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Recent Advances in the Bioherbicidal Potential of Tenuazonic Acid, an *Alternaria* spp. mycotoxin

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Abstract. This review addresses the current knowledge on the phytotoxic roles of tenuazonic acid and its biosynthesis in *Alternaria*. We examine recent advances in the biosynthesis of this toxin produced by *A. alternata* and other fungi; the pathogenicity mechanisms that this molecule displays to exert its bioherbicidal activity; and the risks for human and animal health involved in using tenuazonic acid versus a native mix of toxins produced by *A. alternata*. Finally, we discuss the potential use of tenuazonic acid versus fungal isolates for agricultural weed control.
Keywords: Biological control; fungal metabolites; mycoherbicide; phytotoxins.

Resumen. Esta revisión aborda el estado del arte en el conocimiento acerca de los mecanismos de fitotoxicidad del ácido tenuazónico y su biosíntesis en *Alternaria*. Se examinan los avances más recientes en la biosíntesis de esta toxina producida por *A. alternata* y otros hongos; los mecanismos de patogenicidad que esta molécula emplea para ejercer su actividad bioherbicida; así como los riesgos para la salud humana y animal involucrados en el uso de ácido tenuazónico comparado a una mezcla de las toxinas producidas por *A. alternata*. Finalmente, se discute el uso potencial del ácido tenuazónico versus aislados fúngicos para el control de malezas en la agricultura.
Palabras clave: Control biológico; fitotoxinas; metabolitos fúngicos; micoherbicida.

Introduction

It is well known that weeds can negatively affect agricultural production [1]. Weeds represent one of the greatest limiting factors for crop yield [2] since they can compete for resources such as water, light, nutrients and space, thereby diminishing plant growth [3, 4]. In addition, weeds may harbour other potentially harmful pests and pathogens that can affect economically important crops [5].

Weeds are conventionally controlled using manual, mechanical and chemical methods [5], with the last one being the most widely used [3]. However, the indiscriminate and continuous use of synthetic herbicides generates negative effects on the environment, including their very presence in food, water and soil, as well as the damage they inflict to non-target organisms [6-8]. Furthermore, herbicides negatively impact human health [3,5,6], and their use has been associated with the appearance of weed biotypes resistant to these chemicals [5,

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9, 10]. Not surprisingly, the negative effects caused by herbicides have generated public concern, which has leaded to restrictions on their use [11].

Because of the challenges presented by conventional weed control, the development of alternative techniques is currently needed. One of the most widely accepted techniques is biological control [12], for which fungi and fungal metabolites with herbicidal activity have been suggested [13,14]. The use of microbial metabolites as bioherbicides remains a promising approach since this could solve the restriction problems of working with live microorganisms [15,16].

Alternaria is one of the fungal genera with the greatest bioherbicidal potential [12,17,18], as it can produce a variety of secondary metabolites with phytotoxic, cytotoxic and antimicrobial activities [19]. These phytotoxins are classified into host-selective toxins (HST) or non-host-selective toxins (NHST), based on the susceptibility or resistance of host plants [20]. One of the main NHSTs identified from *Alternaria* is tenuazonic acid (TeA) ((5S)-3-acetyl-5[(2S)-butan-2-yl]-4-hydroxy-1,5-dihydro-1H-pyrrol-2-one) [21-24], which was first isolated by Rosett et al. [25].

TeA bioherbicidal activity was described from an isolate of *Alternaria alternata* as a pathogen of the plant host *Ageratina adenophora* (reviewed in [22]). The phytopathogenic effect of this isolate was mainly attributed to a toxin known as *A. alternata* Crofton-Weed Toxin (AAC) [26,27]. TeA was structurally identified and purified and was determined to be the main active metabolite responsible for the biocontrol effect of AAC [28]. Further studies have identified this phytotoxin as one of the most important virulence factors of *A. alternata* [22, 29].

TeA has been isolated from several different phytopathogenic fungi, including *Alternaria* spp. (particularly *A. alternata, A. longipes* and *A. tenuissima)*, *Aspergillus* spp., *Phoma sorghina* and *Pyricularia oryzae* [20,30-34]. Due to its broad spectrum bioherbicidal activity [16,35], low animal toxicity and low residuality [28], this metabolite is considered to be a potential bioherbicidal agent [16,22]. The main goal of this review is to present the current knowledge regarding TeA mechanisms of toxicity in plants and its biosynthesis and to provide some insight into human safety in order to assess its potential use for weed control.

The role of tenuazonic acid (TeA) in the *Alternaria alternata* mechanism of plant infection

Alternaria spp. can cause disease in numerous economically important crops. These species produce a large amount of primary and secondary metabolites, and several *Alternaria* species produce both host-specific and nonspecific phytotoxins, with negative effects on different cell organelles [36,37].

One of the main phytotoxic compounds produced by *Alternaria* spp. is tenuazonic acid (TeA), which has been isolated from such phytopathogenic fungi as *Pyricularia*, *Phoma*, and *Alternaria* [31,32,38]. TeA is highly phytotoxic to a wide spectrum of plants, causing the reduction of root and shoot length in seedlings [39], as well as a decrease in the chlorophyll content of plant leaves, leading to chlorosis and yellowing in the leaf tissues of monocotyledon and dicotyledon weeds [40].

Studies related to the mode of action of TeA have revealed that this compound inhibits photosynthesis by disrupting the transport of electrons from photosystem II (PSII). In plant cells, PSII damage can lead to the formation of reactive oxygen species (ROS) [41, 42]. TeA-induced ROS species are produced in the chloroplasts and include $^1O_2$, •OH, $O_2^{\bullet-}$ and H_2O_2 [30]. Once they increase in quantity, these ROS disperse throughout the cell and its compartments, causing chlorophyll breakdown, lipid peroxidation, plasma membrane rupture, chromatin condensation, DNA cleavage and organelle disintegration, and eventually the destruction and necrosis of leaf cells [43].

In addition to damaging the host plant, TeA is also involved in maintaining ROS content, host recognition, and the induction of appressoria which infect the host, allowing completion of the infection process. This was demonstrated by Kang et al. [29] on Crofton weed (*Ageratina adenophora*), where PSII damage began even before the mycelium had infected the host leaves. Mutant strains of *A. alternata* lacking TeA formed morphologically different colonies consisting of hyphae with thinner cell walls, had a higher ROS content and lower peroxidase activity, and failed to form appressoria on the host surface. In addition, it was found that the mutant caused disease symptoms when the mycelium was placed on leaves with removed epidermis, demonstrating that TeA may be determinant in recognizing the fungus from the host plant [29]; the authors therefore suggest that the infection process of *A. alternata* begins with the secretion of TeA toxin before infecting its host. TeA toxin inhibits host photosynthetic electron transport in PSII, causing an increase in ROS

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concentration and damaging epidermal and mesophyll cells. Later, the hyphae form the appressoria on the epidermis of the host, with which the fungus begins to colonize the tissues, thereby completing the infection process [29].

Recently, Shi et al. [22] proposed a more specific disease model. When *A. alternata* comes into direct contact with the leaf surface, the TeA toxin secreted by the pathogen penetrates the mesophyll cells and inhibits photosynthetic electron transport by binding to the D1 protein, causing ROS bursting and cell death. Cell contents released by such a cell burst may be used as a source of nutrition for the fungal hyphae, which grow by invading the leaf tissue, and secrete more TeA to kill more cells. Expanding hyphae therefore colonize their host more aggressively and invade living tissue, leading to the visible formation of lesions as a symptom of disease [22].

Biosynthesis of tenuazonic acid in fungi

The most commonly found tetramic acid derivatives are pyrrolidine-2,4-diones, which contain an acyl substituent at C-3. Members of the genus *Alternaria* may produce three tetramic acid (2,-pyrrolidinedione) analogues: TeA, 3-acetyl-5-isopropyltetramic acid, and 3-acetyl-5-isobutyltetramic acid [44].

Tenuazonic acid, the simplest of the tetramic acids, was originally isolated from culture filtrates of the fungus *A. tenuis* (a synonym for *A. alternata*) [25]. It was later found in other members of the same genus such as *Aspergillus* spp. [45], *Epicoccum sorghinum* [32] and *Pyricularia oryzae* [46].

The structure of TeA was elucidated after degradation by ozonolysis followed by acid hydrolysis [47]. The TeA molecule is thought to be composed of an isoleucine and two acetates [48]. Since most tetramic acids are derived from hybrid polyketide synthase (PKS) and non-ribosomal peptide synthetases (NRPS), TeA was also expected to be a product of a PKS–NRPS hybrid enzyme [49]. Using radioactive precursors, it was demonstrated that *A. alternata* first uses L-isoleucine and two acetate molecules to synthesize N-acetoacetyl-L-isoleucine. Further cyclization of this compound then produces TeA [30, 44, 48, 50].

The TeA biosynthetic gene TAS1 was discovered in *P. oryzae* [51]. TAS1 is a non-ribosomal peptide synthetase and polyketide synthase (NRPS–PKS) hybrid enzyme that begins with an NRPS module. The NPRS portion of TAS1 contains the C (condensation)-A (adenylation)-PCP (peptidyl carrier protein) domains. The PKS moiety of TAS1 has a ketosynthase (KS) domain, which is indispensable for its activity and responsible for conducting the final cyclization step in the release of TeA. The C-A-PCP domains condense L-isoleucine and acetoacetyl-CoA into N-acetoacetyl-L-isoleucine. L-isoleucine (L-Ile) binds to the PCP domain followed by catalysis of the adenosylase and condensase domains A and C. This allows the amino group from L-Ile to go through a condensation reaction with the carbonyl group of acetoacetyl-CoA, which creates an amide bond to form N-acetoacetyl-L-isoleucine. Finally, the KS domain recognizes this last compound to initiate the cyclization reaction that produces TeA [51]. The cyclization mechanism mediated by the KS domain to form tetramic acid has been elucidated [52]. TAS1-KS contains the conserved catalytic site composed of the triad Cys179-His322-Asn376. The N-acetoacetyl-L-isoleucine moves from the PCP domain to Cys179, where it is covalently bound via a thioester bond. Docking simulations have shown that this substrate forms a hydrogen bond with Ser324, after which the methylene proton is taken up by His322, triggering a nucleophilic attack on the thioester carbonyl to result in TeA. Finally, Asn376 appears to stabilize the correct conformation of cis-N-acetoacetyl-L-isoleucine for the nucleophilic attack in order to form TeA (Fig. 1) [52,53].

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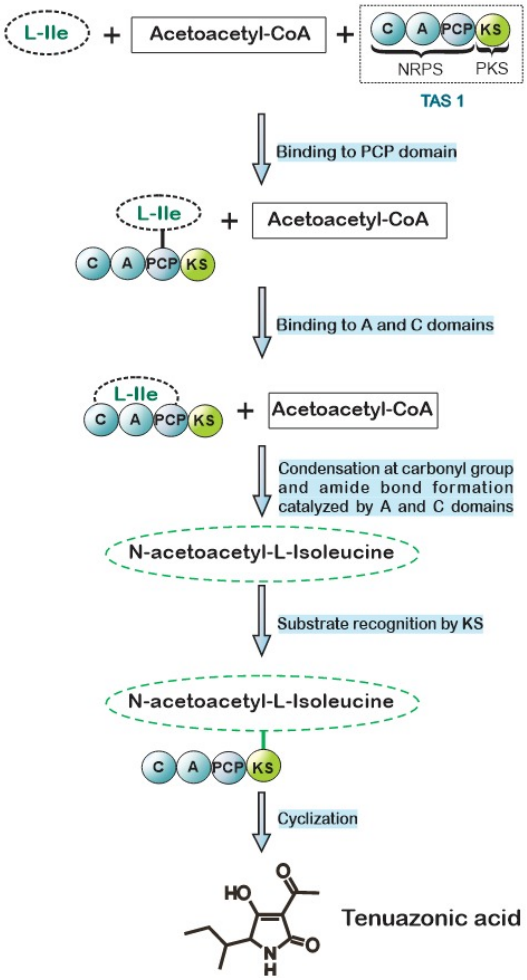

Fig. 1. Biosynthesis of TeA by TAS1.

Addition of L-isoleucine or other amino acids to the culture media may stimulate production of 3-acetyl-5-isopropyltetramic acid (3-AIPTA) and 3-acetyl-5-isobutyltetramic (iso-Tea), both of which are tetramic acids with different substituents at the 5-position. When ^{14}C-carboxyl-labeled L-valine or L-leucine is fed to the culture media of *A. alternata*, derivatives of the tetramic acid 3-AIPTA and iso-TeA are also obtained [44]. 3-AIPTA, which is phytotoxic, can affect photosynthesis by inhibiting PSII electron transport, in addition to inhibiting algal cell growth [54]. Even though 3-AIPTA shows similar mechanisms of toxicity as TeA on weeds, its herbicidal effect is weaker than that of TeA [55]. Iso-TeA is an isomer of TeA that shows toxicity on *Artemia salina* similar to TeA [56], as well as phytotoxicity in rice [57].

Following the description of the biosynthetic pathway of TeA by TAS1 in *P. oryzae* [51], two other genes were discovered: TAS2, a zinc finger transcription factor; and PoLAE1, a homolog of LaeA that acts as a global regulator of secondary metabolism in *Aspergillus* [58]. Deletion mutants of both genes were shown to lose the ability to produce TeA under any form of induction, demonstrating the important regulatory role that these proteins play in TeA synthesis [59].

More recently, two genes involved in TeA synthesis in *A. alternata* were described: AaTAS1, the ortholog of TAS1 from *P. oryzae*; and AaMFS1, a membrane transporter of the major facilitator superfamily (MFS), which is a putative efflux pump for TeA transmembrane transport [24].

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Knockouts of AaTAS1 lose the ability to produce TeA, while knockouts of AsMSF1 show decreased extracellular levels of TeA. One interesting observation with the knockout strains is that DAaTAS1, which did not produce any TeA, significantly decreased its pathogenicity in tomatoes, whereas DAaMSF1 produced a small amount of TeA and did not alter its pathogenicity in tomatoes [24].

The presence of AaTAS1 protein in the cytoplasm is consistent with the hypothesis that it is responsible for the biosynthesis of TeA. The AaMFS1 protein was located on the cell plasma membrane and the intracellular membrane system [24], in agreement with a role in the transmembrane transport of TeA [52]. These findings highlight the importance of mycotoxins in the virulence of *A. alternata* and indicate that the absence of TeA inhibits pathogenicity while low concentrations of TeA can restore the ability of *A. alternata* to infect and colonize plants.

Finally, TeA suppresses the upregulation of AaMSF1 expression levels in the knockout DAaTAS1, suggesting that these two proteins may interact indirectly through TeA [24].

Is TeA safe for humans?

The risk to human health is one of the factors that must be evaluated when working with potential alternative herbicides such as the microorganism *Alternaria*. This is particularly relevant due to the presence of this fungus on crops used for animal or human consumption. *Alternaria* produces TeA as well as a range of different toxins that may be potential harmful food contaminants. Several metabolites have already been reported as toxic compounds [60], and their toxic effects and mechanisms of action have been well described using *in vitro* systems.

Research has been conducted to study the effect on animal and human health of the two most abundant metabolites produced by *Alternaria*, which are TeA and alternariol (AOH). In addition to the phytotoxic effect of TeA, the European Food Safety Authority (EFSA) has reported an LD50 in mice and rats of 80-225 mg per kg of body weight [61]. However, the EFSA reported in 2016 that there are no side effects on human health following daily exposure to a dose of 127-277 ng TeA per kg of body weight [62].

The dibenzo-α-pyrone AOH and its monomethyl ester AME are of more concern for human health than TeA, based on the estimated daily human exposure [62]. Indeed, they can cause DNA-topoisomerase poisoning *in vitro*, meaning that they could become genotoxic at micromolar concentrations [63]. Furthermore, these two compounds are able to induce oxidative stress, which also contributes to its DNA-damaging activity [64,65].

In addition to producing tetramic acids and dibenzo-α-pyrones, *Alternaria* spp. synthesize important amounts of perylene quinones such as alterperylenol (ALP), altertoxins I (ATX-I) and II (ATX-II), and stemphyltoxin III (STX-III). ATX-II is reported to have an even greater impact than AOH as a DNA-damaging and genotoxic compound [66, 67], as it can damage cells *in vitro* at concentrations as low as 0.05 μM [68].

In silico and *in vitro* experiments suggest that AOH may act with perylene quinones to exert estrogenic and antiestrogenic activities, making them possible endocrine disruptors (reviewed in [69]). Unfortunately, there is limited toxicological data for other toxins synthesized by *A. alternata* such as tentoxin (TEN), altersetin (AST), and altenusin (ALS), and studies on the other effects of native combinations of *Alternaria* toxins on human health have been scarce. The chemical diversity of the *A. alternata* native mixture of compounds, the differences in their toxicodynamics and toxicokinetics in animal cells, and the lack of studies in the detection and follow-up of toxins other than TeA, AOH, AME and TEN in human samples (such as urine and breast milk) make it extremely difficult to conclude that native mixtures of these toxins have no effect on human health (reviewed in [69]).

Current status of *Alternaria* spp. as bioherbicides

One of the main limiting factors in modern agriculture worldwide is the emergence and development of weeds that cause considerable losses in crop yield. The appearance of weed biotypes resistant to herbicides in several species and the environmental contamination caused by the inadequate use of synthetic herbicides makes it necessary to find novel, ecologically friendly alternatives [18, 70]. In addition, legislation changes in countries like Mexico have restricted the use of some pesticides of synthetic origin, such as glyphosate [71].

In recent decades, the biological control of weeds with mycoherbicides has received significant attention. Different strains of fungi around the world have been successfully confirmed to control weeds under

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greenhouse and field conditions, some of which have even been patented and are currently commercially available. Genera such as *Alternaria*, *Colletotrichum*, *Fusarium*, *Phoma*, *Puccinia* and *Sclerotinia* have shown the greatest potential as bioherbicides [18,70,72], and exhibit bioherbicidal activity on diverse monocot and dicot weeds [14,73-75]. Despite the success of various fungi in controlling weeds, it is important to conduct a formulation process in order to allow their large-scale application [76].

Different formulations based on *Alternaria* isolates have been evaluated to develop bioherbicides for the control of the weeds *Rumex dentatus* L., *Chenopodium album* L., and *Xanthium strumarium* under laboratory, greenhouse and field conditions [77,78]. The fungus *A. eichhornia* has also been extensively studied for its bioherbicidal activity against water hyacinth, a noxious weed found on bodies of water [79,80]. Recent developments in the field of bioherbicides have resulted in the registration of different formulations in countries including Australia, Canada, China, South Africa, the Netherlands, and the United States [70]. Nevertheless, there are some limitations: while moisture, soil type, temperature and UV light can reduce the efficiency of bioherbicides when applied directly to the field, there are also problems related to the formulation processes needed to guarantee the viability and stability of these agents, in addition to the high costs required to commercialize these products [70, 81]. These limitations have also been noted in mycoherbicides based on *Alternaria* species such as Casst™ (*A. cassiae*) and Smolder® (*A. destruens*) [70, 82]. In spite of advancements in this field, these barriers need to be addressed to ensure the long-term economic and commercial viability of all developed bioherbicides [70].

Culture filtrates and purified natural phytotoxins from *Alternaria* species are also reported to have bioherbicidal potential against different weeds, including *Ageratina adenophora*, *Amaranthus retroflexus*, *Digitaria sanguinalis*, *Echinochloa crus-galli*, *Eclipta* sp. and *Parthenium hysterophorous*. Although these phytotoxins act as commercial herbicides, they work differently at the molecular level, which makes otherwise resistant biotypes susceptible to them [14,27,76,83].

A factor to consider in the use of fungal metabolites as bioherbicidal agents is the needed concentration to develop a biocontrol effect in the plant. The TeA requirement to inhibit plant photosynthesis in PSII by 50 % is 48 μg mL^{-1} [84]. Studies have been carried out with the purpose of increasing phytotoxin production in *Alternaria* spp., reaching maximum TeA yields of approximately ~580 μg g−1 of fungal biomass [85]. In order to make the use of this phytotoxin commercially attractive for weed control, first it becomes necessary to develop possibly a continuous flow fermentation protocol that could help to improve TeA yield by *Alternaria*, and secondly, to work on field spraying/application strategies that could efficiently deliver the phytotoxin into the plant cells to reach the adequate TeA concentrations.

As stated earlier in this review, metabolites from *Alternaria* spp. produce genotoxic and DNA-damaging effects [66,67]. However, as the EFSA reported, no secondary effects were observed on human health at low TeA doses [62]. This highlights the need to understand the mode of action of fungal-derived bioherbicides and proceed with the development of industrial products [73].

We are now at a point where scientific studies on the development of mycoherbicides have significantly advanced around the world, and the field application of registered or unregistered products has increased [18]. To assess the potential of a mycoherbicide, weed researchers must consider the fungi's range, host, and ability to grow and sporulate in culture media, in addition to its genetic stability and virulence. A lack in understanding of these properties will diminish the chance of success for mycoherbicide products, in terms of their commercialization [86]. In addition, several challenges ranging from environmental to political considerations can impact the development of a mycoherbicide. Clearly, one of the most significant problems is related to the release of mycoherbicides into the environment [87]. This issue has raised concerns for both weed scientists and governments, and in each specific case, the host range and environmental impact of the mycoherbicide must be assessed [18].

The use of specific fungal molecules such as TeA as bioherbicides do present some advantages, as supported by various toxicological studies. At the same time, the use of mixtures of compounds produced by specific fungal strains may help to prevent the emergence of weed genetic resistance, but this will require further research and development. Finally, whereas applying fungal strains to control weeds is economically advantageous, this does raise the possibility of unwanted adverse effects in other plant species. The future of bioherbicides is therefore unpredictable at this point, and designs that are more environmentally friendly and safe for human health will require more research in all possible fields, including chemistry.

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