

Review Article

Computational and Structure-Based Insights into Poly (ADP-Ribose) Polymerase (PARP) Inhibitors for Cancer Therapy

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Abstract

Poly (ADP-ribose) polymerase (PARP) inhibitors (PARPi) have become a cornerstone of precision oncology by exploiting synthetic lethality in tumors with homologous recombination deficiency, particularly those harboring BRCA1/2 mutations. Despite substantial clinical success, the long-term effectiveness of PARPi is limited by acquired drug resistance, hematological toxicity, and challenges in achieving isoform selectivity. This narrative review aims to critically synthesize current knowledge on the structural mechanisms of PARP inhibition, pharmacological diversity among clinically relevant PARPi, emerging resistance mechanisms, and the contribution of computational approaches to next-generation inhibitor development. Current evidence indicates that PARPi exert their antitumor effects through both catalytic inhibition of PARylation and PARP trapping, with clinically approved agents, including Olaparib, Rucaparib, Niraparib, and Talazoparib, exhibiting distinct trapping potency, selectivity, toxicity, and therapeutic applications. Emerging resistance mechanisms, including homologous recombination restoration, replication fork stabilization, altered PARP1 trapping, and drug efflux, have shifted drug development toward mechanism-informed therapeutic design. In this context, structure-based computational approaches—including molecular docking, molecular dynamics simulations, pharmacophore modeling, quantitative structure–activity relationship (QSAR), and artificial intelligence-assisted drug design—have become integral to identifying novel scaffolds, improving PARP1 selectivity, optimizing PARP-trapping properties, and prioritizing compounds for experimental validation. Collectively, these advances indicate that integrating structural biology, computational drug design, and resistance biology is essential for developing safer, more selective, and resistance-resilient PARP inhibitors, thereby supporting the next generation of precision cancer therapeutics.

Keywords: PARP Inhibitors (PARPi); Computational Drug Design; Cancer Therapy

Introduction

Poly (ADP-ribose) polymerase inhibitors (PARPi) have transformed the therapeutic landscape of multiple malignancies, particularly those characterized by defects in homologous recombination repair (HRR). The clinical success of PARPi is grounded in the principle of synthetic lethality, whereby inhibition of PARP-mediated DNA repair selectively induces cell death in tumors harboring BRCA1/2 mutations or broader homologous recombination deficiency (HRD) (Lord & Ashworth, 2017). Over the past decade, this concept has expanded from a genetic paradigm into a clinically validated strategy across ovarian, breast, prostate, and pancreatic cancers, establishing PARPi as a cornerstone of precision oncology.

Despite these advances, emerging evidence indicates that the biological and pharmacological behavior of PARPi is more complex than initially appreciated. Early models focused primarily on catalytic inhibition of PARylation and disruption of single-strand break repair. However, subsequent studies have demonstrated that PARP trapping and the stabilization of PARP–DNA complexes is a critical and distinct contributor to cytotoxicity, with substantial variability among clinically approved agents (Murai et al., 2012; Slade, 2020). This has led to a paradigm shift in which PARPi are no longer viewed as uniform inhibitors, but rather as a mechanistically heterogeneous class of drugs with distinct trapping potency, selectivity, and toxicity profiles. Concurrently, resistance to PARPi has emerged as a major clinical challenge. Tumor adaptation occurs through multiple pathways, including restoration of homologous recombination, replication-fork stabilization, altered PARP1 trapping, and changes in drug exposure. These findings highlight that HRD is not a static biomarker but a dynamic and context-dependent state, thereby limiting the predictive value of conventional genomic markers alone (Li et al., 2020; Giudice et al., 2022). As a result, there is increasing recognition that effective use of PARPi requires integration of mechanistic understanding, biomarker refinement, and resistance-aware therapeutic strategies.

At the same time, advances in structural biology and computational chemistry have opened new opportunities for rational drug design. High-resolution characterization of PARP1 domains and inhibitor binding modes has revealed both the strengths and limitations of targeting the highly conserved NAD⁺-binding pocket, particularly with respect to isoform selectivity and off-target toxicity (Illuzzi et al., 2021). In parallel, computational approaches including molecular docking, molecular dynamics simulations, and machine learning are increasingly used to guide scaffold optimization and identify next-generation inhibitors with improved selectivity and pharmacologic profiles (Twala et al., 2025).

This review aims to provide a comprehensive and critical synthesis of current knowledge on PARP inhibitors by integrating multiple dimensions of research. Specifically, this article seeks to: Examine the structural and mechanistic determinants of PARP inhibition and PARP trapping; Compare the pharmacological profiles of clinically relevant PARP inhibitors with appropriate consideration of contextual limitations; Analyze emerging resistance mechanisms and their implications for therapeutic strategies and biomarker development; and Critically evaluate the role of computational approaches in the discovery and optimization of next-generation PARP inhibitors. By bridging these perspectives, this review aims to highlight key challenges, identify opportunities for innovation, and support the rational design of more effective and durable PARP-targeted therapies.

Study methods

This narrative review was conducted to provide a comprehensive and integrative synthesis of current knowledge on poly (ADP-ribose) polymerase (PARP) inhibitors, with a focus on structural mechanisms, pharmacological diversity, resistance biology, and computational drug design approaches. A structured literature search was performed using four major electronic databases: PubMed, Scopus, Web of Science, and Google Scholar. The search

strategy incorporated combinations of relevant keywords and Medical Subject Headings (MeSH) terms, including PARP inhibitors, PARP1, PARP trapping, synthetic lethality, BRCA, DNA repair, drug resistance, molecular docking, molecular dynamics, QSAR, and artificial intelligence in drug discovery. Boolean operators were applied to refine search results and ensure comprehensive coverage across both experimental and computational domains.

The search primarily focused on studies published between 2010 and 2025, reflecting the rapid expansion of research and clinical application in this field. Foundational studies published prior to 2010 were included where necessary to provide essential conceptual background, particularly in relation to synthetic lethality and early PARP inhibitor development. Only articles published in English were considered. The study selection process followed a structured approach aligned with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) principles to enhance transparency.

The initial database search identified 520 records, of which 410 remained after removal of duplicates. Titles and abstracts were screened to exclude studies not directly relevant to PARP inhibitors or the scope of this review, resulting in 52 articles selected for full-text assessment. Full-text articles were evaluated for eligibility based on predefined inclusion criteria. Studies were included if they met at least one of the following criteria: (i) provided structural or mechanistic insights into PARP–ligand interactions, (ii) reported clinical or preclinical data on PARP inhibitors, (iii) investigated resistance mechanisms, or (iv) applied computational approaches to PARP inhibitor discovery or optimization. Studies were excluded if they were not directly related to PARP inhibitors, lacked sufficient scientific rigor, or did not contribute meaningful insights to the objectives of this review. Following full-text evaluation, 19 key studies were included in the final qualitative synthesis.

Although this review is narrative in nature and does not strictly adhere to a systematic review protocol, efforts were made to ensure methodological transparency, reproducibility, and balanced representation of the literature. The included studies were analyzed qualitatively, with emphasis on identifying key mechanistic insights, pharmacologic differences among PARP inhibitors, emerging resistance pathways, and the strengths and limitations of computational approaches in drug discovery. Particular attention was given to integrating findings across structural biology, pharmacology, and translational research to provide a critical and forward-looking perspective on the development of next-generation PARP-targeted therapies.

Biological and Pharmacological Basis of PARP Inhibition

PARP1 in DNA Repair

PARP1 functions as a rapid DNA damage sensor that is preferentially activated at single-strand breaks (SSBs) through coordinated structural and allosteric mechanisms. Upon binding damaged DNA via its zinc-finger-containing DNA-binding domain, PARP1 undergoes conformational rearrangement particularly within the helical subdomain that relieves autoinhibition of the catalytic site and enables NAD⁺-dependent poly(ADP-ribosyl)ation (PARylation) (Twala et al., 2025). PARylation promotes recruitment of DNA repair factors such as XRCC1 and facilitates chromatin remodeling, thereby enabling efficient base excision repair (BER). Crucially, autoPARylation reduces PARP1 affinity for DNA, allowing its dissociation and restoration of catalytic cycling (Lord & Ashworth, 2017; Murai et al., 2012). Beyond a simple repair enzyme, PARP1 integrates structural sensing with enzymatic signaling. Its activity depends on dynamic coupling between DNA-binding and catalytic domains, which regulates access to the nicotinamide-binding pocket and coordinates repair factor recruitment (Illuzzi et al., 2021). This structural plasticity underlies both its physiological role in genome maintenance and its vulnerability to pharmacologic inhibition.

Synthetic Lethality in HRD/BRCA-Deficient Tumors

The therapeutic efficacy of PARP inhibition is grounded in synthetic lethality between PARP-mediated BER and homologous recombination repair (HRR). Unrepaired SSBs that persist into S phase are converted into replication-associated double-strand breaks (DSBs), which require HRR for accurate repair. In HR-proficient cells, these lesions are efficiently resolved; however, in BRCA1/2-mutated or HR-deficient tumors, defective HRR leads to accumulation of lethal genomic instability (Lord & Ashworth, 2017; Murai et al., 2012). Importantly, this paradigm extends beyond canonical BRCA mutations to a broader homologous recombination deficiency (HRD) or “BRCAness” phenotype. Alterations in genes such as RAD51, PALB2, ATM, and other HR-related pathways similarly confer dependence on PARP1-mediated repair (Kim & Yu, 2025). This broader genomic context has important implications for patient selection and biomarker development, as reliance on PARP1 is determined by functional network deficiencies rather than single-gene status alone. Mechanistically, PARP inhibition not only prevents repair but amplifies replication stress, thereby converting endogenous DNA damage into cytotoxic lesions. This dual role repair inhibition and replication destabilization explains the selective vulnerability of HRD tumors.

Catalytic Inhibition versus PARP Trapping

PARP inhibitors (PARPi) were initially conceptualized as catalytic inhibitors that suppress PARylation and impair SSB repair. However, their antitumor activity is now recognized to depend critically on PARP trapping, a distinct mechanism in which PARP1 remains bound to DNA and forms cytotoxic PARP–DNA complexes (Murai et al., 2012). Trapped PARP1 obstructs replication fork progression and prevents fork restart, generating replication-associated DSBs that are more cytotoxic than unrepaired SSBs alone. Importantly, catalytic inhibition and trapping are mechanistically separable: inhibitors with similar catalytic potency can exhibit markedly different trapping efficiencies (Slade, 2020). Clinically relevant PARPi display a hierarchy of trapping potency (Talazoparib >> Niraparib > Olaparib ≈ Rucaparib >> Veliparib), highlighting that pharmacologic effects are not interchangeable across the class (Slade, 2020). Notably, increased trapping correlates with enhanced cytotoxicity but also with increased hematologic toxicity, indicating a trade-off between efficacy and tolerability. Preclinical data further demonstrate that differences in trapping do not necessarily translate into proportional in vivo efficacy at tolerated doses, emphasizing the importance of therapeutic index rather than potency alone (Hopkins et al., 2019). Collectively, these findings redefine PARPi as dual-mechanism agents, in which catalytic inhibition and trapping contribute differentially to therapeutic outcomes.

Structural Basis of PARP Inhibitor Action

PARP1 Catalytic Domain and NAD⁺-Binding Pocket

The structural basis of PARP inhibition resides in the C-terminal catalytic domain, composed of the helical subdomain (HD) and the ADP-ribosyl transferase (ART) subdomain. In the inactive state, the HD occludes access to the NAD⁺-binding site; DNA binding induces conformational rearrangements that expose this pocket and enable catalysis (Twala et al., 2025). Most PARPi act as nicotinamide mimetics, occupying the conserved NAD⁺-binding pocket and forming hydrogen bonds and π – π interactions with key residues. This conserved binding mode explains their high catalytic potency but also presents a major challenge for achieving isoform selectivity across the PARP family (Illuzzi et al., 2021; Lord & Ashworth, 2017). Structural studies further indicate that PARP1 activation involves coordinated domain dynamics rather than static binding, suggesting that effective inhibition may require disruption of these conformational transitions rather than simple active-site occupancy.

Binding Modes of Major PARP Inhibitors

Clinically approved PARPi including Olaparib, Rucaparib, Niraparib, Talazoparib, and Veliparib, share a conserved binding orientation within the catalytic pocket but differ substantially in their chemical scaffolds and peripheral interactions. These structural differences influence binding affinity, selectivity, and pharmacologic behavior (Twala et al., 2025). While all agents target the nicotinamide-binding region, variations in molecular size, rigidity, and substituent positioning affect interactions beyond the core pocket. For example, broader interaction networks can enhance potency but may also reduce selectivity across PARP isoforms. Consequently, compounds such as Rucaparib exhibit broader PARP-family activity, whereas others like Veliparib show relatively greater selectivity but weaker overall potency (Slade, 2020). These findings underscore that shared active-site binding does not equate to pharmacologic equivalence, as subtle structural differences translate into meaningful biological divergence.

Structural Determinants of Trapping and Selectivity

Catalytic inhibition alone does not fully account for PARPi activity. Structural and mechanistic evidence indicates that PARP trapping arises from inhibitor-induced alterations in PARP1–DNA complex stability, rather than simple active-site blockade (Murai et al., 2012). Differences in trapping potency likely reflect the ability of inhibitors to influence PARP1 conformational dynamics, including domain interactions and DNA-binding retention. Talazoparib, for example, exhibits exceptional trapping potency, whereas Veliparib shows minimal trapping despite similar catalytic inhibition, highlighting the importance of structural determinants beyond the catalytic site (Slade, 2020). These effects are thought to involve allosteric modulation linking catalytic-site occupancy to DNA-bound conformations. Because the catalytic pocket is highly conserved, next-generation selectivity strategies focus on less-conserved peripheral regions and domain interfaces. This approach underpins the development of PARP1-selective inhibitors such as AZD5305, which aim to preserve synthetic lethality while minimizing toxicity associated with PARP2 inhibition (Kim & Yu, 2025). Overall, emerging structural insights suggest that optimal PARPi design requires integration of active-site binding, conformational control, and domain-specific selectivity, rather than reliance on catalytic inhibition alone. The emergence of multiple resistance mechanisms has shifted PARP inhibitor development from simply improving catalytic potency toward designing compounds capable of overcoming adaptive tumor responses. Computational approaches now play an increasingly important role in this process by enabling structure-guided optimization of PARP1 selectivity, prediction of resistance-associated binding alterations, identification of novel scaffolds, and prioritization of compounds for experimental validation. Consequently, computational drug design has become an essential component of next-generation PARP inhibitor development rather than merely a supportive discovery tool.

Computational Approaches in PARP Inhibitor Discovery

Molecular docking and virtual screening

Structure-based virtual screening and molecular docking have been central to the early-stage discovery of PARP inhibitors, particularly for identifying compounds capable of engaging the highly conserved nicotinamide-binding pocket of PARP1. These approaches enable rapid exploration of large chemical libraries and provide initial insights into binding poses, hydrogen-bonding interactions, and potential isoform selectivity. However, their primary value lies in prioritization rather than validation, as docking scores alone do not reliably predict biological activity or trapping behavior. A representative example is the multi-stage workflow described by El Hassab et al. (2025), which integrates pharmacophore filtering, docking against both PARP1 and PARP2, and subsequent refinement steps to enrich for PARP1-selective candidates. This strategy highlights a key strength of virtual screening: the

ability to systematically reduce chemical space while incorporating selectivity constraints early in the pipeline. Importantly, the study leverages known structural differences between PARP1 and PARP2 to guide candidate prioritization, illustrating how docking can be enhanced when informed by structural biology. Nevertheless, the predictive limitations of docking are particularly relevant in the PARP field. Because clinically important properties such as PARP trapping and replication-fork interference are not directly encoded in docking scores, these methods cannot capture the full pharmacologic profile of PARP inhibitors. As such, docking should be interpreted as a hypothesis-generating tool, requiring downstream validation through dynamic and experimental approaches (Twala et al., 2025).

Molecular dynamics and free-energy analysis

To address the limitations of static docking models, molecular dynamics (MD) simulations are widely used to evaluate the temporal stability and conformational behavior of PARP1 ligand complexes. MD provides insight into hydrogen-bond persistence, binding-site flexibility, and ligand-induced conformational changes features that are critical for understanding inhibitor potency and selectivity but are not captured in rigid docking models (Wang et al., 2020). In the workflow reported by El Hassab et al. (2025), MD simulations supported the preferential stability of selected compounds in PARP1 relative to PARP2, reinforcing predicted isoform selectivity. More broadly, MD-based analyses are particularly valuable in the context of PARP1 because the catalytic domain exhibits dynamic regulation through allosteric domain interactions, meaning that ligand binding can influence protein conformation beyond the immediate active site (Twala et al., 2025). Free-energy methods, including MM/GBSA and related approaches, further refine these predictions by estimating relative binding affinities. However, their accuracy remains constrained by force-field limitations, sampling depth, and system complexity, particularly for large and flexible systems such as PARP1–DNA–ligand complexes. As a result, MD and free-energy calculations improve mechanistic interpretation but do not eliminate the need for experimental validation.

Pharmacophore modeling, QSAR, and AI-assisted design

Beyond structure-based docking, ligand-based and hybrid computational approaches such as pharmacophore modeling, quantitative structure–activity relationship (QSAR) analysis, and artificial intelligence (AI)-assisted design have become increasingly important in PARP inhibitor discovery. Pharmacophore modeling defines the spatial arrangement of key interaction features required for productive binding and is particularly useful for early-stage filtering and scaffold diversification. In the PARP1-selective workflow described by El Hassab et al. (2025), pharmacophore screening effectively enriched candidate compounds prior to docking and MD refinement, demonstrating its utility in reducing false positives and guiding scaffold selection. QSAR methods complement this by establishing quantitative relationships between molecular descriptors and biological activity, enabling prediction-driven optimization of potency and physicochemical properties. Modern implementations often incorporate three-dimensional structural information and can be integrated with multiscale modeling approaches to improve predictive performance. More recently, AI and machine-learning methods have expanded the scope of computational drug design. These approaches can integrate large-scale chemical and biological datasets to improve target identification, ligand optimization, and biomarker discovery. Importantly, AI is most effective within structured design make test analyze cycles, where it accelerates iteration rather than replacing experimental validation (Vamathevan et al., 2019). Despite these advances, significant limitations remain. Predictive performance depends on data quality, model interpretability, and the ability to capture complex biological phenomena such as PARP trapping and resistance mechanisms. Consequently, the translational value of these approaches lies in prioritization, hypothesis refinement, and integration with experimental workflows, rather than in standalone prediction (Twala et al., 2025; Wang et al., 2020).

Table 1 Strengths and limitations of computational approaches in PARP inhibitor discovery

Method	Strengths	Limitations	Best application
Molecular Docking	Rapid screening	Static protein structure	Hit identification
Molecular Dynamics	Protein flexibility	Computationally expensive	Binding stability
MM/GBSA	Better affinity estimation	Approximation errors	Lead optimization
Pharmacophore Modeling	Scaffold diversity	Depends on known ligands	Virtual screening
QSAR	Activity prediction	Dataset dependent	SAR optimization
AI / Machine Learning	Large-scale prediction	Black-box models, data quality	Compound prioritization

Comparative Analysis of Clinically Relevant and Emerging PARP Inhibitors

Pharmacological Diversity among Clinically Relevant PARP Inhibitors

Although clinically approved PARP inhibitors (PARPi) including Olaparib, Rucaparib, Niraparib, Talazoparib, and Veliparib share a common mechanism of competitive inhibition at the NAD⁺-binding site of PARP1, they are pharmacologically heterogeneous rather than functionally interchangeable. While most agents exhibit comparable catalytic potency in the low-nanomolar range, emerging evidence indicates that differences in trapping efficiency, selectivity, and off-target interactions are more consequential determinants of clinical behavior. Structural analyses demonstrate that variations in molecular scaffolds and peripheral substituents influence not only binding affinity but also family-wide selectivity and polypharmacology. For example, Veliparib exhibits relatively greater selectivity for PARP1/2 but limited trapping capacity, whereas Rucaparib displays broader inhibition across PARP family members, reflecting weaker isoform selectivity. Olaparib and Talazoparib occupy an intermediate position, combining high potency with moderate selectivity (Slade, 2020). These differences have direct clinical implications, as selectivity profiles influence toxicity, drug–drug interactions, and suitability for combination strategies across tumor types (Piombino & Cortesi, 2022).

Selectivity, Toxicity, and Clinical Context

Differences in PARP isoform selectivity further contribute to pharmacologic diversity. While PARP1 is the principal mediator of synthetic lethality, PARP2 inhibition has been implicated in hematologic toxicity, particularly through effects on erythropoiesis. Consequently, inhibitors with broader PARP1/2 activity may exhibit increased toxicity without proportional gains in efficacy (Kim & Yu, 2025). However, clinical interpretation must be approached cautiously. Comparative efficacy across PARPi is confounded by differences in trial design, tumor type, biomarker selection, prior treatment exposure, and therapeutic setting. For example, Olaparib has demonstrated broad utility across ovarian, breast, prostate, and pancreatic cancers, whereas talazoparib's strongest evidence base is in BRCA-mutated breast cancer. Niraparib has shown benefit across broader biomarker-defined ovarian cancer populations, including HRD-positive but BRCA-wild-type disease. These distinctions reflect not only drug properties but also differences in clinical context, limiting direct head-to-head comparison (Piombino & Cortesi, 2022). Accordingly, PARPi should be viewed as a mechanistically related but clinically differentiated class, in which optimal use depends on aligning pharmacologic properties with disease biology and treatment context.

PARP1-Selective Next-Generation Inhibitors

A major recent advance in the field is the development of PARP1-selective inhibitors, which aim to address the limitations of first-generation dual PARP1/2 inhibitors. This strategy is based on the observation that PARP1 is primarily responsible for synthetic lethality in HR-deficient tumors, whereas PARP2 contributes disproportionately to hematologic toxicity. Next-

generation agents, such as AZD5305, are therefore designed to retain PARP1-mediated trapping and antitumor activity while minimizing PARP2 inhibition. This represents a mechanistically informed redesign of the class, rather than incremental optimization of existing scaffolds (Johannes et al., 2021; Kim & Yu, 2025). From a translational perspective, PARP1-selective inhibitors may offer improved tolerability, expanded therapeutic window, and greater compatibility with combination therapies. However, their ultimate clinical value will depend on whether reduced toxicity can be achieved without compromising efficacy, particularly in the context of resistance mechanisms and tumor heterogeneity.

Synthesis and Critical Perspective

Collectively, the evidence indicates that PARP inhibitors should not be considered interchangeable agents defined solely by catalytic potency. Instead, their clinical behavior reflects a multidimensional pharmacologic profile, integrating trapping efficiency, isoform selectivity, toxicity, and disease context. Two key insights emerge: Trapping is a central but double-edged determinant of efficacy, enhancing tumor cytotoxicity while limiting tolerability, and selectivity and therapeutic index are emerging as primary design priorities, particularly in the development of next-generation PARP1-selective inhibitors. These findings support a shift from viewing PARPi as a uniform drug class toward understanding them as a diverse, mechanism-driven therapeutic platform, where rational drug selection and design must balance efficacy, toxicity, and resistance biology. As summarized in Table 2, clinically relevant PARP inhibitors exhibit substantial differences in trapping potency, selectivity, and toxicity, supporting the view that they represent a pharmacologically heterogeneous class rather than interchangeable agents

Table 2 Comparative pharmacologic and mechanistic profiles of clinically relevant and emerging PARP inhibitors

PARP inhibitor	Catalytic potency (PARP1)	PARP trapping potency	PARP1 vs PARP2 selectivity	Key toxicity profile	Representative clinical use	Key pharmacologic implication
Talazoparib	Very high	Very High	Low–moderate	Hematologic toxicity (anemia)	BRCA-mutated breast cancer	High trapping → strong efficacy but narrow therapeutic index
Niraparib	High	High	Moderate	Thrombocytopenia, anemia	Ovarian cancer (maintenance, including HRD+)	Intermediate trapping with broader clinical applicability
Olaparib	High	Moderate	Moderate	GI toxicity, anemia	Ovarian, breast, prostate, pancreatic cancers	Balanced efficacy and tolerability; widely used
Rucaparib	High	Moderate	Low (less selective)	Transaminase elevation, anemia	Ovarian cancer (treatment + maintenance)	Broader PARP-family inhibition may affect toxicity and combinations
Veliparib	Moderate	Low	High (PARP1/2 selective)	Generally better tolerated	Investigational / combination therapy	Weak trapping limits single-agent efficacy but improves tolerability
AZD5305 (next-gen)	High (PARP1)	High (PARP1-selective)	High (PARP1-selective)	Reduced hematologic toxicity (early data)	Emerging (clinical trials)	Designed to preserve efficacy while improving safety

Although Talazoparib demonstrates the strongest PARP-trapping activity, this does not necessarily translate into superior clinical outcomes because greater trapping is associated with increased hematologic toxicity and dose limitations. Conversely, Olaparib and Niraparib provide a more balanced therapeutic profile, while emerging PARP1-selective inhibitors aim

to preserve effective trapping while reducing toxicity. These findings suggest that therapeutic index, rather than maximal trapping potency, should guide future inhibitor development.

Resistance Mechanisms and Design Implications

HR Restoration and Replication-Fork Protection

Resistance to PARP inhibitors (PARPi) is most commonly driven by restoration of homologous recombination (HR), which re-establishes the capacity of tumor cells to resolve replication-associated double-strand breaks. This can occur through secondary (reversion) mutations in BRCA1/2 that restore functional protein, or through loss of end-resection suppressors such as 53BP1, RIF1, REV7, and the Shieldin complex, thereby enabling reactivation of HR despite persistent upstream defects (Giudice et al., 2022). Importantly, resistance is not restricted to full HR restoration. A parallel and mechanistically distinct pathway involves replication-fork protection, whereby stalled forks are stabilized independently of canonical HRR. In this context, reduced nucleolytic degradation of nascent DNA often through altered MRE11 or associated pathways prevents fork collapse and diminishes the cytotoxic consequences of PARP inhibition. As a result, cells may remain HR-deficient yet become PARPi-resistant (Li et al., 2020). Taken together, these findings indicate that resistance arises through two convergent strategies: recovery of DNA repair capacity or attenuation of replication-associated vulnerability. This distinction is critical, as it implies that HRD is not a static biomarker but a dynamic and reversible state, particularly under therapeutic selection pressure.

PARP1 alteration and drug efflux

A second major class of resistance mechanisms involves direct alteration of the drug target or intracellular drug exposure, rather than restoration of DNA repair pathways. Mutations in PARP1 can impair drug efficacy by disrupting DNA binding, interdomain communication, or retention at sites of damage, thereby reducing PARP trapping, which is a key determinant of cytotoxicity (Slade, 2020). Clinically relevant variants, such as those affecting the WGR or catalytic domains, highlight that resistance can arise through loss of trapping rather than loss of catalytic inhibition alone. Alterations in PAR metabolism further contribute to this process. Loss of poly (ADP-ribose) glycohydrolase (PARG) modifies PARylation dynamics and can promote dissociation of PARP1 from DNA, effectively reducing the persistence of trapped complexes. However, this effect is context-dependent, underscoring the complexity of PAR signaling in resistance biology (Giudice et al., 2022). In addition, drug efflux mechanisms, particularly upregulation of ABCB1/P-glycoprotein, reduce intracellular concentrations of PARPi and can confer resistance even in the presence of an intact target. This highlights an important pharmacologic dimension: resistance can emerge not only from genomic adaptation but also from altered drug disposition (Li et al., 2020). Collectively, these mechanisms demonstrate that PARPi resistance extends beyond HR restoration to include target modification and pharmacokinetic escape, emphasizing the need for multidimensional therapeutic strategies.

Implications for next-generation inhibitor design

The diversity of resistance mechanisms has direct implications for the rational design of next-generation PARP inhibitors (Figure 1). First, accumulating evidence indicates that PARP1 is the principal mediator of synthetic lethality, whereas PARP2 contributes disproportionately to hematologic toxicity. This has driven the development of PARP1-selective inhibitors, which aim to preserve antitumor efficacy while improving tolerability (Kim & Yu, 2025). Second, drug design must move beyond optimization of catalytic potency alone. Given the central role of PARP trapping in cytotoxicity, and its modulation in resistance, future compounds should be engineered to achieve an optimal balance of trapping efficiency, isoform selectivity, and safety profile, rather than maximal potency per se. This reflects a shift from enzyme inhibition

toward mechanism-informed pharmacologic design. Third, the emergence of resistance through HR restoration and fork protection supports the use of rational combination strategies, including co-targeting of ATR, WEE1, or other DNA damage response pathways, to either prevent resistance or exploit newly acquired vulnerabilities. In this context, PARPi should be viewed not as standalone agents but as components of a broader network-based therapeutic strategy (Giudice et al., 2022). Overall, these insights underscore that next-generation PARPi development must integrate structural biology, resistance mechanisms, and translational pharmacology, with particular emphasis on overcoming adaptive tumor responses.

PARP inhibitors induce cytotoxicity through catalytic inhibition and PARP1 trapping, leading to replication-fork collapse and double-strand break formation in homologous recombination-deficient (HRD) tumors. Resistance arises through multiple mechanisms, including restoration of homologous recombination (e.g., BRCA1/2 reversion, loss of 53BP1/Shieldin), replication-fork stabilization independent of HR restoration, and reduced drug effectiveness via altered PARP1 trapping, PARG-mediated PAR dynamics, or drug efflux (ABCB1). These mechanisms highlight the dynamic and adaptive nature of PARPi resistance and underscore the need for next-generation PARP1-selective inhibitors, functional biomarkers of HR status, and rational combination strategies targeting compensatory DNA damage response pathways.

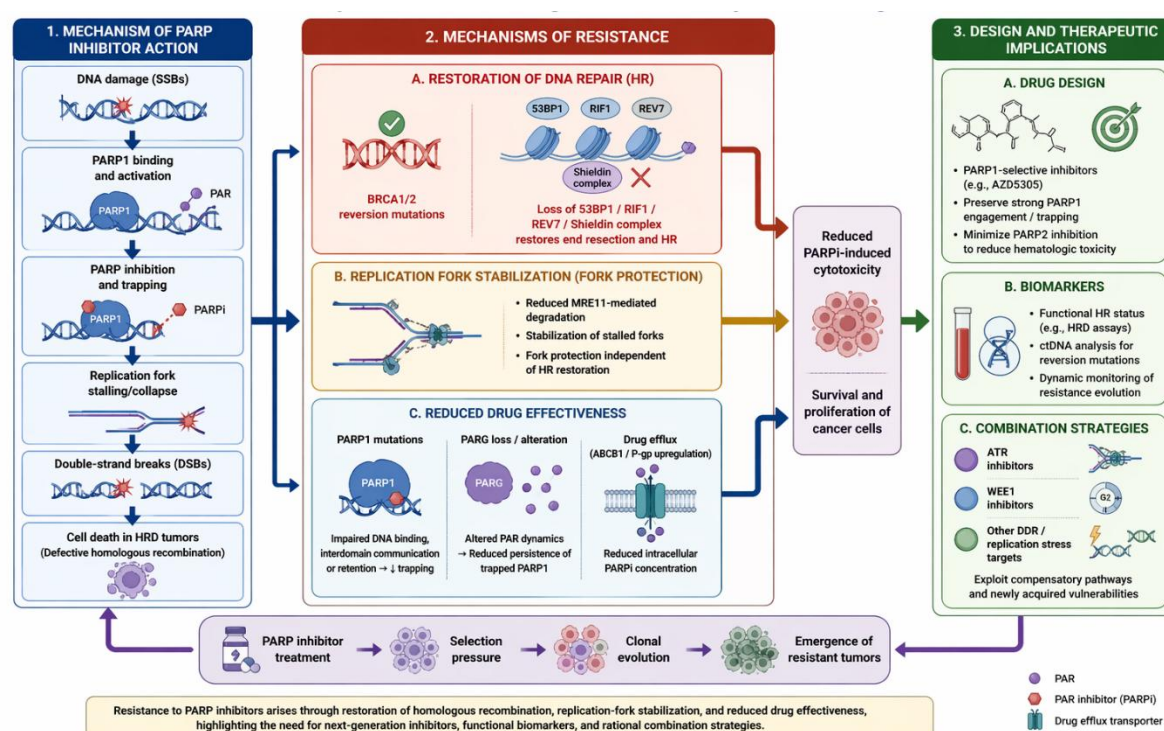


Figure 1 Integrated mechanisms of resistance to PARP inhibitors and their implications for therapeutic strategies (ChatGPT, 2026)

Challenges and Future Perspectives

Selectivity, Toxicity, and Resistance as Design Constraints

The current phase of PARP inhibitor (PARPi) development is no longer focused on demonstrating class efficacy, but on resolving the intrinsic trade-offs between potency, selectivity, toxicity, and durability of response. A central challenge lies in dissociating antitumor activity from systemic toxicity, particularly given that first-generation PARPi typically inhibit both PARP1 and PARP2. While PARP1 is the primary mediator of synthetic lethality in homologous recombination-deficient (HRD) tumors, PARP2 inhibition contributes

disproportionately to hematologic toxicity, especially in rapidly proliferating bone marrow compartments (Slade, 2020). This issue is compounded by the dual role of PARP trapping, which enhances tumor cytotoxicity but also increases toxicity in normal tissues. Preclinical evidence indicates that inhibitors with greater trapping potency do not necessarily confer superior therapeutic benefit at clinically tolerated doses, as increased cytotoxicity is offset by reduced tolerability (Hopkins et al., 2019). These findings highlight that therapeutic index, rather than maximal potency, should guide next-generation PARPi design. Consequently, there has been a strategic shift toward the development of PARP1-selective inhibitors, which aim to preserve PARP1-driven antitumor activity while minimizing PARP2-associated toxicity (Kim & Yu, 2025). However, selectivity alone is unlikely to fully resolve current limitations. Resistance remains a major and multifactorial constraint, arising through restoration of homologous recombination, replication-fork stabilization, reduced PARP1 trapping, alterations in PAR metabolism (e.g., PARG), and drug efflux mechanisms (Giudice et al., 2022; Li et al., 2020). Importantly, these mechanisms demonstrate that resistance is not solely a function of target inhibition failure, but reflects adaptive rewiring of DNA damage response networks and drug exposure dynamics. As such, future PARPi development must move beyond optimizing catalytic inhibition toward mechanism-informed design that anticipates and counteracts resistance pathways.

Translational role of computationally guided design

Computational approaches are increasingly central to addressing these challenges, particularly in enabling early-stage optimization of selectivity, binding mode, and scaffold diversity prior to synthesis. Methods such as molecular docking, molecular dynamics (MD) simulations, pharmacophore modeling, QSAR, and machine-learning-assisted screening allow for rapid prioritization of compounds and hypothesis-driven refinement of PARP1 ligand interactions (El Hassab et al., 2025). These approaches are particularly valuable in the context of PARP inhibitor design because they can incorporate structural differences between PARP isoforms, thereby facilitating the identification of PARP1-selective candidates. In addition, MD simulations provide insight into dynamic conformational behavior and binding stability, which are critical for understanding inhibitor effects beyond static active-site occupancy. However, the translational utility of computational methods remains constrained by several factors. Predictive accuracy depends heavily on structural model quality, force-field assumptions, and sampling limitations, and current approaches are not fully capable of capturing complex biological phenomena such as PARP trapping, replication-fork dynamics, or resistance evolution. As a result, computational predictions must be interpreted as probabilistic rather than definitive, and require systematic experimental validation. Future progress will therefore depend on integrated computational–experimental pipelines, in which *in silico* design is iteratively coupled with structural biology, medicinal chemistry, and functional assays. Such workflows are particularly important for developing next-generation PARPi that are not only selective and potent, but also optimized for therapeutic index and resilience to resistance mechanisms (Kim & Yu, 2025; Twala et al., 2025).

Discussion

The present review indicates that PARP inhibitors (PARPi) should no longer be regarded as a homogeneous class of catalytic inhibitors, but rather as a mechanistically diverse group of agents whose clinical behavior is shaped by the interplay between catalytic inhibition, PARP1 trapping, structural dynamics, and tumor-specific DNA repair dependencies (Illuzzi et al., 2021). This conceptual shift is important because it reframes PARPi from simple enzyme blockers to drugs whose efficacy and toxicity depend on broader pharmacologic and biologic context. A central insight emerging from the literature is that PARP trapping, rather than catalytic inhibition alone, is a major determinant of cytotoxicity. Although clinically approved

PARPi all compete with NAD⁺ at the catalytic site, they differ markedly in their ability to stabilize PARP–DNA complexes (Murai et al., 2012). This distinction is biologically important because trapping enhances replication-fork disruption and DNA damage accumulation, yet it does not translate linearly into clinical benefit. Preclinical evidence suggests that inhibitors with markedly different trapping capacities may achieve comparable antitumor effects at their respective maximum tolerated doses, implying that greater trapping potency can be offset by reduced tolerability. These observations challenge the simplistic assumption that stronger trapping is inherently advantageous and instead indicate that therapeutic index, rather than maximal trapping potency, is the more relevant determinant of clinical utility (Hopkins et al., 2019; Slade, 2020).

From a structural perspective, the high conservation of the NAD⁺-binding pocket explains both the catalytic potency of current PARPi and the persistent challenge of achieving meaningful isoform selectivity (Illuzzi et al., 2021). Although approved agents share a common active-site binding mode, scaffold architecture and peripheral interactions influence family-wide selectivity, trapping behavior, and off-target effects (Twala et al., 2025). This reveals an important limitation of first-generation design strategies: optimization within a highly conserved catalytic pocket inherently constrains selectivity and may contribute to shared toxicity liabilities and overlapping resistance mechanisms. Consequently, next-generation efforts have increasingly focused on exploiting less-conserved peripheral interactions and domain-specific features to improve selectivity and modulate PARP1 retention on DNA (Johannes et al., 2021; Kim & Yu, 2025). The clinical heterogeneity of PARPi reflects this pharmacologic diversity. Differences in trapping potency, selectivity, and off-target activity are associated with distinct toxicity profiles and therapeutic roles across ovarian, breast, prostate, and pancreatic cancers (Slade, 2020). However, interpretation of comparative efficacy remains inherently limited by variation in clinical trial design, biomarker stratification, disease context, and prior treatment exposure. Thus, currently available evidence does not support viewing PARPi as interchangeable agents; rather, they should be considered context-dependent therapeutics whose optimal use depends on the alignment between drug properties and tumor biology (Piombino & Cortesi, 2022).

Beyond biological efficacy, the clinical implementation of PARP inhibitors is also influenced by economic considerations. PARPi remain among the highest-cost targeted anticancer therapies, limiting accessibility in many low- and middle-income countries. Cost-effectiveness analyses suggest that their economic value depends largely on appropriate biomarker-guided patient selection, treatment duration, and healthcare reimbursement policies. Consequently, future precision oncology strategies should integrate both molecular and pharmacoeconomic evidence to maximize clinical benefit while improving healthcare sustainability. Resistance remains a major barrier to durable PARPi benefit and further emphasizes the adaptive nature of tumor response. The literature shows that resistance can emerge through several non-mutually exclusive mechanisms, including restoration of homologous recombination through BRCA1/2 reversion mutations, loss of end-resection suppressors such as 53BP1 or Shieldin, stabilization of stalled replication forks, reduced PARP1 trapping, alterations in PAR metabolism such as PARG loss, and increased drug efflux through transporters such as ABCB1 (Slade, 2020). Importantly, these mechanisms indicate that resistance is not simply a matter of reactivating DNA repair; it can also arise by reducing the cytotoxic consequences of PARP inhibition, especially at the level of replication stress and fork collapse (Li et al., 2020). This has direct implications for biomarker development. Genomic markers of HRD, including BRCA mutations and genomic scar signatures, may not reliably reflect the current functional repair state of tumors after treatment pressure. Accordingly, future biomarker strategies will need to incorporate more dynamic and functional

readouts of HR competency and replication-fork behavior (Giudice et al., 2022; Kim & Yu, 2025).

These mechanistic insights have direct implications for next-generation drug development. The emergence of PARP1-selective inhibitors represents a rational response to the dual challenges of toxicity and resistance. This design strategy is based on the view that PARP1 is the dominant mediator of synthetic lethality, whereas PARP2 contributes more substantially to hematologic toxicity. Compounds such as AZD5305 are therefore better understood not simply as improved analogues of earlier PARPi, but as a mechanistically informed redesign intended to preserve PARP1-dependent antitumor activity while widening the therapeutic window (Johannes et al., 2021). Nevertheless, selectivity alone is unlikely to overcome resistance driven by HR restoration or fork protection, suggesting that future PARPi development will require integration with rational combination strategies, particularly those targeting ATR, WEE1, or broader replication-stress pathways (Giudice et al., 2022; Kim & Yu, 2025).

In this context, computational methods have increasing translational importance. Structure-based and ligand-based approaches including docking, molecular dynamics, pharmacophore modeling, QSAR, and machine-learning-assisted screening can accelerate hit prioritization, scaffold diversification, and selectivity optimization. However, their utility remains bounded by model quality, force-field assumptions, and incomplete representation of complex biological processes such as PARP trapping, replication-fork destabilization, and resistance evolution (Li et al., 2020). Computational predictions remain dependent on the quality of structural data, force-field accuracy, sampling depth, and experimental validation. Consequently, these approaches should be regarded as complementary tools that guide hypothesis generation and lead optimization, rather than as substitutes for laboratory and clinical investigation. Therefore, computational strategies should not be viewed as substitutes for biological validation, but rather as key components of integrated design test refine pipelines that combine structural biology, medicinal chemistry, and functional testing to improve both mechanistic understanding and candidate selection (El Hassab et al., 2025; Kim & Yu, 2025; Twala et al., 2025).

Taken together, this review suggests that future progress in PARP-targeted therapy will depend on a multidimensional strategy that integrates structural pharmacology, resistance biology, biomarker development, and computationally guided design. The next generation of PARPi is therefore likely to be defined not merely by improved catalytic potency, but by enhanced isoform selectivity, better therapeutic index, and greater resilience to adaptive resistance mechanisms (Johannes et al., 2021; Kim & Yu, 2025; Slade, 2020). Such an approach will be essential for extending the benefit of PARP inhibition beyond current indications and for achieving more durable outcomes in biomarker-selected patients.

Conclusion

PARP inhibitors have evolved from simple catalytic inhibitors into a mechanistically complex and clinically diverse class of targeted therapies whose efficacy is governed by the interplay between PARP1 inhibition, PARP trapping, and tumor-specific DNA repair vulnerabilities. While current agents have demonstrated substantial benefit, particularly in homologous recombination-deficient cancers, their clinical utility is constrained by toxicity, incomplete selectivity, and the emergence of resistance. This review emphasizes that PARP1 trapping, therapeutic index, and resistance biology are now central determinants of treatment success, shifting the focus of drug development beyond catalytic potency alone. Emerging strategies including PARP1-selective inhibitors, functional biomarker development, and rational combination therapies targeting DNA damage response pathways represent critical directions for improving efficacy and durability of response. Finally, computationally guided

drug design offers significant translational potential but must be integrated with experimental and clinical validation to address the complexity of PARP biology. Future progress will depend on a multidimensional approach that combines structural insight, pharmacologic optimization, and adaptive resistance management to expand the therapeutic impact of PARP-targeted therapies.

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