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Review

Application and Development of Natural Plant Metabolite Oleanolic Acid in the Nano Era

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Abstract: Like other pentacyclic triterpenoids, oleanolic acid, a natural plant metabolite prevalent in plant peels, stems, and leaves, is regarded as a possible drug candidate. A growing number of studies have shown that oleanolic acid exhibits a variety of beneficial properties, including antiviral, anti-inflammatory, antioxidant, anticancer, and hepatoprotective effects. Additionally, the rapid advance of nanotechnology has dramatically improved oleanolic acid's bioavailability and minimized its disadvantages, leading to unexpected changes in its pharmacological activity and use. Therefore, our aim was to review the progress of research on the distribution and biological properties of oleanolic acid in plants and to discuss new pharmaceutical approaches for oleanolic acid.

Keywords: oleanolic acid; nano; nanoparticles; anti-inflammatory; antitumor

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1. Introduction

It is widely recognized that terpenoids are among the very common and most complex natural chemicals found, richly, in plants in nature, and they have a wide range of pharmacological effects [1]. They are recognized as potential drug compounds, among which sesquiterpenoids, represented by artemisinin, are well-known for their remarkable therapeutic effects on malaria [2]. In recent years, researchers have been focusing more on the extraction, analysis, and structural modification of the isolated active ingredients from the natural products of terpene-containing plants. Additionally, the recent decades have seen a surge in interest in triterpene-rich plant extracts, particularly pure triterpenoids such as bioactive phytochemicals [3–6].

There are two subclasses of triterpenoids based on their chemical structure: pentacyclic triterpenes and tetracyclic triterpenes [7]. Among them, oleanolic acid (OA, Figure 1) and its isomer ursolic acid (UA, Figure 1) are pentacyclic triterpenoid bioactive substances commonly found in fruits and vegetables, and both possess similar physicochemical and biological properties, such as anti-inflammatory, antioxidant, antiviral, anticancer, antidiabetic, hepatoprotective, and cardioprotective effects [8–15]. OA research has gained increasing attention due to its rich biological properties. In the pharmaceutical field, however, its development is hindered, and it is unable to fully exploit its therapeutic effects as a result of its poor water solubility and low bioavailability when taken orally [16]. To address these challenges, a number of new technologies have been developed by researchers, such as preparing new dosage forms of OA and modifying its molecular formula. In particular, nanotechnology, embodied by nanoparticles, as a novel and efficient method of drug preparation, exhibits remarkable effects on improving the dissolution, penetration, and absorption of OA, and its unique combination makes drugs containing OA achieve precise targeting effects [17–19].

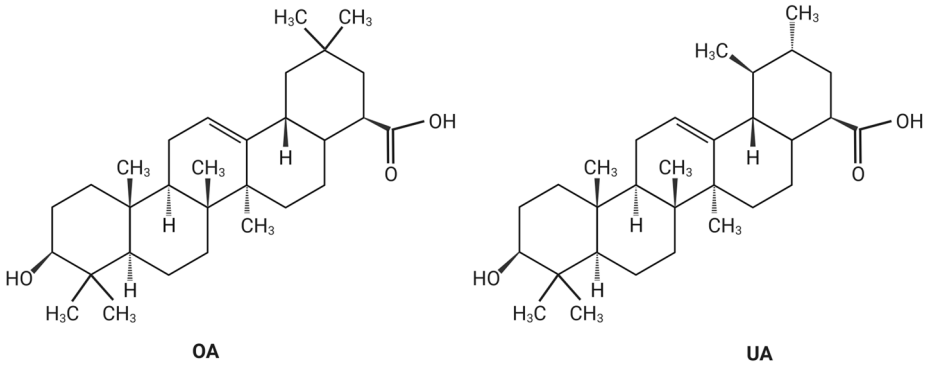

Figure 1. Chemical structures of oleanolic acid and ursolic acid (drawn according to [1]).

In this review, we first examine the most recent findings of OA in vivo and in vitro experimental models, its biological features, and the state of related research and then describe and assess the various methods used to manufacture OA and their bioavailability. The purpose of this study is to serve as a reference for the future research, development, and application of OA.

2. Sources of Oleanolic Acid

Oleanolic acid (3β-hydroxyolean-12-en-28-oic acid) is a natural pentacyclic triterpenoid, with a name that is derived from the plant *Olea europaea*, the primary source of commercial OA preparations at the moment [20]. Pentacyclic triterpenes, important phytochemicals synthesized by the cyclization of squalene in plants, are known as a large class of plant secondary metabolites composed of isoprene (2-methylbutadiene) units [21]. Oleanane, hopane, friedelane, ursane, gammacerane, and lupine are major pentacyclic triterpenes that mainly exhibit antiviral, antitumor, anti-inflammatory, and antioxidant activities [22].

Oleanolic acid can be extracted from different parts of Araliaceae, Asteraceae, Ericaceae, Lamiaceae, Myrtaceae, Oleaceae, Rosaceae, Rubiaceae, Saxifragaceae, and Verbenaceae plants, but its content differs from one plant to another and in different parts of the same plant (Table 1). For instance, studies have shown significant differences in OA content in the fresh leaves and persimmon pulp of different peony varieties [23,24]. Additionally, certain plants have only one organ that contains OA. In birch, for instance, OA is exclusively found in the bark (up to 11 mg/g DW) [25]. OA can also be found in garden thyme and clove plants. Some of the fruit plants where OA has been found and isolated are apple, loquat, grape, elderberry, and sage [25,26]. Notably, a growing number of researchers have examined the abundance of OA in apples, particularly in apple peels, due to their rich content of triterpenoids' active substances and their ubiquity in the daily diet. As shown by the test results, OA and UA are the main triterpenoid active substances in apple peel extract [27,28]. The level of OA in apple flesh is found to reach 0.28 g/100 g in published research [25]. Although apples are an important food source for humans and a raw material in the food industry, only a small fraction of their leaves are used in certain foods, and the vast majority are underutilized as agricultural waste. To explore new sources of natural antioxidants, anticancer, and anti-inflammatory drugs, researchers have developed new methods for the extraction and detection of OA from apples, such as techniques to enhance extraction rates, including ultrasound-assisted extraction, microwave-assisted extraction, and supercritical fluid carbon dioxide [29–31]. Chromatographic techniques that can be used to assess the quantitative and qualitative composition of triterpenoids include high-performance liquid chromatography, gas chromatography, and thin-layer chromatography combined with tandem mass spectrometry [32,33].

Table 1. Natural sources of OA.

Plant Species	Family	Plant Part	Biological Activity	Reference
Betula alba	Betulaceae	Bark	Anti-inflammatory, anti-bacterial, anti-viral, antitumor	[25,34]
Crataegus pinnatifida	Rosaceae	Leaves	Anti-inflammatory, anti-bacterial, anti-viral, antitumor	[25]
Eriobotrya japonica	Rosaceae	Flowers	Not mentioned	[35]
Fabiana imbricata	Solanaceae	Leaves and flowers	Antiviral, antitumor, antihyperlipidemic	[36]
Ligustrum lucidum Ait	Oleaceae	Fruits, leaves	Anti-hepatitis, anti-inflammatory, antioxidative, antiprotozoal, antimutagenic, anticancer	[37–39]
Gentiana lutea	Gentianaceae	Rhizome	Antimicrobial	[14]
Lavandula angustifolia	Lamiaceae	Herbs	Anti-inflammatory, anti-bacterial	[25]
Lantana camara	Verbenaceae	Leaves and flowers	Anti-inflammatory, antioxidative, antiprotozoal	[39]
Melissa officinalis	Lamiaceae	Herbs	Antiviral, hepatoprotective	[25,40,41]
Nerium oleander	Apocynaceae	Leaves	Not mentioned	[25]
Olea europaea L.	Oleaceae	Fruits, bark, leaves	Anticancer, antimicrobial, anti-diabetic	[25,42–45]
Origanum majorana	Lamiaceae	Herbs	Not mentioned	[25]
Panax quinquefolium	Araliaceae	Roots	Anticancer, anti-diabetes, neuroprotection, anti-Aging	[46,47]
Phyllanthus amarus	Phyllanthaceae	Leaves, aerials	Anti-diabetes	[48]
Punica granatum L.	Lythraceae	Fruit	Antioxidant activity	[13]
Rosmarinus officinalis L.	Lamiaceae	Leaves, flowers, stems, branches	Anti-inflammatory, hepatoprotective, gastroprotective, antiulcer	[43]
Rosa laevigata	Rosaceae	Leaves	Anti-inflammatory	[49]
Syzygium aromaticum	Myrtaceae	Leaves, flower buds	Antinociceptive, Anti-inflammatory, antihypertensive, antioxidant	[36,50]
Sambucus nigra	Adoxaceae	Leaves, bark	Anticancer	[25,51]
Satureja montana	Lamiaceae	Herbs	Anticancer, anti-bacterial	[25,52,53]
Siphonodon celastrineus	Celastraceae	Root bark, stems	Anti-inflammatory	[54,55]
Silphium trifoliatum	Asteraceae	Leaves	Anti-bacterial	[46,56]
Salvia officinalis	Lamiaceae	Herbs	Anti-bacterial, anti-inflammatory, anticancer, antioxidative	[25,57,58]
Thymus vulgaris	Lamiaceae	Herbs	Glutaminase inhibitor	[25,59]
Viscum album	Santalaceae	Leaves, stems	Antitumor, analgesic, anti-inflammatory	[39,60,61]
Viburnum chingii	Adoxaceae	Leaves	Antimicrobial	[54,62]

3. Pharmacological Effects of Oleanolic Acid

In spite of its wide range of pharmacological properties, OA's therapeutic potential has only been partially exploited. Studies on triterpenoids have shown that OA exerts beneficial effects through various signaling pathways, such as antiviral, anti-HIV, antibacterial, anticancer, antidiabetic, anti-inflammatory, hepatoprotective, gastroprotective, hypolipidemic, and anti-atherosclerotic effects (Table 2). Apart from its beneficial role in preventing cardiovascular disease, obesity, and metabolic syndrome, OA improves insulin response, maintains beta cell function and survival, and prevents diabetic complications [63,64].

Table 2. Pharmacological actions and signaling pathways of OA.

Signaling Pathway	Biological Activity	Reference
Nuclear factor-κB (NF-κB) signaling pathway	Anti-inflammatory, antitumor	[65–68]
Nod-like receptor pyrin domain containing 3 (NLRP3) signaling pathway	Anti-inflammatory, neuroprotection	[69–71]
Extracellular-signal-regulated kinase (ERK) signaling pathway	Liver protection, antitumor	[72,73]
Protein kinase B/Akt signaling pathway	Antitumor, liver protection	[72,74,75]
Jun N-terminal kinases (JNK) signaling pathway	Antitumor	[1,75]
Orphan receptor γ t signaling pathway	Anti-inflammatory, anti-asthma	[76]
Mitogen-activated protein kinases (MAPK) signaling pathway	Anti-inflammatory	[77,78]
MiR-122/cyclin G1/myocyte enhancer factor 2D (miR-122/CCNG1/MEF2D) signaling pathway	Antitumor	[79]
Cyclic adenosine 3′,5′-monophosphate/protein kinase A (cAMP/PKA) signaling pathway	Lowers blood sugar and blood lipids, protects pancreatic islets	[80]
Phosphatidylinositol 3-kinase/AKT/mammalian target of rapamycin (PI3K/AKT/mTOR) signaling pathway	Anti-osteoarthritis	[81]
Endothelial nitric oxide synthase/Akt/nitric oxide (eNOS/Akt/NO) signaling pathway	Ameliorates high glucose-induced endothelial dysfunction	[82]
Signal transducer and activator of transcription 3 (STAT3) and sonic hedgehog (SHH) signaling pathway	Inhibits colorectal cancer	[83]
Mitogen-activated protein kinase kinase (MEK)/ERK/JNK signaling pathway	Anticancer	[84]
Hippo-Yes-associated protein (Hippo-Yap) signaling pathway	Anti-stomach cancer	[85]
Epidermal growth factor (EGFR)/AKT signaling pathway	Anti-pancreatic cancer	[86]
Nuclear factor erythroid 2-related factor 2 (Nrf-2) signaling pathway	Liver protection, antidiabetic, anti-inflammatory, maintenance of redox and protein homeostasis	[87–89]

3.1. Anti-Inflammatory Effect of OA

The capacity of OA to alter a number of anti-inflammatory pathways has been demonstrated in animal studies and cellular research. It can significantly reduce inflammation and inhibit numerous inflammatory diseases, such as vasculitis, enteritis, and bronchitis [90–93]. The anti-inflammatory effect of OA is exerted through a variety of complex mechanisms.

3.1.1. Inhibition of the Production of Pro-Inflammatory Cytokines

In the context of inflammation and oxidative stress, treatment with OA and its derivatives significantly inhibits the production of pro-inflammatory cytokines (IL-1β, IL-6, IL-8, TNF-α, and MCP-1) [68,94–96]. Researchers found that high-fat diet C57BL/6J female mice given oleanolic acid in water feeders at 0.005% (*w*/*v*) for 16 weeks had a significant reduction in the expression levels of IL-1β, IL-6, and TNFα in adipose tissue [97]. The researchers pretreated BV2 cells with OA (0.5 to 10 μM) for 1 h and then with LPS (100 ng/mL) for 24 h

at 37 °C. The results showed that OA reduced the expression levels of TNF-α, IL-1β, and IL-6 in BV2 cells [98]. Researchers have demonstrated that OA ameliorates experimental autoimmune myocarditis (EAM) in several ways, including by promoting anti-inflammatory cytokines (IL-10 and IL-35), interfering with cardiac-specific autoantibody production, and exerting direct protective effects on cardiac cells [15]. In female C57BL/J6 mice with experimental autoimmune encephalomyelitis, OA has also been revealed to decrease pro-inflammatory mediators (TNF-α, IL-1β, IL-23, IL-17A, chemokine KC, and the growth factor IGF-1) both in serum and colonic tissue, prevent lipid peroxidation and superoxide anion accumulation in intestinal tissue, and induce the expression of the ROS scavenger Sestrin-3 [99].

3.1.2. Increase Antioxidant Production

The anti-inflammatory effect of OA is related to the regulation of antioxidant production. This mechanism is related to the expression of transcription factors Nrf2 and MAP kinase that are oxidative-stress-sensitive [100,101]. OA has also been proven to protect rats from ethanol-induced liver injury by inducing Nrf2-associated antioxidants, thereby maintaining redox homeostasis and modulating ethanol metabolism and inflammatory pathways [102]. As a ubiquitous nuclear transcription factor, NF-κB participates in the transcription of target genes and regulates cell proliferation, differentiation, growth, and apoptosis. As reported in previous studies, OA suppresses inflammation by inhibiting NF-κB signaling and regulating pro-inflammatory cytokines such as TLR-9 and IL-18 [66,103].

3.1.3. Inhibition of Activation of Mitochondria-Associated Inflammatory Vesicles

Mitochondria may be a basic target when OA improves inflammation, as they are organelles that contribute to oxidative stress and neuroinflammation [104]. In mitochondrial organelles, an essential component of innate immune response is DNA synthesis, and mitochondrial DNA binds to NLRP3 containing inflammasome to activate inflammasome [105,106]. There is evidence that OA ameliorates carotid artery injury in diabetic Sprague Dawley rats by inhibiting the NLRP3 inflammasome signaling pathway. Researchers induced a diabetic rat model with streptozotocin (60 mg/kg), followed by 2 weeks of treatment with OA (100 mg/kg/day) injection. OA reversed the hyperglycemia-induced upregulation of the NLRP3 inflammasome components in diabetic rats. In addition, the levels of TNF-α, interleukin (IL)-1β, IL-6, and IL-18 were downregulated in the serum of OA-treated diabetic rats [70]. Additionally, through the inhibition of NLRP3 inflammasome activation, OA attenuates microglia activation and oxidative stress, thereby achieving the neuroprotective effect of OA against ischemic stroke. Researchers found that OA (10 mg/kg, p.o.) attenuates NLRP3 inflammasome activation in a male ICR mouse model of transient middle cerebral artery occlusion. Moreover, OA inhibits the assembly of NLRP3 inflammasome in the injured brain after ischemic stroke [71]. Since various diseases are strongly associated with the activation of NLRP3 and its related molecular regulatory signaling pathways, NLRP3 is an exciting frontier for clinical drug research and development [107]. Effects such as anti-inflammatory or antitumor, which are attributed to inhibiting the signaling pathway of NLRP3 inflammasome, reveal potential targets of OA as an anti-inflammatory agent. In contrast, the highly variable nature of NLRP3 inflammasome agonists allows them to be triggered by many different stimuli, and the specific mechanisms behind this need to be identified in more detail.

3.2. Antitumor Effect of Oleanolic Acid

Compared with synthetic compounds, the natural product OA exhibits rich structural diversity and better preventive and anticancer-drug-like properties. It has become one of the research hotspots for anticancer drug development. OA was found to be effective in treating various tumor cell lines, such as MCF-7 and MCF-7/ADR human breast cancer cells, the 1321N1 astrocytoma cell line, hepatocellular carcinoma, and HCT-116 colorectal cancer cells [108]. The antitumor mechanisms of OA mainly include anticancer cell proliferation,

induction of apoptosis, induction of autophagy, regulation of cell cycle regulatory proteins, inhibition of vascular endothelial growth, anti-angiogenesis, and inhibition of tumor cell migration and invasion (Figure 2). More importantly, the use of OA for cancer treatment was found to be less toxic to cancer cells than to normal cells and more biosafe than other treatments [109]. Therefore, OA exhibits considerable potential in anticancer applications.

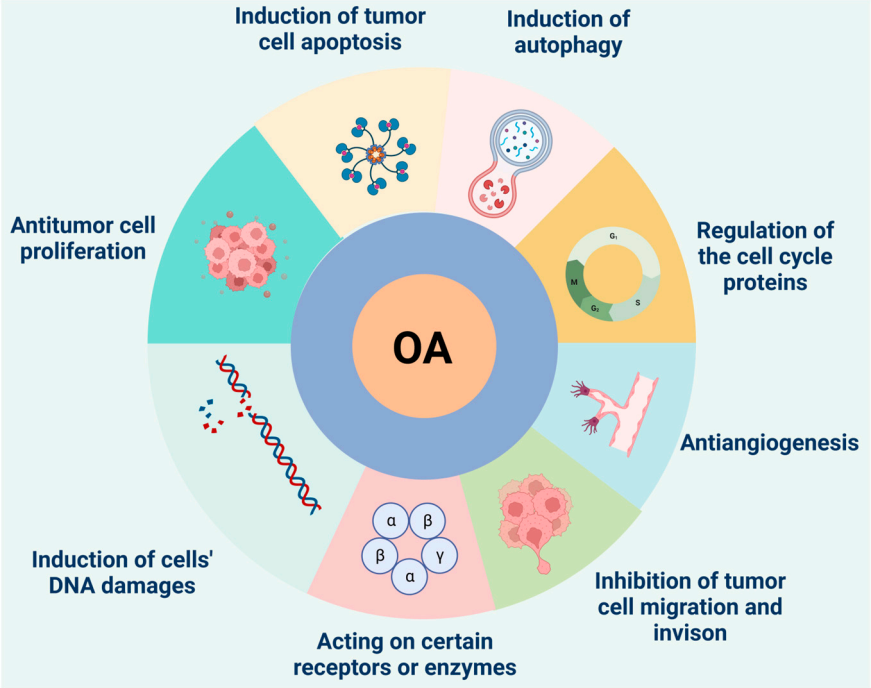

Figure 2. Anticancer ways of OA.

3.2.1. Inhibition of Tumor Cell Proliferation

Oleanolic acid exhibits inhibition of tumor cell proliferation by participating in multiple anticancer signaling pathways and intracellular substance regulation, such as the Akt/mTOR/S6K pathway and the inhibition of macrophage M2 polarization. Mouse model experiments have shown that OA inhibits the proliferation of KRAS-transformed normal cells by attenuating the Akt/mTOR/S6K signaling cascade. In addition, OA also inhibits cancer cell proliferation by suppressing both the mTOR signaling pathway and PI3K/Akt/mTOR signaling pathway [110]. According to experimental findings, OA significantly inhibits the expression of CD163, one of the phenotypic markers of M2 macrophages, and the secretion of IL-10, an anti-inflammatory cytokine produced by M2 macrophages, suggesting that OA's inhibition of cell proliferation occurs through the suppression of the M2 polarization of macrophages [111].

Notably, the reduction in aerobic glycolysis and glycolytic enzymes is suggested to be a mechanism by which OA inhibits tumor cell proliferation. As shown in studies, there is a positive correlation between aerobic glycolysis and cancer cell proliferation, and a high-sugar environment promotes both aerobic glycolysis and cancer cell proliferation [112]. In gastric cancer cells, the proliferation of gastric tumor cells is largely dependent on aerobic glycolysis, whereas OA can reduce HIF-1α-mediated aerobic glycolysis by inhibiting YAP. The specific mechanism is that OA can inhibit glucose uptake and consumption and downregulate the expression of the glycolytic-rate-limiting enzymes HK2 and PFK1 [11]. It is noteworthy that a novel signaling pathway called Hippo-Yap plays a critical role in the growth and progression of tumors, making it a potential therapeutic target for OA in cancer treatment.

There are multiple pathways by which OA inhibits tumor cell proliferation, including reducing the expression of Bcl-2, Cyclin D1, and CKD4, promoting the expression of

Bax and p21, enhancing the activation of p53, etc. [113]. The proliferation of human glioblastoma cells U373 was found to be inhibited by OA when OA activates STAT3 in human macrophages and glioblastoma cells [110]. Moreover, a reduction in gastric cancer cells proliferation is spotted when OA inhibits the expression of cell cycle protein A and cell cycle protein-dependent kinase 2 [114].

3.2.2. Induction of Apoptosis in Tumor Cells

One of the key pathways in tumor therapy is the induction of apoptosis. There is evidence that pentacyclic triterpenoids interfere with multiple stages of cancer development, inhibit tumorigenesis and evolution, and induce apoptosis in several cancers [115,116]. For instance, a variety of tumor cells are induced to undergo apoptosis by OA, including HepG2 cells, human breast cancer MCF-7 cells, HT-29 colon cancer cells, and prostate cancer cells [85,117].

Multiple signaling pathways are involved in the OA-induced apoptosis in tumor cells. One of them is the inhibition of NF-κB activity [118]. OA was shown to inhibit NF-κB expression and regulate the mRNA expression level of the X-linked inhibitor of the apoptosis protein (XIAP) in HuH7 cells compared to untreated cells [119]. Another proven mechanism that promotes apoptosis is that OA inhibits COX-2 overexpression in tumor cells [120]. Here, COX-2 is overexpressed in a variety of tumor cells as a rate-limiting enzyme for prostaglandin synthesis, suggesting its participation in cancer promotion and progression [121]. In human colon cancer HT-29 cells and HepG2 cells, OA is reported to decrease COX-2 protein activity and inducible nitric oxide synthase (INOS) expression, thereby inducing apoptosis [73,122].

3.2.3. Induction of Autophagy

There is an association between OA's anticancer properties and cellular autophagy. As evidenced by the elevated ROS levels in cells after OA treatment, OA-triggered cellular autophagy proceeds in an ROS-dependent manner. A significant inhibition of the growth of HepG2 and SMC7721 cells is achieved as a result of autophagy induction and inhibition of the PI3K/Akt1/mTOR signaling pathway in response to OA treatment [123]. According to another study in bladder cancer T24 cells (ULK1), the mechanisms through which OA causes autophagy include the activation of AMP-activated protein kinase (AMPK), the blocking of the mTOR molecular target, and the increase in UNC-51-like autophagy-activated kinase 1 [124]. There is further evidence that the inhibition of the Akt/mTOR/S6K pathway contributes to OA-induced autophagy [110]. Moreover, most natural compounds were found to induce autophagy primarily through the Akt/mTOR/S6K pathway [125]. There are other autophagy regulatory pathways, such as ERK and JNK, which were shown to be activated in response to OA treatment, indicating their possible association with OA-induced autophagy [126]. It is, therefore, imperative to conduct more research to understand the mechanism of OA-induced apoptosis, which is crucial for the creation of OA-related anticancer medications.

3.2.4. Regulation of Cell Cycle Regulatory Proteins

In different cancers, the expression of cell cycle regulatory proteins may be affected by OA in different ways, resulting in cell cycle arrest at different stages and apoptosis induction in cancer cells. In prostate cancer PC-3, DU145, and LNCaP cells, OA is proven to promote G0/G1 phase cell cycle arrest in a dose-dependent manner by regulating the expression levels of cell-cycle-related proteins. The researchers discovered that certain doses of OA independently inhibit cell cycle progression. In cell lines pretreated with different doses of OA (15, 30, 45, and 60 μM), there was a significant increase in the percentage of cells in the G0/G1 phase but a considerate reduction in the percentage of cells in S phase, as compared to controls [42]. According to previous findings, OA-treated DU145 cells are arrested in G2 because of the activation of p-AKT, p-JNK, p21, and p27, accompanied by the downregulation of p-ERK, cyclin B1, and CDK2 expression. OA-treated MCF-7 cells

are reported to be arrested in G1 owing to the activation of p-JNK, p-ERK, p21, and p27 and the reduction in p-AKT, cyclin D1, CDK4, cyclin E, and CDK2 expression. Moreover, OA-treated U87 cells also exhibit G1 phase arrest caused by the upregulation of p-ERK, p-JNK, p-AKT, p21, and p27 and the downregulation of cyclin D1, CDK4, cyclin E, and CDK2. It is, thus, concluded that OA arrests the cell cycle at different phases and induces apoptosis in cancer cells [74]. According to these results, different cancers are affected differently by OA's effects on the expression of cell cycle regulatory proteins.

In addition, when it acts on certain receptors or enzymes, OA induces different damages to cellular DNA as an active immunomodulatory component, thereby inhibiting the growth migration, invasion, and progression of tumor cells [127].

3.3. Other Pharmacological Effects

OA is not only protective against acute chemical liver injury, but also against chronic liver-disease-induced fibrosis and cirrhosis [128]. There are several altered gene expression patterns and transcription factors that may contribute to this pathway, including farnesoid x receptor (FXR) and Nrf2-, and MT-related genes [129,130]. By encouraging Nrf2 nuclear accumulation, OA can cause Nrf2-dependent gene deinduction, thus protecting the liver from acetaminophen-induced hepatotoxicity [131].

As demonstrated in another study, after 30 days of oral treatment with OA (10 mg/kg/day) and ethanol (4 g/kg/day), a significant reduction in histopathological damage and serum lipid abnormalities as well as biochemical indices of ethanol-induced oxidative stress, such as elevated lipid hydrogen peroxide in the liver, GSH depletion, and decreased antioxidant enzyme activity, was observed in mice [102]. Based on these findings, OA significantly protects against the development of liver injury through various pathways.

Notably, OA displays great potential as a natural compound for the synthesis of potential antidepressant drugs [132]. It is also evidenced to have low side effects when used as an antidepressant, which further excites researchers [133,134]. Thus, OA is increasingly used by researchers to develop antidepressant drugs. In mice exposed to chronic stress, researchers found that OA (20 mg/kg) can activate the hippocampal brain-derived neu-rotrophic factor (BDNF)-ERK-CREB signaling pathway by regulating miR-132, which produced an antidepressant-like effect [135,136]. Another study revealed that OA (40 mg/kg) exhibited antidepressant-like effects in corticosterone-induced depression through downregulation of SGK1 and GR expression and upregulation of the hippocampal BDNF-AKT/mTOR signaling pathway [137].

Other properties of OA, such as anti-prostate cell proliferation, anti-muscle atrophy, and anti-influenza, have also been demonstrated [137–141]. The effects of OA on cardiovascular activities include anti-arrhythmic, immunomodulatory, anti-hyperlipidemic, vasodilatory, anti-inflammatory, and antioxidant [142–144]. In the liver, OA was shown to control glucose 6 phosphates and forkhead box protein O1, thereby normalizing blood glucose levels in rodents with diet-induced obesity or diabetes [145,146]. It was also found that OA inhibits atherosclerosis by downregulating the expression of inducible nitric oxide synthase in apolipoprotein E knockout mice [147]. In conclusion, OA exerts diverse and complex pharmacological effects, making it a promising drug ingredient, but its mechanism requires further investigation.

4. Development and Utilization of Oleanolic Acid

In the biopharmaceutical classification system, pentacyclic triterpenoids are categorized as Class IV medications. As they are almost insoluble in water and have difficulty penetrating biofilms, their pharmacological actions are limited [148]. Another well-known issue of triterpenoids is their low bioavailability. This is primary because their high lipophilicity and water insolubility can significantly decrease the effectiveness of medication absorption in the gastrointestinal system [149]. Thus, researchers are working on exploring new methods to enhance the biopharmaceutical properties of OA. Two principal ways have been found to improve its water solubility, permeability, and bioavailability. One is to

modify the molecular formula of OA to obtain higher biological activity and a wide range of derivatives, which can serve as the basis for the development of new drugs [85,128]. The other is the preparation of new dosage forms of OA, such as nanoparticles, liposomes, solid dispersions, and phospholipid complexes, to improve its dissolution, penetration, and absorption [18]. Among them, nanoparticle drugs are becoming increasingly popular among researchers due to their extended drug circulation time, high bioavailability, targeted delivery, and higher bioavailability.

4.1. Structural Modification of Oleanolic Acid

It is possible to improve bioavailability and expand the scope of application of OA by chemically altering its structure, which is an effective way to develop new drugs. The C-28 position, A ring, and C ring are the main structural modification sites of OA, and derivatives modified at different positions exhibit a variety of pharmacological activities (Figure 3) [128]. Its diverse biological properties, coupled with its high availability and low production cost, make OA an excellent semi-synthetic modified precursor molecule [150].

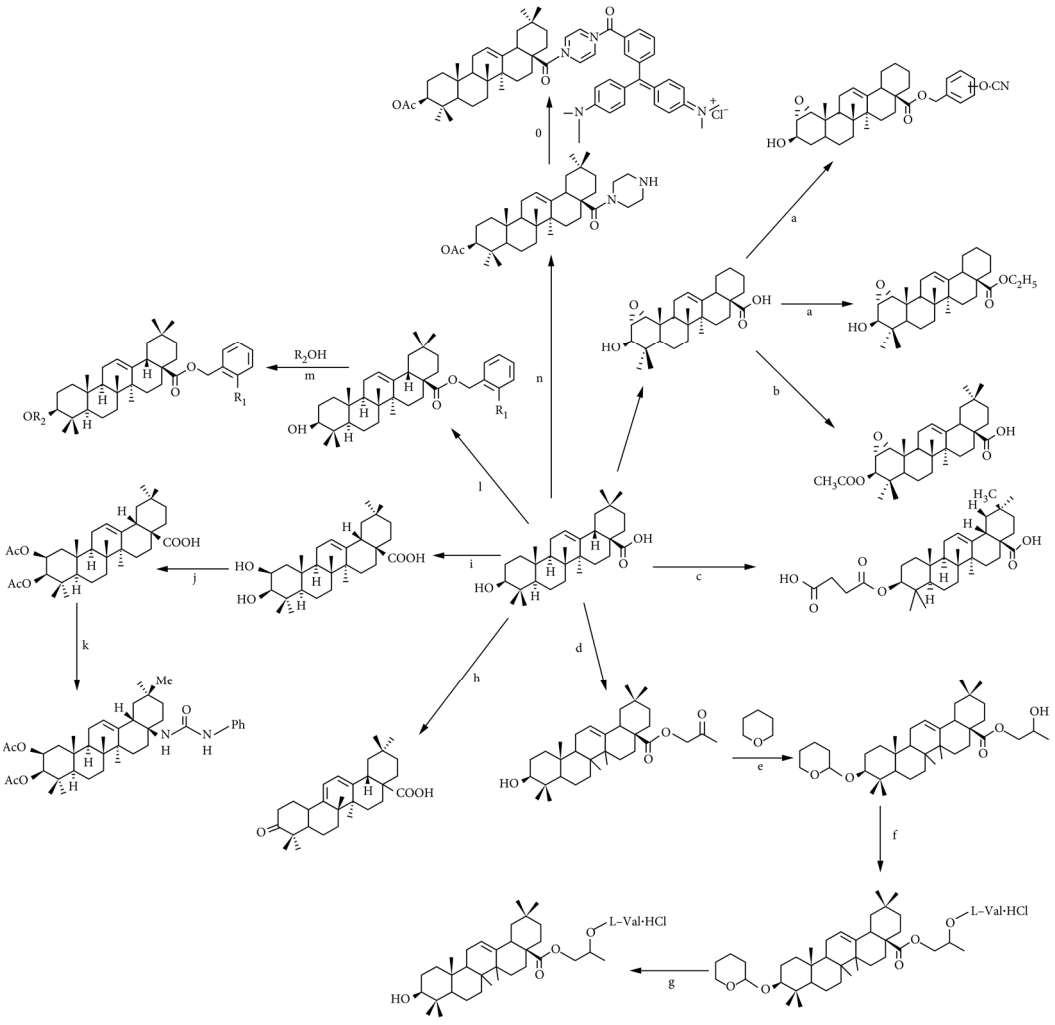

Figure 3. Synthesis of derivatives of oleanolic acid [128].

Many analogs of OA have been synthesized and have exhibited excellent biological activity [128]. Two compounds were prepared from OA isolated from *Syzygium aromaticum* by methylation and acetylation, which have exhibited better in vivo/in vitro anti-inflammatory and membrane stabilization properties, respectively [151–153]. A newly synthesized OA derivative was revealed to have a significant inhibitory effect in vitro and

substantially reduced blood glucose levels compared with OA in in vivo experiments [154]. In lung cancer cells, recently synthesized OA family compound 2 (OLO-2) olean-28 and 13b-olide are shown to promote apoptosis by activating caspase-3, producing ROS, causing DNA damage, and blocking the activation of the ERK, STAT3, AKT, and NF-κB pathways [155]. Another OA derivative, named SZC017, was also prepared by modifying the molecular structure. It can inhibit levels of Akt, phosphorylated-Akt (p-Akt), p-IκBα, total p65, and total p-p65 p-p65 in both the cytoplasm and nucleus and the p65 nuclear translocation to suppress Akt/NF-κB signaling and topoisomerase I and IIα proteins, thus initiating the intrinsic apoptosis of gastric cancer cells [156].

Recently developed OA derivatives have been proven to mitigate OA's weak water solubility, allowing it to demonstrate greater bioavailability. A new OA derivative was revealed to be nearly 20 times more soluble than OA in aqueous solution, release higher amounts of NO in HCC than the normal compound, and exhibit potent anti-HCC activity with little effect on normal hepatocytes [157]. Cyclodextrin encapsulation technology significantly contributes to the synthesis of OA. Tetra-ethylene pentaamine-β-cyclodextrin, a synthetic long-chain amino-β-cyclodextrin derivative, was adopted to prepare OA inclusion complexes, and the finding showed a 2100-fold increase in the water solubility of OA [128]. Researchers also found a drastic promotion of the water solubility of OA by inclusion complexation with amino-appended β-cyclodextrins (ACDs). Moreover, the in vitro anticancer activities of OA against human cancer cell lines HepG2, HT29, and HCT116 are significantly enhanced after the formation of inclusion complexes, and the apoptotic-response results indicate their induction during the apoptosis of cancer cells [158]. This could provide a novel approach to developing novel pharmaceutical formulations of OA. It is noteworthy that the new OA-preparation technique does improve solubility, but its metabolic absorption and bioavailability in vivo have not been sufficiently studied.

While great progress has been made in the structural modification of OA, there are still some issues that need to be explored. Newly synthesized derivatives, for instance, have had few innovative studies, modified dosage forms have not been biologically tested, and OA derivatives have reduced or not significantly improved activity. Taken together, it is necessary to investigate functional groups, pharmacological effects, and unnecessary substituents in chemical-structure modification to make accurate and reasonable modifications.

4.2. Nanoscale Preparation

Nanotechnology has revolutionized the pharmaceutical and biotechnology industries in the 21st century and is seen as a powerful tool for basic research, imaging, and, particularly, enhanced drug delivery. With nano-drug delivery systems, drugs can be delivered at lower doses but perform better therapeutic effects, while improving product bioavailability, safety, and patient compliance [159]. These systems also offer the possibility to deliver highly lipophilic or chemically unstable drugs, thus improving OA's bioavailability, which is hindered by the highly lipophilic and water-insoluble nature of triterpenoids. Moreover, several disadvantages of many natural compounds with poor therapeutic applicability can be addressed by nanocarriers, such as in vivo instability, reduced bioavailability and solubility, low absorption, lack of targeted delivery, and adverse effects. Moreover, nano-based formulations can significantly improve pharmacokinetic parameters and reduce interactions with intracellular proteins, thereby improving the bioavailability of highly lipophilic drugs and achieving targeted delivery to specific sites [160]. In recent years, nanotechnology has been adopted by many researchers to prepare OA.

4.2.1. Nanoliposomes

Liposomes are one of the various nanoparticles that have attracted particular attention because of their structural similarity to biological membranes, high drug loading, and high transport capacity. They possess unique physical and chemical properties as well as high potency and the ability to encapsulate a large number of different molecules [161]. In addition, this type of nanoformulation is highly flexible in preparation, making it possible to

undergo different surface modifications for a wide range of applications in skin applications and gene therapy or as drug delivery systems for different diseases [162]. Nanoliposomes developed from OA show slow release, controlled release, high targeting, reduced toxic side effects, and enhanced antitumor effects [163].

In addition, OA's bioavailability is enormously enhanced after being combined with liposomes (Figure 4). Researchers encapsulated OA in PEGylated liposomes, resulting in good stability, solubility, and diffusion permeability, along with significant drug-carrying capacity and slow in vitro drug release. These OA liposomes have shown superior anticancer activity compared to pure OA and longer drug action through avoidance of Opsonization and macrophage uptake [164]. Chitosan-mediated gold-nanoshell-encapsulated OA liposomes (GNOLs) were also developed by researchers, obtaining a product with an average diameter of 172.03 nm. With a suitable zeta potential, this product is more likely to accumulate in tumor cells. Based on results of in vivo evaluation experiments of GNOLs in U14 tumor-bearing mice, GNOLs exhibit significant inhibitory and pro-apoptotic effects on tumor tissue [163]. Further, liposomes-encapsulated OA is reported to show stronger antitumor activity by synthetic drugs on HeLa cells compared to free OA [158]. The nanoliposome-covered OA is also proved to enhance the anticancer effect by inhibiting proliferation, migration, and invasion [165].

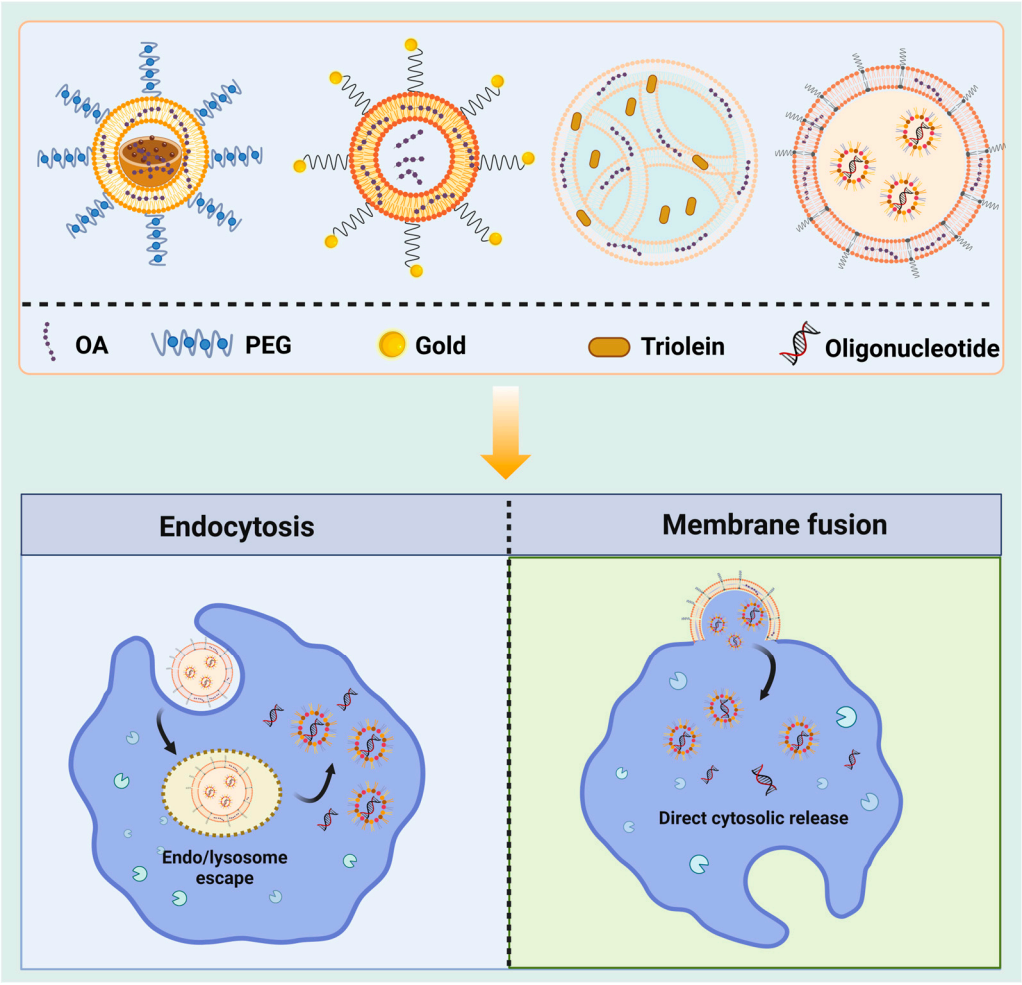

Figure 4. Common modifications and intracellular delivery modes of nanoliposomes.

Oleanolic acid liposomes can attenuate the organ toxicity of related chemotherapeutic drugs. As a result of the combination of OA liposomes and doxorubicin, the effective dose of both compounds is reduced, and the organ toxicity of doxorubicin is also eliminated

without reducing its anticancer effect. Based on histopathological evaluation, liver, kidney, or heart tissues do not show toxic activity, which can be attributed to OA's protective antioxidant properties that protect organs from oxidative stress [166]. A combination of doxorubicin and OA exhibits limited cardiotoxicity without any evidence of histopathological changes in major organs, making it a promising strategy for the future treatment of hepatocellular carcinoma [167].

Notably, some researchers have developed a multivesicular liposome containing OA (OA-MVLs) as a treatment for hepatocellular carcinoma. Compared with pure OA, this compound inhibits the growth of human HepG2 cells and mouse H22 hepatoma more effectively. It exhibits a prolonged drug-circulation time, as a result of the continuous release of active drugs from liposome nanoparticles in in vitro and in vivo experiments. Moreover, OA-MVLs can inhibit the adhesion, migration, and invasion of hepatocellular carcinoma cells at low doses without damaging normal hepatocytes [168].

Taken together, OA-MVLs are considered as a potential drug candidate for cancer treatment in the future as a result of their simple preparation and promising biological effects.

4.2.2. Nanoparticles

Biodegradable polymeric nanoparticles (NPs) offer an excellent option for developing and utilizing OA. In comparison with conventional drug formulations, NPs can slow down the drug release rate, prolong the drug-circulation time, reduce the required dose of drug delivery, and improve the pharmacodynamic effects of a drug in preclinical models [18,128]. In particular, since NPs have an increased permeability and retention effect (EPR), they preferentially collect in tumor and inflammatory tissues, avoiding clearance in the spleen (Figure 5) [169,170]. Incorporating OA into NPs, we can achieve slow release and targetivity, improve antitumor effects, enhance drug safety, and expand drug delivery [17,171,172]. Researchers have developed a novel OA NP-loaded lactoferrin nano-delivery system. OA-NPs disintegrate twice as fast as control OA in in vitro dissolution experiments, and pharmacokinetic studies in rats show a 320.5% relative bioavailability of OA NPs [172]. The ring-opening polymerization (ROP) method was used to synthesize a series of amphiphilic carboxylated cellulose-graft-Poly (L-lactide) (CC-g-PLLA) copolymers that can self-assemble into NPs for delivery of anticancer drug OA. The copolymer (DSPLLA 2.03) NPs display higher drug loading efficiency (24.76 $\pm$ 0.58%). In addition, NPs exhibit better water solubility (16.9 mg/mL) and a prolonged drug release (120 h). In vitro and in vivo studies indicate that NPs maintain cytotoxicity to 4T1 cells and MCF-7 cells and display high antitumor efficiency [173].

Notably, there is a growing interest in the combination therapy with NPs in antitumor studies. It is essential for drug-loaded NPs to avoid elimination by the reticuloendothelial system (RES) to achieve long cycle times. Hydrophilic agents such as polyethylene glycol (PEG) are usually used to modify the surface of NPs to avoid clearance by phagocytosis. This mechanism alters the physicochemical properties of NPs, thus changing the properties of NPs, such as the drug-release profile, biodistribution, and pharmacokinetics [164]. A hydrophobic OA core and a hydrophilic PEG shell were used by researchers to successfully synthesize mPEG-OA NPs that are also capable of encapsulating another anticancer drug hydroxycamptothecin (HCPT) to achieve synergistic effects. As a result, mPEG-OA/HCPT NPs exhibit significantly enhanced anticancer efficacy compared to free drug formulations [174]. Additionally, a range of desirable properties are also exhibited by these co-assembled NPs for co-delivery of anticancer drugs, such as good water solubility, appropriate size, low side effects, and greater bioavailability. Further, researchers constructed a cancer cell membrane-decorated zeolitic-imidazolate framework hybrid nanoparticle (HP) to codeliver cisplatin (DDP) and OA; the results revealed that this platform (HP/DDP/OLA) displays positive feedback in the treatment of bladder cancer (SW780). Moreover, it can enhance apoptosis, while reversing multidrug resistance in SW780 cells, compared to free drugs alone or monodelivery systems [175].

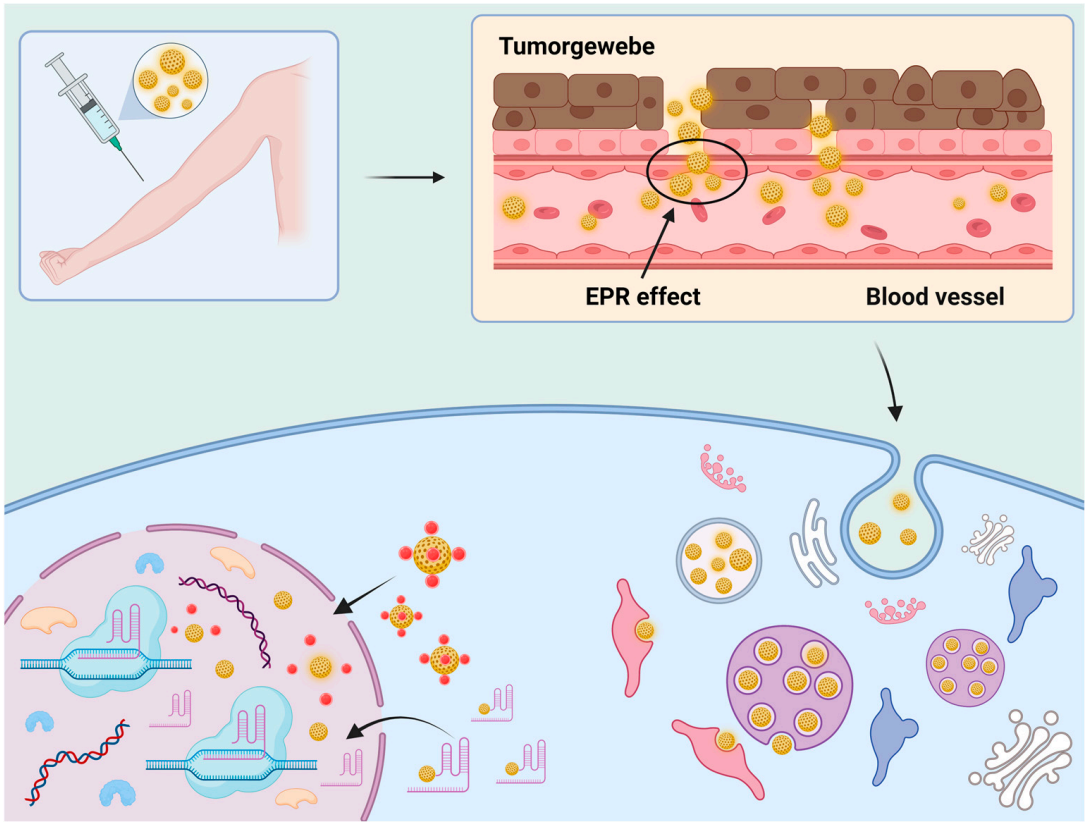

Figure 5. NPs accumulate at tumor sites through EPR effects and targeted delivery systems of NPs.

A pure natural nanomedicine-cum-carrier (NMC) drug delivery system was also designed and fabricated based on bioactive nanomaterials. This system can co-assemble OA and GA into NPs with new morphological characteristics. Natural small-molecule drug carriers retain biological activity and have stronger antitumor effects than non-bioactive drug carriers. Both in vivo and in vitro experiments have confirmed that OA and GA work synergistically to significantly enhance the therapeutic efficacy on tumor therapeutic efficacy. A major reason for this is that OA and GA kill tumors in different mechanisms. In addition, OA/GA NPs are capable of loading up to 15% paclitaxel (PTX). Compared to OA/GA NPs, OA/GA/PTX NPs exhibit enhanced antitumor activity [17].

4.2.3. Other Nanoscale Preparation Methods

An ethanol film hydration was used to prepare OA-loaded hybrid micelles, which were then characterized and evaluated for in vitro release and in vivo drug efficacy. As shown in in vitro drug release studies, approximately 80% of OA was released from the dialysis bag within 24 h, while only 40% of OA micelles was, indicating that the OA micelles achieved a sustained release. In addition, compared to free OA, higher antitumor efficacy was observed with the OA micelles. They also significantly reduced tumor volume and inhibited tumor invasion and migration [176]. Herein, it is safe to conclude that polymer micelles are a promising anticancer-drug delivery system.

OA-loaded nanoemulsions with an average particle size of less than 60 nm were prepared. They were proven to have excellent and stable physical properties based on stability test studies. As evidenced in in vivo experiments, their formulation was non-toxic and non-irritating to the skin. It also had a high skin-penetration ability and can enhance the anti-inflammatory effect of OA. After absorption through the skin, the nanoemulsion made from OA provided a better anti-inflammatory effect [177]. After formulating OA into a nanosuspension, there was an increase of about 550 times in the saturation solubility of OA [178].

In comparison with conventional therapies, nanotechnology has led to greater drug development potential for OA in the treatment of diseases such as cancer. It is possible to further exploit this potential by selecting suitable fabrication methods and nanocarrier-delivery routes to achieve better bioavailability.

5. Conclusions

Oleanolic acid is a natural pentacyclic triterpenoid that can be extracted from various parts of a wide range of plants. Over the past few decades, the potential anti-inflammatory, anticancer, hepatoprotective, and cardioprotective effects of OA and its derivatives have attracted increasing attention from researchers. According to prior studies, OA exerts anti-inflammatory effects by inhibiting the production of pro-inflammatory cytokines, which increases the production of antioxidants or inhibits the activation of mitochondria-associated inflammatory vesicles. Its inflammatory regulatory process involves signaling pathways such as NF-KB and NLRP3. Aside from inhibiting tumor cell proliferation, OA induces apoptosis and autophagy in tumor cells and regulates cell cycle regulatory proteins. It is also possible that the anticancer activity of OA is associated with cell death due to the activation or sensitization of the intracellular pathways of pentacyclic triterpenoids.

Like many other plant compounds, OA possesses many beneficial pharmacological properties. However, its obvious drawbacks cannot be ignored, such as poor water solubility and low bioavailability, which are possibly attributed to the lipophilic nature and low water solubility of OA. Various techniques have been investigated to overcome these drawbacks, such as appropriate structural modification of OA and the application of bio-nanotechnology. In recent years, great progress has been made in the chemical structure modification of OA, and new formulations of OA and its derivatives have sprung up. While sharing some pharmacological properties with OA to some extent, OA derivatives display some distinctive advantages, such as less toxicity, stronger therapeutic effects, and greater bioavailability. As OA NPs are made by nanotechnology, their surface possesses a high modulation that allows them to transport hydrophilic and lipophilic molecules, thus ensuring excellent bioavailability of a drug at specific sites of action. In addition, OA NPs can significantly enhance the solubility of OA and contribute to the distribution of the drug within the body. As compared to monomeric systems, co-assembled NPs and co-loaded hybrid NPs exhibit improved stability and biocompatibility, better responsiveness of drug release, and better performance.

Overall, OA, which is widely found in nature, displays strong biological activity and great research potential. However, there are still some challenges remaining to be addressed in its application into drug development, such as its loading capacity, stability, toxicity, and ability to overcome biological barriers. It is important to utilize appropriate technologies to enhance its biomedical activity. We are confident that with further research and the discovery of new dosage forms, the research and application of OA will be greatly facilitated. More researchers need to explore products that benefit human beings as soon as possible.

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