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Anticancer Potential of Oleandrin: Preclinical Mechanisms, Botanical Origins, and Pharmacokinetic Insights

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Abstract: Oleandrin (OLD) is a lipid-soluble cardiac glycoside derived mainly from the leaves of *Nerium oleander* (Apocynaceae), traditionally used in herbal medicine. Among the various parts of the plant, the leaves contain the highest concentration of OLD. Red-flowered varieties contain higher levels of cardiac glycosides. Although *Thevetia peruviana* (yellow oleander) belongs to the same family, it does not produce OLD. Recent studies show that OLD has significant anticancer potential against various cancers such as breast, prostate, lung, colon, pancreatic, endometrial cancers, melanoma, and osteosarcoma. It works by inducing apoptosis (programmed cell death) via caspase activation, arresting the cell cycle, reducing oxidative stress, and lowering mitochondrial membrane potential. These actions are regulated by key signaling pathways including Wnt/β-catenin, phosphatidylinositol 3-kinase/protein kinase B/nuclear factor-kappa B (PI3K/Akt/NF-κB), and extracellular signal-regulated kinase (ERK). Pharmacokinetic studies reveal that OLD is rapidly absorbed through the oral mucosa and gastrointestinal tract, crosses the blood-brain barrier, and has a half-life of about 2.3 hours. It is mainly metabolized in the liver and intestine, and excreted mostly through feces (66%) and partly through urine (8%). Due to its strong anticancer mechanisms, OLD shows promise as a novel anticancer agent. However, further in vivo studies and clinical trials are necessary to confirm its therapeutic efficacy and safety in humans. Future research should also focus on optimizing its pharmacokinetic properties and minimizing toxicity to enable its transition from experimental models to clinical application.

Keywords: Anticancer; apoptosis; cell proliferation; cytotoxicity; oleandrin;

1. Introduction

Cancer is a broad term that describes a group of diseases characterized by uncontrolled, as well as abnormal growth and proliferation of cells in the body through metastasis (Prendergast et al., 2010). 22% of deaths are caused by a variety of variables, such as tobacco use, whereas 10% are caused by inadequate nutrition, overweight, excessive consumption of alcohol, and other physical carcinogens, such as being exposed to ionizing radiation and environmental pollution. Biological carcinogens like Hepatitis B, Hepatitis C, Epstein-Barr virus, Helicobacter pylori, human papilloma virus infection, and HIV cause about 15% of cancer worldwide. In addition, 5–10% of cancers are caused by genetic defects, which are inherited from the patient's parents (Saini et al., 2020). Global demographics indicate that the number of cancer cases will rise in the next several decades, with more than 20 million additional cases per year anticipated by 2025 (Zugazagoitia et al., 2016). In 2020, there were approximately 10.0 million deaths caused by cancer worldwide and an anticipated 19.3 million new cases of cancer by this time (Ferlay et al., 2021). There is evidence that people with heart failure and cardiovascular disease have an increased chance of developing cancer, which is a significant cause of mortality for people with heart failure (de Boer et al., 2019). An increasing amount of data points to a link between obesity, cancer, and type 2 diabetes (Garg et al., 2014).

While conventional therapies such as radiotherapy, chemotherapy, and surgery have been used but there have also been significant developments in new therapies in recent years, such as radionics, natural antioxidants, targeted therapy, ablation therapy, nanoparticles, ferroptosis-based therapy, chemodynamic therapy, and stem cell therapy (Debela et al., 2021; Jahan Oni et al., 2024; Eity et al., 2024; Chowdhury et al., 2024). One of the key challenges and most promising strategies for future cancer treatment in next-generation precision oncology will be the development of

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personalized combination therapies tailored to the specific pathways or hallmarks driving the tumor biology of individual patients (Zugazagoitia et al., 2016).

Many well-known cancer treatments have been derived from substances found in nature, including irinotecan, vincristine, etoposide, and paclitaxel from plants, actinomycin D and mitomycin C from bacterial cells, and the marine-derived bleomycin. Many of these compounds remain essential in cancer treatment and are expected to remain crucial in the future (Huang et al., 2021). Cardiac glycosides have become a promising option for treating a variety of solid tumors, including lung, breast, liver, colon, gastric, glioblastoma, acute myeloid leukemia, prostate, and pancreatic cancers (Reddy et al., 2020). OLD has been shown to block the growth of numerous types of cancer, with human melanoma and leukemia cells being particularly susceptible to this effect. In contrast, murine malignant cells, normal human epithelial cells, peripheral blood mononuclear cells, and neutrophils are less affected. As a result, OLD holds promise as a powerful anticancer treatment in the future (Kumar et al., 2013). **Fig. 1** exhibits the 2D structure of OLD.

This review explains how the OLD fights against cancer by collecting information from previous research.

2. Methodology

2.1. Search strategy

Using terms like "oleandrin" and "anticancer activity", "Anti-proliferation activity," "Apoptotic effect," "Oxidative stress," "Protective effect," "Cytotoxic activity," "Carcinogenesis," "Anti-angiogenic effect," "Antitumor activity," "Human cancer," "Biological activities," "Biological evaluation," "Chemical features," "Pharmacokinetics," "*In vivo* studies," or "*In vitro* studies." a thorough search was conducted between 2001 and 2024 across numerous highly respected scientific databases, including PubMed, Google Scholar, and Science Direct, to find out relevant information. The sources, biopharmaceutical profile, dose, concentration, test system, predicted anticancer effect, mechanism, and overall conclusion were all included in the comprehensive evaluation of the investigation.

2.2. Inclusion criteria

For this research, specific criteria were followed that focused on the anticancer properties of OLD. *In vivo, in vitro*, or *ex vivo* tests, with or without the use of experimental animals, were considered for research. Additionally, studies were included regardless of whether they detailed the underlying mechanism of action.

2.3. Exclusion criteria

The review's exclusion criteria were appropriately defined to ensure the significance of the reviewed research. Research that contained duplicate data or whose title or abstract did not meet the inclusion requirements was disqualified. Moreover, studies on anticancer activity were not included if they overshadowed the main objective of the current research.

3. Results and Discussion

3.1. Botanical Sources of oleandrin

OLD, a cardiac glycoside that is highly lipid-soluble and is derived from the *Nerium oleander* (Apocynaceae) plant, has great pharmacological qualities and is utilized in traditional herbal therapy. It is commonly used for the treatment of several illnesses, including congestive heart failure, and recently it has attracted a lot of interest because of its broad anti-cancer and innovative anti-viral properties (Zhai et al., 2022). The flowers of *N. oleander* plants are primarily red, white, or pink (Khan et al., 2010). Red-flowered oleanders contain more CGs than white-flowered ones. OLD is present in every part of the *N. oleander* plant, including the stems, leaves, flowers, buds, nectar, and sap (Karawya et al., 1973). The leaves have the largest concentration of OLD, which changes depending on the part of the plant. Despite being a distinct species within the Apocynaceae family, *Thevetia peruviana,* sometimes referred to as yellow oleander, does not produce OLD. The primary active ingredient in yellow oleander is thevetin A (Langford & Boor, 1996).

3.2. Pharmacokinetics of oleandrin

The study of a drug and/or its metabolite kinetics in the body is known as pharmacokinetics. It describes how a medication and its metabolites change over time in serum, plasma, or whole blood, as well as in the target tissue and organs. As the body is such a complicated system, a drug must go through a number of processes in order to be absorbed, distributed, metabolized, and/or eliminated (Ruiz-Gracia et al., 2008).

The process by which the drug leaves the site of administration and enters the bloodstream is known as absorption. OLD has an immediate effect when it is administered orally because initially it is absorbed in the oral mucosa by simple diffusion and then swiftly absorbed in the gastrointestinal system. In humans, OLD has a half-life of 2.3 hours. OLD's lipophilic characteristics make it simple to cross the blood-brain barrier (BBB). As early as 30 minutes after intraperitoneal administration, OLD was found in brain tissues, demonstrating the lipophilic property. OLD had an oral bioavailability of roughly 30% and was quickly absorbed upon administration (maximum blood concentration [C_{max}] at 20 minutes) (Ni et al., 2002). Due to its fast and reversible binding to plasma proteins and poor water solubility, OLD may have a low bioavailability (Jia, 2014).

Drug distribution is the process by which the drug quickly starts to permeate the tissues from the blood capillaries (Gao et al., 2014). The tissue distribution of OLD and its metabolites has not been thoroughly reported because the distribution properties of these substances have primarily been investigated in animal experiments and poisoning cases. According to research done on rats, OLD enters the bloodstream, reversibly attaches to plasma protein, and then circulates throughout the body (Jia, 2014).

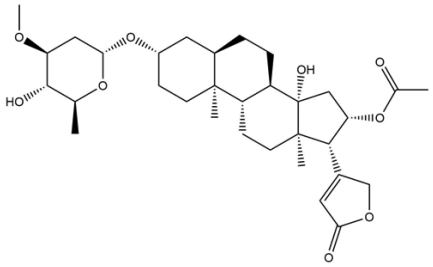

Fig. 1. The two dimensional chemical structure of oleandrin.

Approximately twice the amount of OLD was present in the liver as in the heart or kidney tissues. In mice, OLD may rapidly accumulate in the central nervous system after crossing the blood-brain barrier. In brain tissues, the concentration of OLD is extremely high even after a single injection, and it keeps rising over the span of 24 hours (Ni et al., 2002).

OLD undergoes biotransformation in the liver and small intestine, where liver microsomal enzymes break it down. Before entering the systemic circulation, OLD undergoes significant enzyme metabolism that results in glucuronated or sulfated forms after being partially hydrolyzed to oleandrigenin, which improves absorption (Ni et al., 2002). OLD and its metabolites may be transferred to the basolateral side of the small intestine following conjugation processes that take place in the liver and gut (Gao et al., 2014).

Drug excretion refers to the procedures that physically remove drugs from the body, either unaltered or as products of biotransformation. Urine and bile are the primary mechanisms by which drugs are eliminated (Talevi & Bellera, 2024). Following a 24-hour injection of OLD, 8% of the drug and its metabolites are eliminated in the urine (of which 4.4% and 1.9% are attributed to oleandrigenin and OLD, respectively), and 66% are eliminated in the feces (having the same amounts of OLD and oleandrigenin). Because the majority of the compounds in feces are metabolites from intestinal bacteria, bile excretion is the primary method of OLD's elimination (Ni et al., 2002).

3.3. Anticancer mechanistic pathways

3.3.1. Induction of oxidative stress

Proteins, lipids, and nucleic acids can all be affected by reactive oxygen species (ROS), which can change their mechanism of action. Oxidative stress arises when there is an imbalance between the generation of ROS and anti-oxidative defense, which leads to various diseases like cancer (Jelic et al., 2021). Through mitochondrial disruption, ROS overproduction, antioxidant suppression, and the activation of stress-related apoptotic pathways, OLD promotes oxidative stress and has anticancer effects (Newman et al., 2006).

As per a study conducted by Newman et al. (2006), OLD (0-100μM) with an IC_{50} of 0.03 μM showed a significant increase in intracellular ROS level in BRO cell lines of melanoma cells via inducing apoptosis and also caused oxidative stress along with superoxide radical formation (Newman et al., 2006).

3.3.2. Cytotoxic effects

Cytotoxic chemicals target certain weaknesses in cancer cells, such as abnormal apoptotic pathways, uncontrolled proliferation, and defective DNA repair. One of the main objectives of numerous cancer treatments is to cause cytotoxicity in cancer cells (Pan et al., 2017).

Various investigations revealed that OLD had a significant cytotoxic activity against different cancer cells. In a study, Li et al. (2020) showed that OLD caused significant cytotoxicity against human breast cancer cells including MCF7, SK-BR-3 (50-0.78 nM), and MDA-MB-231 (100-1.56 nM) with an IC_{50} of 24.62, 14.4, and 6.13 nM, respectively (Li et al., 2020). Another study conducted by Ko et al. (2018) showed significant cytotoxicity in breast cancer cell lines, including (RT-R) MBA-MB-231 and MBA-MB 231 (1-500 nM) with IC_{50} of 183 and 72 nM, respectively (Ko et al., 2018). Newman et al. (2007) manifested that OLD could increase cytotoxicity as well as inhibit cell growth in PANC-1 cell lines (0-50 nM) of pancreatic cancer with an IC_{50} of 0.005 μM (Newman et al., 2007). Another study done in BRO cell lines of melanoma by Newman et al. (2006) found a potential cytotoxic effect of OLD (0-100 nM) with an IC_{50} of 0.03 μM (Newman et al., 2006). A study conducted by Pan et al. (2017) showed that, in SW480 cell lines, OLD increased cytotoxicity by causing cell cycle arrest at concentrations of 0.01, 0.02, and 0.05 nM with an IC_{50} of 0.02 μM (Pan et al., 2017). In U2OS and SaOS-2 cell lines, OLD caused cytotoxicity at 0-100nM concentration in osteosarcoma (Ma et al., 2015). OLD increased cytotoxicity of Ishikawa cell lines at 7.5 to 100nM concentration with an IC_{50} of 75.3nM in endometrial carcinoma (Celik et al., 2023).

3.3.3. Apoptotic effects

The equilibrium between programmed cell death and growth is disrupted in cancer, and apoptotic pathway defects allow genetically defective cells to survive. Cancer cells are eventually killed by the majority of cytotoxic, hormonal, and radiation treatments because they cause irreversible cellular damage that leads to apoptosis (Sjöström & Bergh, 2001). OLD induces apoptosis by inhibiting Na+/K+-ATPase, mitochondrial dysfunction, p38 MAPK pathway activation, and upregulation of pro-apoptotic proteins (Li et al., 2020).

As per a study report, the treatment of breast cancer cell lines MCF7, SK-BR-3 (50-0.78 nM) and MDA-MB-231(100 nM-1.56 nM) with OLD showed IC_{50} of 24.65, 14.5 and 6.13 nM, respectively resulted in increased apoptotic cell death through inhibiting cell growth (Li et al., 2020). Another investigation found that OLD caused apoptosis by damaging DNA in lung cancer cell lines (A549, and H1299) at a concentration of 0.01, 0.02, and 0.04 μg/ml (Bao et al., 2016). Another study done in BRO cell lines by Newman et al. (2006) found that OLD (0-100 nM) caused apoptosis in melanoma with IC_{50} of 0.03 μM (Newman et al., 2006). According to a study, OLD causes colorectal cancer cells (SW480) to die to induce mitochondrial-associated pathway apoptosis by targeting Bax and promoting the expression of caspase-3/9 and intracellular Ca^{2+}, as well as the increase of cytochrome c (cyt c) at a concentration of 0.01, 0.02 and 0.05 nM with IC_{50} of 0.02 μM and also causes cell cycle arrest in G2/M phase (Pan et al., 2017). A study revealed that, in U2OS and SaOS-2 cell lines, OLD caused cytotoxicity at 0-100nM concentration in osteosarcoma (Ma et al., 2015). **Fig. 2** illustrates how OLD increase apoptosis.

3.3.4. Induction of autophagy

It is now known that one of the primary regulatory pathways causing autophagy is the Akt/mTOR/p70S6K pathway. Autophagy, not apoptosis, is the mechanism by which PANC-1 cells, a human pancreatic cancer cell line may die (Newman et al., 2007).

As per research, OLD activates stress response pathways like MAPK and JNK and modifies proteins related with autophagy such as LC3-II, at 0-50 nM concentration with IC_{50} of 0.005 μM in PANC-1 cancer cell lines (Newman et al., 2007).

3.3.5. Inhibition of proliferation

Since cancer cells frequently proliferate and divide uncontrollably, one of the primary strategies in cancer treatment is to inhibit cell proliferation. It is possible to reduce tumor size, slow down tumor progression, and enhance patient outcomes by focusing on the processes that cause aberrant cell proliferation (Jelic et al., 2021).

Li et al. (2020) found that OLD inhibits cell proliferation and colony formation and Bcl-2 protein level in breast cancer cell lines MCF7, SK-BR-3 (50-0.78 nM) and MDA-MB-231(100-1.56 nM) with IC_{50} of 24.65, 14.5 and 6.13 nM, respectively (Li et al., 2020). Another study showed that OLD inhibits proliferation and pAkt pathway in PANC-1 cell lines (0-50 nM) of pancreatic cancer with an IC_{50} of 0.005 μM (Newman et al., 2007). OLD inhibits cell proliferation and the EMT pathway in Ishikawa cell lines at 7.5 to 100 nM concentration with an IC_{50} of 75.3 nM in endometrial

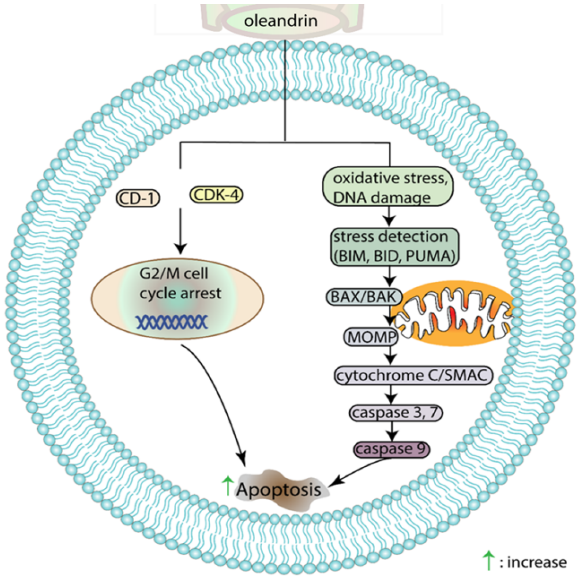

Fig. 2. Oleandrin induces apoptosis by targeting two major pathways: cell cycle arrest and mitochondrial stress. It inhibits CD-1 and CDK-4 activity, leading to G2/M cell cycle arrest, while promoting oxidative stress and DNA damage, which activate stress detection proteins (e.g., BIM, BID, and PUMA). These events result in mitochondrial outer membrane permeabilization (MOMP), release of cytochrome c/ SMAC, and activation of caspases (3, 7, 9), culminating in apoptosis.

carcinoma (Celik et al., 2023).

3.3.6. Inhibition of angiogenesis

Tumor cells develop the capacity to proliferate uncontrollably, withstand apoptosis, maintain angiogenesis, and avoid immune regulation. All of these processes are regulated by STAT proteins, particularly STAT3 and STAT5, which are also consistently activated in an unexpectedly high percentage of human malignancies (Yu et al., 2004). It has been demonstrated that OLD inhibits the NF-κB pathway, which can decrease the release of cytokines related to blood vessel formation, including VEGF and IL-8, which are pro-angiogenic agents (Ko et al., 2018).

A study suggests that OLD inhibits FGF-2 release, MMP 9 expression, and cell growth which leads to inhibition of angiogenesis of cells in PC3 (0.05 ng/mL), DU145 (0.1 ng/mL) cell lines of prostate cancer with IC_{50} of 0.001 to 0.002 µg/ml, respectively (Smith et al., 2001).

3.3.7. Migration and invasion of cells

The spread of cancer from its original site to distant organs is known as metastasis, and it is largely caused by the processes of invasion and migration. One crucial stage in the formation of secondary tumors is the capacity of cancer cells to spread and invade adjacent tissues. The EMT path has been employed by OLD to inhibit invasion. By preventing the growth of cancer cells, inhibition of the EMT process may offer an alternate therapeutic approach (Celik et al., 2023).

According to a study, OLD blocks β-Catenin, MMP-9 enzyme, and pSTAT3 signaling, decreasing colony formation and cell invasion in breast cancer cell lines, including (RT-R) MBA-MB-231 and MBA-MB 231 (1-500 nM) with IC_{50} of 183 and 72 nM, respectively (Ko et al., 2018). Another study showed that OLD inhibits the invasion and migration of cancer cells by inhibiting the EMT pathway. It found that in Ishikawa cell lines, OLD reduces invasion and migration at 7.5 to 100nM concentration with an IC_{50} of 75.3 nM in endometrial carcinoma (Celik et al., 2023). **Table 1** summarizes the anticancer mechanisms of OLD against several cancers, while **Fig. 3** illustrates how OLD decreases cell proliferation, angiogenesis, migration, and invasion in cancer cells.

Table 1. Cancer type, experimental model, tested dose/ concentration, $IC_{50,}$ and anticancer mechanism of oleandrin

Cancer type	Experimental model/ cell lines	Tested dose/ concentrations (R/A)	IC_{50}	Mechanisms/ results	References
Breast Cancer	MDA-MB-231, MCF7 SK-BR-3 (In vitro)	100-1.56 nM 50-0.78 nM 50-0.78 nM	24.62 nM 14.5 nM 6.13 nM	↓Cell proliferation and colony formation, Bcl-2, ↑Cytotoxicity, Bax, Bim, apoptosis, p-ERK, ER stress, eIF2α, ATF4, CHOP, p-PERK, p-eIF2α	Li et al., 2020
Breast Cancer	(RT-R) MDA-MB-231 MDA-MB-231, In Vitro	1-500 nM	183 nM 72 nM	↓OCT3/4,β-Catenin, MMP-9, colony formation, invasion, pSTAT3, ↑Cytotoxicity	Ko et al., 2018

Table 1. *Continued*

Cancer type	Experimental model/ cell lines	Tested dose/ concentrations (R/A)	IC_{50}	Mechanisms/ results	References
Prostate Cancer	PC3 DU145, *in vitro*	0.05 ng/mL 0.1 ng/mL	0.001 µg/ml 0.002 µg/ml	↓FGF-2 release, cell growth	Smith et al., 2001
Lung Cancer	A549 H1299, *in vitro*	0.01 µg/ml 0.02 µg/ml 0.04 µg/ml	-	↓Rad51x, ↑Apoptosis, DNA damage, XRCC1	Bao et al., 2016
Pancreatic Cancer	PANC-1, *in vitro*	0-50 nM	0.005 µM	↓Cell proliferation, pAkt ↑Cytotoxicity, p-ERK, LC3-II, MAPK, JNK, induction of autophagy	Newman et al., 2007
Melanoma	BRO, *in vitro*	0-100 nM	0.03 µM	↓Glutathione, cell growth ↑Cytotoxicity, ROS, apoptosis, superoxide radical formation	Newman et al., 2006
Colon Cancer	SW480, *in vitro*	0.01 µM 0.02 µM 0.05 µM	0.02 µM	↓Pro-caspace-3/-9, Bcl2,GSH ↑Cytotoxicity, apoptosis, Bax, Cyt c, cell cycle arrest in G2/M phase, intracellular Ca2+, caspase-3/-9	Pan et al., 2017
Osteosarcoma	U2OS SaOS-2, *in vitro*	0-100 nM	-	↓β-catenin, colony formation, c-myc, survivin, cyclin D1, MMP-2, and MMP-9 ↑Apoptosis, cytotoxicity	Ma et al., 2015
Endometrial Carcinoma	Ishikawa, *in vitro*	7.5–150 nM	75.3 nM	↓Colony formation, invasion, migration, proliferation, EMT, ZEB1, FN1, ITGB1, VIM, SMAD2, SNAI1,SNAI2, SNAI3, TGFB3, ↑Cytotoxicity,TIMP2,TIMP3, ITGAV and GSK3B	Celik et al., 2023

↑: Increase/Upregulate/Activation; ↓:Decrease/Downregulate/Inactivation; Bcl-2: B cell lymphoma 2; Bax: Bcl-2-associated x protein; Bim: Bcl-2 interacting mediator); pERK: Phosphorylated extracellular signal- regulated kinase; ER stress :Endoplasmic reticulum stress; eIF2α: Eukaryotic translation initiation factor 2 alpha; OCT:Octamer-binding transcription factor; ATF4: Activating Transcription Factor 4; CHOP:C/EBP homologous protein; p-eIF2α: Phosphorylated eukaryotic translation initiation factor 2 alpha; MMP:Matrix metalloproteinase; p-STAT: Phosphorylated signal transducer and activator of transcription; FGF2: Fibroblast growth factor 2; pAKT: Phosphorylated kinase protein-B ; MAPK: Mitogen-activated protein kinase; JNK: c-Jun N-terminal kinase; ROS:Reactive oxygen species; GSH:Glutathione; EMT: Epithelial- mesenchymal transition.

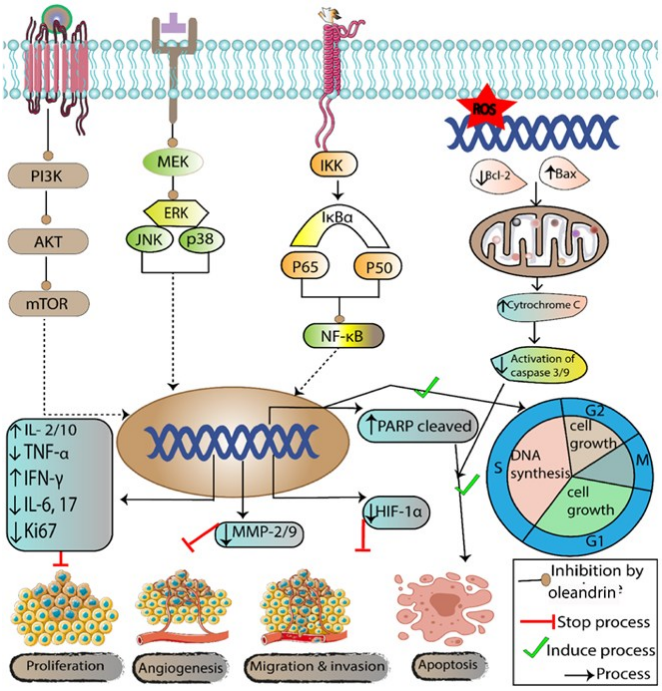

Fig. 3. Oleandrin modulates multiple signaling pathways to suppress cancer progression. It inhibits the PI3K/AKT/mTOR and MEK/ERK pathways, reducing proliferation and angiogenesis while promoting the cleavage of PARP and activation of pro-apoptotic signals (e.g., caspase 3/9). Additionally, it downregulates inflammatory cytokines (e.g., TNF-α, IL-6, IL-17) and matrix metalloproteinases (MMP-2/9), thereby reducing migration, invasion and inducing apoptosis.

4. Conclusion

In conclusion, OLD possesses a significant impact on various types of cancer cell lines like endometrial carcinoma, melanoma, osteosarcoma, breast, colon, pancreatic, and lung cancer. Its ways of preventing cancer include downregulating MMPs, suppressing cell growth through cell cycle arrest, and inducing apoptosis through caspase cascade activation. It decreases cell proliferation, oxidative stress, and colony formation, and enhances cytotoxicity. Its effects are mediated through key signaling pathways, such as PI3K/Akt/NF-κB, Wnt/β-catenin, and ERK. Nevertheless, there is a lack of sufficient clinical studies to support OLD's effectiveness as a cancer treatment. Therefore, clinical validation through well-designed human trials is essential to confirm its therapeutic potential. The discovery of OLD opens new avenues for further investigation, potentially leading to the development and application of cardiac glycosides in treating various diseases. Future research should focus on exploring OLD's clinical applications to enhance current cancer treatment strategies.

Conflict of interest

The authors declared no conflict

Data availability

Data will be made available on request.

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Author's contributions

Conceptualization, M.R., and M.S.; methodology, M.R.; validation, J.S., and M.S.H.; formal analysis, M.I.J.O., and M.S.; data curation, J.S., and M.S.H.; writing—original draft preparation, M.R.; writing—review and editing, M.R.; mechanisms drawing, M.S.; supervision, M.I.J.O.; project administration, M.I.J.O. All authors have read and agreed to the published version of the manuscript.

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