Review

PROTACs in Action: Bridging Chemical Biology and Drug Discovery for Protein Degradation

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Abstract

Proteolysis-targeting chimeras (PROTACs) represent a transformative paradigm in drug discovery, fundamentally altering how we approach protein-targeted therapeutics by harnessing the ubiquitin-proteasome system for selective protein degradation. This comprehensive review examines the evolution of PROTAC technology from its conceptual origins in 2001 to its current clinical validation, with over 30 molecules in various stages of clinical development as of 2024. We explore the mechanistic foundations of PROTAC action, including the catalytic mode of protein degradation that distinguishes event-driven from occupancy-driven pharmacology, and examine the structural design principles governing heterobifunctional architecture, linker optimization, and E3 ligase recruitment strategies. The review analyzes current therapeutic applications across oncology, autoimmune diseases, and neurodegenerative disorders, highlighting the clinical success of compounds like ARV-471 and ARV-110 in Phase III trials. Critical challenges including physicochemical property optimization, resistance mechanisms, and bioavailability limitations are addressed alongside emerging solutions through computational design, artificial intelligence integration, and next-generation platforms including conditional degraders, nano-PROTACs, and expanded E3 ligase recruitment. Recent advances in molecular glue degraders, which represent 66% of FDA-approved degraders, and the development of precision medicine approaches through biomarker-guided therapy are also examined. The review concludes with an assessment of future directions, including E3 ligase repertoire expansion beyond the current focus on CRBN and VHL, targeting of previously undruggable proteins, and the integration of PROTAC technology with combination therapies and precision medicine strategies.

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1. Introduction

The concept of targeted protein degradation has emerged as one of the most significant paradigms shifts in modern drug discovery, offering unprecedented opportunities to eliminate disease-causing proteins through precise manipulation of cellular degradation machinery **(He *et al.* 2025; Yim *et al.* 2024)**. At the forefront of this revolution are proteolysis-targeting chimeras (PROTACs), heterobifunctional molecules that have transformed the traditional approach from protein inhibition to complete protein elimination **(Fan *et al.* 2025; Zhong *et al.* 2024)**. PROTACs represent a fundamental departure from occupancy-driven pharmacology, where drugs must continuously occupy their target to maintain therapeutic effect, to event-driven pharmacology, where a catalytic mechanism enables sustained protein degradation with transient drug exposure **(Faryal *et al.* 2026; Liu *et al.* 2022)**. Owing to this catalytic mechanistic feature, PROTACs could overcome the several limitations of small molecule inhibitors, specifically, the molecules which require deep binding pockets and high target occupancy and have the poor ability to address the non-enzymatic protein function **(Martin-Acosta and Xiao 2021; Nalawansha and Crews 2020)**.

Craig Crews and colleagues in 2001, developed a technology to demonstrate the proof-of-concept for inducing degradation of target protein using chimeric molecules **(Yao *et al.* 2022; Zou *et al.* 2019)**. Since then, the progress of PROTACs has shown exponential growth in both academic and clinical studies **(Bekes *et al.* 2022; Li *et al.* 2022b)**. The first clinical trials with PROTAC began in 2019, owing to the exponential growth as of 2024, there are 30 PROTAC that were identified and used in various stages of clinical trials, for instance, ARV-110 and ARV-471 were in Phase III trials **(Hakem *et al.* 2025; Xi *et al.* 2022)**. Current clinical studies reported that the therapeutic potential of PROTACs with minimal toxicity in limited dose in phase I trials for leading compounds dose range from 420-700 mg **(Kubryn *et al.* 2025; Wang *et al.* 2024b)**. Both androgen and estrogen receptor degrader ARV110 and ARV-471 shows significant success in metastatic castration-resistant prostate and breast cancer respectively and has been validated in clinical trials **(Hamilton *et al.* 2025; Ma and Zhou 2025)**. The significance of PROTAC technology significantly extends in several applications beyond their therapeutic approach, in the field of chemical biology **(Cai *et al.* 2025; Liu *et al.* 2026)**. It has been used for target validation, exploration of known undruggable proteins, and functional protein studies and have opened a new path for developing the effective drug molecules **(Crews 2010; Xie *et al.* 2023)**. PROTAC has the unique ability to reach the target protein and leads to their degradation with spatial and temporal control, hence understanding the protein function and disease mechanisms is very crucial **(Paiva and Crews 2019; Qi *et al.* 2021)**. The current review emphasizes the role of PROTAC technology in chemical biology and drug discovery, and how PROTAC bridges the gap between these domains. Also, we explore the basic mechanistic action of PROTAC, required strategies to design the effective molecules to target protein degradation in both research and clinical aspects **(Zhao *et al.* 2022)**. Recent advance studies including artificial intelligence computational applications and their integration in PROTAC design are also discussed, alongside the next generation platforms, current challenges and opportunities that define the future of transformative technology is also focused on this context **(Park and Jeon 2025).**

2. Mechanisms of Action

2.1. The Ubiquitin-Proteasome System

Protein degradation is significantly influenced by ubiquitin-proteosome system (UPS) hence, it may act as primary control mechanism. In addition, it also maintains the cellular homeostasis by removing the misfolded, surplus and damaged proteins **(Jia *et al.* 2025; Kandel *et al.* 2024)**. This complex mechanism offers the basic information on which PROTAC approach has effectively operates and making deep insights of -

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UPS mechanisms are highly crucial for developing effective degrader. UPS system has highly activated enzymatic cascade mechanism; there are three major classes of enzymes such as E1 activating enzymes, which initiates the process by binding with ATP-dependent activation of ubiquitin via strong high-energy thioester bond **(Melvin *et al.* 2013)**. This activates ubiquitin transferred to another class of enzyme E2 conjugating enzymes via trans-thiolation **(Stewart *et al.* 2016)**. Finally, E3 ubiquitin ligase enzyme enhances the transfer of ubiquitin from E2 to lysine residues on target proteins and producing the polyubiquitin chain which act as degradation signals **(Figure 1)**. Approximately, 600 E3 ligase enzymes were found in human, hence it representing as a largest and most diverse component in the UPS mechanism. This most diversity also being one of the challenges for developing effective PROTAC. These enzymes offer few unique properties like substrate specificity which helpful for determining which protein is target for degradation under specific conditions, besides, it also provides the opportunity to make to design therapeutically effective protein degrader **(Wang *et al.* 2025a)**.

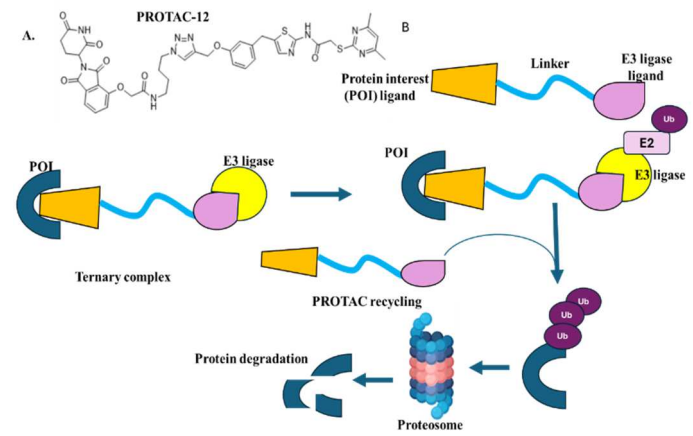

Figure1: Schematic representation of PROTAC-12–mediated targeted protein degradation. PROTAC-12 is a heterobifunctional small molecule composed of a ligand for the protein of interest (POI) linked to an E3 ubiquitin ligase recruiter through an optimized linker. Upon simultaneous binding to the POI and E3 ligase, PROTAC-12 induces ternary complex formation, bringing the target protein into close proximity with the ubiquitination machinery, including the E2 ubiquitin-conjugating enzyme. This interaction promotes transfer of ubiquitin (Ub) molecules to the POI, resulting in polyubiquitination. The polyubiquitinated target is subsequently recognized and degraded by the 26S proteasome, while PROTAC-12 is released and can participate in additional degradation cycles.

2.2. PROTAC Mechanism of Action

Owing to their binding nature PROTACs function as molecular bridges, it binds with their target proteins at the same time it also links the E3 ubiquitin ligase by which it bridges the two proteins and forms a ternary complex. this activated binding enables the E3 ligases to transfer ubiquitin molecules to the target proteins and leads the proteasomal degradation **(Ebadi *et al.* 2025; Li and Crews 2022)**. The formation of ternary complex is crucial for determining the efficacy of PROTAC, because this complex sufficiently stable to allow several ubiquitin transfers and maintaining their spatial orientation for optimal ubiquitination **(Dale *et al.* 2021; Kudo *et al.* 2025)**. The degradation mechanism involves several steps, including the binding of PROTAC with protein of interest or E3 ligases, then formation of binary and ternary complex via recruitment of other component and ubiquitination of target protein, proteasomal degradation, finally recycling of PROTAC **(Konstantinidou *et al.* 2019; Osman *et al.* 2025)**. All these steps have the potential points of optimization that should be considered in developing degrader **(Sincere *et al.* 2023; Wang *et al.* 2020)**.

2.3. Catalytic Mode of Action

The catalytic mechanism of PROTACS offers the number of advantages on the traditional inhibitors. Initially the event-driven nature of protein degradation that transient drug exposure which leads to constant effects as protein resynthesis is essential to restore their target levels. This feature offers the lower dosing frequencies and effectively diminished the side effects. Second, the catalytic mechanism enables sub-stoichiometric dose, where the concentration of PROTAC is very low, however it achieves the effective degradation **(Pettersson and Crews 2019)**. This pharmacological opportunity is helping to targeting the valuable proteins or achieving the systemic drug exposure even in lower dose. This nature offers an additional layer of selectivity, even it binds with multiple proteins degradation those targets can form ternary complexes with E3 ligase. Recent studies on the mechanism have also reported that PROTACs effectively overcome resistance mechanisms associated with traditional inhibitors such as target protein overexpression and mutation that can reduce binding of drug molecules **(Lai and Crews 2017)**.

3. Structural Design Principles

3.1. Heterobifunctional Architecture

Basically, the PROTAC composed of three essential components such as a ligand which bind the protein of interest, and ligand for E3 ubiquitin ligase and a linker molecule that connect these two ligand elements. This heterobifunctional design of PROTAC offers the simultaneous engagement of two major protein, which creating an artificial protein-protein interaction that would not happen naturally **(Bricelj *et al.* 2021)**. The ligand component that binds with target proteins often refers to warhead which can be derived from either known inhibitors, novel chemical compounds or natural ligands. The key requirements are very critical for binding and selectivity of the target protein, though it has less stringent than the traditional inhibitors **(Kim *et al.* 2025)**. This flexibility offers the opportunity to repurposing of weak binders or failed drug candidates as PROTACs. The component of E3 ligase recruits the cellular degradation machinery to the vicinity of target protein. Currently used E3 ligase effectively targets cereblon (CRBN), mouse double minute 2 (MDM2), von-Hippel-Lindau (VHL) and inhibitors of apoptosis proteins (IAPs). The presence of E3 ligase significantly influenced the impact of PROTAC efficiency, and selectivity **(Diehl and Ciulli 2022)**.

3.2. Linker Design and Optimization

Linker molecule is another crucial component of PROTAC; however, it is underappreciated component in the process of drug design. This linker acts as bridges between protein of interest and E3 ligase while preserving the binding affinity of these two ligand molecules and enhances the formation of ternary complex. this linker molecules and its optimization highly balancing the several parameters including, flexibility, composition, binding points and length **(Troup *et al.* 2020)**. The length of the linker optimization initially starts with longer and flexible linkers that gradually shortened to finding the optimal spacing for ternary complex. the typical length of the linker depends on the specific protein-protein interaction geometry that are essential for ubiquitination and can vary dramatically between the different PROTAC pairs **(Han 2020)**. Computational modelling and structural analysis are recently applied to design the linker and predict the optimal geometries. The chemical composition of these linkers also highly influences the PROTAC properties like permeability, solubility and metabolic stability **(Abeje *et al.* 2025)**. For instance, the polyethylene glycol (PEG) provides the excellent solubility in water, enhanced flexibility, but may compromise cell permeability **(Christoforou *et al.* 2025)**. Another linker, alkyl chains offer the enhanced membrane permeability, but the solubility is reduced. Hybrid linkers that incorporating the flexibility and rigid elements that offers the optimal balance of properties. Recently, the developing of

linker-free also emerged as a novel approach to overcome the limitation of traditional linker (Zhao *et al.* 2026).

3.3. E3 Ligase Recruitment Strategies

The selection of appropriate E3 ligases is a critical step in the design the effective PROTACs. Currently, the PROTAC designing highly relies on limited number of E3 ligase ligands with CRBN and VHL ligands that are highly dominating the clinical development. This concentration is essential for effective resistance mechanisms and need for E3 ligase repertories. For example, the CRBN-targeting PROTACs significantly used immunomodulatory drugs (IMiDs) like lenalidomide, thalidomide as E3 ligands, which offers the compact size, and well-characterized binding properties and synthetic accessibility. However, the expression of CRBN varies in several tissue and cell types, potentially limiting the therapeutic window of these PROTACs (Lee *et al.* 2022). In case of VHL-targeting PROTACs performed ligands based on hydroxyproline-containing peptides or their optimized small molecule mimetics. Typically, the VHL ligands results as larger PROTAC and offers the advantage in protein expression pattern and substrate compatibility. The designing of more compact VHL ligands is emerging the E3 ligases that recruitment strategies involved the development of ligases such as RNF114, DCAF11, and DCAF15. These efforts expand the druggable E3 ligase spaces and offer the effective and alternative option for PROTAC development (Diehl and Ciulli 2022).

3.4. Ternary Complex Formation and Stability

Ternary complex formation is the key determinant of PROTAC efficiency; hence the formation of stable and productive complex is crucial in this process. Mainly, this complex involves the thermodynamics and kinetic consideration that are not studied by individual binding interactions. The binding sites and formation of the ternary complex where it thermodynamically favours the individual binary complex also essential for effective degradation (Bai *et al.* 2021). The interaction of POI and E3 ligases components is important for PROTAC ternary complexes are revealed by structural analysis. These interactions are essential for providing the efficient binding energy and specificity to the ternary complex. the concept "Positive cooperativity" is the situation where the ternary complex is significantly enhanced via favourable protein-protein interactions which leads the more degradation (Scott *et al.* 2024). Conversely, the negative cooperativity occurs when the geometric constraints of the ternary complex and resulting the diminished degradation. The advanced computational approach has been employed to predict the geometries of ternary complex, thought it also have the significant limitation in modelling these complex multi-protein systems (Mostofian *et al.* 2023).

4. Computational and AI Approaches

4.1. Computational Design Frameworks

Owing to the complexity of PROTAC development leads the utilization of advanced computational approaches. In the traditional drug design approach, single protein targets are mainly focused and are insufficient for multi-protein system of PROTAC pharmacology (Kubryn *et al.* 2025). Development of PROTAC via computational approaches typically involves the number of steps such as molecular docking to find the binding site and interactions and molecular dynamics simulation to assess the stability of the complex, and free energy calculation to estimate the binding affinities (Tunjic *et al.* 2023). These computational approaches should be optimized to handle the limitation of PROTAC system including the formation of ternary complex and the nature of binding. The crystal structure of PROTAC ternary complex were employed in structure based- design applications to guide the rational design efforts (Danishuddin *et al.* 2023). These structures offer the critical understanding on protein-protein interactions that stabilize the formation of complexes and inform the linker optimization strategies. Though, there is limited number of ternary complexes is one of the significant disadvantages. Homology modelling and docking applications have been used to evaluate the geometries of PROTAC in absence of experimental structures (Hong *et al.* 2025; Rui *et al.* 2023).

4.2. Machine Learning Applications

In the PROTAC development, recent approaches like machine learning have been emerged as efficient tools for design the optimization, which offering the potential to identify the pattern in complex structures-activity relationships that are very difficult to distinguish via traditional approaches. These applications can incorporate the diverse data including the sequence, chemical structures and experimental degradation data. Another AI model deep learning approach also recently employed in the prediction of PROTAC degradation activity based on the chemical structure and target information (Danishuddin *et al.* 2023). These models offer the prediction accuracy of 70-80% in some cases and offers the valuable methods for virtual screening and lead optimization. Though, the size limitation of training datasets remains a significant limitation for model design. Application of reinforcement learning in the optimization of PROTAC structure via iterative design cycles (Wang *et al.* 2025b). These applications can explore the large chemical structure and identify the promising structures and maximize the predicted degradation efficiency while maintaining the favorable pharmaceutical properties. Another approach Graph-based neural network algorithm shows the efficacy in developing the promising PROTAC and represents the molecular structure of PROTAC and interactions with target proteins. This approach offers the opportunity to understand the relationship between complex and chemical structures and biological activity that are not be apparent via traditional approaches (Li *et al.* 2022a).

4.3. Predictive Modeling and Virtual Screening

Predictive modelling is another major computational approach highly applied to predictive models for PROTAC activity; these models are highly focused on the degradation efficiency, pharmaceutical properties and selectivity based on the chemical structures of target protein. The successful models effectively accelerated the development of PROTAC by reducing the requirement for extensive synthesis and testing. The prediction of novel PROTAC structure via virtual screening applications from large chemical libraries (Liu *et al.* 2025). These methods combine the molecular docking and pharmacophore prediction and machine learning algorithms to predict the effective molecules for experimental validation. The integration of artificial intelligence and experimental applications has been used for the development of active learning applications to optimize the PROTAC structure via iterative cycles of prediction, synthesis and testing (Koirala *et al.* 2025). These methods effectively diminish the number of compounds that need to optimization the structures. Recent advanced applications like transfer-based neural networks specifically employed for PROTAC generation. These methods predict the novel PROTAC structures with optimized pharmacokinetic properties via reinforcement learning demonstrating the efficacy of AI-driven development approaches (Luo *et al.* 2025).

5. Therapeutic Applications and Clinical Development

5.1. Oncology Applications

In the field of oncology applications, PROTAC is used as promising therapeutic molecules that accounting for most clinical programs. for instance, the ARV-110, is the first PROTAC in the clinical trials that act as estrogen and androgen receptor degraders. It effectively targeting nuclear hormone receptors and used for the treatment of metastatic castration-resistant prostate cancer (Anaya *et al.* 2025). The compound effectively

encouraging efficiency in phase II trials, with specific benefits observed in AR mutated patients that conder resistance to traditional therapies. Hence the success of ARV-110 has been validated the PROTAC application for clinical development. ARV-471 is another sex hormone receptors degrader, specially targets the estrogen receptor which is also applied in phase III trials for ER-positive breast cancer (Table 1). The compound has effectively enhanced the efficiency of PROTAC compared to the conventional estrogen receptor degraders **(Snyder *et al.* 2025)**. Beyond the hormone receptors, PROTAC has been applied in several oncology targets including transcription factors, protein kinases and epigenetic regulators. Recently developed PROTACs that are used in clinical trials effectively targets the BRD4, BTK and other oncology targets, which demonstrate the wide range of approaches. For successful completion of phase I trial compounds such as CFT8634 (BRD9 degrader) and NX-2127 (BTK degrader) require further validation **(Fan *et al.* 2025)**.

Table 1. Currently used PROTACs in Clinical Trials for various Diseases

Drug	Target	Status	Timeline
BGB-16673	BTK	Phase III	Phase III launched Apr 2025
ARV-110	AR	Phase II	Phase I/II initiated earlier (circa 2019-2021)
ARV-766	AR	Phase II	Phase 1/2 started: September 2, 2021
GT-20029	AR	Phase II	Phase I (US/China): Dosing first subject Feb 2022
KT-474	IRAK4	Phase II	Phase I: Study start Feb 23, 2021
PRT3789	BTK	Phase II	Phase II start: ~2024–2025
CFT1946	BRAF	Phase II	Phase II start: 2023–2024
ASP-3082	KRAS G12D	Phase I	Phase I start: 2024
ABBV-101	BTK	Phase I	Phase I start: 2022–2023
ARV-393	ER	Phase I	Phase I-first human start: Q2 2024
BG-60366	EGFR	Phase I	NA
HRS-1358	AR	Phase II	Phase II start: 2023–2024

5.2. Autoimmune and Inflammatory Diseases

In the context of autoimmune and inflammatory disease PROTAC application shows significant progress specially for targets which involved in immune cell activation and signaling. Due to their ability to achieve the target protein provide significant advantages over traditional immunosuppressive approaches. For instance, KT-474 is specifically designed to target IRAK4 and has been used in Phase II clinical trials for the treatment of hidradenitis suppurativa and atopic dermatitis **(Galla *et al.* 2024)**. The dose dependent studies of this compound reported that it significantly degrades the IRAK4 in peripheral blood mononuclear cell and efficiently reduce the inflammatory cytokines production in patients. The pharmacodynamics studies with PROTAC observed the protein degradation and downstream effects beyond the detectable drug levels. This phenomenon is highly responsible for the catalytic mechanism of action of PROTAC and offers the effective therapeutic advantages including the dose-reducing frequency and sustained efficacy. The expression E3 ligases specifically in tissues may offers the new way for targeting the immune cells same time it protects the other tissues. This tissue-specific feature may reduce the systemic immunosuppression associated with traditional therapies **(Agarwal *et al.* 2025)**.

5.3. Neurodegenerative Diseases

Neurodegenerative disorders are another promising field where the application of PROTAC is significantly employed to eliminate the aggregated or misfolded proteins that are highly responsible for neurodegeneration. Tau-targeting PROTAC is one of the widely accepted one to address the tauopathies including Alzheimer's diseases **(Zhou *et al.* 2025)**. These PROTACs selectively target the hyperphosphorylated tau species and leads its degradation without affecting the normal tau function which represents a precision approach in the field of neurodegenerative disease management. In context of Huntington's disease, PROTAC applications are effectively focused on selective degradation of mutant huntingtin proteins, but it is preserving the wild-type function **(Yao *et al.* 2024)**. This approach offers the wide range of therapeutic benefits and avoiding the toxicity associated with complete removal. However, in neurodegenerative disease, blood-brain barrier is one of the significant challenges while delivering the PROTACs to the central nervous system. Hence, the designing an effective brain-penetrant PROTACs are highly required for careful optimization of other physicochemical properties and may benefit from advanced delivery strategies **(Mohapatra *et al.* 2024)**.

5.4. Clinical Development Challenges

The clinical development of PROTACs has the potential to targets the proteins with selectivity, though it has unique challenges that differ from the traditional small molecule drugs. Owing the complexity of protein degradation, the finding of novel approaches is highly required for biomarker development, dose selection and safety assessment. To address the challenges in PROTAC pharmacology, recent advanced studies such pharmacodynamic modelling has been applied, this models efficiently quantify the target occupancy, deconvolve the degradation from inhibition effects and find the downstream pharmacodynamics responses **(Gioiello *et al.* 2025)**. Biomarker advancement for PROTAC clinical trials expects techniques to observe target protein levels and degradation kinetics. This may include the development of pharmacodynamic assays, imaging approaches, and circulating biomarkers that can specify real-time information about drug activity Several chemical biology studies used PROTACs as facilitators for functional integration of proteins and revealing the phenotypes. PROTACs demonstrate the direct translation of chemical biology to clinically relevant therapeutics **(Liu *et al.* 2024)**. Several case studies have been conducted with AR degrader, ER degrader and IRAK4 degrader which demonstrate the mechanistic understanding of PROTAC degradation and formation of ternary complex. Understanding the dual role of PROTACs as functional biology probes and therapeutic candidates, reinforcing the special position at the interface of chemical biology and drug discovery **(Nunes *et al.* 2019)**.

6. Challenges and Limitations

6.1. Physicochemical Property Challenges

Owing to the heterobifunctional feature of PROTAC offers the molecules that violate traditional drug-like criteria, provides the significant limitations for pharmaceutical development **(Cai *et al.* 2025)**. Typically, the molecular weight of PROTACs ranges from 700-1500 Da, but, over the 500 Da limit suggested by Lipinski's Rule of Five **(An and Fu 2018; Antermite *et al.* 2023)**. The increased size of the PROTACs is due to the higher number of hydrogen bond donors and acceptors, which also increase the polar surface area and increase the log P values **(Syahputra *et al.* 2025)**. The violation of drug-likeness criteria may influence the practical challenge for PROTAC development, and adequate oral bioavailability **(Edmondson *et al.* 2019)**. Recent studies reported that identification of specific physicochemical parameters which correlates with oral absorption, which is important for limiting the exposed hydrogen bond donors **(Hornberger and Araujo 2023; Rej *et al.* 2024)**. According to Beyond Rule of Five (bRo5) PROTACs minimize the hydrogen bond donors, molecular flexibility, and achieving appropriate polarity ratios **(Egbert *et al.* 2019; Ermondi *et al.* 2021)**.

6.2. Oral Bioavailability Optimization

In order to improve the oral bioavailability of PROTAC, several strategies have been developed, such as modification of structural aspects and enhanced the cellular permeability. The creation of intracellular hydrogen bonds that can reduce the molecular polarity in membrane environments **(Abeje *et al.* 2025)**. The chameleonic behavior of PROTAC adopting several conformations in aqueous membrane permeability. In addition, prodrug strategies also been applied to improve the PROTAC bioavailability following absorption. This approach has reported the significant increase the oral bioavailability for several PROTACs. Formulation approaches like nanosuspensions, amorphous solid dispersion and lipid-based system have been developed to overcome the solubility limitations and significantly improve the oral absorption of PROTACs with maintain their degradation activity **(Zhao and Dekker 2022)**.

6.3. Resistance Mechanisms

Drug resistance mechanisms is one of the challenges that limits the clinical success of PROTACs and limits the therapeutic efficacy. These resistance mechanisms are diverse and may alter the target protein expression, and function of E3 ligase or proteosome activity. Alteration or mutant in target protein significantly reduce the binding affinity of PROTAC by which it enhances the resistance mechanism **(Kim *et al.* 2022)**. However, the constraint for only temporary binding may make this mechanism less problematic for PROTAC compared to traditional compounds. Additionally, PROTAC can target multiple sites on the same protein which give the opportunity to overcome single-site resistance mutations. E3 ligase downregulation or mutation also have been observed as resistant mechanisms in therapeutic approaches **(Bouvier *et al.* 2024)**. The development PROTAC that targeting alternative E3 ligases offers the strategies to overcome this resistance. Dysfunction and proteosome inhibition also confer the PROTAC resistance by preventing the degradation of ubiquitinated proteins Even though the PROTACs used as effective targeted therapy, resistance the remains a biologically predictable and challenging rather than a solved problem. But the mechanism of resistance is multifactorial which significantly involving alterations of target protein, cellular adaptation and E3 ligase machinery **(Danishuddin *et al.* 2023)**.

7. Future Directions and Emerging Technologies

7.1. Next-Generation PROTAC Platforms

The next-generation PROTAC Platform application provides the advances in both design strategy and technological advancement. Conditional PROTACs have emerged as emerging technologies to achieve improved selectivity and reduced off-target effectiveness via spatial and temporal control of protein degradation activity. The incorporation of light-activated PROTAC with photo caging groups used to remove the specific wavelength of light and enabling precise control over degradation timing and location **(Wang *et al.* 2024a)**. This approach also used to require temporal control of protein. For instance, the hypoxia-responsive PROTAC offers another conditional application, that utilizing linkers are that effectively cleaved under low-oxygen conditions under tumor microenvironments. Cell-penetrating PROTAC incorporates the incorporating peptides to enhance cellular uptake. This approach significantly the enhance the tissue specificity, particularly with limited vascular access or high drug efflux ability, in addition to this it effectively addresses the fundamental challenges **(Yim *et al.* 2024)**.

7.2. Nano-PROTAC Platforms

Nano-PROTAC platforms is the combination of nanotechnology with PROTAC development for processing the enhanced drug delivery, improved pharmacokinetics and diminished toxicity. Nano-PROTAC platform composed of several approaches such as encapsulation, conjugation and development of self-assembling PROTAC nanostructures. Liposomal formulation of PROTAC also increased the bioavailability and distribution while reducing the systemic exposure. This formulation can also offer the sustained reducing systemic exposure **(Wu *et al.* 2025)**. Also, this formulation releases the PROTAC and may enables enhanced accumulation in target tissues via passive or active targeting mechanisms. Polymeric nanoparticles provide the additional supports for PROTAC delivery with controlled release of kinetic and incorporate targeting ligands for improved selectivity. Another approach, semi-responsive polymers release PROTAC in response to specific cellular condition offers an advanced application to selective drug delivery **(Moon *et al.* 2023)**.

7.3. Artificial Intelligence and Machine Learning

The integration of artificial intelligence and machine learning application significantly transform the PROTAC design and optimization. The integration of advanced applications provides the potential to accelerate the identification novel design strategies, improve success rates that may be apparent via traditional approaches. These models explore wide range of chemical spaces and propose structure that optimize the multiple objectives simultaneously, including degradation activity, selectivity and pharmaceutical properties **(Lin *et al.* 2026)**. Deep learning application in the production of PROTAC have achieved 70-80% of the accuracy and provides the valuable tools for virtual screening and lead optimization. The continued development of these applications combined with selective datasets are expected to further enhancement of accuracy. Reinforcement learning approaches also been used to optimize the PROTAC structures via iterative design cycles for identifying successful compounds **(Han and Sun 2023)**.

7.4. Expanding E3 Ligase Diversity

The selection of E3 ligase in the PROTAC development represents the crucial steps in this field. Around 300 genes were encoded E3 ligases in the human genome, the current focus on handful of well-characterized ligases were significantly used for degradation machinery. High-throughput screening application has been used for the identification E3 ligase ligands via success rates remain low owing to the challenging nature of the protein-protein interaction **(Liu *et al.* 2023)**. Heterobifunctional screening libraries is the alternative screening approaches that used DNA-encoded libraries to find the E3 ligase binders. Development of tissue-specific E3 ligases strategies offers the enhanced selectivity for PROTAC therapy, this approach effectively controls the differential expression patterns of E3 ligases, where the expression was controlled by external stimuli, represent another approach to achieving the selective protein degradation **(Michaelides and Collie 2023)**.

7.5. Precision Medicine and Biomarker Development

The production of efficient precision medicine approaches with application of PROTAC guided biomarkers now beginning to emerge. These approaches mainly involve the finding of patient population most likely to benefit from specific PROTAC treatment based on the biomarker profiles, both genetic and proteomic markers **(Rutherford and McManus 2024; Zhang *et al.* 2025)**. This biomarker based PROTAC treatment directly quantifies the target protein level and assesses the pathway modulation and downstream response. Hence the development of standardized biomarkers is crucial for effective and successful PROTAC therapy **(Kamaraj *et al.* 2024)**. Production of personalized PROTAC therapies based on individual patients requires some characteristics features including mutation in target protein or E3 ligase expression profiles. This strategy significantly enhances the therapeutic efficacy while diminishing the toxicity **(Mancarella *et al.* 2023; Wang *et al.* 2025c)**.

7.6. Combination Therapies

The application of combination therapy with PROTACs is recently has attention as an important strategic direction for maximizing therapeutic effectiveness while diminishing the drug resistance. These approaches significantly increase the therapeutic values with traditional therapeutics and multiple PROTACs targeting different proteins degradation **(Sincere *et al.* 2023)**. Mechanistic studies of combination of PROTAC with kinase inhibitors revealed that the combination therapy can overcome the drug resistance and enhanced the therapeutic efficacy. This approach highly addresses the cellular reprograming that occurs during chronic PROTAC exposure, and multitarget PROTAC can simultaneously degrade the multiple proteins and disease networks than single-target proteins **(Burke *et al.* 2022)**.

8. Conclusion

The application of PROTAC for targeted protein degradation has undergone remarkable transformation since 2001. As of now around 30 compounds were in clinical trials due to their conceptual framework and clinically validated therapeutic modality. The present review has emphasised the fundamental mechanism of action and function of PROTAC, the strategic approach to develop the promising target specific molecules. To expand the utility of this approach in current therapeutic approach, the understanding of mechanistic foundations of PROTAC action and exploitation of the UPS is highly required. This information offers the catalytic approach for elimination of misfold proteins that provides the distinct advantages over conventional therapeutic approaches. The event-driven approach of protein degradation offers the sustainable therapeutic efficacy from transient drug exposure and improve the safety profile as well. Hence, the design principles of PROTAC application recently matured significantly with advanced linker chemistry, E3 ligase recruitment strategies. The integration of recent advancement like artificial intelligence and machine learning approaches is highly accelerating the finding of effective and optimal PROTAC structures and diminishing the empirical burden of traditional optimization approaches. Although these successes, there is significant challenges in the development of PROTAC, due to their limitation in physicochemical property, oral bioavailability, and the resistance mechanism. Hence there is need more focus on this to address these challenges via innovative approaches including developing conditional degraders, expansion of E3 ligase diversity, and nano-PROTAC platforms. The future technology integration in PROTAC with next-generation platforms may offers the enhanced selectivity, pharmaceutical properties, and expanded therapeutic applications. The integration specific and unique strategies of medicine and combination therapies may expand the therapeutic potential of targeted protein degradation. In future, the development of PROTAC should have great attention specifically, the three approaches like, E3 ligase, incorporation of AI-driven application and implementing precision medicine and exploring combination therapy application to improve the clinical benefit. PROTACs have been applied in various therapeutic approaches, but still their translation to the clinical phases has several obstacles. The key challenges like optimization of pharmacokinetic and penetration into the tissues, and minimizing off-target degradation is also should be addressed to offer the safe, efficient and widely accessible PROTAC therapeutics. The bridging of two different domains such as chemical biology and drug discovery via PROTAC application also represents a paradigm shift in how we approach protein targets and therapeutic intervention. It creates a new path and opportunities for addressing the undruggable protein while providing the powerful tools for understanding the function of protein in health and disease.

9. Disclosure Statements

9.1. Author Contribution

RV: Data collection, literature review, manuscript preparation along with Conceptualization, supervision, manuscript writing and revision. The corresponding author have read and approved the final manuscript.

9.2. Declaration of Generative AI

No generative artificial intelligence (AI) or AI-assisted technologies were used in the preparation, writing, analysis, or interpretation of this review article. The content presented is the original work of the authors, developed through critical analysis and synthesis of the scientific literature.

9.3. Ethics approval (for clinical/animal studies)

Not applicable. This review article is based solely on the analysis and synthesis of previously published literature and does not involve any new studies with human participants or animal subjects. Therefore, ethical approval from an institutional review board or ethics committee was not required.

9.4. Informed Consent Statement

Not applicable. This review article does not involve human participants, patient data, or identifiable personal information; therefore, informed consent was not required.

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No new data were generated or analyzed in this study. All information presented in this review article is derived from previously published literature, and the relevant sources are cited within the manuscript.

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