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Review on: Repurposing Phenytoin and Its Derivatives for Ovarian Cancer Management: Current Insights and Future Directions

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Abstract : Ovarian cancer is one of the most serious gynecological malignancies because most patients are diagnosed at an advanced stage when treatment options become limited. Although surgery and chemotherapy remain the primary treatments, many patients eventually develop resistance to drugs such as cisplatin and paclitaxel, resulting in poor long-term outcomes. Drug repurposing has gained attention as an effective strategy because it allows the use of existing approved medicines for new therapeutic purposes, reducing both development time and cost. Phenytoin, traditionally used as an antiepileptic drug, has shown promising anticancer effects by blocking voltage-gated sodium channels, reducing tumor cell invasion, and inducing apoptosis in various cancer types. Hydantoin derivatives, structurally related to phenytoin, also demonstrate enhanced cytotoxicity and better molecular targeting. This review provides an overview of current insights into the potential role of phenytoin and its derivatives in managing ovarian cancer, highlighting their mechanisms of action, preclinical evidence, limitations, and future therapeutic opportunities.

Keywords: Phenytoin, Hydantoin derivative, Ovarian cancer, Drug repurposing, Sodium channels, Apoptosis, Nano-Drug delivery, Chemoresistance.

INTRODUCTION

Ovarian cancer remains the eighth most common cancer in women and is responsible for a large number of cancer-related deaths worldwide because early symptoms are usually vague and difficult to detect [1]. More than 70% of patients are diagnosed at an advanced stage, where the chances of metastasis and recurrence are very high [2]. Although chemotherapy with platinum-based drugs is effective initially, most patients develop chemoresistance within months, which makes the disease more difficult to treat [3]. Drug repurposing is a promising strategy that identifies new therapeutic uses for existing approved drugs, allowing researchers to bypass early toxicity testing and reduce overall development time [4]. This approach is useful in ovarian cancer, where safe and fast alternatives are required due to the aggressive nature of the disease [5]. Phenytoin, a commonly used antiepileptic drug, has gained attention because voltage-gated sodium channels (VGSCs)—its primary neurological target—are also found in many cancer cells, including ovarian cancer [6]. Blocking these channels can reduce cancer cell motility, proliferation, and metastatic potential [7]. Hydantoin derivatives, including phenytoin, have shown strong anticancer properties in multiple experimental studies [8]. By modifying the hydantoin ring, new compounds with enhanced cytotoxicity and multi-pathway inhibition have been discovered [9]. Because ovarian cancer requires multi-target therapy due to its complex progression patterns, phenytoin-based compounds represent a strong candidate for drug repurposing research [10].

CHEMICAL STRUCTURE AND PHARMACOLOGICAL BASIS

Phenytoin belongs to the hydantoin class of heterocyclic compounds characterized by a five-membered ring with two carbonyl groups that contribute to its chemical stability and biological activity [11]. The structure includes two phenyl groups attached at carbon-5, which increase lipophilicity and allow the drug to cross cell membranes efficiently [12]. Because of this property, phenytoin can interact with intracellular signaling pathways that regulate cancer growth and metastasis [13].The hydantoin nucleus is highly modifiable, and small changes on the N-1, N-3, or C-5positions can significantly increase binding affinity, cytotoxicity, and selectivity toward cancer cells [14]. Medicinal chemistry studies show that adding electron-withdrawing groups, halogens, or aromatic rings improves anticancer potency in various hydantoin analogues [15]. These structural features make phenytoin a suitable scaffold for new drug development in ovarian cancer therapy [16].One of the primary anticancer mechanisms of phenytoin is the inhibition of voltage-gated sodium channels (VGSCs), especially Nav1.5, which is commonly overexpressed in ovarian, breast, and colon cancers [17]. These channels regulate electrical activity, but in cancer cells, they promote motility, invasion, and metastatic progression [18]. By blocking sodium influx, phenytoin reduces membrane depolarization and suppresses cancer cell movement, thereby reducing metastatic potential [19].

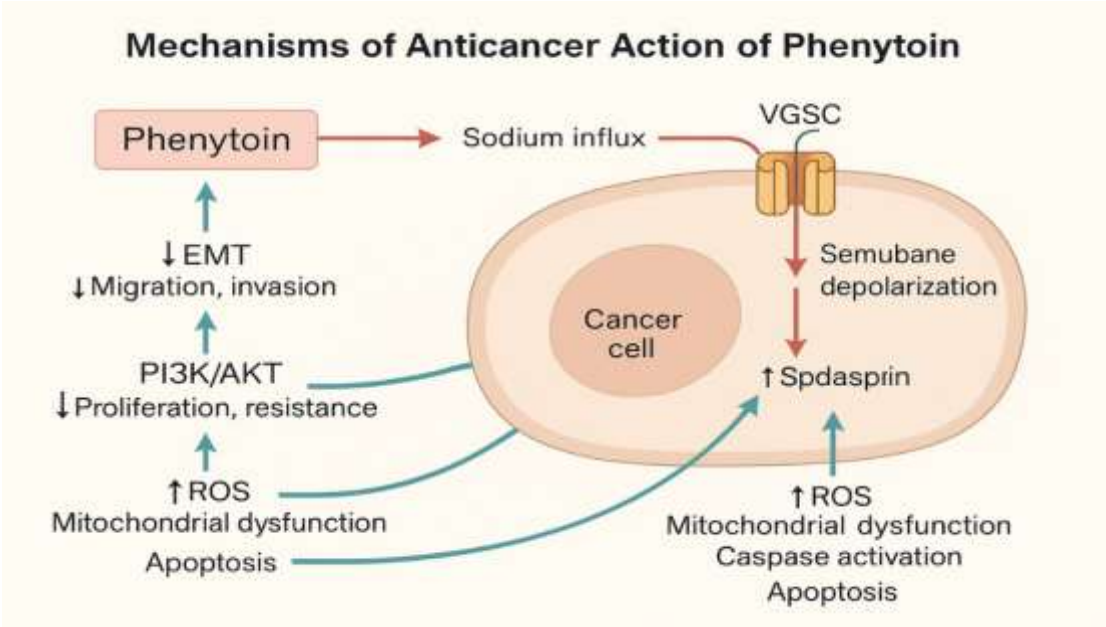

Fig. Mechanism of Anticancer Action of Phenytoin

Phenytoin also interferes with intracellular signaling pathways involved in cancer survival. It inhibits the PI3K/AKT and MAPK pathways, which are essential for ovarian cancer proliferation and resistance to chemotherapy [20]. Inhibition of these pathways results in growth arrest and reduces the ability of cancer cells to evade apoptosis [21]. Moreover, phenytoin increases reactive oxygen species (ROS), disrupts mitochondrial function, and activates caspase-dependent apoptosis, further promoting cancer cell death [22]. Another important mechanism is the suppression of epithelial–mesenchymal transition (EMT), a process in which cancer cells gain invasive and stem-like characteristics. Sodium-channel blockade downregulates EMT markers such as vimentin and N-cadherin while restoring epithelial markers such as E-cadherin [23]. This leads to reduced migration and limited metastatic spread [24].

EVIDENCE OF PHENYTOIN ACTIVITY IN CANCER MODELS

Laboratory research shows that phenytoin reduces proliferation and invasion in various cancer types, including breast, colon, lung, prostate, and ovarian cancer cell lines [25]. In ovarian In cancer cell models such as SKOV3 and OVCAR3, phenytoin decreases cell viability, induces apoptosis, and slows down migration in dose-dependent experiments [26]. These findings support the idea that sodium-channel inhibition can weaken ovarian cancer progression [27]. Animal studies demonstrate further benefits. In mouse xenograft models, tumors treated with phenytoin showed smaller tumor volumes, reduced angiogenesis, and decreased metastatic nodules compared to untreated controls [27]. Importantly, phenytoin administration did not cause major systemic toxicity, suggesting a favorable safety profile for repurposing in cancer therapy [28]. Clinical observations also report that patients with epilepsy receiving phenytoin sometimes show slower tumor growth or reduced cancer incidence compared to patients receiving other anticonvulsants [29]. Although not yet conclusive, these population-level findings encourage more targeted clinical research to validate phenytoin's anticancer potential in ovarian cancer [20].

HYDANTOIN DERIVATIVES AND THEIR ANTICANCER POTENTIAL

Hydantoin derivatives are structurally related compounds that often show stronger anticancer activity than phenytoin itself [30]. Small changes to the hydantoin ring—such as adding halogens, aromatic groups, or heterocyclic fragments—can significantly improve cytotoxicity and selectivity for cancer cells [1]. These modifications enhance cell penetration, strengthen receptor binding, and increase the ability of the compound to interfere with proliferation pathways [31]. Some hydantoin derivatives exert anticancer effects by increasing oxidative stress, altering mitochondrial function, and activating caspase-mediated apoptosis in tumor cells [21]. Others inhibit DNA synthesis and disrupt cell division cycles, leading to cell-cycle arrest in the G0/G1 or G2/M phases [32]. A few advanced derivatives also inhibit tubulin polymerization, which prevents proper chromosome separation during mitosis, resulting in mitotic arrest and cell death [33].

Type of Hydantoin Derivative	Structural Modification	Primary Anticancer Mechanism	Effects on Cancer Cells
Basic hydantoin derivatives	Small substitutions on hydantoin ring	Increased oxidative stress; mitochondrial disruption	↑ ROS, ↑ apoptosis, ↓ proliferation
Halogenated / aromatic hydantoins	Halogens, aromatic rings, heterocycles	Enhanced receptor binding and cytotoxicity	↑ Selectivity, ↑ cell penetration, ↓ tumour growth
Cell-cycle inhibitory hydantoins	Modifications at N-1 / N-3 / C-5	Inhibition of DNA synthesis; cell-cycle arrest	G0/G1 or G2/M arrest, ↓ mitosis
Tubulin-inhibiting hydantoins	Bulky aromatic ligands	Disruption of tubulin polymerisation	Impaired chromosome separation; mitotic arrest; apoptosis
Metal-based hydantoin complexes	Platinum (Pt) and other metal conjugation	DNA binding and enhanced DNA damage	Strong apoptosis in resistant tumours; effective in platinum-resistant ovarian cancer

Table 1: Anticancer Activities of Hydantoin Derivatives

Metal-based hydantoin derivatives, particularly platinum–hydantoin complexes, demonstrate even stronger anticancer effects because they bind to DNA more efficiently and induce apoptosis in resistant tumors [34]. This can be especially helpful in platinum-resistant ovarian cancer, where standard drugs lose effectiveness [35]. Hybrid compounds like β-carboline–hydantoin analogues also inhibit metastatic pathways such as EMT and reduce the invasive behavior of cancer cells [36].

COMBINATION THERAPY POTENTIAL WITH CHEMOTHERAPEUTIC AGENTS

Combination therapy is widely used in cancer treatment because it targets different pathways simultaneously and reduces the risk of drug resistance [37]. In ovarian cancer, adding phenytoin to existing chemotherapy regimens may provide additive or synergistic benefits, particularly due to its sodium-channel-blocking properties [38]. Blocking sodium channels can weaken the cancer cell's internal stability, making it more sensitive to cytotoxic drugs [39].

Phenytoin has shown synergy with **cisplatin**, one of the main chemotherapy drugs used in ovarian cancer. Sodium-channel inhibition increases DNA fragmentation and makes cancer cells more vulnerable to cisplatin-induced DNA damage [40]. This allows lower doses of cisplatin to achieve similar effects, potentially reducing toxicity while maintaining treatment efficacy [41].

Phenytoin also enhances the effects of **paclitaxel**, a drug that stabilizes microtubules and prevents cell division [42]. Because some hydantoin derivatives disrupt microtubules, combining them with paclitaxel produces stronger mitotic arrest and apoptosis in cancer cells [43]. Additionally, phenytoin may improve responses to **PARP inhibitors**, especially in BRCA-mutated ovarian cancer, by reducing cancer cells' DNA repair ability and increasing stress sensitivity [44].

These findings suggest that phenytoin can act as a **chemosensitizer**, improving the performance of standard chemotherapy and potentially reducing recurrence rates in ovarian cancer patients [45].

NANOFORMULATION AND TARGETED DELIVERY APPROACHES

Nanotechnology is an emerging approach in oncology because it improves drug delivery, reduces toxicity, and increases drug concentration specifically at tumor sites [46]. Nano-carriers can protect phenytoin from rapid metabolism and enhance penetration into ovarian tumors, which often spread across the peritoneal cavity [32]. Using nanocarriers also allows controlled drug release over time, ensuring steady therapeutic levels [47].

Liposomes are one of the most widely used nanocarriers and are effective in delivering phenytoin and hydantoin derivatives [48]. Liposomal formulations increase circulation time, enhance tumor uptake, and reduce exposure to healthy tissues [20]. Polymeric nanoparticles such as PEG- or PLGA-based systems also help stabilize phenytoin and improve cellular uptake in ovarian cancer cells [49].

Targeted nanoparticles containing ligands such as **folate**, **transferrin**, or **peptides** can specifically bind to receptors that are overexpressed in ovarian cancer cells [50]. For example, folate-tagged phenytoin nanoparticles deliver the drug directly to ovarian tumor tissues, increasing cytotoxicity and reducing systemic side effects [51]. Some hydantoin-loaded nanocarriers also enhance ROS production and apoptosis, making them more effective against chemoresistant tumors [43]. Overall, nanoparticle-based delivery systems can significantly improve the therapeutic performance of phenytoin and make it more effective as a repurposed anticancer drug in ovarian cancer [52].

CLINICAL CHALLENGES AND LIMITATIONS

Despite promising laboratory evidence, several challenges must be addressed before phenytoin can be used clinically for ovarian cancer therapy [9]. One of the major concerns is its **narrow therapeutic window**, meaning that small changes in dose can cause toxicity or reduced effectiveness [37]. This complicates treatment planning, especially in cancer patients who often have altered liver function or are taking multiple medications [53].

Phenytoin undergoes metabolism through cytochrome P450 enzymes, particularly CYP2C9 and CYP2C19. Many chemotherapy drugs also rely on similar metabolic pathways, increasing the risk of drug–drug interactions [42]. Such interactions may reduce phenytoin effectiveness or increase toxicity, which highlights the importance of therapeutic drug monitoring [15].

Another limitation is the lack of **high-quality clinical trials** evaluating phenytoin for ovarian cancer. Most available data comes from cell-based studies, animal experiments, or observational findings in epileptic patients. Although these results are encouraging, controlled clinical studies are needed to confirm safety, optimal dosing, and effectiveness in real ovarian cancer patients [24].

Ovarian tumors are biologically complex and often develop resistance to therapy. Phenytoin works primarily through sodium-channel inhibition, so its effectiveness may vary depending on tumor genetics, channel expression, and microenvironmental factors. Therefore, identifying predictive biomarkers — such as Nav1.5 and related channel expressions — will be essential for selecting patients who are most likely to benefit [32].

FUTURE PERSPECTIVES

Future research should focus on improving phenytoin's selectivity, delivery, and clinical applicability for ovarian cancer therapy. Developing new hydantoin derivatives with better toxicity profiles, stronger anticancer effects, and multi-targeting properties could significantly enhance treatment outcomes. Molecular docking and computational modeling can help design derivatives that bind more effectively to cancer-specific targets [35].

Nanotechnology also offers promising opportunities. Advanced nano formulations such as liposomal-phenytoin, PEG-nanoparticles, and folate-targeted carriers can improve tumor accumulation and reduce systemic toxicity. Combining phenytoin with immunotherapy, PARP inhibitors, or cold plasma treatment may further improve treatment outcomes in drug-resistant ovarian cancer [54].

Clinical translation requires Phase I/II trials to study safe dosage ranges, pharmacokinetics, and combinations with current chemotherapy regimens. Personalized medicine approaches using biomarker testing may help identify patient subgroups who can benefit the most from phenytoin-based treatments [55].

CONCLUSION

Phenytoin and its hydantoin derivatives have significant potential for repurposing as anticancer agents, especially in ovarian cancer where new therapeutic strategies are urgently needed. Their ability to inhibit sodium channels, induce apoptosis, prevent metastasis, and enhance chemotherapy responses makes them valuable candidates for further exploration. Although laboratory and animal studies show promising results, clinical trials are essential to fully validate their role in ovarian cancer therapy.

With advancements in drug delivery technologies, structural modifications, and combination therapy strategies, phenytoin-based treatments may provide a cost-effective and efficient approach to managing ovarian cancer in the future [56].

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