



The Roles of Phytoalexin as Responsive Factors in Plant Disease Resistance and Its Benefit on Human Health

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Abstract

Despite limited experimental evidences and findings it has been suggested that phytoalexins plays major roles in disease resistance as some form of natural products which serves as antimicrobial metabolites of low molecular weight secretion which inhibit the growth of fungi pathogens while some are toxic to bacteria, nematodes and other organisms. This review whose aim is to provide a comprehensive overview of Phytoalexins as critical responsive factor in plants disease resistance is revised to explores the genetic basis of phytoalexins biochemical diversity, regulatory mechanisms that governs their biosynthesis, distribution, accumulation patterns using modern molecular biology tools and it's significance to human health. This review provides an overview of the roles of phytoalexins a compound in plant defense and their diversity in selected plants families exploring the structural forms of its various groups as well as modes of accumulation from remote precursors through de novo synthesis of enzymes and complex defence mechanisms involving the actions of biotic and abiotic elicitors. This article further highlight their biosynthesis and mechanisms of action delving into the distinctive metabolic pathways involved in the formation of novel synthetic phytoalexin models, mediated by enzymatic reactions and elicitor influences, shedding light on the complex interactions underlying plant defense strategies. Conclusion is drawn to emphasizes the potential of modern molecular tools in the elucidation of the mechanisms of phytoalexin synthesis and its accumulation, through the manipulation of gene(s) directly involved in their biosynthetic pathways. to produce the compounds for human therapeutic treatment for the promotion of human health.

Keywords: Antimicrobial, de novo, elicitors, metabolites, *indole-Phytoalexins*

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Introduction

Phytoalexins are a group of chemically diverse low molecular weight or broadspectrumantimicrobial compounds synthesized by plants in response to pathogenic attacks, such as infections, stress, and climate changes (Schmelz et al., 2014). Phytoalexins as a key player in plant defense against pathogens can be described as a class of plant-derived compounds playing a fundamental role in plant defense against pathogens and infection (Desmedt et al., 2020). These compounds exhibit toxicity to specific pathogens, including fungi, bacteria, and viruses, thereby playing a vital role in plant immunity. The mechanism of accumulation is described through de novo synthesis, enzymatic biocatalysis activities, and the influence of biotic and abiotic elicitors will not only help plants fight threats or stressors but has enhanced immeasurable benefits to human health in critical areas such as reducing oxidative stress, fighting cancer, managing diabetes, killing parasites, protecting the heart, central nervous system as well as supporting growth and muscular development.

Phytoalexins accumulate near both resistant and susceptible necrotic tissues by the influence of a high substance known as elicitors which induce the host plant defense responses over microbial infections or other stressors viz a viz physical attacks as they inhibit pathogen development also by restricting fungal growths. These compounds can also deter biotic invasions (like bacteria, nematodes and viruses) and abiotic stresses (like heavy metals, UV radiation and mechanical damage). They can also effectively protect plants by inhibiting sporulation, hyphal growth and spore germination of phytopathogenic fungi because they possess the ability of demethylating or hydroxylating the aromatic rings in the Phytoalexins to render them inactive (Pu et al., 2021; Ahuja et al., 2012). The need to enhance plant disease resistance and the optimization of resource allocation between growth and defense mechanisms can be achieved through the targeted induction of specific genes responsible for the biosynthesis and accumulation of phytoalexins. These secondary metabolites, which belong to diverse chemical classes such as flavonoids, stilbenoids, and terpenoids tend to play a crucial role in plant immunity (Alseekh et al., 2020).

This review whose aim is to provide a comprehensive overview of Phytoalexins as critical responsive factors in plant disease resistance is revised to explore the genetic basis of phytoalexins biochemical diversity, regulatory mechanisms that govern their biosynthesis, distribution, accumulation patterns using modern molecular biology tools and it's significance to human health. By identifying key genes involved in plant resistance and susceptibility, we seek to understand how phytoalexins contribute to antimicrobial defense mechanisms with emphases to recent advances, we will also discuss the role of phytoalexins in plant immunity, their biosynthetic pathways, and the regulatory networks governing their production.

Method

The following are the details of the research methods applied:

Identification of Relevant Literature Sources:

A systematic search was conducted in various scientific databases (e.g., Scopus, Web of Science, PubMed, Google Scholar) using relevant keywords such as "phytoalexin", "plant disease resistance", "antimicrobial metabolites", "plant defense mechanisms", "phytoalexin biosynthesis", "phytoalexin genetic basis", "phytoalexin human health", and combinations of these keywords.

Searches were also conducted in specialized journals in the fields of phytopathology, plant biochemistry, and pharmacology. References of the articles found were also checked to identify other relevant studies

(snowballing).

Literature Selection

Inclusion criteria were set to select articles that were relevant to the review topic. These criteria may include: Original research articles (if there is relevant experimental data to be discussed in the context of the review). Review articles (to gain a broader perspective and identify knowledge gaps).

Relevant scientific reports and books.

Articles discussing the mechanism of action of phytoalexins in plant disease resistance. Articles discussing the potential benefits of phytoalexins for human health. Articles discussing the genetic aspects and regulation of phytoalexin biosynthesis. Exclusion criteria were also set to filter out irrelevant articles.

Data Extraction and Information Synthesis:

Important information from the selected articles was extracted and compiled. Extracted data may include: Types of phytoalexins discussed. Role of phytoalexins in resistance to specific pathogens in specific plants. Mechanisms of phytoalexin biosynthesis and regulation. Genetic aspects underlying phytoalexin diversity. Potential pharmacological activities of phytoalexins on human health (e.g., anticancer, antimicrobial activities).

Research methods used in the reviewed studies.

The collected information is then analyzed and synthesized to identify trends, patterns, knowledge gaps, and key points related to the role of phytoalexins in plant disease resistance and their benefits to human health.

Review Structure:

The synthesized information is systematically and logically arranged in the form of a review article. The structure of a review article usually includes: Introduction (background and purpose of the review). Discussion (thematic sections that discuss various aspects of phytoalexins according to the focus of the review).

Results and Discussion

It was reported that the predominant defense mechanisms as immune response in plants against pathogene infection are categorized into three types in line with the (Zheng et al., 2024), order of layers such as the pathogen-associated molecular pattern (PAMP) and her triggered immunity (PTI) which is a reinforcement of some complex microbial compounds. Like flagellin lipopolysaccharides and chitins collectively form pattern recognition receptors (PRRs) that may lead to the activation of mitogen activated protein kinase (MAPK) Cascades, reactive oxygen species ROS and cellulose biochemical compounds (Alpkvist et al., 2024). However, the second layer as reported to be the Effector-triggered immunity (ETI) as mediated by nucleotide-binding leucine-rich (NLR) proteins which initiate hypersensitive response (HR) over detection of pathogen-derived effectors and in turn causes cell death as measures to contain infection. The advance layer describes plants to exhibit a defense response through the exosome-mediated cross-kingdom RNA (CKRI) system, whereby facilitated small RNAs (sRNAs) will be transferred to interfere between host and pathogen to suppress virulence-related expression of

genes in a well-coordinated defense strategy. The biosynthesis of Phytoalexins is catalysed by enzymes such as phenylalanine ammonia lyase (PAL), Cinnamate 4-hydrolase, and 4-coumarate: CoA ligase). The key to understanding the biosynthetic pathways of phytoalexins and the enzymes involved provides valuable insights into the expression of plant responses to infection by pathogens (Kaur et al., 2022).

Terpenoid phytoalexins, in particular, are widely distributed across various plant species, including tobacco, sweetpotato, cauliflower, ornamental, calabash, cellerygrasses, tomatoes, bamboo, ginger, figs, pears, Spinach, morninglory, Jatropha, soybean, sunflower, marigold, linseed, carrots, beets, okra, pulses, cacao, mulberry, Roses, trawberry, citrus, sweet potato, tomato, pepper, grapevine, cotton among others whose phytoalexin types and forms of accumulation are identified here in this review in accordance with their botanical and/or scientific names Table 1. These compounds have been shown to exhibit antimicrobial and antifungal properties, making them an essential component of plant defense mechanisms. The role of phytoalexins in plant disease response has significant implications for human health. Phytoalexins have been found to possess antioxidant, anti-inflammatory, and anticancer properties, making them potential candidates for the development of novel therapeutics.

Phytoalexins biosynthesis is found to follow a multi-step pathway where precursor molecules, derived from primary metabolites accumulate under the influence of elicitors to undergo enzymatic modification to produce the final product. Each step in this pathway requires specific reactants and enzymes that catalyze reactions towards ensuring a smooth progression from the initial precursor to the bioactive Phytoalexins. These biosynthesis reactions activated by specific genes are essential for plant immunity, allowing the rapid production of Phytoalexins to inhibit pathogen growth which in turns enhances human survival. Elicitors are molecules that trigger plants to initiate the accumulation of phytoalexins with the aim of defending them against infections. Under normal conditions, the process of Phytoalexins synthesis is stimulated by the activation of certain elicitors which initiate the transcription of genes responsible for biosynthetic reactions when signal of the presence of microorganisms and the plant potency in the recognition of the pathogens which can trigger a series of biochemical reaction pathways (Allen & Thomas, 1971). Elicitors can be classified into two main types: biotic and abiotic. While biotic elicitors originate from the invading microorganism parasite hence endogenous while on the contrary abiotic elicitors come from the host plant itself which is described as exogenous depending on the interaction between the plant and the microorganism (Yadav & Islam, 2023). The use of modern molecular biology tools has enabled researchers to understand how Phytoalexins are influence to develop disease resistant plants from remote precursors through the de novo synthesis of enzymes and identification or expression of elicitor genes that are related to stress and disease responses. Understanding these control mechanisms is crucial as scientists can modify specific genes involved for the genetic manipulation of phytoalexins productions or their specific signaling to enhance disease resistance (Saber Riseh et al., 2024). According to a recent report series of biochemical pathways which have been utilized in production of different Phytoalexins, with the majority being derived from the phenylpropanoids (Shikimic) pathways described as organic compounds and other secondary metabolites synthesized from the Amino acid phenylalanine and while the latter is involved in response to plant disease resistance i.e flavonoids, Lignin, anthocyanins, flavonoids, anthocyanins in Figure 2 to Figure 4.

Phenylpropanoids And Shikimic Acid Pathways

Generally, Phenylpropanoid pathways consist of three steps mediated by the enzymes phenylalanine ammonia lyase (PAL), cinnamic acid 4-hydroxylase (C4H), and 4 coumarate: CoA ligase (4CL). Figure 1 Molecular structures of the corn, sorghum and rice plants Phytoalexins.

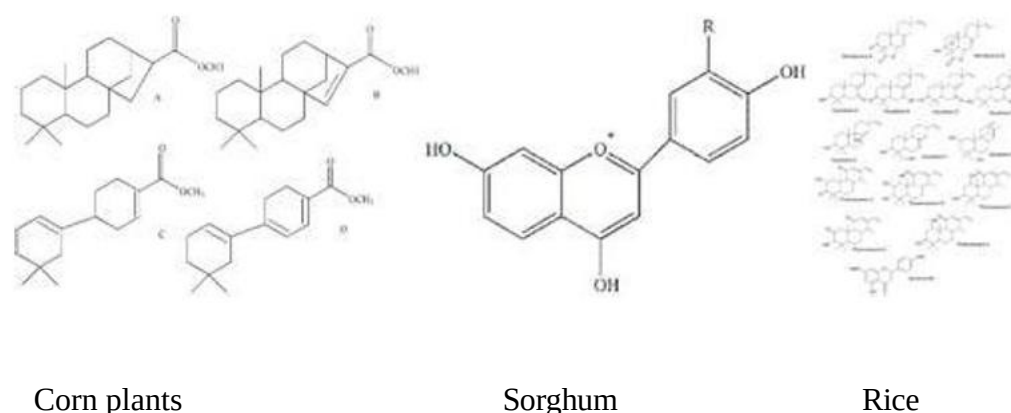


Figure 1. Molecular structures of the corn, sorghum and rice plants

The aromatic amino acid phenylalanine through an enzyme phenylalanine ammonia-lyase (PAL) has been shown to facilitate the deamination of phenylalanine into trans-cinnamic acid (cinnamate) leading to the synthesis of key intermediates such as p-coumaroyl-CoA Figure 2. The pathway continues with the hydroxylation of trans-cinnamic acid by cinnamic acid 4-hydroxylase (C4H) to produce p-coumaric acid, and Finally, 4CL converts p-coumaric acid into p-coumaroyl-CoA which in turns leading to the formation of various phenolics and/flavonoid compounds such as Gallic acid, coumarine, Resveratrol spilbenes, aurones, flavones, isoflavones, flavonols, and anthocyanins. Playing essential inhibitory role for plant antimicrobial, antioxidant and structural activities enhancing growth and pathogen defense strategies. Many phenylpropanoids (PP)-derived compounds also offer human health benefits such as antiviral, antiparasitic, anti-inflammatory and potential anti-cancer properties (Zhang et al., 2023).

Methylerythritol Phosphate Mep and Mevalonic Acid Mva Pathway

In contrast to their animal counterparts the methylerythritol phosphate pathway MEP and the optional Mevalonic acid pathways MVA are metabolic routes in plant cells occurring in the plastids and the protoplasm. The geranylgeranyl diphosphate production in rice probably occurs in the plastids by methylerythritol phosphate pathway while the sesquiterpenes and triterpenes are normally synthesized in the cytoplasm through the mevalonate pathways. Diterpenoid phytoalexins are expected to arise through the diphosphate geranylgeranyl methylerythritol. Unlike, the phenylpropanoids pathways, Phytoalexins can also be produced through methylerythritol phosphate, mevalonic acid pathways (Figure 3). Diphosphate and the Monoterpenoids indole Alkaloids MIA biosynthesis Figure 4 whose products are very crucial for plant defense producing bioactive compounds that protect against pathogens and environmental stress. During cellular respiration in the mitochondria electron carriers like NADH and FADH₂ are involved in the generation of acetyl-CoA through the kreb cycle forming key precursor whose role in the beginning of the mevalonic acid MVA was successful by facilitating electron passing through the electron transport chain to produce energy in the form of adenosine triphosphate ATP to trigger the biosynthesis pathway. Successive enzymatic reactions, including those catalyzed by HMG-CoA synthase (HMGS) and HMG-CoA reductase (HMGR), leading to the formation of mevalonate. Mevalonate undergoes phosphorylation and decarboxylation by mevalonate kinase (MK), phosphomevalonate kinase (PMK), and mevalonate-5-diphosphate decarboxylase (MPDC) to yield isopentenyl pyrophosphate (IPP).

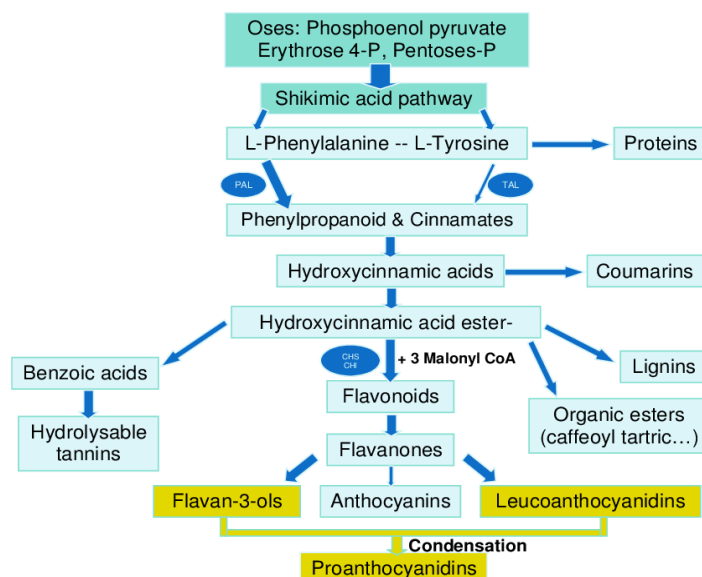


Figure 2. Phenylpropanoic-polymalonic and their Shikimic acid Pathways

Through the action of IPP isomerase (IPPI), IPP is converted into dimethylallyl pyrophosphate (DMAPP), a precursor for various isoprenoid compounds via different routes, which can be harmonized in a third alternative pathway playing key roles in the biosynthesis of some vital compounds known as isoprenoids in plants, animals, and microbes alike. In an alternative pathway, 1-deoxy-D-xylulose 5-phosphate (DXP) is synthesized from glyceraldehyde-3-phosphate and pyruvate via DXP synthase (DXS). DXP is further processed into 2-C-methyl-D-erythritol 4-phosphate (MEP) by DXP reductoisomerase (DXR) and undergoes a series of transformations via enzymes such as IspD, IspE, and IspF to form (E)-4-hydroxy-3-methylbut-2-enyl diphosphate (HMBPP). HMBPP is then reduced by IspH to generate both IPP and DMAPP.

Monoterpenoids, Indole Alkaloids, Mia or Indole Phytoalexins Pathways

Monoterpenoid indole alkaloids (MIAs) are complex nitrogen-containing compounds found in plant families such as Annonaceae, Apocynaceae, Loganiaceae, and Rubiaceae. Various cytochrome P450 monooxygenases (Ambrin et al., 2020). This process produces a wide range of MIAs with significant medicinal properties. For example, catharanthine and vindoline are precursors to the anti-cancer drugs vinblastine, vincristine, as well as ajmalicine and reserpine, which are recommended to treat hypertension and psychiatric disorders, respectively. The structural diversity and biological activities of MIAs make them valuable in the development of therapeutic agents for numerous human diseases. For examples key enzymes and genes identified in the Monoterpenoids Indole Alkaloids (MIA) biosynthesis pathways of *Catharanthus roseus* and *Rauvolfia serpentina* are numerous such as Geraniol10-hydroxylase(G10H), catalyze the conversion of geraniol to 10-hydroxygeraniol, Secologanin synthase (SLS) which catalyze the conversion of loganic acid to Secologanin, Tryptophan decarboxylase(TDC) involves in the decarboxylation of Tryptophan, strictosidine synthase (STR) catalyzes the condensation of tryptamine and secologanin Strictosidine β -glucosidase (SGD): involved in the hydrolysis of strictosidine, terbasonine 16- hydroxylase (T16H) catalyzes the hydroxylation of tabersonine. Desacetoxyvindoline-4-hydroxylase (D4H) involved in the hydroxylation of desacetoxyvindoline, Deacetylvindoline-4-O-acetyltransferase (DAT) catalyzes the acetylation of deacetylvindoline, Vinorine synthase (VS) catalyzes the conversion of polyneuridine aldehyde to vinorine. Acetylajmalan esterase

(AAE) is involved in the hydrolysis of acetylajmalan, Raucaffricine-O- β -glucosidase (RG) catalyzes the hydrolysis of raucaffricine, and Perakine reductase (PR) is an enzyme involved in the reduction of perakine. among others who catalyze the Monoterpenoid Indole Alkaloids pathways in the diagrams, as other enzymes colored in red actually represented in breaking arrows, Figure 3. Catharantine and vinblastine have often been reported as powerful anti-carcinogenic, anti-viral, and anti-fungal agents.

These alkaloids play some very crucial roles in medical treatment, particularly in combating cancer and infectious diseases due to bacteria or viruses. Moreover, strictosidine, an essential precursor in alkaloid biosynthesis, exhibits remarkable anti-retroviral activity, making its molecular model hold significant potential for applications for HIV, papilloma, Chikungunya virus, Zika virus treatment, and the development of effective medication. Plants produce a wide range of amino acid-derived defensive compounds that serve as potent antimicrobial agents, offering valuable insights for drug discovery. Among these, antimicrobial peptides (AMPs) such as defensins, thionins, and knottins disrupt microbial membranes, interfere with intracellular pathways, and enhance immune responses (Wang et al., 2024; Farvardin et al., 2024). Alkaloids, including berberine and quinoline derivatives, target bacterial DNA replication and efflux pumps, while Phenylpropanoids, such as coumarins and flavonoids, exhibit antibacterial and antiviral activity by inhibiting enzyme function. Additionally, phytoalexins and phytoanticipins play crucial roles in plant immunity and human health, with compounds like resveratrol and glucosinolates demonstrating antifungal and antibacterial properties. These natural molecules, with their diverse structures and mechanisms of action, provide a promising avenue for overcoming antimicrobial resistance (AMR) and guiding the rational design of new antimicrobial drugs. Their ability to target multiple pathways makes them superior to some conventional antibiotics, reinforcing their potential as future therapeutic agents (Sethulekshmi et al., 2022). The tomato plant (*Solanum lycopersicum* L.) produces cholesterol-derived steroidal alkaloids, namely tomatine and tomatidine, which demonstrate potent fungistatic activity against *Candida* spp. Notably, these compounds exhibit minimal toxicity to human cells, making them highly promising for therapeutic use.

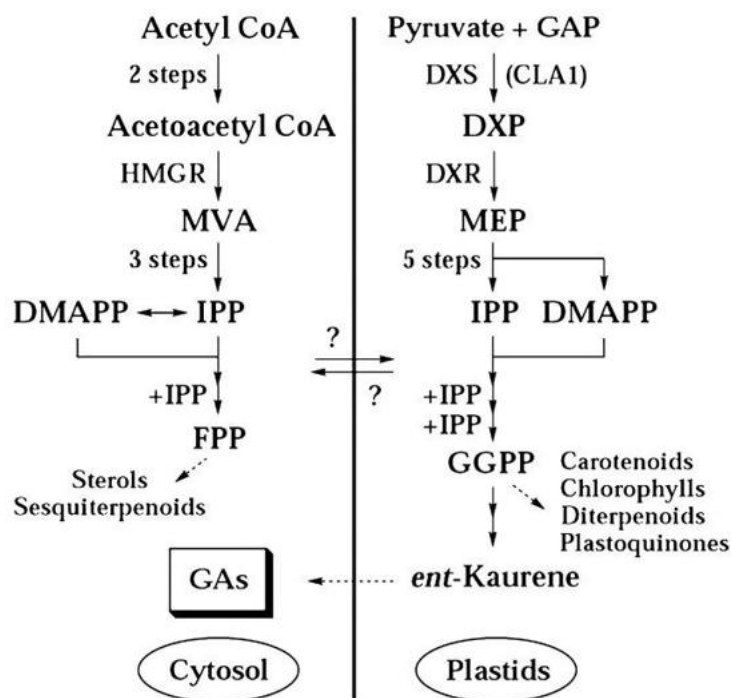


Figure 3. Methylerythritol phosphate (MEP) and Mevalonic acid pathways (MVA)

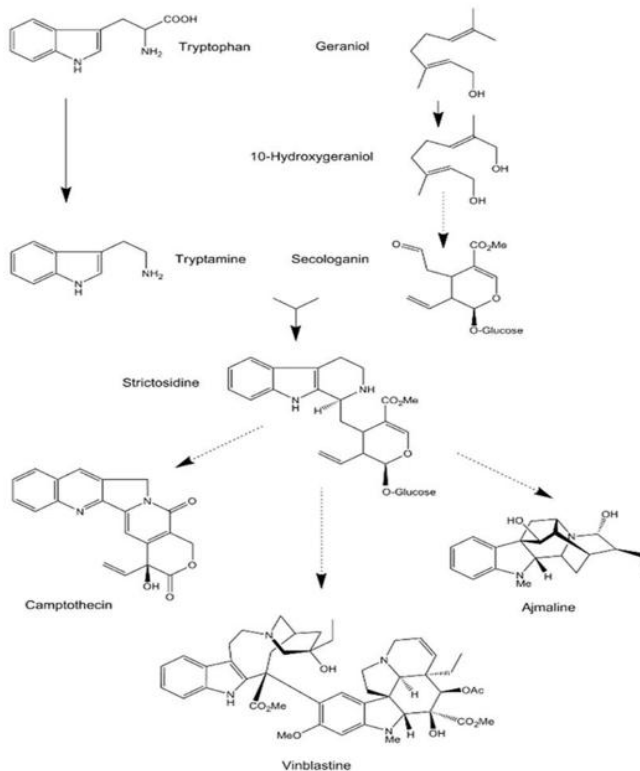


Figure 4. Monoterpenoids indole Alkaloids MIA or indole Phytoalexins Pathway

Tomatidine, in particular, possesses strong antiviral properties, effectively inhibiting viruses particles by blocking multiple rounds of viral replication. This inhibition occurs after viral entry into mammalian cells and may persist for up to 24 hours post-infection, offering a critical window for therapeutic intervention. These natural compounds present significant potential for the development of novel antiviral, antifungal, anti-cancer treatments and/or medication reinforcing the importance of plant-derived bioactive molecules in modern medicine (Elnour & Abdurahman, 2024; Kiełtyka-Dadasiewicz et al., 2024).

Grapevines *Vitis vinifera* a predominant Photoalexins which belongs to the Stilbene family trans-resveratrol (trans-3,5,4'-trihydroxystilbene (RES)). a prominent phytoalexin called resveratrol, a stilbene polyphenol with antioxidant and estrogen-like properties RES described as polyphenol, containing two phenol rings joined by a double styrene bonds in their cellular model has been shown to possess significant free radicals scavenging properties. RES reduces elevated malondialdehyde (MDA) and nitrite levels, restores depleted glutathione (GSH) and can reduce amyloid A β fibril formation in vitro by promoting remodeling of this peptide into a non-toxic structure of high molecular weight, possibly by activation of AMP-activated protein kinase (AMPK) by the calcium/Calmodulin-dependent protein Kinase-beta, which is an important anti-aging pathway and has been linked to various health benefits, for example cardiovascular and muscular health. It interacts with various proteins and organelles, including mitochondrial respiratory complexes. Resveratrol's effects on human health are diverse, ranging from cancer and neurodegeneration to cardiovascular and muscular health. In a recent development Anigopreissin A, a dimeric derivative of resveratrol, has been reported to inhibit reverse transcriptase in nevirapine-resistant HIV strains (Sharma et al., 2022). and in a further related development, (-)- hopeaphenol, a tetrameric resveratrol produced by *Shorea ovalis* (Dipterocarpaceae) has exhibited virulence responsive anti-viral features by blocking the type III secretion systems of Gram-negative pathogens, including *Pseudomonas aeruginosa* and *Yersinia pseudo-tuberculosis*. Additionally, (-)-hopeaphenol prevents the growth of the intracellular bacterial pathogen like *Chlamydia trachomatis*, which causes the sexually transmitted disease chlamydia. Various resveratrol-derived monomers and dimers have also demonstrated bactericidal activity against Gram-positive food spoilage bacteria, such as *Listeria monocytogenes*, with cell membrane damage identified as a result of the consequence of the damage done by the mode of action. Phytoalexins strengthen plant immunity and can be enhanced through synthetic biology, gene manipulation and metabolic analysis to improve crop disease resistance and support global food security (Han et al., 2025). In addition, streamlining isolation processes and reducing costs will facilitate further studies, including the exploration of biosynthesis by-products for developing antiviral and antibacterial medications for promoting human health.

Conclusion

Phytoalexins, secondary metabolites in plants, play a crucial role in the defense mechanism against diseases. Although experimental evidence is still limited, phytoalexins have been shown to have antimicrobial activity against fungal pathogens and toxicity to other organisms. This study aims to provide a comprehensive review of phytoalexins as important responsive factors in plant disease resistance. Furthermore, this study highlights the genetic basis of phytoalexin biochemical diversity, regulatory mechanisms of their biosynthesis, distribution, and accumulation patterns by using modern molecular biology tools, and their significance for human health. This article also discusses structural diversity, accumulation mechanisms from precursors through the synthesis of novel enzymes, and complex defense mechanisms triggered by biotic and abiotic elicitors. The conclusion of the study emphasizes the potential of modern molecular biology tools in unraveling the mechanisms of phytoalexin

synthesis and accumulation, as well as the possibility of manipulating the genes involved to produce therapeutic compounds for human health.

Conflict of interest

No conflict of interest

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