

Non-proteinogenic amino acids potential use as allelochemicals¹

Uso potencial de aminoácidos não-proteinogênicos como aleloquímicos

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Abstract - From existing amino acids, twenty are directly involved in the formation of proteins. The others are known as non-proteinogenic amino acids (NPAA). The NPAA have different functions, including anti-herbivory activity, antimicrobial, protection from stress, cell signaling, nitrogen storage, as toxins against invertebrates and vertebrates and as allelochemicals. Plants are able to release these metabolites in the soil, which may influence the growth and development of neighboring plants, both positively and negatively. The objective of this review is to describe the chemical characteristics, the allelopathic potential and selectivity for crops of non-proteinogenic amino acids m-tyrosine, L-DOPA, methionine sulfoximine and azetidine.

Keywords: m-tyrosine; L-3,4-dihydroxyphenylalanine; MSO; azetidine-2-carboxylic acid

Resumo - Dos aminoácidos existentes, vinte estão envolvidos diretamente na formação de proteínas. Os demais são conhecidos como aminoácidos não-proteinogênicos (AANP). Os AANP possuem diferentes funções, incluindo atividade anti-herbivoria, antimicrobiana, proteção contra o estresse, sinalização celular, armazenamento de nitrogênio, como toxinas contra invertebrados e vertebrados e, também, como aleloquímicos. As plantas são capazes de liberar esses metabólitos no solo, os quais podem influenciar o crescimento e desenvolvimento de plantas vizinhas, tanto positiva como negativamente. O objetivo dessa revisão é descrever as características químicas, o potencial alelopático e a seletividade para culturas dos aminoácidos não-proteinogênicos m-tirosina, L-DOPA, metionina sulfoximina e azetidino.

Palavras-chaves: m-tirosina; L-3,4-dihidroxifenilalanina; MSO; ácido carboxílico-2-azetidino

Introduction

The overall structure of amino acids involves a grouping amine and a carboxylic group, containing carbon, hydrogen, nitrogen and oxygen. There are thousands of amino acids and it is estimated that about 250 are found in plants, especially in the genres leguminosae, sapindaceae, aceraceae, hippocastenaceae and cucurbitaceae (Vranova et al., 2011). However, only 20 amino acids are involved directly in protein structure (Bell, 2003). Other molecules are known as non-proteinogenic amino acids (NPAA; Matsumoto, 2011).

The NPAA have different functions, including anti-herbivory activity, antimicrobial, allelochemical, stresses protection, cell signaling, nitrogen storage and as toxins against invertebrates and vertebrates (Bell, 2003). Despite these important functions, the attention of the research to the NPAA only intensified with the identification of their importance in metabolism, gene regulation and protection of plants. In addition, NPAA can be decisive in the ecosystem structure and function (Vranova et al., 2011).

Plants release special metabolites in the soil, which may influence the growth and

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development of neighboring plants, both positively and negatively (Soares et al., 2012). This phenomenon is called allelopathy, defined as the ability of plants to protect themselves using natural compounds (Gniazdowska & Bogatek 2005) and also chemically interact with other living beings (Weir et al. 2004). Allelopathy is a phenomenon known for many years and a wide range of allelochemicals have been identified (Matsumoto, 2011). Among these allelochemicals there are some NPAA. The objective of this review is to describe the chemical characteristics, the allelopathic potential and selectivity for crops of non-proteinogenic amino acids m-tyrosine, L-DOPA, methionine sulfoximine and azetidine.

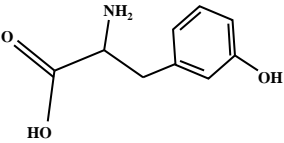
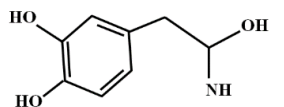
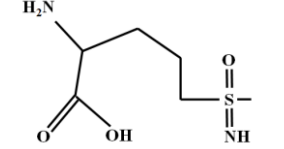
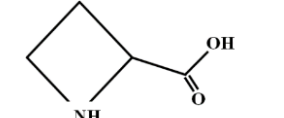
Meta-tyrosine

Meta-tyrosine (3-hydroxy methyl alanine; and tyrosine; Table 1) is an analog of

the proteinogenic amino acid, ATP-tyrosine (tyrosine). It is classified as an aromatic NPAA. For the physical-chemical characteristics of the compound, pKa 2.00 and log Kow -2.30 (OCD, 2015) we can infer that it is movable both by xylem and phloem of plants. M-tyrosine was identified as amino acid free of *Festuca rubra* L. and *Euphorbia myrsinites* (Bertin et al., 2007).

In vitro assays show that tyrosine is toxic to a wide variety of plant species. Nevertheless, its degradation by soil microorganisms can minimize the allelopathic effects in natural systems (Kaur et al., 2009). However, the large number (>1% of fresh weight) of m-tyrosine produced and released by the roots of some cultivars of *Festuca sp.* (Bertin et al., 2007) suggests that this amino acid plays an important role in the eco-physiology of these grasses.

Table 1. General characteristics of non-proteinogenic amino acids.

Name	Chemical structure	pKa*	Log Kow*	Mechanism of action
m-Tyrosina		2,00	-2,30	¹ Formation of defective proteins
L-DOPA		2,32	-2,39	² Formation of ROS
Methionine sulfoximine		2,28	-1,87	³ Inhibitor of glutamine synthetase
Azetidine		2,35	-3,09	⁴ Formation of defective proteins

1 Bertin et al., 2007; 2 Nishihara et al., 2004; 3 Gill & Eisenberg, 2001; 4 Trotter et al., 2002; * OCD, 2015.

In plants of *F. rubra*, m-tyrosine is found in the seeds, leaves and especially the roots (Bertin et al., 2007). This happens due to increased enzyme activity in the conversion of phenylalanine into m-tyrosine in the roots

(Huang et al., 2012). The biosynthesis of m-tyrosine involves two metabolic pathways the catalytic and non-catalytic. The catalytic route involves the shikimic acid pathway (Huang et al., 2012). In *Streptomyces coeruleorubidus*, m-

tyrosine is catalyzed by phenylalanine 3-hydroxylase reaction (Zhang et al., 2011). In contrast, in plants of *Euphorbia myrsinitis* m-tyrosine is synthesized by transamination m-hydroxyphenylpyruvate (Muller & Schutte, 1967).

In order to identify possible metabolic precursors in the synthesis of m-tyrosine in seedling of *F. rubra*, 100 μ M of phenylalanine, phenylpyruvic acid, tyrosine and shikimic acid solutions were added. There was increased production of m-tyrosine, compared to the control only when phenylalanine was added (Huang et al., 2012). When *F. rubra* received phenylalanine marked (U-13 C9, 15 N) in solution, it was found that almost 30% of L-tyrosine was marked (Huang et al., 2010).

The enzyme that catalyzes the hydroxylation of phenylalanine to m-tyrosine belongs to the cytochrome P450 monooxygenase family. These enzymes are inhibited by ABT (1-aminobenzotriazole) and ancymidol (α -cyclopropyl- α -[p-methoxyphenyl]-5-methyl pyrimidine alcohol). When these inhibitors were applied to plants of *F. rubra*, the level of m-tyrosine was reduced between 12% and 40% compared to untreated plants (Huang et al., 2012).

The formation of m-tyrosine by non-catalytic way in plants is not well known. In animal cells, m-tyrosine is accumulated during oxidative stress by non-enzymatic oxidation of phenylalanine (Fell et al., 1979). The abundance of m-tyrosine in mammalian tissues indicates oxidative stress and cell aging (Molnar et al., 2005; Matayatsuk et al., 2007).

L-tyrosine amino acid inhibits the growth of roots, changing phytohormones signaling, particularly auxin (Bertin et al., 2007; Bertin et al., 2009). However, expression of the auxin responsive gene *DR5-GUS* was not affected by m-tyrosine in six mutants of *Arabidopsis* auxin responsive, suggesting that m-tyrosine does not interfere directly in the metabolism or auxin activity (Bertin et al., 2007).

Due to its chemical structure, tyrosine also interferes in plant amino acids metabolism. There is evidence that in protein synthesis, m-tyrosine is incorporated in bacteria instead of phenylalanine (Aronson e Wermus, 1965), in mammalian cells (Gurer-Orhan, 2006; Matayatsuk et al., 2007) and vegetables (Rodgers et al., 2002). For example, in *Vigna radiata* phenylalanine tRNA synthetase catalyzes also up to 25% of m-tyrosine instead of phenylalanine (Rodgers et al., 2002). Incorrect incorporation of m-tyrosine in protein can affect their three-dimensional structure, and thus interfere with the function regulation of protein phosphorylation by tyrosine (Luan, 2002). Furthermore, the presence of m-tyrosine promotes tyrosine cross-links with cell walls (Held et al., 2004).

M-tyrosine present in the soil solution inhibits the root growth of monocots and dicots species. The content of organic matter, between 2 and 4%, does not affect its biological activity. However, the allelopathic effects of m-tyrosine is inversely proportional to the content of nitrogen present in the soil solution. M-tyrosine half-life in the soil lies between 24 and 48 hours, depending on the type of soil and the nitrogen content (Bertin et al., 2009).

L-DOPA

L-DOPA (L-3,4-dihydroxyphenylalanine; Table 1) is a compound with high allelopathic activity (Vadivel & Janardhanan, 2001) and is present in species of the Fabaceae family. For instance, *Mucuna pruriens* L. contains L-DOPA in proportions of up to 4% (m/m) of its leaf content. In seeds of this species, the proportion of this amino acid affects up to 7% (m/m) (Nishihara et al., 2004). The molecule physicochemical characteristics, with pKa 2,30 and log Kow -2,39 (OCD, 2015) allow inferring that their mobility is both in the xylem and in the phloem of plants.

L-DOPA is a catecholamine formed from hydroxylation of tyrosine (Soares et al.,

2012). In animals, it is an important molecules precursor, including neurotransmitters dopamine, noradrenaline and adrenaline; and the pigment melanin (Matsumoto, 2011). In plants, L-DOPA inhibits the growth of seedling roots, having little or no effect on the aerial parts or on the germination (Fujii, 2003). In fact, L-DOPA present in the soil at a concentration of 0.1 mM inhibits more than 50% of the roots growth of 19 species, including *Brassica* sp., *Digitaria ciliaris*, *Cucumis* sp., *Lycopersicum esculentum* (Nishihara et al., 2004; Hachinohe & Matsumoto, 2007).

In plant L-DOPA is oxidized by polyphenol oxidase (PPO), generating superoxide. The resulting superoxide is converted to H₂O₂ by the superoxide dismutase and/or transition metals (such as Fe and Cu and Fe (II)), which trigger the Fenton reaction (Kostrzewa et al., 2002; Mittler, 2002; Matsumoto 2011). Reactive oxygen species (ROS) formed can cause lipid peroxidation, damage to proteins and to DNA integrity, leading to programmed cell death (Pattison et al., 2002).

Selectivity between species may happen due to differential PPO activities (Hachinohe and Matsumoto, 2007). Plant species on which the PPO activity is enhanced favor L-DOPA to be oxidized to melanin and produce high amount of reactive oxygen species (Mushtaq et al., 2013a). In the susceptible species, L-DOPA causes oxidative damage due to the presence of reactive oxygen species (Matsumoto, 2011). In lettuce, L-DOPA (0.1 and 1 mM) doubled the PPO activity (Mushtaq et al., 2013a). Plants of *Cucumis sativus* and *Glycine max* presented inhibition of root growth and increased PPO activity after addition of L-DOPA (Soares et al., 2011; Mushtaq et al., 2013b). In lettuce, L-DOPA (1 mM) increased about 4 times the production of O₂⁻ and H₂O₂ compared to untreated control. Lipid peroxidation also increased with the addition of L-DOPA (Mushtaq et al., 2013a).

Other species with smaller PPO activity can metabolize L-DOPA in other non-toxic

metabolites. Plants of *Echinochloa crus-galli* L. and *Lolium perenne* L. are tolerant to L-DOPA due to its degradation (Nishihara et al., 2004).

Methionine sulfoximine

Methionine sulfoximine (2-amino-4- (S-sulfonamide-methyl) butanoic acid; MSO) is an analog of glutamate. MSO is an effective inhibitor of glutamine synthetase (GS; Table 1; Poitry et al., 2000; Bhatnagar et al., 2001; Gill and Eisenberg, 2001). From crystallography studies, it was found that MSO and phosphinothricin (PPT) have similar characteristics in inhibiting GS (Gill and Eisenberg, 2001). Both MSO and PPT are able to connect in the same way at the GS action site (Gill & Eisenberg, 2001). In a test with GS leaves of *Pisum sativum* L., adding MSO and glutamate was competitive with the substrate of the enzymatic reaction (Evstigneeva et al., 2003). Compatible with pKa 2.28 and log Kow -1.87 (OCD, 2015) of MSO, it appears that this molecule has great mobility in the phloem of plants.

MSO sensitive plants have inhibited the GS enzyme, promoting ammonium accumulation in cytotoxic levels (De Block et al., 1987). For instance, plants of *Arabidopsis thaliana* sprayed with 2.5 µM of MSO showed tenfold increase in ammonium levels and consequently there was growth inhibition and induction of necrosis (Maughan & Cobbet, 2003). Tolerance of plants to MSO is due to its degradation capacity. Plants *A. thaliana* transgenic containing phosphinothricin acetyl transferase detoxicated enzyme are insensitive to MSO (Maughan & Cobbet, 2003).

Azetidine

The carboxylic-2-azetidinone acid (AZC; Table 1) is a homolog of proline, but it is a cyclical NPAA. This compound is found in Liliaceae (mainly in *Convallaria majalis* and *Polygonatum multiflorum*) and beetroot (*Beta vulgaris*) (Peterson & Fowden 1963; Rubenstein

et al., 2006). AZC is found in up to 7% of *Convallaria majalis* leaves mass (Peterson & Fowden 1963) and up to 5% in beet (Rubenstein et al., 2006). According to the physicochemical characteristics of AZC, pKa 2.35 and log Kow - 3.09 (OCD, 2015), it appears that its mobility happens through the xylem and phloem of plants. AZC is highly toxic to many organisms because it is incorrectly incorporated into proteins instead of proline, modifying the three dimensional structure of proteins, including collagen, keratin and hemoglobin (Trotter et al., 2002).

Final Remarks

The increase in cases of weeds resistant to herbicides has challenged scientists to develop new approaches to their management. The NPAA, primarily m-tyrosine, L-DOPA, MOS and AZC presented potential to manage weed flora by the use in rotation of vegetable crops that produce them.

In addition, these compounds and other allelochemicals can be used as precursors in the synthesis of new herbicidal molecules. However, the fact that some NPAA can replace "useful" amino acids in proteins suggests that their toxicological profile is probably not favorable for the development of herbicides.

Our review showed NPAA with different mechanisms of action and that present allelochemical potential. It is believed that the next stages of field trials would analyze the conditions and factors that minimize infestations when using crop rotations with cultivated species that synthesize high amount of those NPAA.

Another line of investigation that would likely result in lasting solution to the weed management would be the development of cropping systems with those NPAA producing crops integrated with the chemical method of weed management.

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