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PATHOGENESIS-RELATED PROTEINS IN PLANTS: MOLECULAR FEATURES, FUNCTIONAL DIVERSITY, AND BIOTECHNOLOGICAL APPLICATIONS

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Abstract *Pathogenesis-related (PR) proteins are critical components of the plant immune system, rapidly accumulating in response to pathogen attack and various stresses. Since their first identification in tobacco infected with Tobacco Mosaic Virus (TMV), these inducible proteins have been classified into multiple families based on sequence and functional characteristics. PR proteins exhibit a range of biochemical activities – including cell-wall degrading enzyme activities (e.g., chitinases, glucanases), antimicrobial peptide functions (e.g., defensins, thionins), and protease inhibition – that contribute to direct pathogen suppression and modulation of defense signaling. Advances in molecular cloning have enabled transgenic expression of PR genes in susceptible crops, often leading to enhanced resistance against fungi, bacteria, oomycetes, and viruses. Beyond plant immunity, some PR proteins display multifunctional properties relevant to stress tolerance and pharmacology. This review summarizes current understanding of PR protein classification, molecular features, induction by biotic/abiotic cues, and their application in crop protection, while highlighting opportunities and challenges in harnessing PR proteins for biotechnology.*

Keywords: *Pathogenesis-related (PR) proteins; chitinases; glucanases; defensins; thionins; fungi, bacteria, oomycetes; viruses*

Introduction

Recent molecular studies suggest that PR proteins operate as downstream markers of the salicylic-acid-dependent defense cascade, and their induction often coincides with the activation of systemic acquired resistance in distal tissues (Edreva, 2005). Initially, PR proteins were discovered in tobacco against TMV and were called 'b-proteins (Gianinazzi et al., 1970; Van Loon and Van Kammen, 1970). In 1980, these putative defensive proteins as were named as "Pathogenesis Related Proteins (PR)". Pathogenesis-related proteins are mainly expressed by resistant plants and induce a hypersensitive necrosis response (HR) against pathogens. Later, it was proved that PRs were not only expressed under biotic stress but also against abiotic stress environments. When PRs were found to accumulate in tobacco under hypersensitive reaction, more research was conducted in this area, and all physical, biochemical, genetic, and molecular properties of PRs were studied (Datta and Muthukrishnan, 1999).

PRs have particular physical and biochemical properties upon which they are distinguished. Their molecular weight ranges between 6-43 kDa; hence, they are low molecular weight proteins. They can be extracted from plant cells and are stable in low pH conditions, usually below 3 (Datta and Muthukrishnan, 1999; Van Loon and Van Kammen, 1970). Other distinguished properties, like their thermostability and high resistance to proteases, are due to their compact molecular framework comprising four alpha helices and four beta sheets in which beta sheets run antiparallel between alpha helices. Nuclear magnetic resonance (NMR) studies showed that these alpha helices and beta sheets form a tightly packed bipartite core having an 'alpha-beta-alpha' configuration and are stabilized by hydrogen and hydrophobic interactions (Fernández et al., 1997). Many PR proteins contain conserved disulfide bridges stabilizing their tertiary structure, a feature that contributes to their remarkable resistance to temperature fluctuations and proteolytic cleavage. Comparative structural studies in rice, tobacco, and Arabidopsis reveal that these proteins maintain their bioactivity even after prolonged exposure to acidic environments, a property uncommon among typical cytosolic proteins.

Transcriptomic analysis also indicates that acidic PR isoforms preferentially accumulate in the apoplast, whereas basic isoforms are more common in vacuoles and intracellular compartments. Their secretion usually follows the classical ER–Golgi route, supporting the view that PR proteins function primarily as extracellular defense molecules (Van Loon and Van Kammen, 1970). Other cellular locations are the primary cell wall, the secondary cell wall, and, in case of fungal infection, cell wall papillae (Benhamou et al., 1991; Jeun, 2000; Jeun and Buchenauer, 2001). Early concept proposed by Asselin and coworkers stated that PRs were confined to photosynthesizing plant tissues only (Asselin et al., 1985), but later research showed that they are present in leaves, roots, stems, and flowers of plants (Van Loon and Van Kammen, 1970). Research allowed the detection of PR proteins in roots of cucumber treated with a *Trichoderma harzianum* strain T-203 (Yedidia et al., 2000), and new chitinase lysozyme, and PRs have been isolated and characterized from *Medicago sativa* roots, which function in the cleavage of Nod factors of *Rhizobium meliloti* (MINIC et al., 1998). Not only biotic factors but abiotic factors are also involved in the induction of PRs in plants; these include inorganic salts, chemicals like salicylic acid, fatty acids, and polyacrylic acid, physical factors like UV-B radiation, freezing temperature, injury, osmotic shock, water excess, and drought, are involved in PRs induction (Van Loon and Van Kammen, 1970);(EDREVA, 1990) (Tamás et al., 1997) (Pääkkönen et al., 1998) (Buchel and Linthorst, 1999) (Fujibe et al., 2000). Under drought or salinity stress, plants accumulate reactive oxygen species (ROS), and PR proteins—particularly PR-2, PR-3, and PR-5—are frequently upregulated as part of the ROS-scavenging and cell-wall strengthening responses. Some PR genes are also temperature-responsive, showing rapid induction under cold shock due to ABA-mediated signaling. Besides these environmental factors, plant hormones like jasmonic acid, abscisic acid, ethylene, and auxin also play an important role in PRs induction.

Salicylic acid (SA) signaling is typically linked with defense against biotrophic pathogens and drives the classical systemic acquired resistance (SAR) program, including strong induction of PR-1/PR-2/PR-5(Alazem and Lin, 2015). In contrast, jasmonic acid (JA) and ethylene (ET) frequently act synergistically to promote defenses against necrotrophs and herbivores, activating many chitinases/defensins and other antimicrobial PRs. Abscisic acid (ABA) primarily mediates abiotic stress responses (drought, salinity, and cold) and can either suppress or potentiate immunity by crosstalk with SA and JA/ET pathways, thereby fine-tuning PR gene expression depending on the stress context (Buchel and Linthorst, 1999) (Fujibe et al., 2000). The discovery of PRs opened the door for a novel research field. The research on the genetics of PRs in plants showed that the genes belong to a tiny multigene family and the expression of synthesis of PRs is regulated at the transcriptional level (Edreva, 2005). The PR-promoters consist of various cis- regulatory elements that mediate PR gene expression. The cis-regulatory elements are GCC box, MRE-like sequence, G box, SA-responsive element, and W box (Zhou, 1999). Most PR promoters recruit WRKY transcription factors that bind to W-box elements, whereas NPR1—acting as a central immune regulator—bridges SA signaling with transcriptional activation of several PR gene families. Grafting experiments showed that PRs are produced *in-situ* that depicts that they are site-specific and are produced where they are needed and are not transported to other sites after their synthesis (Gianinazzi, 1982).

During SAR, locally produced signals trigger SA accumulation in distal tissues, leading to NPR1 activation and broad PR-gene transcription in uninfected leaves (Edreva, 2005). Early ROS bursts serve as second messengers that amplify defense via redox changes and MAPK signaling, and they also influence NPR1 activity through cellular redox status. WRKY factors cooperate with NPR1 (and associated co-regulators such as TGAs) at PR promoters to integrate SA with JA/ET crosstalk and produce context-specific PR expression patterns (Gianinazzi, 1982). Recent genome-wide analyses in rice, citrus, and grapevine have identified dozens of PR gene members with diverse regulatory motifs, highlighting their expanded roles beyond pathogen defense. Functional studies in transgenic tomato, soybean, and tobacco have demonstrated that constitutive or inducible expression of individual PR genes can markedly reduce disease severity. Plants of the family *Nicotiana glutinosa*, having the N-resistance gene, upon infection with tobacco mosaic virus leads to hypersensitivity that prevents further spread of the virus. Spread is restrained due to the formation of lesions. In addition to this, plants have an inbuilt resistance mechanism called SAR (systemic acquired resistance). Van Loon studied the correlation between the presence of PR proteins and the onset of SAR mechanism. This review focuses on the classification of PR families across plant species and integrates classical discoveries with recent genomic, transcriptomic, and functional studies. The aim is to provide a consolidated understanding of PR classification, distribution across taxa, molecular cloning efforts, transgenic applications, and emerging opportunities for using PR-based defenses in crop improvement.

Characterization of PR proteins

A 10,000-fold increase in PR proteins has been observed in infected plant tissue. This high expression of PR-genes can indicate the defensive response of plants. Since PR proteins have been extensively studied in tobacco plants, this article will contain the classes of PR proteins with reference to the biological system of tobacco.

General classes are Acidic PR1Ps and Basic PR1Ps.

Structural Classes are as follows:

1. Plant β-1,3-Glucanases (PR-2)
2. Plant Chitinases (PR-3, PR-4, PR-8, PR-11)
3. PR-5 Family- Thaumatin-Like Proteins
4. PR-6 Family: Proteinase Inhibitors

First-class beta 1,3 glucanases cleave the glucosidic bond between 1,3 glucans. These enzymes are abundant in seed plants. Their expression is also observed in uninfected plants under complex and diverse environmental and developmental conditions. There are many structural classes of B-1,2 Glucanases, having different sizes and regulation patterns. All of these glucanases are important for plant reproductive function. Another, stylar and endosperm contain these. Besides all these functions, these enzymes have shown antifungal activity in vitro. Chitinases hydrolyze the residues of the fungal cell wall component chitin. Thus, these are antifungal.

PR-5 Family proteins are extremely sweet in taste and move slowly on polyacrylamide gel. This family consists of thaumatin-like proteins that accumulate under osmotic stress and function as antifungal and anti-freezing agents.

The next family containing proteinase inhibitors is much more stable and shows defensive properties upon insect or pathogen attack. These plant proteins inhibit proteinases whose function in pathogenicity is important.

Table 1: Classification of PR proteins. This table summarizes major PR families and lists their key properties/activities, representative members and commonly used gene symbols

Family	Properties	Type/Member	Gene symbol
PR-1	Unknown	Tobacco PR-1a	ypr1
PR-2	β -1,3 glucanase	Tobacco PR-2	ypr2
PR-3	Chitinases type I, II, IV,V, VI.VII	Tobacco P, Q	ypr3
PR-4	Chitinase type I, II	Tobacco R	ypr4
PR-5	TLPS thaumatin like proteins	Tobacco S	ypr5
PR-6	Protease Inhibitor	Tomato inhibitor-1	ypr6
PR-7	End proteinase	Tomato P69	ypr7
PR-8	Chitinase type III	Cucumber chitinase	ypr8
PR-9	Peroxidase	Tobacco lignin forming peroxidase	ypr9
PR-10	Ribosome inactivating proteins	Parsley PR-1	ypr10
PR-11	Chitinase type 1	Tobacco class V chitinase	ypr11
PR-12	Defensins	Radish R5 AFP-3	ypr12
PR-13	Thionins	*Arabidopsis* TH.12-1	ypr13
PR-14	Lipid transfer protein	Barley LTP-4	ypr14

Many other families are also recognized, summarized in table 2.

Discovery of PRs in different plant families

Across plant taxa, pathogen infection or stress frequently leads to de novo accumulation of host-derived PR proteins in infected tissues and, in many cases, in distal organs during systemic signaling (Van Loon and Van Kammen, 1970; van Loon, 1985). After the original description of virus-induced PR proteins in tobacco, homologous PR families have been reported in numerous plant families and are now widely used as molecular markers of activated defense responses (Antoniw et al., 1980; Redolfi and Cantisani, 1984). PR accumulation often correlates with localized necrosis or hypersensitive reactions, but can also be triggered by elicitors and abiotic stresses (Wagih and Coutts, 1981). Table 2 summarizes representative examples of PR proteins identified in different plant species, their putative functions, inducing agents, and key references.

Table 2: PR proteins reported in different plant families. The table compiles representative species, number of PRs detected, proposed functions, inducing pathogens/stresses and references

Plant Name	No. of PRs	Function	Against	References
Amaranthaceae Family				
Gomphrena globosa	5	unknown	TBSV, Mineral deficiency and light exposure	(Pennazio, 1981)
Chenopodiaceae Family				

Beta vulgaris	1(1a/B5Q TD3)	unclear	Beet necrotic yellow vein virus	(Webb et al., 2014)
Compositae Family				
Gynura aurantiaca	2-3	unknown	citrus exocortics viroid	(Conejero et al., 1979)
Helianthus annus	PR2, PR3	β1,3glucanase, Chitinase	Aspirin stress	(Jung et al., 1993)
Cruciferae Family				
Arabidopsis thaliana	PR1, PR5	Unknown, Thionin activity	*Trichoderma harzianum*	(Pečenková et al., 2017)
Brassica nigra	PR2, Q,S	Chitinase and thaumatin like	*Phoma lingam*	(Dixelius, 1994)
Brassica oleracae	PR2	β1,3glucanase	*Peronospora parasitica*	(Ziadi et al., 2001)
Raphanus raphanistrum	PR2,3	β1,3glucanase, Chitinase	*Alternaria alternate*, *Fusarium oxysporum*	(Khanal et al., 2014)
Brassica nupus	PR1	unknown	Trichoderma harzianum, Sclerotinia sclerotiorum	(Alkooranee et al., 2017)
Cucurbitaceae Family				
Cucumis sativus	2-3	Chitinase activity	Tomato spotted wilt virus	(Tas and Peters, 1977; Wagih and Coutts, 1982)
Gramineae Family				
Hordeum vulgare	2	Chitinase plus β1,3glucanase or like antibiotic nikkomycin	Yeast species	(Grenier et al., 1993; Reiss and Bryngelsson, 1996)
Zea mays	PR10,8 others	Chitinase glycanohydrolase activity	*Aspergillus flavus*, mercuric chloride stress	(Chen et al., 2006; Nasser et al., 1988)
Triticum aestium	PR4 PR1,3 and 5	Ribonuclease activity Chitinases and thaumatin like	*Fusarium culmorum* Ethylene Stress	(Caporale et al., 2004) (Freitas et al., 2003)
Malvaceae Family				
Gossypium hirsutum	PR1 PR5 PR12	Unknown Thaumatin like Involved in JA and ET dependent defense signaling pathway	*Verticillium dahliae*	(Du et al., 2017)
Papilionaceae Family				
Medicago sativa	PR10	RNase activity, ligand interactor and posttranslational modifiers	P. syringae pv pisi, salicylic acid stress, Alfalfa mosaic virus	(Alblas and De, 1986)
Pinaceae Family				
Picea abies	PR-P PRm-6	Endochutinase β1,3glucanase	Ozone exposure	(Kärenlampi et al., 1994)
Rutaceae Family				
Citrus sinensis	PR2,3,5,7, 9,14,15,16	β1,3glucanase, Chitinase, Thaumatin like, Aspartic proteinase, lignin forming	*Xylella fastidiosa, Citrus leprosis virus, Phytophothora parasitica*	(Campos et al., 2007)

		peroxidases, lipid tranferin proetrin, oxalte oxidase		
Solanaceae Family				
Nicotiana debneyi	PR1	Unknown	*Tobacco Mosaic virus*	(Ahl et al., 1982; Ahl and Gianinazzi, 1982)
Nicotiana tabacum	PR4,5,9,11	Chitinase, Thaumatin like, lignin forming peroxidases	*Tobacco Mosaic virus*	(Campos et al., 2007; Gianinazzi et al., 1977)
Solanum tunersum	2	Unknown	*citrus exocortics viroid*	(Conejero et al., 1979)
Umbelliferae Family				
Apium graveolens	1	Unknown	*Viriod*	(Henriquez and Sänger, 1982)
Petroselinum	PR1-4	β1,3glucanase, Chitinase	Ozone and Heat shock	(Eckey-Kaltenbach et al., 1997)
Vitaceae Family				
Vitis vinifera	PR-1	Unknown	*Botrytis cinerea, Plasmopora viticola*	(Enoki and Suzuki, 2016)
Vitis pseudo reticulata	PR10.1	Ribonuclease activity	*Erysiphe necator*	(Xu et al., 2014b)

Cloning of PRs from plants

PR proteins are induced against specific pathogens or environmental stress; these proteins were isolated and purified from the plants and cloned into specific vectors under control promoters and transformed into susceptible plants, making them resistant to pathogens. Most of these proteins are specific to control different types of stresses (biotic or abiotic stress). B-1, 3-Glucanase is a particular pathogenesis-related protein that is expressed by sugarcane and assist to activate its defense system during the pathogen-plant interaction. It helps to generate resistance against smut in sugarcane. It's two of the genes called ScGluA1 and ScGluD1, have been identified, and their cDNA sequences were retrieved from the GenBank nucleotide database. PCR of these specific genes was performed, purified, and then cloned into PMD18-T vector (Su et al., 2013). PR 10 genes encode for the proteins that help to resist biotic and abiotic stresses. A cDNA had been cloned from Spinacia oleracea L. (Spinach) that encodes for PR 10 proteins called SoPR10. After obtaining the full-length sequence, a PCR run is performed against specific primers, and then these sequences are cloned into PMD18-T vector. (Bai et al., 2014)

A member of PR-5 group, called Thaumatin-like proteins (TLP-D34) were induced in different plants to respond to stress. Its antifungal activity assist to produce disease resistance in plants. It has been isolated from rice and cloned into the vector pGL2 under the control of CaMV promoter (Datta et al., 1999). P23 is a PR-5 protein of tomato and is produced when there is infection of citrus exocortis viroid. PR-5 protein was cloned from the VFN8 genomic library by using a specific PrP23 probe. This construct was cloned into tomato-specific vectors (PBI121) at the restriction site of Hind3. PR-5 sequences were flanked by neomycin phosphotransferase that provides resistance against the kanamycin antibiotic (Fagoaga et al., 2001). PR-1a is a protein that is produced in tobacco under stress conditions. The cDNA clone encoding the full sequence of PR-1a protein was subcloned into pCGN1761 with the help of the restriction enzyme EcoR1. These plasmids having PR1 gene were then transformed into Agrobacterium *tumefaciens* (Alexander et al., 1993). Another PR-protein isolated from barley was chitinases that helps to protect barley from infection by pathogens. These chitinases, having a molecular weight of 35kDa were cloned into a particular vector, and then their expression in Escherichia coli was checked. These chitinases act as a major antifungal agent against different fungal species i.e., Alternaria sp. Etc. That's why they are used to increase resistance in rice, tea, clover, and tobacco against fungus (Kirubakaran and Sakthivel, 2007). PR-10 has been found essential in antifungal, antiviral, and antibacterial processes. PR-10 is present in different plants e.g., wheat, rice, Zea mays, etc. This gene has isolated from Zea mays and cloned into the expression vector pET26b and then expressed in Escherichia coli, particularly in Rosetta DE3. (Zandvakili et al., 2017)

Transgenic Containing PRPs

Plant pathogen proteins have been studied since the 1980s. And cloning these transgenes into transgenic plants has been a successful story. Some of the transgenic plants are discussed below:

1. Tobacco
2. Tomato
3. Rice
4. Potato
5. Apple
6. Oranges
7. Soya bean
8. Grapevine
9. Cucumber
10. Strawberry
11. *Chrysanthemum* (Takatsu et al., 1999)

1. Tobacco

Both PR1a and GRP are glycine-rich Plant-Related Pathogen proteins and are induced when TMV infects the plant. Their functions are unknown. But they work on the principle of acquired resistance. Many PRPs are used in transgenic experiments to induce defense against pathogens, where their genes are usually fused with GUS reporter gene (Condit and Meagher, 1986; GRÜNER and PFITZNER, 1994; Linthorst et al., 1989; Van Huijsduijnen et al., 1986; Varner and Cassab, 1986). Genome-derived pathogen-related proteins GRP, PR-1a, and complementary DNA PR-S have been expressed in Samsun NN tobacco cells. 35S promoter of CMV (Cauliflower Mosaic Virus) was used as transcriptional control. RNA and protein gel blotting showed positive insertion of a gene, which was then proceeded for self-pollination and seed formation. But the later generations of these transgenics showed no positive defense against TMV (Tobacco Mosaic Virus) or AMV (Alfalfa Mosaic Virus) (Linthorst et al., 1989; Vierheilig et al., 1995). Transformation of PR1a and PR-S generated a total of nine kanamycin-resistant plants, and GRP generated 11. And after infection of transgenic Tobacco plants with TMV (Figure 1) and AIMV, there was no clear resistance against the viruses (Linthorst et al., 1989). Transgenics with PR-1a, PR-3, PR-4, and PR5 transgenesis were also checked to see if they can provide defense against Glomus mosseae, a vesicular-arbuscular mycorrhizal fungus. As a result, a transgenic plant was observed with constitutive expression of a protein with (beta)-1,3-glucanase activity, which was an acidic isoform of tobacco PR-2. (Ryals et al., 1994; Vierheilig et al., 1995; Ward et al., 1991).

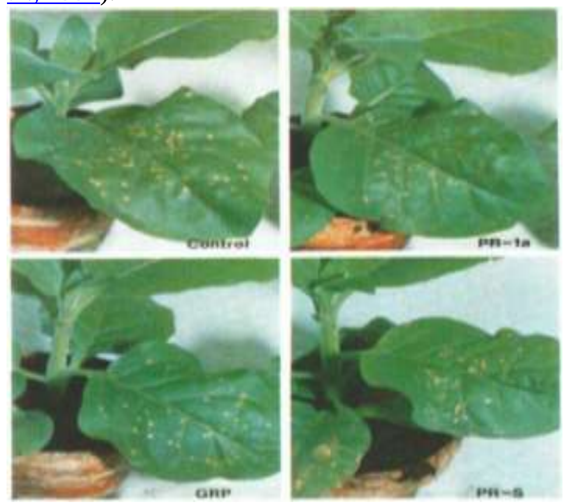

Figure 1 Infection of transgenic tobacco with TMV (Linthorst et al., 1989)

In other research, the transgenic tobacco was made tolerant against two oomycete pathogens (Figure 2), *Peronospora tabacina* and *Phytophthora parasitica*, via PR1a protein (Alexander et al., 1993). The plasmid made for PR1 transgenesis was transformed via *Agrobacterium*. Plants used *Nicotiana tabacum* to check for kanamycin resistance. The effect of PR1a was checked against *Tobacco Mosaic Virus, Potato Virus Y, Cercospora nicotianae, Phytophthora parasitica var. nicotianae, Pseudomonas syringae pv. tabaci* and *Peronospora tabacina* (Figure 3). The transgenic line did not differ from the control, and all showed the symptoms except against two oomycete pathogens *P.tabacina* causative agent of blue mold disease, and *P.parasitica* var. nicotianae causative agent of blank shank disease (Alexander et al., 1993).

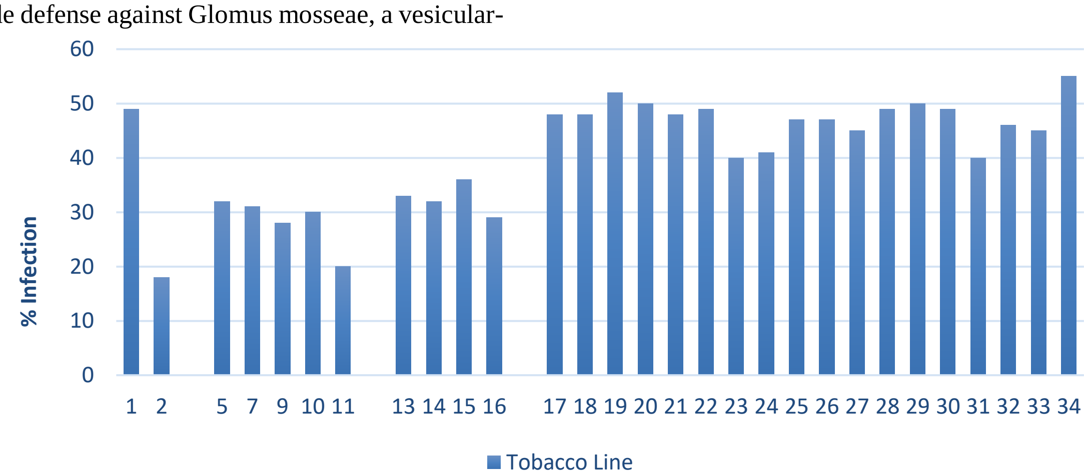

Figure 2 Blue mold disease ratings. Plant were scored for the percentage of total leaf area infected 7 days after infection (Alexander et al., 1993)

Figure 3 P. parasitica-infected tobacco plants. The two non-transgenic plants showed wilting. The third PR1a transgenic showed little wilting, and the fourth transgenic showed no symptoms (Alexander et al., 1993)

2. Tomato

The *Arabidopsis* NPR1 gene was inserted in tomato cultivar as a transgene, and the plant protein provided dual function of heat tolerance and protection against Tomato Mosaic Virus (ToMV). All the horticulture traits and morphology of transgenic lines were normal for up to four generations. The symptoms that appear on infection of ToMV, like Fusarium Wilt, Bacterial Wilt, Gray leaf Spot, and Bacterial Spot, were greatly reduced (Alexander et al., 1993). One of the major reasons for a significant crop loss is an oomycete plant pathogen (*Phytophthora citrophthora*) of citrus plants. P23, a pathogen-related protein group PR-5 was transformed in Citrus sinensis L. Obs. cv. Pineapple (Tomato) under CaMV 35S promoter. The continuous lowering in lesion production was observed as compared to control plants (Fagoaga et al., 2001; Rodrigo et al., 1991).

3. Rice

Rhizoconia solani is the rice fungus that causes Sheath Blight (ShB) and causes potential loss of rice crop in Asia (Datta et al., 1999; Ou, 1985). The infection starts from the plant surface as cushions and then spreads over the entire plant body through its hyphae, causing necrotic damage. When there is a pathogen infection in a plant, stress, elicitors, and developmental signals, Thaumatin-like receptors (TLP) are induced in them. TLPs are one of a group of Pathogen Related Protein (PR-5) (Bryngelsson and Green, 1989; Datta et al., 1999; King et al., 1988; Pierpoint et al., 1987; Singh et al., 1987; Van Loon et al., 1987). The overexpression was induced in transgenic lines of elite indica rice cultivars to make it competent against sheath blight disease (Figure 4) under the transcriptional control unit of CaMV 35S promoter (Datta et al., 1999).

Figure 4 Biological assay of control and transgenic rice showing disease symptoms; left Control rice plant showing disease symptom, right transgenic rice showing partial disease symptom (Datta et al., 1999)

The effect of PR-3 in transgenic cultivars of elite indica rice was also a success story in enhancing resistance against sheath blight. This was a PEG-mediated transformation system (Datta et al., 2001).

4. Potato

A related research with transgenic potato showed enhanced tolerance against light blight fungus *Phytophthora infestans* when osmotic-like protein (PR-5) was inserted into it (Zhu et al., 1996).

5. Apple

Agrobacterium-mediated transformation was performed by which pathogen-related protein gene was inserted in 'Galaxy' an apple scion cultivar, and apple rootstock M.26. This was to increase their defense against *Erwinia amylovora*, a causative agent of fire blight in apples (Ko et al., 1999; Ko et al., 2000).

6. Orange

One of the major reasons for a significant crop loss is an oomycete plant pathogen (*Phytophthora citrophthora*) of citrus plants. P23 is P-5 protein naturally produced in tomato against this fungus. In a study, resistance was made to induce resistance in sweet orange and checked for its resistance to *Phytophthora citrophthora*. The transgenic orange cultivar showed potential protection from the oomycete as compared to control samples (Fagoaga et al., 2001; Rodrigo et al., 1991).

7. Soya bean

Class 10 PR protein, GmPR10, was found to be expressed in *Glycine max* (Soya bean) when infected with *Phytophthora sojae* where its abundance was higher in leaves than in stems and roots. When transgenic Soya bean and Tobacco plants were overexpressing GmPR10, they produced complete resistance in both of them against P.sojae and *P.nicotianae* Breda, respectively.(Xu et al., 2014a)

8. Grapevine

Agrobacterium was used to transform RCC2 (Rice Chitinase Gene) into *Vitis Vinifera* L. cv. Neo Muscut). This transgenic grapevine plant showed resistance against the fungi *Uncinula necator,* which causes powdery mildew. Symptoms of disease were there, but very little as compared to control plants (Yamamoto et al., 2000). This saved the yield loss due to powdery mildew, gray mold rot, downy mildew, and anthracnose, as grapes are used for wine, raisins, and most importantly for table sugar. This transgenesis was successful against powdery mildews.

9. Cucumber

cDNA of RCC2 gene was transformed via *Agrobacterium* into cucumber (*Cucumis sativus* L.), which was under the control of 35S promoter of Cauliflower Mosaic Virus. 200 transgenics were grown. 60 out of them were investigated to have RCC2 gene in them, as they had elongated shoots. All were positive. Out of them, 20 were taken into the experiment to check the resistance against *Botrytis cinerea* (gray mold). And 75% of them showed high resistance, and three of the cucumber transgenic strains exhibited complete resistance. (Tabei et al., 1998; Yamamoto et al., 2000)

10. Strawberry

Fragaria × *ananassa* (strawberry) plants are usually attacked by gray mold *Botrytis cinerea*. They were transformed by *Agrobacterium* for the thaumatin II cDNA (*thauII*) under the transcriptional unit of 35S promoter of CaMV. 14 transgenics were then tested for resistance against *Botrytis cinerea* by using **a** conidial suspension for introducing infection. All 14 showed hgh resistance as compared to control non-transgenic Lones (Asao et al., 1997; Schestibratov and Dolgov, 2005; Yamamoto et al., 2000). A similar type of transgenic strawberry *Fragaria* × *ananassa* Duch cv. Toyonaka in Japan, were constructed by the expression of Rice Chitinase Gene in them via agrobacterium mediated transformation. It was also done under 35S promoter of CaMV. The disease cured was a pathogenic fungus, *Sphaerotheca Humuli* that causes powdery mildew in strawberries. It was a successful experiment. (Schestibratov and Dolgov, 2005; Yamamoto et al., 2000).

PRs as a drug

Different classes of plant pathogenesis-related proteins are studied extensively as a control of agents causing human diseases **(**González-Lamothe et al., 2009**)**. Chitinases belong to the third family of plant pathogenesis related protein **(**Kombrink and Somssich, 1997**)** and are involved in the hydrolysis of the cell wall components of fungi and insect exoskeleton i-e Chitin. Chitinases are usually induced after fungal infection in plants **(**Sahai and Manocha, 1993**)**. Studies suggest the use of chitinase in the treatment of fungal infection along with antifungal drugs **(**Rathore and Gupta, 2015**)**. According to one study, they can be used to detect fungal infections in humans **(**Vega and Kalkum, 2011**)**. Another group of pathogenesis-related proteins that are reported to be active against human pathogens is phytoalexins. For example, many important crops from *Brassicaceae* family of plants produce phytoalexins. Many of these phytoalexins are important due to their antifungal nature **(**González-Lamothe et al., 2009**)**. Camalexin, one of the phytoalexins from *Brassicaceae* is reported to kill prostate cancer cells by apoptosis **(**Smith et al., 2014**)**. Many phytoalexins have been described as anticarcinogenic, with cardiovascular activities and antioxidant. Maslinic acid is a phytoalexin extracted from olives, has been reported to be effective against tumors, diabetes, and heart diseases **(**Lozano-Mena et al., 2014**)**. Family Poaceae produces 3-deoxyanthocyanidins and flavonoid phytoalexins, which have a protective role against gastrointestinal cancer **(**Yang et al., 2009**)**. Brassinin, an indolic phytoalexin from *Brassica campestris* inhibited the proliferation of colorectal cancer cells in humans in vitro **(**Kello et al., 2014**)**. Another important phytoalexin is extracted from grape skin called resveratrol. Various studies have reported its antitumor and antiproliferative activities **(Athar et al., 2007) (Jang et al., 1997) (Fulda and Debatin, 2004)**. Resveratrol has shown its anticancer properties against lung carcinoma, hepatoma, and intestinal tumors. Some phytoalexins, e.g., stilbenes and indoles, protect from cardiovascular diseases **(**Jeandet et al., 2014**)**. Proteinase inhibitors are another class of pathogenesis related protein usually induced by insect bite in plants. They are also found in seeds and tubers **(**Kombrink and Somssich, 1997**)**. Proteinase inhibitors are present in potato tubers, and these proteinase inhibitors can be used for the treatment of peri-anal dermatitis in humans. It works by inhibiting proteolytic activity in human feces **(**Ruseler-van Embden et al., 2004**)**.

Cholecystokinin (CCK) is a satiety agent in humans that is secreted in response to a meal and decreases food consumption in humans. It stimulates the production of trypsin from the pancreas, which then stops further production of CCK. To reduce food intake in obese people proteinase inhibitor from potato was reported to inhibit trypsin, which led to an increase in CKK level. Increase the level of CKK, then decrease the food intake (Hill et al., 1990). Thionins are sulfur-containing plant proteins induced by fungal and bacterial infection. Thionin from *Arabidopsis thaliana* can inhibit the growth of *Escherichia coli, Candida albicans, Staphylococcus aureus,* and many transformed human cell lines

(Loeza-Ángeles et al., 2008). Potato and wheat thionins were found to be effective against the human pathogen *Leishmania donovani* (Berrocal-Lobo et al., 2009). *In one study thionin from Capsicum annuum* showed activity against various human pathogens, including fungal and bacterial pathogens. They were effective against *P. aeruginosa, E. coli, C. tropicalis, S. cerevisiae,* and *C. albicans* (Taveira et al., 2014). Lipid transfer proteins of *Brassica campestris* inhibit reverse transcriptase of HIV-1. Antiproliferative activity of these proteins against breast cancer cells and hepatoma has also been reported (Lin et al., 2007). According to one study, lipid transfer protein from *Narcissus tazetta* can inhibit the plaque-forming ability of respiratory syncytial virus (RSV) and host cell lysis induced by influenza A virus. It also has antiproliferative activity against human acute promyelocytic leukemia cells (HL-60) (Ooi et al., 2008). Lipid transfer proteins from coffee and pepper have antifungal properties against *Candida* genus fungal strains. Osmotin, which belongs to the fifth class of PRP, is a cysteine-rich protein. Adiponectin, a protein produced by adipocytes, and its reduction in the human body can cause insulin resistance, obesity, and atherosclerosis. Osmotin from plants can mimic the adiponectin in the human body, which can recognize its receptor, performing its function. So osmotin might be used for treatment of obesity and insulin resistance in humans (Miele et al., 2011) (Viktorova et al., 2012).

Dual function of pathogen-related proteins

Many pathogens attack a wide range of plants and result in threatening diseases that decrease the annual crop production. Plants have advanced mechanisms in response to these pathogenic attacks, like the PRPs, pathogenesis-related proteins, and the host plant signal transduction. These proteins are activated in response to the numerous pathogen attacks and stress conditions like metal stress, cold, salinity, drought, and UV-light. These proteins produce several dual functions like disease resistance, antifungal activity, defense mechanism, cell wall strengthening, and enzymatic functions. PR proteins are divided into 17 families according to their biological properties and functions (Singh et al., 2014). Tobacco (*Nicotiana tabacum cv*. Wisconsin 38) has pathogen related protein PR1a gene, which has a 5'flanking region at position 1533 identified by PCR. Two constructs, 1533 and 906, were integrated at the upstream part of the PR1a gene with the GUS reporter gene in the tobacco genome. All the transformants showed the increased expression of the GUS reporter gene even after the induction of TMV (tobacco mosaic virus) or treatment with acetylsalicylic acid. The transcriptional activation of the PR1a promoter region -906 to -335 helps in the defense mechanism against the pathogen and also promotes plant development. The PR1a region activation perform dual function, such as the promotion of developmental and environmental signals (GRÜNER and PFITZNER, 1994). PR proteins of plants, which are located in the nucleotide binding site-leucine –rich repeat (NBS-LRR) helps in the detection of the pathogen as well as provide resistance by activating the SAR (systemic associated resistance) mechanism. Plant NBS-LRR detects the effector elements (a virulence Avr protein) (Chisholm et al., 2006), which cause the virulence by binding with the pathogen-associated proteins. As a result of binding, conformational changes occur in the amino terminal and LLR domains with the formation of ADP for ATP by the NBS domain, down regulate the pathogen resistance signaling. NBS-LRR senses the pathogen attack and also provide resistance to the plant (DeYoung and Innes, 2006).

The important disease resistance (R) genes class, which encodes (NB-LRR) proteins provide crop resistance to multiple pathogens during breeding in interfamily. NB-LRR type R genes like RPS1 and RPS4 from Arabidopsis perform a function in two *solanaceae (Nicotiana benthamiana* and *Solanum lycopersicum*), but also in the two *Brassicaceae (Brassica Rapa* and *Brassica napus).* The transformation of the dual genes RPS1/RPS4 not only produces resistance or immunity from the bacterial effector molecules but also produces protection against fungal pathogens like *Colletotrichum higginsianu* in *Brassicaceae* and *Colletotrichum orbiculare* in cucumber. The transfer of R genes in interfamily produces resistance to the wide range of pathogens (Narusaka et al., 2013).

There are many pathogens related proteins with their dual functions, which are described in Table 3.

Table 3: Dual functions of PR proteins. Examples of PR families that contribute to disease resistance while also supporting tolerance to abiotic stress or insect attack, with host plants and target organism

Protein family	Dual Function	Function	Plant	Against	References
PR1 (CABPR1)	Disease resistance and tolerance to heavy metal stress	Activate transduction pathway and hypersensitive reaction.	Transgenic tobacco	*Phytophthora nicotianae, Ralstonia solanacearum and Pseudomonas syringae*	(Sarowar et al., 2005) (Van Loon and Van Strien, 1999)
PR2 (β-1,3-glucanases)	Disease resistance as well as increase antioxidant capacity	Catalyzed endo-type hydrolytic cleavage of 1, 3-β-D-glucosidic linkages in β-1, 3-	transgenic *Linum usitatissimum* (flax)	*Fusarium oxysporum* and *F. culmorum*	(Wojtasik et al., 2013) (Walsh et al., 2000)

		glucans causes death of pathogens.			
PR3 (Chitinases)	Defense mechanism and overexpression of chitinases and β-1,3-glucanases	Catalyzed the hydrolysis of β-1, 4-linkage of the *N*-acetyl glucosamine polymer of chitin.	*Citrus limon*	*Alternaria alternata*	(Henrissat and Bairoch, 1993) (Fanta et al., 2003)
PR5 TLP gene	Antifungal activity with enhanced stress resistance in crop plants	Osmotic stress, anti-freezing, and anti-fungal activity.	Transgenic tobacco plant	*Rhizoctonia solani*	(Singh et al., 2013) (Liu et al., 1994)
PR6 (Protease inhibitors) SAPIN2a	Increased resistance to the lepidopteron insects and great economic growth of the tomato, corn and pepper etc.	Natural killer of proteases	Transgenic tobacco plant	*Helicoverpa armigera* and *Spodoptera litura*	(Luo et al., 2009) (Koiwa et al., 1997)
PR7 (GhCP1) & (AtCP2)	Insecticidal property with programmed cell death	Denature proteins of the pathogens.	*Gossypium hirsutum* and *Arabidopsis*	cotton bollworm larvae	(Mao et al., 2013)

Conclusion

Pathogenesis-related (PR) proteins form a fundamental part of the plant defense system, acting as early responders to both pathogens and environmental stresses. Their biochemical diversity, structural stability, and inducible expression allow plants to mount effective protective responses. Advances in molecular studies have clarified their roles in pathogen inhibition, stress tolerance, and defense signaling. Transgenic and functional studies also show that PR genes can strengthen crop resistance without major growth penalties. However, several PR families still require a deeper mechanistic understanding. Future research integrating genomics, protein engineering, and gene-editing tools will help optimize PR-based resistance strategies. Overall, PR proteins remain essential components for improving plant resilience in modern agriculture.

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Declaration

Data Availability statement

All authenticated data have been included in the manuscript.

Consent for publication

Not applicable

Declaration of Competing Interests

The authors declare that they have no conflict of interest.

Author Contribution Statement

All authors contributed to this work. Muhammad Hammad: Conceptualization, Investigation, Original Draft Writing. Muhammad Shafiq: Supervision, Validation, Reviewing and Final Editing. Mohsin Ali: Methodology, Data Curation, Visualization. Farzeen Zehra Kheemji, Gul Shair, SHUH Sherazi, and Muhammad Shakeel: Literature Support, Draft Improvement. Afifa Israr: Reviewing and Editing. Nimrah Farooq: Writing Assistance and Figure Organization.

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