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Defense Genes Induced by Pathogens and Abiotic Stresses in *Panax ginseng* C. A. Meyer

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Korean ginseng is a medicinally important perennial herb from the family *Araliaceae*. It has been cultivated for its highly valued medicinal properties for over 1,000 years in east Asian countries such as China, Korea, and Japan. Due to its longtime cultivation in shady areas, ginseng is frequently exposed to pathogenic infections. Plants protect themselves from microbial pathogens using an array of defense mechanisms, some of which are constitutively active, while others are activated upon pathogen invasion. These induced defense responses, controlled by defense-related genes, require tradeoffs in terms of plant fitness. We hypothesize that ginseng, as with other plants, possesses regulatory mechanisms that coordinate the activation of attacker-specific defenses in order to minimize fitness costs while attaining optimal resistance. Several classes of defense-related genes are induced by infection, wounds, irradiation, and other abiotic stresses. Both salicylates and jasmonates have been shown to cause such responses, although their specific roles and interactions in signaling and development are not fully understood in ginseng. This review summarizes possible defense-related genes in ginseng based on their expression patterns against biotic and abiotic stresses and describes their functional roles.

Keywords: *Panax ginseng*, Ginseng, Pathogens, Pathogenesis-related, Jasmonic acid, Defense-responsive gene

INTRODUCTION

Ginseng (*Panax ginseng* C. A. Meyer) is an important plant in East Asia, where nearly every species has been employed medicinally. In Chinese, ginseng literally means "man-herb," which can be translated as "the essence of man." In 1883, the genus *Panax* was added to the name, in which *pan* means "all" and *axos* means "cure." Thus, the meaning of *Panax ginseng* is "all-healing man-herb" [1]. In China and Korea, the plant has been utilized for over 2,000 years as a tonic, a stimulant, and to foster stress-resistance [1]. The active constituents contained in most ginseng species include ginsenosides, polysaccharides, peptides, polyacetylenic alcohols, and fatty acids [2]. Pharmaceutical-grade ginseng has been found to improve antibody-dependent cytotoxicity [3], ameliorate lung pathology [4], bolster learning in mice [5], potentiate vaccination against the common cold and influenza [6], inhibit the development of reverse tolerance to morphine [7], prevent free-radical damage to pulmonary vascular endothelium cells [8], exert anti-stress effects [9], inhibit mutagenesis [10], potentiate the generation of nerve fibers [11], and produce anti-aging effects [12].

The older is the ginseng plant, the greater is its medici-

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nal value due to the increase in secondary metabolites that occurs over long periods of successive cultivation (4-5 years). This increased metabolite content is likely due to repeated exposure to environmental stress. While plants react to the multitude of biological, chemical and environmental stresses with a battery of defenses, abiotic stresses are one of the main factors that limit crop yield. The agricultural changes of the modern era, including increased use of chemical fertilizers and irrigation, have increased abiotic stresses such as temperature, UVB radiation (280-320 nm), salinity, drought, and heavy metals. The cumulative effect of these increased stresses has been drastic loss of annual crop yields [13].

To overcome the yield loss caused by abiotic stresses, plants possess a variety of avoidance and tolerance mechanisms. Plants are nutritional substrates for a wide range of parasites, including fungi, bacteria, viruses, nematodes, and insects. In response, plants have evolved systems to facilitate pathogen recognition and induction of the appropriate defenses. These responses include migration of nuclei and organelles to the invasion site [14], production of reactive oxygen species [15], mechanical strengthening of the cell wall, and synthesis of antibiotics (phytoalexins). These responses are often accompanied by programmed cell death, which is known as a hypersensitive response [16]. Both biotic and abiotic stresses have common signal and response pathways in plants and thereby can influence each other through cross-talk (for recent review, [17]). Current research is underway to understand the whole gene networks activated by stress, with the aim of improving knowledge about the medicinally important ginseng plant.

UNDERSTANDING THE DEFENSE MECHANISMS IN GINSENG

Studies regarding ginseng defense mechanisms can benefit genetic engineering by identifying and isolating genes related to the defense response. In order to overcome environmental stresses, plants have evolved structural, chemical, and inducible defense mechanisms to survive different challenges [18]. Structural defense involves the protective function of the cuticle layer, which consists of cutin, a complex polymer of esterified fatty acids coated with waxes, and the rigid molecule lignin. The second line of defense involves the hypersensitive response and its concomitant oxidative burst, accumulation of secondary metabolites, signaling for increased activity of antioxidant enzymes, and the induction of pathogenesis-related proteins [19,20].

Previously, a genomic project to identify *P. ginseng* genes constructed a cDNA library consisting of approximately 20,000 cDNAs [21]. The researchers obtained expressed sequence tags from clones prepared from the hairy root, flower bud, leaf, embryonic callus, and root of *P. ginseng* in order to characterize possible defense-related genes. In this paper, we review the research on these defense-related genes and discuss their roles in the plant's response to environmental stress. We limited our review to published research on the genes, proteins, and metabolites that have been experimentally demonstrated to be part of ginseng's self-defense response.

PATHOGENESIS-RELATED PROTEIN

Pathogenesis-related proteins (PRs) were originally classified on the basis of their characteristics as plant proteins induced in pathological situations, although the term "PRs" has come to refer to all induced proteins and their homologues involved in incompatible host-pathogen interactions [20,22]. PRs were first observed in tobacco plants infected with tobacco mosaic virus [23] and were initially classified into 17 classes [20] based on molecular weight, iso-electric point, localization, sequence analysis, biological activity, and serology [22,24,25]. Most PRs exhibit antimicrobial activity; their accumulation in the plant reflects the resistance response. Recently, van Loon *et al*. [20] introduced the term "inducible defense-related proteins" to specify the originally anticipated definition of PRs. Although the specific functions of PRs are not fully understood, several are postulated to play roles in the prevention of pathogen invasion. In ginseng, five genes encoding PRs have been isolated and characterized, as recapitulated below.

PgPR2 (β-glucanase)

β-1,3-glucanases (EC 3.2.1.39) comprise a PR-2 family that is rapidly triggered by and accumulates in response to pathogen attack, elicitor treatment, and hormonal responses [26]. These proteins catalyze the hydrolytic cleavage of 1,3-β-D-glucosidic bonds in β-1,3-glucans. The β-1,3-glucanase gene was first cloned and characterized in the rice plant [27]. In the tomato plant, Wubben *et al.* [28] found evidence of the accumulation of β-1,3-glucanases in both compatible and non-compatible pathogen interactions. In ginseng, the coding sequence of *Pg-glu1* (molecular weight 46 kD) showed 60% identity with tomato, tobacco, and potato β-1,3-glucanases [29]. The optimal pH for Pg-glu1 activity was found to be between 4.5 and 6.5. *Pg-glu1* expression was significantly

higher in shoots upon wounding and after application of ethylene, cytokines, salicylic acid, and fungal elicitors. The increased expression after salicylic acid application may be due to a common signaling pathway shared with tobacco *GL9* [30], tobacco *PR-2d* [31], and *Arabidopsis BG2* [32].

In another report, *Pg-glu1* was transformed into ginseng calli using *A. rhizogenes's* oncogene (*rolC)*, which up-regulated the expression and activity of β-1,3-glucanases in comparison to those in non-transformed calli. These results confirm the efficacy of the *rolC* gene in the transformation of a PR gene in *P. ginseng.* Of note, β-1,3-glucanase activity was overcome by phytopathogens within a short period of time. Consequently, the combination of β-1,3-glucanases with chitinase is apparently more effective in degrading fungal cell walls [33].

PgPR3 (chitinase)

Chitinase (EC3.2.1.14) belongs to the diverse group of PR genes that includes PR3, 4, 8 and 11. It catalyzes the hydrolysis of β-1,4-linked N-acetylglucosamine and N-acetylmuramic acid, which are different forms of lysozyme. Chitinase has the ability to degrade fungal cell walls; several investigators have focused on the use and manipulation of chitinase genes to enhance the ability of a plant to resist fungal pathogens. Chitinases are classified into six different classes based on their primary structures [34]. In ginseng, the chitinase gene PgChi-1 has been identified and characterized [35]. This gene's amino acid sequence has confirmed similarity with pear (76%), bitter melon (77%), and cotton (76%) chitinases. The highest transcription level of *PgChi-1* is in the ginseng root rather than the leaf or stem. It has been determined that chitinase expression is induced by several stressors, including wounding, salicylic acid, ethylene, auxins, cytokinins, and heavy metal salts [36,37]. In particular, the transcription level of *PgChi-1* was found to be elevated after wounding and exposure to heavy metals, oxidative stress, osmotic stress, salicylic acid, jasmonic acid, fungal infection, and nematode infection [35]. This study suggests that ginseng's chitinase gene belongs to family 19, class I.

PgPR5 (thaumatin-like protein)

Thaumatin is a low-calorie (virtually calorie-free) protein sweetener and flavor modifier that was first discovered as a mixture of proteins isolated from the katemfe fruit (*Thaumatococcus daniellii* Bennett) of West Africa [38]. Some of the proteins in the thaumatin family are natural sweeteners roughly 2,000 times more potent than sugar. Proteins in the PR-5 family are known as "thaumatin-like proteins" due to their homology with the sweet-tasting protein thaumatin [39]. The PR-5 family consists of thaumatin-like and osmotin-like proteins, which have been found to be involved in plant defenses against infections [40]. In addition, it has been reported that PR-5 proteins play roles in development [41], protection against osmotic stress [42,43], and cold tolerance [44]. The thaumatin domain has been found in species as diverse as rice and *Caenorhabditis elegans*. Research has shown that PR-5 accumulates in plants during stressful conditions. A novel *PgPR5* with an 87% similarity to *Actinidia deliciosa* was identified from the leaf of the ginseng plant. In ginseng, *PgPR5* was found to be induced by cold, infection, and application of salt or heavy metals [45], although its functional role has not been elucidated. Further research is warranted to identify additional ginseng PR-5 proteins and to compare them at the structural and functional levels.

PgPR6 (protease inhibitor)

Among the PRs, PR-6 has been found to act as a protease inhibitor that plays an essential role in plant defense [19]. Plant protease inhibitors are small proteins present in both dicots and monocots [46,47] that are often rich in cysteine and lysine, contributing to the nutritional quality [48]. Protease inhibitors have been associated with a variety of activities, including suppression of pathogenic nematodes like *Globodera tabaccum*, *Globodera pallida*, and *Meloidogyne incognita* [49]; inhibition of spore germination and mycelium growth of *Alternaria alternata* [50]; and response to pathogenic fungi such as *Trichoderma reesei* [51]. These attributes make protease inhibitors an ideal choice for use in the development of transgenic crops resistant to pathogens.

Families of protease inhibitors have been found to be specific for each of the four mechanistic classes of proteolytic enzymes. Based on the active amino acid in the "reaction center" [52], these families are classified as serine, cysteine, aspartic, and metallo-proteases. Although serine protease inhibitors have been studied in the most detail [53], researchers have characterized the cysteine protease inhibitor *PgCPI* in ginseng [54]. They found that *PgCPI* is moderately induced by osmotic stress, abscisic acid, and jasmonic acid; and significantly induced by light, UV radiation, methyl jasmonate, and wounding. The wounding that leads to the activation of protease inhibitors was designed to mimic the chewing of herbivorous insects, a stressor that has been carefully studied in the tomato [55,56]. In ginseng, infection with *Botrytis cinerea*, *Colletotrichum gloeosporoides*, or a nematode induced *PgCPI* [54]. It is hypothesized that protease inhibitors block

the synthesis of chitin in the fungal cell wall by inhibiting the synthesis of an enzyme required to activate chitin synthase [57]. PgCPI has also been found to inhibit the activity of the enzyme papain, which researchers use to test a protein's function as a cysteine protease inhibitor. Researchers have used DNA blots to show that *PgCPI* exists as a multi-gene family (three copies) [54]. The discovery of novel protease inhibitors is important to refine our understanding of their many functions.

PgPR10 (ribonuclease)

PR-10 proteins have been described as a ubiquitous class of intracellular pathogenesis-related proteins belonging to the family of small, homologous, primarily acidic proteins [19]. These proteins are highly homologous with a large family of food and tree pollen allergens [58]. The findings from several studies suggest that PR-10 proteins are involved in mechanisms of plant defense, development, and steroid hormone-mediated disease resistance [59-62]. First described in parsley, intracellular pathogenesis proteins [63] are transcribed in response to fungal infections and wounding. They have been renamed as PR-10 proteins [22].

In ginseng, one study sequenced two distinct PgPR10 proteins, both of which contained ribonuclease superfamily domains [64]. In fact, the full coding genomic DNA sequence of *PgPR10* has been isolated and characterized in detail at the transcription level. In addition, several purified PR10 proteins have demonstrated RNase activity *in vitro* [65-67]. In tobacco, research has characterized transgenic lines overexpressing *PgPR10-2* and found the protein to possess RNase activity as well as tolerance to various salt and biotic stresses [68]. If PR-10 proteins do indeed function as RNases, they likely possess specific RNA substrates or require activation, as their unregulated activity could injure plant tissues.

PR-LIKE PROTEINS

PgPGIP (polygalacturonase inhibiting protein)

Polygalacturonase-inhibiting protein (PGIP) is a pathogenesis-related protein first described by Weurman [69]. PGIPs are leucine-rich repeat proteins associated with the cells of all dicotyledonous plants [70] and a few pectin-rich monocotyledonous plants [71]. PGIPs have been shown to specifically bind and inhibit fungal endopolygalacturonases, which are important fungal virulence factors [72]. This particular inhibition is considered crucial to a plant's defense against fungi [73-76].

In ginseng, a *PgPGIP* that showed sequence identity with proteins from chickpea (70.3%), *Arabidopsis* (68.4%), and cotton (60.6%), with ten leucine-rich repeat domains was recently characterized [77]. The mature form of PGIP is characterized by the presence of ten leucine-rich repeat domains that represent over two-thirds of the protein; this motif forms a solvent-exposed surface of parallel β-sheets that mediates protein-protein interactions [74,78,79]. These studies found that mRNA transcripts of this gene accumulated over time during a compatible host-pathogen interaction. Interestingly, wounding did not induce weak constituent expression, whereas fungal infection strongly up-regulated its transcription level.

In the strawberry plant, one study found clear induction of *PGIP* due to infection with *B. cinerea*, whereas wounding failed to impact the transcription level [80]. In the potato plant, PGIP accumulation increased five-fold after infection with *Phytophthora infestans* [81]. PGIPs are known to exist in many copies in different groups of plants [82,83], as well as in *ginseng* [77]. In particular, ginseng's *PgPGIP* has shown a wide spectrum of inhibitory effects against many pathogenic fungi, including *Colletotrichum gloeosporoides*, *Rhizoctonia solani*, *Fusarium oxysporum*, and *Phythium ultimum*. Taken together, these data suggest that *PgPGIP* is an excellent candidate gene for studying ginseng's signaling pathway triggered by fungal pathogens.

PgGST (glutathione S-transferase)

The first discovered glutathione S-transferases (GSTs, EC 2.5.1.18) have been identified and characterized in insects, bacteria, and in many plants based on their ability to metabolize exogenous toxins. GSTs selectively bind glutathione and homologues such as homoglutathione (g-Glu–Cys–b-Ala) and hydroxymethyl glutathione (g-Glu–Cys–Ser), commonly found in legumes and grasses [84]. GSTs detoxify a variety of hydrophobic and electrophilic compounds by catalyzing their conjugations with glutathione [85]. In plants, GSTs are categorized as type I (Phi), II (Zeta), III (Tau), or IV (Theta) based on the phylogenetic tree and the genetic distance attained in the evolutionary relationship [86].

In ginseng, research has found *PgGST* to be induced by exposure to metals, plant hormones, heavy metals, and high light irradiance (Kim *et al*. unpublished results). The functions of GST appear to be directly cytoprotective, suggesting their importance in supporting normal development and periods of environmental stress [87]. In *Arabidopsis*, GST is expressed rapidly and systematically via pathogen-derived signals [88]. Thus, in general, GST can be considered a PR-like gene [89] as well as a

free radical scavenger [90]. Further study of *PgGST* and its role in oxidative stress will help to elucidate ginseng's defense response pathways.

OTHER DEFENSE-RELATED GENES

PgSPD (spermidine synthase)

Spermidine synthase (EC 2.5.1.16) catalyzes the transfer of a propylamine group in the biosynthesis of spermidine, a positively-charged polyamine [91]. Spermidine plays a major role in the plant life cycle, including development and response to environmental stresses [92,93]. In ginseng, the putative gene encoding spermidine was isolated and showed 84% similarity with lotus plant spermidine [94]. Tissue expression patterns of *PgSPD* were found in ginseng roots, flower, bud, stem and leaves. Researchers observed moderate elevation of *PgSPD* mRNA transcription after the application of abscisic acid, jasmonic acid, mannitol, and heavy metals; they observed greater increases after cold and salt stress. HPLC polyamine analysis of cold- and salt-treated plants showed high polyamine content.

Of the three major polyamines, spermidine is most closely associated with stress tolerance in plants [95]. Spermidine genes have been isolated and characterized from *Arabidopsis thaliana*, *Lycopersicon esculentum*, *Cucumis sativus*, and *Zea mays* [96-99]. Spermidine may exert several functions in stressed plants, including direct protection and regulation of stress-related signaling [100]. Research has found that spermidine causes inward rectification of rectifier K^+ channels and certain Ca^{2+}-permeable channels, which modulate plasma membrane ion channels by preventing NaCl-induced K^+ efflux. This may help plants adapt to salty conditions [101,102]. The use of *PgSPD* in genetic engineering may improve ginseng crops by modulating polyamine biosynthesis.

MLP151 (major latex protein)

Major latex proteins are lacticifer-specific, low molecular-weight polypeptides first isolated from the seeds of the opium poppy [103]. These proteins are present exclusively in latex, making them useful markers to investigate the expression regulation of laticifer-specific genes [104]. *Arabidopsis* contains 15 proteins related to the major latex protein. Researchers have isolated *MLP151* from ginseng [105], with a pI of 4.86 and a calculated molecular weight of 16.87 kDa. Although the function of the major latex protein in plants is unknown, its expression patterns are similar to those of certain intracellular pathogenesis-related proteins [106]. Some intracellular pathogenesis-related proteins possess strong allergenic properties and exhibit antibacterial, antifungal, or ribonuclease activity [65]. It has been found that *MLP* expression increases most significantly after wounding and pathogen attack [107].

Ginseng research has shown that ginseng's *MLP151* is differentially expressed in the plant's organs. It was also reported that the transcription level was significantly increased by light and mannitol and drastically decreased by salicylic acid, H_2O_2, wounding, darkness, and oxidative stress [105]. These data suggest that *MLP151* protects plant cells through mechanisms distinct from those activated by salicylic acid and ROS signals. It also appears that the regulation and functions of these proteins vary by defense mechanism. Based on these characteristics, major latex proteins can be considered defense-related proteins with properties similar to those of PR proteins.

PgGAD (glutamate decarboxylase)

Glutamate decarboxylase (GAD, EC 4.1.1.15) catalyzes the conversion of L-glutamate to c-aminobutyric acid (GABA), a four-carbon, non-protein amino acid found in virtually all prokaryotic and eukaryotic organisms. GABA is synthesized via the alpha-decarboxylation of glutamate in an irreversible reaction catalyzed by the cytosolic enzyme GAD [108]. In plants, a number of abiotic stresses stimulate rapid accumulation of GABA, such as mechanical damage, cold, shock, hypoxia, cytosolic acidification, and water stress [109]. A unique feature of plant GAD is the presence of a calmodulin-binding domain near the C-terminal [110,111]. We isolated *GAD* in ginseng, which shows a conserved motif and 76-85% homology with the GADs of other plants including tomato, *Arabidopsis*, and petunia [112]. *PgGAD* appears to be constitutively expressed in ginseng stems. The mRNA transcription level of *PgGAD* was up-regulated dramatically by cold and wounding, but declined drastically with oxidative stress [112].

In plants, cytosolic Ca^{2+} levels tend to increase in response to cold shock, heat shock, salinity, drought, touch, and osmotic stress [113]. In addition, intracellular Ca^{2+} levels increase in response to several environmental factors. As the H^+ concentration increases, the Ca^{2+} in calmodulin activates GAD, thereby increasing the intracellular GABA concentration [110,114,115]. Kaplan *et al*. [116] used micro-array analysis to investigate gene expression during cold stress. They found increased GAD transcription levels of two GAD genes in *Arabidopsis* [116], thus demonstrating a characteristic transcript abundance-regulated response. In ginseng, the activity of *PgGAD* has

Table 1. List of characterized defense-related genes from *Panax ginseng* and their behaviors under different stresses

Defence related genes	Coding protein/enzyme	Stress response	Asscession no.	Reference
PgPR2	β-1,3-Glucanases	Wounding, ethylene, cytokines, SA, fungal elicitors	DQ015705	Kiselev et al. 2006 [29]
PgPR3	Chitinase	Wounding, oxidative stress, osmotic stress, JA, nematode, cytokines, SA, fungal elicitors	FJ790420	Pulla et al. 2010 [35]
PgPR5	Thaumatin-like proteins	Salt, cold, heavy metals, pathogen	GQ452234	Kim et al. 2009 [45]
PgPR6	Cystein proteinase	Wounding, light, UV, MeJA, fungal elicitors	GU001147	Jung et al. 2010 [54]
PgPR10	Ribonuclease	Fungal, nematode, salt	GU086324	Pulla et al. 2010 [68]
PgPGIP	Polygalacturonase inhibiting protein	Pathogens	GQ351365	Sathiyaraj et al. 2009 [77]
PgGST	Glutathione S transferase	Oxidative stress, heavy metals, herbicides	EU625298	Kim 2008 [119]
PgSPD	Spermidine synthase	Salt, cold	GQ229380	Parvin et al. 2009 [94]
PgMLP151	Major latex protein	Light, mannitol	EU939308	Sun et al. 2009 [105]
PgGAD	Glutamate decarboxylase	Wounding, cold	GU324938	Lee et al. 2009 [112]
PgCaM	Calmudulin	Mannitol, oxidative stress, ABA, heavy metal	FJ825754	Wasnik et al. 2009 [117]
PgCAT	Catalase	Mannitol, oxidative stress, chilling, heat	EU327037	Purev et al. 2010 [118]

SA, salicylic acid; JA, jasmonic acid; UV, ultraviolet; MeJA, methyl jasmonate; ABA, abscisic acid.

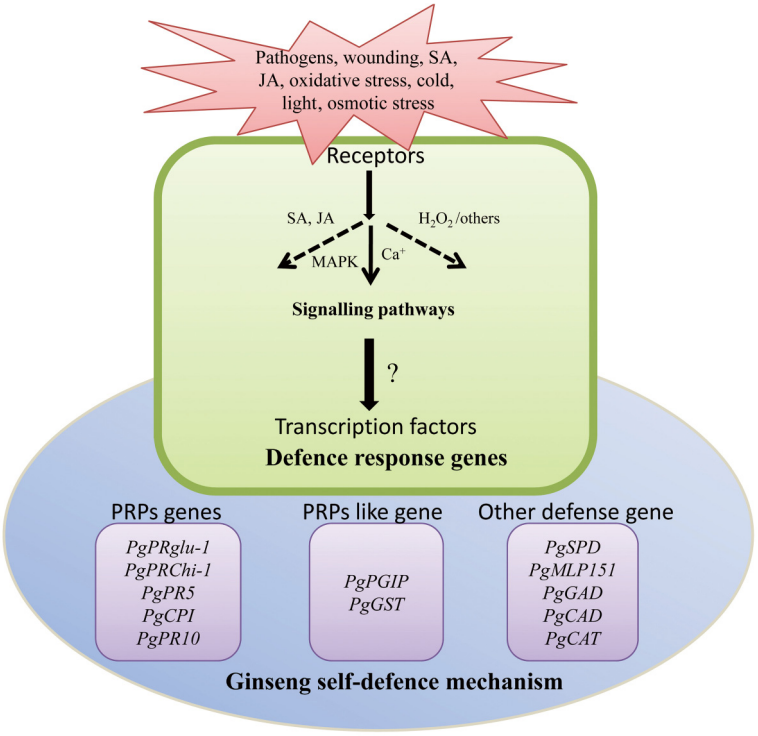

Fig. 1. Schematic diagram shows ginseng's self-defense mechanisms against various biotic and abiotic stresses. These genes may be triggered in response to integrated signaling networks involving jasmonic acid (JA), salicylic acid (SA), Mitogen-activated protein kinase (MAPK), or Ca^+ under unfavorable conditions [29,35,45,54,77,94,112]. These genes may act as potential markers based on their responses to a specific factor.

been found to increase in response to cold and wounding. An important area of future research is the study of this cold signaling mechanism in ginseng *PgGAD*.

CONCLUSION

This is the first review of ginseng self-defense mechanisms dealing exclusively with components that have potential significance in elucidating the complex system of innate plant immunity. Ginseng's PR proteins consist of a variety of families with members that differ in occurrence, expression, and biological activities (Table 1). Some genes appear to cause salicylic acid/jasmonic acid-dependent defense responses, contributing to pathogen

defense. While some members suppress specific pathogens, others restrict pathogen growth in general [22]. Ginseng research has clarified the various functions of certain defense-related genes against phytopathogens. The schematic illustration depicted in Fig. 1 incorporates the components of ginseng's self-defense mechanisms outlined in this review. These mechanisms are grouped into categories based on their properties. This information is valuable to ginseng researchers that study the functional significance of ginseng's self-defense mechanisms.

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