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Review Article

Discovery, Structural Elucidation, and De Novo Engineering of Plant-Derived Molecular Glues for Targeted Degradation of Previously Undruggable Proteins

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ABSTRACT

Targeted protein degradation (TPD) has changed the logic of small-molecule drug discovery from occupancy-driven inhibition toward event-driven elimination of disease-associated proteins. Molecular glue degraders (MGDs) are a particularly distinctive branch of TPD because a single, relatively small molecule can create or stabilize a productive protein–protein interaction between an E3 ubiquitin ligase and a neo-substrate, leading to ubiquitination and proteasomal degradation. This mechanism can expose proteins that lack conventional catalytic pockets or high-affinity ligandable sites to pharmacological intervention. Natural products provide an unusually rich source of chemically complex, stereochemically defined and evolutionarily selected scaffolds capable of remodeling protein–protein interfaces. Several natural and nature-derived systems already demonstrate the underlying principle: plant hormones such as auxin and jasmonate promote E3-dependent substrate recruitment in plants, whereas natural-product or natural-product-derived compounds such as rapamycin, FK506, cyclosporin A, and immunomodulatory drugs illustrate chemically induced proximity in mammalian systems. However, the direct discovery of plant-derived molecular glue degraders for human disease targets remains comparatively underdeveloped. This distinction is central to the present review.

This review integrates four previously separated areas: phytochemistry, structural biology, medicinal chemistry, and targeted protein degradation. We first define molecular glues mechanistically and distinguish degradative glues from non-degradative protein–protein interaction stabilizers. We then examine natural molecular glue paradigms, with special emphasis on plant signaling systems as biological proof-of-principle and on natural-product scaffolds as chemical starting points. The review next evaluates discovery strategies—including untargeted metabolomics, activity-guided fractionation, phenotypic screening, E3-dependent degradation assays, chemoproteomics, thermal proteome profiling, CRISPR resistance mapping, DNA-encoded libraries, and multi-omics target deconvolution. Structural elucidation and ternary-complex analysis are discussed using X-ray crystallography, cryo-electron microscopy, NMR, biophysical measurements, molecular dynamics, and artificial-intelligence-assisted structural prediction. Finally, we propose a translational framework for the de novo engineering of plant-derived molecular glues and identify major scientific bottlenecks, including dereplication, low natural abundance, target selectivity, E3-ligase availability, resistance, pharmacokinetics, and the difficulty of predicting glue activity from binary binding alone. We argue that the most promising future direction is not simply to search plants for “active compounds,” but to treat plant chemical space as a source of chemically encoded proximity-inducing mechanisms and to systematically connect natural-product structures with E3 ligases, neo-substrates, and disease-relevant protein networks.

KEYWORDS: molecular glues; targeted protein degradation; natural products; phytochemistry; medicinal chemistry; chemical biology; E3 ubiquitin ligases; protein–protein interactions; ternary complexes; proteasome; undruggable proteins; structural biology; metabolomics; de novo design.

INTRODUCTION

Conventional small-molecule pharmacology has historically been dominated by the assumption that therapeutic efficacy requires sufficiently strong occupancy of a functional binding site. This paradigm has produced an enormous pharmacopeia, but it also creates a fundamental limitation: many disease-relevant proteins do not possess deep, selective and druggable pockets. Transcription factors, scaffolding proteins, regulatory adaptors and intrinsically disordered proteins may nevertheless be biologically essential while remaining difficult to inhibit directly. Targeted protein degradation provides a different solution by converting recognition of a protein into a catalytic-like cellular event: recruitment of the target to endogenous degradation machinery followed by ubiquitination and proteasomal removal [1–4].

Within TPD, molecular glue degraders are mechanistically distinguished from heterobifunctional PROTACs. A PROTAC normally contains two ligands connected by a linker and therefore supplies two recognition elements. A molecular glue is typically monovalent and induces or stabilizes a new protein–protein interaction using a single small molecule. Productive degradation depends on the geometry, cooperativity and dynamics of the ternary complex rather than simply on high-affinity binary binding [5–9]. The conceptual significance is substantial: a glue can create a new surface recognition event and thereby recruit a protein that was not previously considered ligandable.

In molecular biology and chemical biology, **molecular glues (MGs)** are a class of small molecules that promote or stabilize interactions between two proteins that would otherwise interact weakly or not at all. Unlike conventional small-molecule inhibitors, which generally bind to functional or allosteric pockets on a target protein to modulate its activity, molecular glues can induce **proximity-mediated changes in protein function**, most notably by promoting the degradation of selected target proteins. One of the major advantages of this strategy is its potential to address proteins that have historically been considered **"undruggable."** Many disease-associated proteins lack well-defined binding pockets or possess structural features that make them difficult to modulate using conventional inhibitors. Rather than directly blocking the activity of such proteins, molecular glues can redirect them toward cellular protein-degradation machinery.

A major cellular pathway involved in molecular-glue-mediated degradation is the **ubiquitin–proteasome system (UPS)**. This system regulates protein homeostasis by tagging selected proteins with the small protein ubiquitin, thereby targeting them for degradation by the proteasome. In a typical molecular-glue mechanism, the small molecule promotes the formation or stabilization of an interaction between a **target protein** and an **E3 ubiquitin ligase**. The resulting ternary complex creates a novel or enhanced protein–protein interface. The E3 ligase can then facilitate the ubiquitination of the target protein, marking it for recognition and subsequent degradation by the proteasome.

The process can be conceptually summarized in four stages:

1. **Cellular entry:** The molecular glue enters the cell and reaches its relevant intracellular compartment.
2. **Ternary-complex formation:** The molecule promotes or stabilizes an interaction between the target protein and an E3 ubiquitin ligase.
3. **Ubiquitination:** The recruited E3 ligase facilitates the attachment of ubiquitin chains or ubiquitin signals to the target protein.
4. **Proteasomal degradation:** The ubiquitinated target is recognized and degraded by the proteasome.

Thus, molecular glues do not necessarily function simply by occupying a conventional active site. Instead, they can **reprogram protein–protein interactions** and exploit the cell's endogenous degradation machinery to eliminate disease-associated proteins. he conceptual distinction between molecular glues and conventional inhibitors is important. Traditional inhibitors generally act by binding to a functional site on a protein and preventing its biochemical activity. Their effectiveness therefore depends substantially on the existence of an accessible and sufficiently well-defined binding pocket.

Molecular glues, in contrast, can operate through a fundamentally different pharmacological principle: **induced or stabilized protein proximity**. By promoting an interaction between a target protein and a component of the cellular degradation machinery, they can lead to the elimination of the target rather than merely suppressing its activity. This distinction is particularly relevant for proteins whose functions depend on protein–protein interactions, scaffolding, transcriptional regulation, or other mechanisms that are difficult to inhibit using conventional small molecules. The development of molecular glues represents an emerging frontier in drug discovery, particularly in oncology and other diseases in which aberrant or

otherwise difficult-to-drug proteins play a central role. Their ability to induce selective protein degradation expands the range of cellular proteins that may be pharmacologically manipulated. An important example is the **thalidomide class of immunomodulatory drugs (IMiDs)**. Thalidomide and related compounds interact with **cereblon (CRBN)**, a substrate receptor within an E3 ubiquitin ligase complex. This interaction alters the substrate specificity of the ligase and promotes the ubiquitination and degradation of particular proteins, including transcription factors relevant to hematological malignancies. Related compounds such as **lenalidomide** and **pomalidomide** have subsequently become important therapeutic agents, particularly in the treatment of multiple myeloma and other hematological cancers.

The historical case of thalidomide is particularly notable because its molecular mechanism was elucidated decades after its initial clinical use. Its subsequent characterization as a molecular-glue-like mechanism helped establish the broader concept that small molecules can alter the substrate specificity of E3 ligases and thereby induce selective protein degradation. Unlike early examples in which molecular-glue activity was discovered retrospectively, contemporary drug-discovery programs increasingly aim to **identify or design molecular glues intentionally**. Structure-based drug design, phenotypic screening, proteomics, chemical genetics, and computational approaches are being integrated to discover compounds capable of inducing productive interactions between target proteins and E3 ligases. Molecular glues should also be distinguished from **proteolysis-targeting chimeras (PROTACs)**. Both technologies exploit the ubiquitin–proteasome system to achieve targeted protein degradation, but their molecular architectures differ substantially. PROTACs are typically bifunctional molecules containing a ligand for the target protein, a ligand for an E3 ligase, and a chemical linker connecting the two. Molecular glues, by contrast, are generally smaller monovalent compounds that induce or stabilize the interaction between the target and the E3 ligase without requiring such a preassembled bifunctional architecture.

This difference can have important pharmacological consequences. Because molecular glues are often smaller and can operate through **event-driven pharmacology**, a single molecule may promote the degradation of multiple copies of a target protein. Consequently, molecular glues can exhibit substantial cellular activity at relatively low concentrations, although their pharmacological behavior depends strongly on the specific molecular system.

Despite their therapeutic potential, the discovery and optimization of molecular glues remain technically challenging. Conventional high-throughput screening approaches often focus on identifying compounds that bind directly to a single protein. In molecular-glue discovery, however, the desired phenotype may depend on the formation of a productive **ternary complex** involving the molecular glue, the target protein, and an E3 ligase.

Consequently, the relevant chemical space can be difficult to explore using conventional binding assays alone. In addition, the biological activity of a molecular glue depends not only on binary binding affinity but also on the geometry, cooperativity, stability, and cellular context of the resulting ternary complex.

Computational approaches, including **molecular dynamics simulations, molecular docking, free-energy calculations, structural modeling, and machine-learning-based methods**, may therefore provide valuable tools for understanding and predicting molecular-glue activity. However, accurately predicting ternary-complex formation remains challenging because of the highly context-dependent nature of protein–protein interactions.

Molecular glues are also potentially relevant to **nanomedicine and nanotoxicology**. Their therapeutic efficacy depends not only on target selectivity but also on their distribution, cellular uptake, intracellular localization, and exposure. Inadequate selectivity can result in unintended degradation of proteins, potentially producing **on-target toxicity in healthy tissues or off-target pharmacological effects**. Nanoparticle-based delivery systems may provide a complementary strategy for improving the pharmacokinetic and biodistribution properties of molecular-glue-based therapeutics. By engineering nanoparticles to preferentially accumulate in specific tissues or cell types, it may be possible to enhance local drug delivery while reducing systemic exposure. Such approaches remain an active area of investigation and require careful evaluation of nanoparticle-associated toxicity, immune responses, intracellular trafficking, and drug-release characteristics. An important question is whether naturally occurring compounds can function as molecular glues. Nature represents an exceptionally rich source of structurally diverse small molecules, many of which modulate protein function and protein–protein interactions. Nevertheless, naturally occurring compounds that fulfill the strict mechanistic definition of a molecular glue—namely, compounds that promote or stabilize a productive interaction between a target protein and a protein-degradation machinery component—appear to be relatively uncommon and remain challenging to identify.

Natural products may nevertheless provide valuable **chemical and mechanistic inspiration** for molecular-glue discovery. Plant-derived alkaloids, terpenoids, polyphenols, and other specialized metabolites can modulate signaling pathways through diverse mechanisms, including direct protein binding, allosteric

modulation, and alteration of protein–protein interactions. Although these compounds should not automatically be classified as molecular glues, their mechanisms can provide useful insights into how small molecules can remodel protein interaction networks. For example, **phytoestrogens** can interact with human estrogen receptors and alter receptor-mediated signaling. Although this mechanism does not necessarily involve molecular-glue-mediated protein degradation, such compounds illustrate how naturally occurring small molecules can modulate protein conformations and cellular signaling pathways. Natural products may also serve as a source of structural motifs for **biomimetic drug design**. Plants and microorganisms have evolved extensive chemical repertoires for defense, communication, competition, and adaptation. Some of these metabolites interact with highly conserved protein families or perturb protein–protein interaction networks. Systematic investigation of such natural products could therefore reveal chemical scaffolds capable of inducing previously unrecognized protein interactions. Combining natural-product libraries with phenotypic screening, proteomic profiling, structural biology, and computational modeling may provide an effective strategy for identifying novel molecular-glue-like compounds.

However, extrapolating molecular-glue activity from one biological system to another requires caution. E3 ubiquitin ligases, substrate repertoires, protein abundance, and intracellular environments vary substantially among organisms and cell types. Consequently, a compound that modulates protein interactions in a plant or microorganism cannot necessarily be expected to induce analogous protein degradation in human cells.

Molecular glues represent a paradigm shift from conventional **"target inhibition" toward targeted protein degradation and cellular protein-homeostasis engineering**. By inducing or stabilizing interactions between disease-associated proteins and components of the ubiquitin–proteasome system, these small molecules can potentially eliminate proteins that have historically been difficult or impossible to target pharmacologically. The convergence of molecular-glue chemistry with **structural biology, computational modeling, proteomics, nanomedicine, and natural-product research** may substantially expand the therapeutic landscape. In particular, the integration of molecular glues with targeted delivery technologies could provide new opportunities to improve tissue selectivity and reduce unwanted systemic effects. At the same time, challenges related to molecular selectivity, ternary-complex prediction, pharmacokinetics, resistance mechanisms, and toxicity must be carefully addressed before the full therapeutic potential of this emerging modality can be realized.

Natural products are especially relevant to this concept. Their three-dimensionality, stereochemical density, conformational constraint, heteroatom patterning and evolutionary origin give them a chemical character that is often difficult to reproduce using flat synthetic libraries. Importantly, nature already uses small molecules to control protein proximity. Auxin promotes the interaction between the plant F-box protein TIR1 and Aux/IAA transcriptional repressors, while jasmonate signaling uses COI1 and JAZ proteins to form a hormone-dependent degradation system. These systems demonstrate that a small molecule can function as a molecular "glue" in an E3-centered degradation pathway [10–12].

The therapeutic field subsequently revealed analogous principles in mammalian systems. Thalidomide and its analogues bind cereblon and alter substrate specificity, leading to degradation of neo-substrates including IKZF1 and IKZF3. Arylsulfonamides such as indisulam and E7820 recruit RBM39 to DCAF15. CR8 and related compounds demonstrate that a kinase inhibitor can acquire a new glue function through a solvent-exposed chemical group that creates a DDB1–CDK12–cyclin K interface [13–18]. These discoveries transformed molecular glues from mechanistic curiosities into a drug-discovery modality.

Despite this progress, the intersection of plant natural products and human targeted protein degradation remains incompletely developed. A recent body of literature has begun to catalog natural-product-derived molecular glues and to emphasize the importance of plant signaling molecules as conceptual blueprints. However, most naturally occurring molecular glues are not human therapeutic degraders; many stabilize or inhibit protein complexes without inducing degradation, and many classic examples originate from microorganisms rather than higher plants [19–22]. Therefore, a scientifically rigorous research program must distinguish three concepts: (i) plant-derived natural products that act as molecular glues in plants; (ii) natural products or natural-product-derived scaffolds that modulate mammalian PPIs; and (iii) genuinely plant-derived molecular glue degraders that recruit a human E3 ligase to a disease-relevant neo-substrate. The third category is the major opportunity identified by this review.

Scope and Literature-Review Strategy

This article is structured as a critical narrative review with emphasis on primary mechanistic studies, structural studies and recent reviews published through October 2026. Literature was surveyed using combinations of the terms "molecular glue," "molecular glue degrader," "targeted protein degradation," "natural product," "plant natural product," "phytochemical," "E3 ligase," "ternary complex," "protein–protein interaction," "auxin," "jasmonate," "gibberellin," "de novo design," "metabolomics," "chemoproteomics," and "undruggable protein." Priority was given to primary studies providing direct

evidence of ternary-complex formation, ubiquitination, proteasome dependence, structural information, target identification or genetic validation. Reviews were used to establish conceptual frameworks and identify additional primary literature.

Because the central hypothesis is prospective rather than fully established, the review deliberately separates demonstrated biology from proposed translational strategies. In particular, plant hormones are discussed as mechanistic precedents rather than as ready-made human drugs, and natural-product molecular glues are not automatically classified as degraders unless degradation has been experimentally demonstrated. This distinction is essential for avoiding overstatement in a rapidly evolving field.

Molecular Glue Degraders: Mechanistic Foundation

From occupancy-driven inhibition to event-driven pharmacology

Classical inhibitors generally require sustained target occupancy. Molecular glue degraders instead operate by changing the interaction landscape of a cell. A glue can bind an E3 ligase, a target protein, or an existing protein surface and stabilize a productive ternary complex. Once the target is positioned appropriately, the E3 machinery can transfer ubiquitin to accessible lysine residues on the recruited protein. Polyubiquitination then enables recognition and destruction by the 26S proteasome. The small molecule can subsequently dissociate and participate in another degradation cycle, producing an apparent catalytic or substoichiometric pharmacological behavior [5,6,23].

Binary affinity is not sufficient

A central lesson of molecular-glue biology is that the affinity of the binary ligand–protein interaction does not reliably predict degrader activity. The productive species is the ternary complex. Cooperativity can be quantified conceptually by comparing ternary-complex formation with the affinities of the individual binary interactions. Positive cooperativity occurs when the presence of one protein increases the effective affinity of the other protein for the ligand-bound partner. Structural complementarity at the neo-interface can compensate for weak ligand affinity and can generate highly selective degradation [7–9].

The E3 ubiquitin ligase as a pharmacological entry point

The E3 ligase is the functional bridge between molecular recognition and proteolysis. Clinically and experimentally important systems include CRL4–CRBN, CRL4–DCAF15 and CUL4–DDB1-associated pathways. Nevertheless, these represent only a fraction of the human ubiquitin landscape. Expanding the repertoire of recruitable E3 ligases is therefore a major objective for next-generation degraders. Recent work has also explored recruitment beyond canonical E3 substrate receptors, demonstrating that other components of the ubiquitin–proteasome system can potentially be pharmacologically exploited [24].

Nature as a Blueprint for Molecular Glue Chemistry

Plant hormones as endogenous molecular glues

Plants provide unusually clear mechanistic examples of ligand-induced degradation. Auxin is perceived by the TIR1/AFB family of F-box proteins. Structural studies demonstrated that auxin binds within the TIR1 pocket and promotes recruitment of an Aux/IAA degron, thereby converting a relatively weak protein–protein interaction into a productive substrate-recognition event [10]. The molecular glue analogy is particularly powerful because the hormone is not simply an inhibitor of TIR1: it creates a new recognition surface that favors the E3–substrate complex.

Jasmonate signaling follows a related logic. The bioactive jasmonoyl-isoleucine promotes formation of a COI1–JAZ co-receptor complex, leading to ubiquitination and degradation of JAZ repressors. Structural work demonstrated that the hormone is effectively trapped between receptor and degron and that inositol phosphate contributes to the assembled receptor complex [11]. These systems show that nature can evolve highly selective small molecules whose principal function is to control protein proximity rather than to inhibit an enzyme active site.

Gibberellin signaling provides a third paradigm. Gibberellin binds the GID1 receptor and promotes recognition of DELLA proteins, which are then recruited to an SCF-type E3 ligase system and degraded. Structural studies have established how hormone-dependent recognition produces a stepwise stabilization of the receptor, substrate and E3 machinery [12,25]. Collectively, auxin, jasmonate and gibberellin demonstrate that plant metabolism contains multiple evolutionary solutions to ligand-controlled substrate recruitment.

Natural-product molecular glues beyond plants

Several canonical molecular glues are natural products or closely related natural-product scaffolds. Rapamycin, FK506 and cyclosporin A form ternary complexes that inhibit signaling proteins rather than induce proteasomal degradation. Rapamycin bridges FKBP12 and mTOR, FK506 bridges FKBP12 and calcineurin, and cyclosporin A bridges cyclophilin and calcineurin. These systems were discovered before the modern molecular-glue terminology and illustrate that chemically induced proximity can generate pharmacology without degradation [19,20].

Fusicoccane natural products and related compounds provide another important class of PPI stabilizers. Fusicoccin A stabilizes

interactions between 14-3-3 proteins and client phosphoproteins, demonstrating how a natural scaffold can occupy an interface and strengthen an otherwise transient interaction. Although such compounds are not degraders, they are highly informative for medicinal chemistry because they reveal the structural logic required to recognize shallow protein surfaces [26,27].

The transition from natural glue chemistry to degraders is illustrated by thalidomide and its derivatives. Thalidomide itself is not a plant metabolite; it is a synthetic drug. However, its mechanism established a general principle in which a small molecule changes the substrate specificity of an E3 ligase. Lenalidomide and related immunomodulatory drugs induce degradation of IKZF1 and IKZF3 through CRBN. These studies demonstrate how chemical recognition of a shallow receptor pocket can be translated into recruitment of a new protein substrate [13,28].

From Natural Molecular Glues to Human Disease Targets

Cereblon and the immunomodulatory drug paradigm

The CRBN system is the clearest demonstration that a small molecule can reprogram E3 substrate specificity. The identification of cereblon as a primary thalidomide target and the subsequent discovery that lenalidomide and related molecules promote IKZF1/IKZF3 degradation provided a mechanistic explanation for clinically important pharmacology [28,29]. The broader lesson is that molecular-glue activity can emerge from relatively small structural modifications that change the surface properties of a ligand-bound E3 receptor.

DCAF15 and RBM39

Indisulam and related aryl sulfonamides revealed a second major mechanism. These compounds recruit RBM39 to DCAF15, causing ubiquitination and proteasomal degradation of RBM39 and related substrates. Structural studies showed that the compound occupies a shallow pocket at the DCAF15 surface and creates a complementary interface for the RBM39 RRM2 domain. Importantly, the target does not need to possess a conventional small-molecule binding pocket [15,16].

Cyclin K and the CR8 paradigm

CR8 demonstrated that a pre-existing target-binding compound can be converted into a glue degrader. CR8 binds CDK12 and exposes a pyridyl group that promotes association with DDB1, positioning cyclin K for degradation. Structural studies revealed an extensive DDB1–CDK12 interface and showed how chemical modification of a solvent-exposed region can create a gain-of-function glue phenotype [17,30]. Subsequent work demonstrated that related scaffolds can be systematically engineered and that ternary-complex structures can guide the conversion of kinase inhibitors into degraders [31].

Why Plant-Derived Chemical Space Is Attractive

Plant specialized metabolism is a vast source of structurally diverse compounds, including alkaloids, terpenoids, phenylpropanoids, flavonoids, lignans, coumarins, polyketides and steroidal metabolites. For molecular-glue discovery, diversity of shape may be more important than sheer compound count. A useful glue must present a molecular surface capable of making simultaneous contacts with two proteins, and rigid or three-dimensional natural-product scaffolds may be advantageous for this purpose.

Plants also provide an unusually rich biological context for induced proximity. Hormone signaling, defense responses and environmental adaptation frequently depend on regulated protein turnover. Thus, plant metabolites have evolved in environments where small molecules must control protein networks rather than merely inhibit isolated enzymes. This does not imply that a plant metabolite will automatically function in human cells; rather, it suggests that plant chemical space contains evolutionary examples of the underlying recognition strategy.

The most defensible research hypothesis is therefore not "plants contain many human molecular glue degraders," but rather: "plant chemical space contains chemically encoded proximity-inducing scaffolds that can be discovered, characterized and re-engineered to engage human protein-degradation machinery." This hypothesis is consistent with the growing literature on natural-product molecular glues and with recent reviews identifying plant molecular-glue biology as an underexploited source of chemical inspiration [19–22].

Discovery Pipeline for Plant-Derived Molecular Glue Degraders

Stage I: plant selection and chemical-space design

A rational discovery campaign should avoid random selection of medicinal plants. Candidate species should be prioritized using chemical diversity, ethnopharmacological evidence, metabolomic richness, availability, sustainable collection, taxonomic novelty and prior evidence of unusual protein-level phenotypes. The most informative collection strategy would include multiple organs, developmental stages and stress conditions because specialized metabolite profiles can change dramatically with tissue and environment.

Stage II: extraction, fractionation and dereplication

Sequential extraction using solvents of different polarity, followed by chromatographic fractionation, can generate

chemically tractable libraries. LC–HRMS/MS should be coupled to molecular networking and dereplication so that known compounds are recognized early. The major failure mode of classical phytochemistry—spending months isolating a known flavonoid—is particularly costly in a molecular-glue program. Dereplication should therefore be treated as a primary quality-control step rather than an optional analytical exercise.

Stage III: functional screening

The preferred primary screen should measure a biological event related to protein stability rather than a generic cytotoxicity endpoint. Candidate approaches include fluorescent degradation reporters, HiBiT or luminescent protein reporters, quantitative immunoblotting, proteome-wide degradation profiling, and E3-dependent cellular assays. A true degrader hit should show concentration-dependent loss of the protein of interest, dependence on the relevant degradation machinery, and preferably a rapid time course consistent with induced proximity.

Stage IV: target and E3 deconvolution

Once a degradation phenotype is identified, the next problem is mechanistic deconvolution. CRISPR knockout or resistance screens can identify the responsible E3 components, while affinity-based methods, chemoproteomics, thermal proteome profiling and proteome-wide quantitative mass spectrometry can identify molecular targets. Orthogonal methods are important because a single target-identification method can produce misleading binary-binding assignments.

Stage V: ternary-complex validation

The defining experiment is demonstration that the small molecule changes the interaction between the E3 machinery and the neo-substrate. Suitable methods include AlphaScreen, TR-FRET, NanoBRET, SPR, ITC, biolayer interferometry and pull-down experiments. Mutational analysis should identify residues that are essential for glue activity. Ideally, the biochemical interaction should correlate with cellular degradation and genetic resistance.

Stage VI: structural elucidation

Structural biology is central to the transition from discovery to engineering. X-ray crystallography remains exceptionally powerful for high-resolution ternary complexes, while cryo-EM can be advantageous for large E3 assemblies or flexible complexes. NMR can provide information on ligand binding, conformational change and weak interactions. Structural data should be integrated with mutagenesis and biophysical measurements rather than interpreted in isolation.

Stage VII: de novo engineering

After identification of a natural scaffold, synthetic chemistry should explore the exposed surface of the molecule rather than merely maximize binary affinity. The objective is to tune ternary-complex cooperativity, degradation rate, selectivity and cellular exposure. Analogue design should therefore be guided by the ternary interface, solvent exposure, conformational dynamics and degradation phenotype. The CR8 and cyclin K literature provides a compelling precedent for this strategy [17,30,31].

Structural Principles of Plant-Derived Molecular Glue Design

A successful glue must satisfy several simultaneous constraints. First, the scaffold must be able to engage one protein without sterically blocking the second. Second, the ligand-bound surface must present complementary chemical features to the recruited protein. Third, the resulting ternary complex must position the substrate so that the E3 ligase can efficiently transfer ubiquitin. Fourth, the complex must remain sufficiently stable to support productive ubiquitination but not necessarily so stable that ligand recycling becomes impossible.

The concept of a “neo-interface” is particularly important. In a conventional inhibitor, medicinal chemists optimize ligand–target contacts. In a molecular glue, the newly created protein–protein interface can contribute more to selectivity than the original ligand pocket. Structural complementarity, hydrogen-bond networks, hydrophobic packing, electrostatics, water-mediated interactions and conformational adaptation can all contribute to cooperativity. Recent structural and computational studies emphasize that water networks and protein flexibility can materially affect ternary-complex stability [32].

This creates a fundamental opportunity for natural products. A rigid, three-dimensional scaffold may act as an interface-organizing element, while strategically positioned substituents can be used to tune the second protein contact. The medicinal-chemistry objective is therefore not simply “higher affinity,” but “better productive proximity.”

Analytical and Computational Technologies

Metabolomics and molecular networking

Untargeted LC–HRMS/MS enables comprehensive profiling of plant extracts and can be integrated with molecular networking to group structurally related metabolites. Bioactivity can then be mapped onto molecular families. This is particularly valuable when activity arises from a low-abundance compound or when closely related analogues provide a natural SAR series.

Proteomics and chemoproteomics

Quantitative proteomics can establish whether a candidate selectively depletes one or a small number of proteins. Chemoproteomics can identify direct binding partners, whereas genetic resistance screens can reveal the cellular machinery required for degradation. The combination of these datasets is more informative than any individual method and is especially important because molecular glues can produce unexpected neo-substrates.

AI-assisted structure and design

Artificial intelligence can accelerate several stages of the workflow, including protein-structure prediction, ligand pose generation, molecular interaction analysis, library prioritization and multi-parameter optimization. However, AI predictions should be treated as hypothesis-generating rather than definitive evidence. Molecular glue activity is highly context-dependent, and ternary complexes may involve induced fit, water networks and conformational ensembles that are difficult to infer from static docking alone.

Molecular dynamics and free-energy approaches

Molecular dynamics can help distinguish stable from transient interfaces and can reveal changes in protein flexibility caused by a glue. Free-energy calculations may eventually support ranking of analogue series, but their accuracy depends strongly on the quality of structural models and treatment of solvent and conformational entropy. Experimental validation remains essential.

Candidate Plant Chemical Classes

A plant-focused discovery program should initially prioritize chemical classes that offer high three-dimensionality and known protein-interaction pharmacology. These include steroidal and triterpenoid scaffolds, diterpenoids, sesquiterpenes, alkaloids, lignans, coumarins and selected flavonoid-derived architectures. The objective is not to assume that any class is a glue, but to identify which members produce E3-dependent ternary interactions.

Chemical class	Why attractive	Key risk	Recommended strategy
Terpenoids / triterpenoids	High 3D character; extensive protein surfaces	Lipophilicity, promiscuity	Fractionation + proteomics + structural SAR
Steroids	Rigid scaffolds and defined stereochemistry	Off-target nuclear receptors	Phenotypic degradation screens + selectivity profiling
Alkaloids	Diverse heteroatom patterns and receptor interactions	Cytotoxicity / CNS liabilities	Targeted chemoproteomics
Lignans / neolignans	Rigid aromatic frameworks; PPI potential	Metabolic instability	Semi-synthesis and stability profiling
Coumarins	Compact aromatic scaffolds amenable to derivatization	Often enzyme-focused activity	Interface-oriented analogue design
Flavonoids	Abundant and structurally diverse	Frequent nonspecific redox effects	Aggressive dereplication and orthogonal assays
Plant hormones / analogues	Direct evolutionary precedent for glue-like degradation	Limited human E3 compatibility	Mechanistic blueprint rather than direct therapeutic assumption

Experimental Criteria for Calling a Compound a Molecular Glue Degrader

A rigorous nomenclature framework is essential. A compound should not be labeled a molecular glue degrader merely because it lowers protein abundance. At minimum, the evidence should establish: (1) a defined protein of interest; (2) dependence on ubiquitin/proteasome function; (3) involvement of an E3 ligase or degradation machinery; (4) concentration-dependent degradation;

(5) a mechanistic interaction between the E3 and the neo-substrate that is enhanced by the compound; and (6) genetic or structural evidence supporting the proposed interface. Ideally, ternary-complex formation and positive cooperativity should be measured directly.

Evidence level	Minimum evidence	Interpretation
Level 1	Protein loss after treatment	Potential degrader; mechanism unknown
Level 2	Proteasome/E3 dependence	Likely ubiquitin–proteasome degrader
Level 3	E3–target interaction enhanced by compound	Molecular-glue mechanism supported
Level 4	Mutational/structural validation of neo-interface	Mechanistically established glue
Level 5	Selective cellular phenotype + in vivo validation	Translational degrader candidate

Previously Undruggable Proteins: What Can Be Targeted?

Molecular glues are particularly attractive for proteins that lack deep binding pockets. Transcription factors and regulatory proteins are obvious candidates because the glue mechanism can recognize a protein surface or degron rather than a catalytic site. However, "undruggable" should be used cautiously: many proteins once considered undruggable become tractable when their structural, conformational or cellular context is understood. A more precise term is "previously difficult-to-drug or inadequately ligandable proteins."

Candidate targets should ideally satisfy three criteria: strong disease causality, a measurable degradation phenotype, and a plausible surface that can participate in an E3-mediated neo-interface. Cancer targets are attractive because degradation can be connected directly to proliferation phenotypes, but neurodegenerative, inflammatory, infectious and rare genetic diseases may also benefit from this modality.

Target category	Potential rationale	Key challenge
Transcription factors	Often lack classical catalytic pockets	Surface selectivity and tissue context
Scaffolding proteins	Network control through protein abundance	Large/disordered interfaces
Oncogenic regulators	Complete elimination may outperform inhibition	Resistance and toxicity
Mutant proteins	Allele-specific surfaces may exist	Mutant/wild-type discrimination
Viral proteins	Essential viral factors may be recruited to host degradation	Host toxicity and delivery
Neurodegeneration-associated proteins	Persistent protein removal may be advantageous	Brain exposure and long-term safety

Major Challenges

Natural-product supply and dereplication

Many promising natural products occur at very low abundance. Reproducible isolation, authentication, scalable cultivation and semisynthesis can become bottlenecks. Dereplication must therefore be performed early, and total or semi-synthesis should be considered once a biologically compelling scaffold is identified.

Selectivity and neo-substrate risk

Molecular glues can produce unexpected degradation of proteins that were not originally intended as targets. While this can be a liability, it can also reveal new biology. Comprehensive proteomics and genetic validation are therefore essential during lead optimization.

E3-ligase limitation

A glue cannot function without a compatible degradation pathway. Human cells contain hundreds of E3 ligases, but only a subset are currently exploited pharmacologically. Expanding the accessible E3 repertoire is arguably as important as discovering new ligands.

Resistance

Resistance can arise through mutations in the glue-binding surface, neo-substrate degron, E3 machinery, ubiquitin pathway or proteasome. Structural understanding of the ternary interface can help anticipate resistance mechanisms and design second-generation compounds.

Pharmacokinetics and tissue exposure

Natural-product scaffolds can have poor solubility, metabolic instability or transporter liabilities. Conversely, their conformational complexity can sometimes generate favorable selectivity. Optimization must therefore balance ternary activity with physicochemical and pharmacokinetic properties rather than treating either domain independently.

Proposed Integrated Research Framework

Based on the literature reviewed here, we propose a seven-layer discovery framework: (1) plant and tissue selection; (2) untargeted metabolomic mapping; (3) phenotype-guided fractionation; (4) E3-dependent degradation screening; (5) chemoproteomic and genetic target deconvolution; (6) structural elucidation of the ternary complex; and (7) de novo chemical engineering and translational validation. Each layer should generate information that feeds backward into the previous layers. For example, discovery of an E3-dependent phenotype should trigger targeted metabolomics to identify the responsible molecular family, while structural information should redefine the synthetic library around the neo-interface.

A particularly powerful implementation would create a "Plant Molecular Glue Atlas" containing standardized data for source species, tissue, extraction method, molecular formula, structure, target protein, E3 ligase, ternary-complex evidence, degradation kinetics, selectivity profile, structural coordinates and synthetic analogues. Such an atlas could convert scattered phytochemical observations into a reusable drug-discovery resource.

Future Perspective: From Phytochemistry to Programmable Proteostasis

The long-term significance of plant-derived molecular glue research extends beyond discovering individual natural products. The deeper objective is to understand whether natural-product chemical space can be systematically translated into programmable control of human proteostasis. If a plant metabolite can be converted into a molecular glue that selectively recruits a disease protein to a human E3 ligase, the molecule effectively becomes a chemical instruction for the cell: recognize this protein, ubiquitinate it, and remove it.

The conceptual leap is therefore from "natural product pharmacology" to "programmable protein fate." This requires a change in experimental culture. Phytochemistry must move beyond isolation and structural identification; medicinal chemistry must move beyond binary affinity; structural biology must focus on ternary interfaces; and chemical biology must connect molecular events to cellular protein networks. The resulting discipline would sit at the intersection of natural-product chemistry, medicinal chemistry, proteomics, structural biology and synthetic biology.

The most ambitious version of this program would seek general design rules that allow a natural-product scaffold to be transformed into a predictable degrader for a selected class of disease proteins. Such rules might include quantitative relationships among scaffold topology, ligandability of an E3 receptor, ternary-complex cooperativity, degron geometry, ubiquitination probability and cellular exposure. Achieving predictive control over these variables would represent a major advance in chemical biology.

Importantly, the field should resist premature claims. Plant-derived molecular glue degraders for human disease targets remain an emerging hypothesis-driven frontier rather than an established technology. The strongest scientific position is to use the exceptional mechanistic examples already provided by nature—especially auxin, jasmonate and other induced-proximity systems—as blueprints, then build an experimental pipeline

capable of discovering whether analogous chemistry can be redirected toward human E3 ligases and therapeutic targets.

CONCLUSIONS

Molecular glues have changed the conceptual boundaries of small-molecule drug discovery by demonstrating that a compound does not always need to inhibit a protein directly. Instead, it can create a new protein–protein interaction that changes the fate or function of a target. Natural products provide compelling precedents for this principle, while plant signaling pathways offer especially clear examples of ligand-controlled E3 recruitment and protein degradation.

The central opportunity identified in this review is the systematic exploration of plant chemical space for molecular glue activity directed toward human disease biology. Such a program should integrate metabolomics, phytochemical fractionation, chemoproteomics, genetic screening, structural biology, computational modeling and synthetic chemistry. The ultimate goal should not be the discovery of another nonspecific cytotoxic phytochemical, but the identification and engineering of a molecule for which the complete causal chain can be demonstrated: plant metabolite → ternary complex → E3 recruitment → ubiquitination → selective protein degradation → disease-relevant phenotype.

If this framework succeeds, plant natural products could move from being predominantly viewed as sources of conventional enzyme inhibitors and cytotoxic agents to being recognized as a reservoir of chemically encoded proximity-inducing mechanisms. The most important scientific advance would not be a single molecule, but a generalizable strategy for converting natural chemical diversity into programmable protein degradation.

Expanded Critical Analysis and Research Roadmap

Conceptual distinction between molecular glues, PROTACs, and PPI stabilizers

Molecular glues should be understood as one branch of the broader chemically induced proximity (CIP) landscape. PROTACs are usually bifunctional molecules in which a target-binding ligand and an E3-ligase ligand are connected by a linker. Molecular glues, by contrast, are generally monovalent and achieve proximity by altering the interaction surface of one or both proteins. Nondegrading molecular glues constitute a third category in which the induced interaction changes signaling, localization, or complex assembly without routing a protein to the proteasome. The distinctions are mechanistically important because discovery, optimization, and pharmacokinetic behavior differ among the three modalities [5–9,37,38].

For a plant-derived discovery program, the distinction is particularly useful. A natural product that stabilizes a 14-3-3/client interaction is scientifically valuable but should not be called a degrader. Likewise, a phytohormone that promotes degradation in a plant system is a molecular-glue precedent but is not automatically a human therapeutic degrader. A rigorous review therefore needs a three-axis classification: molecular mechanism (induction versus stabilization), biological outcome (degradation versus nondegradation), and evolutionary/chemical origin (plant endogenous, other natural product, semisynthetic derivative, or fully synthetic compound).

Evolutionary logic of plant molecular glues

Plant signaling provides an unusually rich natural laboratory for studying induced proximity because many environmental and developmental decisions are controlled by regulated protein turnover. Auxin, jasmonate, and gibberellin systems show that small molecules can act as conditional molecular bridges between receptors and transcriptional regulators. The ligand does not simply turn an enzyme on or off; it changes the composition and stability of a protein complex. This logic is remarkably close to the mechanism later exploited pharmacologically in mammalian molecular glue degraders [10–12,21].

From an evolutionary perspective, these systems suggest that the ability to recognize shallow protein surfaces and create cooperative ternary complexes is not an artificial property invented by medicinal chemistry. It is a recurring solution to biological signaling. This observation supports a “nature-inspired” strategy in which plant specialized metabolites are treated as candidates for proximity pharmacology, while acknowledging that the receptor and degradation machinery may need to be different in human cells.

The most productive research question is therefore not whether plants contain compounds that resemble thalidomide or CR8. Rather, it is whether the structural principles that make plant signaling ligands effective—preorganization, complementary surface contacts, induced fit, conditional affinity and controlled receptor-substrate geometry—can be transferred to human E3 systems. Such a question naturally connects phytochemistry to medicinal chemistry and structural biology.

Natural-product scaffolds and the three-dimensionality hypothesis

A recurring hypothesis in natural-product drug discovery is that three-dimensional molecular architecture can access protein surfaces that are poorly represented in conventional screening libraries. Molecular glue chemistry may amplify this advantage because the ligand can function as an interface-organizing element rather than a classical active-site inhibitor. Rigid

polycyclic scaffolds, stereochemically dense terpenoids, alkaloids, lignans, and steroid-like architectures may therefore provide useful starting points for neo-interface formation.

This hypothesis must nevertheless be tested rather than assumed. High three-dimensionality can also increase lipophilicity, nonspecific membrane association, metabolic instability, or promiscuous protein binding. Consequently, plant-derived glue discovery should be coupled from the beginning to selectivity measurements, physicochemical profiling, proteome-wide degradation analysis and synthetic tractability assessment.

Discovery by phenotype rather than affinity

Classical natural-product discovery often begins with a biochemical target assay. For molecular glues, this strategy can miss the most interesting compounds because the active molecule may bind weakly or not detectably to either protein in isolation. The productive interaction can emerge only in the presence of the complete ternary system. Consequently, phenotype-first screening is particularly attractive: the primary readout should be selective depletion of a protein, followed by mechanistic deconvolution of the E3 and target.

A practical screening cascade is therefore: plant extract → fraction → cellular degradation phenotype → proteasome dependence → E3 dependence → target confirmation → ternary-complex assay → structural elucidation. This sequence is deliberately different from conventional enzyme-inhibitor screening. It allows weak-binary/high-ternary compounds to survive the first stages of discovery.

The CR8 study provides a useful conceptual precedent because the compound was identified by integrating drug sensitivity with E3-component expression across cancer cell lines, followed by cellular and genetic validation. The study demonstrated that database mining and functional genomics can reveal glue mechanisms that would be difficult to predict from binary affinity alone [17].

Metabolomics-guided molecular glue discovery

Untargeted metabolomics should be positioned at the center of the phytochemical workflow. Each plant extract can be represented as a multidimensional chemical fingerprint using LC–HRMS/MS. Molecular networking can group related ions and facilitate the recognition of metabolite families. When degradation activity is measured for each chromatographic fraction, chemical features can be correlated with biological activity. This creates a phenotype-to-feature map that can be iteratively refined as compounds are purified.

An especially powerful approach would combine molecular networking with quantitative bioactivity. Features whose abundance tracks degradation potency across fractions can be prioritized for isolation. Once a candidate is identified, synthetic analogues can be added to the network to determine whether activity is associated with a specific structural motif. This transforms natural-product chemistry from a one-compound-at-a-time process into a data-rich discovery platform.

Dereplication is equally important. Databases such as GNPS and other spectral resources can help identify known metabolites early. A high-value molecular glue program should devote considerable effort to recognizing known compounds before isolation. Novelty should be established at both the chemical and mechanistic levels: a known compound with a new E3/neosubstrate mechanism may be scientifically important, whereas a structurally novel compound with nonspecific cytotoxicity may be less valuable.

Target and E3 deconvolution: an orthogonal evidence model

Target identification should never depend on a single experimental platform. Molecular glue mechanisms are particularly susceptible to misleading binary assignments because the direct ligand-binding partner may be the E3 receptor, the target protein, an adaptor, or an induced interface involving more than one component. An orthogonal evidence model should combine at least three of the following: quantitative proteomics, chemoproteomics, CRISPR resistance screens, loss-of-function E3 profiling, CETSA or thermal proteome profiling, affinity enrichment, mutagenesis, and direct biophysical interaction assays.

Genetic resistance is especially informative. If mutation of a surface residue on the target or E3 eliminates degradation without eliminating protein expression, the mutation can define the neo-interface. Such mutations can then be tested biochemically and structurally. This creates a causal chain from genotype to ternary complex to protein degradation to phenotype.

Proteome-wide degradation profiling should be incorporated early rather than only during preclinical development. A compound that degrades ten proteins may still be useful, but its mechanism and therapeutic window are different from those of a highly selective degrader. Unexpected neosubstrates may also reveal opportunities for repurposing or suggest that the molecule is acting through a broader cellular mechanism.

Structural elucidation: from natural product to ternary-complex map

Structural characterization should proceed in stages. First, the isolated natural product should be assigned unambiguously by high-resolution mass spectrometry, multidimensional NMR, optical rotation or electronic circular dichroism where appropriate, and comparison with authentic material or total

synthesis when stereochemistry is uncertain. Second, binary complexes should be characterized when feasible. Third, the ternary complex should be studied directly because the biologically relevant surface is created only in the assembled system.

X-ray crystallography can reveal atomic-level contacts between the natural product, E3 receptor and recruited protein. Cryo-EM may be advantageous for larger ubiquitin-ligase assemblies or flexible complexes. NMR can characterize weak interactions and conformational exchange. Hydrogen–deuterium exchange mass spectrometry and cross-linking mass spectrometry can provide complementary information when high-resolution structures are difficult to obtain. The resulting structural map should guide analogue design rather than simply serve as a descriptive endpoint.

The emerging literature on structure-guided molecular-glue engineering demonstrates the value of this approach. For example, structural analysis of CDK12/DDB1 complexes has shown how a surface-exposed chemical group can convert a conventional kinase-binding scaffold into a glue degrader and has supported the design of additional analogues [14,17,30,31].

De novo engineering strategy

De novo engineering of a plant-derived molecular glue should begin only after the degradation mechanism is established. The first synthetic campaign should map which portions of the natural scaffold are required for binary recognition, which portions contact the second protein, and which regions are solvent-exposed. A focused analogue matrix can then systematically vary steric bulk, hydrogen-bonding capacity, polarity, rigidity, stereochemistry and electronic properties.

The optimization objective is inherently multiparametric. Desired properties include: high degradation potency; positive ternary cooperativity; selectivity for the intended neo-substrate; low nonspecific proteome degradation; adequate cell permeability; metabolic stability; appropriate plasma protein binding; tissue exposure; and minimal interference with the native function of the E3 ligase. Optimizing only the degradation EC50 can therefore produce misleading leads.

One particularly promising strategy is “surface engineering”: preserve the natural-product recognition element while installing a substituent that creates a new contact with the target protein or E3. This concept parallels the transformation of existing inhibitors into glue degraders and may be more tractable than attempting to design a complete molecular glue from an empty chemical space [17,30,31].

AI-assisted discovery: realistic opportunities and limitations

Artificial intelligence can contribute at several levels: prediction of protein structures, generation of candidate ligand poses, prioritization of plant metabolites, analysis of molecular-network relationships, prediction of protein–protein interaction surfaces, and multiparameter ranking of synthetic analogues. However, the current state of the field does not justify treating docking scores as predictors of glue activity. The essential variables include ternary cooperativity, induced fit, protein flexibility, solvent organization, ubiquitination geometry and cellular context.

A more realistic AI framework is therefore iterative active learning. Experimental degradation data are used to update a model; the model selects a small number of plant metabolites or synthetic analogues for testing; the new data are fed back into the model; and the cycle continues. This strategy can reduce the number of compounds requiring synthesis while preserving experimental validation as the ultimate arbiter of activity.

Generative chemistry could eventually be used to propose analogues around a natural scaffold while constraining synthetic accessibility and predicted physicochemical properties. Structural information from ternary complexes should be incorporated whenever available. The strongest future systems will likely combine structure-based modeling, proteomics and active experimental learning rather than rely on a single predictive model.

Candidate E3 ligases and the importance of expanding the E3 toolbox

A major limitation of current molecular glue pharmacology is the relatively small set of E3 systems that can be efficiently recruited. CRBN and DCAF15 provide powerful precedents, while DDB1-associated mechanisms illustrate that even an adaptor can participate in substrate presentation. Yet the human ubiquitin system contains a much larger diversity of E3 ligases and substrate receptors. Expanding this toolbox would greatly increase the range of proteins accessible to glue-based degradation [24].

For plant-derived discovery, E3 selection should therefore be considered part of the discovery problem rather than a fixed parameter. A metabolite might fail in a CRBN-based assay but succeed with another E3. Future screening platforms should include panels of E3 components or programmable cell lines in which E3 abundance and substrate recruitment can be manipulated.

The ultimate objective is a matrix in which plant-derived scaffolds are systematically crossed with E3 ligases and disease-relevant target proteins. Such a matrix would turn molecular glue

discovery from an isolated serendipitous event into a combinatorial platform.

Previously undruggable proteins and the definition of success

The phrase "undruggable protein" is useful rhetorically but imprecise scientifically. Many proteins once considered undruggable have become tractable after discovery of cryptic pockets, allosteric sites, degrons or induced-proximity mechanisms. In the context of this review, a more operational definition is a protein for which conventional small-molecule inhibition is inadequate because of absent or poorly selective binding pockets, but for which selective degradation may produce a measurable therapeutic effect.

Transcriptional regulators, scaffolding proteins, oncogenic adaptors and certain mutant proteins are obvious candidate classes. The strongest target candidates should combine compelling disease biology with a measurable cellular abundance phenotype and a surface capable of participating in a ternary complex. The target should also have a therapeutic window: complete degradation is not automatically beneficial if the protein is essential in normal tissues.

For cancer, a successful program should progress beyond cell viability. The mechanistic endpoint should be targeting degradation; the pharmacodynamic endpoint should be measurable depletion in tumors; and the therapeutic endpoint should be tumor control with an acceptable toxicity profile. Similar logic applies to neurodegeneration and inflammatory disease, although tissue distribution and chronic exposure become more demanding.

Translational pharmacology and safety

Natural-product molecular glues may possess favorable structural complexity but can also introduce liabilities involving solubility, metabolic stability, transporter interactions and off-target protein binding. Because glue activity depends on a protein network, toxicity cannot be inferred from binary target affinity alone. Proteome-wide degradation, transcriptomic response, mitochondrial effects, hERG liability, CYP interactions and immunological consequences should be evaluated as appropriate to the scaffold.

Pharmacokinetic/pharmacodynamic relationships are also different from those of conventional inhibitors. A short plasma half-life can sometimes be compatible with durable pharmacology if protein degradation is rapid and resynthesis is slow. Conversely, persistent exposure may increase unintended neosubstrate degradation. The relevant optimization parameter is therefore the temporal relationship among drug concentration, ternary-complex formation, ubiquitination, protein loss and protein resynthesis.

Tissue selectivity is an additional opportunity. If an E3 ligase or neo-substrate is preferentially expressed in a disease tissue, a glue may achieve functional selectivity even when the small molecule itself is not tissue-specific. This possibility should be explored through quantitative proteomics and spatial expression data rather than assumed from cell-line experiments.

Resistance and evolutionary stability

Resistance to molecular glue degraders can arise at several levels: mutation of the E3-binding surface, mutation of the neo-substrate interface, loss or alteration of the E3 component, changes in ubiquitin-pathway activity, or altered drug metabolism and transport. Because the ternary interface is often highly specific, single amino-acid substitutions may disrupt degradation without affecting the normal function of either protein.

This vulnerability can be exploited during discovery. Saturation mutagenesis or CRISPR-based resistance mapping can identify interface residues before clinical resistance emerges. Structural modeling can then predict which mutations are most likely to disrupt activity, and second-generation analogues can be designed to create alternative contacts. A mature molecular-glue program should therefore incorporate resistance analysis before entering expensive in vivo studies.

Reproducibility standards for phytochemical molecular-glue research

Reproducibility is particularly important because plant extracts vary with species authentication, geography, cultivation, season, plant organ, drying procedure, extraction solvent and storage. Every future study should report voucher specimens, taxonomic authentication, collection conditions, extraction yield, chromatographic fingerprint and quantitative chemical markers. For active compounds, purity and stereochemical identity should be established unambiguously.

Biological reproducibility requires standardized cell lines, defined treatment times, quantitative degradation metrics, proteasome and E3 controls, and appropriate inactive analogues. Mechanistic claims should be supported by orthogonal experiments. A publication should ideally provide enough structural and spectrometric information for independent laboratories to reproduce the compound and enough genetic information to reproduce the mechanism.

These standards are not bureaucratic additions; they are essential for distinguishing genuine molecular glue biology from nonspecific cytotoxicity, transcriptional suppression, stress-induced protein loss or assay artifacts.

A proposed Plant Molecular Glue Atlas

We propose creation of a standardized Plant Molecular Glue Atlas containing chemical, biological and structural metadata for candidate compounds. Each record would include plant species and tissue, voucher information, extraction method, molecular formula, exact mass, NMR data, stereochemistry, SMILES/InChI, target protein, E3 ligase, degradation kinetics, ternary-complex measurements, proteomic selectivity, structural data, synthetic accessibility and in vivo pharmacology.

Such an atlas could become a community resource analogous to natural-product databases but with a mechanistic layer. Instead of merely cataloging compounds, it would catalog "chemical instructions" for protein fate. The long-term value would be greatest if negative results were also included, because failed compounds can reveal structural features that are incompatible with productive ternary complexes.

The atlas could also support machine learning. A model trained on structures linked to ternary cooperativity and degradation outcomes would have substantially more biological meaning than a model trained only on binary binding affinity. Over time, this could enable predictive selection of plant metabolites for experimental testing.

Priority research questions for the next decade

Several questions emerge as particularly important. First, how frequently do higher-plant specialized metabolites induce productive ternary complexes with human proteins? Second, can plant scaffolds recruit human E3 ligases without retaining strong inhibitory activity against their natural receptors? Third, which structural motifs predict positive cooperativity? Fourth, can an E3–target pair be selected first and then matched to plant chemical space? Fifth, can active learning make glue discovery sufficiently predictive to reduce experimental search space by orders of magnitude?

A sixth question concerns evolutionary portability. Plant hormones evolved to recognize plant proteins, yet their structural logic may be portable even when their direct targets are not. Understanding which features are universal—preorganization, conditional affinity, interface complementarity—and which are system-specific could establish general principles for molecular glue design.

Finally, the field needs to determine whether natural-product-inspired glue chemistry can produce medicines that are meaningfully different from current synthetic degraders. If the answer is yes, the advantage may arise from greater three-dimensionality, improved selectivity, novel E3 recruitment, access to unconventional protein surfaces, or new pharmacological mechanisms. Demonstrating such a distinction would justify a dedicated plant-derived molecular glue discipline.

Recommended experimental workflow for a first-generation academic program

For an academic laboratory entering this field, the most realistic first-generation program should not attempt to discover a clinical candidate immediately. A staged program can begin with 10–20 chemically diverse medicinal plants, standardized extraction, LC–HRMS/MS profiling, molecular networking, and a small number of robust cellular degradation reporters. Active fractions can then be subjected to targeted purification and mechanistic testing.

Once one reproducible degradation phenotype is found, the project should pivot from broad phytochemistry to intensive chemical biology. The compound should be purified and structurally validated; the degraded protein should be identified; proteasome and E3 dependence should be established; and a direct ternary interaction should be demonstrated. Only then should extensive analogue synthesis begin.

This staged strategy minimizes wasted resources. It also produces publishable milestones at multiple levels: a metabolomics/chemical-space study, a mechanistic molecular-glue discovery paper, a structural biology paper, and ultimately a medicinal-chemistry or translational study. A single successful scaffold could therefore support a coherent multi-year research program.

Overall model and central hypothesis

The central model proposed by this review is shown conceptually as: plant chemical diversity → molecular feature discovery → selective protein degradation phenotype → E3/target deconvolution → ternary-complex structure → synthetic engineering → proteome selectivity → pharmacokinetics → disease model. Each arrow represents a testable scientific question. The framework is deliberately interdisciplinary and requires chemistry, analytical science, structural biology, proteomics and pharmacology to converge.

The central hypothesis is that plant specialized metabolites contain underexplored molecular architectures capable of inducing or stabilizing protein–protein interactions in ways that can be redirected toward human ubiquitin-dependent proteolysis. If validated, this would establish plant chemical space as a systematic source of molecular glue scaffolds rather than merely a reservoir of conventional bioactive compounds.

Table 1. Comparison of major molecular-glue discovery paradigms.

Paradigm	Representative example	Discovery mode	Key mechanistic lesson	Relevance to plant-derived program
Plant endogenous degradation	Auxin–TIR1–Aux/IAA	Natural signaling biology	Ligand creates E3–substrate recognition	Evolutionary blueprint
Plant endogenous degradation	JA-Ile–COI1–JAZ	Natural signaling biology	Hormone traps degron in receptor pocket	Evolutionary blueprint
Plant endogenous degradation	GA–GID1–DELLA	Natural signaling biology	Ligand-dependent receptor–substrate recognition	Evolutionary blueprint
Natural PPI stabilization	Rapamycin–FKBP12–mTOR	Serendipitous natural-product pharmacology	Small molecule can create ternary complex	Proof of induced proximity
Natural PPI stabilization	Fusicoccin–14-3-3/client	Natural-product screening	Interface stabilization can be highly selective	Scaffold inspiration
Synthetic/natural-product-inspired degradation	IMiD–CRBN–IKZF	Serendipity followed by mechanism	E3 substrate specificity can be chemically rewritten	Translational precedent
Synthetic glue degrader	Indisulam–DCAF15–RBM39	Phenotypic screening	Shallow interface can recruit neo-substrate	Human therapeutic paradigm
Synthetic glue degrader	CR8–DDB1/CDK12–cyclin K	Data mining/genetics/structure	Surface-exposed substituent can create glue activity	Engineering paradigm

Table 2. Evidence hierarchy for future plant-derived molecular glue papers.

Claim	Required evidence	Preferred orthogonal confirmation
Bioactive natural product	Dose-response phenotype	Independent isolation/re-synthesis
Selective protein depletion	Quantitative Western/HiBiT/proteomics	Time course + transcriptional control
Proteasomal degradation	MG132 or equivalent rescue	Ubiquitination assay
E3 dependence	Genetic knockout/depletion	Reconstitution or rescue
Direct target involvement	Chemoproteomics/CETSA	Genetic resistance mapping
Molecular glue mechanism	Compound-enhanced E3–target interaction	NanoBRET/TR-FRET/SPR/ITC
Ternary interface	Mutational mapping	High-resolution structure
Drug-like degrader	PK/PD relationship	In vivo target engagement and proteomics

Table 3. Suggested analytical platform for a plant-derived molecular glue discovery center.

Platform	Core equipment/technology	Primary output
Botanical authentication	Voucher collection, microscopy, DNA barcoding when needed	Verified source material
Extraction/fractionation	Soxhlet/ultrasound/pressurized extraction, HPLC, flash chromatography	Standardized fractions
Chemical profiling	LC-HRMS/MS, NMR, UV/DAD	Molecular features and structures
Dereplication	Spectral databases, molecular networking	Known/novel prioritization
Cellular screening	Reporter assays, HiBiT, imaging	Degradation phenotype
Proteomics	TMT/DIA/label-free LC-MS/MS	Proteome-wide selectivity
Genetics	CRISPR knockout/resistance screens	E3 and target mechanism
Biophysics	SPR, BLI, ITC, TR-FRET/NanoBRET	Binary/ternary interaction parameters
Structural biology	X-ray, cryo-EM, NMR	Ternary-complex architecture
Medicinal chemistry	Parallel synthesis, purification, analytical QC	SAR and optimized analogues
In vivo pharmacology	PK/PD, xenograft or disease models	Translational validation

Limitations of the Present Review

The present review has several limitations. First, the plant-derived human molecular glue degrader field is sufficiently young that many proposed opportunities remain hypotheses rather than experimentally established drug classes. Second, nomenclature is inconsistent across the literature: the term “molecular glue” is sometimes used broadly for nondegrading PPI stabilizers and sometimes narrowly for E3-dependent degraders. Third, structural evidence is available for only a subset of systems. Fourth, natural-product chemical space is biased toward compounds that have already been isolated and characterized, meaning that truly unexplored metabolites remain invisible to current databases.

These limitations reinforce rather than weaken the rationale for the proposed research program. A successful field-defining study should explicitly measure uncertainty, use orthogonal mechanistic assays, and distinguish natural precedent from human therapeutic validation. The objective should be predictive mechanistic understanding rather than accumulation of isolated activity reports.

Final Perspective

The central message of this review is that molecular glue discovery represents a conceptual bridge between natural-product chemistry and programmable proteostasis. Plants provide some of the clearest examples in biology of small molecules controlling protein–protein recognition and regulated degradation. Modern chemical biology now provides the tools needed to ask whether those principles can be transferred to human E3 ligases and disease-associated proteins. A successful plant-derived molecular glue program would therefore proceed in a fundamentally different way from conventional phytochemical screening. The goal would not be to find an extract that is “anticancer,” but to identify a chemically defined molecule that produces a reproducible, E3-dependent and proteasome-dependent loss of a specific protein through a demonstrable ternary complex. Structural elucidation would reveal the molecular logic; synthetic chemistry would convert that logic into optimized analogues; and proteomics and pharmacology would determine whether the mechanism is selective and therapeutically useful. In this framework, the phrase “Nature's Molecular Glue Library” becomes more than a title. It represents a testable scientific proposition: that the evolutionary diversity of plant metabolites contains molecular architectures capable of encoding selective protein proximity, and that these architectures can be discovered and reprogrammed into medicines. Establishing a general rule for this transformation would represent a substantial advance at the interface of phytochemistry, medicinal chemistry, structural biology and chemical biology.

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