


Toxins in plant pathogenesis: Understanding the role of toxins in host–pathogen interaction

Seweta Srivastava^{1*}, Akhilesh Chandrapati¹, Aakash Gupta¹, Meenakshi Rana¹, Arun Karnwal², Kanuri Komala Siva Katyayani³, Raghavendra Reddy Manda⁴, Dipshikha Kaushik⁵, Shaptadvipa Bhattacharjee⁶, Ravindra Kumar⁷

¹Department of Plant Pathology, School of Agriculture, Lovely Professional University, Phagwara, Punjab, India.

²Department of Microbiology, School of Bioengineering & Biosciences, Lovely Professional University, Phagwara, Punjab, India.

³College of Agriculture, Assam Agricultural University, Jorhat, Assam, India.

⁴Laboratory of Entomology, Wageningen University and Research, Wageningen, Netherlands.

⁵Department of Plant Pathology, Krishi Vigyan Kendra, Morigaon Assam Agricultural University, Morigaon, Assam, India.

⁶Department of Plant Breeding and Genetics, Krishi Vigyan Kendra, Morigaon Assam Agricultural University, Morigaon, Assam, India.

⁷Crop Protection Division, ICAR-Indian Institute of Wheat and Barley Research, Karnal, Haryana, India.

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ABSTRACT

The present-day concept of toxins in pathogenesis has acquired an important place in the arena of plant pathology. Because once the toxic metabolite of the pathogen is identified and characterized, it opens up many ways for combating the pathogen. Microbes use toxins as a weapon to cause damage and eventually destroy host cells. Plant pathogenic bacteria and fungi damage their host by producing diffusible toxins. These toxins induce several symptoms such as chlorosis, necrosis, water soaking, and wilting, which lead to the death of the plants. These toxins (secondary metabolites) are dangerous to the plants even in minute concentrations, and many of the toxins reproduce at least a few symptoms of relevant fungal or bacterial diseases. Plant pathogens use toxins as weapons to infect susceptible hosts. There has been significant progress in understanding these microbial toxins' nature, structure, and their mode of action, which is discussed in this article. In addition to being employed to determine plant disease resistance, screening for disease-resistant mutants, and to manage disease, studying pathogenic toxins and their underlying mechanisms for pathogenicity is crucial to understand the host–pathogen interactions.

1. INTRODUCTION

Since the latter half of the 19th century, pathogenic fungi and bacteria have been known to generate chemical substances that cause symptoms to recur on test plants when the pathogen fails to thrive on it [1]. Nevertheless, in the middle of the 21st century, research on the toxins released by plant diseases and their impact on plants finally started to pick up steam [2,3]. The crucial role that toxins play in plant pathogenesis has long been a matter of debate. The comprehension of biological experiments intended for clarifying the role of pathogenic bacteria and fungi in disease production has been hindered by their inability to purify and chemically characterize their metabolites, despite the fact that many of these microorganisms have been demonstrated to include them in their culture filtrates [4,5].

Plant pathogen metabolism generates non-enzymatic substances known as phytopathogenic toxins, which are toxic to plants [6].

*Corresponding Author:

Seweta Srivastava,
Department of Plant Pathology, School of Agriculture, Lovely Professional University, Phagwara, Punjab, India.
E-mail: seweta.21896@lpu.co.in

These poisons have the ability to completely kill a plant's regular physiological processes at very low concentrations. Toxins produced by phytopathogenic fungi can have a significant impact on the emergence of plant diseases and consequently harm the host plants [7]. Most phytopathogenic toxins are secondary metabolites with low molecular weight that can cause wilting, growth suppression, chlorosis, necrosis, and leaf spotting, among other particular symptoms [8]. Toxins that are phytopathogenic have a complicated mode of action. It primarily affects the host plant's cell membrane, mitochondria, and chloroplasts (Cp), which kills the plant or disrupts with its metabolism [9]. Furthermore, it prevents the host plant from synthesizing proteins and nucleic acids, which can lead to physiological problems, cell death, and ultimately the plant's own demise [10]. Furthermore, it prevents the host plant from synthesizing proteins and nucleic acids, which can lead to physiological problems, cell death, and ultimately the plant's own demise [10]. Understanding how pathogens and plant hosts interact, as well as how to use pathogenic toxins to detect plant disease resistance, find disease-resistant mutants, and management of plant diseases, all depend greatly on how well we are able to study the mechanisms of pathogenic toxins in pathogenicity [11-14]. Reviews of phytopathogenic microbes and their toxins have been few thus far [9].

Several plant pathogens produce toxins that harm host plants. Some toxins can cause almost all the peculiar symptoms of a plant disease [15]. These toxins (secondary metabolites) are deadly to plants even at very low concentrations, and many of them intensify fungal or bacterial disease symptoms [16]. Few toxins show increased toxicity only against the hosts of toxin-producing pathogens whereas in some cases, a pathogen’s potential to produce toxin is related to its disease-causing ability [17]. Toxins are host specific or non-host specific. Few toxins are active on many plant species and are considered as non-host selective, while some of the toxins act on one species, called host-specific toxins, like victorin. Yoder (1980) classified plant pathogen toxins as a pathogenic or virulence factor based on their involvement in disease development [18].

Toxin has been involved in pathogenesis all the way back to Anton de Bary, who strengthened the theory of plant disease generally called as “theory of toxins.” The theory of toxin suggests that a pathogen-induced toxin causes all disease symptoms. This theory was largely refuted, as more information about plant diseases was gathered. Afterward, the toxin theory of plant diseases was reinvigorated by the discovery of the host-specific toxin like victorin. The toxin can harm or kill the host by directly affecting the living host cells [19].

2. CLASSIFICATION OF TOXINS

According to Wheeler and Luke [20], there are three types of toxins, namely phytotoxins, vivotoxins, and pathotoxins as mentioned in Table 1.

3. EFFECT OF TOXINS ON PLANT TISSUES

3.1. Changes in Cell Wall Permeability

All diseased plant tissues show changes in cell wall permeability [24]. Some show this effect before any visible symptom of the disease. Some toxins kill plant cells by altering plasma membrane permeability, allowing water and electrolytes to leak out and the toxin to enter [25]. Cell wall permeability is affected by lycomarasmin, fusaric acid, picolinic acid, and victorin [26,27]. In the case of victorin, even at very low concentrations, the toxin makes sensitive tissues more permeable, which causes the cells to leak. As a result, they cannot store salts and other substances. Similar results can be acquired with resistant plants but only when the toxin concentration is high. Gaumann (1958) believed that leaf cell permeability was a primary factor in wilt

diseases. In tomato plants, fusaric acid affects the semi-permeability of the plasma membrane, allowing metal ions, amino acids, and peptides to escape in the cell’s transpiration stream and damaging osmotic and turgor pressure [28]. Gottlieb observed the fluid in tomato plants attacked by *Fusarium lycopersici* enhanced marrow cell water permeability by nearly 3 times higher than the healthy tomatoes [29].

3.2. Disruption of Normal Metabolic Process of Plants

Toxins or antibiotics intervened with enzyme systems and produced derangement of vital metabolites [30]. Linskens detected K, Ca, Na, and amino-acid leakage from lycomarasmin and fusaric acid-affected leaves. Many physiological activities of host cells are disrupted due to changes in cell wall permeability. The disturbed salt balance in the protoplasm causes an increase in respiration [31]. Loss of water and other substances cause enzyme system malfunction, resulting in cell death. Gnanam (1956); Sadasivan and Saraswathi-Devi (1957); and Sadasivan and Kalyanasundaraan (1959) reported ionic imbalance in *Fusarium*-infected cotton plants [32-34]. Pyricularin inhibits the polyphenol oxidase system, and victorin decouples oxidative phosphorylation. With heavy metal ions, fusaric acid and picolinic acid can create chelating complexes, inhibiting the enzyme system that needs those metals to function. Toxin-resistant tissues either inactivate the toxin or have an alternative enzyme system for normal function [35].

Obstruction with the growth regulator system of the plant may cause stimulation of the growth of plant parts. Conversely, few toxins interfere root growth such as *Fusarium moniliforme* that gives rise to a thermostable toxin even in the soil around the roots, which causes roots’ browning and restricted development. The toxin also produces plant growth regulating and phytotoxic impact on plant system [36].

4. TOXINS SELECTIVELY SPECIFIC TO HOST

4.1. Victorin (HV)-Toxin

Victorin was one of the first HSTs discovered, and its toxicity (effects at 10 pM), rapid cell effects, and high specificity made it the archetype HST [37]. As a consequence of the development and extensive usage of the Victoria oat variety and its derivatives, the fungus *Cochliobolus* (*Helminthosporium victoriae*) was 1st time visible in 1945–1946 and has been the cause of it [38]. The *Vb* gene for resistance to crown rust, which is infected by *Puccinia coronata* f.sp.

Table 1: Difference between pathotoxin, phytotoxin, and vivotoxin with examples [21].

Pathotoxins	Phytotoxins	Vivotoxins
Discovered by Wheeler and Luke, 1963 [20].	Discovered by Wheeler in 1975 [22].	Discovered by Dimond and Waggoner, 1953 [23].
Pathotoxins are toxins that play a significant part in causing plant disease. They are secreted by the plant pathogen or by the contact between host and pathogen.	Phytotoxins are the toxic compounds secreted by living organisms and their role in disease is simply suspected rather than confirmed.	Vivotoxins are secreted in the diseased host by either the pathogen or its host plant.
Pathotoxins, when utilized to a sensitive host at low concentration, should either show all or most of the symptoms of the plant disease. The host range and resistance/susceptibility spectrum of the toxin and the pathogen ought to be identical. The pathogenicity should be directly related to the pathogen’s ability to secrete toxin.	The function of phytotoxins in plant disease development is suspected because the release of the toxins and the pathogenicity of the disease-causing agent have no relationship.	Vivotoxins have a partial significance in the cause of plant disease. Reproducible isolation of the toxin from the infected host and induction of at least some of the disease symptoms when inoculated to a healthy plant.
They may be non-specific or specific.	They are non-specific.	These are generally non-specific.
Examples:- Tab-toxin: <i>Pseudomonas tabaci</i> HMT toxin: <i>Drechslera maydis</i> race T	Examples:- Alternaric acid: <i>Alternaria solani</i> Cochliobolin: <i>Cochliobolus</i> spp.	Examples:- Fusaric acid: <i>Fusarium</i> spp. Pyricularin: <i>Pyricularia oryzae</i>

avenae, was present in these oats. The *Vb* gene has not been genetically distinguished from *Pc-2*, a gene for resistance against crown rust pathogen [39,40], indicating that the two genes may be identical.

Victorin's ability to operate as a particular elicitor for the generation of phytoalexins, known as avenanthramides, in oat cultivars expressing the *Pc-2* gene is what makes it so intriguing [41,42]. *Cochliobolus victoriae* infects sensitive oat plants' basal portion, produces toxin then inoculated to the leaves, and resulted in plant death, whereas other varieties of oat's and other plants that were evaluated were either resistant to the fungus and toxin or were moderately sensitive to it. Producing toxins in mushrooms is controlled by a single *TOX3* gene. The toxin causes numerous changes at histological and metabolic levels in the host, such as structural alterations of the cell wall, cellular electrolyte losses, enhanced respiration, reduced development, and protein synthesis, in addition to other visible symptoms of disease brought on by the pathogen. Ion, salt, and acid leakage from the tonoplast of mitochondria cause increased respiration in victorin-treated tissues [43].

Furthermore, in culture, only toxin-producing isolates of fungus are pathogenic to oats, while non-pathogenic isolates do not secrete toxins. Victorin is a complex, partially cyclic chlorinated pentapeptide [38]. Victorin is highly mobile in plants [44]. Victorin appears to bind to various proteins in the cell plasma membrane, but how it affects susceptible plants' metabolism remains unknown [45]. Victorin primarily affects cell wall permeability [20].

Victorin inhibits the photorespiratory enzyme glycine decarboxylase, which cleaves RUBISCO and leads to cell death by exchanging protons between Cps, mitochondria, and peroxisomes as mentioned in Figure 1 [46]. Victorin also causes laddering of DNA and condensation of heterochromatin, the common signs of apoptosis [47-49]. Victorin shrinks cells and lowers mitochondrial membrane potential, according to Curtis and Wolpert (2004), without compromising the integrity of the plasma membrane or the tonoplast [50]. Animals undergo Victorine-like apoptosis as a result of calcium ion efflux, oxidative burst, serine and cysteine proteases, and nuclease activity [47-49]. Therefore, transcriptional and/or metabolic reprogramming of host cells, which results in the stimulation of a cellular suicide pathway, is probably what causes victorin-induced cell death [45].

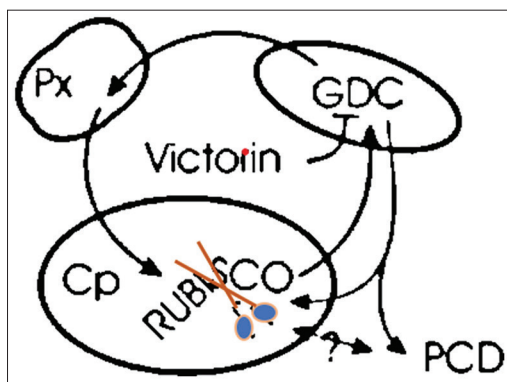


Figure 1: Victorin is an exceptionally potent inhibitor of glycine decarboxylase, which is crucial to the photorespiratory cycle. This cycle involves the interchange of products from the RUBISCO oxygenase reaction between the peroxisome, mitochondrion, and chloroplast. Treatment with victorin causes RUBISCO to cleave and causes programmed cell death (PCD). How the RUBISCO cleavage connects to the PCD mechanism is unknown.

4.2. T-Toxin or *Cochliobolus heterostrophus* Toxin (HMT Toxin)

The *C. heterostrophus* (T-variety) produced the T-toxin and is a contributing factor to the exceptional virulence of Texas male sterile cytoplasm-bearing maize and is the cause behind Southern Corn Leaf Blight (SCLB) [51]. There are two pathogenic varieties of *C. heterostrophus*. In 1925, Race O was previously identified as a maize pathogen [52]. Race T was first developed in the US in 1968. It is identical to other *C. heterostrophus* breeds other than its capacity to manufacture T toxin. By 1970, it only targeted Texas male corn in the Corn Belt [53]. Three decades later, we are aware that the Tox1 locus, which is absent from the O race of *C. heterostrophus*, is the primary distinction between the T and O races of this organism. Since the T race is derived from race O [54-56], a molecular knowledge of the Tox1 locus in T and O must advance the knowledge of how a new pathogenic fungus race evolves [57] whereas, corn with normal cytoplasm is fungus as well as toxin resistant. Both *C. heterostrophus* T susceptibility and resistance are received from the mother (in the cytoplasmic genes). The potential of *C. heterostrophus* T to secrete T-toxin and its pathogenicity in TMS maize are both controlled by an identical gene. T-toxin improves virulence but is not essential for the disease causing ability of *C. heterostrophus* race T [51].

T-toxin is a blend of long linear polyketols (35–45 carbon) with a 41-carbon main component [58]. The toxin acts on the mitochondria of sensitive cells, rendering them defective and inhibiting synthesis of ATP. T toxin binds to a protein molecule (URF 13) on sensitive inner membrane of mitochondria as shown in Figure 2 [59,60]. Plants with Texas-type cytoplasmic male infertility may contain a minute rearrangement in their mitochondrial chromosome encoding the URF13 protein (*T-URF13* gene). Normal maize cytoplasm lacks this gene and protein. Yoder and Gracen (1975) found that in maize lines infected with cytoplasmic male sterility, the presence of T toxin causes the URF13 protein to generate pores in the inner mitochondrial membrane [61], which results in diffuse tissue necrosis, presumably by apoptosis [62]. The pores create the loss of integrity of mitochondria, mitochondrial membrane, selective permeability, and cause disease [63].

4.3. HC-Toxin or *Helminthosporium carbonum* Toxin

Cochliobolus carbonum causes leaf spot of maize and secretes host-specific toxin HC, which shows toxicity only on selective maize lines, was isolated and crystallized by Pringle and Scheffer [64]. Although the HC toxin's exact mode of action is unknown, however, it is the only toxin whose genetic, pharmacological, and molecular origins are known. The HC toxin has a molecular formula that approaches $C_{32}H_{50}N_6O$ [65]. A gene (*Hm1*) in resistant maize lines produces the HC-toxin reductase enzyme, which lowers and causes detoxification of the toxin [Figure 3]. Sensitive maize lines are tolerant to the HC toxin despite lacking *Hm1* gene. According to experimental findings, HC toxin exerts its effects by delaying the onset of gene expression alterations required to establish responses to artificially induced differences. The secondary metabolic abnormalities seen with *H. victoriae* toxin are not present in corn tissue inoculated with *H. carbonum* toxin [66]. It loses its unique toxicity due to its relative instability. Reduced water solubility and nitrogen loss seem to be connected to this activity loss [65].

4.4. HS-Toxin or *Helminthosporoside*

The toxin's structure is reported as a 2-hydroxycyclopropyl-a-D-galactopyranoside [67]. *Helminthosporium sacchari*, causing eye spot

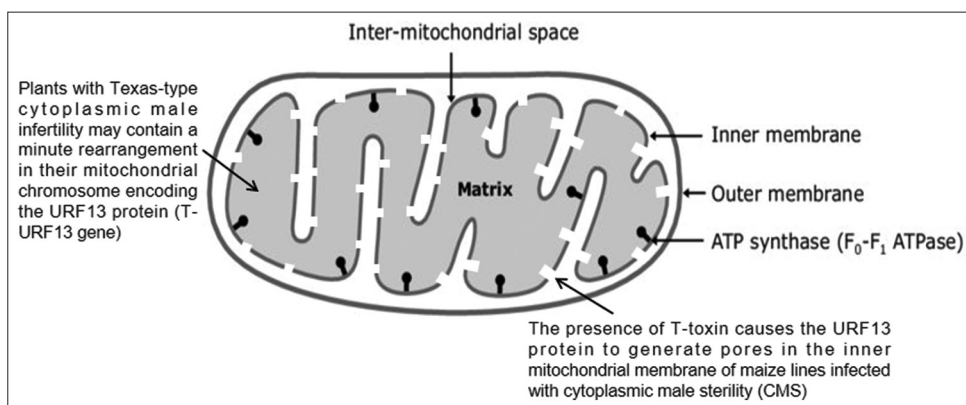


Figure 2: T-toxin binds to a protein molecule (URF 13) on sensitive inner membrane of mitochondria.

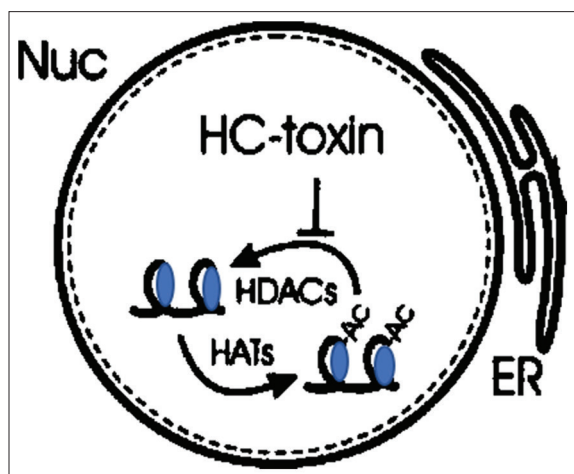


Figure 3: Histone deacetylases are known to be inhibited by HC-toxin in the nucleus (Nuc), which leads to a hyperacetylation of histones through histone acyltransferases. It is believed that this causes alterations in gene expression that stops antifungal chemicals from being synthesized.

disease, is particularly virulent on seedlings of specific sugarcane cultivars [68]. The host-selective toxin secreted by the disease-causing fungus causes reddish-brown streaks on sensitive leaves [69]. The toxin alters Cps and cell wall permeability in sensitive hosts but not in resistant ones. The protein in resistant lines has no affinity for the toxin [68].

They did not, however, conduct synthesis to verify this structure. The history of leaf temperature seems to have an impact on toxin sensitivity. The toxin is made tolerable by brief foliar pre-treatments at temperatures above or below the growth temperature. This study also shows that toxin generation in pure fungal crops cultivated in the existence of serinol (2-amino-1, 3-propanediol) is expanded significantly to 1,000 times when the fungus is cultivated amid sugarcane suspension crops from disease-susceptible or resistant varieties [70].

4.5. PC-Toxin or Periconia Toxin

Milo disease or Periconia blight caused by a soil-borne pathogen *Periconia circinata* attacks only milo type of grain sorghum (*Sorghum vulgare* var. *subglabrescens*). In 1948, Leukel established that the milo disease was caused by a toxin that was host specific. Only virulent strains produce a low-molecular-weight polypeptide toxin [71]. Two host-selective polypeptide toxins, called A and B, were extracted from the culture filtrates [64].

Toxin A, the main toxin (molecular weight <2000), has a non-amino acid fraction. It induces metabolic change in sensitive corn tissue in a similar way to that of the *H. victoriae* toxin [72]. There is evidence that it contains three or more related and selectively toxic compounds with different chemical properties. Acid hydrolysis of one of these compounds produced alanine, aspartic acid, glutamic acid, and serine in a ratio of 6:4:2:2. In structure and biological activity, it appears equivalent to T-toxin. The toxin causes rapid loss of K⁺-ions and other materials through leakage of the plasma membrane of susceptible tissues but has no effect on resistant tissues. It does not act on isolated mitochondria, Cps, and nucleic activities and directly affects protein synthesis [73].

4.6. AM-Toxin or *Alternaria mali* Toxins

The *Alternaria alternata* pathotype that causes the Alternaria apple leaf spot (formerly known as *A. mali*) produces AM-Toxins [74,75]. The newly discovered and described *AMT* gene, which is only found in the *A. alternata* apple pathotype isolates, plays a critical part in the production of the AM toxin. Two AM toxin biosynthetic genes are designated, namely *AMT1* and *AMT2* [74,76]. Non-ribosomal peptide synthetase is encoded by *AMT1*, and aldo-keto reductase is encoded by *AMT2* [76,77]. The crucial cell organelles known as Cps are where AM poisons mostly cause tissue damage [Table 2] [78].

The cyclic depsipeptide toxin molecule often exists as a combination of three forms [79,80]. Other plant pathogen toxins, such as the HC toxin of *C. carbonum* race 1 [81] and the tentoxin of *Alternaria tenuis*, also contain this type of structural chemical compound of the cyclic depsipeptide [82]. The resistant apple cultivars are able to withstand more than 10,000 times the normal amount of toxins without developing any symptoms. Sensitive cells' plasma membranes grow in the infoldings as a result of the AM toxin, and the cells exhibit substantial electrolyte loss. The interface between the cell wall and the plasma membrane is where toxins first emerge to be toxic, but the AM toxin also causes a rapid loss of chlorophyll [Figure 4], indicating that this toxin has multiple sites of action [83].

4.7. AK-Toxin or Phyto Alternarin

Alternaria kikuchiana produced the AK-toxin that causes the black spot of the Japanese pear (*Pyrus serotina*). The pathogen only affects the Nijissciki cultivar and its descendants [Table 2]. Tanaka [84] made the very first mention of toxin's role in disease causing and latterly by other workers in Japan [85-89]. Three selective toxins designated as phyto-alternarin A, B, and C have been obtained from the culture filtrates of the fungus [90].

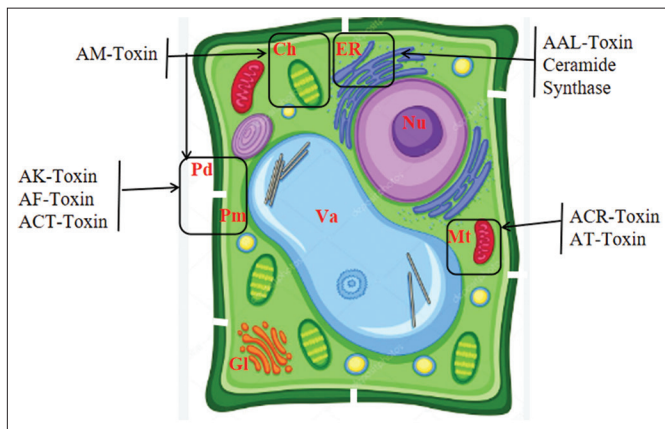


Figure 4: Schematic presentation of target sites of host-specific toxins (HSTs) produced by *Alternaria alternata*. Ch, chloroplast; ER, endoplasmic reticulum; Gl, Golgi apparatus; Mt, mitochondrion; Nu, nucleus; Pd, plasmodesmata; Pm, plasma membrane; Va, vacuole.

The mechanism of action of AK-Toxin is similar to that of victorin. Scientists isolated an HST called AK-toxin, simultaneously monitoring host selectivity during isolation, and found that their toxin preparation satisfied the HST criteria [91-94]. The same preparations of AK toxin were always extracted from filtrates of pathogenic isolate cultures from different regions of Japan. The AK toxin preparation was highly toxic to ten cultivars, including Nijisseiki, but not to 26 other cultivars of pears and non-host plants. This spectrum of toxicity in Japanese pear cultivars coincided with pathogen susceptibility. All *A. alternata* isolates that produce AK toxin may cause black spots on sensitive pear leaves [93,94]. AK toxin was released by germinating pathogen spores, but no free AK toxin was detected in the dormant spores. Toxin AK caused venous necrosis on leaves sensitive to 0.01 µg/mL but not on leaves resistant even to 100 µg/mL [Figure 4].

4.8. PM-Toxin

In conjunction with SCLB, a new disease, Yellow Leaf Blight of Maize [124], caused by *Mycosphaerella zeae-maydis* [125], has been recognized. The SCLB outbreak of 1970 devastated maize fields due to T-race of *C. heterostrophus*. A second fungus, *Phyllosticta zeae-maydis*, with the same biological specificity, appeared by coincidence. Race T produces toxin T, while *Phyllosticta zeae-maydis* produces PM-toxin [109,126], both host-selective polyketide toxins required for super-virulence [127]. *M. zeae-maydis* is also specific for maize T and produces the toxin PM [128,129]. Host-specific maize pathotoxins with linear C33 or C35 poly-ketol structures were generated by *Phyllosticta maydis* [130].

5. NON-SPECIFIC TOXINS

5.1. Tabtoxin

Tabtoxin has been first reported by Johnson and Murwin [131] and confirmed by Clayton [132] to be produced by the bacterium *Pseudomonas syringae* pv. *tabaci*, which causes the wildfire disease of tobacco. Pathovar *tabaci* strains can be found on different hosts, like beans and soybeans [133,134], and by other pathovars of *P. syringae*, that are found on coffee, maize, and oats. Necrotic spots are caused by toxin-producing strains on leaves, and each spot has a yellow halo encircling it. Not only do sterile culture filtrates of the organism and pure toxin elicit symptoms similar to tobacco wildfire, but they also do so in a wide range of plant species from other families [135]. Oftentimes

P. syringae pv. *tabaci* strains yield mutants (Tox-) that are incapable of producing the toxin. Tox-strains create necrotic leaf spots lacking a yellow halo and have decreased virulence. *Pseudomonas angulata*, the causative agent of tobacco angular leaf spot, is indistinguishable from toxic strains and is currently believed to be a non-toxic variant of *P. syringae* pv. *tabaci* [136].

Wooley *et al.* [137] reported the first isolation of tabtoxin, and Stewart [138] published an appropriate structure. The common amino acid threonine and the hitherto unidentified amino acid tabtoxinine combine to form the dipeptide known as tabtoxin. The active toxin, tabtoxinine, is released when the inactive toxin, tabtoxin, breaks down within the cell. The structure of tabtoxin is composed of tabtoxinine-b-lactam [2-amino-4-(3-hydroxy-2-oxoazacyclobutan-3-yl)butanoic acid] and threonine. A different kind of tabtoxin known as [2-serine] tabtoxin [139] is also created in trace amounts as an analog that has a serine molecule substituted in place of a threonine molecule. Both forms of tabtoxin are produced in a physiologically inert state, but they can be easily transformed into the active tabtoxinine-b-lactam moiety by cleaving serine or threonine using certain aminopeptidases found in the plant or bacteria. The target enzyme glutamine synthetase, which catalyzes the conversion of glutamic acid to glutamine in amino acid metabolism, is inhibited by the active moiety tabtoxinine-b-lactam [Figure 5]. The aforementioned inhibition causes an aberrant build-up of ammonia in tobacco cells, which gives rise to the recognizable chlorosis [140].

5.2. Phaseolotoxin

Phaseolotoxin (N-sulfodiaminophosphinyl-ornithyl-alanyl-homoarginine) is a phytotoxic secondary metabolite produced by *P. syringae* pv. *phaseolicola* that causes halo blight of beans [141]. The primary hosts are lima beans, red kidney beans, cranberry yellow beans, green beans, scarlet runner, kudzu vine, and *Proteus vulgaris* common [142]. Sawada and Fujikawa reported that this toxin is also produced by *P. syringae* pv. *actinidiae*, the causative agent of kiwifruit bacterial cancer [143].

Infected plants exhibit both localized and systemic chlorotic symptoms at the same rates. These symptoms were resulted in restricted growth of freshly expanded leaves, regulated apical dominance, and ornithine production. Systemic infections are uncommon but more frequently manifest in some dry bean varieties as juvenile leaflets that curl, become yellow, and eventually die [144]. The Pht region, an island of pathogenicity, contains 23 genes arranged in five transcriptional units: Two monogenic units (argK, phtL) and three arranged as operons (phtA, phtD, phtM), the majority of which have unidentified functions. The products of a few of these genes are involved in the production of phaseolotoxin [141].

By interacting with the active site and deactivating the ornithine carbamoyl transferase enzyme, which ordinarily transforms ornithine into citrulline, a precursor of arginine, the toxin damages cells as shown in Figure 5 [145]. Phaseolotoxin, however, also appears to inhibit the biosynthesis of pyrimidine nucleotides, reduce ribosome activity, interfere with lipid synthesis, modify membrane permeability, and cause the accumulation of large starch granules in Cps [83].

5.3. Tentoxin

The *A. alternata* (formerly known as *A. tenuis*), which was first described by George Templeton *et al.* [146], is the source of tentoxin. It is a cyclic tetrapeptide that is documented for binding with Cp-coupling factor, and involved in the process of energy transfer in Cps

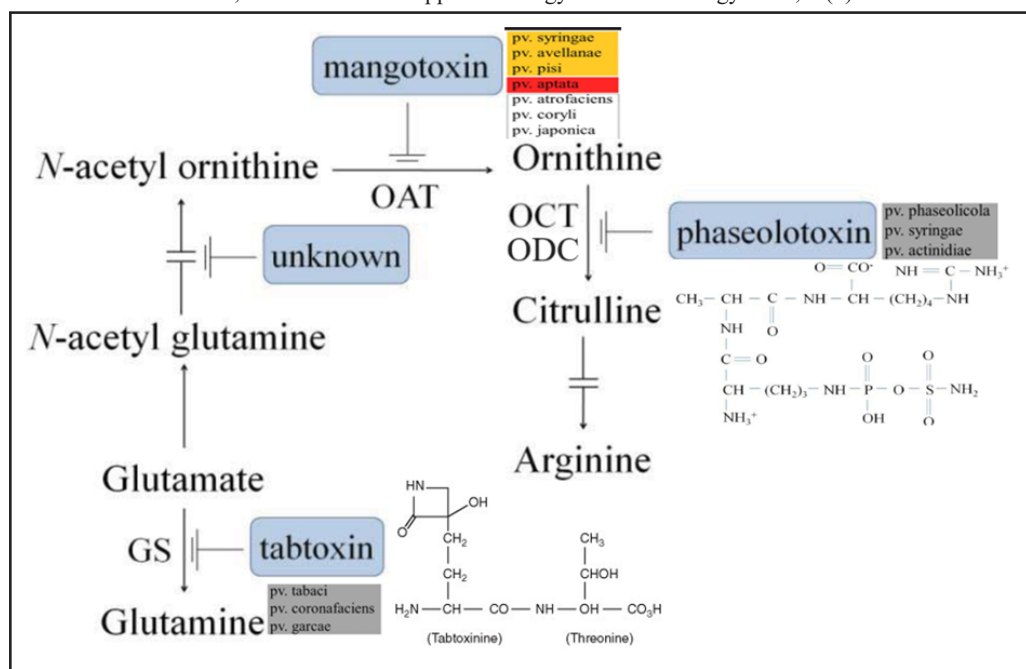


Figure 5: The production of mangotoxin and its enzymatic target. An illustration of the processes involved in the manufacture of polyamines and arginine-glutamine. The several pathovars responsible for the synthesis of the various antimetabolite toxins are demonstrated along with the enzymatic targets of the various antimetabolite toxins, including mangotoxin. OAT, ornithine N-acetyltransferase; OCT, ornithine carbamoyltransferase; ODC, ornithine decarboxylase; and GS, glutamine synthetase

by activating it. Additionally, it inhibits the conversion of ADP into ATP that occurs under the influence of light [147]. Tentoxin interferes with the normal growth of Cps and causes chlorosis in species that are sensitive to its effects. It leads to the production of less chlorophyll. Additionally, but unrelatedly, tentoxin suppresses the action of polyphenol oxidases, which are involved in a number of plants defense systems [148].

5.4. Cercosporin

Cercospora and numerous other fungi produced cercosporin toxin. It is associated with the infections and leaf spots that appear on a wide variety of cultivated plants, such as *Cercospora zinnia* leaf spots and gray corn leaf spots [149]. A photosensitizing perylenequinone called cercosporin absorbs light energy, transforms it into an energetically active state, and combines with molecular oxygen to create activated oxygen, which damages host plant membranes and feeds the intercellular pathogen by providing nutrients. The toxicity of photosensitizers is due to oxidative damage to a plant cell's lipids, proteins, and nucleic acid and kills plants, thus increasing the pathogen's virulence [150]. Fungal spores and mycelium produce pyridoxine (vitamin-B6), which neutralizes it by combining with one oxygen atom and allowing them to withstand against the cercosporin toxicity [151].

Cercosporin production is mediated by multiple signal transduction pathways [152]. Calcium and calmodulin signaling may be involved in the generation of cercosporin, according to studies utilizing pharmacological inhibitors [153]. The development of cercosporin in *C. zeae-maydis* was also linked to a gene encoding a MAP kinase, according to a study [154]. Additionally, the transcription factor CRG1 controls the production of cercosporin [155].

5.5. Tagetitoxin

P. syringae pv. *tagetis*, which produces this toxin, was first identified as a pathogen affecting calendula production in Denmark in 1955 [156].

It is also the cause of bacterial leaf spots and apical chlorosis in several species of the Compositae family, including African marigold (*Tagetes erecta* L.), sunflower (*Helianthus annuus* L.), common ragweed (*Ambrosia artemisiifolia* L.), Jerusalem artichoke (*Helianthus tuberosus* L.), dandelion (*Taraxacum officinale* Weber), bush plant (*Silphium perfoliatum* L.), and another species of sunflower (*Helianthus salicifolius* A. Diter) [157-161]. Mitchell and Durbin [162] first postulated an eight-membered ring as the chemical structure of the TGT; however, this was soon changed to a two cyclic structure on the basis of NMR and mass spectrometry (shown right) [163]. Tagetitoxin has the chemical formula - C₁₁H₁₇N₂O₁₁PS [162].

The toxin results in unexpected apical chlorosis, necrotic leaf patches, and even a chlorotic halo. It functions by preventing Cp RNA polymerase III from acting [164,165]. Based on their capacity to create tagetitoxin, pathogens are categorized into three classes: Class 1 and 2 strains may cause the toxin to be produced in plants, but Class 3 strains cannot [166].

5.6. Fusicoccin (FC)

Fusicoccum amygdali causes almond and peach twig rust that causes the leaves of an infected shoot to wilt and dries out and causes cancer around infected buds and nodes [167]. The phytotoxin called FC produced by fungi induces symptoms of downy mildew when introduced into the xylem [168]. The toxin is a carbocyclic terpene glycoside [169]. The main metabolite FC A induces the wilt in the plant tissues at concentrations up to 0–1 µg/mL, currently undergoing phytotoxicity tests. FC toxin B, C, and D and aglycone are comparatively very less phytotoxic than FC A. The phytotoxicity of FC A is non-selective, although highly active when given through the vascular system [170].

FC affects cellular transport systems and increases the absorption of several anions, sugars, and amino acids by affected cells. The toxin is regarded as the first clear example of wilt toxin because it has been shown to reproduce physiological causes of wilt, not just the wilt symptoms. It also elevates opening of stomatal, respiration, and enlargement of cell [171].

Table 2: List of *A. alternata*-produced host-specific toxins known to date.

Alternaria pathotype	Toxin Produced	Target site of toxin	Type of disease and host	Genes Involved	Chemical Structure/ Characteristics	Reference
Apple pathotype (<i>Alternaria mali</i>)	AM-toxin Type-I Type-II Type-III	Membrane protein; chloroplasts	apple blotch Apple	<i>AMT</i> genes	Cyclic peptide	[95,96]
Sunflower pathotype (<i>A. alternata</i>)	AS-toxin Type-I	Not known	Leaf spotting Sunflower	Not known	Tetrapeptide	[97]
Pathotype of Japanese pear (<i>Alternaria kikuchiana</i>)	AK-toxin Type-I Type-II	Sulfhydryl-bearing molecules in membrane protein	Black spotting Japanese pear	<i>AKT</i> genes	Epoxy-decatrienoic esters	[98-100]
Rough Lemon pathotype (<i>Alternaria citri jambhiri</i>)	AC-toxin ACR-toxin Type-I	Mitochondria	Leaf spotting citrus rootstocks	<i>ACRT</i> genes	Terpenoid	[101,102]
Tangerine pathotype (<i>Alternaria citri tangerine</i>)	ACT-toxin Type-I Type-II	Membrane proteins	Brown spotting Tangerines and Mandarins	<i>ACTT</i> genes	Epoxy-decatrienoic esters	[100,103]
Strawberry pathotype (<i>Alternaria alternata</i> f. <i>sp. fragariae</i>)	AF-toxin Type-I Type-II Type-III	Microsomal phospholipase A ₂	Black spotting Strawberry	<i>AFT</i> genes	Epoxy-decatrienoic esters	[104,105]
Tobacco pathotype (<i>Alternaria alternata</i> f. <i>sp. longiceps</i>)	AT-toxin Type-I Type-II	Mitochondria	Brown spotting Tobacco	<i>ATT</i> genes	Not known	[95,106]
<i>Alternaria jesenskiae</i> and <i>Cochliobolus</i> (<i>Helminthosporium carbonum</i>)	HC-toxin	Mitochondrial membrane	Leaf spotting and ear rotting <i>Zea mays</i>	<i>A. jesenskiae</i> <i>TOXE</i> , <i>A. jesenskiae</i> <i>TOXA</i> , <i>A. jesenskiae</i> <i>TOX2</i> genes	Cyclic tetrapeptide	[107,108]
Tomato pathotype (<i>A. alternata</i> f. <i>sp. lycopersici</i>)	AL-toxin Type-Ta Type-Tb	Aspartate carbamoyl transferase; sphinganine N-acetyltransferase	Stem canker Tomato	<i>ALT</i> genes	Aminopentol esters	[109-112]
Brassica pathotype (<i>A. brassicicola</i>)	AB-toxin	Not known	Black leaf spotting <i>Brassica</i> species	Not known	Protein	[113,114]
<i>A. brassicae</i>	Destruxin-A, Destruxin-B, ABR-toxin	Vacular H ⁺ -ATPase	Gray leaf spotting <i>Brassica</i> species	<i>DtxS</i> genes	Not known	[115-118]
Peach pathotype (<i>A. alternata</i>)	AP-toxin	Not known	Black spotting Peach	Not known	Not known	[119]
<i>A. panax</i>	AP-toxin	Not known	Alternaria blight American ginseng	Not known	Not known	[120,121]
Knapweed (<i>A. alternata</i>)	Maculosin toxin	Ribulose-1, 5-bisphosphate carboxylase	Black leaf blight knapweed	Not known	Cyclic peptide	[122,123]

A. alternata: *Alternaria alternata*

5.7. Marticin

It is a pathotoxin produced by *Fusarium* sp. of the Mortierella group. Highly pathogenic strains of the pea pathogen, *Fusarium solani* f.sp. *pisi*, produce large quantities of a marticin [172]. In detail, marticin toxin was initially inspected by Hardegger and Pfiffner. The two compounds, marticin, and isomarticin are acquired from the acid part of extract of fungus in which the isomarticin predominates [173].

Less pathogenic strains produce less phytotoxic compounds javanicin and fusarubin. However, marticin was obtained from diseased plant tissues in sufficient amount to induce wilted necrosis [174]. Kern proposed that the phytotoxic action of marticin could be due to its inhibition of malate or citric acid dehydration in the citric acid cycle [175].

5.8. Lycomarasmin

Tomato wilt is solely caused by *Fusarium oxysporum* f.sp. *lycopersici*. Lycomarasmin and fusaric acid were discovered filtrates of the culture of fungus causing tomato wilt by Gaumann *et al.* in 1952 [176]. Tomato wilt symptoms mimic the toxic damage caused by the combined effects of these two toxins. The researchers also mentioned the wilt toxin vasofuscarin, which is thought to contribute to the progression of disease [177]. Lycomarasmin is a polypeptide having the empirical formula C₉H₁₅O₇N₃ and a molecular weight of 277.3. Lycomarasmin was proposed by Woolley (1948) as the modified tripeptide [178].

Waggoner and Dimond (1953) reported that the toxin inactivates the growth factor strepogenin, which counteracts its effects. After being applied to tomato cuttings, purified lycomarasmin works as a chelating

Table 3: List of other microbial toxins, their influence on the host or tissues, and their mode of action [44,198-200].

Toxin	Pathogen	Host	Chemical Structure/ Characteristics	Specificity	Mode of Action	Reference
Alternaric acid, altersolanol, macrosporin, and zinniol	<i>Alternaria solani</i>	Potato and Tomato	Di-basic acid Alternaric acid	Non-specific Phytotoxin	The role is doubtful in disease development, wilting, necrosis, and chlorosis occur	[83,198,199]
Colletotinin	<i>Colletotrichum fuscum</i>	Anthracnose of <i>Digitalis</i>	Same as alternaric acid, polysaccharide and peptide attributes	Non-specific Phytotoxin	Disrupts cell permeability or affects pectic enzymes	[200,201]
Diaporthin	<i>Endothia parasitica</i>	Chestnut	Structure similar to isocoumarins	Phytotoxin	Necrosis of the conducting vessels	[202]
Helminthosporal	<i>Helminthosporium sativum</i>	Wheat and Barley	Sesquiterpenoid	Non-specific phytotoxin	Interferes with the respiration of root tissues of wheat and barley	[203,204]
Ophiobolin A (formerly known as Cochliobolin)	<i>Helminthosporium oryzae</i>	Rice	Oxalic acid	Non-selective Phytotoxin	Phenol metabolism gets hampered	[83,205]
Oxalic acid	<i>Aspergillus niger</i> , <i>Sclerotinia sclerotiorum</i>	Crown rot of Groundnut seedlings	Oxalic acid	Phytotoxin	Necrosis	[198,200,206]
Fumaric acid	<i>Rhizopus</i> sp.	Hull rot of almonds causes rotting of the fruit mesocarp	Either fumaric acid or its derivatives	Non-specific Phytotoxin	The toxin extends from the damaged fruits and causes lightening in neighboring leaves and twigs	[207,208]
Hydrogen cyanide (HCN)	Unidentified Psychrophilic Basidiomycetous Fungus	White crown rot or snow mold of Alfalfa	HCN	Phytotoxin	Necrosis	[209]
Thaxtomins (Thaxtomin A and B)	<i>Streptomyces</i> spp.	Scab of Potato	Amino-acid derivatives	Non-specific Phytotoxin	Plant cell hypertrophy and cell death at levels resembling those in scab lesions on field-infected potato tubers	[210,211]
Albicidin	<i>Xanthomonas albilineans</i>	Leaf scald of Sugarcane	Peptide antibiotic	Non-specific Phytotoxin	Interfere with the cleavage-relegation step of ATP-dependent DNA at the gyrase A subunit	[212,213]
Syringomycin and Syringostatin	<i>Pseudomonas syringae</i> pv. <i>syringae</i>	Leaf spots and cankers of stone fruits	Cyclic lipodepsinona peptides	Non-specific	Lysis of cellular membrane resulting in necrosis.	[44,214-216]
Coronatine	<i>Pseudomonas syringae</i> pv. <i>atropurpurea</i> , <i>tomato</i> , <i>glycinea</i> , <i>morsprunorum</i> , <i>maculicola</i>	Tomato, canker of cherry and plum, bacterial blight of soybean	α -Amino acid, coronamic acid and coronafacic acid	Non-specific	Light-dependency chlorosis, necrosis and stunting of plant tissues. Hypertrophy of potato tuber tissues and causes loosening of cell wall	[44,217,218]
<i>Pseudomonas (Ralstonia) solanacearum</i> toxin	<i>Pseudomonas (Ralstonia) solanacearum</i>	Potato	Polysaccharide	Pathotoxin	Block water flow in the vascular system	[198,200,219]
Amylovorin	<i>Erwinia amylovora</i>	Apple and Pear (Fire blight)	98% Galactose in Polymeric forms and 0.3% protein	Specific Phytotoxin	Causes blighting apple and pear	[200,220]
SV-toxins I and II	<i>Stemphylium vesicarium</i>	Brown spot disease of European Pear	Structure of these toxins is still unknown	Specific	Cause veinal necrosis in susceptible cultivars of the pear at low concentration	[221,222]
Phomalide, Phomalairdenone and Depsilairdin	<i>Phoma lingam</i>	Lesions on Canola (<i>Brassica napus</i>)	Cyclic depsipeptide	Specific	Causes lesion and blackening of lower stems and decay	[223,224]

agent and creates an iron-containing, water-soluble, unstable complex that is transported to the leaves [179]. Common symptoms are brought on by iron that is released into the leaves. Iron makes the poison more toxic, whereas copper makes it less hazardous. Enhanced water permeability of the epidermis and increased transpiration of tomato cuttings are brought on by lycomarasin in the presence of iron [180].

5.9. Fusaric Acid

The existence of this toxin was originally noted in 1934 from *Fusarium heterosporum*; nearly 20 years later, Gauman *et al.* (1952) also observed its presence from *F. oxysporum* f.sp. *lycopersici*, *F. oxysporum* f.sp. *vasinfectum*, and *Gibberella fujikuroi*, recognized its poisonous character [176]. After that, numerous *Fusarium* formae specialis of the elegance group, including *F. oxysporum* f.sp. *lycopersici*, *batatis*, *conglutinans*, *cubense*, *lini*, *vasinfectum*, *udum*, and *F. moniliforme*, have been found to contain this phytotoxic metabolite [181-185].

It is categorized as a non-specific vivotoxin and is the most researched wilt toxin produced by a pathogen. It does not, however, manifest every indication of wilt. It is now widely acknowledged that fusaric acid is not a byproduct of autolysis but rather is created during the intense development phase [186]. Fusaric acid is secreted by developing hyphae, although the majority of it is released after mycelial autolysis begins [187,188].

Additionally, in the tissue extract, direct screening of this metabolite of afflicted plants has been performed and has been successful to a significant degree [189]. It has also been noted that some species produce the toxin in the rhizosphere soil of tomato plants [190]. Contrarily, some publications [183] claim that although the same pathogen secretes fusaric acid in culture solution, not in the host tissues. They added that this toxin did not contribute to pathogenicity. Fusaric acid is claimed to play a variety of roles in plants. It disturbs the cell wall permeability and leads to the complex formation of copper and iron in the host cell tissues. This throws off the cell's ionic balance and enzymatic activities. By enzymes chelation or making the respiration-related enzymes inactive, it changes the plant's breathing pattern [191].

5.10. Pyricularin

Blast rice disease, caused by *Pyricularia oryzae* (*Magnaporthe grisea*), is characterized by leaf spots, collar, and culm rot [192]. Rice crop infected with *P. oryzae* can release up to nine toxins, depending on the fungal strain and the host range. Pyricularin is more toxic to the fungus itself than to the host plants, and the fungus produces a specific protein to inactivate the antifungal property of the toxin, but not the phytotoxic property [193-195]. Since picolinic acid affects vulnerable types more than resistant ones, the other toxin, pyricularin, is more active and partially specific. Together with picolinic acid, pyricularin serves as an important factor in blast disease by inhibiting the resistance, or the hypersensitive reaction [196]. Polyphenols and oxidases are increased by the toxin. One of the main rice plant polyphenols, chlorogenic acid, reduces the toxicity [197]. Some other microbial toxins, their influence on the host or tissues, and their mode of action are mentioned in Table 3.

6. CONCLUSION

The toxins described previously play a significant portion in the disease development and able to cause all or majority of the symptoms typical of the particular disease in plants that are susceptible. During pathogenesis, microorganisms produce the majority of these toxins.

Hence, it may be concluded that the toxin concept can be applied in controlling the diseases of plants. Once identify the toxic compounds, their structure, nature, and mode of action, it easily counteracts that the effect of the toxin can be done. The toxins can also be used for screening resistant varieties on a large scale in less time. The study of toxins helps to know the cause of pathogenesis at the host's molecular level. This information will help us in our breeding program of evolving disease-resistant varieties of crop plants. Future research on these toxins will help us better understand and evaluate how plants and pathogens interact, as well as provide us with fresh approaches to disease prevention. Laboratory research on the use of plant-pathogenic microbial toxins is still ongoing. It is anticipated that the application of bioengineering techniques, such as tissue culture and cell engineering, will solve this difficulty and hasten the development of useful uses for natural toxins. All these researches in biotechnology and molecular biology field are to bring novel strategies in disease management.

7. AUTHORS' CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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Data is available with the authors and shall be provided upon request.

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