Botanica
ISSN 2538-8657
https://doi.org/10.35513/Botlit.2022.1.2
2022, 28(1): 4–14

Review

Pipecolic acid in plants: biosynthesis, signalling, and role under stress

Fatma Nur Koc, Burcu Seckin Dinler*

Sinop University, Faculty of Arts and Sciences, Department of Biology, Sinop, Turkey
*Corresponding author. E-mail: bseckin@sinop.edu.tr

Abstract

Koc F.N., Seckin Dinler B., 2022: Pipecolic acid in plants: biosynthesis, signalling, and role under stress. – Botanica, 28(1): 4–14. https://doi.org/10.35513/Botlit.2022.1.2

Plants protect themselves by developing defensive responses against various biotic and abiotic stress factors throughout their lives. As a result, they create a stress response called 'systemic acquired resistance' (SAR) under pathogen infection. Pipecolic acid is one of the critical signalling molecules in regulating systemic acquired resistance, and it is a product of L-lysine metabolism in all organisms. It is synthesised not only by plants but also by microorganisms, animals and fungi. Many studies have been carried out to understand pipecolic acid's biosynthesis, transport and role in plants under biotic stress. But recent studies report that pipecolic acid also functions as a stress response in plants under abiotic stress. This paper reviews the historical development of studies on pipecolic acid, its biosynthesis, and its function in plants under stress conditions and systemic acquired resistance.

Keywords: abiotic stress, biotic stress, L-lysine, N-hydroxy-pipecolic acid, systemic acquired resistance (SAR).

INTRODUCTION

Plants are affected by various stress factors throughout their lives. They are exposed to many abiotic factors such as extreme temperature changes (hot and cold), drought, over salinity, lack of nutrients, and toxic metals (Zhang et al., 2021). The exposed abiotic factors are the most critical environmental components that affect the distribution and productivity of plants (Zhang et al., 2018). Otherwise, herbivore organisms, parasites, and microorganisms are biotic factors that adversely affect the plant life cycle. Animals and organisms that live as parasites, fed by plant tissues such as nematodes, harm their development by preventing the removal and use of nutrients required for the plant. Microorganisms that infect plant tissues are replicated in tissue, causing the plant to become ill and die (Iqbal et al., 2021). So, plants have developed many defence mechanisms to protect themselves and survive the adverse effects of the biotic and abiotic stress factors.

Plants have developed a complex immune system that can activate the defence mechanism in local and non-infected areas to cope with the infestation of microbial pathogens (Gao et al., 2021). There are two types of local defence mechanisms against pathogen infections; immunity (PTI) triggered by the molecular model associated with the pathogen and immunity (ETI) triggered by the effector (Zhang et al., 2020). Furthermore, both PTI and ETI can start the production of long-distance signal molecules to stimulate

the systemic acquired resistance (SAR) mechanism (Gao et al., 2021).

The 'systemic acquired resistance' (SAR) mechanism is considered the essential plant defence mechanism, which is broad-spectrum and long-lasting to protect the distant tissues of plants under pathogen infection. The most critical feature of the SAR mechanism is the communication between infected tissue and other healthy tissue (Shah et al., 2014). The SAR mechanism that provides this communication has been shown to signal molecules such as salicylic acid (SA) and SA variant (methyl salicylate) candidate signal molecules, a plant hormone (Gao et al., 2015). In subsequent years, the presence of stronger signal molecules in the SAR mechanism has been detected. Other signal molecules involved in the SAR mechanism are glycerol 3 phosphate (G3P), azelaic acid (AzA), pipecolic acid (Pip), N-hydroxy-pipecolic acid (NHP), nicotinamide adenine dinucleotide (NAD), nicotinamide adenine dinucleotides (NDP), and nicotinamide adenine dinucleotide phosphate (NADP) and dehydroabietic (Gao et al., 2021). The transfer of SAR signal molecules from infected tissue to non-infected tissues through phloem ensures strong defence communication.

SA is a plant hormone that plays a vital role in organising local and systemic immunity. In early studies, SA was considered a long-distance signal due to the accumulation of pathogenesis and infected leaves in the flourishing content. However, further studies have shown that SA is not a critical signal molecule, although it is necessary to warn the SAR (Shah & Zeier, 2013). In the studies made, it is stated that when SA production and accumulation are blocked, plants make them more susceptible to pathogen infection (Wang & Xiang, 2020). Therefore, SA and subsequent signals are necessary to control diseases caused by pathogens that exhibit a biotrophic phase in their life cycles, especially when they receive nutrients from living plant cells (Shah et al., 2014).

Pip, a derivative and non-protein amino acid of L-lysine, plays a role in forming a SAR response (Zhang et al., 2020). Pip is a critical molecule of plant immunity, stimulated by the accumulation of phytoalexin, the processing of SA biosynthesis, and defence gene expressions. Studies show that plants under the pathogen attack Pip accumulates in infected and non-infected tissues (Návarová et al., 2012; Wang et al., 2018). However, Pip's role in the SAR has not been fully explained despite the work carried out.

NHP, an essential molecule of the SAR mechanism, is formed by the hydroxylation of pipecolic acid (Hõrak, 2021). NHP interacts with SA to produce an effective response to the SAR mechanism (Bernsdorff et al., 2016; Hartmann et al., 2017). Pip, NHP, and SA accumulate in infected tissues and non-infected tissues in plants under pathogen infection (Bernsdorff et al., 2016; Gao et al., 2021; Zeier, 2021), and they are indicated to be critical signal molecules in the formation of plant immunity (Klessig et al., 2018). However, its functions in the SAR mechanism have not yet been fully elucidated. Some studies in recent years have shown that pipecolic acid is also synthesised in plants under abiotic stress. However, the effects of pipecolic acid under abiotic stress are not fully understood. This study aims to draw attention to the roles of Pip and its derivative in plants under stress and highlight its features.

HISTORY OF PIPECOLIC ACID STUDIES IN PLANTS

Pipecolic acid is a non-protein amino acid naturally synthesised in plants, animals, fungi, and microorganisms. In 1891, Ladenburg produced pipecolic acid for the first time by reducing picolinic acid with sodium and ethanol. It was dissolved using optically active tartaric acid and obtained partially racemised L-pipecolic acid by oxidation of conhydrine (Morrison, 1952). In two separate studies in 1947 (Dent et al., 1947) and 1950 (Steward & Thompson, 1950), a non-protein amino acid with the properties of pipecolic acid was identified in two-dimensional paper chromatography of potato tuber and other plant sources. Morrison (1953) and Zacharius et al. (1954) have isolated pipecolic acid from *Trifolium repens* and *Phaseolus vulgaris*, respectively, showing its presence in biological materials. Yatsu & Boynton (1959) applied maleic hydrazide, a plant growth regulator, and osmotic stress to strawberries and measured the pipecolic acid level in the plant leaves for the first time. Pálfi and Dézsi (1968) have defined pipecolic acid as a marker of abnormal protein metabolism in diseased plants. In the following years, a study on rat brains has reported that pipecolic acid is a product of lysine metabolism (Chang, 1976) (Table 1).

Table 1. Historical chronology of the discovery of pipecolic acid (isolation, biosynthesis, roles in the development of plant growth and under stress conditions)

Studies and results	References
Pip was produced by the reaction of picolinic acid with sodium and ethanol.	Ladenburg, 1891
Partial L-pipecolic acid was obtained by the oxidation of conhydrine.	Willstatter, 1901
An unidentified non-protein amino acid with the properties of pipecolic acid was identified in paper chromatography.	Steward & Thompson, 1950; Dent et al., 1947
Pip was isolated from *Trifolium repens* plant.	Morrison, 1953
Pip was isolated from *Phaseolus vulgaris* plant.	Zacharius et al., 1954
Pip level was measured under maleic hydrazide and osmotic stress.	Yatsu & Boynton, 1959
Pip is a marker of abnormal protein metabolism in diseased plants.	Pálfi & Dézsi, 1968
Pip is a product of lysine metabolism.	Chang, 1976
Pip has a function as a neurotransmitter.	Charles, 1986
Pip is important in stimulating flowering in *Lemna gibba.*	Fujioka et al., 1987
Pip has an essential role in SAR.	Song et al., 2004
Pip is an osmoregulatory amino acid in non-halophilic plants.	Moulin et al., 2006
Pip is a critical regulator of plant immunity.	Návarová et al., 2012
Exogenous Pip application increased the resistance of the tobacco plant under the pathogen infection.	Vogel-Adghough et al., 2013
Pip accumulates in the xylem sap and leaves of the infected soybeans	Abeysekara et al., 2016
Pip accumulation in the roots may suppress root growth.	Caddell et al., 2020
Exogenous application of NHP triggers SAR generation.	Yıldız et al., 2021
Ald1 mutant tomato plant under drought stress is more tolerant than *fmo1* mutant tomato plant.	Wang et al., 2021

In a study on rat brains (Charles, 1986), it has been reported that pipecolic acid functions as a neurotransmitter. In 1987, a survey on *Lemna gibba*, an aquatic plant, reported that pipecolic acid effectively stimulated flowering (Fujioka et al., 1987). In their research on *Arabidopsis thaliana* ald1 mutant, Song et al. (2004) have shown that Pip plays an essential role in regulating SAR. A study conducted in 2006 identified that pipecolic acid is an osmoregulatory amino acid in non-halophilic plants under various osmotic stress conditions (Moulin et al., 2006). Návarová et al. (2012) have shown that Pip is a critical regulator of plant immunity. Exogenous Pip application on tobacco plants has shown an increase in resistance to infection (Vogel-Adghough et al., 2013). In a survey of soybean (*Glycine max* L.) infected with *Fusarium virguliforme*, it has been reported that pipecolic acid accumulates in xylem sap and leaves because of stimulation of plant immunity (Abeysekara et al., 2016).

In the study of drought-stressed sorghum plants, it has been reported that high Pip accumulation in sorghum roots/rhizosphere suppresses root growth (Caddell et al., 2020). Yıldız et al. (2021) have shown that the NHP, created by the hydroxylation of the Pip, is a signal molecule required to complete and rearrange the SAR response in *Arabidopsis* plant. Lastly, Wang et al. (2021) have examined the function of the ALD1 gene, which catalyses the production of pipecolic acid from L-lysine, and the FMO1 gene, which catalyses the hydroxylation of pipecolic acid under drought stress. They have asserted that *ald1* mutant tomato plants have a higher tolerance to drought stress than *fmo1* mutant tomato plants (Table 1).

PIPECOLIC ACID BIOSYNTHESIS

Pipecolic acid has two natural enantiomers: L-Pipecolic acid and D-Pipecolic acid (Fig. 1). Both enantiomers are the products of L-Lysine (Vranova et al., 2013). Since the amino acid L-Lysine has an amino group in both the α-position and the ε-position, they are synthesised in plastids by two different biosynthesis pathways: the 1,2-dihydroxy-pipecolic acid (P2C) pathway and the 1,6-dihydroxy-pipecolic acid (P6C) pathway. In pathogen stimulation in the P2C pathway, also known as the KAC pathway, L-lysine is converted to α-ketoacid ε-amino α-ketocaproic acid (KAC) by a reaction catalysed by a lysine ami-

notransferase enzyme encoded by AGD 2-like defence response protein 1 (ALD1) gene. As a result of the dehydration of KAC, 1,2-dihydroxy-pipecolic acid (1,2-DP or P2C) is formed. In the next step, L-pipecolic acid is formed from 1,2-DP with the activation of the SAR deficient 4 (SARD4) gene, which encodes a homolog of bacterial ornithine cyclodeaminase (Fig. 2 A) (Hartmann et al., 2017; Shan & He, 2018).

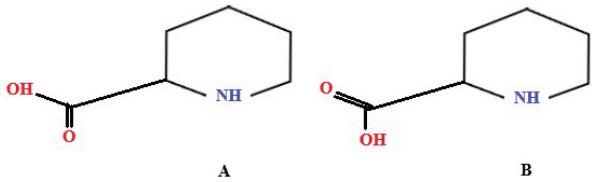

Fig. 1. L-Pipecolic acid (A) and D-Pipecolic acid (B) (modified from Vranova et al., 2013)

In the saccharopine pathway or P6C pathway, 1,6-dihydroxy-pipecolic acid (1,6-DP or P6C) is formed from α-aminoapidic semialdehyde (AAS), which is an intermediate step in the α-aminoadipic acid (Aad) production pathway from L-lysine. During pathogen infection, 1,6-DP then transforms into L-Pip and is vital in stimulating the systemic acquired resistance mechanism. In the first step of the pipecolic acid synthesis, saccharopine is formed from L-lysine with the lysine ketoglutarate reductase (LKR) gene activation. In the next step, hydrolysis of saccharopine occurs with the reaction catalysed by a hydrolase enzyme encoded by the saccharopine dehydrogenase (SDH) gene. α-aminoapidic semialdehyde is formed from hydrolysed saccharopine. The promoter region of the LKR/SDH gene contains elements that respond to abscisic acid (ABA) and jasmonic acid (JA) (Fig. 2 B). Studies have shown that exogenous ABA and methyl-jasmonate application increase the expression of these genes. In the second step, 1,6-DP is formed by a spontaneous reaction from α-aminoapidic semialdehyde. Pipecolic acid is formed by the reaction catalysed by sarcosine/pipecolate oxidase from 1,6-DP (Zeier, 2013, Neshich et al., 2013, Hartmann & Zeier, 2018). The saccharopine pathway has been associated with stress response in *Arabidopsis* and rapeseed. It has been determined that the LKR/SDH gene expression increases under salt and osmotic stress in these plants (Moulin et al., 2000).

A bioactive derivative N-hydroxypipecolic acid

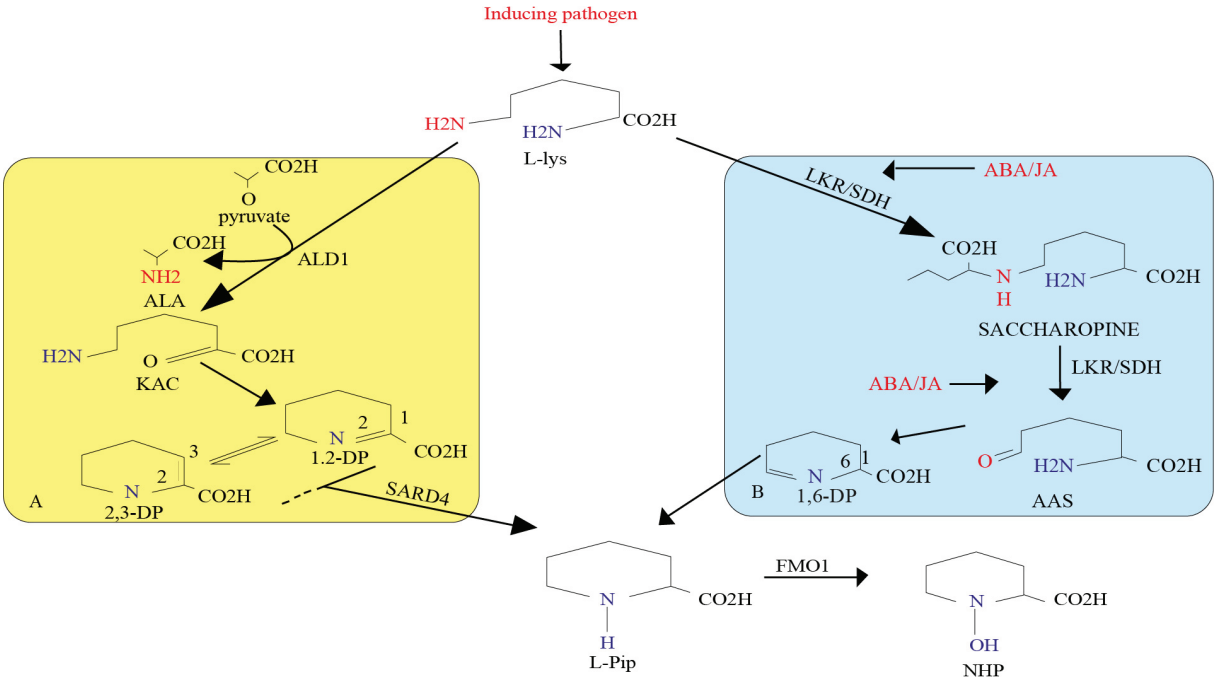

Fig. 2. Pipecolic acid biosynthesis; P2C (1,2-dihydroxy-pipecolic acid) pathway (A) and P6C (1,6-dihydroxy-pipecolic acid) pathway (B): L-lys (L-lysine), KAC (α-ketoacid ε-amino α-ketocaproic acid), 1,2-DP (1,2-dihydroxy-pipecolic acid), 2,3-DP (2,3-dihydroxy-pipecolic acid), AAS (α-aminoapidic semialdehyde), 1,6-DP (1,6- dihydroxy-pipecolic acid), L-Pip (L-pipecolic acid), NHP (N-hydroxy-pipecolic acid) (modified from Hartmann & Zeier, 2018)

(NHP) is formed by increasing pipecolic acid content in plastids under stress conditions. This reaction is activated by Flavin-Dependent Monooxygenase 1 (FMO1) (Chen et al., 2018) (Fig. 2). Návarová et al. (2012) have asserted that the ald1 mutant *Arabidopsis* plant is defective for the SAR response, and it could stimulate the SAR response only with the exogenous pipecolic acid application. They also have asserted that the pipecolic acid exogenously applied to the roots of the wild-type *Arabidopsis* plant could largely stimulate the resistance in the leaves. In a study on transgenic rice plants, the overexpression of the ALD1 gene, which is involved in Pip biosynthesis, has been shown to increase the plant's defence mechanism against *Magnaporthe oryzae* infection (Jung et al., 2016). Similarly, the previous studies on *sard4* mutant *Arabidopsis* plants have shown that the SARD4 gene is essential for Pip biosynthesis, and the *sard4* mutation slows down Pip biosynthesis and causes the overaccumulation of 2,3-DP, which is formed as a result of isomerisation of 1,2-DP (Ding et al., 2016; Hartmann et al., 2017). In the study, it has been reported that SARD1 and CBP60g genes regulate SA biosynthesis in plants under pathogen infection (Sun et al., 2015). Sun et al. (2018) have reported that the Calmodulin Binding Transcription Factor (CAMTA) family suppress the biosynthesis of Pip and NHP by negatively affecting the expression of SARD1 and CBP60g. With the FMO1 gene expression, Pip hydroxides and creates NHP. Studies have shown that the UGT76B1 gene should be expressed in the glycosylation of NHP. The loss of function in the UGT76B1 gene has been shown to stop the accumulation of NHP-OGlc (Mohnike et al., 2021).

PIPECOLIC ACID IN SYSTEMIC ACQUIRED RESISTANCE

SAR is generally studied as a leaf-to-leaf response of two parallel and related pathways, linked to SA and Pip or its bioactive form NHP, AzA, NO, ROS, and G3P (Kachroo & Kachroo, 2020). The transport of signal molecules in the SAR mechanism plays an essential role in forming the SAR mechanism in tissues. It has been suggested that SA and its volatile derivative form (MeSA) of the SAR mechanism are key candidate signal molecules (Ádám et al., 2018) and that SA's presence is necessary to form a SAR response in distant tissues (Métraux et al., 1990; Gaffney et al., 1993). In subsequent studies, it has been stated that SA accumulates in infected and non-infected tissues but has been compromised by bacterial SA hydroxylase NahG. Both SA-brokerage and SAR mechanism-driven protection has been compromised (Vlot et al., 2009; Liu et al., 2011). It has also been assumed that the SA, which is systemically moving, is carried in an apoplastic way in the *Arabidopsis thaliana*. Its long-distance transport is insufficient in setting up the SAR mechanism (Vernooij et al., 1994; Lim et al., 2016). Therefore, it is believed that the SA has been coordinated to form the SAR mechanism with other signal molecules (Lim et al., 2020). During the infection, it was observed that the SAR mechanism was weak in plants that could not accumulate SA. However, studies have found that the SAR mechanism cannot be created in mutant plants that cannot produce SA (An & Mou, 2011). Therefore, SA accumulation is considered necessary for a strong SAR response against pathogen infections in the plant (Gaffney et al., 1993; Nawrath & Métraux, 1999; Bernsdorff et al., 2016).

Návarová et al. (2012) have determined that Pip accumulation is shown before the SA accumulation. While SA and Pip/NHP paths are considered two paths in parallel, recent studies have indicated that both paths are coordinated (Gao et al., 2015). In parallel with these findings, Lenk et al. (2019) have demonstrated that the external Pip application has an effect that increases NO concentration in barley plant under the *P. syringae* infection. These results show that Pip has raised the number and alerted the SAR and that Pip is at the head of the NO-ROS-AzA-G3P flow harness (Wang et al., 2018; Lenk et al., 2019). The ALD1 genes expressed in the P2C route form de-hydroxy-pipecolic acid from Lys and the SARD4 genes in reducing the de-hydroxy-pipecolic acid to Pip. In the studies conducted, it has been determined that mutations in the ALD1 gene prevent Pip accumulation and SAR formation. However, it has been stated that SARD4 mutant plants can accumulate Pip even in low quantities and have partial SAR response (Ding et al., 2016). In previous studies, the cucumber plants treated with pipecolic acid stimulated the SAR response against *Podosphaera xanthii*, *P. syringae*

infection (Belu et al., 2021; Pazarlar et al., 2021).

Recent studies indicate that Pip and NHP are strong signal molecules that can replace the SA (Hartmann et al., 2017). It has been found in studies that encouraged the systemic acquired resistivity mechanism of pipecolic acid to be established, strengthening plant immunity (Lenk et al., 2019). Schnake et al. (2020) have reported that NHP accumulation in leaves is faster than Pip build-up, and SAR response is vital in plants under *P. syringae* infection. Studies have shown that ALD1 and FMO1 genes, which refer to the NHP biosynthesis, are required for SA accumulation (Mishina & Zeier, 2006; Cecchini et al., 2015). Yıldız et al. (2021) have demonstrated that the external NHP application significantly stimulates the SA biosynthesis. ALD1 and FMO1, although the genes are non-SA-independent, could be upregulated directly by SA (Cecchini et al., 2015). In addition, while SA-deficient mutants have been determined not to produce a SAR response, NHP-deficient *ald1* and *fmo1* mutants have shown that the same situation does not occur (Hartmann et al., 2018; Shields et al., 2022).

It has also been observed that the amount of NHP and its conjugate derivative NHP-Glc, accumulate in the leaves after infection in the *Arabidopsis* plants (Holmes et al., 2019; Chen et al., 2018; Hartmann & Zeier, 2018). In the studies conducted, it has been observed that the amount of free NHP increases as a result of mutations in the UGT76B1 gene, that plant growth is suppressed and that there is an increase in SAR response (Bauer et al., 2021; Cai et al., 2021; Holmes et al., 2021). The NHP is considered an essential molecule for understanding the signalling between molecules in the SAR mechanism and detecting species-specific pathogens in plants.

In their study on soybean (*Glycine max* L.), Abeysekara et al. (2016) have asserted that Pip accumulates in the systemic tissues in response to *Fusarium virguliforme* infection and positively regulates the SA biosynthesis. Exogenous Pip application has been shown to stimulate the expression of Pathogenesis-Related 1 (PR1) protein, SA accumulation, and the resistance against *Pseudomonas syringae* pv. *maculicola* (Psm). However, it has been shown that exogenous Pip application alone is insufficient for SA production in local and systemic tissues. Still, it positively affects the SA production under a pathogen stimulus. Accordingly, it has been reported that exogenous Pip application in pathogen infection effectively stimulates resistance due to the increased SA accumulation and signalling (Návarová et al., 2012). It is known that the *Arabidopsis* genome encodes the calmodulin-binding transcription activator (CAMTA) genes, which are related to plant immunity (Bouché et al., 2002). These genes, especially CAMTA1, CAMTA2, and CAMTA3, are directly related to plant immunity (Kim et al., 2013). Sun et al. (2020) have reported that camta1-3 mutant *Arabidopsis* shows disease resistance dependent on SA and Pip/NHP.

Pip activation stimulates nitric oxide (NO) and reactive oxygen species (ROS) in the SAR pathway. NO and ROS stimulate the activation of other molecules involved in SAR. The accumulation of ROS promotes the release of 18-carbon (C-18) membrane lipids, resulting in the accumulation of 9-carbon (C-9) azelaic acid (AzA) (Vlot et al., 2021). In a previous study on the *Arabidopsis* plant, it has been reported that the amount of AzA increases in the petiole secretion during pathogen infection. It has been reported that, with exogenous AzA application, AzA is transported in a symplastic way, inducing both SA- and Pip/NHP- dependent defence responses (Jung et al., 2009; Yu et al., 2013). The increased amount of AzA stimulates the accumulation of glycerol-3-phosphate (G3P), a product of lipid metabolism. AzA-dependent resistance and SAR depend on the accumulation of G3P (Fig. 3).

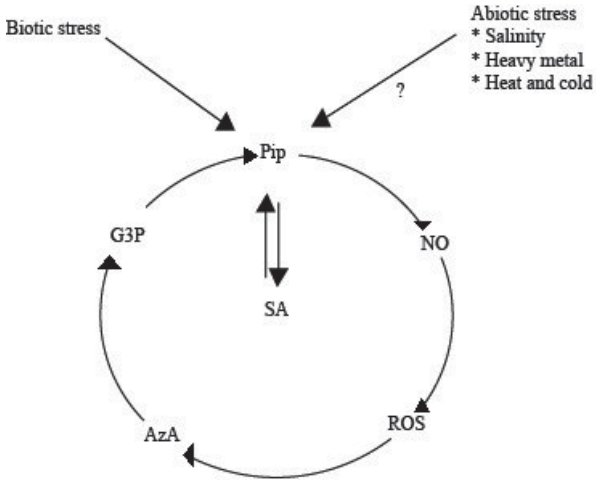

Fig. 3. Relationship between Pip with biotic and abiotic stress; Pip (pipecolic acid), NO (nitric oxide), ROS (reactive oxygen species), AzA (azelaic acid), G3P (glycerol-3-phosphate)

CONCLUSIONS

Pipecolic acid is known to act as a local/basal signal in SAR by stimulating the production of salicylic acid under biotic stress. It can be used as a signal molecule to increase plant tolerance. Previous studies on pipecolic acid have shown that this molecule may have a role in increasing the resistance of plants against stress. However, these studies on pipecolic acid focused on its function under biotic stress but have not been thoroughly examined under abiotic stress, especially salt, cold, heavy metal and heat. Therefore, this review wants to draw attention to the gap in this subject. Also, there is a need for more profound research in plant physiology, biochemistry, plant molecular biology and agriculture.

REFERENCES

Abeysekara N.S., Swaminathan S., Desai N., Guo L., Bhattacharyya M.K., 2016: The plant immunity inducer pipecolic acid accumulates in the xylem sap and leaves of soybean seedlings following *Fusarium virguliforme* infection. – Plant Science, 243: 105–114. https://doi.org/10.1016/j.plantsci.2015.11.008

Ádám A.L., Nagy Z.Á., Kátay G., Mergenthaler E., Viczián O., 2018: Signals of systemic immunity in plants: progress and open questions. – International Journal of Molecular Sciences, 19(4): 1146. https://doi.org/10.3390/ijms19041146

An C., Mou Z., 2011: Salicylic acid and its function in plant immunity F. – Journal of Integrative Plant Biology, 53(6): 412–428. https://doi.org/10.1111/j.1744-7909.2011.01043.x

Bauer S., Mekonnen D.W., Hartmann M., Yildiz I., Janowski R., Lange B., Geist B., Zeier J., Schäffner A.R. 2021: UGT76B1, a promiscuous hub of small molecule-based immune signalling, glucosylates N-hydroxypipecolic acid, and balances plant immunity. – The Plant Cell, 33(3): 714–734. https://doi.org/10.1093/plcell/koaa044

Belu N., Fufeng A.B., Nunn G.M., Spelman R.M., Hirjikaka D., Martin M.B., Xiao N.W., Dhaliwal M., Dan-Dobre M., Poleatewich A., Cameron R.K., 2021: Systemic acquired resistance (SAR)-associated molecules induce resistance in lab-and greenhouse-grown cucumber. – Physiological and Molecular Plant Pathology, 113:101592. https://doi.org/10.1016/j.pmpp.2020.101592

Bernsdorff F., Döring A.C., Gruner K., Schuck S., Bräutigam A., Zeier J., 2016: Pipecolic acid orchestrates plant systemic acquired resistance and defense priming via salicylic acid-dependent and-independent pathways. – The Plant Cell, 28(1): 102–129. https://doi.org/10.1105/tpc.15.00496

Bouché N., Scharlat A., Snedden W., Bouchez D., Fromm H., 2002: A novel family of calmodulin-binding transcription activators in multicellular organisms. – Journal of Biological Chemistry, 277(24): 21851–21861. https://doi.org/10.1074/jbc.M200268200

Caddell D.F., Louie K., Bowen B., Sievert J.A., Hollingsworth J., Dahlberg J., Purdom E., Northern T., Coleman-Derr D., 2020: Drought shifts sorghum root metabolite and microbiome profiles and enriches the stress response factor pipecolic acid. – The Preprint Server for Biology (*bioRxiv*). https://doi.org/10.1101/2020.11.08.373399

Cai J., Jozwiak A., Holoidovsky L., Meijler M.M., Meir S., Rogachev I., Aharoni A., 2021: Glycosylation of N-hydroxy-pipecolic acid equilibrates between systemic acquired resistance response and plant growth. – Molecular Plant, 14(3): 440–455. https://doi.org/10.1016/j.molp.2020.12.018

Cecchini N.M., Jung H.W., Engle N.L., Tschaplinski T.J., Greenberg J.T., 2015: ALD1 regulates basal immune components and early inducible defense responses in Arabidopsis. – Molecular Plant-Microbe Interactions, 28(4): 455–466. https://doi.org/10.1094/MPMI-06-14-0187-R

Chang Y.F., 1976: Pipecolic acid pathway: the major lysine metabolic route in the rat brain. – Biochemical and Biophysical Research Communications, 69(1): 174–180. https://doi.org/10.1016/S0006-291X(76)80288-4

Charles A.K., 1986: Pipecolic acid receptors in rat cerebral cortex. – Neurochemical Research, 11(4): 521–525. https://doi.org/10.1007/BF00965321

Chen Y.C., Holmes E.C., Rajniak J., Kim J.G., Tang S., Fischer C.R., Mudgett M.B., Sattely E.S., 2018: N-hydroxy-pipecolic acid is a mobile metabolite that induces systemic disease resistance in *Arabidopsis*. – Proceedings of the National Academy of Sciences, 115(21): E4920–E4929. https://doi.org/10.1073/pnas.1805291115

Dent C.E., Stepka W., Steward F.C., 1947: Detection of the free amino-acids of plant cells by partition chromatography. – Nature, 160: 682. https://doi.org/10.1038/160682a0

Ding P., Rekhter D., Ding Y., Feussner K., Busta L., Haroth S., Xu S., Li X., Jetter R., Feussner I., Zhang Y., 2016: Characterization of a pipecolic acid biosynthesis pathway required for systemic acquired resistance. – The Plant Cell, 28(10): 2603–2615. https://doi.org/10.1105/tpc.16.00486

Fujioka S., Sakurai A., Yamaguchi I., Murofushi N., Takahashi N., Kaihara S., Takimoto A., 1987: Isolation and identification of L-pipecolic acid and nicotinamide as flower-inducing substances in Lemna. – Plant and Cell Physiology, 28(6): 995–1003. https://doi.org/10.1093/oxfordjournals.pcp.a077402

Gaffney T., Friedrich L., Vernooij B., Negrotto D., Nye G., Uknes S., Ward E., Kessmann H., Ryals J., 1993: Requirement of salicylic acid for the induction of systemic acquired resistance. – Science, 261; 754–756. https://doi.org/10.1126/science.261.5122.754

Gao Q.M., Zhu S., Kachroo P., Kachroo A., 2015: Signal regulators of systemic acquired resistance. – Frontiers in Plant Science, 6: 228. https://doi.org/10.3389/fpls.2015.00228

Gao H., Guo M., Song J., Ma Y., Xu Z., 2021: Signals in systemic acquired resistance of plants against microbial pathogens. – Molecular Biology Reports, 1–13. https://doi.org/10.1007/s11033-021-06344-7

Hartmann M., Zeier J., 2018: L-lysine metabolism to N-hydroxypipecolic acid: an integral immune-activating pathway in plants. – The Plant Journal, 96(1): 5–21. https://doi.org/10.1111/tpj.14037

Hartmann M., Kim D., Bernsdorff F., Ajami-Rashidi Z., Scholten N., Schreiber S., Zeier T., Schuck S., Reichel-Deland V., Zeier J., 2017: Biochemical principles and functional aspects of pipecolic acid biosynthesis in plant immunity. – Plant Physiology, 174(1): 124–153. https://doi.org/10.1104/pp.17.00222

Hartmann M., Zeier T., Bernsdorff F., Reichel-Deland V., Kim D., Hohmann M., Scholten N., Schuck S., Bräutigam A., Hölzel T., Ganter C., Zeier J., 2018: Flavin monooxygenase-generated N-hydroxypipecolic acid is a critical element of plant systemic immunity. – Cell, 173(2): 456–469. https://doi.org/10.1016/j.cell.2018.02.049

Holmes E.C., Chen Y.C., Sattely E., Mudgett M.B., 2019: Conservation of N-hydroxy-pipecolic acid-mediated systemic acquired resistance in crop plants. – bioRxiv, 537597. https://doi.org/10.1101/537597

Holmes E.C., Chen Y.C., Mudgett M.B., Sattely E.S., 2021: *Arabidopsis* UGT76B1 glycosylates N-hydroxy-pipecolic acid and inactivates systemic acquired resistance in tomato. – The Plant Cell, 33(3): 750–765. https://doi.org/10.1093/plcell/koaa052

Hõrak H., 2021: How to achieve immune balance and harmony: glycosyltransferase UGT76B1 inactivates *N*-hydroxy-pipecolic acid to suppress defense responses. – The Plant Cell, 33 (3): 453–454. https://doi.org/10.1093/plcell/koaa053

Iqbal Z., Iqbal M.S., Hashem A., Abd_Allah E.F., Ansari M. I., 2021: Plant defense responses to biotic stress and its interplay with fluctuating dark/light conditions. – Frontiers in Plant Science, 12, 297. https://doi.org/10.3389/fpls.2021.631810

Jung H.W., Tschaplinski T.J., Wang L., Glazebrook J., Greenberg J.T., 2009: Priming in systemic plant immunity. – Science, 324(5923): 89–91. https://doi.org/10.1126/science.1170025

Jung G.Y., Park J.Y., Choi H.J., Yoo S.J., Park J.K., Jung H.W., 2016: A rice gene homologous to *Arabidopsis* AGD2-LIKE DEFENSE1 participates in disease resistance response against infection with *Magnaporthe oryzae.* – The Plant Pathology Journal, 32(4): 357. http://dx.doi.org/10.5423/PPJ.NT.10.2015.0213

Kachroo A., Kachroo P., 2020: Mobile signals in systemic acquired resistance. – Current Opinion in Plant Biology, 58: 41–47. https://doi.org/10.1016/j.pbi.2020.10.004

Kim Y., Park S., Gilmour S.J., Thomashow M.F., 2013: Roles of CAMTA transcription factors and salicylic acid in configuring the low-temperature transcriptome and freezing tolerance of Arabidopsis. – The Plant Journal, 75(3): 364–376. https://doi.org/10.1111/tpj.12205

Klessig D.F., Choi H.W., Dempsey D.M.A., 2018: Systemic acquired resistance and salicylic acid: past, present, and future. – Molecular Plant-MicrobeInteractions, 31(9): 871–888. https://doi.org/10.1094/MPMI-03-18-0067-CR

Ladenburg A., 1891: Ueber die Piperidincarbonsäu-

ren. – Berichte der Deutschen Chemischen Gesellschaft, 24(1): 640–643.

Lenk M., Wenig M., Bauer K., Hug F., Knappe C., Lange B., Timsy Häußler F., Mengel F., Dey S., Schäffner A., Vlot A.C., 2019: Pipecolic acid is induced in barley upon infection and triggers immune responses associated with elevated nitric oxide accumulation. – Molecular Plant-Microbe Interactions, 32(10): 1303–1313. https://doi.org/10.1094/MPMI-01-19-0013-R

Lim G.H., Shine M.B., de Lorenzo L., Yu K., Cui W., Navarre D., Hunt A.G., Lee J.Y., Kachroo A., Kachroo P., 2016: Plasmodesmata localizing proteins regulate transport and signaling during systemic acquired immunity in plants. – Cell Host & Microbe, 19: 541–549. https://doi.org/10.1016/j.chom.2016.03.006

Lim G.H., Liu H., Yu K., Liu R., Shine M.B., Fernandez J., Burch-Smith T., Mobley J.K., Mcletchie N., Kachroo A., Kachroo P., 2020: The plant cuticle regulates apoplastic transport of salicylic acid during systemic acquired resistance. – Science Advances, 6(19): eaaz0478. https://doi.org/10.1126/sciadv.aaz0478

Liu P.P., von Dahl C.C., Klessig D.F., 2011: The extent to which methyl salicylate is required for signaling systemic acquired resistance is dependent on exposure to light after infection. – Plant Physiology, 157(4): 2216–2226. https://doi.org/10.1104/pp.111.187773

Métraux J.P., Signer H., Ryals J., Ward E., Wyss-Benz M., Gaudin J., Raschdorf K., Schmid E., Blum W., Inverardi B., 1990: Increase in salicylic acid at the onset of systemic acquired resistance in cucumber. – Science, 250: 1004–1006. https://doi.org/10.1126/science.250.4983.1004

Mishina T.E., Zeier J., 2006: The *Arabidopsis* flavin-dependent monooxygenase FMO1 is an essential component of biologically induced systemic acquired resistance. – Plant Physiology, 141(4): 1666–1675. https://doi.org/10.1104/pp.106.081257

Mohnike L., Rekhter D., Huang W., Feussner K., Tian H., Herrfurth C., Zhang Y., Feussner I., 2021: The glycosyltransferase UGT76B1 modulates N-hydroxy-pipecolic acid homeostasis and plant immunity. – The Plant Cell, 33(3): 735–749. https://doi.org/10.1093/plcell/koaa045

Morrison R.I., 1952: Naturally occurring L-pipecolinic acid. – The Biochemical Journal, 50(3): 14–15.

Morrison R.I., 1953: The isolation of L-pipecolinic acid from *Trifolium repens*. – Biochemical Journal, 53(3): 474–478.

Moulin M., Deleu C., Larher F., 2000: L-Lysine catabolism is osmo-regulated at the level of lysine-ketoglutarate reductase and saccharopine dehydrogenase in rapeseed leaf discs. – Plant Physiology and Biochemistry, 38(7–8): 577–585. https://doi.org/10.1016/S0981-9428(00)00777-4

Moulin M., Deleu C., Larher F., Bouchereau A., 2006: The lysine-ketoglutarate reductase–saccharopine dehydrogenase is involved in the osmovx-induced synthesis of pipecolic acid in rapeseed leaf tissues. – Plant Physiology and Biochemistry, 44(7–9): 474–482. https://doi.org/10.1016/j.plaphy.2006.08.005

Návarová H., Bernsdorff F., Döring A.C., Zeier J., 2012: Pipecolic acid, an endogenous mediator of defense amplification and priming, is a critical regulator of inducible plant immunity. – The Plant Cell, 24(12): 5123–5141. https://doi.org/10.1105/tpc.112.103564

Nawrath C., Métraux J.P., 1999: Salicylic acid induction–deficient mutants of Arabidopsis express PR-2 and PR-5 and accumulate high levels of camalexin after pathogen inoculation. – The Plant Cell, 11(8): 1393–1404. https://doi.org/10.1105/tpc.11.8.1393

Neshich I.A., Kiyota E., Arruda P., 2013: Genome-wide analysis of lysine catabolism in bacteria reveals new connections with osmotic stress resistance. – The ISME Journal, 7(12): 2400–2410. https://doi.org/10.1038/ismej.2013.123

Pálfi G., Dézsi L., 1968: Pipecolic acid as an indicator of abnormal protein metabolism in diseased plants. – Plant and Soil, 29(2): 285–291. https://doi.org/10.1007/BF01348946

Pazarlar S., Sanver U., Cetinkaya N., 2021: Exogenous pipecolic acid modulates plant defence responses against *Podosphaera xanthii* and *Pseudomonas syringae* pv. *lachrymans* in cucumber (*Cucumis sativus* L.). – Plant Biology, 23(3): 473–484. https://doi.org/10.1111/plb.13243

Schnake A., Hartmann M., Schreiber S., Malik J., Brahmann L., Yildiz I., von Dahlen J., Rose L.E.,

Schaffrath U., Zeier J., 2020: Inducible biosynthesis and immune function of the systemic acquired resistance inducer N-hydroxypipecolic acid in monocotyledonous and dicotyledonous plants. – Journal of Experimental Botany, 71(20): 6444–6459. https://doi.org/10.1093/jxb/eraa317

Shah J., Zeier J., 2013: Long-distance communication and signal amplification in systemic acquired resistance. – Frontiers in Plant Science, 4: 30. https://doi.org/10.3389/fpls.2013.00030

Shah J., Chaturvedi R., Chowdhury Z., Venables B., Petros R.A., 2014: Signaling by small metabolites in systemic acquired resistance. – The Plant Journal, 79(4): 645–658. https://doi.org/10.1111/tpj.12464

Shan L., He P., 2018: Pipped at the post: pipecolic acid derivative identified as SAR regulator. – Cell, 173(2): 286–287. https://doi.org/10.1016/j.cell.2018.03.045

Shields A., Shivnauth V., Castroverde C.D.M., 2022: Salicylic Acid and N-Hydroxypipecolic Acid at the Fulcrum of the Plant Immunity-Growth Equilibrium. – Frontiers in Plant Science: 841688. https://doi.org/10.3389/fpls.2022.841688.

Song J.T., Lu H., McDowell J.M., Greenberg J.T., 2004: A key role for ALD1 in activation of local and systemic defenses in Arabidopsis. – Plant Journal, 40: 200–212. https://doi.org/10.1111/j.1365-313X.2004.02200.x

Steward F.C., Thompson J.F., 1950: The nitrogenous constituents of plants with special reference to chromatographic methods. – Annual Review of Plant Physiology, 1: 233–264. https://doi.org/10.1146/annurev.pp.01.060150.001313

Sun T., Zhang Y., Li Y., Zhang Q., Ding Y., Zhang Y., 2015: ChIP-seq reveals broad roles of SARD1 and CBP60g in regulating plant immunity. – Nature Communications, 6(1): 1–12. https://doi.org/10.1038/ncomms10159

Sun T., Busta L., Zhang Q., Ding P., Jetter R., Zhang Y., 2018: TGACG-binding factor 1 (TGA 1) and TGA 4 regulate salicylic acid and pipecolic acid biosynthesis by modulating the expression of systemic acquired resistance deficient 1 (SARD 1) and calmodulin-binding protein 60g (CBP 60g). – New Phytologist, 217(1): 344–354. https://doi.org/10.1111/nph.14780

Sun T., Huang J., Xu Y., Verma V., Jing B., Sun Y., Orduna A.R., Tian H., Huang X., Xia S., Schafer L., Jetter F., Zhang Y., Li X., 2020: Redundant CAMTA transcription factors negatively regulate the biosynthesis of salicylic acid and N-hydroxypipecolic acid by modulating the expression of SARD1 and CBP60g. – Molecular Plant, 13(1): 144–156. https://doi.org/10.1016/j.molp.2019.10.016

Vernooij B., Friedrich L., Morse A., Reist R., Kolditz-Jawhar R., Ward E., Uknes S., Kessmann H., Ryals J., 1994: Salicylic acid is not the translocated signal responsible for inducing systemic acquired resistance but is required in signal transduction. – The Plant Cell, 6(7): 959–965. https://doi.org/10.1105/tpc.6.7.959

Vlot A.C., Sales J.H., Lenk M., Bauer K., Brambilla A., Sommer A., Chen Y., Wenig M., Nayem S., 2021: Systemic propagation of immunity in plants. – New Phytologist, 229(3): 1234–1250. https://doi.org/10.1111/nph.16953

Vranova V., Lojkova L., Rejsek K., Formanek P., 2013: Significance of the natural occurrence of L- versus D-pipecolic acid: a review. – Chirality, 25(12): 823–831. https://doi.org/10.1002/chir.22237

Vogel-Adghough D., Stahl E., Návarová H., Zeier J., 2013: Pipecolic acid enhances resistance to bacterial infection and primes salicylic acid and nicotine accumulation in tobacco. – Plant Signaling & Behavior, 8(11): e26366. https://doi.org/10.4161/psb.26366

Wang P., Xiang M., 2020: Research progress of NPR genes in signal pathway of salicylic acid mediated plant disease resistance. – In: E3S Web of Conferences, EDP Sciences, 145, 01038. https://doi.org/10.1051/e3sconf/202014501038

Wang Y., Schuck S., Wu J., Yang P., Döring A.C., Zeier J., Tsuda K., 2018: A MPK3/6-WRKY33-ALD1-pipecolic acid regulatory loop contributes to systemic acquired resistance. – The Plant Cell, 30(10): 2480–2494. https://doi.org/10.1105/tpc.18.00547

Wang P., Luo Q., Yang W., Ahammed G.J., Ding S., Chen X., Wang J., Xia X., Shi K., 2021: A Novel Role of Pipecolic Acid Biosynthetic Pathway in Drought Tolerance through the Antioxidant System in Tomato. – Antioxidants, 10(12): 1923. https://doi.org/10.3390/antiox10121923

Willstätter R., Kraut H., Erbacher O., 1901: Oxy-

dation des Conydrins – Berichte der Deutschen Chemischen Gesellschaft, 34: 3166. https://doi.org/10.1002/cber.190103402290

Yatsu L., Boynton D., 1959: Pipecolic acid in leaves of strawberry plant as influenced by treatments affecting growth. – Science, 130(3379): 864–865. https://doi.org/10.1126/science.130.3379.864

Yildiz I., Mantz M., Hartmann M., Zeier T., Kessel J., Thurow C., Gatz C., Petzsch P., Köhrer K., Zeier J., 2021: The mobile SAR signal N-hydroxypipecolic acid induces NPR1-dependent transcriptional reprogramming and immune priming. – Plant Physiology, 186(3): 1679–1705. https://doi.org/10.1093/plphys/kiab166

Yu K., Soares J.M., Mandal M.K., Wang C., Chanda B., Gifford A.N., Fowler J.S., Navarre D., Kachroo A., Kachroo P., 2013: A feedback regulatory loop between G3P and lipid transfer proteins DIR1 and AZI1 mediates azelaic-acid-induced systemic immunity. – Cell Reports, 3(4): 1266–1278. https://doi.org/10.1016/j.celrep.2013.03.030

Zacharius R.M., Thompson J.F., Steward F.C., 1954: The detection, isolation and identification of L(-)-pipecolic acid in the non-protein fraction of beans (*Phaseolus vulgaris*). – Journal of the American Chemical Society, 76: 2908–2912. https://doi.org/10.1021/ja01640a015

Zeier J., 2013: New insights into the regulation of plant immunity by amino acid metabolic pathways. – Plant, Cell & Environment, 36(12): 2085–2103. https://doi.org/10.1111/pce.12122

Zeier J., 2021: Metabolic regulation of systemic acquired resistance. – Current Opinion in Plant Biology, 62: 102050. https://doi.org/10.1016/j.pbi.2021.102050

Zhang Y., Lv Y., Jahan N., Chen G., Ren D., Guo L., 2018: Sensing of abiotic stress and ionic stress responses in plants. – International Journal of Molecular Sciences, 19(11): 3298. https://doi.org/10.3390/ijms19113298

Zhang H., Qiu Y., Li M., Song F., Jiang M., 2020: Functions of pipecolic acid on induced resistance against *Botrytis cinerea* and *Pseudomonas syringae* pv. tomato DC3000 in tomato plants. – Journal of Phytopathology, 168(10): 591–600. https://doi.org/10.1111/jph.12938

Zhang H., Zhu J., Gong Z., Zhu J.K., 2021: Abiotic stress responses in plants. – Nature Reviews Genetics, 1–16. https://doi.org/10.1038/s41576-021-00413-0

FNK https://orcid.org/0000 0001 5906 3274
BSD https://orcid.org/0000 0001 6289 380X