular processes, including angiogenesis, metabolism, metastasis, proliferation, and apoptosis. By blocking the PI3K/AKT pathway, OA suppresses the AKT proteins in the gastric cancer cell line AGS[14]. By promoting the production of autophagic vesicles and upregulating the expression of autophagy-related

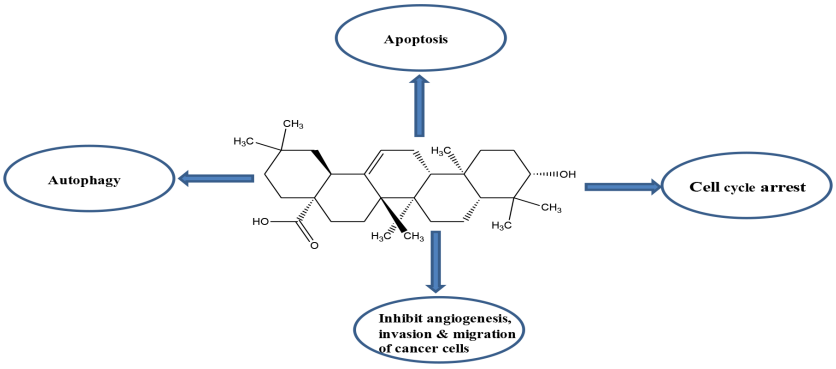


Figure 1. Mechanism of action of oleanolic acid anticancer activity.

proteins, OA dramatically inhibited the development of HepG2 and SMC7721 cells. These effects are mediated through the PI3K/AKT/mTOR pathway[15,16].

Uncontrolled cell proliferation is caused by abnormal cell cycle regulator function, which makes them appealing therapeutic targets in cancer treatment[17,18]. Numerous studies have shown that OA can arrest different stages of the cell cycle arrest, such as G1 cell cycle arrest in HCT15, U87, and K562 cell lines, S phase and G2/M phase cell cycle arrest in Panc28 and HepG2 cells, and eventually cancer cell death[18]. Table 1 summarises oleanolic acid's anticancer properties both *in vitro* and *in vivo*.

Table 1. *In vitro* and *in vivo* anticancer activity of oleanolic acid

Type of Cancer	Study design	Study models	Dose and route of administration	Molecular mechanisms	References
Liver cancer/ HCC	*In vitro*	SMMC-7721	-	Reduce intracellular mitochondrial membrane potential, ATP concentration and induce apoptosis. Reduce the expression of p-Akt and p-mTOR	9
Liver cancer/ HCC	*In vitro*	HepG2	-	Block the JNK/p38 signalling pathway, cause cell cycle arrest, and trigger mitochondrial death	24
Liver cancer/ HCC	*In vitro*	Hep3B, Huh7 and HA22T	-	Strong anti-angiogenic properties that prevent cell invasion and migration	25
Liver cancer/ HCC	*In vitro*	HuH7	-	Suppress NF-κB activity and alter X-linked Inhibitor of Apoptotic Protein (XIAP) mRNA expression	26
Liver cancer/ HCC	*In vitro*	HepG2 and SMC7721	-	Induce autophagic cell death via PI3K/Akt/mTOR and ROS-dependent pathway	27
Liver cancer/ HCC	*In vitro*	HepG2	-	Causes cell cycle arrest and mitochondrial-dependent apoptosis	28
Liver cancer	*In vivo*	HepG2, mice	75 or 150 mg/kg/day, i.p. for 3 weeks	Causes cell cycle arrest mediated by ERK–p53 and mitochondrial-dependent apoptosis	17
Bladder cancer	*In vitro*	T24 and EJ	-	Induced protective autophagy through the AMPK-mTOR-ULK1 signalling pathway	19
Breast cancer	*In vitro*	MCF-7 and MDA-MB-231	-	Induced apoptosis and cell cycle arrest	20,21
Breast cancer	*In vivo*	Mouse Luc 4T1, mice	40 mg/kg, p.o. for 11 days	Regulated the lactic acid bacteria, which enhanced to maturation of immune cells and exerted anti-cancer activity	35
Glioblastoma	*In vitro*	U87	-	Cell cycle arrest and apoptosis induction	21
Glioblastoma	*In vitro*	U373-MG	-	Prevent cell division by inhibiting STAT3 activity	23
Gastric cancer	*In vitro*	MKN-45 and SGC-7901	-	Inhibits yes-associated protein, which lowers HIF-1α-mediated, aerobic glycolysis-associated proliferation	22
Pancreatic cancer	*In vitro*	Panc-28	-	Induce ROS-mediated mitochondrial and lysosomal pathway, apoptosis and cell cycle arrests	29
Prostate cancer	*In vitro*	DU145	-	Cell cycle arrest and apoptosis induction	21
Prostate cancer	*In vivo*	DU145, mice	50 µg/mouse, i.m., total of 4 injections of OA in 2-day intervals	Apoptosis induction and cell cycle arrest via the ERK/ JNK/AKT pathway	21
Prostate cancer	*In vitro*	PC-3, DU145, and LNCaP	-	Control the PI3K/Akt pathway, apoptotic expression levels, and proteins linked to the cell cycle	30
Rectal cancer	*In vitro*	HCT-15 and HT-29	-	Inhibit NOX2/ROS/HIF-1α axis signalling	31
Skin cancer	*In vitro*	A375	-	Inhibit EGFR and trigger apoptosis mediated by caspase 3 that is dependent on the mitochondria	32
Non-Small Cell Lung Cancer (NSCLC)	*In vitro*	A459, H460, and B16F10 melanoma cells	-	Reduced the development of lung metastases brought on by melanoma and the expression of angiogenic Vascular Endothelial Growth Factor (VEGF)	33
Lung cancer	*In vitro*	A549	-	Induce mitophagy through PINK1/Parkin axis pathway	34
Breast cancer	*In vivo*	Mouse Luc 4T1, mice	40 mg/kg, p.o. for 11 days	Regulated the lactic acid bacteria, which enhanced to maturation of immune cells and exerted anti-cancer activity	35

2.2 Anti-Diabetic Activity

In diabetic animal models, oleanolic acid has been shown to enhance insulin action, suppress gluconeogenesis, and boost glucose utilisation. It enhances the transmission of the insulin signal while inhibiting oxidative stress-induced gluconeogenesis and hepatic insulin resistance. Its protective effect on extracellular signal-regulated kinase phosphorylation and mitochondrial activity is responsible for these effects.

Furthermore, OA controls a number of biological pathways linked to the etiology of diabetes. It alters NF-kappa B activity, slows down the polyol pathway and the synthesis of advanced glycation end products, activates M3 muscarinic receptors, and affects the G protein-coupled bile acid receptor. Crucially, OA does not have adipogenic effects like some other anti-diabetic or anti-obesity medications do. Accordingly, OA may offer a more effective and promising therapeutic approach for the management of diabetes and related metabolic disorders[36-38]. Takeda G protein-coupled receptor 5 (TGR5) is expressed by pancreatic β-cells. Insulin release is increased, and beta cell activity is impacted by TGR5 activation. In mice given a high-fat diet, OA increases glucose tolerance by functioning as a TGR5 agonist and reducing insulin and blood glucose levels. By activating TGR5, OA increases intracellular cAMP levels and stimulates the synthesis of insulin through a PKA-dependent mechanism[39].

2.3 Antibacterial Activity

One element of a plant's protection against pathogens is oleanolic acid. OA showed antibacterial efficacy by disrupting the cell membranes of Listeria monocytogenes, Enterococcus faecium, and Enterococcus faecalis. The bacterium L. monocytogenes is the cause of listeriosis, a foodborne disease that kills a significant number of people.

Oleanolic acid demonstrated modest antimicrobial activity, effectively inhibiting *Staphylococcus aureus* at a concentration of 62.5 µg/ml. It also exhibited inhibitory effects at a concentration of 31.2 µg/ml (MIC) against *Salmonella enterica*, *Escherichia coli*, and *Shigella dysenteriae*. The MIC range of 1.9-3.9 µg/mL of the positive reference, kanamycin sulfate, was almost identical to the MIC range of 0.9-7.8 µg/mL for 3-epioleanolic acid, which demonstrated a more powerful antibacterial activity[38, 40-41].

2.4 Antiviral Activity

OA exhibited antiviral properties against a variety of viruses. HIV-1 protease could be blocked by OA[42]. This inhibition successfully halted the HIV life cycle by causing the development of immature and non-infectious virions. OA may target non-structural protein 5B (NS5B), an RNA-dependent RNA polymerase (RdRp), an essential enzyme in HCV replication[43-44]. According to reports, OA prevents early infection with Herpes Simplex Virus (HSV) types I and II[45]. The UL8 protein, which is a part of the HSV-1 virus's viral helicase-primase complex, is dysregulated by OA. Viral replication depends critically on the UL8 protein[46].

2.5 Hepatoprotective Activity

One of OA's noteworthy bioactivities is its ability to shield the liver against toxicity. In China, it is marketed as an over-the-counter hepatic medication. By lowering serum ALT and AST levels, OA and its derivatives have hepatoprotective effects. Activating nuclear factor erythroid 2-related factor 2 (Nrf2) via reprogramming the liver is one of the ways that OA protects against various hepatotoxicants. One transcription factor that controls genes involved in detoxification and antioxidant pathways is Nrf2 activation. Enzymes Nqo1 and HO-1 are induced, phase-2 detoxification conjugation is increased, GSH production and conjugation are encouraged, and toxins are transported out of hepatocytes to aid in hepatoprotection. Nrf2 also reduces CYP2E1 activity, reducing the bioactivation of toxic compounds like CCL_4 and acetaminophen, potentially reducing hepatotoxicity. Additionally, Nrf2 activation reduces Oatp1b2 expression, which may reduce the uptake of toxic substances like phalloidin. TGR5 activation can lead to proinflammatory cytokines, potentially implicating cholestasis. OA appears to have a threshold for safety, with lower doses and shorter durations being associated with hepatoprotection, while higher doses and longer durations can lead to hepatotoxicity. For instance, oral dosages of less than 100 mg/kg are safe for mice for 4 days, rats for 7-14 days, or rats for 10-60 mg/kg for 30 days. In albino mice or rats, oral dosages above 225 mg/kg for 10 days, 100 mg/kg for 30 days, or 45-135 mg/kg for 90 days may cause hepatotoxicity[6, 47-49].

Pregnane X receptor and constitutive androstane receptor promoters, which control the catalytic activity

of certain enzymes like CYP3A4 and CYP2B6, have been shown to change their activities in response to OA. Thus, reducing unfavourable interactions between CYP450 transcriptional inducers and medicinal medication, which is responsible for liver injury[50].

One of the main causes of death worldwide, Alcoholic Liver Disease (ALD), has been linked to oxidative stress as a major pathophysiological factor. OA is crucial in avoiding oxidative damage brought by alcohol. Pro-inflammatory cytokines like TNF-α and IL-6 were inhibited by OA, while anti-oxidative mechanisms, including NRF-2, HO-1, SOD-1, and GR expression, were increased. One important enzyme in alcohol-induced toxicity, which produces toxic aldehydes and free radicals, CYP2E1, is inhibited by OA[51-52].

2.6 Cardioprotective Effect

Clinical trials are currently lacking, with the majority of research being done on preclinical models of hypertension, *ex vivo* investigations using aortic rings, and some *in vitro* experiments using cell cultures. When oleanolic acid was administered to hypertensive animals, the increase in systolic blood pressure was considerably reduced. Furthermore, oleanolic acid's hypotensive actions are linked to nephroprotection and a strong diuretic-natriuretic activity. *In vitro* studies have revealed a variety of signalling pathways that affect the release of vasodilation mediators, including altering LOX-1, lowering NADPH oxidase, and increasing HO-1 and NRF2 expression[53-54].

2.7 Antioxidant Activity

In preclinical studies, oleanolic acid lowers the level of malonaldehyde and increases glutathione peroxidase and superoxide dismutase activity. The molecular mechanism reported that OA participates in the activation of Nrf2 and a few enzymes, such as CAT and PRX. Since oxidative stress is linked to the development of chronic illnesses, OA's antioxidant properties are crucial for the control and cure of numerous illnesses[55].

2.8 Anti-inflammation Activity

OA decreases the activation of the nuclear factor erythroid-related factor 2 (NRF-2) and NF-κB pathways, suppresses inflammatory mediators such as IL-1β, IL-6, and TNF-α, and modifies oxidative stress by scavenging reactive oxygen species. It also inhibits COX, LOX and the HMGB1 signalling pathways, reducing inflammation and protecting cells from oxidative damage[56-59]. Also, oleanolic acid irreversibly inhibited secretory phospholipase by forming the complex, explaining its anti-inflammatory properties[10].

2.9 Hair Promoter

OA lowers the concentration of dihydrotesterone, tumour necrosis factor-alpha, and the enzyme 5α-reductase, which will slow down alopecia. Furthermore, it stimulates the Wnt/β-catenin pathway, which in turn promotes hair matrix and, eventually, cell proliferation[60].

2.10 Skin Protector from Inflammatory Matter

Oleanolic acid serves as a skin protector by inhibiting the activation of aryl hydrocarbon receptors, thereby reducing the levels of proinflammatory cytokines and preventing the accumulation of autophagosomes induced by particulate matter. As a result, oleanolic acid can shield the skin from exposure to particulate matter, diminishing skin inflammation and wrinkles[61]. The evidence showed that OLA can suppress hypertrophic scarring by reducing the collagen (I and III) and TGF-β1, with increased levels of Matrix Metalloproteinase (MMP)-1 in scar tissue when treated at 22 days at different concentrations. Therefore, it may be effective for human hypertrophic scarring. Preliminary evidence suggests that oleanolic acid can block the synthesis of a specific form of testosterone in skin that triggers an increase in sebum production. Oleanolic acid might also be able to improve the skin barrier function and reduce inflammation, and has promise in treating atopic dermatitis and helping sensitive skin types. Moreover, its mechanism in atopic dermatitis is to suppress the expression of cytokines (chemotactic and Th2). More research is needed to validate its effect on skin disorders[62-63].

2.11 Neuroprotective Activity

Significant increases in CaMKII and Brain-Derived Neurotrophic Factor (BDNF) expression were seen in the OA therapy, indicating possible advantages for neuronal survival and proliferation. It also enhanced the expression of genes related to myelination and

Table 2. Pharmacological activity of oleanolic acid

Disease	Molecular mechanisms	References
Diabetes mellitus	Alters NF-kappa B activity, slows down the polyol pathway and the synthesis of advanced glycation end products, activates M3 muscarinic receptors, and affects the G protein-coupled bile acid receptor	36-38
Diabetes mellitus	Activate TGR5, increases intracellular cAMP levels and stimulates the synthesis of insulin through a PKA-dependent mechanism.	39
Antibacterial activity	Disrupts the bacterial cell membrane, inhibits growth	41
Antioxidant	Hepatoprotective activity was studied *in vitro* on immunological liver injury of primary cultured rat hepatocytes. OA showed hepatoprotective activity	47
Cardioprotective	Reduces cardiac inflammation, promotes anti-inflammatory cytokines, and has antioxidant effects	53
Antioxidant	Increases SOD, GPx, and CAT; reduces MDA and ROS. Reduces oxidative stress in multiple tissues	55
Hair promoter	Lowers the concentration of dihydrotesterone, tumour necrosis factor-alpha, and enzyme 5α-reductase, which will slow down alopecia.	60
Neuroprotective	Antioxidant and anti-inflammatory effects modulate neuroinflammation	67

remyelination, suggesting the possibility of nerve repair, and decreased neuroinflammation by inhibiting pro-inflammatory cytokines.

Also, it has the ability to trim down serum HMGB1 levels by hindering the transfer of HMGB1 from the nucleus to the cytoplasm. This will reduce the inflammation in the brain injury and neuronal apoptosis in the case of subarachnoid haemorrhage.

In a study, animals treated with 6-Hydroxydopamine (HDA) demonstrated a functional deficit, and their striatal dopamine levels decreased. These effects were mitigated by OA therapy within 7 days prior to injury and 1 day after damage. Furthermore, rats treated with OA either before or after the injury recovered from membrane depolarisation brought on by HDA, suggesting that OA pre-administration shields dopamine neurons from HDA's harmful effects. This implies that OA could be utilised to treat Parkinson's disease or as a preventative measure[64-65]. The primary factors influencing OA's neuroprotective properties are its anti-inflammatory, anti-apoptotic, and antioxidant activities[66-67]. The pharmacological effect of OA with a mechanism of action is summarised in Table 2 and Figure 2.

2.12 Preclinical Pharmacokinetics of Oleanolic Acid

Oleanolic acid exhibited low permeability in Caco-2 cell permeation studies. OA *in vivo* absorption is most likely mediated by passive diffusion, as indicated by the absence of directional effects.

In another study, reports that when oleanolic acid was taken orally at doses of 25, and 50 mg/kg, there was no significant difference in Tmax, $t_{1/2}$, dose-normalised Cmax (66-74 ng/ml based on 25 mg/kg), and dose-normalised AUC (5.4-5.9 microg min/ml based on 25 mg/kg). Oral dosages of 25 and 50 mg/kg had very low absolute oral bioavailability (0.7%). Limited elimination through the urine is suggested by the low amount of urine excretion for both oral and intravenous dosages[68].

Oleanolic acid had dose-linear pharmacokinetics following intravenous administration at doses of 0.5, 1 and 2 mg/kg, as demonstrated by unaltered dose-normalised AUC (16.0-17.9 µg/ min/ml), CL (28.6-33.0 ml/min/kg), $t_{1/2}$ (41.9-52.7 min) and Vss (437-583 ml/kg).

Due to inadequate absorption and metabolic clearance, OA was shown to have a low oral bioavailability. Intravenous administration shows predictable kinetics, but caution and monitoring are crucial for safe application[69].

2.13 Combination of Oleanolic Acid with Other Agents

Combining oleanolic acid with other bioactive compounds or therapeutic agents has been explored to enhance its pharmacological efficacy and reduce side effects. Oleanolic acid and ursolic acid, both naturally

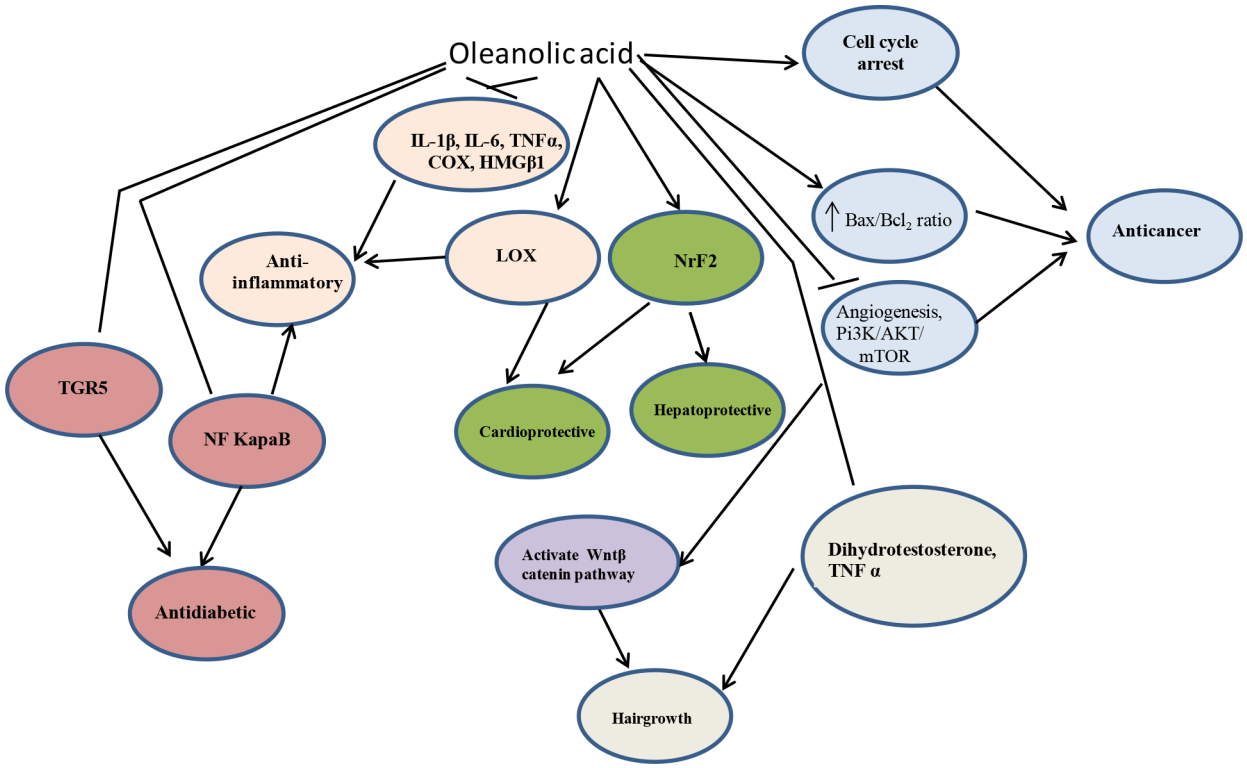


Figure 2. Summary of the pharmacological effects of oleanolic acid, with the mechanism.

occurring triterpenoids, share similar structures and biological activities. According to studies, combining these two substances may have a stronger impact by preventing colon cancer cells from migrating via downregulating the MMPs pathway[70].

In cancer therapy, oleanolic acid has been studied for its potential to sensitize cancer cells to chemotherapy drugs like doxorubicin. The combination has been shown to significantly enhance the cytotoxic effects of doxorubicin in pancreatic and melanoma cancer cells more than that of the treatment alone[71-72].

In diabetes research, combining oleanolic acid with metformin has been investigated for improving insulin sensitivity and glucose metabolism. This combination may offer potential benefits in treating type 2 diabetes by enhancing the glucose-lowering effects and protecting pancreatic β-cells from oxidative damage[73].

2.14 Clinical Studies of Oleanolic Acid

Despite significant preclinical data supporting the efficacy of oleanolic acid, there is limited large-scale clinical evidence for its use in human diseases. OA was given to hyperlipidemic patients for four weeks in a clinical study (four tablets taken once, three times a day). Before and after OA therapy, the patients' blood samples were taken. Triglycerides (TG), Low-Density Lipoprotein (LDL), and Total Cholesterol (TC) all sharply declined in serum following OA dosing. The results of DNA microarray analysis demonstrated that following OA therapy, there was a significant shift in the expression of 21 mRNAs. Following OA therapy, bioinformatics analysis revealed that 4 mRNAs had a substantial down-regulation and 17 mRNAs had an up-regulation. OA may therefore help with hyperlipidemia[74]. The clinical studies with oleanolic acid are summarised in Table 3.

To determine whether frequent use of olive oil enhanced with OA is beneficial in preventing diabetes, another clinical investigation was carried out. In order to determine the incidence of new-onset type 2 diabetes mellitus (T2DM), prediabetic patients were randomised to receive either OA-enriched olive oil (equal to a dose of 30 mg OA/day) or the same oil that was not enriched (control group). According to the findings, there were 48 new T2DM onset episodes overall, 31 in the control group and 17 in the patients in the OA-enriched, OA-treated group. Hence, pre-diabetic patients who consumed OA-enriched olive oil had a lower chance of

Table 3. Clinical studies with oleanolic acid

S. No.	Disease	Dose of oleanolic acid and route of administration	Serum marker	Remarks	References
1	Hyperlipidemia	4 tablets once, three times a day for 4 weeks	Serum TG, LDL, and TC declined	4 mRNAs down-regulation and 17 mRNAs up-regulation, Hyperlipidemia	74
2	Diabetes mellitus	30 mg per day	-	OA-enriched olive oil had a lower chance of acquiring type 2 diabetes	75-76
3	Chronic hepatitis	Oral oleanolic acid treatment for 3 months	Improved ALT, AST, and the incidence of cirrhosis	Helped in the prevention of type 2 diabetes	77

acquiring type 2 diabetes, indicating that OA may be utilised as a functional food and treatment to prevent type 2 diabetes[75-76].

Oral oleanolic acid treatment for three months improved liver function markers, including serum Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), and the incidence of cirrhosis, in a study including patients with chronic hepatitis[77].

3. Potential Challenges

Future research on Oleanolic Acid (OA) faces several pivotal challenges that demand multidisciplinary solutions. A primary concern is OA's inherently low bioavailability, which must be improved through innovative formulation techniques and strategic structural modifications. Simultaneously, in-depth mechanistic investigations are crucial to unravel its precise molecular targets and signalling pathways, especially its interactions with critical regulators such as NF-κB, AMPK, and PPARγ.

OA holds considerable potential in combination therapies, where it may enhance the efficacy of standard treatments or help overcome drug resistance in diseases like cancer and diabetes. However, clinical translation requires large-scale, well-designed human trials, along with comprehensive safety assessments, to determine optimal therapeutic dosages and evaluate long-term safety.

Due to its dual antioxidant and anti-inflammatory effects, OA is also a promising agent for dermatological and cosmetic applications. Nevertheless, issues related to compound stability and effective delivery must be addressed. Additionally, to support growing global demand and ensure environmental sustainability, the development of scalable and eco-friendly production methods—such as plant cell culture and synthetic biology approaches—is increasingly important.

4. Conclusion

Global shifts in disease patterns and microbial resistance have intensified research focus on bioactive plant compounds and their derivatives. This has catalysed significant scientific interest in developing novel therapeutics from natural sources, with OA—a pentacyclic triterpenoid—receiving particular attention due to its diverse pharmacological properties.

Extensive studies demonstrate OA's efficacy in attenuating and ameliorating multiple pathological conditions. Consequently, substantial research efforts have been directed toward developing optimized. OA formulations and derivatives with enhanced bioavailability, potency, and reduced toxicity. Notably, OA's natural abundance, high biological activity, and multifunctional therapeutic potential present compelling research opportunities.

While clinical investigations on OA remain limited relative to preclinical studies, existing evidence indicates promising therapeutic applications for liver disorders, metabolic syndromes, cardiovascular diseases, oncology, and inflammatory conditions. Further comprehensive clinical studies are essential to conclusively establish its safety, mechanistic pathways, and efficacy across diverse health contexts.

5. Author Contribution

Aarti S. Zanwar: Conceptualisation, and final review, Writing and Literature Search; Sachin B Zanwar, Ashim Kumar Sen: Reviewing and Verification; Sushil S. Burle, Krupa Joshi: Data collection and manuscript editing;

Kirti V. Patel, Dhanya B. Sen, Rajesh A. Maheshwari: Critical revision and expert insights. All authors have read and agreed to the published version of the manuscript.

6. References

1. Dincheva I, Badjakov I, Galunska B. New Insights into the research of bioactive compounds from plant origins with nutraceutical and pharmaceutical potential. Plants (Basel). 2023; 12(2):258. https://doi.org/10.3390/plants12020258 PMid:36678971 PMCid:PMC9860645
2. Wan XL, Lu YF, Xu SF, Wu Q, Liu J. Oleanolic acid protects against the hepatotoxicity of D-galactosame plus endotoxin in mice. Biomed Pharmacother. 2017; 93:1040-1046. https://doi.org/10.1016/j.biopha.2017.07.045 PMid:28738497
3. Castellano JM, Ramos-Romero S, Perona JS. Oleanolic acid: Extraction, characterisation and biological activity. Nutrients. 2022; 14(3):623. https://doi.org/10.3390/nu14030623 PMid:35276982 PMCid:PMC8838233
4. Shanmugam, MK, Dai X, Kumar AP, Tan BKH, Sethi, G, Bishayee A. Oleanolic acid and its synthetic derivatives for the prevention and therapy of cancer: Preclinical and clinical evidence. Cancer Lett. 2014; 346(2):206-216. https://doi.org/10.1016/j.canlet.2014.01.016 PMid:24486850 PMCid:PMC4004441
5. Pollier J, Goossens A. Oleanolic acid. Phytochemistry. 2012; 77:10-15.
6. Liu J, Lu YF, Wu Q, Xu SF, Shi FG, Klaassen CD. Oleanolic acid reprograms the liver to protect against hepatotoxicants, but is hepatotoxic at high doses. Liver Int. 2019; 39(3):427-39. https://doi.org/10.1111/liv.13940 PMid:30079536
7. Janicsak G, Veres K, Kakasy AZ, Mathe I. Study of the oleanolic and ursolic acid contents of some species of the Lamiaceae. Biochem Syst Ecol. 2006; 34:392-396. https://doi.org/10.1016/j.bse.2005.12.004
8. Tang ZY, Li Y, Tang YT, Ma XD, Tang ZY. Anticancer activity of oleanolic acid and its derivatives: Recent advances in evidence, target profiling and mechanisms of action. Biomed Pharmacother. 2022; 145:112397. https://doi.org/10.1016/j.biopha.2021.112397 PMid:34798468
9. Zhou W, Zeng X, Wu X. Effect of oleanolic acid on apoptosis and autophagy of SMMC-7721 hepatoma cells. Med Sci Monit. 2020; 26:e921606-1. https://doi.org/10.12659/MSM.921606
10. Sen A. Prophylactic and therapeutic roles of oleanolic acid and its derivatives in several diseases. World J Clin Cases. 2020; 8(10):1767. https://doi.org/10.12998/wjcc.v8.i10.1767-1792. PMid:32518769 PMCid:PMC7262697
11. Duan L, Yang Z, Jiang X. Zhang, J. Guo, X. Oleanolic acid inhibits cell proliferation migration and invasion and induces SW579 thyroid cancer cell line apoptosis by targeting forkhead transcription factor A. Anticancer Drugs. 2019; 30:812-820. https://doi.org/10.1097/CAD.0000000000000777 PMid:30882397
12. Xu F, Na L, Li Y, Chen L. Roles of the PI3K/AKT/mTOR signalling pathways in neurodegenerative diseases and tumours. Cell Biosci. 2020; 10:1-12. https://doi.org/10.1186/s13578-020-00416-0 PMid: 32266056 PMCid:PMC7110906
13. Li L, Wei L, Shen A, Chu J, Lin J, Peng J. Oleanolic acid modulates multiple intracellular targets to inhibit colorectal cancer growth. Int J Oncol. 2015; 47(6):2247-2254. https://doi.org/10.3892/ijo.2015.3198 PMid: 26459864
14. Onorati AV, Dyczynski M, Ojha R, Amaravadi RK. Targeting autophagy in cancer. Cancer. 2018; 124:3307-3318. https://doi.org/10.1002/cncr.31335 PMid:29671878 PMCid:PMC6108917
15. Lee JH, Yoo ES, Han SH, Jung GH, Han EJ, Jung SH, *et al*. Oleanolic acid induces apoptosis and autophagy via the PI3K/AKT/mTOR pathway in AGS human gastric cancer cells. J Funct Foods. 2021; 87:104854. https://doi.org/10.1016/j.jff.2021.104854
16. Zheng K, He Z, Kitazato K, Wang Y. selective autophagy regulates cell cycle in cancer therapy. Theranostics. 2019; 9(1):104-125. https://doi.org/10.7150/thno.30308 PMid:30662557 PMCid:PMC6332805
17. Wang X, Bai H, Zhang X, Liu J, Cao P, Liao N, *et al*. Inhibitory effect of oleanolic acid on hepatocellular carcinoma via ERK-p53-mediated cell cycle arrest and mitochondrial-dependent apoptosis. Carcinogenesis. 2013; 34:1323-1330. https://doi.org/10.1093/carcin/bgt058 PMid:23404993
18. Castellano JM, Guinda A, Delgado T, Rada M, Cayuela JA. Biochemical basis of the antidiabetic activity of oleanolic acid and related pentacyclic triterpenes. Diabetes. 2013; 62(6):1791-1799. https://doi.org/10.2337/db12-1215 PMid:23704520 PMCid:PMC3661625
19. Song Y, Zhang P, Sun Y, Li X, Chen L, Xiao Y, *et al*. AMPK activation-dependent autophagy compromises oleanolic acid-induced cytotoxicity in human bladder cancer cells. Oncotarget. 2017; 8(40):67942-67954. https://doi.org/10.18632/oncotarget.18980 PMid:28978086 PMCid:PMC5620226
20. Chakravarti B, Maurya R, Siddiqui JA, Bid HK, Rajendran SM, Yadav PP, *et al*. *In vitro* anti-breast cancer activity of ethanolic extract of *Wrightia tomentosa*: Role of pro-apoptotic effects of oleanolic acid and ursolic acid. J Ethnopharmacol. 2012; 142(1):72-79. https://doi.org/10.1016/j.jep.2012.04.015 PMid:22855944
21. Kim GJ, Jo HJ, Lee KJ, Choi JW, An JH. Oleanolic acid induces p53-dependent apoptosis via the ERK/JNK/AKT pathway in cancer cell lines in prostatic cancer xenografts in mice. Oncotarget. 2018; 9(41):26370-26386. https://doi.org/10.18632/oncotarget.25316 PMid:29899865 PMCid:PMC5995180

22. Li Y, Xu Q, Yang W, Wu T, Lu X. Oleanolic acid reduces aerobic glycolysis-associated proliferation by inhibiting yes-associated protein in gastric cancer cells. Gene. 2019; 712:143956. https://doi.org/10.1016/j.gene.2019.143956 PMid:31271843
23. Fujiwara Y, Komohara Y, Kudo R, Tsurushima K, Ohnishi K, Ikeda T, *et al*. Oleanolic acid inhibits macrophage differentiation into the M2 phenotype and glioblastoma cell proliferation by suppressing the activation of STAT3. Oncol Rep. 2011; 26(6):1533-1537. https://doi.org/10.3892/or.2011.1454 PMid:21922144
24. Gao C, Li X, Yu S, Liang L. Inhibition of cancer cell growth by oleanolic acid in multidrug resistant liver carcinoma is mediated via suppression of cancer cell migration and invasion, mitochondrial apoptosis, G2/M cell cycle arrest and deactivation of JNK/p38 signalling pathway. J Buon. 2019; 24(5):1964-1969.
25. Lin CC, Huang CY, Mong MC, Chan CY, Yin MC. Antiangiogenic potential of three triterpenic acids in human liver cancer cells. J Agric Food Chem. 2011; 59(2):755-762. https://doi.org/10.1021/jf103904b PMid:21175131
26. Shyu MH, Kao TC, Yen GC. Oleanolic acid and ursolic acid induce apoptosis in HuH7 human hepatocellular carcinoma cells through a mitochondrial-dependent pathway and downregulation of XIAP. J Agric Food Chem. 2010; 58(10):6110-6118. https://doi.org/10.1021/jf100574j PMid:20415421
27. Shi Y, Song Q, Hu D, Zhuang X, Yu S, Teng D. Oleanolic acid induced autophagic cell death in hepatocellular carcinoma cells via PI3K/Akt/mTOR and ROS-dependent pathway. Korean J Physiol Pharmacol. 2016; 20(3):237-243. https://doi.org/10.4196/kjpp.2016.20.3.237 PMid:27162477 PMCid:PMC4860365
28. Zhu YY, Huang HY, Wu YL. Anticancer and apoptotic activities of oleanolic acid are mediated through cell cycle arrest and disruption of mitochondrial membrane potential in HepG2 human hepatocellular carcinoma cells. Mol Med Rep. 2021; 23(6):440. https://doi.org/10.3892/mmr.2021.12079 PMid:33846804 PMCid:PMC8060796
29. Wei J, Liu M, Liu H, Wang H, Wang F, Zhang Y, *et al*. Oleanolic acid arrests cell cycle and induces apoptosis via ROS-mediated mitochondrial depolarization and lysosomal membrane permeabilization in human pancreatic cancer cells. J Appl Toxicol. 2013; 33(8):756-765. https://doi.org/10.1002/jat.2725 PMid:22678527
30. Li X, Song Y, Zhang P, Zhu H, Chen L, Xiao Y, *et al*. Oleanolic acid inhibits cell survival and proliferation of prostate cancer cells *in vitro* and *in vivo* through the PI3K/Akt pathway. Tumor Biol. 2016; 37(6):7599-7613. https://doi.org/10.1007/s13277-015-4655-9 PMid:26687646
31. Guo Y, Han B, Luo K, Ren Z, Cai L, Sun L. NOX2-ROS-HIF-1α signaling is critical for the inhibitory effect of oleanolic acid on rectal cancer cell proliferation. Biomed Pharmacother. 2017; 85:733-739. https://doi.org/10.1016/j.biopha.2016.11.091 PMid:27938946
32. Ghosh S, Bishayee K, Khuda-Bukhsh AR. Oleanolic acid isolated from ethanolic extract of Phytolacca decandra induces apoptosis in A375 skin melanoma cells: Drug-DNA interaction and signaling cascade. J Integr Med. 2014; 12(2):102-114. https://doi.org/10.1016/S2095-4964(14)60015-7 PMid:24666676
33. Lúcio KA, Rocha GD, Monção-Ribeiro LC, Fernandes J, Takiya CM, Gattass CR. Oleanolic acid initiates apoptosis in non-small cell lung cancer cell lines and reduces metastasis of a B16F10 melanoma model *in vivo*. PLOS One. 2011; 6(12):e28596. https://doi.org/10.1371/journal.pone.0028596 PMid:22174843 PMCid:PMC3235133
34. Castrejón-Jiménez NS, Leyva-Paredes K, Baltierra-Uribe SL, Castillo-Cruz J, Campillo-Navarro M, Hernández-Pérez AD, *et al*. Ursolic and oleanolic acids induce mitophagy in A549 human lung cancer cells. Molecules. 2019; 24(19):3444. https://doi.org/10.3390/molecules24193444 PMid:31547522 PMCid:PMC6803966
35. He K, Meng X, Su J, Jiang S, Chu M, Huang B. Oleanolic acid inhibits the tumor progression by regulating Lactobacillus through the cytokine-cytokine receptor interaction pathway in 4T1-induced mice breast cancer model. Heliyon. 2024; 10(5), e27028. https://doi.org/10.1016/j.heliyon.2024.e27028 PMid:38449659 PMCid:PMC10915379
36. Wang X, Li YL, Wu H, Liu JZ, Hu JX, Liao N, *et al*. Antidiabetic effect of oleanolic acid: A promising use of a traditional pharmacological agent. Phytother Res. 2011; 25(7):1031-1040. https://doi.org/10.1002/ptr.3385 PMid:21254272
37. Dash S, Pattnaik G, Sahoo N, Kar B. The promising role of oleanolic acid in the management of diabetes mellitus: A review. J Appl Pharm Sci. 2021; 11(9):149-157.
38. Kim S, Lee H, Lee S, Yoon Y, Choi KH. Antimicrobial action of oleanolic acid on *Listeria monocytogenes*, *Enterococcus faecium*, and *Enterococcus faecalis*. PLoS One. 2015; 10:e0118800. https://doi.org/10.1371/journal.pone.0118800 PMid:25756202 PMCid:PMC4355482
39. Xue C, Jia H, Cao R, Cai W, Hong W, Tu J, *et al*. Oleanolic acid improved intestinal immune function by activating and potentiating bile acids receptor signaling in *E. coli* -challenged piglets. J Animal Sci Biotechnol. 2024; 15(1):79. https://doi.org/10.1186/s40104-024-01037-0 PMid:38760843 PMCid:PMC11102245
40. Ayeleso TB, Matumba MG, Mukwevho E. Oleanolic acid and its derivatives: Biological activities and therapeutic potential in chronic diseases. Molecules. 2017; 22(11):1915. https://doi.org/10.3390/molecules22111915 PMid:29137205 PMCid:PMC6150249
41. Wrońska N, Szlaur M, Zawadzka K, Lisowska K. The synergistic effect of triterpenoids and flavonoids-new approaches for treating bacterial infections? Molecules. 2022;

27(3):847. https://doi.org/10.3390/molecules27030847 PMid:35164112 PMCid:PMC8838219
42. Bachar SC, Mazumder K, Bachar R, Aktar A, Al Mahtab M. A review of medicinal plants with antiviral activity available in Bangladesh and mechanistic insight into their bioactive metabolites on SARS-CoV-2, HIV and HBV. Front Pharmacol. 2021; 12:732891. https://doi.org/10.3389/fphar.2021.732891 PMid:34819855 PMCid:PMC8606584
43. Khwaza V, Oyedeji OO, Aderibigbe BA. Antiviral activities of oleanolic acid and its analogues. Molecules. 2018; 23(9):2300. https://doi.org/10.3390/molecules23092300 PMid:30205592 PMCid:PMC6225463
44. Serra C, Lampis G, Pompei R, Pinza M. Antiviral activity of new triterpenic derivatives. Pharmacol Res. 1994; 29(4):359-366. https://doi.org/10.1016/1043-6618(94)80057-X PMid:7971687
45. Mukherjee H, Ojha D, Bag P, Chandel HS, Bhattacharyya S, Chatterjee TK, *et al*. Anti-herpes virus activities of *Achyranthes aspera*: An Indian ethnomedicine, and its triterpene acid. Microbiol Res. 2013; 168(4):238-244. https://doi.org/10.1016/j.micres.2012.11.002 PMid:23218996
46. Jannus F, Sainz J, Reyes-Zurita FJ. Principal bioactive properties of oleanolic acid, its derivatives, and analogues. Molecules. 2024; 29(14):3291. https://doi.org/10.3390/molecules29143291 PMid:39064870 PMCid:PMC11279785
47. Kinjo J, Okawa M, Udayama M, Sohno Y, Hirakawa T, Shii Y, *et al*. Hepatoprotective and hepatotoxic actions of oleanolic acid-type triterpenoidal glucuronides on rat primary hepatocyte cultures. Chem Pharm Bull (Tokyo). 1999; 47(2):290-292. https://doi.org/10.1248/cpb.47.290 PMid:10071859
48. Xu GB, Xiao YH, Zhang QY, Zhou M, Liao SG. Hepatoprotective natural triterpenoids. Eur J Med Chem. 2018; 145:691-716. https://doi.org/10.1016/j.ejmech.2018.01.011 PMid:29353722
49. Chen P, Zeng H, Wang Y, Fan X, Xu C, Deng R, *et al*. Low dose of oleanolic acid protects against lithocholic acid-induced cholestasis in mice: Potential involvement of nuclear factor-E2-related factor 2-mediated upregulation of multidrug resistance-associated proteins. Drug Metab Dispos. 2014; 42(5):844-852. https://doi.org/10.1124/dmd.113.056549 PMid:24510383
50. Lin YN, Chen CJ, Chang HY, Cheng WK, Lee YR, Chen JJ, *et al*. Oleanolic acid-mediated inhibition of pregnane x receptor and constitutive androstane receptor attenuates rifampin-isoniazid cytotoxicity. J Agric Food Chem. 2017; 65(39):8606-8616. https://doi.org/10.1021/acs.jafc.7b02696 PMid:28945086
51. Liu J, Wang X, Liu R, Liu Y, Zhang T, Fu H, *et al*. Oleanolic acid co-administration alleviates ethanol-induced hepatic injury via Nrf-2 and ethanol-metabolizing modulating in rats. Chem Biol Interact. 2014; 221:88-98. https://doi.org/10.1016/j.cbi.2014.07.017 PMid:25111957
52. Kim KA, Lee JS, Park HJ, Kim JW, Kim CJ, Shim IS, *et al*. Inhibition of cytochrome P450 activities by oleanolic acid and ursolic acid in human liver microsomes. Life Sci. 2004; 74(22):2769-2779. https://doi.org/10.1016/j.lfs.2003.10.020 PMid:15043991
53. Sureda A, Monserrat-Mesquida M, Pinya S, Ferriol P, Tejada S. Hypotensive effects of the triterpene oleanolic acid for cardiovascular prevention. Curr Mol Pharmacol. 2021; 14(6):935-942. https://doi.org/10.2174/1874467213999201230211544 PMid:33390142
54. Senthil S, Sridevi M, Pugalendi KV. Cardioprotective effect of oleanolic acid on isoproterenol-induced myocardial ischemia in rats. Toxicol Pathol. 2007; 35(3):418-423. https://doi.org/10.1080/01926230701230312 PMid:17455091
55. De Stefani C, Vasarri M, Salvatici MC, Grifoni L, Quintela JC, Bilia AR, *et al*. Microemulsions enhance the *in vitro* antioxidant activity of oleanolic acid in RAW 264.7 cells. Pharmaceutics. 2022; 14(10): 2232. https://doi.org/10.3390/pharmaceutics14102232 PMid:36297667 PMCid:PMC9610975
56. Yang EJ, Lee W, Ku SK, Song KS, Bae JS. Anti-inflammatory activities of oleanolic acid on HMGB1 activated HUVECs. Food Chem Toxicol. 2012; 50(5):1288-1294. https://doi.org/10.1016/j.fct.2012.02.026 PMid:22386814
57. Dharmappa KK, Kumar RV, Nataraju A, Mohamed R, Shivaprasad HV, Vishwanath BS. Anti-inflammatory activity of oleanolic acid by inhibition of secretory phospholipase A2. Planta Med. 2009; 75(03):211-215. https://doi.org/10.1055/s-0028-1088374 PMid:19085684
58. Li W, Guo Y, Zhang C, Wu R, Yang AY, Gaspar J, *et al*. Dietary phytochemicals and cancer chemoprevention: A perspective on oxidative stress, inflammation, and epigenetics. Chem Res Toxicol. 2016; 29(12):2071-2095. https://doi.org/10.1021/acs.chemrestox.6b00413 PMid:27989132
59. Nkeh-Chungag BN, Oyedeji OO, Oyedeji AO, Ndebia EJ. Anti-inflammatory and membrane-stabilizing properties of two semisynthetic derivatives of oleanolic acid. Inflammation. 2015; 38:61-69. https://doi.org/10.1007/s10753-014-0007-y PMid:25173889
60. Zhang B, Zhang W, Luo J, He J, Zheng X, Zhu S, *et al*. Effects of oleanolic acid on hair growth in mouse dorsal skin mediated via regulation of inflammatory cytokines. J Appl Biomed. 2023; 21(1):48-57. https://doi.org/10.32725/jab.2023.003 PMid:37016778
61. Kim YJ, Lee JE, Jang HS, Hong SY, Lee JB, Park SY, *et al*. Oleanolic acid protects the skin from particulate matter-induced aging. Biomol Ther (Seoul). 2021; 29(2):220. https://doi.org/10.4062/biomolther.2020.106 PMid:32952129 PMCid:PMC7921861
62. Fu H, Yen FL, Huang PH, Yang CY, Yen CH. Oleanolic acid nanofibers attenuated particulate matter-induced oxidative stress in keratinocytes. Antioxidants. 2021; 10(9):1411.

https://doi.org/10.3390/antiox10091411 PMid:34573043 PMCid:PMC8469115
63. Kang YM, Kim HM, Lee M, An HJ. Oleanolic acid alleviates atopic dermatitis-like responses *in vivo* and *in vitro*. Int J Mol Sci. 2021; 22(21):12000. https://doi.org/10.3390/ijms222112000 PMid:34769428 PMCid:PMC8584529
64. Mabandla MV, Nyoka M, Daniels WM. Early use of oleanolic acid provides protection against 6-hydroxydopamine induced dopamine neurodegeneration. Brain Res. 2015; 1622: 64-71. https://doi.org/10.1016/j.brainres.2015.06.017 PMid:26111646
65. Ndlovu BC, Daniels WM, Mabandla MV. Amelioration of L-Dopa-associated dyskinesias with triterpenoic acid in a Parkinsonian rat model. Neurotox Res. 2016; 29:126-134. https://doi.org/10.1007/s12640-015-9567-3 PMid:26459303
66. Caltana L, Rutolo D, Nieto ML, Brusco A. Further evidence for the neuroprotective role of oleanolic acid in a model of focal brain hypoxia in rats. Neurochem Int. 2014; 79:79-87. https://doi.org/10.1016/j.neuint.2014.09.011 PMid:25280833
67. Wasim M, Bergonzi MC. Unlocking the potential of oleanolic acid: Integrating pharmacological insights and advancements in Delivery systems. Pharmaceutics. 2024; 16(6):692. https://doi.org/10.3390/pharmaceutics16060692 PMid:38931816 PMCid:PMC11206505
68. Lu YF, Wan XL, Xu Y, Liu J. Repeated oral administration of oleanolic acid produces cholestatic liver injury in mice. Molecules. 2013; 18(3):3060-3071. https://doi.org/10.3390/molecules18033060 PMid:23470335 PMCid:PMC6270117
69. Jeong DW, Kim YH, Kim HH, Ji HY, Yoo SD, Choi WR, *et al*. Dose-linear pharmacokinetics of oleanolic acid after intravenous and oral administration in rats. Biopharm Drug Dispos. 2007; 28(2):51-57. https://doi.org/10.1002/bdd.530 PMid:17163409
70. Piet M, Paduch R. Ursolic and oleanolic acids in combination therapy inhibit migration of colon cancer cells through down-regulation of the uPA/uPAR-dependent MMPs pathway. Chem Biol Interact. 2022; 368:110202. https://doi.org/10.1016/j.cbi.2022.110202 PMid:36191607
71. Esmaeili H, Sabet MN, Mosaed R, Chamanara M, Hadi S, Hazrati E, *et al*. Oleanolic acid increases the anticancer potency of doxorubicin in pancreatic cancer cells. J Biochem Mol Toxicol. 2023; 37(10):e23426. https://doi.org/10.1002/jbt.23426 PMid:37345903
72. Puenea G, Almajan-Guța BO, Chioibaș R, Macașoi I, Geamantan A, Dinu Ș, *et al*. Evaluation of oleanolic acid, doxorubicin and their association in the treatment of melanoma: Enhanced efficacy and antiangiogenic potential. Farmacia. 2023; 71(6):1295-1304. https://doi.org/10.31925/farmacia.2023.6.21
73. Wang X, Chen Y, Abdelkader D, Hassan W, Sun H, Liu J. Combination therapy with oleanolic acid and metformin as a synergistic treatment for diabetes. J Diabetes Res. 2015; 2015(1):973287. https://doi.org/10.1155/2015/973287 PMid:25789330 PMCid:PMC4350965
74. Han-Qiong LU, Jie SH, Cai-Ping CH, Xiao MA, Chao LI, Chun-Xiao XU, *et al*. Lipid-lowering effects of oleanolic acid in hyperlipidemic patients. Chin J Nat Med. 2018; 16(5):339-346. https://doi.org/10.1016/S1875-5364(18)30065-7 PMid:29860994
75. Santos-Lozano JM, Rada M, Lapetra J, Guinda Á, Jiménez-Rodríguez MC, Cayuela JA, *et al*. Prevention of type 2 diabetes in prediabetic patients by using functional olive oil enriched in oleanolic acid: The Prediabole study, a randomised controlled trial. Diabetes Obes Metab. 2019; 21(11):2526-2534. https://doi.org/10.1111/dom.13838 PMid:31364228
76. Luo Q, Wei Y, Lv X, Chen W, Yang D, Tuo Q. The effect and mechanism of oleanolic acid in the treatment of metabolic syndrome and related cardiovascular diseases. Molecules. 2024; 29(4):758. https://doi.org/10.3390/molecules29040758 PMid:38398510 PMCid:PMC10892503
77. Gutiérrez-Rebolledo GA, Siordia-Reyes AG, Meckes-Fischer M, Jiménez-Arellanes A. Hepatoprotective properties of oleanolic and ursolic acids in antitubercular drug-induced liver damage. Asian Pac J Trop Med. 2016; 9(7):644-651. https://doi.org/10.1016/j.apjtm.2016.05.015 PMid:27393091