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REVIEW ARTICLE

Plant-Derived Bioactive Proteins and Peptides as Emerging Therapeutics: Current Evidence and Potential Translational Challenges

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Abstract

Medicinal plants have long served as a cornerstone of traditional therapies, primarily recognized for their rich repertoire of secondary metabolites. Beyond these small molecules, plants produce a diverse array of proteins endowed with potent bioactive properties that remain comparatively underexplored in modern drug discovery. This review aims to consolidate and highlight the current knowledge on major families of plant-derived proteins and peptides with medicinal value, with particular emphasis on their mechanisms of action, therapeutic limitations, mitigation strategies, and translational potential. A narrative literature survey was conducted using peer-reviewed studies to feature plant proteins/peptides, such as lectins, pathogen-related proteins, RIPs, proteases, etc., with reported medicinal values. The review highlights how plant proteins exert therapeutic effects through defined molecular interactions, including enzymatic catalysis, selective membrane disruption, receptor binding, immune modulation, and interference with pathogen or cancer-associated cellular processes, resulting in antiviral, antifungal, anticancer, anti-inflammatory, and immunomodulatory activities. It is believed that the evolutionary diversification and lineage-specific expansion of these protein families have generated extensive functional variability, increasing the likelihood of identifying molecules with novel or enhanced bioactivity. Advances in genomics, proteomics, and recombinant expression technologies have further accelerated protein discovery, functional characterization, and bioengineering, enabling improved specificity, stability, and delivery. Collectively, the evidence supports plant-derived proteins as a versatile and multifunctional class of biomolecules that complement conventional small-molecule therapeutics, while underscoring the need for systematic characterization, optimized production strategies, and well-designed preclinical and clinical studies to support their future application in disease prevention, management, and biomedical innovation.

Keywords: Plant proteins; Bioactive molecules; Therapeutic potential; Immunomodulation; Anticancer; Antiviral

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Introduction

Medicinal plants have been used as therapeutic resources across human civilizations, forming the foundation of traditional medical systems such as Ayurveda, Traditional Chinese Medicine, Unani, African traditional medicine, and ethnomedicine worldwide [1]. Historically, the pharmacological value of medicinal plants has been attributed predominantly to low-molecular-weight secondary metabolites, including alkaloids, flavonoids, terpenoids, phenolics, and glycosides. These compounds have yielded numerous modern drugs and lead molecules [2,3]. Consequently, this metabolite-centric view has overshadowed another biologically powerful class of plant-derived molecules: proteins and peptides. In recent decades, accumulating biochemical, molecular, and pharmacological evidence has demonstrated that plants produce a wide array of proteins with potent and

highly specific bioactivities relevant to human health [4]. Unlike secondary metabolites, proteins often act through well-defined molecular mechanisms, such as enzymatic catalysis, receptor binding, membrane disruption, or direct modulation of immune and signaling pathways. These characteristics confer high target specificity and biological efficacy, frequently at nanomolar concentrations [5].

Most medicinally relevant plant proteins originate from conserved gene families involved in innate plant defense, stress responses, or nutrient storage. These include lectins, ribosome-inactivating proteins, pathogenesis-related (PR) proteins [6], antimicrobial peptides 7, proteases, protease inhibitors, and seed storage proteins 8. From an evolutionary perspective, many of these protein families have undergone lineage-specific expansion and diversification, particularly in plants exposed to strong biotic pressures such as pathogens and herbivores. This evolutionary plasticity has generated extensive functional diversity, increasing the likelihood of discovering proteins with novel or enhanced bioactivities [6,8]. Technological advances in genomics, transcriptomics, proteomics, and recombinant protein expression have dramatically accelerated the discovery and functional characterization of plant protein families. High-quality plant genome assemblies have revealed extensive expansion of bioactive protein families, particularly in medicinal and stress-adapted species. At the same time, protein engineering, molecular docking, and targeted delivery systems are overcoming historical limitations related to toxicity, immunogenicity, and stability [9,10].

Although numerous reviews have examined individual classes of plant-derived bioactive proteins in detail, the literature remains fragmented across protein families. This review consolidates the major bioactive plant protein groups within a single structured framework, enabling cross-family comparison of mechanisms and translational challenges. By emphasizing shared principles and common development constraints, it provides an integrated reference to guide future therapeutic and industrial applications. In this review, we highlight the major types and classes of proteins and peptides with potential medicinal value, explore their possible mechanisms of action, and discuss the challenges and limitations associated with their biotechnological and medicinal applications.

Materials and Methods

Literature search strategy

This review was conducted as a narrative, non-systematic literature review focusing on protein-based molecules from plant sources with reported or proposed medicinal value, as the available data remained fragmented and hard to harmonize under a systematic review framework. The literature survey aimed to capture foundational mechanistic studies, representative experimental evidence, and recent advances relevant to therapeutic applications rather than to exhaustively quantify outcomes. Primary literature searches were performed using major scientific databases, including PubMed, Web of Science, Scopus, and Google Scholar, and refined via Boolean operators. The search was conducted using combinations of controlled vocabulary and free-text terms, such as: "plant proteins, plant-derived antimicrobial proteins, plant defensins, pathogenesis-related proteins, ribosome-inactivating proteins, lectins, mechanism of action, antifungal, antiviral, anticancer, mode of action, therapeutic application, clinical potential." To ensure mechanistic depth, priority (inclusion criteria) was given to (i) peer-reviewed original research articles describing biochemical, structural, molecular, or cellular mechanisms; (ii) studies reporting experimentally validated bioactivities in vitro, in vivo, or in early-phase clinical contexts; and (iii) review articles used to contextualize protein families and identify foundational references. Exclusion criteria included: (i) studies that were agricultural-based only with no relevance to biomedical or therapeutic applications, or (ii) obtained from non-peer-reviewed sources. Furthermore, no strict publication date limits were imposed; however, recent studies were given particular emphasis.

Figure development and visualization

The figures presented in this review were generated using a text-to-figure visualization tool of Figurelabs.ai (Available from: https://figurelabs.ai, Last accessed Jan, 2026), which converts structured textual descriptions into schematic illustrations. The textual inputs provided to the tool were derived exclusively from detailed mechanistic information curated from peer-reviewed research articles. The tool was used solely to facilitate the visual representation of established or experimentally supported pathways, while all biological interpretations, pathway definitions, molecular interactions, and mechanistic frameworks were manually curated, validated, and summarized by the authors. No mechanistic conclusions or biological inferences were generated by the visualization tool itself.

Plant-Derived Proteins and Peptides

Lectin Protein Families

Plant lectins are non-enzymatic, carbohydrate-binding proteins that recognize and reversibly bind specific mono- or oligosaccharide moieties without altering their covalent structure. They are ubiquitous in the plant kingdom and are particularly abundant in seeds, bulbs, rhizomes, bark, latex, and leaves. Molecular weights of plant lectins typically range from ~10 kDa to >120 kDa, depending on oligomeric state and domain composition. Structurally, most lectins are oligomeric proteins composed of identical or closely related subunits, which enhances multivalent carbohydrate binding and biological potency [11]. From a physiological perspective, plant lectins function primarily in defense against pathogens, herbivores, and insects, as well as in symbiotic recognition and intracellular signaling [12]. Their high stability, resistance to proteolysis, and strong affinity for glycoconjugates underpin both their ecological function and their biomedical relevance. The medicinal

potency of plant lectins is closely linked to their tissue localization and expression level. Seed lectins are often present at high concentrations, enabling strong bioactivity upon ingestion or extraction [13]. Lectins localized in latex or epidermal tissues tend to exhibit higher toxicity and antimicrobial potency, reflecting their role as immediate defense molecules [14].

Plant lectins have been extensively investigated for their diverse medicinal potential. This encompasses anticancer activities such as the induction of apoptosis, cell-cycle arrest, and inhibition of angiogenesis, as well as antiviral effects through the blockade of viral entry and membrane fusion [15]. In addition, lectins exhibit immunomodulatory properties [16], enabling them to either activate or suppress immune responses, and display broad antimicrobial and antifungal activities [14]. They were also studied for their potential effects as antiulcer agents and antinociceptives [17-20]. Owing to their high specificity for carbohydrate moieties, plant lectins are also widely employed as diagnostic and targeting tools in glycobiology and oncology. Several lectins are already established as research reagents, and several candidates are currently undergoing preclinical or clinical evaluation for therapeutic applications [21]. Plant lectins are classified based on sequence homology, three-dimensional fold, and carbohydrate specificity. Structural aspects of major lectin families with established or emerging medicinal relevance are summarized in Table 1.

Mechanism of action

Plant lectin families exhibit diverse yet convergent mechanisms of action that underpin their therapeutic potential (Figure 1). Legume lectins, such as concanavalin A (*Canavalia ensiformis*) and phytohemagglutinin (*Phaseolus vulgaris*), selectively bind aberrant surface glycans overexpressed on cancer cells, including the Thomsen–Friedenreich antigen, triggering mitochondrial apoptosis via cytochrome c release and caspase activation, while also inducing autophagy through BNIP3 upregulation and suppression of PI3K/Akt/mTOR signaling [30]. In parallel, their strong mitogenic activity promotes T-lymphocyte proliferation and cytokine secretion (e.g., IL-2, IFN-γ), thereby amplifying antitumor immune responses. Hevein (Hevea brasiliensis) and related small chitin-binding lectins exert potent antimicrobial effects by binding chitin in fungal cell walls, disrupting cell wall biosynthesis, and causing hyphal rupture. Additionally, hevein domains can activate innate immune cells, inducing oxidative bursts in neutrophils, and have been exploited as targeting motifs in nanoparticle-based drug delivery systems to enhance chemotherapeutic uptake [31,32]. Hevein-like lectins identified in spike moss (*Selaginella moellendorffii*) have been investigated as potential inhibitors of SARS-CoV-2 and several early viral variants. These lectins are proposed to impede viral entry by interacting with terminal N-acetylgalactosamine residues on the spike glycoprotein (S1), thereby interfering with ACE2-mediated host cell attachment [28]. Jacalin (*Artocarpus integra*) exerts therapeutic effects by binding O-glycosylated CD45, which triggers the ERK/p38 MAPK pathways to induce IL-2 production and T-cell proliferation. It simultaneously inhibits HIV-1 infection by sterically blocking the gp120–CD4 interaction and, in oncological models, promotes apoptosis by suppressing Lyn kinase activity. Furthermore, it stimulates macrophages to release cytotoxic TNF-α and reactive oxygen species via NF-κB activation, enhancing anti-tumor immunity [33-36]. Finally, GNA (*Galanthus nivalis*) functions as a potent antiviral agent by binding to high-mannose glycans on viral envelope proteins, such as gp120 in HIV-1, effectively neutralizing the virus and blocking entry/fusion into host cells. In oncology, GNA induces apoptosis and autophagy by binding to cell-surface receptors and internalizing to the mitochondria, where it triggers ROS production, cytochrome c release, and the activation of p38/p53 signaling pathways. It also serves as a specialized carrier molecule in transgenic medicine, facilitating the oral delivery and absorption of fused therapeutic proteins across biological barriers like the gut epithelium [37,38].

Limitations, mitigation strategies, and therapeutic relevance

Plant lectins share common translational limitations, primarily off-target glycan binding, mitogenicity or immunogenicity, and potential cytotoxicity due to broad carbohydrate specificity, which complicate systemic clinical use [39]. Current mitigation strategies focus on protein engineering (domain truncation, point mutations to reduce nonspecific binding), targeted delivery, dose control, and conjugation to carriers to improve selectivity and safety [40]. Looking forward, their clinical future is most promising in highly controlled contexts. Such as topical applications, localized anticancer targeting, antiviral blocking at mucosal surfaces, and use as diagnostic or targeting modules rather than standalone therapeutics, where lectin–glycan specificity can be exploited while minimizing systemic exposure and toxicity [41]. On clinical context, plant lectins have reached clinical evaluation with markedly different levels of translational maturity. Extracts of *Viscum album* containing mistletoe lectins have been investigated as adjunctive therapies in oncology, with several clinical studies reporting improvements in quality-of-life parameters. However, the evidence remains heterogeneous, and methodological limitations and ongoing debate preclude definitive conclusions regarding clinical efficacy [42-44]. While lectins from other sources, such as Griffithsin (from red algae *Griffithsias* sp.), a mannose-binding lectin produced recombinantly in plants, have completed Phase I trials as a topical microbicide, demonstrating excellent safety, minimal systemic absorption, and strong promise for prevention of HIV-1 and other sexually transmitted viral infections [45]. Other plant lectins like Abrin (*Abrus precatorius*) and Ricin-B–containing systems remain at the preclinical stage; despite potent anticancer activity in experimental models, their intrinsic toxicity currently confines their clinical potential to engineered immunotoxins or targeted delivery platforms rather than standalone therapeutics [46].

Ribosome-Inactivating Protein (RIP) Families

Ribosome-inactivating proteins (RIPs) are a class of plant-derived enzymes that irreversibly inhibit protein synthesis by depurinating a highly conserved adenine residue in the sarcin–ricin loop of large ribosomal RNA. This N-glycosidase activity renders ribosomes incapable of interacting with elongation factors, leading to translational arrest and, ultimately, cell death [47]. RIPs are widely distributed in higher plants and are particularly abundant in medicinal species known for their antiviral and anticancer properties [48]. The tissue localization and expression levels of RIPs strongly influence their biological and medicinal effects. RIPs concentrated in seeds and storage tissues are typically associated with defense against predators and pathogens, resulting in high intrinsic toxicity. Conversely, RIPs expressed in vegetative tissues often display more regulated activity and lower toxicity. Intracellular compartmentalization, such as vacuolar sequestration, further limits autotoxicity in plant cells while preserving defensive function [49].

RIPs have been intensively investigated for a broad range of biomedical applications, notably as antiviral agents against HIV-1, HBV, HSV, and emerging viruses such as SARS-CoV-2, as well as anticancer molecules capable of suppressing tumor growth and inducing apoptosis [50]. They have also been developed as immunotoxins for targeted cancer therapy and, in historical and limited clinical contexts, explored as abortifacient and antifertility agents [51], while continuing to serve as powerful experimental tools for studying ribosome function and cell death pathways. The medicinal activity of RIPs is fundamentally based on their ability to depurinate a specific adenine residue in ribosomal RNA, resulting in irreversible inhibition of protein synthesis. In cancer cells, this translational arrest activates apoptotic signaling through both intrinsic mitochondrial and extrinsic death receptor pathways, accompanied by oxidative stress, DNA damage responses, and caspase activation [52]. In antiviral contexts, RIPs suppress viral replication by inhibiting viral protein synthesis and, in some cases, directly targeting viral RNA or replication complexes. Type-II RIPs achieve enhanced cellular entry via lectin-mediated endocytosis, whereas type-I RIPs rely on alternative uptake routes such as pinocytosis and are therefore under active investigation due to their more favorable balance between efficacy and safety [53]. In immunotoxin-based strategies, the catalytic RIP domain is conjugated to targeting molecules to enable the selective elimination of malignant cells, making mechanistic understanding a central factor in the clinical advancement of RIP-derived therapeutics (Figure 2) [54].

RIPs are typically basic proteins with molecular weights ranging from ~25 kDa to over 60 kDa, depending on domain composition. They are exceptionally stable, resistant to proteolysis, and retain activity under a wide range of pH and temperature conditions [55]. These biochemical properties, combined with their potent biological activity, underline both their therapeutic potential and their inherent toxicity. Plant RIPs are traditionally classified into three major types based on their structural organization and cellular targeting capacity, which are summarized in Table 2.

Table 1: Structural aspects of major plant lectin families endowed with medicinal values

Lectin Family	Subunit Size	Oligomeric State	Fold/ Topology	Metal Ion Requirement	Carbohydrate-Binding Site Features	Disulfide Bonds	Structural Stability	Structure–Function Implications	Ref
Legume (L-type) lectins	250–300 aa (~25–30 kDa)	Dimers or tetramers (50–120 kDa)	β-sandwich (jelly-roll–like)	Ca^{2+} and Mn^{2+} essential	Shallow binding pocket formed by loop regions; metal ions stabilize sugar coordination	Few or none	High thermal and pH stability	Multivalency via oligomerization enables receptor cross-linking, immune cell activation, and apoptosis signaling.	22,23
Jacalin-related lectins (JRLs)	15–35 kDa	Monomers, dimers, or tetramers	β-prism I	None required	Compact, deep carbohydrate-binding pocket with aromatic residues for galactose stacking	Rare	Moderate; sensitive to proteolysis	Strong glycan specificity underlies antiviral envelope recognition; mutations reduce mitogenicity without loss of binding.	24,25
Ricin B-like (R-type) lectins	~130 aa per B-chain domain	Part of heterodimeric type II RIPs	β-trefoil fold	None	Two galactose-binding sites per domain; high avidity	None	High	Efficient cell internalization makes them ideal targeting moieties for immunotoxins	26
GNA-type lectins	12–15 kDa	Dimers or tetramers	β-prism II	None	Multiple mannose-binding pockets are arranged symmetrically	None	Very high (protease-resistant)	High affinity for high mannose glycans enables potent viral entry inhibition	27
Hevein lectins	30–45 aa (4–8 kDa)	Monomeric or multimeric	Small cysteine-rich fold	None	Linear groove recognizing GlcNAc/chitin oligomers	Multiple (3–4)	Extremely high	Disulfide-stabilized scaffolds confer resistance to degradation and strong antifungal activity	28,29

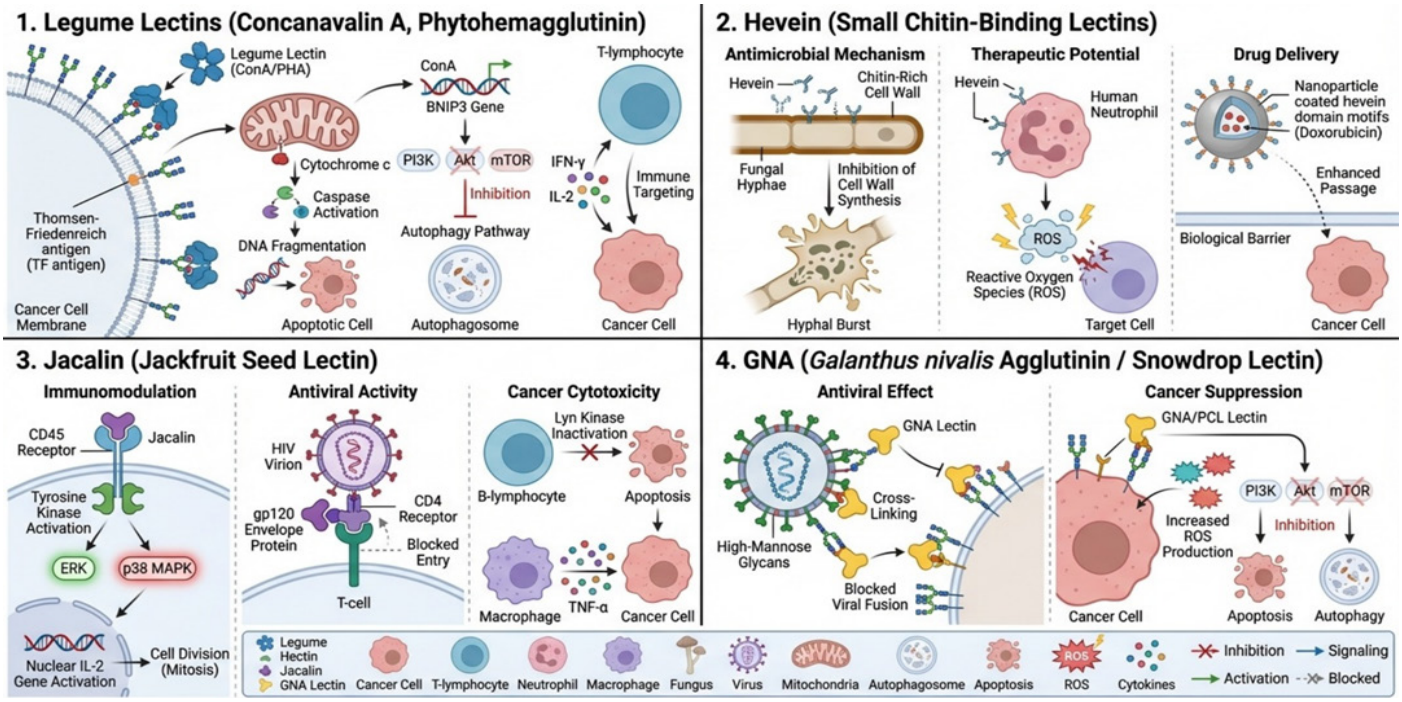

Figure 1: Possible mechanism of action of major plant lectin families: Schematic representation of the principal, experimentally supported mechanisms by which plant lectins exert biological effects, including carbohydrate-mediated cell surface binding, receptor cross-linking, immune cell activation, inhibition of viral entry, and induction of apoptosis. The figure highlights representative pathways common to major bioactive lectin families.

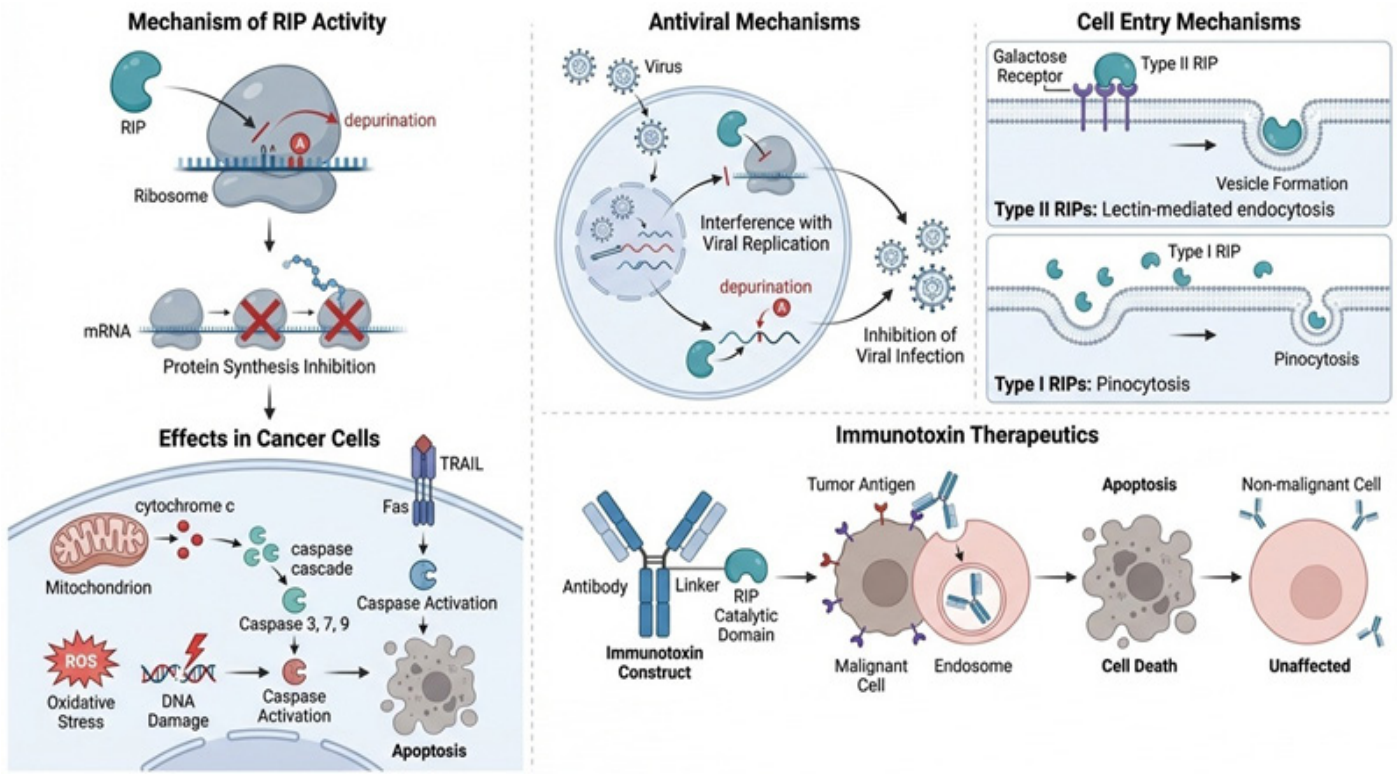

Figure 2: Ribosomal inactivating proteins (RIPs) mechanism of action: Overview of the canonical catalytic mechanism of plant RIPs, illustrating ribosomal depurination, translational arrest, and initiation of apoptotic cell death. The figure emphasizes core molecular events common to RIP classes.

Limitations, mitigation, and clinical trials of RIPs

Plant ribosome-inactivating proteins (RIPs) from classes I, II, and III exhibit substantial therapeutic promise. But their clinical translation is constrained by several well-defined limitations. The principal challenge is toxicity, which is most pronounced for type-II RIPs due to lectin-mediated cellular uptake and efficient retrograde transport, leading

to off-target ribosomal inactivation in healthy tissues. Even type-I RIPs, while lacking a binding subunit, can cause nonspecific cytotoxicity at higher doses, and all RIP classes raise concerns regarding immunogenicity, systemic inflammatory responses, and poor therapeutic index. Additional limitations include inefficient intracellular delivery for type-I and type-III RIPs, rapid clearance, and difficulties in achieving tumor- or virus-specific selectivity. For type-III RIPs, incomplete or uncontrolled proteolytic activation may further reduce predictability and efficacy [63]. To mitigate these limitations, multiple engineering and delivery strategies have been developed. The most advanced approach involves immunotoxin design, where the catalytic RIP domain (commonly the A chain of type-II RIPs or full type-I RIPs) is conjugated to monoclonal antibodies, growth factor ligands, or nanocarriers to enable cell-specific targeting and minimize systemic exposure. Deglycosylation, site-directed mutagenesis, and epitope masking have been used to reduce immunogenicity, while PEGylation and nanoparticle encapsulation improve pharmacokinetics and stability. For type-III RIPs, controlled activation through engineered cleavage sites offers a promising route to enhance safety. Collectively, these mitigation strategies shift RIPs from broadly cytotoxic plant toxins toward precision biological payloads suitable for targeted therapy [63]. In terms of clinical trial status, native plant RIPs have not progressed as standalone therapeutics due to safety concerns. However, RIP-derived immunotoxins have advanced into early-phase clinical trials, particularly in oncology. Ricin A-chain–based and abrin-derived immunotoxins have been evaluated in Phase I/II studies for hematological malignancies and solid tumors, demonstrating proof-of-mechanism but also dose-limiting toxicities that halted broader development. Type-I RIPs, owing to their more favorable safety profile, remain under active preclinical and translational investigation, especially for antiviral and cancer applications. Type-III RIPs are currently confined to experimental and preclinical stages but are increasingly viewed as attractive next-generation scaffolds for safer RIP-based therapeutics. Overall, while no RIP-based drug has yet achieved regulatory approval, continued advances in targeting, delivery, and protein engineering sustain strong clinical interest in RIPs as modular cytotoxic agents rather than conventional drugs [63,64].

Pathogenesis-Related (PR) Protein Families

Pathogenesis-related (PR) proteins constitute a diverse group of plant proteins that are induced in response to biotic stresses such as pathogen infection, herbivory, and wounding, as well as abiotic stresses including salinity, drought, and oxidative stress. Initially characterized in tobacco during hypersensitive responses, PR proteins are now recognized as ubiquitous components of plant innate immunity [65]. Beyond their defensive role in planta, many PR protein families exhibit bioactivities of direct relevance to human health, including antifungal, antibacterial, antiviral, anticancer, and immunomodulatory effects. This arises from multiple mechanisms, including direct membrane disruption, enzymatic degradation

Table 2: Main characteristics of RIP classes

RIP Type	Structure	M.Wt. (kDa)	Domain structure	Catalytic Site	Cellular Uptake	Examples	Biochemical Stability	Intrinsic Toxicity (Structural Basis)	Translational Suitability	References
Type-I RIPs	Single-chain monomeric protein	~25–30	N-glycosidase catalytic domain only	Conserved active-site residues (e.g., Tyr, Glu, Arg) forming the depurination pocket	Inefficient uptake via pinocytosis or non-specific endocytosis	Bryodin I (Bryonia dioica), Luffin-A/B (Luffa cylindrica), Dianthin (Dianthus caryophyllus), Momordin (Momordica charantia)	High thermal and pH stability; protease-resistant	Moderate; absence of lectin domain limits cellular entry	Favorable scaffold for conjugation-based targeting strategies	[47,56-59]
Type-II RIPs	Heterodimer A–B toxin linked by a disulfide bond	~60–65 (A: ~30; B: ~30–35)	A chain: catalytic N-glycosidase; B chain: ricin B-like lectin	Conserved rRNA depurination active site in A chain	Efficient receptor-mediated endocytosis via glycan binding	Ricin (Ricinus communis), Abrin (Abrus precatorius), Volkensin (Adenia volkensii)	Extremely stable; resistant to denaturation	Very high; lectin-mediated uptake enhances cytosolic delivery	A-chain is widely used after detachment from the B-chain	[26,60,61]
Type-III RIPs	Inactive precursor requiring proteolytic activation	~35–45 kDa precursor	Catalytic RIP domain + removable peptide segments	Latent active site exposed after cleavage	Limited uptake; activity dependent on maturation	Maize RIPs (Zea mays)	High stability in precursor form	Low to moderate; restricted activation	Promising platform for engineering safer RIP derivatives	[62]

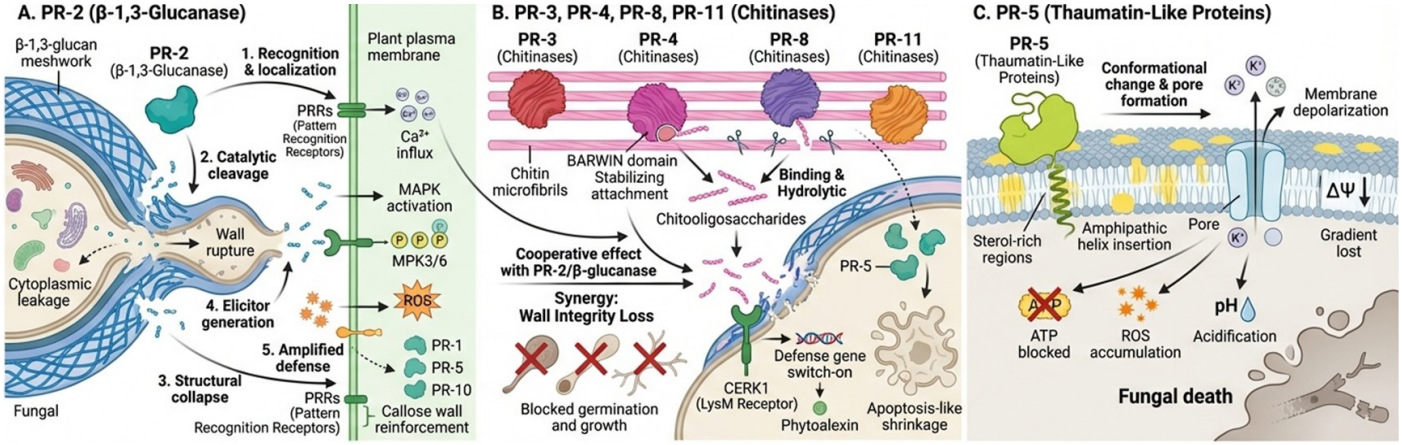

Figure 3: Antifungal activity (cell wall and membrane disruption) of some pathogen-related proteins.

of pathogen structural components, generation of immunogenic fragments, and modulation of host immune responses. Anticancer effects are often mediated through induction of apoptosis, oxidative stress, and interference with cell signaling pathways (Figure 3) [66]. PR proteins are typically low- to medium-molecular-weight proteins (10–40 kDa), often secreted or localized to the apoplast, vacuole, or extracellular matrix. Their stability, inducibility, and frequent enrichment in medicinal plants underpin their prominence among bioactive plant protein families. They are classified into multiple families (PR-1 to PR-17) based on sequence homology, biochemical activity, and immunological properties [67]. Among these, several families have been particularly well-studied for medicinal relevance.

Examples of bioactive PR families

PR-1 proteins (CAP superfamily)

PR-1 proteins are among the most strongly induced defense proteins in plants and belong to the CAP (Cysteine-rich secretory proteins, Antigen 5, and PR-1) superfamily. They are relatively small proteins, typically 14–17 kDa, containing conserved cysteine residues that form disulfide bonds, which stabilize their structure. These proteins are predominantly localized in the extracellular space or apoplast, where they can directly interact with pathogens. Functionally, PR-1 proteins exhibit robust antifungal and antibacterial activities, often acting through sterol-binding and membrane-disruptive mechanisms. While immunomodulatory functions of PR-1 proteins have been primarily characterized in plants, comparative studies of CAP-domain proteins in animals indicate conserved structural features associated with immune modulation, supporting a plausible but indirect mechanistic parallel [68-70].

PR-2 proteins (β-1,3-glucanases)

PR-2 proteins are β-1,3-glucanases that hydrolyze glucans in fungal cell walls, contributing to plant defense. These enzymes typically range from 30 to 40 kDa and possess well-defined catalytic domains that mediate glucan degradation. They are mainly localized in the apoplast and vacuole. Beyond their direct antifungal activity, PR-2 proteins generate bioactive oligosaccharides that function as immune elicitors, promoting immunostimulatory and antimicrobial responses 71.

PR-3, PR-4, and PR-8 proteins (chitinases)

PR-3, PR-4, and PR-8 proteins are chitinase-containing PR proteins that hydrolyze chitin, a key structural component of fungal cell walls and insect exoskeletons. These enzymes typically range from 25 to 35 kDa and often include chitin-binding domains that enhance substrate recognition and catalytic efficiency. They are localized in the apoplast, vacuole, and occasionally within intracellular compartments, allowing them to target pathogens at multiple cellular sites. Beyond their strong antibacterial properties, such as Brassica juncea (BjCHI1) [72], antifungal and insecticidal activities [73]. Chitinases have been explored for antitumor and immunomodulatory applications [74], as their ability to degrade glycan-containing structures can trigger immune responses and disrupt tumor cell integrity.

PR-5 proteins (thaumatin-like proteins)

PR 5 proteins, also called thaumatin-like proteins (TLPs), are small (~20–26 kDa) defense proteins stabilized by multiple disulfide bonds that adopt a conserved β fold related to the intensely sweet thaumatin protein. They accumulate in the apoplast and vacuole, where they interact with invading pathogens, displaying robust antifungal activity. This is achieved through mechanisms that include β-glucan binding and membrane permeabilization, contributing to the disruption of pathogen cell integrity. In addition to their well established role in plant innate immunity, several studies indicate broader bioactivities; specific plant TLP (i.e., Osmotin; Nicotiana tabacum) has been acting as a plant sentinel and has possible functional agonist of mammalian adiponectin, potentially offering therapeutic value for obesity, diabetes, and related metabolic and inflammatory disorders [75,76].

PR-6 proteins (protease inhibitors)

PR 6 proteins comprise plant serine protease inhibitors such as Kunitz-type inhibitors (KTIs) and Bowman-Birk inhibitors (BBIs), typically small proteins of 8–25 kDa often stabilized by disulfide bonds and highly abundant in seeds

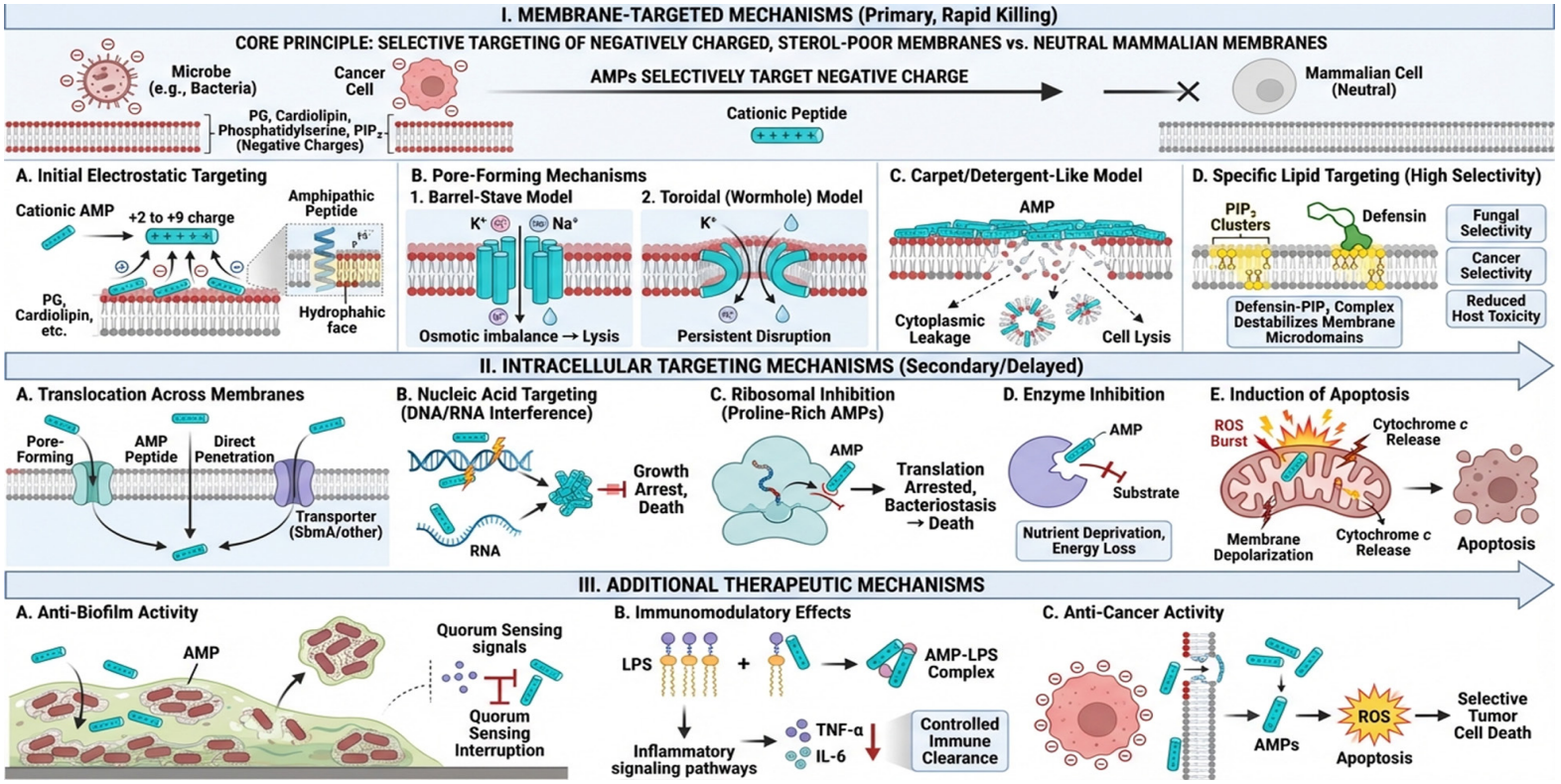

Figure 4: Possible mechanism of action of AMPs/ACPs as therapeutic agents: Conceptual overview of dominant peptide–membrane interactions, including electrostatic binding, pore formation, and membrane destabilization, which underlie antimicrobial and cytotoxic activity. Additional mechanisms such as intracellular targeting, reactive oxygen species induction, and immunomodulatory effects are described in the text and may vary among peptide families.

and storage tissues. These inhibitors block the activity of pathogenic and digestive serine proteases, thereby disrupting protease-mediated processes in microbes and pests and contributing to innate defense. Beyond their plant defensive roles, substantial evidence supports medicinal bioactivity of these inhibitors: soybean-derived BBIs and KTIs have been shown to modulate cell signaling and inhibit proliferation in various cancer models, and they also exhibit anti-inflammatory effects by targeting proteases involved in immune pathways, suggesting utility in inflammatory and tumor contexts [77-79].

Limitations, mitigation strategies, and therapeutic relevance

Plant pathogenesis-related (PR) proteins (PR1–PR6) possess intrinsic antimicrobial, antifungal, and immunomodulatory activities, making them attractive as therapeutic candidates; however, their clinical translation is limited by several factors. Many PR proteins are highly immunogenic or allergenic, having been shown to bind human IgE and elicit hypersensitivity reactions, thereby restricting systemic administration [80,81]. In addition, PR proteins exhibit poor pharmacokinetic properties, including rapid proteolytic degradation, short plasma half-life, and limited tissue penetration, resulting in reduced in vivo efficacy compared with in vitro antimicrobial activity [81,82]. Mechanistic ambiguity further complicates development, particularly for PR1 proteins, whose antifungal or cytotoxic actions have only recently been linked to sterol-binding and membrane disruption, limiting rational therapeutic optimization [70]. To mitigate these challenges, current approaches focus on peptide truncation to remove allergenic epitopes, recombinant expression of minimal active domains, and nanoparticle-based delivery systems to improve stability and targeted activity while reducing immunogenicity [83]. Although no native PR proteins have yet advanced to late-phase clinical trials, PR-derived peptides and engineered variants have been reported to have selective antifungal and anticancer activity in mammalian cell and animal models, supporting their potential as lead scaffolds for next-generation biologics rather than direct therapeutic agents [78].

Antimicrobial and Cytotoxic Peptide Families

Plant antimicrobial and cytotoxic peptides (AMPs and ACPs) are small, typically cysteine-rich proteins ranging from 2 to 10 kDa that serve as first-line defense molecules against a broad spectrum of pathogens, including bacteria, fungi, viruses, and insects. These peptides are highly stable due to extensive disulfide bonding and exhibit amphipathic structures that allow direct interaction with microbial membranes. In addition to antimicrobial activity, many of these peptides display cytotoxicity toward mammalian cancer cells and immunomodulatory properties, highlighting their biomedical potential. AMPs are often constitutively expressed in seeds, roots, leaves, and epidermal tissues, with inducible upregulation under biotic or abiotic stress. Plant AMPs exert their medicinal effects primarily through membrane disruption, pore formation, and induction of oxidative stress. Cationic and amphipathic properties allow selective targeting of negatively charged microbial and tumor cell membranes. Some AMPs additionally interact with intracellular targets, modulate immune responses, and inhibit viral replication, demonstrating multifunctional therapeutic potential (Figure 4) [84,85]. Plant AMPs are classified based on sequence motifs, structural folds, cysteine patterns, and biological activity.

Examples of plant AMPs/ACPs

Defensins

Plant defensins are small (~5 kDa), cysteine-rich peptides of 45–54 amino acids characterized by a conserved cysteine-stabilized α-helix/β-sheet (CSαβ) fold, maintained by four to five disulfide bridges that confer exceptional stability and amphipathicity. These peptides accumulate in multiple tissues, including seeds, leaves, roots, and flowers, and exemplify a versatile class of innate defense molecules. Functionally, plant defensins exhibit broad-spectrum antimicrobial activity against bacteria and fungi, which is attributed to their highly cationic surfaces that preferentially bind to the negatively charged membranes of these microorganisms. This leads to pore formation, membrane depolarization, and subsequent cell death. Beyond antimicrobial effects, defensins have been reported to exert anticancer cytotoxicity by targeting tumor cell membranes and inducing reactive oxygen species (ROS), as well as immunomodulatory effects, including upregulation of chemokine expression in mammalian cells, highlighting their translational potential in biomedicine [86-88].

Thionins

Thionins are small (~5 kDa), highly basic, cysteine-rich peptides stabilized by three to four disulfide bridges and are predominantly found in seeds and vegetative tissues of plants. These peptides exhibit potent antifungal and antibacterial activities through direct interaction with negatively charged microbial membranes, where their amphipathic helices insert into lipid bilayers, leading to membrane permeabilization and cell lysis. In addition to antimicrobial effects, thionins have been reported to display cytotoxicity, in part through similar membrane-disruptive mechanisms and induction of cell death in tumor cells [89,90].

Cyclotides

Cyclotides are a unique class of 28–37 amino acid cyclic peptides characterized by a cystine knot motif in which six cysteine residues form three disulfide bonds, creating exceptional structural stability. They are predominantly found in plant families such as Rubiaceae and Violaceae and accumulate in seeds, leaves, and flowers, where they contribute to innate defense. These peptides exhibit a range of bioactivities, including antimicrobial, antiviral, and anticancer effects, with their cyclic backbone conferring remarkable resistance to proteolytic degradation. Mechanistically, cyclotides interact with lipid bilayers, disrupting membrane integrity and causing leakage and cell death; certain members also interfere with viral entry and replication processes, highlighting their therapeutic potential [91,92].

Hevein-Like Peptides

Hevein-like peptides are a family of small (~4–8 kDa) cysteine-rich plant proteins. They contain conserved chitin-binding domains and are stabilized by multiple disulfide bonds, which gives them a compact and protease-resistant structure. These peptides were first identified in the latex of the rubber tree (Hevea brasiliensis) and are also found in other tissues such as bark and epidermal

layers, where they contribute to innate defense by binding chitin in fungal cell walls and insect exoskeletons, thereby inhibiting pathogen growth and compromising cell wall integrity. In addition to antifungal and broader antimicrobial effects, some hevein-like peptides have been implicated in modulating plant immune signaling and may influence host defense responses through interactions with pathogen enzymes and elicitation of defense pathways [84,93].

Limitation, mitigation strategies, and clinical progress

Despite their strong in vitro antimicrobial and cytotoxic activities, the practical applications of plant-derived AMPs and ACPs remain constrained by several intrinsic limitations. These peptides are highly susceptible to proteolytic degradation in biological and environmental matrices, resulting in short half-lives and poor bioavailability, particularly under in vivo or field conditions [94]. Their cationic and amphipathic nature, while essential for microbial killing, often compromises selectivity, leading to hemolytic activity and cytotoxic effects on mammalian cells at therapeutically relevant concentrations, thereby narrowing the therapeutic window [95]. In addition, peptide activity is frequently reduced in complex biological fluids due to binding to serum proteins or ionic shielding, limiting efficacy beyond controlled in vitro assays. From a production standpoint, chemical synthesis and purification of cysteine-rich plant peptides remain costly, while recombinant expression can suffer from low yields, misfolding, or host toxicity [96]. To address the stability, toxicity, and bioavailability constraints outlined above, current efforts focus on rational peptide engineering and advanced delivery technologies. Chemical modifications such as D-amino acid substitution, peptide cyclization, PEGylation, and sequence optimization substantially improve protease resistance, circulation time, and target selectivity while reducing hemolytic and off-target cytotoxicity. In parallel, encapsulation in nanoparticles, liposomes, or hydrogels protects AMPs/ACPs from degradation and enables controlled or site-specific release, particularly in infection sites or tumor microenvironments [97]. Synergistic combinations with conventional antibiotics further lower effective doses and mitigate toxicity while enhancing efficacy against multidrug-resistant pathogens [98]. Although AMPs have great therapeutic potential, their transition into human clinical trials remains significantly limited compared to animal-derived counterparts. The majority of plant AMP research is currently localized in the preclinical stage or focused on agricultural biotechnology.

Proteases and Protease Inhibitor Families

Plant proteases and protease inhibitor families constitute a diverse and medically significant group of proteins that encompass proteolytic enzymes, antioxidant enzymes, and metabolic enzyme inhibitors, each contributing to distinct therapeutic outcomes. Cysteine proteases such as papain from Carica papaya [99], bromelain from Ananas comosus [100], and ficin from Ficus carica [101] are well-characterized proteolytic enzymes with molecular weights ranging from 20–35 kDa, stabilized by disulfide bridges, and localized primarily in latex, fruit pulp, or vacuoles. These enzymes exhibit anti-inflammatory activity through modulation of cytokine pathways, fibrinolytic activity by cleaving fibrin clots, and anticancer effects by inducing apoptosis and disrupting tumor extracellular matrices [99-101]. Complementing these are plant antioxidant enzymes, including superoxide dismutases, catalases, and peroxidases, which mitigate oxidative stress by converting reactive oxygen species into harmless products. Notable examples, such as horseradish peroxidase (Armoracia rusticana) and Moringa-derived catalases and peroxidases, are reported to have potent radical-scavenging activity, protect cellular components from oxidative damage, and have been investigated for cardiovascular, neuroprotective, and anticancer applications [102-104]. Finally, metabolic enzymes and their natural inhibitors, particularly α-amylase and α-glucosidase inhibitors from Phaseolus vulgaris and Morus alba, contribute to glycemic regulation and obesity management by slowing carbohydrate digestion and reducing postprandial glucose spikes. Across all these protein families, tissue localization, post-translational stabilization, and concentration directly influence bioactivity, with higher accumulation in seeds, fruits, or latex correlating with enhanced therapeutic efficacy [105,106]. Mechanistically, these proteins act by enzymatically cleaving specific substrates, neutralizing reactive oxygen species, and inhibiting key metabolic enzymes.

Limitations, mitigation strategies, and clinical progress

The therapeutic application of plant proteases and protease inhibitor families is constrained by limited specificity, unfavorable pharmacokinetics, and safety concerns. Many plant protease inhibitors exhibit promiscuous inhibition across related protease families, increasing the risk of off-target effects and disruption of essential host proteolytic processes, particularly in coagulation and digestion. Their proteinaceous nature further results in short in vivo half-lives, poor oral bioavailability, and high susceptibility to proteolytic degradation, while immunogenicity and anti-nutritional effects, such as inhibition of human trypsin and chymotrypsin, raise additional safety concerns. Variability in plant-derived preparations and the high cost of producing homogeneous recombinant inhibitors further complicate standardization and scale-up [107]. To overcome these challenges, current strategies emphasize precision engineering and targeted delivery. Structure-based drug design and peptidomimetic approaches are being used to improve specificity and proteolytic stability, while nano-formulations (liposomes, nanoparticles, hydrogels) enhance protection from degradation and extend systemic circulation. Combination therapies that pair protease inhibitors with chemotherapy or immunotherapy reduce required dosages and limit resistance, while targeting compensatory proteolysis pathways (e.g., aggresome–autophagy systems) mitigates adaptive escape mechanisms. Reflecting these advances, several plant-derived or plant-inspired protease inhibitors have progressed into clinical

evaluation, including the Bowman–Birk inhibitor (BBI) for cancer prevention. It has been evaluated in early-phase clinical trials, including Phase II studies for oral leukoplakia, as a potential chemopreventive agent. While these trials have been reported to be safe and have shown some biomarker modulation, definitive evidence for cancer prevention efficacy remains limited [108,109]. Collectively, these developments indicate that while native plant proteases and inhibitors face translational barriers, engineered and selectively delivered derivatives could achieve clinical relevance.

Other Enzymes with Biomedical Applications

Plant-derived enzymes extend beyond proteases to include a variety of catalytic proteins with direct biomedical relevance, such as lipases, phosphatases, and nucleases. These enzymes typically range from 20 to 60 kDa, are stabilized by disulfide bonds or cofactor binding, and are localized in seeds, leaves, or specialized secretory tissues. Lipases from *Coriandrum sativum* and *Elaeis guineensis* exhibit antithrombotic and lipid-lowering activities by catalyzing the hydrolysis of triglycerides and phospholipids, thereby modulating lipid metabolism in vivo. Phosphatases, including acid and alkaline phosphatases from Allium cepa and *Pisum sativum,* have been investigated for their roles in bone health, signal transduction modulation, and detoxification of phosphate-containing xenobiotics. Nucleases, such as ribonucleases and deoxyribonucleases from *Cucumis sativus* and *Ricinus communis*, exhibit antiviral and anticancer properties by degrading nucleic acids in targeted pathogens or tumor cells, inducing apoptosis or inhibiting viral replication. The therapeutic potential of these enzymes is further enhanced by tissue-specific expression, post-translational modifications, and inherent stability under physiological conditions. The biomedical activity is mediated by substrate-specific hydrolysis, modulation of cellular signaling pathways, and induction of programmed cell death, making plant enzymes versatile tools for therapeutic development and industrial biotechnology [110-112].

Storage Proteins and Nutraceutical Bioactive Proteins

Plant storage proteins, traditionally considered nutrient reservoirs, have emerged as important bioactive molecules with medicinal and nutraceutical applications. These proteins, including globulins, albumins, and legumins, generally range from 20 to 70 kDa per subunit and are enriched in seeds, tubers, and nuts, often forming multimeric complexes that confer stability and slow-release properties. Beyond their nutritional value, storage proteins from *Phaseolus vulgaris*, *Glycine max*, and *Arachis hypogaea* exhibit immunomodulatory, antioxidant, and anti-inflammatory effects. Specific subunits can bind carbohydrates or interact with immune receptors, modulating cytokine secretion and enhancing host defense mechanisms. Additionally, certain storage proteins act as natural enzyme inhibitors or carry latent antimicrobial peptides, contributing to protection against microbial contamination and metabolic dysregulation. Their medicinal effects are mediated through interactions with cellular targets, modulation of oxidative stress pathways, and inhibition of pathogenic enzymes, while high stability and abundance in seeds make them amenable to extraction and formulation as nutraceuticals. These features position storage proteins as dual-function molecules that provide both dietary benefits and therapeutic potential [113-115].

Future Perspectives of Bioactive Plant Proteins

Bioactive plant proteins are emerging as a promising frontier in both the pharmaceutical and nutraceutical industries (Table 3). Advances in high-throughput genomics, transcriptomics, and proteomics have enabled rapid identification and functional characterization of novel protein candidates, while recombinant expression systems allow scalable production. Currently, several plant proteins are in preclinical or early clinical phases, including lectin-derived immunotoxins for targeted cancer therapy, enzyme-based antiviral agents, and peptide-based antimicrobial formulations. Nutraceutical applications are also expanding, with seed storage proteins and enzyme inhibitors incorporated into functional foods and dietary supplements for glycemic control, cardiovascular health, and immune support [5].

Despite this progress, several challenges limit broader industrial adoption. Proteins often exhibit limited stability, potential immunogenicity, and batch-to-batch variability, which necessitate careful engineering, formulation, and delivery strategies. Innovations such as protein engineering, glycoengineering, encapsulation, and conjugation to targeting moieties are being applied to improve stability, bioavailability, and specificity. Furthermore, regulatory frameworks for protein-based therapeutics and nutraceuticals are evolving, requiring rigorous safety and efficacy evaluation [116].

Cross-Cutting Strategies for Toxicity Reduction and Functional Preservation

While individual protein families exhibit distinct translational limitations, several cross-cutting biotechnological strategies have emerged to reduce toxicity while maintaining therapeutic bioactivity. These approaches operate at structural, molecular, and formulation levels. At the structural level, protein engineering strategies such as site-directed mutagenesis, domain truncation, and epitope deletion are used to minimize off-target binding and immunogenicity while preserving catalytic and binding domains. Deimmunization algorithms and in-silico epitope mapping further allow rational redesign of plant proteins to reduce T-cell activation potential while preserving functional conformation. Chemical modification approaches, including PEGylation, glycoengineering, and backbone cyclization, improve serum half-life, reduce proteolytic degradation, and mask immunogenic epitopes. PEGylation has been shown to decrease systemic toxicity

and renal clearance while maintaining catalytic efficiency in several protein therapeutics [117].

Advanced formulation systems have become central to translational development. Encapsulation within liposomes, polymeric nanoparticles, micelles, dendrimers, or hydrogel matrices enhances stability, protects against enzymatic degradation, and enables sustained or site-specific release. These delivery systems can reduce systemic exposure while maintaining high local concentrations at disease sites. Targeted delivery represents another critical strategy. Conjugation to monoclonal antibodies, receptor ligands, or cell-penetrating peptides improves cellular selectivity and minimizes collateral toxicity. In RIP-derived immunotoxins, removal of lectin domains combined with antibody-guided targeting significantly enhances therapeutic index [118-120]. Controlled activation systems, including protease-cleavable linkers and tumor microenvironment-responsive designs, further refine safety by ensuring activation occurs predominantly at pathological sites [121].

Collectively, advances in protein engineering, chemical modification, and nanotechnology-based delivery systems are transforming inherently potent yet potentially toxic plant proteins into controllable biologic platforms with improved pharmacokinetics, reduced immunogenicity, and preserved target specificity, thereby enhancing their therapeutic index and translational feasibility. Future progress will depend on genomics-driven discovery of novel protein scaffolds, high-throughput functional screening, precision-targeted and stimulus-responsive delivery strategies, and rational combinatorial approaches with small-molecule drugs. Achieving clinical and industrial impact will require coordinated interdisciplinary collaboration across plant biology, structural biology, pharmacology, and bioengineering, positioning bioactive plant proteins as a sustainable and multifunctional reservoir for next-generation therapeutics and nutraceuticals [122].

Conclusion

Plant-derived proteins represent a versatile and rapidly growing class of bioactive molecules with broad potential for therapeutic and nutraceutical applications. Their inherent specificity, stability, and multifunctional bioactivity provide opportunities for developing novel interventions that complement existing small-molecule drugs. Technological advances in genomics, proteomics, protein engineering, and targeted delivery systems are enabling scalable production and improved safety profiles, bringing many candidates closer to industrial and clinical realization. While challenges such as immunogenicity, stability, and regulatory hurdles remain, ongoing innovations in protein design, formulation, and delivery are mitigating these limitations. The evolutionary diversity of plant protein families offers a rich resource for discovering novel bioactivities and mechanisms, particularly against cancer, infectious diseases, inflammation, and metabolic disorders. Integration of plant protein research with pharmaceutical development, functional foods, and nutraceutical industries promises to expand the pipeline

Table 3: Summary of main plants' bioactive proteins and their reported biological activities, challenges, and possible medicinal translation

Protein Family	Main Indications (Reported/Investigated)	Key Limitations	Furthest Clinical Stage Reported
Lectins	Anticancer (apoptosis induction, immune activation), antiviral (HIV-1, SARS-CoV-2 entry inhibition), immunomodulation, antimicrobial, anti-inflammatory	Off-target glycan binding; mitogenicity; immunogenicity; systemic cytotoxicity; narrow therapeutic index	Early-phase clinical trials (e.g., mistletoe extracts; recombinant griffithsin Phase I as a topical microbicide)
Ribosome-Inactivating Proteins (RIPs)	Anticancer (immunotoxins), antiviral (HIV-1, HBV, HSV), experimental cytotoxic payloads	High intrinsic toxicity (especially Type II RIPs); immunogenicity; delivery challenges; narrow safety margin	Phase I/II trials for RIP-derived immunotoxins; no approved standalone RIP therapeutics
Pathogenesis-Related (PR) Proteins	Antifungal and antibacterial; anticancer (apoptosis induction); anti-inflammatory; metabolic regulation (e.g., BBI chemoprevention)	Allergenicity (IgE binding); limited pharmacokinetics; rapid degradation; incomplete mechanistic clarity (for some PR classes)	Early-phase clinical evaluation for specific derivatives (e.g., Bowman–Birk inhibitor Phase II for oral leukoplakia); most remain preclinical
Antimicrobial / Cytotoxic Peptides (AMPs/ACPs)	Antibacterial; antifungal; antiviral; anticancer (membrane disruption, ROS induction); immunomodulation	Proteolytic instability; hemolysis and off-target cytotoxicity; reduced activity in biological fluids; production cost	Primarily preclinical (in vitro and animal models); no advanced human trials reported
Proteases & Protease Inhibitors	Anti-inflammatory; fibrinolytic; anticancer adjunct; metabolic regulation (glycemic control, weight management)	Limited specificity; off-target proteolysis; short half-life; anti-nutritional effects (for some inhibitors); formulation challenges	Clinical use in nutraceutical contexts; BBI early-phase trials; several enzyme preparations used as supplements rather than regulated drugs
Other Enzymes (Lipases, Phosphatases, Nucleases)	Lipid modulation; bone health; antiviral; anticancer (nucleic acid degradation)	Limited clinical validation; delivery constraints; specificity concerns; immunogenic potential	Preclinical/experimental stage
Storage Proteins / Nutraceutical Proteins	Immunomodulatory; antioxidant; anti-inflammatory; metabolic support	Limited direct therapeutic validation; variability in preparations; regulatory classification challenges	Nutraceutical/functional food applications; not as advanced as regulated biologics

of biologically active agents. Continued interdisciplinary collaboration and strategic investment in research, high-throughput screening, and translational studies will be key to unlocking the full therapeutic and commercial potential of plant-derived bioactive proteins.

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Availability of data and materials

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CRediT author statement

MEMO: Conceptualization; Data curation; Formal analysis; Validation; Visualization; Writing-original draft; Writing-review and editing.

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