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# Nanoformulations of Pentacyclic Triterpenoids: Chemoprevention and Anticancer

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## ABSTRACT

One of the greatest difficulties of the twenty-first century is finding safe and effective anticancer medicines. The global incidence of cancer is constantly increasing, endangering the lives of millions of people. Cancer is caused by a variety of reasons, including inappropriate hormone regulation, genetic abnormalities lifestyle and occupational parameters. Plants are the most reliable source of medicine for disease therapy. Anticancer properties can be found in a variety of natural phytochemicals substances. Pentacyclic triterpenoids have been discovered to have anti-inflammatory, blood sugar-regulating, antiviral, antioxidant, cardioprotective, neuroprotective, antiparasitic, growth-stimulating, and antitumor capabilities in recent investigations. Moreover notably, triterpenoids have recently become one of the most relevant issues due to their selective damaging effects on cancer cells while remaining nontoxic to normal cells. Oleanolic acid, lupeol, betulinic acid, ursolic acid are pentacyclic triterpenoids that are generally found in plants, mainly fruits and vegetables, and are extracted and isolated using a variety of methods and chromatography platforms. This review summarized the chemoprevention and remedy of some pentacyclic triterpenoids nanoparticles in many tumors.

**Key words:** Pentacyclic triterpene; Lupeol; Betulinic acid; Ursolic acid; Oleanolic acid; Nanoformulations; Biological effects; Antitumor.

## INTRODUCTION

Cancers are frequently characterized by an unexplained cause, high genetic instability, high histological heterogeneity, a lack of specific biomarkers and a high level of local aggressiveness or spreading, all of which are difficult for contemporary medicine to deal with (Burrell et al. 2013; Li et al. 2020). Despite advancements in pharmaceutical sciences and the discovery of novel medications for specific forms of cancer, several of issues limit their application. Toxicity to normal cells, medication resistance, and a lack of adequate circulation in the body all contribute to the conclusion that cancer is one of the leading causes of death globally (Attia et al. 2019). Apoptosis, a cell's natural death mechanism, is a possible target for cancer treatment. Caspases are used in both the intrinsic and extrinsic pathways to carry out apoptosis by cleaving hundreds of proteins. The apoptotic process is frequently suppressed in cancer by a variety of mechanisms, including antiapoptotic protein overexpression and proapoptotic protein under expression. Many of these alterations result in innate resistance to chemotherapy, the most common anticancer treatment (Danial and Korsmeyer 2004).

Anticancer therapies are frequently based on inhibiting cancer cell proliferation and inducing the apoptosis process to eliminate cancer cells. It is critical that these properties must be restricted to cancer only, with no other side effects on cells that are normal (Pfeffer and Singh 2018). The stimulation of proapoptotic molecules and the inhibition of antiapoptotic molecules are two typical therapeutic targeting techniques. Death-receptor ligands, BCL-2 inhibitors, XIAP inhibition, and alkylphospholipid analogues that act as apoptotic signals are some of the targets that have been studied (Hassan et al. 2014). There has been a surge in interest in plant-derived compounds in recent years that have biological and pharmacological properties that are desired (Dias et al. 2012).

Nanotechnology entails the creation of structures with diameters ranging from 1 to 100 nanometers. Drug delivery vehicles, contrast agents and diagnostic gadgets are all being developed with nanomaterials and several are currently being tested in clinical studies (Kim et al. 2010). Many researchers are interested in nano-formulations of medicinal medicines for drug delivery applications. These nano-formulations improve the characteristics of traditional medications while being tailored to the individual delivery site (Jeevanandam et al. 2016). Nano-formulations such as dendrimers,

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polymeric nanoparticles, liposomes, nano-emulsions and micelles are gaining popularity in the pharmaceutical sector for improved medication formulation. For the creation of nano-formulations to deliver pharmaceuticals in biological systems, a wide range of synthetic methods are available. The size and shape of the particle formulation, the biological characteristics of the medication, and the targeted site all influence the production processes used (Petros and DeSimone 2010).

Studies on pentacyclic triterpenoids have gotten a lot of attention all over the world. fruit`s coat and herbs are the site of them, such as apples, cranberries, olives, and rosemary. Tetracyclic triterpenes and pentacyclic triterpenes are the two types of triterpenes acid, and pentacyclic triterpenes being the most abundant. Tetracyclic triterpenoids contain a methylatedsteroids. Pentacyclic one is categorized as lupane, ursane and oleane, etc. (Muffler et al. 2011). Triterpenes were first used to describe a mixture of isomeric hydrocarbons with the atomic formula $C_{10}H_{16}$ derived from the basic oils found within tissue, tree and plant`s sap. However, there is a trend to refer to hydrocarbons and their oxygenated derivatives as terpenoids, which is a more common term. In any case, certain authors presently use the term terpene to refer to terpenoids (Jäger et al. 2009). In the Western world, average daily consumption of triterpenes is estimated to be around 250 mg, whereas in Mediterranean countries, the average daily intake might be as high as 400 mg. So now, about 30,000 triterpenes have been identified. Plants have a large number of triterpenes, the majority of which are predominantly pentacyclic (seeds, roots, stem park, leaves or the wax like coating of numerous fruits and herpes, like thyme, mistletoe, wild jujupe or lavender). They're also observed in animals and fungi (Patocka 2003).

**General Properties of Terpenoids**

The majority of terpenoids are odorous, colored liquids that seem to be lighter than water and dispersed in nature. Some of them seem to be solids, including camphor. Most are soluble in an organic solvent but insoluble in water. Optical activity is present in the vast majority of them. They are usually unsaturated cyclic or open-chain elements with one or more double bonds and a boiling point of 150-180$^{o}$C. As a result, they undergo additional reactions with halogen, hydrogen, acids, and others. Antiseptic properties can be found in a variety of substances. Hydrogenation and polymerization are inhibited by them. All of the oxidizing agents are successful in oxidizing them. The great majority of terpenoids produce isoprene as one of the outcomes of heat breakdown (Yadav et al. 2014).

Triterpenes are terpenes with 30 carbon atoms that are made up of six isoprene units. These are plant secondary metabolites that are widely distributed throughout the plant kingdom. Triterpenoids can be found in a variety of plant components, including leaves, fruit peels, and stem bark. Terpenes and terpenoids are biosynthesized in higher plants and organisms using the isoprene (2-methylbutadiene) unit. Terpenes have a fundamental molecular formula that is multiples of C5H8 (Croteau 1998). Unfortunately, pentacyclic triterpenes have low water solubility and, as a result, low bioavailability. These pharmacological qualities could be improved by making changes to their original structures as well as inventing new delivery systems based on the most recent nanotechnological advances. The goal of developing nanocarrier-delivery systems is to increase the transport capacity of bioactive chemicals by improving their solubility, bioavailability and stability in vivo, as well as ensuring tumor targeting while reducing toxicity and side effects (Kaps et al. 2021).

**Physiological and Pharmacological Activities of Pentacyclic Triterpenoids**

Pentacyclic triterpenoids have a wide range of physiological and pharmacokinetic features, which include anti-inflammatory, antiviral, antibacterial, antioxidant activities along with raising glutathione levels, antioxidizing enzymes, and antioxidants, also (JC Furtado et al. 2017). Reactive oxygen species (ROS) blocking properties and accretion the formation of antioxidant enzymes via Nrf2 is one of the aspects of oleanolic acid (OA) (Pollier and Goossens 2012). The major class of pentacyclic triterpenoids, their structure and examples illustrated in (Table 1). Genotoxicity is caused by ROS produced by radiation. Ursolic acid inhibits UVB-induced oxidative alterations like lipid peroxidation, oxidative stress, and damage to DNA, and hence serves as a strong nerve relaxant (Cargnin and Gnoatto 2017). Immune management, blood sugar regulation, blood pressure reduction, and antitumor activity have all been discovered in several studies (Yan et al. 2014). It is well-known for its ability to prevent and treat tumors via natural ingredients, along with its minimal toxicity and excellent efficacy. Many antitumor properties of triterpenoids have been discovered in vivo and in vitro, comprising suppression of cell proliferation, signal transduction impacts, apoptosis, suppression of matrix metalloproteinase production, and tumor invasion (Bishayee et al. 2011).

Pentacyclic triterpenoids have been shown to suppress tumorigenesis in vivo and in vitro, promoting apoptosis and cell cycle stop, according to several studies. Pentacyclic triterpenoids have a variety of physiological and medicinal properties, particularly antiangiogenic and cell differentiation impacts, which are linked to anticancer properties. By suppressing ROS, pentacyclic triterpenoids have antioxidant properties. Numerous previous researches have revealed that lupane, oleanane, and ursane have anticancer effects (Yan et al. 2014). Receptors that are considered as cancer therapeutics targets such as hydrocarbon, androgen, and vascular endothelial growth factor. Nuclear factor-kB (NF-kB) enhancement and signal moving, cell growth, cell death, angiogenesis, mitochondrial malfunction, and MDR genes` regulation and proteins` management are all suppressed by triterpenoids (Kanda and Yokosuka 2015). This review discusses the antitumor activity of nanoformulations of numerous subtypes of triterpenoids, like oleanolic acid, maslinic acid, and urosolic acid, as well as the progress of antitumor mechanisms (Table 2).

**Types of Terpenoids Lupeol**

Lupeol is a type of pentacyclic triterpene that may be derived from a range of plants, including cabbage, pepper, and cucumber. Many pharmacological properties of lupane type pentacyclic triterpenoids have been discovered in vivo

**Table 1:** Major class of pentacyclic triterpenoids, their structure and examples

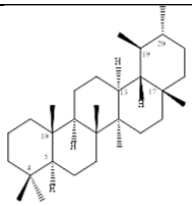
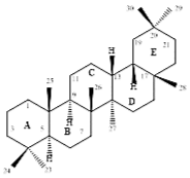
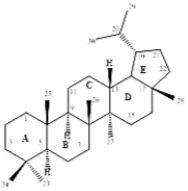
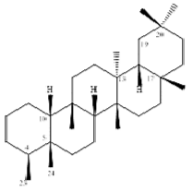
| Main Group | Structure | Examples | References |
|---|---|---|---|
| Ursane |  | Ursolic acid, α Amyrin | Cargnin and Gnoatto (2017) |
| Oleanane |  | Oleanolic acid, 18 $\beta$ - Glycyrrhetinic acid, $\beta$ Amyrin | Pollier and Goossens (2012) |
| Lupane |  | Betulinic acid | Bishayee et al. (2011) |
| Friedelane |  | Friedelin, Celastrol | Mandal et al. (2012) |

**Table 2:** Some pentacyclic triterpenoids with anticancer activity and their mechanisms

| Pentacyclic triterpenoids nanoparticles | Animal model/ cell line | Effects | References |
|---|---|---|---|
| Betulin Gold nanoparticles | A375, B164A5, 1BR3, and HaCaT cell lines | Increased cytotoxicity and induction of apoptosis. | Mioc et al. (2018) |
| Betulinic acid Polymeric nanoparticles | PANC-1 cell line and Ehrlich Ascites Carcinoma in Swiss albino male mice | Decreased cell proliferation, enhanced ROS production, induction of apoptosis, and reduced tumor volume. | Saneja et al. (2019) |
| Betulinic acid Self-assembled nanoparticles | A2780 cell line | Increased cytotoxicity and decreased cell proliferation. | Colombo et al. (2020) |
| Oleanolic acid Hybrid nanoparticles | MGC-803 and NIT3T3 cell lines | Increased stability, biocompatibility and tumor-targeting, and induction of apoptosis. | Li et al. (2020) |
| Oleanolic acid Polymeric nanoparticles | SGC7901 cell line | Decreased cell proliferation, decreased cyclooxygenase 2 (COX-2) expression and increased caspase-3 activity. | Zhang et al. (2013) |
| Ursolic acid Mesoporous silica nanoparticles | HepG2 cell line | Suppress cell proliferation and topoisomerase | Li et al. (2017) |
| Urosolic acid Poly (ursolic acid) nanoparticles | CT26 and NIH 3T3 CT26 tumor-bearing male Sprague Dawley rats and CT26 tumor-bearing male BALB/c mice | Increased stability, accumulation in cancer tissues, cytotoxicity and cellular uptake, and inhibition of the cell cycle and tumor progression. | Ou et al. (2020) |

and in vitro experiments, including potent antitumor & anti-inflammatory properties. Multiple reports demonstrate that lupane type pentacyclic triterpenoids have a strong anti-mutation impact, and they can also prevent Genomic damage induced by chemical reagents. Furthermore, investigations have shown that lupane type pentacyclic triterpenoids inhibit tumor growth by modulating the Bax/Bcl2 ratio in nude mice with high metastatic human melanoma (Yan et al. 2014). The mechanisms of lupeol against cancers by inducing apoptosis are represented in Fig. 1.

Lupeol has limited water solubility. The creation of nanomaterials is one option for overcoming this. There are several methods for making nanomaterials. Emulsification/solvent evaporation is one of them. Few papers on lupeol nanoencapsulation have been published; the first trial attempted to nanoencapsulate lupeol using interfacial polycondensation and spontaneous emulsification processes, resulting in particles larger than 600nm (Redeş et al. 2011). Lupeol retains NF-B in the cytosol and prevents its translocation to the nucleus, but the nanonutraceutical has the reverse effect, with NF-B levels in the cytosol decreasing and NF-B levels in the nucleus increasing as the treatment dose increases. These findings imply that the biological effects of nanonutraceuticals should be carefully considered and that similar dosages of the active chemical and lupeol in nanonutraceuticals may result in improved benefits (Danhier et al. 2009). Caco-2 endocytosis of PLGA nanoparticles appears to be clathrin-mediated in several studies (Reix et al. 2012). The most effective anti-inflammatory effects were found at the largest dose of pure lupeol and the lowest dose of a nanonutrient complex. This unusual behavior could be due to a higher bioavailability of lupeol enclosed in the cell interior (Cháirez-Ramírez et al. 2015).

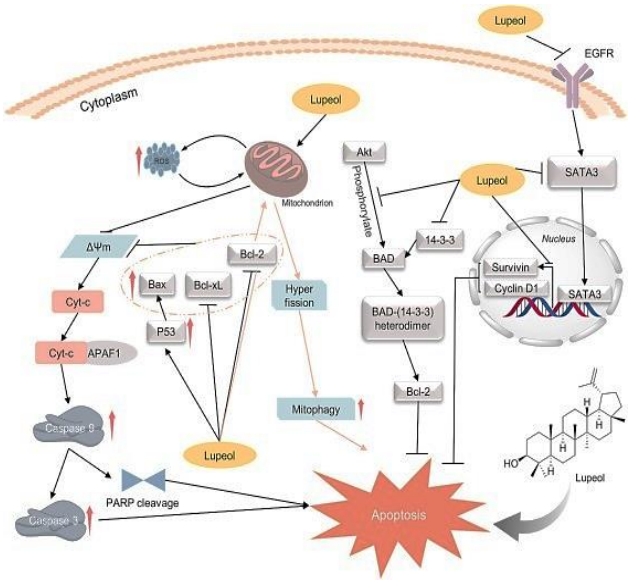



**Fig. 1:** The mechanisms of lupeol against cancers by inducing apoptosis (Liu et al. 2020).

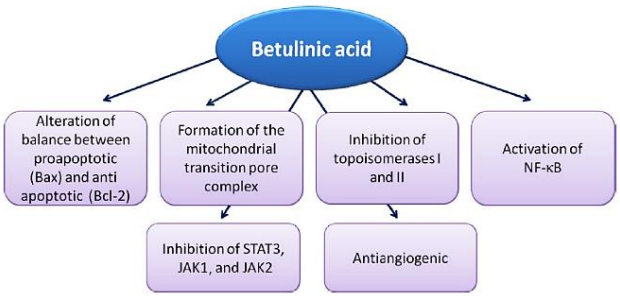



**Fig. 2:** The action pathways of betulinic acid against cancer (Salvador et al. 2014).

**Betulinic Acid (BA)**

It induces cell death via taking actions through the mitochondrial membrane via an internal pathway that produces ROS and activates the pro-apoptotic p38 MAPK and SAP/JNK kinases, which are engaged via a range of mechanisms together with cell growth, expression of a gene, differentiation and cell death. The plant Bacopa monnieri contains betulinic acid, which has anti-inflammatory properties through inhibiting the cyclo-oxygenase-2 (COX-2) enzyme and lowering COX-2-mediated prostanoid mediators (Williams et al. 2014). In vivo, betulinic acid possesses anticancer properties as resulted in a decrease in tumor development and decreased lung metastasis, ovarian and prostate cancers. Due to the proteasome-dependent degradation of transcription factors specificity proteins, prostate cancer cells treated with betulinic acid had lower levels of VEGF. Its complex chemical structure makes it an excellent substrate for a variety of changes. This allows for the creation of appropriate derivatives with the desired properties (Salvador et al. 2014). The action pathways of betulinic acid against cancer are represented in Fig. 2.

The poor solubility of BA, combined with other frequent constraints such as high blood clearance and low selectivity, has a negative impact on its efficacy in vivo. A nano-delivery method capable of successfully navigating physiological and cellular barriers and ensuring the delivery of the payload to the mitochondria for maximum impact is required to improve the therapeutic efficiency of the medicine on cancer cell mitochondria (Dahoumane et al. 2017). In vitro cytotoxicity studies in MCF7 and PANC-1 cells revealed that BA-loaded PLGA-mPEG NPs were more harmful than free BA. Increased cellular apoptosis, mitochondrial membrane potential loss, production of elevated reactive oxygen species, and cell cycle arrest all supported BA NPs' higher cytotoxicity. As a result, in vivo tests in the Ehrlich tumor (solid) model after intravenous injection revealed that BA NPs outperformed native BA in anticancer effectiveness. Furthermore, Ehrlich tumor mice treated with BA NPs showed no biochemical, hematological, or histological toxicity. These findings suggested that BA-loaded PLGA-mPEG NPs could be useful in a variety of applications (Saneja et al. 2017).

Several reports investigated the anticancer properties of BA-loaded liposomes in HepG2 cells. After being introduced to liposomes, both BA were able to stop the cell cycle from progressing into the G1 phase. Surprisingly, liposomes with encapsulated BA are more powerful than free BA solutions when it comes to antiproliferative action. BA-loaded liposomes caused apoptosis via the mitochondrial route, according to more comprehensive research, which could lead to idiopathic apoptosis (Shu et al. 2019). Another study compared the impacts of polyethylene glycol (PEG) and poly-L-lysine-graft-polyethylene glycol (PLL-g-PEG) copolymers on the mitochondrial targeted delivery of betulinic acid (BA) using mitochondriotropic TPP+-functionalized epigallocatechin gallate (EGCG)-capped gold NPs (AuNPs). In the human Caco-2, HeLa and MCF-7 cancer cell lines, and testing their cellular absorption, mitochondrial localization, and efficacy as therapeutic delivery platforms for BA. In vitro, these nanocomplexes suppressed the cancer cell proliferation compared to the free BA. High amplitude mitochondrial depolarization, caspases 3/7 activation, and an associated arrest at the G0/G1 phase of the cell cycle were all identified as mechanisms of action (Oladimeji et al. 2021).

**Ursane-type Triterpenoids**

β-Boswellic acid and A-Boswellic acid are ursane-type triterpenoids that suppress 12-O-tetradecanoylphorbol-13-acetate that led to inflammation in animals. Apart from inhibiting the effects of LPS, β-Boswellic acid is a specific inhibitor of COX-1 with IC50 values of 15 mol/lit. Furthermore, the platelet-type 12-LOX catalysis is reduced 2-fold by these pentacyclic triterpenoids. 2-diketone of 12-ursene derived from Boswellia serrata. Triana and Planch (Burseraceae) suppress important inflammatory mediators such TNF- α, IL-6 and IL-1 without phosphorylating c-jun N-terminal kinase or p38 (Jiang et al. 2020). Multiple molecular targets modulated by ursolic acid are represented in Fig. 3.

Ursolic acid (UA) is the most often utilized ursane-type chemical in pharmacies. Its functional groups are identical to those of the OA. The peel of fruits and the leaves of herbs are the most common sources of UA. Caldeira de Araujo Lopes et al. (2013) made PEGylated UA-loaded liposomes with UA resulting in liposomes that might last up to 60 days. Zhao et al. (2015), on the other hand, created PEGylated UA-loaded liposomes containing

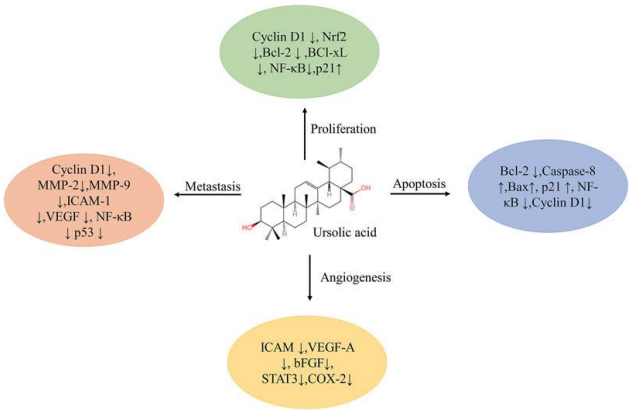



**Fig. 3:** Multiple molecular targets modulated by ursolic acid (Wang et al. 2021).

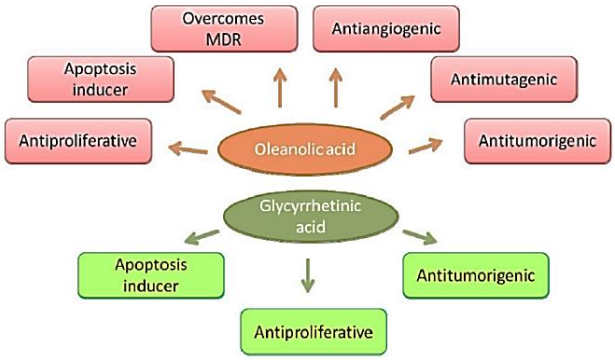



**Fig. 4:** Anti-inflammatory impacts of oleanolic acid and its derivatives (Yoo et al. 2017).

soya lecithin and cholesterol, which delayed the release time and only released 53.6 percent of the total UA content within three days. The findings revealed that Liposomes can have their surfaces functionalized to improve their stability and drug release. Wang et al. (2017a) shown that a chitosan coating on a liposomal surface can increase liposomal stability. Depending on the pH value, modify the UA release profile. Furthermore, in a cancer context, the accumulation of UA-loaded liposomes modified by chitosan was observed to be substantially higher than that of free UA.

HepG2 cells and a normal L-02 cell line were incubated with UA-loaded polymer micelles (PMs), the antiproliferative inhibitory parameter (IC50) was lower than with free UA at the same dosage. The results of anti-hepatocarcinoma activity testing in H22 xenograft mice were consistent with prior findings, and PMs were more effective tumor inhibitors and had a greater impact on mouse survival times than free UA. Though 5-flurouracil (5-FU) had a similar inhibitory effect, the survival time was significantly longer (Wang et al. 2017a). In SGC7901 cells, it was founded that UA-loaded mPEG-PCL NPs had a higher inhibitory action (IC50) than free UA solutions. The remarkable anticancer efficacy of NPs was attained by the inhibition of cyclooxygenase 2 and caspase-3 activation which are both overexpressed in gastric cancer (Zhang et al. 2013). Another report revealed that in comparison to free UA, the incubation of hepatocellular carcinoma with produced UA-loaded NPs (PVP-b-PCL NPs) decreased the IC50 values. PVP-b-PCL NPs had a significantly longer half-life than mPEG-PCL NPs (Zhang et al. 2015).

**Oleanolic Acid (OA)**

OA is a natural substance made up of pentacyclic triterpenoids that have been obtained from a wide variety of food and medicinal plants. OA metabolites, such as 2-cyan-3, 12-dioxo- oleanane- 1, 9, diene-28 acid (CDDO) and CDDOMe, are commonly detected in several plants, including ginseng, licorice, clove, and panax pseudoginseng, and have significant anticancer effects (Fig. 4) (Yoo et al. 2017). Antioxidant, anti-tumor, anti-inflammatory and anti-diabetic actions are just a few of the pharmacological properties of OA. Because of its hepatoprotective properties, it has been employed as a liver medication (Wang et al. 2013). C30H48O3, 456.7 g/mol is the chemical structure and weight of OA. It has been shown to inhibit cancer cell growth in various in several models. It extracted from Glossogyne tenuifolia was shown to have low antioxidant activity and modest cytotoxicity in MCF-7 breast cells. It also suppressed the growth of tumor in mice and HepG2 cell line (Mu et al. 2015).

Expression of miR-122, that acts as a tumor suppressor in several cancers such as lung cancer cells, was also promoted by OA. OA enhanced apoptosis and ROS generation in human cervical cancer cells (HeLa). Tumor inhibition rate at nude mice transplanted with pancreatic cancer L3.6PL cells can reach 74.2 percent after intragastric administration of CDDOMe (Song et al. 2015). Soybean saponins are oleanane type pentacyclic triterpenoids that induce apoptosis in HeLa, HepG2, and HCT15 cells, inhibiting their proliferation. HEPG2 cells have an LC50 of 0.6mg/mL (Salvador et al. 2017), while HeLa cells have an LC50 of 0.4 mg/mL. 3-Odglucopyranosylhederagenin 23-Odribofuranoside is another form of oleanane molecule that has been shown to inhibit tumor cell development (Juang and Liang 2020). oleanolic acid has been shown to diminish the occurrence of azoxymethane-induced aberrant crypt foci in rats and explained that by suppression of COX-2 and inducible nitric oxide synthase in relation to drop in cells in the S phase (Salvador et al. 2014).

In another report researchers used a protective PEG covering to encapsulate OA in liposomes. When HeLa cells were given these PEGylated liposomes nanoformulation, the cytotoxic effect was increased on HeLa cells in comparison to non-PEGylated nanocarriers or pure OA, PEGylated liposomes had the best anticancer efficacy in vitro (Gao et al. 2012). Wang et al. (2017b) used octreotide to modify OA-loaded liposomes (Oct) in A549 cells, the drug delivery system (DDS) with Oct was found to have better antiproliferative action and cellular uptake than the DDS without Oct. The HepG2 cells were incubated with the co-loading of OA and DOX into the liposomal formulation. The key advantage of this system was the attenuation of the toxic effect of DOX on cardiomyocytes, while the synergistic anticancer effect of the DDS was noticeable at the same time (Sarfraz et al. 2017). Wang et al. (2020) synthesized a self-assembled nanoparticle platform encapsulating 10-hydroxycamptothecin (HCPT) based on an amphiphilic oleanolic acid polyprodrug, poly[oligo(ethylene glycol) methyl ether methacrylate]-b-poly (oleanolic acid methacrylate) (POEGMA-b-POAMA) and hydrophobic OA prodrug monomers. Furthermore, 4T1 cells and MCF-7 cells showed increased cell cytotoxicity, and 4T1 cells were able to absorb it

efficiently. Furthermore, in vivo antitumor efficacy testing revealed that the POEGMA-b-POAMA/HCPT NPs exhibited a high antitumor efficacy with minimal side effects when used to treat the 4T1 mouse breast tumor xenograft tumor. There was a strong cytotoxic effect on 4T1 and MCF-7 cells.

**Conclusions**

In conclusion, the nano-delivery system is a potentially viable platform for pentacyclic triterpenoid nanoparticles and highlights mitochondrial targeting as an option in cancer therapy. There is substantial proof that pentacyclic triterpenoid aiming a range of signalling mechanism that leads to an anticarcinogenic effect. Evidence from several studies indicated the ability of pentacyclic triterpenoid nanoformulation in the chemoprevention and therapy of various tumours has been highlighted in this review. In the future we suggested a combination of one of the pentacyclic triterpenoid nanoformulation derivatives with other chemotherapeutic drugs can have a powerful therapeutic impact. New technologies will continue to be employed in the synthesis of pentacyclic triterpenoid nanoformulation with the advancement of research and the rapid development of science and technology. This will open up new avenues for the development of new anticancer medications, as well as provide significant social and economic benefits.

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