Exploring the therapeutic potential of oleanolic acid and its derivatives in cancer treatment: a comprehensive review

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Abstract

Oleanolic acid (OA) is a triterpenoid that occurs naturally and may be isolated from various plants. Analogs of oleanolic acid can be produced artificially or naturally. The current treatments have limited selectivity and may also impact normal cells. OA and its derivatives provide a promising cancer treatment platform with greater selectivity and less toxic effects. As a result of their enhanced sensitivity, selectivity, and low toxicity, they are great options for focusing on particular biological pathways and reducing the growth of tumor cells. The effects of OA and derivatives of OA on various cancer types have been investigated. However, breast and hepatocellular malignancies are the most studied cancers. In breast cancer, derivatives such as saikosaponin A (SSa), saikosaponin B (SSb), and SZC014 influence key pathways such as the Janus kinase/signal transducer and activator of transcription (JAK/STAT), protein kinase-B (Akt), and nuclear factor-kappa B (NF-κB) pathways, inhibiting metastasis, angiogenesis, and cell migration, respectively. When a para-aminobenzoic acid (PABA)/nitric oxide (NO) derivative of OA is administered to HepG2 cells, the reactive oxygen species (ROS)/mitogen-activated protein kinase (MAPK)-mediated mitochondrial pathway causes apoptosis. Nanoformulations incorporating OA, such as OA-paclitaxel (PTX), show potential for suppressing tumor progression by inhibiting drug efflux mechanisms. Thus, exploring the interactions of OA and a few of its derivatives with various cellular pathways offers a promising approach to combating different types of cancer. This review delves into the potential of oleanolic acid and its derivatives in retarding cancer progression through their interactions with diverse cellular pathways.

Abbreviations

4-HNE	4-Hydroxynonenal
ABTS	2,2'-Azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt
ACSL4	Acyl-CoA synthase long-chain family member 4
ADR	Adriamycin
AH-Me	Achyranthoside H methyl ester
ALT	Alanine aminotransferase
AMPK	Adenosine monophosphate-activated protein kinase
ARE	Antioxidant response elements
AST	Aspartate aminotransferase
Atg5	Autophagy-related gene 5
Bax	Bcl-2-associated X-protein
BCDC	*Bupleurum chinese* DC
Bcl-2	B-cell lymphoma 2
β-gal	Beta-galactosidase
BUN	Blood urea nitrogen
CAR	Chimeric antigen receptors
CCL2	Chemokine ligand 2
CCM	Cancer cell membrane
CDDO	2-Cyano-3,12-dioxoolean-1,9-dien-28-oic acid
CDDO-Ea	2-Cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid ethyl amide
CDDO-Im	1-[2-Cyano-3-,12-dioxooleana-1,9(11)-dien-28-oyl] imidazole
CDDO-Me	Methyl-2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oate
CDDP	Cis-diamminedichloroplatinum(II)
CDH	Cadherin

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CDK2	Cyclin-dependent kinase 2
COX-2	Cyclooxygenase-2
CUK	α-Cyano-substituted α, β unsaturated ketone
CXCL16	Chemokine (C-X-C motif) ligand 16
DAPT	N-[N-(3,5-difluorophenacetyl)-1-alanyl]-S-phenylglycine t-butyl ester
DDS	Drug delivery system
DMBA	7,12-Dimethylbenz[a]anthracene
DOX	Doxorubicin
Dox@HSA-OA	Human serum albumin nanoparticle-mediated tumor-targeted doxorubicin/oleanolic acid combination therapy
DPPH	2,2-Diphenyl-1-picrylhydrazyl
DR4	Death receptor 4
DR5	Death receptor 5
DRβ-H	D Rhamnose-hedrin (3b-[(a-L-arabinopyranosyl)-oxy]olean-12-en-28-oicacid)
DVL2	Dishevelled segment polarity protein 2
EAC	Ehrlich ascites carcinoma
EGFR	Epidermal growth factor receptor
EGFR^{LTC}	Epidermal growth factor receptor L858R/T790M/C797S
EMT	Epithelial–mesenchymal transition
EMT-6	Experimental mammary tumour-6
ERK	Extracellular signal-regulated kinases
ERS	Endoplasmic reticulum stress
EsA	Esculentoside A
EZH2	Enhancer of zeste homolog 2
FADD	Fas-associated death domain protein
FITC	Fluorescein isothiocyanate
FLIP	FLICE (FADD-like IL-1β-converting enzyme)-inhibitory protein
FOXA1	Forkhead box A1
FTH1	Ferritin heavy chain
FXR	Farnesoid X receptor
FZD7	Frizzled class receptor 7
GEM	Gemcitabine
GPX4	Glutathione peroxidase 4
GSH	Glutathione
GSK3	Glycogen synthase kinase 3
HA	Hypocrellin A
HER2	Human epidermal growth factor receptor 2
HIF	Hypoxia inducible factors
HIMOXOL	Methyl 3-hydroxyimino-11-oxoolean-12-en28-oate
HO-1	Heme oxygenase 1
HNP	Hybrid nanoparticles
HPV	Human papilloma virus
HSA-NPs	Human serum albumin nanoparticles
HSD17B1	17 Beta-hydroxysteroid dehydrogenase type-1
hTERT	Human telomerase reverse transcriptase
ICAM-1	Intercellular adhesion molecule 1
IFD	Induced fit docking
IKK	IκB kinase
iNOS	Inducible nitric oxide synthetase
ITGB1	Integrin beta 1
JAG1	Jagged1
JNK	C-Jun N-terminal kinase
Keap-1	Kelch-like enoyl-CoA hydratase-associated protein 1
LC3B-I/II	Light chain 3B I/II
LDH	Lactate dehydrogenase
LHB	Luteinizing hormone beta
LRP6	Low-density lipoprotein receptor-related protein 6
MAA	Maackia amurensis agglutinin
MAL-2	Maackia amurensis lectin 2
MAPK	Mitogen-activated protein kinases
MDA	Malondialdehyde
MDR1	Multi-drug resistance 1
MDS	Molecular dynamic simulation
MDI	Metered-dose inhaler
MMP	Matrix metalloproteinases
MMP	Mitochondrial membrane potential
MMP3	Matrix metallopeptidase 3
NAC	N-acetylcysteine
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NO	Nitric oxide
NOXs	Nicotinamide adenine dinucleotide phosphate oxidases
N-RAS	Neuroblastoma rat sarcoma viral oncogene homolog
NRF2	Nuclear factor erythroid 2-related factor 2
NSCLC	Non-small cell lung cancer
OA	Oleanolic acid
OAME	Oleanolic acid methyl ester
OAO	Oleanolic acid oxime
OECD	Organization for Economic Cooperation and Development
OEOA	Olean-12-eno[2,3-c] oxadiazol-28-oic acid
PABA	Para-aminobenzoic acid
p-Akt	Phosphorylated protein kinase B
PARP	Poly(adenosine diphosphate-ribose) polymerases
PBMC	Peripheral blood mononuclear cells
PCNA	Proliferating cell nuclear antigen
PCR	Polymerase chain reaction
PDA	Pancreatic ductal adenocarcinoma

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PD-L1	Programmed cell death ligand 1
P-gp	P-glycoprotein
PINK1	Phosphatase and tensin homolog-induced kinase 1
p-mTOR	Phosphorylated mammalian target of rapamycin
PTK2	Protein tyrosine kinase 2
PTX	Paclitaxel
PXN	Paxillin
PXR	Pregnane X receptor
Rh123	Rhodamine 123
RNPC	RNA-binding protein companion of MCPIP1
ROS	Reactive oxygen species
SMAA	3-Succinyloxyiminoolean-12-en-28-oic acid
SMAEB	3-Succinyloxyiminoolean-12-en-28-oic acid benzyl ester
SMAEM	3-Succinyloxyiminoolean-12-en-28-oic acid methyl ester
SMAM	3-Succinyloxyiminoolean-12-en-28-oic acid morpholide
SOD	Superoxide dismutase
SOX9	SRY (Sex-determining region Y)-box
SPINK1	Serine protease inhibitor Kazal type 1
SRB	Sulforhodamine B
SSd	Saikosaponin D
STAT1	Signal transducer and activator of transcription 1
STAT3	Signal transducer and activator of transcription 3
TAM	Tumor-associated macrophages
TEAD	Transcription enhancer factor (TEA) domain transcription factor
TET3	Tet methylcytosine dioxygenase 3
TfR1	Transferrin receptor 1
Th17 cells	T helper 17 cells
TNBC	Triple-negative breast cancer
TNF-α	Tumor necrosis factor alpha
TrxR	Thioredoxin reductase
TS	Tea saponins
UA	Ursolic acid
UGTs	UDP-glucuronosyltransferases
VASP	Vasodilator-stimulated phosphoprotein
V-CAM 1	Vascular cell adhesion molecule 1
VEGF	Vascular endothelial growth factor
Wnt	Wingless-related integration site
XIAP	X-chromosome-linked inhibitor of apoptosis protein
YAP	Yes-associated protein
ZBTB10	Zinc finger and Broad-Complex, Tramtrack, and Bric-a-Brac domain-containing protein 10
ZIF	Zeolitic imidazolate framework
Z-VAD-FMK	Carbobenzoxy-valyl-alanyl-aspartyl-[O-methyl]-fluoromethylketone

Introduction

Triterpenoid oleanolic acid (3β-hydroxy-olea-12-en-28-oic acid) (OA) is extracted from more than 1600 different plants. It demonstrates anti-inflammatory, antioxidant, anticancer, antimicrobial, and many other properties, as shown in Fig. 1 (Han et al. 2021). It can be found in nature as an aglycone of triterpenoid saponins or as a free acid. It is commonly present with its isoforms such as ursolic acid (UA), moronic acid, or betulinic acid (Kang et al. 2020). OA is sourced from clove leaves, pomace, clove blossoms, mistletoe sprouts, and several other plants (Kang et al. 2017). By activating the Akt/Foxg1 pathway, saikosaponin D (SSd), a naturally occurring triterpenoid derived from *Bupleurum falcatum L.*, induces the downregulation of neurogenesis and cognitive impairment (Lixing et al. 2017). *Radix Bupleuri* is separated to produce Saikosaponin A (SSa). According to Liu et al. (2018b), it lessens heart fibrosis and decreases cardiac dysfunction. Many different plants contain the triterpene pomolic acid, which helps to fight glioblastoma and tumors via apoptosis. (Guimarães et al. 2017). According to Zhang et al. (2017), 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid ethyl amide (CDDO-Ea) has a cytoprotective impact by attenuating the accumulation of ROS and increasing heme oxygenase-1 (HO-1) activity. Bardoxolone methyl substituted with an α-cyano-substituted α, βunsaturated ketone (CUK) in its ring has greater therapeutic efficacy and safety than its parent molecule (Huang et al. 2017).

OA is vital in the treatment of Alzheimer's, hyperglycemia, diabetes, atopic dermatitis, wound healing, and antimicrobial activity (Fig. 1). According to Han et al. (2021), OA protects microglia from Alzheimer's disease and reduces cognitive decline. The inflammatory response induced by allergies is reduced by OA through the release of cytokines caused by mast cells (Kang et al. 2020). According to Kang et al. (2017), OA exploits the peroxisome proliferator-activated receptorꞓ (PPARꞗdi as an antagonist to prevent cartilage deterioration caused by hyperglycemia. It provides protection against renal oxidative stress and kidney damage and can be utilized to treat diet-induced prediabetes (Gamede et al. 2021). By lowering the levels of high-mobility group box 1 (HMGB1), OA exhibits a hepatoprotective effect (Wang et al. 2019c). To ameliorate atopic dermatitis, it inhibits the Akt, Nuclear Factor kappa light-chain-enhancer of activated B cells (NF-κB), and Signal Transducer and Activator of Transcription 1 (STAT1) signaling pathways (Kang et al. 2021).

Fig. 1 Role of oleanolic acid in the treatment of diseases such as Alzheimer's, hyperglycemia, diabetes, atopic dermatitis, wound healing, and antimicrobial activity
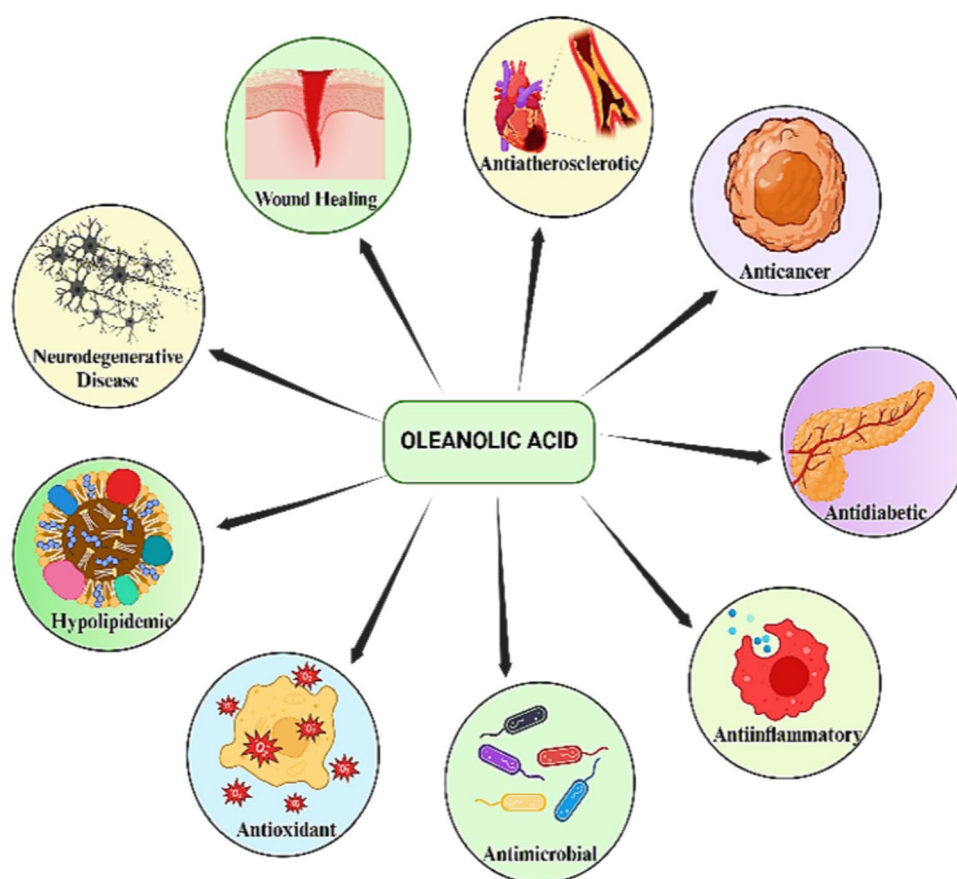
Globally, nearly 10 million deaths due to cancer were recorded in 2020 (Debela et al. 2021). Cancer treatments often include surgery, radiation, and chemotherapy. However, these methods are limited by the potential negative impact on native cells and the potential for resistance to arise with continued use. Techniques to reduce harm and increase therapeutic sensitivity are being developed to address these issues (Debela et al. 2021).

Anticancer drug discovery was revolutionized with the use of natural products. Irinotecan, vincristine, paclitaxel, and etoposide are a few plant-derived anticancer drugs whereas actinomycin D and mitomycin C are bacteria-derived. As the landscape of cancer therapy is expanding, new opportunities are being sought for the development of natural anticancer drugs and for exploring their utility as therapeutics (Huang et al. 2021). The compound OA and its derivatives are relatively nontoxic. They are crucial components for cancer therapy since they can interact with a variety of biological processes. In triple-negative breast cancer (TNBC), SSd inhibits proliferation by inducing apoptosis via the Wingless-related integration site (Wnt)/β-catenin pathway (Wang et al. 2018). When combined with aspirin, OA oxime morpholide derivatives decrease cytotoxicity, downregulate NF-kB levels, and aid in the prevention of liver cancer (Krajka-Kuźniak et al. 2019b).

When treating non-small cell lung cancer, UA and OA may target the p62 protein and mitophagy (Castrejón-Jiménez et al. 2019). OA triggers apoptosis in melanoma cells via the NF-kB pathway (Woo et al. 2021). It inhibits tumor initiation and development by affecting phosphatidylinositide 3-kinase (P13K)/Akt/mammalian target of rapamycin (mTOR)/NF-kB signaling pathways. It activates autophagy via the extracellular signal-regulated kinase/c-Jun N-terminal kinase/mitogen-activated protein kinase (ERK/JNK/p38 MAPK) signaling pathways. SZC015, a derivative of OA, activates an intrinsic apoptotic pathway by up-regulating poly (ADP-ribose) polymerase (PARP), caspase 3 and 9, and increases Bcl-2 Associated X-protein (Bax)/Bcl2 expression. OA suppresses angiogenesis by inhibiting the expression of STAT3 and sonic hedgehog signaling pathways (Žiberna et al. 2017). Multiple such examples demonstrate that OA and its derivatives can act as potent anti-cancer moieties.

This review focuses on several cellular pathways that OA and its derivatives use to induce apoptosis and slow cancer growth. These advancements might help create more effective and innovative. These advancements might help create more effective and innovative therapeutic approaches.

Breast cancer

Breast cancer is more prevalent among women and ranks 5th in cancer-related deaths. As of 2020, GLOBOCAN reported about 2.3 million fatalities. The World Health Organization states that approximately 18 different types of histological breast cancer are known. Some of the frequently used therapeutic strategies include surgery, radiation therapy, and endocrine therapy (Łukasiewicz et al. 2021).

Achyranthoside H methyl ester (AH-Me), a derivative of OA shows increased cytotoxicity towards MCF-7 and MDA-MB-453 cells. 1-[2-cyano-3-,12-dioxooleana-1,9(11)-dien-28-oyl] imidazole (CDDO-Im) causes DNA damage via ROS production and thus induces apoptosis in BRCA1 null and estrogen receptor-negative breast cancer cells (Fukumura et al. 2009). CDDO-Im downregulates the growth and metastasis of breast cancer by blocking the Epidermal growth factor receptor (EGFR)/Signal Transducer and Activator of Transcription 3 (STAT3)/Sox-2 pathways in Tumor-associated macrophages (TAMs) (Yang et al. 2013).

Chu and colleagues studied the effect of SZC014, on Breast cancer cells. SZC014 has anticancer effects by impairing the cell cycle, inhibiting inflammation, and inhibiting cell death, which are linked to the Akt and NF-kB pathways. SZC014 decreases breast cancer cell viability and displays minimal toxicity towards mammalian epithelial cancer cell lines, showing that it has greater specificity for breast cancer cells. SZC014 reduced the viability of these cells more strongly than OA. It suppresses cell migration and colony formation. Cell fragmentation and shrinkage of apoptotic cells were observed after SZC014 treatment. When the Bax/Bcl2 ratio increases, procaspase 3 and procaspase 9 levels are suppressed, and Poly (Adenosine Diphosphate-ribose) polymerases (PARP) cleavage increases after the cells are treated with SZC014. This causes G1 phase arrest in the cells. The Akt pathway is a dominant target of SZC014. SZC014 inhibits the activity of cyclooxygenase 2 (COX-2), a protein that promotes angiogenesis and cancer cell proliferation. SZC014 inhibits the nuclear translocation of p65. N-acetylcysteine (NAC), an active scavenger of SZC014 inhibits SZC014-induced apoptosis (Chu et al. 2017). Cheng et al. described another OA derivative namely D Rhamnose-Hedrin (3b-[a-L-arabinopyranosyl)-oxy] olean-12-en-28-oicacid) (DRβ-H). This is an oleanane type of triterpenoid with anticancer properties. The RNA binding region (RNP1, RRM) containing (RNPC1), an RNA-binding protein, is attenuated in highly invasive breast cancer. DRβ-H showed cytotoxic effects at higher concentrations. It increased the levels of RNPC1 and E-cadherin after 24 h

of treatment shown by western blotting. Knockdown of RNPC1 reduced the upregulation of these two proteins, after DRβ-H treatment. It also diminishes the antimetastatic activities of DRβ-H (Cheng et al. 2017).

P-glycoproteins (P-gp), ATP-driven transmembrane transporters, are found at relatively high concentrations in multiple types of cancers. The side effects of P-gp inhibitors limit their application in cancer treatment. *Bupleurum chinense DC* (BCDC) inhibits P-gp and Multidrug resistance 1 (MDR1)/mRNA. SSd is used to reverse multidrug resistance (MDR). MCF-7/Adriamycin (ADR) cells are affected concurrently with SSd and ADR. SSd downregulates the expression of P-gp and MDRI mRNA. SSd restores the accumulation of Rhodamine 123 (Rh123), which demonstrates that the reversal of MDR by SSd is due to its effect on P-gp-mediated transport (Li et al. 2017). In TNBC, the progesterone receptor, human epidermal growth factor receptor 2 (HER2), and estrogen receptor are negatively expressed. SSd inhibits the proliferation of HCC1937 cells and represses TNBC cell line proliferation has inhibitory effects, however, SSb and SSc show less cytotoxicity, indicating that the configuration of the C-16 position is important for the cytotoxic effect of sapogenin. Treatment with SSd increased nuclear condensation, programmed-cell death, and cleaved caspase 3 levels. Cotreatment with SSd and carbobenzoxy-valyl-alanyl-aspartyl-[O-methyl]-fluoromethylketone (z-VAD-fmk) an inhibitor of caspase, decreased cleaved caspase 3 and PARP levels to a greater extent than treatment with SSd alone, suggesting that SSd causes apoptosis. The inhibitory effect of SSd is due to its impact on the Wnt/β-catenin pathway. Nuclear and cytoplasmic fractions show reduced β-catenin levels. Cotreatment with SSd and Lithium chloride, an activator of β-catenin increases cell viability, demonstrating that the effect of SSd is mediated by a reduction in β-catenin (Wang et al. 2018).

Another study showed that cell adhesion molecules (CAMs), which belong to the integrin family, promote invasion and adhesion of cells. In addition, CAMs are overexpressed during the invasion and proliferation of cells. The FERM fragment integrin subunit of focal adhesion kinase (FAK) assists in these processes. FAK assists in the advancement of breast cancer. Methyl 3-hydroxyimino-11-oxoolean-12-en28-oate (HIMOXOL) and 12α-bromo-3-hydroxyimonooolean28 13-olide (Br-HIMOLID) attenuate cell metabolism and show greater cytotoxicity than the parent compound. These compounds decrease cancer cell migration and invasion potential. HIMOXOL and Br-HIMOLID also decreased the expression of integrin beta-1 (ITGB1) and integrin 1. Br-HIMOLID downregulates FAK and its phosphorylated forms. The antimigratory effect of OA analogs is due to their ability to downregulate proteins such as ITGB1, protein tyrosine kinase 2 (PTK2), and the Paxillin (PXN) gene (Lisiak et al. 2017). Another

study showed that HER2 is overexpressed in breast cancers. HIMOXOL and Br-HIMOLID, semisynthetic analogues of OA, induce cancer cell death through apoptosis and autophagy. These analogs are modified at the C3, C11, and C28 positions. HIMOXOL and Br-HIMOLID reduced cell viability to a greater extent than the parent moiety. Br-HIMOLID was toxic only after 3 days of incubation. HIMOXOL and Br-HIMOLID decreased colony-forming ability at all concentrations. Cell cycle analysis of SK-BR-3 cells revealed that OA treatment caused stagnation at the G0/G1 phase and decreased the number of cells in the S phase. Br-HIMOLID increases the number of apoptotic cells. Bax, PARP, and cyclin D levels increase at higher concentrations of Br-HIMOLID. Br-HIMOLID increases LC3-II/LC3-I ratio, the mammalian target of rapamycin (mTOR) negatively regulates autophagy, which is marked by decreased levels of p62. OA, HIMOXOL, and Br-HIMOLID attenuate cell migration (Lisiak et al. 2021).

Lantana camara is a medicinal plant from which triterpenoids such as Lantadene A, B, and C are derived. These compounds demonstrate antimicrobial, anti-insecticidal, and antifungal properties. Lantadene A and B show elevated radical scavenging activity. Both compounds decreased the viability of MCF-7 cells. Lantadene C and icterogenin also demonstrate anti-proliferative activity. Lantadene B is important for cell cycle arrest and caspase 9 induction. Lantadene B decreases cells in the G2/M phase while increasing cells in the early stages of the cell cycle (Shamsee et al. 2018).

Esculentoside A (EsA) is a triterpene that shows anti-inflammatory activity by targeting S3a, a ribosomal protein. It also shows anti-proliferative and anti-metastatic potential. It impairs tumor growth by inhibiting cancer stem cells. Experimental mammary tumor-6 (EMT-6) mammosphere cells exhibit stem cell properties and can be used as a CSC anticancer target. EsA at increasing concentrations inhibits mammosphere formation in murine and breast cancer cells. Apoptotic cells increased following EsA treatment. EsA significantly reduces the expression of proteins that confer stem-like properties. The levels of proteins that antagonize apoptosis decrease, and the levels of proteins that assist in apoptosis increase after EsA treatment. It also downregulates IL-6, pSTAT3, and STAT3 expression (Liu et al. 2018a).

STAT3 helps promote metastasis by mediating the Janus kinase/signal transducer and activator of the transcription (JAK/STAT) pathway. Activated STAT3 promotes matrix metallopeptidase 3 (MMP3) expression. Saikosaponin (SS), a triterpenoid, is responsible for the pharmacological activities of *Bupleurum*. STAT3 and vasodilator-stimulated phosphoprotein (VASP) show elevated expression in cancer cells. Treatment with SSb reduces the levels of c-myc and cyclin D1, which are involved in the STAT3

pathway and are regulators of cell proliferation. pSTAT3 and VASP expression also decreased in the MCF-7 cell line and cells with NSC74859. The VASP level increases when STAT3 is phosphorylated by IL6. Treatment of cells with ministered with SSb decreases MMP protein expression (Ma et al. 2019).

Another study showed that TAMs assist in tumor progression and cell survival. TAMs recruit monocytes to tumor sites via chemokines and promote angiogenesis. TAMs suppress T cell expression and prevent their survival, augmenting immunosuppression in the tumor environment. Methyl-2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oate (CDDO-Me) inhibits TAM infiltration into the tumor environment, prevents the secretion of chemokines, and elevates Tumor necrosis factor alpha (TNF-α) expression. It also increases the CD8 + :CD4 + T-cell ratio. CDDO-Me decreases the expression of TAM markers, such as CD206 and CD115. It reduces proangiogenic and IL-6 levels while increasing TNF-α expression. The activity of the chemokine (C-X-C motif) ligand 16 (CXCL16), increases, and the levels of chemokines such as chemokine ligand 2 (CCL2) decrease. The levels of matrix metalloproteinases (MMP2) and Arg1, which assist immunosuppressive TAMs, are attenuated after treatment with CDDO-Me. CDDO-Me also increases IL-1β levels, which assist in T-cell activation. CD3 + cells positive for the CD8 marker were significantly increased. After treatment with CDDO-Me, the spleens of mice exhibit reduced numbers of CD3 + CD4 + cells and increased numbers of CD3 + CD8 + cells (Ball et al. 2020). Zhou and his group studied CDDO-Me and investigated how it affects the Wnt/β-catenin pathway. The Wnt/β-catenin pathway is often dysregulated in multiple cancer types, including breast cancer. CDDO-Me targets nuclear factor erythroid-2 related factor-2, JAK/STAT, NF-kB, etc. Treatment of tumor cells with CDDO-Me attenuates tumor growth and inhibits the Wnt/β-catenin pathway. OA, CDDO, and CDDO-Me antagonize this pathway. CDDO-Me reduces the transcriptional activity of proteins that assist in signalling pathways. It may also act on the upstream region of Dishevelled Segment Polarity Protein 2 (DVL2) and β-catenin. When CDDO-Me is used, cells treated with Wnt exhibit decreased levels of phosphorylated low-density lipoprotein receptor-related protein 6 (pLRP6), pDVL2, LRP6, DVL2, β-catenin, etc. CDDO-Me reduces Wnt target gene expression. Its effect on LRP6 and Frizzled class receptor 7 (FZD7) does not depend on transcriptional regulation but relies on the lysosomal pathway. Glycogen synthase kinase 3 (GSK3) is not essential for the effect of CDDO-Me on signaling pathways. CDDO-Me reduces breast cancer cell viability and attenuates tumor sphere formation (Zhou et al. 2020a) (Fig. 2) (Table 1).
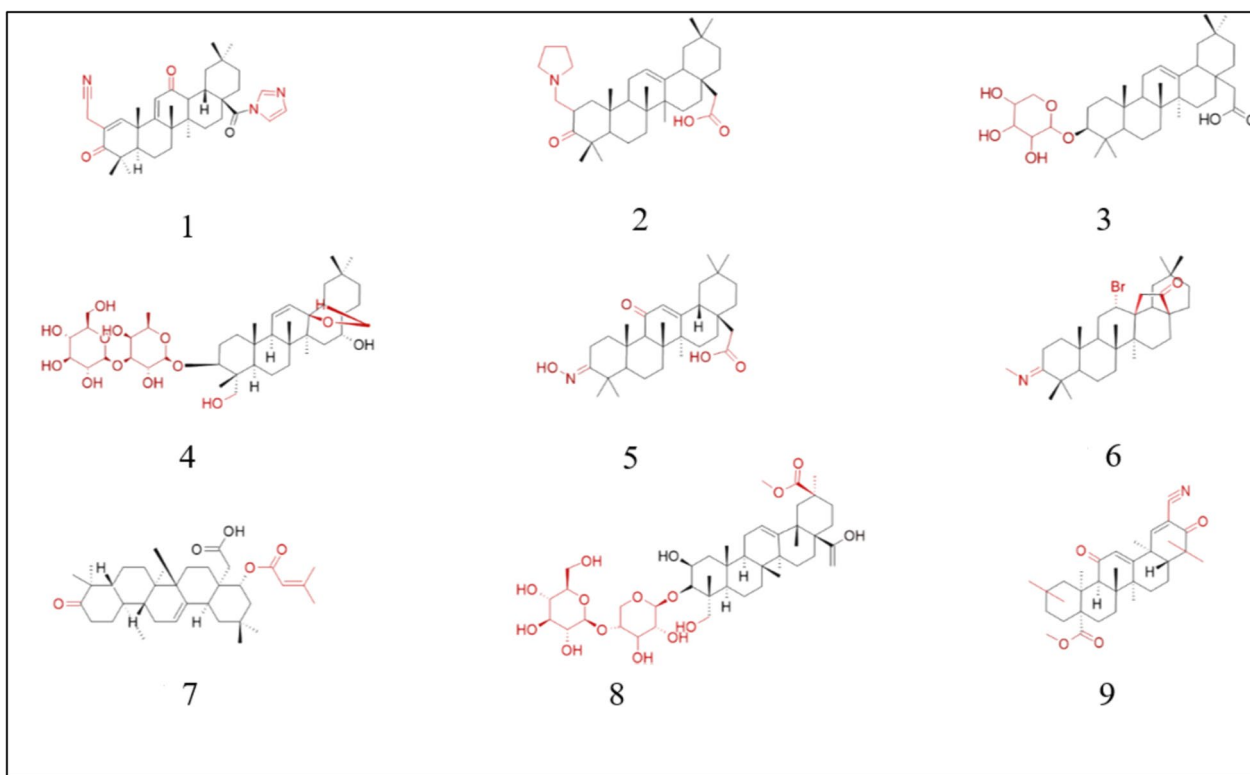
Fig. 2 Structures of OA derivatives effective against breast cancer. 1: CDDO-Im; 2: SZC014; 3: DRβ-H; 4: SSd; 5: HIMOXOL; 6: BrHI-MOXOL; 7: Lantadene B; 8: Esculentoside A; 9: CDDO-Me

Table 1 OA derivative and its effect on breast cancer

Name of the derivative	IC50	Pathway/gene/RNA involved	Source	References
1-CDDO-Im	10–30 μM	EGFR/STAT3/Sox-2 pathways	Synthetic	(Hyer et al. 2005, Kim et al. 2011, So et al. 2013, Yand et al., 2013)
2-SZC014	9.8 μM	Akt pathway NF-kB pathway	Synthesized	(Chu et al. 2017)
3-DRβ-H	> 20 μM	RNPC1 proteins E-cadherin proteins	*Clematis ganpiniana*	(Cheng et al. 2017)
4-SSd	13.06 μM	P-gp Wnt/β-catenin pathway, PARP	*Bupleurum chinense*	(Li et al. 2017) (Wang et al. 2018)
5-HIMOXOL 6-BrHIMOLID	4.25 μM 5.81 μM	ITGB1 protein Integrin 1 protein	Semi-synthetic	(Lisiak et al. 2017) (Lisiak et al. 2021)
7-Lantadene B	112.2 μM	Bax, PARP, p62, and cyclin D levels	*Lantana camara*	(Shamsee et al. 2018)
8-Esculentoside A	177.68 μM	IL-6 protein PSTAT3 protein STAT3 protein	Root of *Phytolacca esculenta*	(Liu et al. 2018a)
9-CDDO-Me	0.51 μM	Wnt/β-catenin pathway, CXCL16, CCL2, IL-6	Synthetic	(Zhou et al. 2020a) (Ball et al. 2020)
OA-PTX nanoparticle	7.66 μM	P-gp	Synthetic	(Bao et al. 2020)

Cervical cancer

In developing countries, cervical cancer is common among women. Most cases are found in developing countries. Cervical cancer mostly results from long-term infection with human papillomavirus (HPV). HPV16 and 18 cause 70% of cancer cases. New molecules and therapies are being discovered as treatments for cervical cancer (Edathara et al. 2020).

Epifriedelinol is a compound that shows excellent anti-inflammatory and antioxidant properties. It is isolated from *Aster tataricus'* roots and *Vitex penduncularis's* leaves. Yang and colleagues observed the effects of epifriedelinol on C-33A and HeLa cell lines. The cell viability decreased with increasing concentrations of epifriedelinol. It also elevated caspase 3, 8, and 9 enzyme activity and cytosolic cytochrome c in both cell lines. Epifriedelinol also affects how the B-cell lymphoma 2 (Bcl-2) family of proteins is expressed, increasing the activity of Bad, Bim, and Bak proteins, and reducing the activity of others, such as the Bcl-xL and Bcl2 proteins. It also downregulates the expression of inhibitors of apoptosis proteins (Yang et al. 2017). Potočnjak and colleagues studied the combinatorial effect of cisplatin and OA. Cisplatin is a commonly employed agent for treating a wide range of cancers. However, it can cause cardiotoxicity, nephrotoxicity, and hepatotoxicity. Since the kidney is the major route of elimination, cisplatin often accumulates there and causes damage to the kidneys through ROS production. OA aids in repairing this damage and enhances the cervical cancer cells' sensitivity to cisplatin. Cisplatin-treated mice exhibited elevated kidney damage and increased creatinine and blood urea nitrogen (BUN) concentrations in the serum, and these effects were attenuated by treatment with increasing concentrations of OA. OA attenuates 4-hydroxynonenal (4-HNE) and HO-1 levels, which are oxidative stress markers and prevents the loss of superoxide dismutase (SOD) activity. Higher doses of OA decreased tumor necrosis factor-alpha (TNF-α), autophagy-related gene 5 (Atg5), and light chain 3B (LC3B-I/II) levels in cisplatin-treated mice. OA also decreases the levels of p21 and results in limited caspase 3 and 9 cleavage and PARP in the kidney. Higher doses of OA decreased the expression of Extracellular signal-regulated kinases (ERK) and the IC50 values. Treating HeLa cells with OA and cisplatin suppresses the expression of the Bcl-2 protein while increasing LC3B-II expression (Potočnjak et al. 2019).

Edathara and colleagues studied the effects of OA and esculetin on HeLa cell lines. The cytotoxic effects on the cell line were studied using a sulforhodamine B (SRB) assay at different concentrations of OA and esculetin. These genes affect the expression of cell cycle regulatory genes. Beta-galactosidase (β-gal) assay revealed that they were able to increase cell senescence, and semiquantitative polymerase chain reaction (PCR) results showed that OA and esculetin elevated tumor suppressor gene expression and downregulated proliferation regulator levels. Wound healing assays revealed that the migratory activity of cells decreased, and Wnt signalling-associated gene expression also significantly decreased in cells treated with OA and esculetin. Annexin V-Fluorescein isothiocyanate (FITC)/PI staining revealed that most of the cells treated with a combination of the two agents underwent apoptosis. Treatment with OA and esculetin led to the localization of the p16 and p53 genes in the cytoplasmic and perinuclear regions, revealing their apoptotic effects (Edathara et al. 2020). Ferroptosis is an essential process that prevents and kills tumor growth, especially in kidney and liver cancer. Therefore, the induction of ferroptosis in tumor cells is an essential therapeutic strategy. Ferroptosis is regulated by the Acyl-CoA synthase long-chain family member 4 (ACSL4) gene. OA treatment causes the accumulation of Fe2 + and malondialdehyde (MDA) and a reduction in tumor size. Glutathione (GSH) levels also decreased in mice treated with OA. With increasing concentrations of OA, HeLa cell viability decreases, and ROS levels increase. OA treatment increased ACSL4 and transferrin receptor 1 (TfR1) activity and decreased ferritin heavy chain (FTH1) and glutathione peroxidase 4 (GPX4) expression in both tumors and HeLa cells. Inhibiting the expression of

Table 2 OA derivative and its effect on cervical cancer

| Name and structure of the derivative	IC50	Pathway/gene/RNA involved	Source	References
10-Epifriedelinol	428.4 μM	Bcl-xL proteins Bcl2 pathway	*Aster tataricus'* roots *Vitex penduncularis's* leaves	(Yang et al. 2017)
Cisplatin-OA	10 μM	Bcl-2 protein LC3B-II expression	Synthetic	(Potočnjak et al. 2019)
11-oleanolic acid	43.44 μM	p16, p53, Wnt pathway, ACSL4, TfR1, FTH1, GPX4	Olive plant	(Edathara et al. 2020) (Xiaofei et al. 2021)
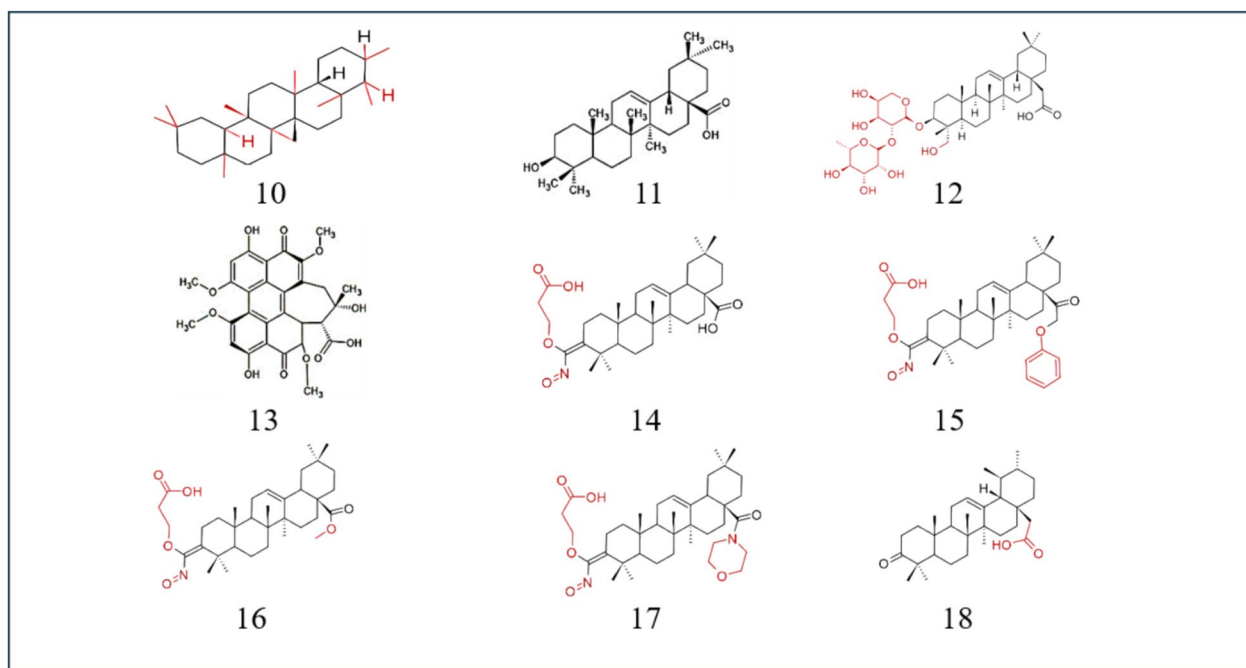
Fig. 3 Structures of OA derivatives effective against cervical and hepatocellular cancer. 10: epifriedelinol; 11: OA; 12: α-hedrin; 13: HA; 14: SMAA; 15: SMAE; 16: SMAEM; 17: SMAM; 18: ursolic acid

ACSL4 reduced OA-mediated ferroptosis in this cell line (Xiaofei et al. 2021) (Table 2) (Fig. 3).

Gastric cancer

Gastric cancer is common among Asian and South American populations. It has been shown to result in low survival rates. According to the Lauren classification, there are three main subtypes, but according to the WHO, there are four main subtypes. *H. pylori* and Epstein−Barr virus are among the major causative agents of gastric cancer (Sexton et al. 2020).

The interaction between programmed cell death ligand-1 (PD-L1) and programmed cell death protein-1 helps control tumor immunity. The DNA methyltransferase 5-azacytidine regulates PD-L1 expression in breast cancer. OA at higher concentrations decreases the survival of MKN-45 cells augmented with IL-1 and attenuates PD-L1 expression. Treatment of MKN-45 cells with OA restored IL-2 levels, which indicates that T-cell activity mediates OAs' cytotoxic effect on gastric cancer cells. OA significantly decreases demethylase activity in cells treated with IL-1 and downregulates PD-L1. OA leads to the downregulation of PD-L1 by inhibiting Tet methylcytosine dioxygenase 3 (TET3) expression. OA also inhibits the NK-kB signalling essential for attenuating PD-L1 via the demethylation of MKN-45 cells (Lu et al. 2020). Current studies showed that Treg and T helper 17

(Th17) cells are integral parts of the tumor microenvironment, and any imbalance may lead to immunosuppression in tumors. IL-6 and miRNAs regulate the Treg/Th17 imbalance in gastric cancer cells. OA also has an inhibitory effect on gastric cancer cells. qPCR results showed that in gastric cancer tissue, the miR-98-5p level decreased. In gastric cancer tissue, Treg and Th17-related factor expression levels are increased. Patients with gastric cancer have peripheral blood mononuclear cells (PBMCs) with a reduced balance of Treg/T helper 17 cells (Th17 cells). The demarcation of Treg/Th17 cells is impaired by the administration of OA, which also promotes miR-98-5p expression in the PBMCs of cancer patients. The differentiation of Treg/Th17 cells is impaired when miR-98-5p is overexpressed. miR-98-5p negatively regulates IL-6 expression. Therefore, OA regulates Treg/Th17 cell balance by regulating the expression of miR-98-5p (Xu et al. 2021). (Table 3).

Hepatocellular cancer

Among the different types of cancers, globally hepatocellular carcinoma (HCC) ranks as the third leading cause of death. Exposure to hepatitis B or hepatitis C and aflatoxin B1 are the major risk factors for developing hepatocellular carcinoma (Gee et al. 2018). Hepatocellular cancer treatment typically includes chemotherapy, radiofrequency ablation, etc. However, recurrence and multidrug

Table 3 OA derivative and its effect on gastric cancer

Name of the derivative	IC50	Pathway/gene/RNA involved	Source	References
11-OA	> 30 μM	IL-1 protein PD-L1 expression NK-kB signaling IL-6, miR-98-5p	Olive plant	(Lu et al. 2020) (Xu et al. 2021)
HN/CDDP/OA	16.7 μM	P-gp, apoptosis pathway	Synthetic	(Li et al. 2020)

resistance are very common, leading to the need for more efficient therapies (Li et al. 2018). Drug resistance is often caused by increased expression of P-gp, a drug transporter (Kayouka et al. 2019).

Nuclear factor erythroid 2-related factor 2 (Nrf2) which is a regulator of antioxidant and detoxifying enzymes, shows increased expression after OA treatment. The action of Nrf2 is partly mediated by farnesoid X receptor (FXR) and via NF-κB-activated pathways inhibition (Dzubak et al. 2006). Regulation of the mitochondrial pathway and X-chromosome-linked inhibitor of apoptosis protein (XIAP) promotes OA-mediated apoptosis in HuH7 cells (Shyu et al. 2010). OA modified to have azaheterocyclic groups to the A-ring shows cytotoxicity against hepatocellular cancer and BEL-7404 cell lines. The ROS/MAPK-mediated mitochondrial pathway induces apoptosis in HepG2 cells treated with a Para-aminobenzoic acid (PABA)/NO derivative of OA. Enhanced cytotoxicity is observed in HepG2 and Col-02 cells treated with OA modified with a nitro group at the C-17 position and 1-en-2-cyano-3-oxo in the A ring (Mallavadhani et al. 2013). Wang and the group demonstrated that Vascular endothelial growth factor (VEGF) and intracellular adhesion protein expression are attenuated in liver cancer after treatment with OA, which reduces viability and induces cell apoptosis. Epithelial–mesenchymal transition (EMT) is vital in tumor progression, and OA helps in inhibiting this process through the modification of inducible nitric oxide synthetase (iNOS). OA causes dimerization of iNOS, which elevates the production of NO. OA limits the ability of HCC cells to migrate and invade, which relies on the production of NO. Administration of OA reduces vimentin levels, which is a mesenchymal identifier, and elevates E-cadherin levels, which is an epithelial identifier. OA promotes the nitrification of EMT-related proteins, thus antagonizing EMT in hepatocellular cancer cells. Moreover, OA enhances antitumour activity and increases the activity of regorafenib, which is an inhibitor of angiogenesis, on vimentin, MMP2/9, and E-cadherin. Increased iNOS production enhances survival of individuals with hepatocellular cancer (Wang et al., 2019a). A recent study showed that P-gp is absent in highly invasive breast cancer cells but is present in liver cancer cells. OA decreases the viability of cells, and this effect is not impacted by verapamil, a P-gp inhibitor, in breast cancer cells. OA attenuates the survival of HepG2 cells to a greater extent in the presence of verapamil. This is due to the blocking of the efflux pump that causes OA to accumulate (Kayouka et al. 2019).

Zhou and colleagues showed how OA represses hepatocellular cancer cell growth and induces cell death and nuclear condensation in cells. OA reduces ATP levels, suggesting mitochondrial dysfunction. Bcl-2 expression is reduced, and Bax expression is increased, indicating enhanced apoptosis. P62 levels decrease, and LC3-II and Beclin-2 levels increase, indicating elevated autophagy in cells treated with OA. Akt/mTOR pathway-induced autophagy is restricted after treatment with OA. When an autophagy inhibitor is coadministered with OA, cell proliferation and apoptosis are decreased (Zhou et al. 2020b). A current study showed that essential biological pathways are regulated by miRNA gene expression, which serves as an important target for anticancer drugs. EMT is promoted by the deletion of miR-122, which leads to Hepatocellular cancer progression. OA, although not a common activator in the pathway, enhances the expression of miR-122. In addition, HepG2 cells treated with OA exhibit decreased migration and invasion rates due to increased miR-122 levels and downregulated EMT (He et al. 2021). Hosny and colleagues studied 7,12-dimethylbenz[a]anthracene (DMBA), which has tumorigenic and genotoxic effects due to the production of ROS. Few OA derivatives help inhibit DMBA-induced carcinogenesis. OA scavenges 2,2'-Azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt (ABTS) and 2,2-Diphenyl-1-picrylhydrazyl (DPPH), indicating its antioxidant properties. It inhibits Ehrlich ascites carcinoma (EAC) and HepG2 cell line proliferation. OA increases Alanine aminotransferase (ALT), AST, proliferating cell nuclear antigen (PCNA) expression, and antioxidant levels while attenuating MDA, TNF-a, NF-kB, COX-2, and VEGF expression in mice treated with DMBA. They also showed attenuated Bcl-2 expression and elevated Caspase-3 and Beclin-1 levels. Treatment with OA improves the hepatocellular architecture (Hosny et al. 2021).

Doxorubicin (DOX) is commonly administered as an anticancer agent. DOX and OA show poor solubility in the body. This is overcome by using liposomes, which show enhanced absorption and higher drug-loading capacity. Treatment with both drugs simultaneously increased the cytotoxicity by several-fold compared to either drug alone. OA release was found to be highest in DMEM and decreased in acidic buffer. Liposome treatment shows improved cytotoxicity

and anticancer effects. The number of viable cells also decreased upon treatment with the drug. DOX is most efficient in diminishing tumor growth, and DOX-encapsulated liposomes show greater cytotoxicity than OA-DOX-encapsulated liposomes. Glutathione peroxidase activity was detected only in cells treated with OA-DOX-encapsulated liposomes, indicating protection against ROS. The administration of free DOX and DOX-encapsulated liposomes resulted in the least amount of glutathione peroxidase activity. The levels of biochemical markers involved in organ toxicity increase after the administration of DOX; however, OA-DOX-encapsulated liposomes show little alteration in the expression of these markers (Sarfraz et al. 2017).

CYP450 influences some of the effects of OA, which causes the release of NO by O_2-vinyl diazenium diolates, thus exerting anticancer effects. Compound 5 (Zou et al. 2017) inhibits the proliferation of SMMC-7721 and HepG2 cells, and the highest level of NO is produced by this compound in SMMC-7721 cells; however, it does not affect normal liver cells. NO levels decrease when a CYP450 inhibitor or NO scavenger is used. The compound shows increased solubility compared to OA due to the addition of a galactosyl group to OA (Zou et al. 2017). Gee and colleagues studied how CDDO-Me affects the STAT3 pathway. CDDO-Me helps attenuate STAT3 expression, involved in the development of hepatocellular cancer. A variant of the surface marker found on the hepatitis B virus, W4P, promotes the progression of cancer via the STAT3 pathway. CDDO-Me shows cytotoxicity toward cells expressing this variant. It suppresses tumor growth, colony formation, and migration and induces the apoptosis of these cells, showing its anticancer activity. CDDO-Me suppresses the activation of STAT3 via W4P, a large surface protein Luteinizing Hormone Beta (LHB). CDDO-Me decreases cyclin D1 levels and increases p53 and p21 expression. These proteins are needed for STAT3 activation, and their alterations repress STAT3. CDDO-Me suppresses IL-6 production, which is involved in the inflammatory response; in turn, it prevents the progression of hepatocellular cancer (Gee et al. 2018). Another study showed that α-hedrin reduces cell survival and causes apoptosis through the accumulation of ROS and the depletion of GSH in hepatocellular cancer cells. It increases the levels of proapoptotic proteins and proteins associated with mitochondria-mediated apoptosis. The tumor volume and apoptosis increase with α-hedrin at higher concentrations (Li et al. 2018). Wang and group described the role of hypocrellin A (HA). HA shows anticancer activity through photodynamic effects. It can be used to increase the potency of OA as an anticancer agent. HA reduces cell density and causes cells to become rounded when administered. Yes-associated protein (YAP) and Transcription Enhancer Factor (TEA) Domain Transcription Factor (TEAD) levels and their target protein expression are attenuated after treatment with HA.

Downregulation of YAP reduces hepatocellular cancer cell proliferation. HA combined with OA more strongly inhibits proliferation and migration and reduces YAP and TEAD levels in hepatocellular cancer cells (Wang et al. 2019b).

Among the different morpholide derivatives of OA, 3-succinyloxyiminoolean-12-en-28-oic acid (SMAA) has the greatest cytotoxicity, and 3-succinyloxyiminoolean-12-en-28-oic acid benzyl ester (SMAEB) has the least. 3-succinyloxyiminoolean-12-en 28-oic acid methyl ester (SMAEM) and SMAA reduce the expression of p50, while 3-succinyloxyiminoolean-12-en-28-oic acid morpholide (SMAM) and SMAEB reduce p65 levels. These proteins are involved in the NF-κB pathway. The reduction in p65 levels is correlated with SMAMs' impact on COX-2. A reduced level of STAT5A/B in the nucleus and an increase in the nucleus are linked to the actions of SMAEB and SMAM. SMAA and SMAM increase proapoptotic protein expression, while all morpholide derivatives of OA reduce antiapoptotic protein levels (Krajka-Kuźniak et al. 2019a). Yao and colleagues studied how OA and UA affect UDP-glucuronosyltransferases (UGTs), which are metabolic enzymes involved in phase II metabolism. UGT1A1 is one of the primary UGT isoforms. Variations in these enzymes may alter drug metabolism. Transcription factors such as pregnane X receptor (PXR) and chimeric antigen receptor (CAR) regulate its expression. The UGTIA3 and UGT1A4 substrates are activated by OA and Ursolic acid (UA). Studies have been performed to understand its effect on HEPG2 cells. OA and UA upregulate the expression of UGTIA1/A3/A4/A9. OA induces PXR expression in HEPG2 cells but has no effect on CAR expression. PXR is responsible for the regulation of UGTIAs in cells treated with OA and UA. Silencing PXR reduces the induction of UGT1A1. UGT1A1 expression mediated by CAR is not influenced by OA or UA (Yao et al. 2019). Krajka-Kuźniak and colleagues demonstrated that Oleanolic acid oxime (OAO) derivatives exhibit enhanced anti-inflammatory properties due to increased hydrophilicity. Its combination with aspirin enhances its properties. The NF-κB pathway is often associated with inflammation-induced carcinogenesis. This pathway mainly regulates the IL-6 gene. COX-2 helps promote the progression and invasion of cancer cells. Therefore, its downregulation is necessary for inhibiting cancer progression. These oxime derivatives prevent the proliferation of HepG2 cells. OA conjugates with aspirin and aspirin itself show less cytotoxicity than OA and its oxime derivatives. OA derivatives, particularly morpholides, are excellent therapeutic agents. p50 and p65 levels in the NF-κB pathway decrease after treatment with OAO derivatives. The morpholide derivative of OAO conjugates with aspirin to reduce the NF-κB subunit levels to a great extent. This conjugate acts as a chemopreventive agent. A decrease in the amount of IκB kinase inhibits NF-κB pathway activation. Through the NF-κB

Table 4 OA derivative and its effect on hepatocellular cancer

Name of the derivative	IC50	Pathway/ gene/ RNA involved	Source	References
11-OA	–	Nrf2, NF-Kb, ROS/MAPK-mediated mitochondrial pathway	Olive plant	(Dzubak et al. 2006)
	> 50 μM	P-gp		(Kayouka et al. 2019)
	65 μM	vimentin, MMP2/9 and E-cadherin		(Wang et al. 2019a)
	26.91 μM	Bcl2,P62, LC3-II		(Zhou et al. 2020b)
	14.07 μM	miR-122		(He et al. 2021)
	4.25 μM	Bcl-2, LC3-II, Beclin-2, Akt/mTOR pathway, VEGF, MDA, TNF-α, NF-Kb, COX-2		(Hosny et al. 2021)
OA-DOX liposome	78.03 μM	Glutathione peroxidase activity, ROS production	Synthetic	(Sarfraz et al. 2017)
9-CDDO-Me	> 1.25 μM	IL-6 proteins STAT3 proteins	Synthetic	(Gee et al. 2018)
12-α-hedrin	18.45 μM	Mitochondrial pathway	Hedera species Nigella species	(Li et al. 2018)
13- HA	–	YAP proteins TEAD proteins	Hypocrella Bambusae Shiraia bambusicola	(Wang et al. 2019b)
14-SMAA	38 μM	NF-κB pathway	Synthetic	(Krajka-Kuźniak et al. 2019a, b)
15-SMAEB	100 μM	NF-κB pathway	Synthetic	(Krajka-Kuźniak et al. 2019a, b)
16-SMAEM	100 μM	NF-κB pathway	Synthetic	(Krajka-Kuźniak et al. 2019a, b)
17-SMAM	46 μM	NF-κB pathway	Synthetic	(Krajka-Kuźniak et al. 2019a, b)
18-Ursolic acid	–	UGTs, PXR, CAR	Apples, thyme, oregano	(Yao et al. 2019)
OAO-Asprin	> 150 μM	COX-2, IL-6, NF-kb	Synthetic	(Krajka-Kuźniak et al. 2019a, b)
CDDP/OA-LCC NPs	2 μM/35 μM	ALT, AST, mTOR pathway, NF-Kb, AMPK pathway	Synthetic	(Khan et al. 2019)

(**–**) not available

pathway, OAO derivatives suppress the main inflammatory components, and their conjugation with aspirin enhances this effect (Krajka-Kuźniak et al., 2019b) (Fig. 3) (Table 4).

Melanoma

Melanoma is a type of cancer associated with melanocytes that produce pigments in the skin and other areas, such as the uvea. Melanoma accounts for a small number of skin cancers but is highly associated with death. The low survival rate is due to its high metastatic activity and resistance to chemotherapeutic agents. It mostly occurs due to mutations in the BRAF V600 or neuroblastoma rat sarcoma viral oncogene homolog (N-RAS) genes. Melanoma has been treated with a variety of treatments, including radiation therapy and chemotherapy. However, these therapies tend to have side effects, and therefore, an inclination towards natural products has been observed in recent years. OA shows excellent anticancer and anti-inflammatory properties (Caunii et al. 2017).

Liu and colleagues studied that altering the sugar group linked to the aglucone of OA affects tumor progression (Liu et al. 2013). Apoptosis is induced by CDDO by increasing the amount of cytoplasmic free Ca2 + in COLO 16 cells.

CDDO and CDDO-Im induce apoptosis in multidrug-resistant cells via MMP loss, the production of superoxide, the release of cytochrome c and several other factors (Hail et al. 2004). CDDO-Me and CDDO-Im promote glutathione synthesis to shield human keratinocytes from the toxicity induced by 2-chloroethyl ethyl sulfide, a sulfur mustard analog (Abel et al. 2011).

UA dose-dependently attenuates the growth of SK-MEL-2 cells at increasing concentrations. UA also affects the cell cycle progression of aneuploid and diploid cells. At lower concentrations, the diploid cells were evenly distributed across all the phases, while the aneuploidy cells were mostly concentrated at G2/M phase. S phase arrest takes place and finally the cells undergo destruction at high concentrations. The flow chamber method evaluates the adhesion of cells to certain molecules, such as Intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1(V-CAM 1), involved in tumor progression. Treatment with UA slightly altered the adhesion to the VCAM substrate and significantly altered the adhesion to the ICAM substrate. Compared with UA, OA has a greater impact on reducing the vascular density and the number of blood vessels in each area. Treatment with OA reduces the melanoma-associated angiogenesis reaction. Although OA

is more potent as an angiogenic inhibitor than UA, its meta-static ability was not attenuated by either agent (Caunii et al. 2017).

Woo and colleagues studied how OA affects the NF-kB pathway. The survival of A375P melanoma cells was reduced with elevated concentrations of OA. OA also induced apoptosis in A375P and A375SM cells. Cleaved PARP showed greater expression in both cell lines treated with OA. Bax expression increases, and Bcl-2 expression decreases in A375SM cells, with no significant difference in expression in A375P cells. OA induces apoptosis through the regulation of p-NF-κB, an essential regulator of the NF-κB pathway. OA inhibits melanoma cell proliferation in vivo. The liver and kidneys are not affected after treatment with OA, demonstrating its nontoxic nature (Woo et al. 2021) (Table 5).

Non-small cell lung cancer

Globally non-small cell lung cancer (NSCLC) shows a prevalence of 13%. NSCLC is a commonly occurring lung cancer. Adenocarcinoma, large cell carcinoma, and squamous cell carcinoma are the most common forms of lung cancer. In recent years, immunotherapy and targeted therapy have become more and more popular for treating NSCLC (Araghi et al. 2023). VEGF expression is attenuated, and apoptosis is induced by OA in NSCLC and multidrug-resistant cells (Lucio et al. 2011). Cellular GSH is inhibited, and gamma-glutamylcysteine synthase activity decreases in cells administered with OA combined with radiation. CDDO-Me induces apoptosis via cytochrome c release and the attenuation of FLICE (FADD-like IL-1β-converting enzyme)-inhibitory protein (FLIP), which is an endogenous antagonist of caspase-8 (Zou et al. 2007). Song and colleagues studied how ROS causes damage to DNA and eventually cell death by acting on various signalling pathways. STAT3 is active in multiple forms of cancer, lung cancer included, making it a suitable target. Several OA derivatives are being used in treating NSCLC. SCZ017 is a derivative of OA that shows selective cytotoxicity toward lung cancer cells and reduces

their viability. It elevates the level of apoptosis, which is induced with the help of caspase-3, and by elevating Bax/Bcl2 levels. The LC3-II/I ratio and Beclin-2 level were elevated by SZC017. These are hallmarks of autophagy. SZC017 targets the Akt pathway and decreases Akt and pAkt levels. This decreases the level of p-STAT3 in the nucleus. SZC017 leads to ROS production and the accumulation of calcium in cells. The ROS produced is inhibited with the help of NAC, which also increases the STAT3 and Akt levels and downregulates the proteins involved in autophagy. ROS regulate the apoptotic and autophagic pathways and inhibits the STA3 and Akt pathways (Song et al. 2017).

Inhibiting cancer cell autophagy reduces cell growth and helps overcome resistance to chemotherapy. Autophagy inhibitors are applied to fight cancer tumors. α-Hederin, a natural saponin, also has anticancer properties. α-Hederin upregulates LC3B-II in NSCLC, indicating an increase in the number of autophagosomes. It elevates p62 levels, demonstrating that α-Hederin is an inhibitor of autophagy and causes the accumulation of autophagosomes. The pH of lysosomes is increased in NSCLC after α-Hederin treatment, indicating the suppression of late autophagy and cathepsin D maturation in lysosomes. Paclitaxel combined with α-Hederin had greater inhibitory effects than paclitaxel alone. These compounds also increase the levels of cleaved PARP and caspase-3, indicating that caspase-centred cell death is induced in chemo-resistant cells. ROS accumulate due to the impact of α-Hederin on paclitaxel, which causes cell death (Zhan et al. 2018).

Three main groups, cyclins, their kinases, and their inhibitors, regulate the cell cycle. SSd upregulates the activity of some of these genes. c-Jun N-terminal kinase (JNK) expression increases at the sites of proliferation and apoptosis. The JNK inhibitor and SSd are combined, and their effect on cancer cells is determined. They cause cells to accumulate in the sub-G1 and sub-G2 phases, which increases apoptosis and prevents proliferation, respectively. SSd induces apoptosis via the JNK pathway. SSd and JNKi work synergistically to negatively regulate proliferation and positively regulate apoptosis. SSd alone elevates the levels of cell cycle regulator genes and JNK/pJNK activity. P53 is downregulated by

Table 5 OA derivative and its effect on melanoma

Name of the derivative	IC50	Pathway/gene/RNA involved	Source	References
9-CDDO-Me	–	MMP	Synthetic	(Abel et al. 2011)
1-CDDO-Im	–			
18-UA	58.43 μM	ICAM-1 V-CAM 1	Apples, bilberries, cranberries, elderflower, peppermint, lavender, oregano, thyme, hawthorn, and prunes	(Caunii et al. 2017)
11-OA	100 μM	NF-kB pathway, Bax, Bcl2	Olive plant	(Woo et al. 2021)
Dox@HSA-OA NPs	–	EGFR, caspase-3, caspase-7, Bcl2	Synthetic	(Kumbham et al. 2022)

(–) not available

JNK/pJNK, which indicates that SSd upregulates p53 levels. JNk inhibitors and SSd attenuate each other's impacts on the expression of other members (Chen et al. 2018). Wu and colleagues demonstrated the effect of SSd on NSCLC. SSd greatly inhibits the growth of NSCLCs and reduces their numbers. The initial phase of the cell cycle shows increased cell numbers and cells in G2/M decrease. SSd attenuated Cyclin D1 and CDK4 levels and elevated P27 levels. It increases the number of apoptotic cells. The levels of proliferation markers such as STAT3 are decreased, and the levels of apoptotic markers such as p44/42 and cleaved caspase-3 are elevated (Wu et al. 2020).

EGFR mutations are mostly observed in such cancers. EFGR inhibitors are often used to treat patients with this type of cancer. However, resistance to these inhibitors develops over time, paving the way for the use of OA, which shows antitumour activity against these cell lines. NO has antitumour effects and can be combined with OA to increase cytotoxicity. OA is more potent against the A549 cell line than against the other cell lines. The addition of a nitrosyl group at the end of the ester chain of OA increases its potency and enhances the spectrum of OA. The presence of an NO donor increases the activity of OA. The hybrids of OA-NO show increased cytotoxicity due to the presence of a 3-acetyl-OA (OAc-3) functional group. The inhibition of EGFR-L858R/T790M/C797S (EGFR-LTC) kinase depends on the function of the NO donor and

the structure of the triterpenoid. The greater the amount of NO released, the greater the cell growth and proliferation are inhibited. OA/hederagenin and NO increase its activity against non-small cell lung cancer cell lines (Chen et al. 2019).

Another study showed that higher doses of ursolic and OA cause a reduction in the viability of A549 cells, with UA being more cytotoxic. LC3-II levels increase with increasing incubation time, indicating that autophagy occurs. The LC3-II/LC3-1 ratio is elevated to a greater extent with uric acid. Treatment with UA and OA increases alterations in mitochondria, indicating that autophagosomes are being formed. Cells treated with UA exhibit fragmented mitochondria in autophagosomes, indicating mitophagy. UA and OA increase p62 and LC3 levels. Phosphatase and Tensin Homolog -induced kinase 1 (PINK1) and Parkin are markers of mitophagy. Both compounds elevated PINK1 expression, demonstrating that PINK1 is recruited to the mitochondrial membrane. Parkin levels increase with OA but are not affected by UA. UA induces autophagy via the AKT/mTOR pathway, while OA uses a different mechanism. Both acids stimulate ROS production. Acid-mediated inhibition of autophagy increases Nrf2 expression. Treatment of cells with OA or UA and an autophagy inhibitor significantly increased the number of cells with a low MMP, which decreased the cells' metabolic potential (Castrejón-Jiménez et al. 2019) (Fig. 4) (Table 6).
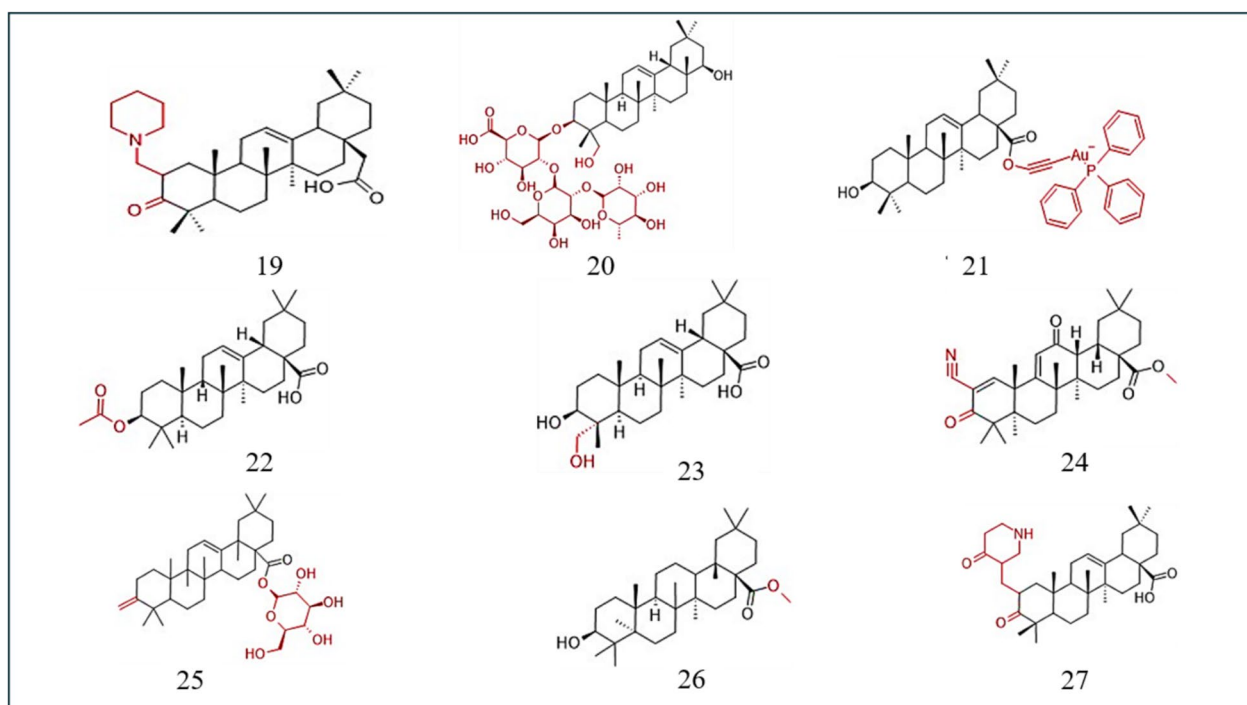

Fig. 4 Structure of OA derivative effective against non-small cell lung, ovarian and other types of cancers. 19: SZC017; 20: Soyasaponin 1; 21: Gold-OA derivatives conjugation; 22: 3-O-acetyloleanolic acid; 23: CDDO; 24: Hederagenin; 25: Dextrose-OA; 26: OAME; 27: K73-03

Table 6 OA derivative and its effect on non-small cell lung cancer

Name of the derivative	IC50	Pathway/gene/RNA involved	Source	References
9-CDDO-Me	–	FLIP, caspase-8, cytochrome c, VEGF	Synthetic	(Samudio et al. 2006, Zou et al. 2007)
19-SZC017	9.66 μM	STA3 proteins Akt proteins	Synthetic	(Song et al. 2017)
12-α-hedrin	32.43 μM	PARP proteins Caspase-3 proteins	Hedera helix	(Zhan et al. 2018)
4-SSd	–	JNK pathway	Radix Bupleuri	(Chen et al. 2018) (Wu et al. 2020)
OA/hedragenin and NO combination	–	EGFR	Synthetic	OA/hedragenin and NO
18-UA	40 μM	AKT/mTOR pathway	Apples, bilberries, cranberries, elderflower, peppermint, lavender, oregano, thyme, hawthorn, and prunes	(Castrejón-Jiménez et al. 2019)
11-OA	40 μM	PINK1/Parkin pathway	Olive plant	(Castrejón-Jiménez et al. 2019)

(**–**) not available

Ovarian cancer

Ovarian cancer (OC) is a highly malignant type of gynecological cancer. However, due to its internal nature and multiple side effects, there are very few available therapies (Bian et al. 2020). Epithelial ovarian cancer accounts for most ovarian cancers. Ovarian cancer has a high chance of reoccurring with a low rate of survival (Jia et al. 2017). Chemotherapy based on paclitaxel and platinum, followed, or preceded by cytoreductive surgery, is the most commonly employed therapy (Sung et al. 2018).

The growth of A2780 ovarian cancer cells is attenuated by CDDO-Im via the JAK/STAT3 pathway. IL-6 secretion is reduced by CDDO-Me in paclitaxel- and cisplatin-resistant ovarian cancer cell lines and induces apoptosis via STAT3-regulated genes (Duan et al. 2009). It generates ROS in ovarian cancer cells and inhibits phosphorylated protein kinase B (p-Akt), p-mTOR, NF-Kb, p65 and antiapoptotic protein expression (Gao et al. 2011, Gao et al. 2013).

Tea saponins (TSs) have an antiproliferative effect and reduce the viability of OVCAR-3 and A2780/CP70 cells but are less cytotoxic to IOSE-364 cells. TS has a better impact than cisplatin. It inhibits colony formation and reduces the number of cells. TS increases apoptosis and causes nuclear condensation and fragmentation. Caspase-3/7 activity is increased, and pro-caspase-3 levels are decreased. TS induces apoptosis via the Bcl-2 family and not via the intrinsic apoptotic pathway. Apoptosis is induced independently of the extrinsic pathway, which relies on FAS-associated death domain protein (FADD) and death receptor 5 (DR5). VEGF expression is decreased via a hypoxia-inducible factor (HIF1-β)-independent pathway (Jia et al. 2017). Sung and colleagues reported that elevated levels of sialyl transferase and sialylated markers in tumor cells are hallmarks

of cancer. Maackia amurensis agglutinin (MAA) upregulation and α2,3-linked sialylation are often observed in higher stages of cancer. Soyasaponin 1 (Ssa1) represses α2,3-linked sialylation, MAA, and Maackia amurensis lectin-2 (MAL-2) in epithelial ovarian cancer cell lines. This downregulation reduces the motility of the cells. Cell growth and multiplication are not impacted by sialylation. The cell adhesion marker cadherin (CDH) 1 was elevated, and CDH2 expression decreased. The sialyl transferase levels are manipulated by α2,3 sialylation inhibitors, demonstrating that targeting this sialylation can attenuate the migratory activity of these cells (Sung et al. 2018).

Bian and colleagues showed how OA derivatives complexed with gold affect the thioredoxin system. Cell proliferation is regulated by the thioredoxin system, which consists of thioredoxin (Trx), thioredoxin reductase (TrxR), and NADPH. Thioredoxin targeting is a promising treatment for ovarian cancer. Auranofin, a gold compound, inhibits the thioredoxin system and shows antitumour potential by interacting with the sulphur or selenium groups of TrxR. To improve the safety of metal-based treatments of ovarian cancers, they are complexed with pentacyclic triterpenes. The gold complex with an OA derivative shows the highest cytotoxicity against ovarian cancer cells. The ovarian cancer cell line showed the greatest toxicity among other cell lines. This complex inhibits TrxR, owing to its gold centre, but shows less activity than auranofin. Mitochondrial membrane potential (MMP) levels are low after treatment with the complex, indicating that mitochondrial dysfunction contributes to cell death induced by the complex. The complex induces the colocalization of ROS and endoplasmic reticulum stress (ERS) with increasing concentrations. The levels of ER chaperones and markers of ERS are elevated in the presence of the gold complex. This compound increases

ROS levels, which actuates ERS, possibly leading to apoptosis. The pro-apoptotic protein expression is elevated, and the levels of pro-survival proteins are decreased. Cyclin A and cyclin-dependent kinase 2 (CDK2) levels are reduced, indicating a dependency on ROS production for the anticancer activity of the compound. Lactate dehydrogenase (LDH) is released from cells, resulting in compromised membrane integrity. NAC increases the cytotoxicity of the complex and inhibits ROS production. This complex activates ERS and produces ROS. The Trx system is necessary for maintaining redox balance, and inhibition of TrxR can offset this balance. This effect is overcome by the use of an ERS inhibitor, such as salubrinal, which inhibits ROS production. Salubrinal can also counteract the apoptotic potential of the complex. Overall, the complex inhibits tumor growth by attenuating the expression of TrxR (Bian et al. 2020) (Fig. 4) (Table 7).

Other types of cancer

Bladder carcinoma

Novel methods are being developed for the treatment of bladder carcinoma; drug delivery systems (DDS) are also being developed. One such system is based on zeolitic imidazolate framework (ZIF) nanoparticles, which exhibit excellent properties. The cancer cell membrane (CCM) was modified to improve the targeting of the DDS. DDP is the most commonly used chemical drug; however, it can have many side effects, which can be overcome by the use of OA, which has an anticancer effect through the activation of the adenosine monophosphate-activated protein kinase (AMPK) pathway. Efficient homing can be achieved by linking Zn2 + in ZIF to phosphate groups on CCM. The hybrid nanoparticles (HNPs) of CCM-decorated ZIF with OA/DDP showed enhanced biocompatibility and drug release due to the unique ability of ZIF to respond to changes in pH. Combination therapy can achieve the same cytotoxicity at lower doses. The HP/DDP/OA group exhibited increased apoptosis, with a greater number of cells in G0/G1 phase arrest and fewer in the S phase. MDR can be reversed by OA by reducing P-gp expression. Which allows the accumulation of DDP. DDS increases the anticancer activities of OA and DDP (Chen et al. 2020).

Colorectal cancer

3-O-acetyloleanolic acid increases the expression of colorectal cancer DR5 to cause HCT-116 cells to undergo apoptosis. (Yoo et al. 2012). The rectal cancer cell lines exhibited high sensitivity to OA, CDDO, and CDDO-Me. Cell proliferation is inhibited by OA. OA increases ROS generation in a concentration-dependent manner. NADPH oxidase (NOX) expression is elevated in HCT-15, CaCo-2, and HT-29 cells. OA silencing suppresses the ability of OA to induce ROS generation and inhibit cell proliferation. OA decreases cyclin D1 and CDK2 expression; however, this effect is suppressed by NOX silencing. OA induces increased activity of HIF-1α in CaCo-2 cells but suppresses its activity in HCT-15 and HT-29 cells. When HIF-1α is overexpressed, the inhibitory effect of OA on HCT-15 and HT-29 cell proliferation is attenuated. OA inhibits cell proliferation by downregulating HIF-1α. Suppression of HIF-1α is carried out by overexpression of NOX2 and ROS production induced by OA (Guo et al. 2017). α-Hederin is a triterpenoid saponin that brings about apoptosis in colorectal cancer cells. The survival and clonogenic ability of HCT116 and HCT8 cells decreased with increasing concentrations of α-hederin. α-Hederin induces apoptosis via the mitochondrial pathway. α-Hederin elevates LC-3 expression and increases the number of autophagosomes, indicating that it promotes autophagy in these cells. It also promotes tumorigenicity in vivo via autophagy. The Phosphorylated mammalian target of rapamycin (p-mTOR), p-ULK1, p-P70S6K, and P62 protein levels are reduced by α-hederin, while the p-AMPK and beclin-1 levels are reduced. Silencing of AMPK reversed this effect. The ROS inhibitor NAC reversed the increase in ROS production and the activation of the AMPK/mTOR pathway induced by α-hederin, indicating that NAC reverses α-hederin-induced autophagy. 3-MA, an autophagy inhibitor, inhibits α-hederin-induced autophagosome formation and decreases cell viability (Sun et al. 2019).

Table 7 OA derivatives and its effect on ovarian cancer

Name of the derivative	IC50	Pathway/gene/RNA involved	Source	References
1-CDDO-Im 9-CDDO-Me	– –	p-Akt, p-mTOR, NF-Kb, p65, IL-6, JAK/ STAT pathway	Synthetic	(Gao et al. 2011, Gao et al. 2013)
Tea saponins	5.9 µg/ml	VEGF,DR5,FADD	Camillia plants	(Jia et al. 2017)
20-Soyasaponin 1	–	α2,3-linked sialylation,MAA,MAL-2	*Desmodium styracifolium*	(Sung et al. 2018)
21-Gold-OA derivatives conjugation	10.24 µM	TrxR, LDH, Cyclin A, CDK2	Synthethic	Bian et al. (2020)

(**–**) not available

Glioma and glioblastoma

These types of tumors show poor reactivity to chemotherapeutics. The proliferation of glioblastoma and neuroblastoma cells is blocked by CDDO, CDDO-Me, and CDDO-Im. The activation of caspase-3 and mitochondrial proteins by all the CDDO analogues induces apoptosis in a few paediatric solid tumor lines (Alabran et al., 2008). The growth of both U373 and human macrophages is attenuated by the suppression of CD163, IL-10, and STAT3 phosphorylation (Fujiwara et al. 2011).

Head and neck cancer

Cisplatin is also commonly used in head and neck cancer (HNC) treatment. This type of cancer affects the upper aerodigestive tract. A combination of surgery, radiotherapy, and chemotherapy has been used to treat this type of cancer. However, MDR often develops. Antioxidant response elements (AREs) are often bound by Nrf2s' promoter, which maintains redox homeostasis. Anticancer therapy focuses on increased ROS levels and antioxidant pathways as targets. Hederagenin, a triterpenoid, induces apoptosis via the mitochondria-mediated intrinsic pathway and helps overcome cisplatin resistance. It decreases the viability of both cisplatin-resistant and cisplatin-sensitive cells. It elevates Bax expression and decreases Bcl2 levels in cells. It activates most caspases except caspase 8. The apoptotic effect is caused by the suppression of the NF-κB pathway and $\Delta\Psi$m. HED causes GSH depletion and subsequent ROS accumulation in HNC cells. It increases p53 levels in HN9-resistant and HN9-sensitive cells. HED reduced the levels of Nrf2-ARE antioxidant pathway-related proteins. It elevates Kelch-like ECH-associated protein 1 (Keap-1) levels and attenuates p62 levels. Keap- 1 knockdown causes Nrf2 elevation, which inhibits the effect of HED on HNC cells. HED inhibited the increase in Nrf2 in cisplatin-resistant cells. HED has a cytoprotective effect and does not cause harm to normal tissues. One possible target for the therapy of chemoresistant HNC cells may be the Nrf2 pathway (Kim et al. 2017).

Hematological malignances

Cleave poly (ADP-ribose) and augment caspase-9 and caspase-3 activity, resulting in apoptosis induced by synthetic derivatives of OA (Zhang et al. 2007). Olean-12-Eno[2,3-c] oxadiazol-28-oic acid (OEOA) causes differentiation and arrest in the G1 phase in human leukemia cells (Ng et al. 2013). Leukemia and Burkitt's lymphoma cell lines exhibit inhibited growth when treated with oleanolic vinyl boronates (Moreira et al. 2013). CDDO has a greater effect than PPAR-gamma ligands on inducing differentiation and apoptosis via caspase activation and loss of the MMP. CDDO-Me affects

NF-κB activation and gene products, which helps suppress leukemia cell proliferation. CDDO-Me and CDDO hinder the NF-kB pathway by blocking IκB kinase (IKK)-β activity (Ahmad et al. 2006).

Osteosarcoma

Osteosarcoma is a type of malignant bone tumor that is most commonly observed among adolescents and young adults. Dextrose-OA, a derivative of OA, shows excellent anti-OS activity. By blocking the Notch pathway, OA triggers apoptosis by triggering both caspase-dependent and caspase-independent mechanisms. OA decreases cell viability and proliferation. Saos-2 cells are more strongly affected by OA than are MG63 cells. The expression of Hes-1, a target gene in the Notch pathway, was attenuated in cells treated with OA. OA suppresses Jagged1 (JAG1)-mediated apoptosis, and this effect is enhanced by the Notch inhibitor N-[N-(3,5-difluorophenacetyl)-1-alanyl]-S-phenylglycine t-butyl ester (DAPT), indicating that Notch plays a role in preventing cell proliferation. OA causes mitochondrial depolarization, which can be rescued by the addition of JAG1 ligands. OA induces a reduction in ROS, which is blocked by JAG1, the production of ROS stimulates OA-driven apoptosis and a decrease in membrane potential (Xu et al. 2018). Chen and colleagues studied how the Wnt1 signalling pathway promotes cell proliferation and invasion. Osteosarcoma progression is linked to Wnt1 signalling activation, along with elevation of c-myc, matrix metallopeptidases, and cyclin-D1, which are genes associated with cell proliferation. Wnt1 overexpression is regulated by SRY (Sex-determining Region Y)-Box (SOX9) in osteosarcoma. OA has been shown to have anti-osteosarcoma effects. OA reduces the viability, colony formation ability, and invasion of U2OS and KHOS cells. OA brings about cell death in osteosarcoma cells by promoting caspase 3 activation. OA downregulates SOX9, β-catenin, and Wnt1 expression, which can be reversed by SOX9 silencing (Chen et al. 2021).

Prostate cancer

Prostate cancer is a hallmark of cancers among men Androgen deprivation therapy is often employed for this type of cancer. Oleanolic acid methyl ester (OAME) is a derivative of OA assessed for its antitumour potential. OAME decreases the proliferation, colony formation ability, and viability of PC-3 cells and other Prostate cancer cell lines. G2 phase arrest is seen. Phosphatidylserine is expressed on the outer membrane, and DNA is fragmented in cells treated with OAME, indicating apoptosis. OAME reduces the MMP, causes cytochrome c production, and caspase 3 activation. OAME causes ROS production in PC-3 cells. These effects brought about by OAME have also been observed in vivo

(Abdelmageed et al. 2017). Treatment of prostate cancer cell lines with CDDO-Me and CDDO-Im inhibited growth due to the elevated activity of Death receptor 4 (DR4) and DR5, which serve as surfaces for TRAIL (Hyer et al. 2008). CDDO-Me also inhibits Human Telomerase Reverse Transcriptase (hTERT) expression and the Akt/NF-kB/mTOR pathway (Liu et al. 2012).

Pancreatic cancer

Pancreatic tumors are one of the most lethal types of tumors. Several approaches have been developed to improve patient survival, with limited success. Gemcitabine (GCB) is the drug most often employed for treating pancreatic ductal adenocarcinoma (PDA). The serine protease inhibitor Kazal type-1 (SPINK1) promotes cancer progression and helps in developing resistance to the drugs employed for chemotherapy. Silencing of miR-421 results in SPINK1 overexpression. OA induces cytotoxicity and cell death in pancreatic cancer cells via a mechanism stimulated by 5-fluorouracil. CDDO-me improves cytotoxicity against cells by generating ROS, superoxide anions, and hydrogen peroxide and improves cytotoxicity against cells by generating ROS. OA induces cytotoxicity and apoptosis in pancreatic cancer cells via a mechanism mediated by 5-fluorouracil. STAT3 and IKK activity is suppressed by CDDO derivatives. CDDO-Me causes ROS production, increasing the protein repressor level of Zinc finger and Broad-Complex, Tramtrack, and Bric-a-Brac domain-containing protein 10 (ZBTB10) and attenuating the expression of cell cycle-regulating proteins (Liby et al. 2010). Treatment of AsPC-1 cells with K73-03, a novel synthetic derivative of OA, reduced their viability, proliferation rate, and colony formation ability. The expression of LC3 and Beclin-1 was upregulated in OA-treated cells, indicating the occurrence of autophagy in these cells. K73-03 increases depolarization of the mitochondrial membrane potential and increases protein degradation. It triggers the apoptosis of these cells by affecting apoptotic proteins. K73-03 upregulates MiR-421 expression in AsPC-1 cells. In pancreatic cancer cells, the SPINK1 level is low in miR-421, and K73–03 helps to reverse this effect epigenetically. Enhancers of zeste homolog 2 (EZH2) and H3K27me3 levels are attenuated in these cells. MiR-421 inhibition reverses the impact of K73-03 on SPINK1 expression. SPINK1 silencing limits cell proliferation-induced autophagy, causes mitochondrial dysfunction, reduces cell mass, reduces ATP production, and enhances the apoptotic rate. SPINK1 silencing increases the potency of K73–03-mediated inhibition of this pathway. K73-03 attenuates cell proliferation by elevating SPINK1 levels to a greater extent than GCB. Autophagy is suppressed by SPINK1 overexpression, which also causes mitochondrial dysfunction and the suppression of ATP production. In cells overexpressing SPINK1, K73-03 inhibits

tumor growth and enhances apoptosis. K73-03 decreases SPINK1 expression to a greater extent than does GCB (Shopit et al. 2020).

Renal cancer has a significant death rate. An increase in cytotoxicity and resistance to drugs limits the application of chemotherapy. OA, CDDO, and CDDO-Me show high sensitivity to rectal cancer cell lines. Cell proliferation is inhibited by OA. OA increases ROS generation in a concentration-dependent manner. Nicotinamide Adenine Dinucleotide Phosphate oxidases (NOXs) expression is elevated in HCT-15, CaCo-2, and HT-29 cells. Its silencing suppresses OAs' ability to increase ROS generation and attenuate cell growth. OA decreases cyclin D1 and CDK2 expression, however, this effect is suppressed by the silencing of NOX. OA induces increased activity of HIF-1α in CaCo-2 cells, while it suppresses its levels in HCT-15 and HT-29 cells. When HIF-1α is overexpressed, the downregulatory activity of OA on HCT-15 and HT-29 cell growth is attenuated. OA inhibits cell proliferation by downregulation of HIF-1α. Inhibition of HIF-1α is carried out by overexpression of NOX2 and ROS production brought about by OA (Guo et al. 2017). Another study shows that 2–3% of the malignancies worldwide are brought about by renal cell cancer (RCC). Treatments include partial nephrectomy and nephrectomy. SSd is a triterpenoid that displays anti-inflammatory, anti-infectious, and anti-cancer effects. EGFR is overexpressed in RCC. SSd helps suppress this activity. SSd suppresses cell viability, colony formation ability, and proliferation in 769-P and 786-O cells. SSd cause G0/G1 phase arrest and induces apoptosis in 769-P and 786-O cells. It inhibits the expression of EGFR pathway-related genes. EGFR/p38 Mitogen-activated protein kinases (MAPK) signaling pathway is suppressed by SSd to suppress cell growth (Cai et al. 2017).

Thyroid cancer

Among the endocrine types of thyroid cancer, thyroid cancer accounts for 1–2% of systematic cancers and is the most prevalent OA that causes apoptosis via the Bax/Bcl2 pathway. Forkhead box A1 (FOXA1) is a protein found in the thyroid and is overexpressed in thyroid cancer. Thus, studies have been performed to understand how OA suppresses FOXA1 expression. OA reduces cell viability and causes nuclear condensation and fragmentation in SW579 cells. It induces apoptosis by elevating the Bax/Bcl2 levels. The cell proliferation, invasion, and clonogenic abilities of SW579 cells were reduced. OA elevates E-cadherin and suppresses vimentin. FOXA1 promotes colony formation, invasion, and migration in cells. OA elevates p-Akt levels and attenuates FOXA1 expression via the PI3K/Akt pathway (Duan et al. 2019).

OA nanoparticle and its effect on different types of cancers

Over the past ten years, OA has advanced significantly, especially in fields like toxicity studies, chemical changes, pharmacological research, separation and purification, and therapeutic application of OA. However, the clinical uses of OA are currently very limited due to its volatility, hydrophobic nature, and low bioavailability. The biological aspect of nanotechnology has led to the development of nanoparticulate medication delivery, which could produce effective OA formulations for therapeutic use. The OA's bioavailability and dissolving rate are improved by the nanoparticulate drug delivery system, which offers a workable formulation technique for clinical applications (Chen et al. 2011).

Breast cancer

Recently Nanoparticles have been used for the treatment of cancer due to their unique properties, such as sustained release, greater specificity, and targeting, and improved bioavailability. OA can form nanoparticles through self-assembly, which can then be used for encapsulating drugs such as paclitaxel. Synergistic treatment is possible because OA and paclitaxel (PTX) both display anticancer effects via different mechanisms and OA, an inhibitor of P-gp, increases the concentration of PTX, which is a substrate for P-gp. Nanodrug formulation improves the antitumour efficacy of OA due to enhanced cellular uptake. When administered, PTX-OA nanoparticles decrease the size of the tumor and suppress cell proliferation (Bao et al. 2020).

Gastric cancer

Li and the group demonstrated how cis-diamminedichloroplatinum (II) (CDDP) and OA NPs help enhance cancer treatment. CDDP is the most commonly used chemotherapeutic agent and exerts its anticancer effect by forming DNA adducts that inhibit DNA transfection. Cisplatin often causes drug resistance. Cisplatin in combination with OA helps to overcome this limitation. HNP with CDDP and OA (HN/CDDP/OA) show high bioavailability and are thus suitable as DDS. The combination of CDDP and OA reduces the dosage and enhances the anticancer effect compared to when CDDP and OA are administered alone. The combined effect of both drugs elevates apoptosis levels and promotes G0/G1 phase arrest. The incorporation of OA into a drug delivery system helps to MDR and enhances its accumulation in MGC-803 cells for improved activity. OA reverses MDR by downregulating the expression of P-gp proteins. HN/CDDP/OA shows pH-responsive release at approximately 5.5 and targets specific tumors (Li et al. 2020).

Hepatocellular cancer

Calcium carbonate acts as a perfect delivery system due to its biocompatibility and biodegradability. Studies have investigated the effect of lipid-coated cisplatin/oleanolic acid calcium carbonate NPs (CDDP/OA-LCC NPs) on HCC cells. Both CDDP and OA reduced cell viability with increasing concentrations. A 2:35 ratio of CDDP to OA was used for efficient drug loading in the NPs. These NPs are encapsulated in a pH-sensitive carrier that selectively releases the drug. The combined NPs showed the greatest cytotoxicity. CDDP/OA-LCC NPs interact with cells efficiently and cause nuclear condensation and disintegration, characteristic of apoptotic cells. The cytotoxicity of the combined NPs was higher than that of the individual NPs. The quantity of cells in the G0/G1 and sub-G1 stages increased as a result of these NPs, with few cells in the G2/M phase, indicating increased apoptosis. The combined treatment maintained lower levels of ALT and aspartate aminotransferase (AST), indicating low hepatocellular cytotoxicity. OA shows hepatoprotective effects and counters the impact of ROS elevation. Suppression of mTOR pathway activation and the NF-κB pathway and alteration of the AMP-activated protein kinase (AMPK) pathway induces apoptosis (Khan et al. 2019).

Melanoma

Another study showed that protein nanoparticles, such as human serum albumin nanoparticles, (HSA-NPs) have good biocompatibility, high drug loading efficiency, and avoid detection by the immune system, making them excellent carriers of anticancer agents. Human serum albumin nanoparticles interact with proteins derived from the tumor, which are acidic and have higher cysteine content and show increased activity in many cancer cells. DOX in combination with chemotherapeutic agents is used as an efficient combination therapy. HSA-NPs conjugated with OA and Dox have synergistic effects on murine melanoma and oral cancer cell lines. The amount of drug released from the HSA-NPs was greatest after 3 days, and at a pH of 5.0, administration with free Dox and Dox conjugated to HSA-NPs showed greater fluorescence signal when viewed under a fluorescence microscope after 4 h, indicating greater cellular uptake of the drug. The cell viability and IC50 values of the cell lines decreased with increasing time after treatment with HSA NP-mediated tumor-targeted Dox/OA combination therapy Human Serum Albumin Nanoparticle-mediated tumor-targeted Doxorubicin/ OA combination therapy (Dox@HSA-OA). The Annexin V assay showed that Dox@HSA-OA induced greater apoptosis than free Dox and HSA-OA in

both cell lines. Both cell lines treated with Dox@HSA-OA NPs bring about G_2/M arrest. Dox penetration was greater with Dox@HSA-OA NPs than with free Dox. Dox@HSA-OA showed greater increases in t1/2 and Cmax with reduced clearance than free Dox. Dox@HSA-OA reduced tumor size, increased DNA fragmentation and decreased the expression of the antiapoptotic marker Ki-67. Compared with cells treated with free Dox, cells treated with Dox@HSA-OA NPs showed greater upregulation of caspase-3 and caspase-7 and negative regulation of EGFR and Bcl-2 proteins (Kumbham et al. 2022) (Table 8).

Structure–activity relationship of OA derivatives

The addition of triphenylphosphine cations (TPP +) or tricyclohexylphosphine cations (TCP +) (29–30 Fig. 5) along various positions of the chain of 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid (CDDO) at the 28th COOH position, improves the anticancer properties against the HCT-116, MCF-7, and A549 cell lines (Ju et al. 2021). The conversion of the α, β-unsaturated carbonyl derivative of OA to an amide at 28-COOH, had a greater antiproliferative effect on the MCF-7, HeLa, and HepG2 cell lines. Compound 30 shows greater activity against HepG2 cells, and compound 31 (Fig. 5) retards MCF-7 cell growth (Wang et al. 2020). Hydroxamate derivatives of OA have a cytotoxic impact against multiple cancer types. Compound 32 (Fig. 5) is an excellent candidate against the 518A2 cell line (Wiemann et al. 2016). Meng and his group synthesized derivatives of OA by introducing certain fragments of PDGF receptor inhibitors at the C-2 or C-3 position. Compounds 33 and 34 (Fig. 5) inhibited SGC-7901 and A549 cell lines (Meng et al. 2021). Adding a phenyl-urea moiety with a linker at

Table 8 OA derivatives and its effect on other types of cancer

| Type of cancer	IC50	Name and structure	Pathway/ gene/ RNA involved	Source	References
Bladder carcinoma	15.8 μM	HP/DDP/OA NP	P-gp	Synthetic	(Chen et al. 2020)
Colorectal cancer	–	12-α-hederin	p-mTOR protein, p-ULK1 protein, p-P70S6K protein, p62 protein, mitochondrial pathway	Hedera helix	(Sun et al. 2019)
	21.85 μM	21-3-O-acetyloleanolic acid	DR5	Synthetic	(Yoo et al. 2012)
Glioma and glioblastoma	–	22-CDDO	CD163, IL-10, and STAT3	Synthetic	(Fujiwara et al. 2011)
	–	9-CDDO-Me			
Head and neck cancer		23-Hederagenin	Mitochondria-mediated Intrinsic pathway NF-κB pathway	Chenopodium quinoa plant	(Kim et al. 2017)
Hematological malignancies	–	24-CDDO	IKK-β, NF-kB	Synthetic	(Ahmad et al. 2006)
	–	9-CDDO-Me			
Osteosarcoma	–	25-Dextrose-OA	Notch signaling pathway	Synthetic	(Xu et al. 2018)
	–	11-OA	SOX9, β-catenin, and Wnt1	Olive plant	(Chen et al. 2021)
Prostate	50 μM	26-OAME	Caspase 3	Leucas cephalotes	(Abdelmageed et al. 2017)
	7 μM	9-CDDO-Me	Akt/NF-kB/mTOR pathway, DR4, DR5	Synthetic	(Hyer et al. 2008)
Pancreatic	–	11-OA	STAT3 and IKK	Olive plant	(Liby et al. 2010)
	–	9-CDDO-Me		Synthetic	
	-	27-K73-03	SPINK1 gene	Synthetic	(Shopit et al. 2020)
	1.6 μM		EGFR pathway	Radix Bupleuri	(Cai et al. 2017)
Renal cancer	–	24-CDDO	NADPH oxidases	Synthetic	(Guo et al. 2017)
	–	9-CDDO-Me			
	42.20 μmol/l	4-SSd	EGFR pathway	Radix Bupleuri	(Cai et al. 2017)
Thyroid cancer	–	11-OA	PI3K/Akt pathway,FOXA1,Bax/Bcl2	Olive plant	(Duan et al. 2019)

(–) not available

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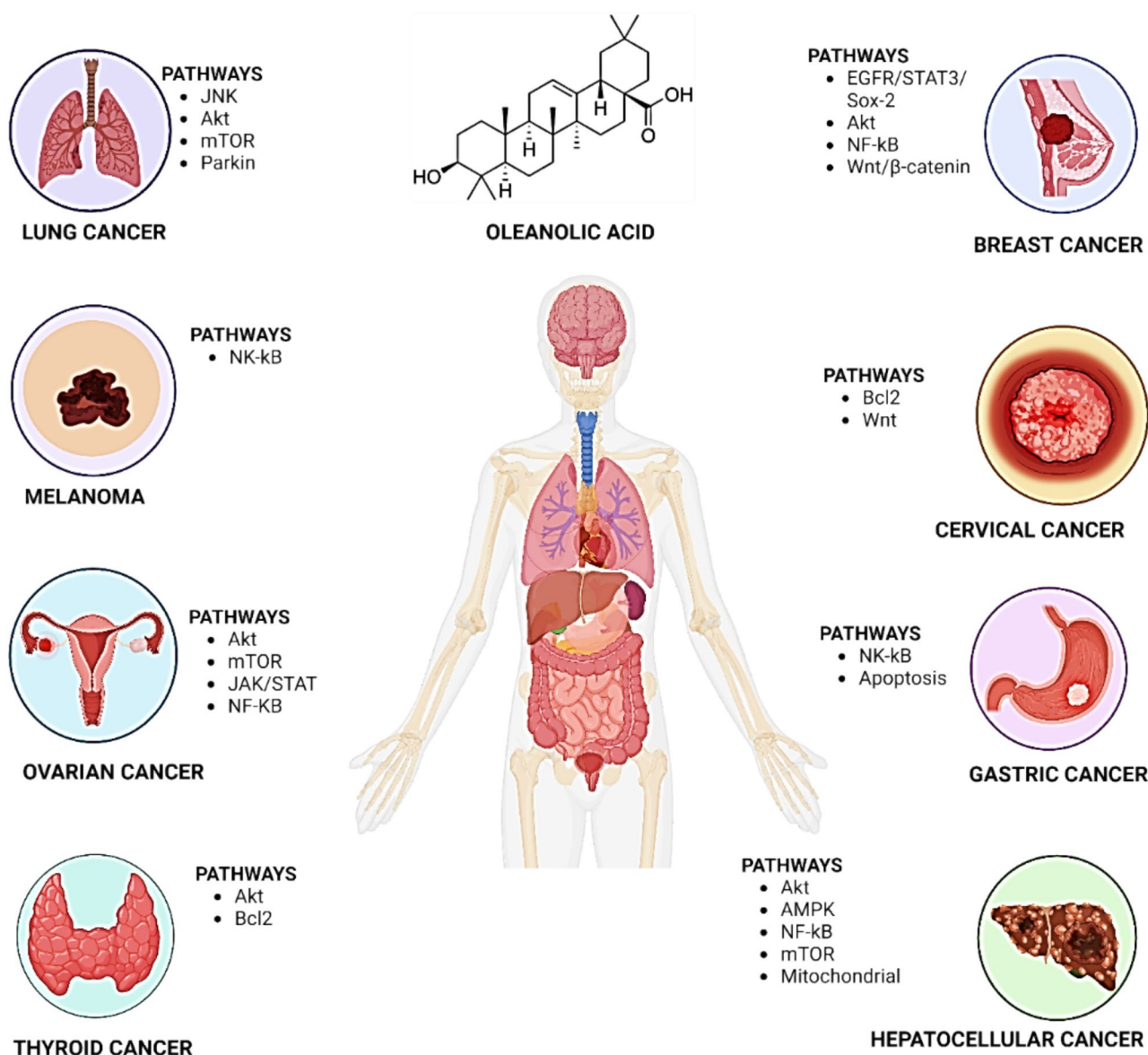
Fig. 5 Effect of oleanolic acid and its derivatives on different cancer pathways

the C-28 position increases its inhibitory activity against VEGFR-2 (Song et al. 2021). When a conjugated double bond is added to the C-ring of OA, the anticancer activity is enhanced against the MCF-7, HeLa, human renal adenocarcinoma (ACHN), and DU-145 cell lines. Compound 35 (Fig. 5), which is a derivative of OA, was synthesized by inserting an O2 vinyl diazenium diolate-based group that releases nitric oxide (NO) and has greater cytotoxic effects on HepG2 cells (Zou et al. 2017). The addition of a rhodamine group at the C-28 position using a piperazinyl linker to OA enhances its activity against the 518A2, A2780, HT29, MCF7, and 8505C cell lines (Yang et al. 2022). OA triazole-conjugate compound 36 (Fig. 5) shows greater anti-proliferative activity against SW480 cells than OA

(Chouaib et al., 2019). Insertion of an acetyl-substituted L-arabinose moiety enhances the antiproliferative activity of OA derivatives against HL60 and A431 cells (Zhong et al. 2021). OA derivatives that are dimeric and connected at C-28 show greater activity toward multiple cell lines (Cheng et al. 2015). Parra and colleagues synthesized 264 compounds from OA and maslinic acid. These derivatives strongly affected the growth of the HT29 and B16-F10 cell lines. Several of the cytotoxic derivatives exhibited low IC50 values. The addition of a long chain ω-amino acid at the 28th carbon carboxylic group and the addition of a small acyl group at the C-3/C-2 hydroxyl group of the A-ring improve the cytotoxic effects of the derivatives (Parra et al. 2014) (Fig. 6).
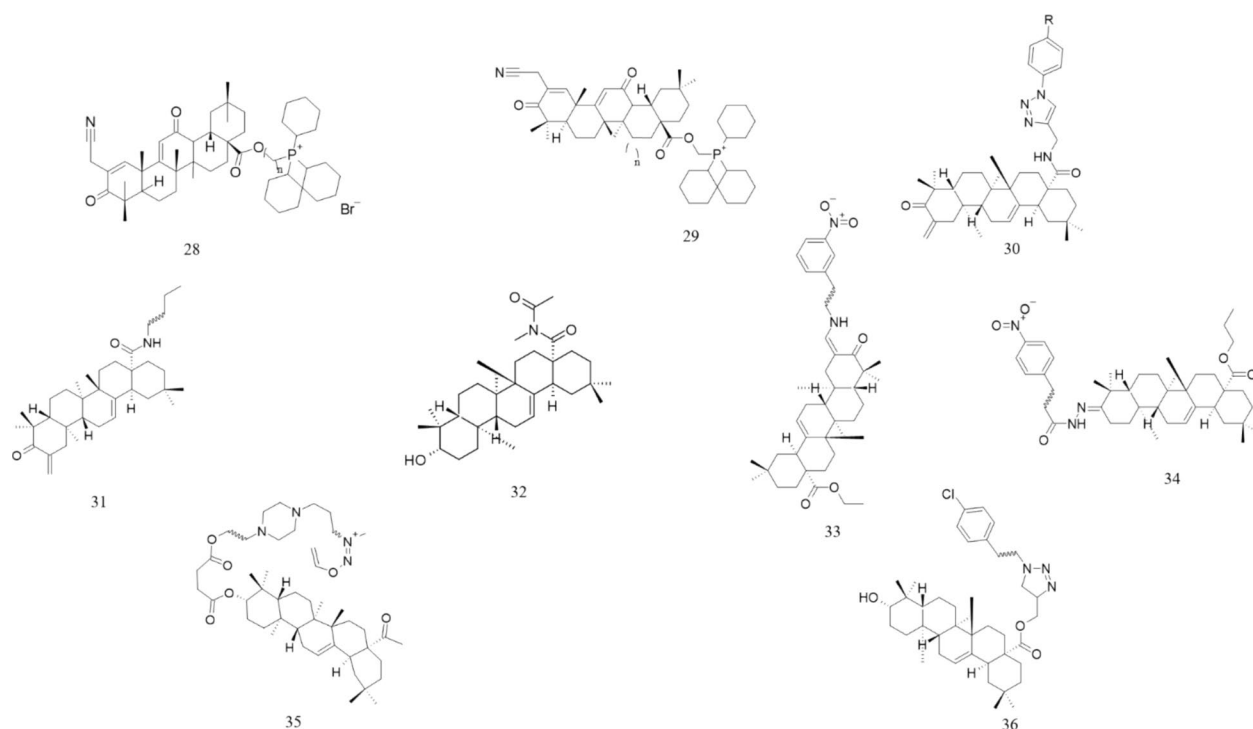
Fig. 6 Structure–activity relationship of OA derivatives. 28, 29: Addition of TPP + or TCP + at different positions in the CDDO chain. 30, 31: Conversion of the α, β-unsaturated carbonyl derivative of OA to an amide at 28-COOH. 32: Hydroxamate derivative of OA. 33, 34: Introduction of PDGF receptor inhibitors at the C-2 or C-3 position. 35: Insertion of an O2 vinyl diazenium diolate-based group. 36: OA triazole-conjugate

In-silico analysis of OA and its derivatives

To get a better understanding of molecular interactions of OA and its derivatives with various target proteins, in-silico analysis is done. Fontana and the group synthesized novel OA and Lupeol derivatives. They performed molecular docking, to determine the interaction of these derivatives with key proteins, such as NF-kB involved in leukemia progression. The derivatives showed high binding affinity for NF-kB and other related proteins. Using interactions with residues in the proteins' active site, such as hydrophobic bonds, π-π stacking, and hydrogen bonding. Modification in the derivatives structures enhanced their binding affinity, suggesting potential features critical for therapeutic efficacy, These derivatives inhibit the NF-kB pathway, impairing leukemia progression (Fontana et al. 2022). Another study showed that nummularic acid (NA) (Fig. 7 compound 37) is a plant-derived compound with strong potential as a selective inhibitor of proteins involved in the apoptotic pathways. NA forms highly stable complexes, showing binding energies of − 8.5 kcal/mol with BAX (2K7W), − 8.2 kcal/mol with BCL-2 (1K3K), − 1.9 kcal/mol with NF-κB (1NFK), and − 8.4 kcal/mol with P53 (1AIE). NA shows binding affinities and interactions similar to standard inhibitors such as doxorubicin, lapatinib, and vincristine. According

to pharmacokinetic and ADME assessment, NA shows desirable physiochemical properties with great gastrointestinal absorption, moderate BBB permeability, null hepatotoxicity, and cytochrome inhibition. NA is a potential biomolecule for pharmaceutical formulations that fight cancer, with lower toxicity and greater bioavailability (Majid et al. 2022).

Molecular docking, molecular dynamic simulation (MDS), and pharmacokinetic studies were done to evaluate β-sitosterol (Fig. 7 compound 38) and OA as anti-cancer agents by inhibiting human estrogenic 17 beta-hydroxysteroid dehydrogenase type-1 (HSD17B1. Each candidate satisfied the non-toxic criterion, according to pharmacokinetic tests, molecular docking, and MDS studies showed a strong inhibitor's interaction with HSD17B. Two essential residues in the process of enzyme inhibition are Leu149 and Pro187. Each inhibitor's –OH and –COOH groups were essential for maintaining the inhibitor–HSD17B1 interaction. These findings show that OA and β-sitosterol are potential candidates for HSD17B1 inhibition (Kristanti et al. 2022) Senol et al. clarified that the biological activity of phenyl rings is influenced by their position and kind of substituents. Higher potency is exhibited by compounds that have a CF3 or NO2 group in the meta- or para-position of the phenyl ring. The drug-likeness parameters of the most potent compounds (Fig. 7 39i, ii, and iii), fall under Lipinski's and Jorgensen's
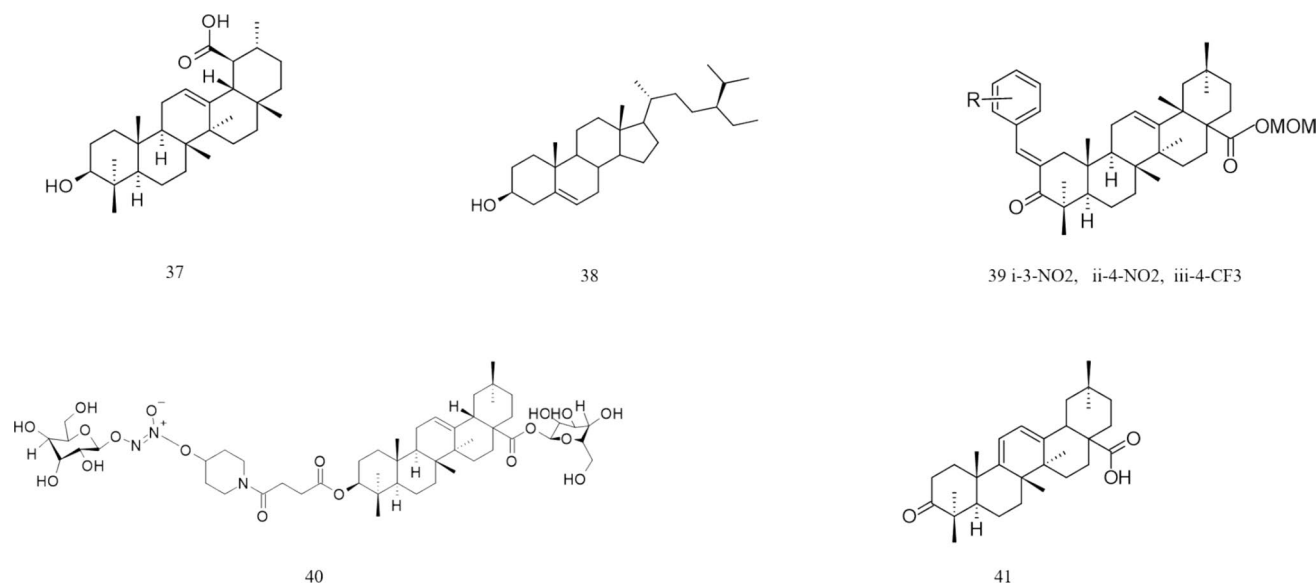
Fig. 7 Structures of OA derivatives 37. nummularic acid, 38. β-sitosterol, 39. Derivatives of α, β-Unsaturated Ketones Based on OA, 40. O$_2$-glycosylated diazeniumdiolate OA derivative, 41. Oxy-Di-OA

rules. Molecular docking was accomplished using the induced fit docking (IFD) protocol and assessed their affinity for protein targets such as PARP1, mTOR, and P13K. Results indicated that compound Fig. 7 39i showed the greatest affinity for PARP1 (IFD score: – 10.505 kcal/mol), and compound Fig. 7 39ii displayed the greatest affinity for mTOR AND PI3K (IFD scores: –10.291 and –10.897 kcal/mol respectively) These three compound show greatest affinity and their complexes are stable with the protein targets. Molecular dynamics studies showed that the binding pocket of the target proteins showed high stability for the active compounds. These results underscore the compounds' potential for developing inhibitors for prostate cancer (Senol et al. 2023).

In-silico docking studies were done to evaluate the affinity of OA with three biodegradable proteins—bovine serum albumin (BSA) (4JK4), bovine lactoferrin (1BLF), and bovine beta-lactoglobulin (3NPO), showed that OA showed highest binding affinity to BSA (− 8.2 kcal/mol), followed by beta-lactoglobulin (− 7.5 kcal/mol), and lactoferrin (− 6.2 kcal/mol). The methyl groups of OA interact with ILE297 and ARG336, by forming alkyl-alkyl bonds. OA's cyclohexane and cyclohexene rings also showed these interactions with the ARG336, LEU304, and HIS337 residues. Albumin is the most suited protein carrier for OA among the tested options based on its strong binding affinity and energy (Shukla et al. 2023). Malleogu and the group showed that UA displays strong binding affinity and is a potential modulator of EMT-related targets. Higher fluctuations were observed for Snail-UA (Cα: 9.390 Å), Slug-UA (Cα: 5.869 Å), and Fibronectin-UA (Cα: 1.759 Å), with

corresponding values for backbone, side chain, and heavy atoms reported. B-factor values also indicated structural flexibility. Root-mean-square deviation values of UA with Snail, Slug, and Fibronectin were low, indicating stable complexes. The 50 ns MDS trajectory revealed consistent hydrophobic and ionic interactions across the complexes, emphasizing UA's strong affinity and stability in the active sites of these proteins. Hence UA can act as a potential anti-metastatic drug (Mallepogu et al. 2023).

Patent, clinical trials, and pre-clinical trials of OA and its derivatives

Patents CN102151275A (Lin et al. 2011), CN102114022A (Lin et al. 2011), CN102114023A (Lin et al. 2011), CN102133219A (Lin et al. 2011), and CN102114021A (Lin et al. 2011) claims OAs' application in pancreatic, colorectal, ovarian, cervical cancer, and breast cancer treatment respectively. Patent CN102838652A shows that few OA derivatives act as anti-cancer agents in liver, colon, leukemia, and oral cancers (Liu et al., 2012). OA–uridine/pyrimidine conjugates are claimed as anticancer drugs in patents CN102633855A (Cheng et al. 2012) and CN102633856A (Cheng et al. 2012), respectively. To ascertain these OA derivatives' anticancer capabilities, they were synthesized and evaluated against a range of cancer cell lines. Patent CN102532246 A displays the role of OA aminoamide derivatives in breast cancer therapy (Shen et al. 2012). OA amidate derivatives and a number of 2-substituted OA derivatives are made and utilized pharmaceutically according to patents WO2013079018A1 and WO2013079024A1 (Xu

et al. 2013). A synthesis method for OA saponin that is effective in treating tumors is claimed in patent CN103483411A (Zhu et al. 2014). Patent CN103585158A reveals a pharmaceutical composition that, at 20 μM, markedly reduced the proliferation of the rat liver cancer cell RH-35 and HepG2 cells. The composition contained OA and sulforaphane, an anticancer ingredient extracted from broccoli (Wang et al. 2014). Patent KR1020200045126 summarizes OA derivates as agents against glioblastoma (Kang-min et al. 2018). Patents CN114409725A and CNN114380884A demonstrate OA derivatives as anticancer agents (Yanqiu et al. 2022). Table 9 summarizes the patents on OA and its derivatives.

In a phase I clinical experiment, CDDO's action in cancer cells was assessed (Speranza et al. 2012). The dose tolerance and pharmacokinetic profile were determined for a few patients. CDDO was elevated in the plasma and reached a steady state within 48 h. When administered for one year, Bardoxolone methyl showed excellent tolerance and minimal toxicity in a phase 3 trial (Hong et al. 2012). OA was mixed in the diet of C57BL/6 mice, and its effects and activity were studied. OA shows low oral bioavailability owing to abysmal gastrointestinal absorption, leading to first-pass metabolism in the liver. Formulating OA as a sodium caprate OA and freeze-dried polyvinylpyrrolidone increases its interstitial absorption and dissolution rate in Caco-2 cells. The synthesis of water-soluble amino acid analogues of OA improves its oral bioavailability. The bioavailability of OA nanosuspensions was elevated in NSCLC lines (Li et al. 2011).

In-vivo toxicity

Huang and group studied the O2-glycosylated diazeniumdiolate OA derivative (Fig. 7 compound 40), which demonstrated anti-tumor efficacy and a promising safety profile in mice. Mice were given intravenous injections of six different doses (200, 180, 162, and 145.8 mg/kg) in an acute toxicity test, and their survival was tracked for 14 days. Only two mice survived at the maximum dose (200 mg/kg), although no deaths or aberrant behavior were seen at a low dosage (145.8 mg/kg). Compared to a similar chemical, compound 40 (Fig. 7) calculated LD50 was 173.3 mg/kg, which is substantially greater, indicating that it is a safer drug. BALB/c nude mice with subcutaneous SMMC-7721 tumors received treatment with compound 40 (Fig. 7) (3 mg/kg intravenously, three times per week for three weeks) in a different anti-HCC trial. Without changing body-weight, treatment with compound 40 (Fig. 7) dramatically decreased tumor size and weight compared to the control. These findings show that in comparison to a chemical based on furoxan, compound 40 (Fig. 7) is a powerful inhibitor of HCC tumors with reduced toxicity (Huang et al. 2012). Xiang and team investigated the acute toxicity of 3-oxours-oleana-9(11), 12-dien-28-oic acid (Oxy-Di-OA) (Fig. 7 compound 41) in male Kunming

mice weighing 20 ± 2 g via intraperitoneal injection and gavage. The mice were split into six groups based on size and weight, and they were given unlimited access to water during their 12-h fast. The maximal dose of 900 mg/kg Oxy-Di-OA was produced in bean oil for the intraperitoneal injection assay. Different groups received doses of 178, 422, 600, 750, and 900 mg/kg, while one group received bean oil as a control. For the first hour, mice were monitored constantly; after that, they were monitored sporadically for 4 h, then every 24 h, and every seven days to look for any indications of toxicity or death. The LD50 was determined using the Käber method, obtaining a 714.83 mg/kg value with a 95% confidence interval of 639.73–798.73 mg/kg. At high dosages, symptoms included sluggishness and a reduction in aggression. Different doses of Oxy-Di-OA were given in the gavage experiment, whereas bean oil was given to one group as a control. The LD50 for gavage administration was higher than 2000 mg/kg, indicating minimal toxicity, and observations followed a similar timeframe. According to the findings, Oxy-Di-OA is comparatively safe at lower dosages; for additional in vivo research, 600 mg/kg is deemed innocuous (Xiang et al. 2017).

Saini and team carried out an acute toxicity study (OECD guideline 425) on female Wistar rats who were exposed to UA and OA using a metered-dose inhaler (MDI). Three male and three female rats were included in each of the two groups of rats—the control and treatment groups. For up to 14 days, the animals were monitored for clinical indications of toxicity at 1-h intervals for the first 4 h and then at 4-h intervals for the next 24 h. The treatment groups did not behave abnormally, and no fatalities or negative side effects were noted. A minor rise in blood calcium levels and variations in mean corpuscular hemoglobin concentration were the only notable alterations observed in serum biochemistry or hematology, and body and organ weights stayed constant when compared to controls. Although the lung tissue of the rats subjected to MDI exhibited congestion, hemorrhagic lesions, deformed alveolar tissue, and localized mononuclear cell infiltration, the histopathological analysis did not identify any notable changes in essential organs. Overall, the study showed that rats did not show acute toxicity to either UA or OA (Saini et al. 2022). Stepnik and group determined the potential toxicity of OA (715 μg/mL) in the zebrafish embryo using the acute toxicity test, following Organization for Economic Cooperation and Development (OECD) recommendations for chemical testing (Test No. 236) An hour after fertilization, zebrafish embryos were examined for transparency, shape, and viability. Only eggs that satisfied all requirements—namely, being round, viable, and fully transparent—were selected and transferred to 12-well plates (Sarstedt, Germany). Two groups at random—the experimental and control groups, were separated and held in each well for the whole duration of the trial, which was

Table 9 Patents on OA and its derivative

Structure	Patent Number	Cancer	References
	CN102151275 A	Pancreatic cancer	Lin et al., 2011
	CN102114022 A	Colorectal cancer	
	CN102114021 A	Breast cancer	
	CN102114023 A	Ovarian cancer	
	CN102133219 A	Cervical cancer	
	CN102838652 A	Hepatocellular cancer	Liu et al., 2012
	CN102633855 A	Hepatocellular cancer	Cheng et al., 2012
OA- pyrimidine conjugates	CN102633856 A	Hepatocellular cancer	
	CN102532246 A	Breast cancer	Shen et al., 2012
	WO2013079018A1	Antitumor	Xu et al., 2013
	WO2013079024A1	Antitumor	
	CN103483411 A	Prostate, lung, leukaemia	Zhu et al., 2014
OA-sulforaphane combination	CN103585158 A	Hepatocellular cancer	Wang et al., 2014
OA derivative and TRAIL	KR20200045126A	Glioblastoma	Kang-min et al., 2018
OA A ring derivatives	CN114409725A	Antitumor	Yanqiu et al., 2022
	CN114380884A	Antitumor	Yanqiu et al., 2022

up to 96 h. In two batches of embryos (three wells per batch, $n = 5$–7 per well), 3000 μL of the zebrafish medium (control group) or 715 μg/mL of OA supplemented (experimental group) were used. After 23, 47, 71, and 95 h of incubation, the death rate was calculated. Incubation times of 71 and 95 h were used to measure hatchability. Following a 95-h incubation period, the following morphological defects were evaluated: posture, jaw development, eye size, hemorrhage, yolk sac necrosis, heartbeat, and heart/yolk edema. Thus, it can be said that OA at a level of 715 μg/mL is not harmful to the growing organism in vivo because it has no effect on morphology, mortality, hatchability, or muscle function (Stepnik et al. 2023).

Discussion and future prospective

OA and its derivatives, whether derived from natural sources such as *Bupleurum falcatum* L. or synthesized chemically, have been extensively researched for their anticancer properties. This paper delves into their impact on various cancer types, with a focus on hepatocellular carcinoma (HCC) and breast cancer. In HCC, OA-DOX-encapsulated liposomes shield against reactive oxygen species (ROS), while modifications such as the addition of a galactosyl group enhance the solubility and increase the anticancer efficacy of these liposomes. Compounds such as CDDO-Me and α-hedrin exhibit promising effects by targeting inflammation, proliferation pathways, and apoptosis in HCC cells. Additionally, OA and its morpholide derivatives have the potential to suppress crucial cancer pathways, such as the NF-κB pathway, thereby impacting drug metabolism and antagonizing EMT. Similarly, in breast cancer, derivatives such as SSa, SSb, and SZC014 influence key pathways such as the JAK/STAT, Akt, and NF-κB pathways, leading to the inhibition of metastasis, angiogenesis, and cell migration, respectively. With further research being conducted on a variety of cancer types, these results point to the therapeutic potential of OA and its derivatives in the treatment of cancer.

Furthermore, these compounds hold promise beyond HCC and breast cancer, with ongoing investigations in other cancer types. By targeting multiple cellular pathways, such as the Akt/mTOR, JAK/STAT, and Wnt/β-catenin, pathways, OA, and its analogues offer a multifaceted approach to cancer therapy, potentially enhancing specificity and sensitivity to treatment. Compounds such as CDDO-Me inhibit tumor progression and survival through various mechanisms, including immune modulation and interference with chemokine signalling. Nanoformulations incorporating OA, such as OA-PTX, show potential for suppressing tumor progression by inhibiting drug efflux mechanisms. Overall, this study underscores the potential of OA and its analogues as novel therapeutic agents for cancer treatment, highlighting the importance of further research to elucidate their full therapeutic potential across diverse cancer types.

Data availability Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Declarations

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