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# Shikimic Acid Pathway in Biosynthesis of Phenolic Compounds

*Norma Francenia Santos-Sánchez, Raúl Salas-Coronado, Beatriz Hernández-Carlos and Claudia Villanueva-Cañongo*

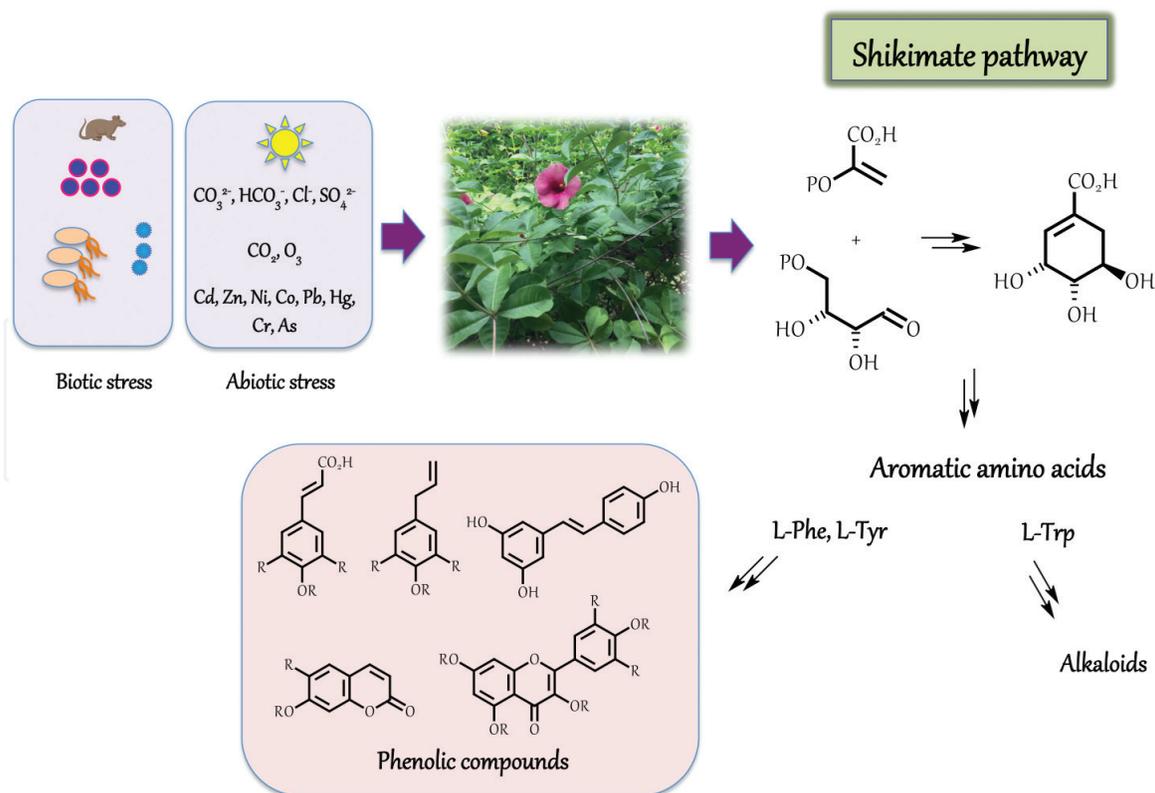
## Abstract

Phenolic compounds are secondary metabolites found most abundantly in plants. These aromatic molecules have important roles, as pigments, antioxidants, signaling agents, the structural element lignan, and as a defense mechanism. The expression of phenolic compounds is promoted by biotic and abiotic stresses (e.g., herbivores, pathogens, unfavorable temperature and pH, saline stress, heavy metal stress, and UVB and UVA radiation). These compounds are formed via the shikimate pathway in higher plants and microorganisms. The enzymes responsible for the regulation of phenolic metabolism are known, and shikimic acid is a central metabolite. The shikimate pathway consists of seven reaction steps, beginning with an aldol-type condensation of phosphoenolpyruvic acid (PEP) from the glycolytic pathway, and D-erythrose-4-phosphate, from the pentose phosphate cycle, to produce 3-deoxy-D-arabino-heptulosonic acid 7-phosphate (DAHP). A key branch-point compound is chorismic acid, the final product of the shikimate pathway. The shikimate pathway is described in this chapter, as well as factors that induce the synthesis of phenolic compounds in plants. Some representative examples that show the effect of biotic and abiotic stress on the production of phenolic compounds in plants are discussed.

**Keywords:** shikimate pathway, phenolic compounds, biosynthetic routes, phenylpropanoid metabolism

## 1. Introduction

The secondary metabolism is a biosynthetic source of several interesting compounds useful to chemical, food, agronomic, cosmetics, and pharmaceutical industries. The secondary pathways are not necessary for the survival of individual cells but benefit the plant as a whole [1]. Another general characteristic of secondary metabolism is that found in a specific organism, or groups of organisms, and is an expression of the individuality of species [2]. The secondary metabolism provides chemical diversity to organic molecules with low molecular weight that are related by the respective pathways; such organic molecules are called secondary metabolites. The secondary metabolites are often less than 1% of the total carbon in plant molecules [3]. These organic molecules isolated from terrestrial plants are the most studied, and their syntheses have an important role in the protection against

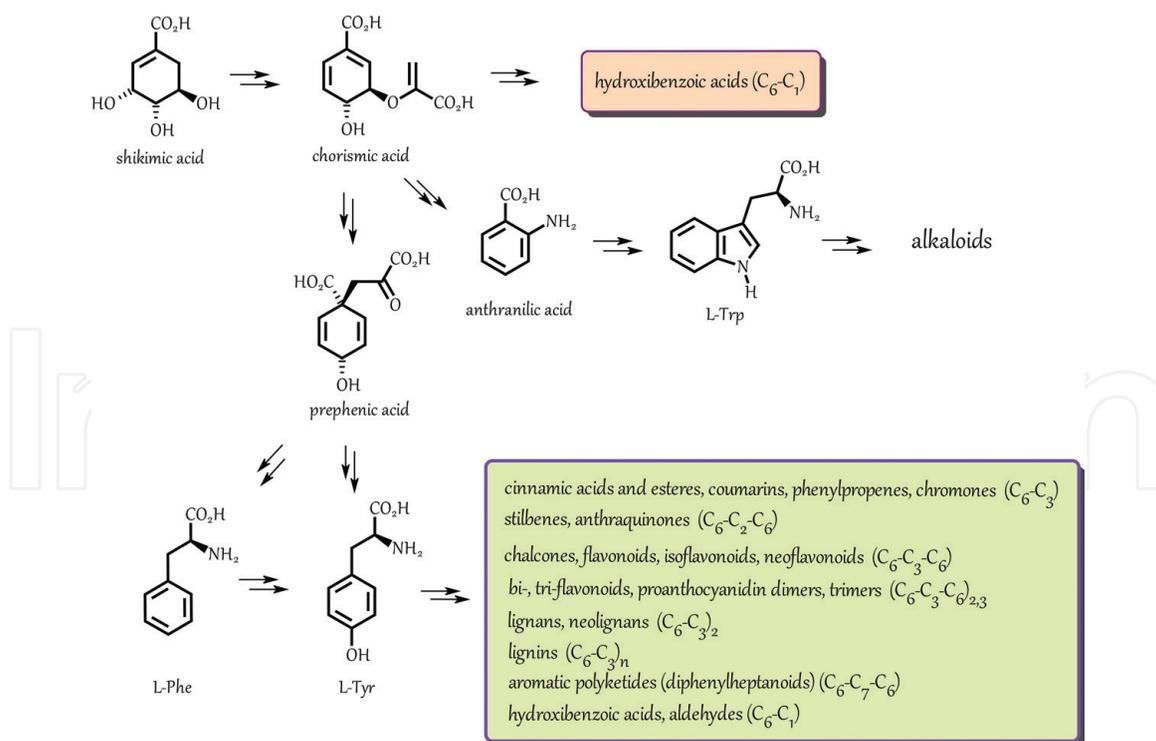


**Figure 1.** Phenolic compound biosynthesis promoted by biotic and abiotic stresses (e.g., herbivores, pathogens, unfavorable temperature and pH, saline stress,  $\text{CO}_2$ ,  $\text{O}_3$ , heavy metal stress, and UVB and UVA radiation).

pathogens, unfavorable temperature and pH, saline stress, heavy metal stress, and UVB and UVA radiation [3]. Secondary metabolism reflects plant environments more closely than primary metabolism [4]. There are three principal kinds of secondary metabolites biosynthesized by plants: phenolic compounds, terpenoids/isoprenoids, and alkaloids and glucosinolates (nitrogen- or sulfur-containing molecules, respectively) [5]. Phenolic compounds are biosynthesized by the shikimate pathway and are abundant in plants. The shikimate pathway, in plants, is localized in the chloroplast. These aromatic molecules have important roles, as pigments, antioxidants, signaling agents, electron transport, communication, the structural element lignan, and as a defense mechanism [6], **Figure 1**. The seven steps of the shikimate pathway and the metabolites for branch point are described in this chapter, as factors that induce the synthesis of phenolic compounds in plants. Some representative examples that show the effect of biotic and abiotic stress on the production of phenolic compounds in plants are discussed.

## 2. The shikimate pathway

The shikimate biosynthesis pathway provides precursors for aromatic molecules in bacteria, fungi, apicomplexan, and plants, but not in animals [2, 7]. Shikimic acid is named after the highly toxic Japanese *shikimi* (*Illicium anisatum*) flower from which it was first isolated [8]. This biochemical pathway is a major link between primary and secondary metabolism in higher plants [6]. In microorganisms, the shikimate pathway produces aromatic amino acids L-phenylalanine (L-Phe), L-tyrosine (L-Tyr), and L-tryptophan (L-Trp), molecular building blocks for protein biosynthesis [9]. But in plants, these aromatic amino acids are not only crucial components of protein biosynthesis; they also serve as precursors for diverse secondary metabolites that are important for plant growth [10]. These secondary metabolites are called

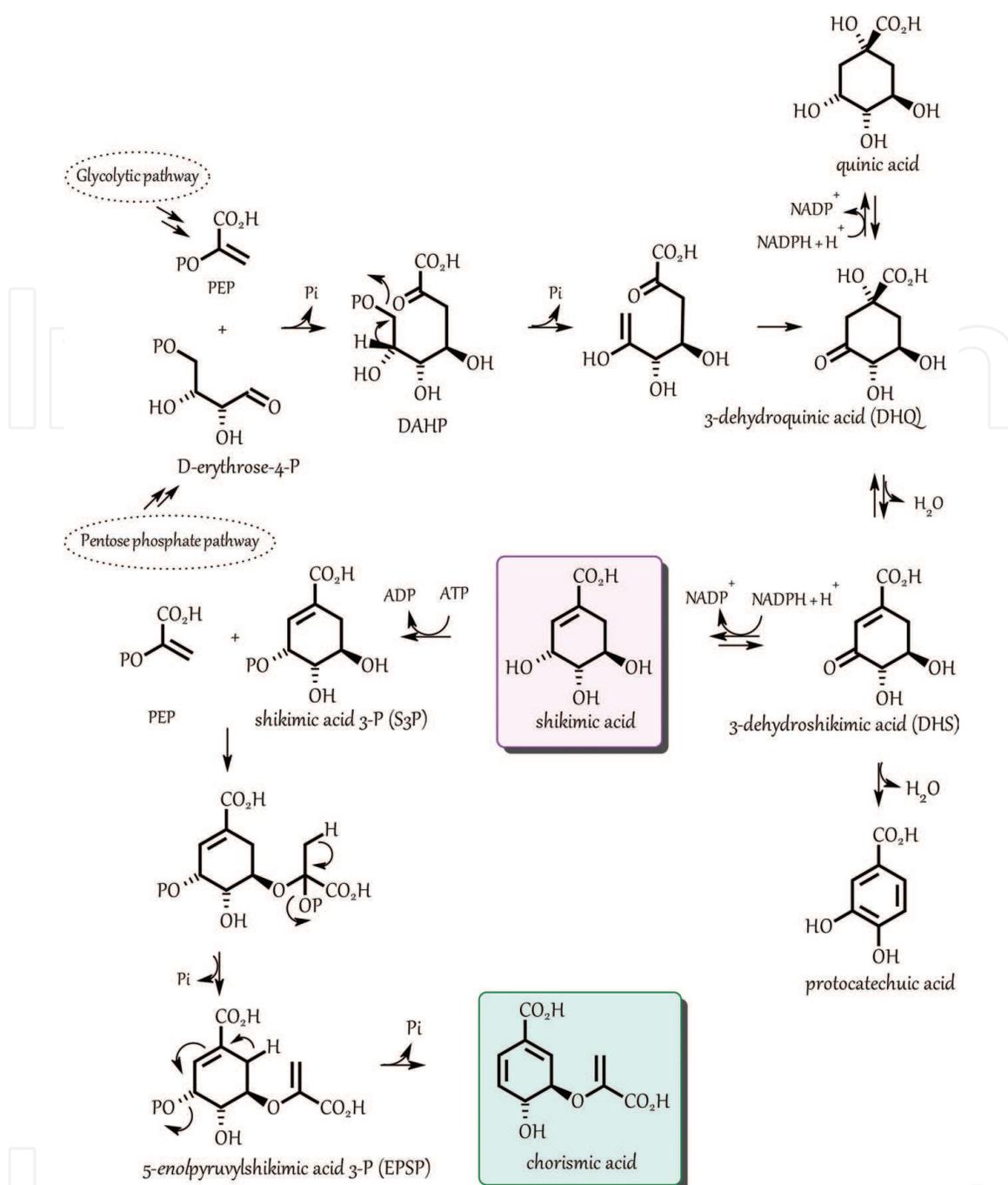


**Figure 2.** The shikimic and chorismic acids are the common precursors for the synthesis of L-Phe, L-Tyr, and L-Trp and diverse phenolic compounds.

phenolic compounds and are synthesized when needed by the plant [11]. These molecules play an important role in the adaptation of plants to their ecosystem, and their study advances biochemical techniques and molecular biology [3, Bourgaud]. The principal aromatic phenolic compounds synthesized from L-Phe and L-Tyr are cinnamic acids and esters, coumarins, phenylpropenes, chromones (C<sub>6</sub>-C<sub>3</sub>), stilbenes, anthraquinones (C<sub>6</sub>-C<sub>2</sub>-C<sub>6</sub>), chalcones, flavonoids, isoflavonoids, neoflavonoids (C<sub>6</sub>-C<sub>3</sub>-C<sub>6</sub>), and their dimers and trimers, respectively (C<sub>6</sub>-C<sub>3</sub>-C<sub>6</sub>)<sub>2,3</sub>, lignans, neolignans (C<sub>6</sub>-C<sub>3</sub>)<sub>2</sub>, lignans (C<sub>6</sub>-C<sub>3</sub>)<sub>n</sub>, aromatic polyketides, or diphenylheptanoids (C<sub>6</sub>-C<sub>7</sub>-C<sub>6</sub>) [12]. L-Trp is a precursor of alkaloids in the secondary metabolism [2]. Additionally, diverse hydroxybenzoic acids and aromatic aldehydes (C<sub>6</sub>-C<sub>1</sub>) are biosynthesized via branch points in the shikimate pathway, **Figure 2**. Phenolic compounds biosynthesized from the shikimate pathway have structural versatility.

The shikimate pathway consists of seven sequential enzymatic steps and begins with an aldol-type condensation of two phosphorylated active compounds, the phosphoenolpyruvic acid (PEP), from the glycolytic pathway, and the carbohydrate D-erythrose-4-phosphate, from the pentose phosphate cycle, to give 3-deoxy-D-*arabino*-heptulosonic acid 7-phosphate (DAHPS), **Figure 3**. The seven enzymes that catalyze the pathway are known: 3-deoxy-D-*arabino*-heptulosonate-7-phosphate synthase (DAHPS; EC 4.1.2.15, now EC 2.5.1.54), 3-dehydroquinate synthase (DHQS; EC 4.2.3.4), 3-dehydroquinate dehydratase/shikimate dehydrogenase (DHQ/SDH; EC 4.2.1.10/EC 1.1.1.25), shikimate kinase (SK; EC 2.7.1.71), 5-enolpyruvylshikimate 3-phosphate synthase (EPSPS; EC 2.5.1.19), and chorismate synthase (CS; EC 4.2.3.5) [13], **Table 1**.

The shikimate pathway has special characteristics that are present only in bacteria, fungi, and plants. The absence of the pathway in all other organisms provides the enzymes catalyzing these reactions with potentially useful targets for the development of antibacterial agents and herbicides. For example, 5-enolpyruvylshikimate 3-phosphate synthase (EPSP-synthase) catalyzes the transfer of the enolpyruvyl (carboxyvinyl) moiety from PEP to shikimic acid 3-phosphate (S3P) [6].



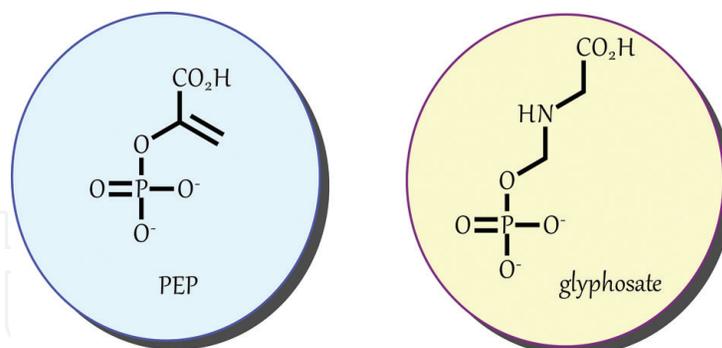
**Figure 3.**  
Shikimate pathway.

In the second reaction step, DAHP loses phosphate (Pi); the enolic-type product is cyclized through a second aldol-type reaction to produce 3-dehydroquinic acid (DHQ). The 3-dehydroquinic acid synthase (DHQS) catalyzes this cyclization in the shikimate pathway. The DHQ dehydrates to produce 3-dehydroshikimic acid (DHS) (3-dehydroquinic acid dehydratase); this compound has a conjugated double carbon-carbon, **Figure 3**. The protocatechuic and the gallic acids (C<sub>6</sub>-C<sub>1</sub>) are produced by branch-point reactions from DHS [2]. The fourth step in the pathway is a reduction reaction of DHS with reduced nicotinamide adenine dinucleotide phosphate (NADPH), **Figure 3**. The fifth section of the pathway is the activation of shikimic acid with adenosine triphosphate (ATP) (shikimate kinase, SK) to make shikimic acid 3-phosphate (S3P). The sixth chemical reaction is the addition of PEP to S3P to generate 5-enolpyruvylshikimic acid 3-phosphate; the enzyme that catalyzes this reaction step, 5-enolpyruvylshikimate 3-phosphate synthase (EPSPS), has been extensively studied. The reason for this interest is because glyphosate [*N*-(phosphonomethyl)

Reaction step	Substrate	Enzyme/cofactor	Product
1	Phosphoenolpyruvate (PEP), erythrose-4-phosphate	3-Deoxy-D-arabino-heptulosonate-7-phosphate synthase (DAHPS; EC 4.1.2.15, now EC 2.5.1.54)/ Co <sup>2+</sup> , Mg <sup>2+</sup> or Mn <sup>2+</sup> [15]	3-Deoxy-D-arabino-heptulosonic acid 7-phosphate (DAHP), Pi
2	3-Deoxy-D-arabino-heptulosonic acid 7-phosphate (DAHP)	3-Dehydroquinase synthase DHQS (EC. 4.2.3.4)/Co <sup>2+</sup> , NAD <sup>+</sup> [15, 16]	3-Dehydroquinic acid (DHQ), Pi
3	3-Dehydroquinic acid (DHQ)	3-Dehydroquinase dehydratase (DHQ dehydratase EC 4.2.1.10) [15]	3-Dehydroshikimic acid (DHS), H <sub>2</sub> O
4	3-Dehydroshikimic acid (DHS), NADPH + H <sup>+</sup>	Shikimate dehydrogenase (SDH; EC 1.1.1.25) [18–21]	Shikimic acid, NADP <sup>+</sup>
5	Shikimic acid, ATP	Shikimate kinase enzyme (SK; EC 2.7.1.71)	Shikimic acid 3-phosphate (S3P), ADP
6	Shikimic acid 3-phosphate (S3P), PEP	5-Enolpyruvylshikimate 3-phosphate synthase, also called aroA enzyme (EPSPS; EC 2.5.1.19) [25]	5-Enolpyruvylshikimate 3-phosphate (EPSP), Pi
7	5-Enolpyruvylshikimate 3-phosphate (EPSP)	Chorismate synthase (CS; EC 4.2.3.5)/FMNH <sub>2</sub> [2, 19, 30, 31]	Chorismic acid, Pi

*Pi, phosphate; NAD<sup>+</sup>, oxidized nicotinamide adenine dinucleotide; NADPH, reduced nicotinamide adenine dinucleotide phosphate; FMNH<sub>2</sub>, reduced flavin mononucleotide.*

**Table 1.**  
 Substrates, enzymes, and products of the shikimate pathway.



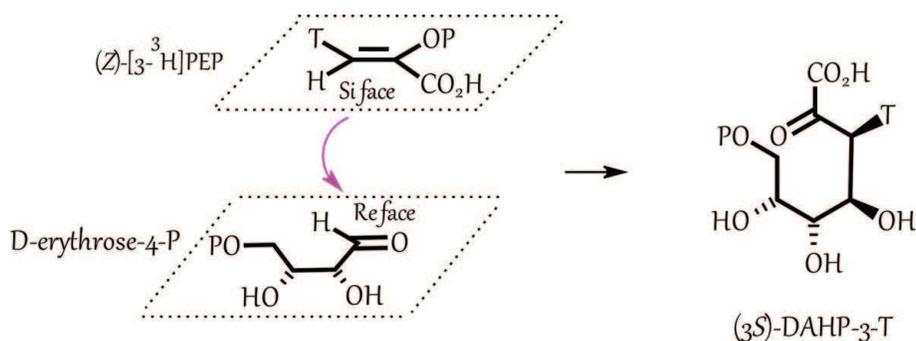
**Figure 4.**  
 PEP and glyphosate (powerful inhibitor of the 5-enolpyruvylshikimate 3-phosphate synthase, EPSPS).

glycine] is a powerful inhibitor of EPSPS [2], so glyphosate has been used as a broad-spectrum systemic herbicide. It is an organophosphorus molecule, phosphonic acid, and glycine derivative that has a similar molecular structure to PEP, **Figure 4**.

The last reaction step of the shikimate pathway is the production of chorismic acid from catalytic action on the chorismate synthase (CS). This reaction is a 1, 4-*trans* elimination of Pi, to yield the conjugated molecule, chorismic acid, **Figure 3**.

## 2.1 Synthesis of 3-deoxy-D-arabino-heptulosonic acid 7-phosphate (DAHP)

The first reaction of the shikimate pathway is an aldol-type condensation of PEP and carbohydrate erythrose-4-P, to give 3-deoxy-D-arabino-heptulosonic acid

**Figure 5.**

Stereochemistry of the condensation reaction of (Z)-[3-<sup>3</sup>H]PEP and D-erythrose-4-phosphate by DAHP synthase [14].

7-phosphate (DAHP), **Figures 3 and 5**. A new stereogenic center is generated in the condensation product DAHP catalyzed by the 3-deoxy-D-arabino-heptulosonate-7-phosphate synthase enzyme (DAHPS; EC 4.1.2.15, now EC 2.5.1.54). Results of enzymatic kinetic and labeled PEP with tritium (Z)-[3-<sup>3</sup>H] PEP suggest that the nucleophilic attack of PEP is from the *Si* face of PEP to the *Re* face of the carbonyl group of D-erythrose-4-P, **Figure 5** [14]. Two isoenzymes of DAHPS have been found for the catalysis of this first reaction step. One isozyme needs only Mn<sup>2+</sup>, and the other, either Co<sup>2+</sup>, Mg<sup>2+</sup>, or Mn<sup>2+</sup> for the catalysis [15].

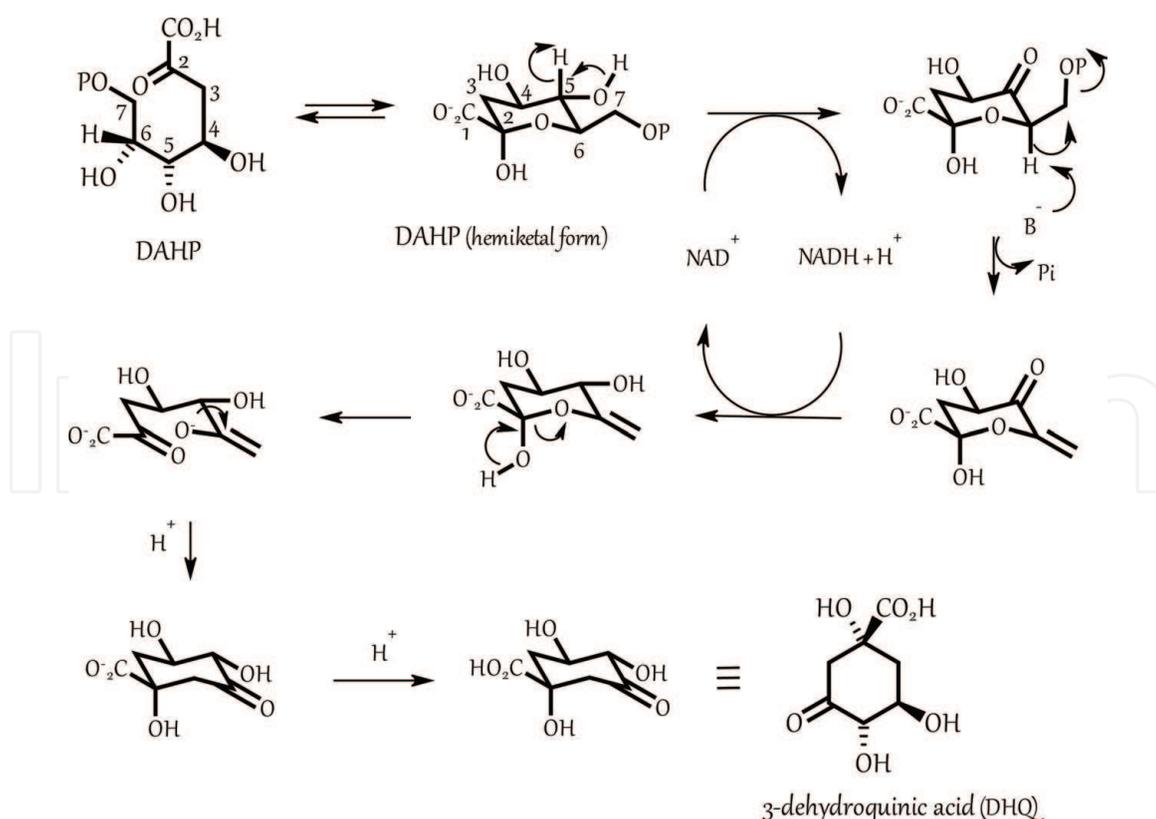
## 2.2 Synthesis of 3-dehydroquinic acid (DHQ)

The second reaction of the shikimate pathway is an intramolecular aldol-type reaction cyclization, where the enol (C6-C7) of DAHP nucleophilically attacks the carbonyl group (C2), to produce a six-member cycle, the 3-dehydroquinic acid (DHQ), **Figures 3 and 6**. The enzyme that catalyzes this reaction, 3-dehydroquininate synthase DHQS (EC. 4.2.3.4), is a carbon-oxygen lyase enzyme that requires Co<sup>2+</sup> and bound oxidized nicotinamide adenine dinucleotide (NAD<sup>+</sup>) as cofactors [15, 16]. The Co<sup>2+</sup> is essential for the catalytic activity of DHQS. Bender et al. [16] found that DHQS, from *Escherichia coli*, is a monomeric metalloenzyme that contains tightly bound Co<sup>2+</sup>, and DHQS is deactivated with ethylenediaminetetraacetic acid (EDTA). The presence of the substrate (DAHP) blocks the inactivation by EDTA. The NAD<sup>+</sup> cofactor dissociates from the DHQS enzyme rapidly in the presence of DAHP [16]. The reaction mechanism of the enzyme-catalyzed conversion of DAHP to DHQ involves five transformations from the DAHP hemiketal form, a pyranose: (1) oxidation of the hydroxyl at C5 adjacent to the lost proton that requires NAD<sup>+</sup> (NAD<sup>+</sup> need never dissociate from the active site), (2) the elimination of Pi of C7 to make the α,β-unsaturated ketone, (3) the reduction of C5 with NADH + H<sup>+</sup>, (4) the ring opening of the enol to yield an enolate, and (5) the intramolecular aldol-like reaction to produce DHQ. All five-reaction steps occur through the function of DHQS, **Figure 6**.

The reduction reaction of DHQ leads to quinic acid at this branch point in the shikimate pathway. Quinic acid is a secondary metabolite that is free, forming esters or as part of alkaloids such as quinine. Quinic acid is found in high quantities in mature kiwi fruit (*Actinidia chinensis* and other species of *Actinidia*) and is a distinguishing characteristic of fresh kiwi fruit [7]. Also, the quinic acid is abundant in roasted coffee [17].

## 2.3 Synthesis of 3-dehydroshikimic acid (DHS) and shikimic acid

The third and fourth reaction steps of the shikimate pathway are catalyzed by a bifunctional enzyme: 3-dehydroquininate dehydratase/shikimate dehydrogenase



**Figure 6.**  
 Reaction mechanism of DAHP (hemiketal form) to 3-dehydroquinic acid (DHQ) by 3-dehydroquinase DHQS (EC. 4.2.3.4) [16].

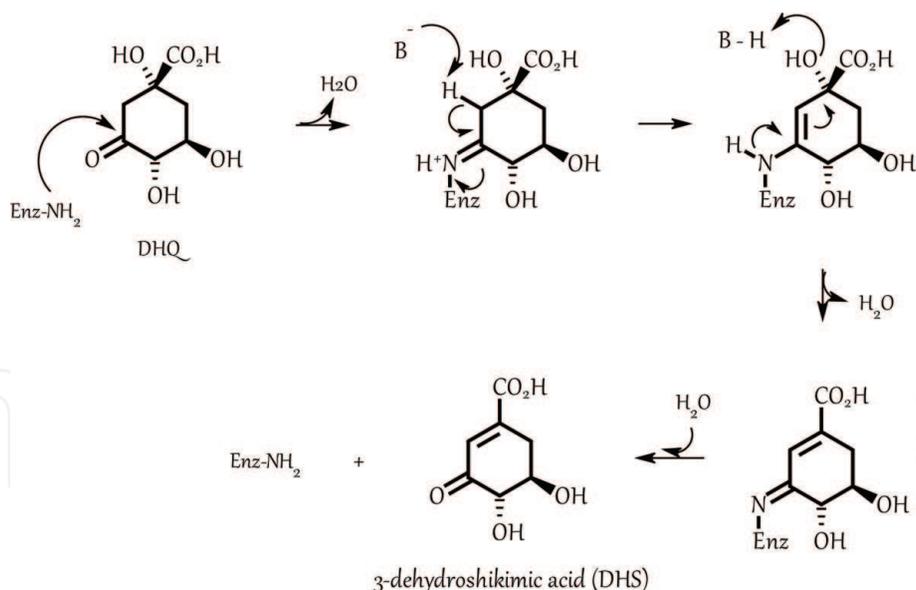
(DHQ dehydratase/SDH; EC 4.2.1.10/EC 1.1.1.25). The DHQ dehydratase enzyme is a hydro-lyase kind, and the SDH is an oxidoreductase enzyme. The DHQ dehydratase, in the third reaction step, converts DHQ into 3-dehydroshikimic acid (DHS) by eliminating water, and this reaction is reversible, **Figure 7**. The DHS is converted to shikimic acid in the fourth reaction step, by the reduction of the carbonyl group at C-5 by the catalytic action of SDH with NADPH, **Figure 3**. The biosynthesis of DHS is a branch point to shikimic acid and to the catabolic quinate pathway. If the DHS dehydrates, it produces protocatechuic acid (C<sub>6</sub>-C<sub>1</sub>) or gallic acid, **Figure 3**. Gallic acid (C<sub>6</sub>-C<sub>1</sub>) is a hydroxybenzoic acid that is a component of tannins [2].

Two structurally different kinds of 3-dehydroquinase dehydratase are known: type I (not heat-stable) and type II (heat-stable). Type I enzyme is present in bacteria and higher plants, and type II is found in fungi, which have both types of enzymes [18, 19]. The catalytic mechanism of the type I DHQ dehydratase has been detected by electrospray MS [20]. This catalytic mechanism involves the amino acid residue Lys-241 that forms a Schiff base with the substrate and product, **Figure 7** [21]. The fourth step is the reduction of DHS with NADPH that enantioselectively reduces the carbonyl of the ketone group of DHS to produce shikimic acid (shikimate dehydrogenase, SDH), **Figure 3**.

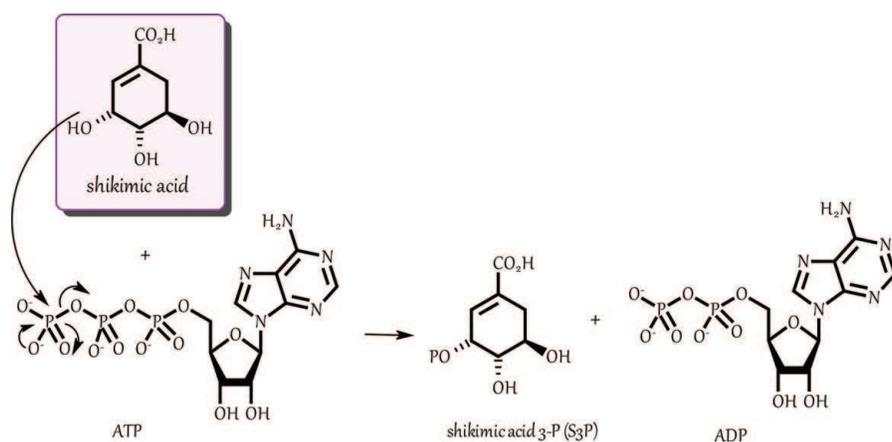
Sigh and Christendat [22] reported the crystal structure of DHQ dehydratase/SDH from the plant genus *Arabidopsis*. The crystal structure has the shikimate bound at the SDH and the tartrate molecule at the DHQ dehydratase. The studies show that Asp 423 and Lys 385 are key catalytic amino acids and Ser 336 is a key-binding group.

## 2.4 Synthesis of shikimic acid 3-phosphate (S3P)

The shikimate kinase enzyme (SK; EC 2.7.1.71) catalyzes the phosphorylation of the shikimic acid, the fifth chemical reaction of the shikimate pathway, and the products are shikimic acid 3-phosphate (S3P) and ADP, **Figures 3** and **8**.



**Figure 7.** Reaction mechanism to produce 3-dehydroshikimic acid (DHS) by type I DHQ dehydratase enzyme [21].



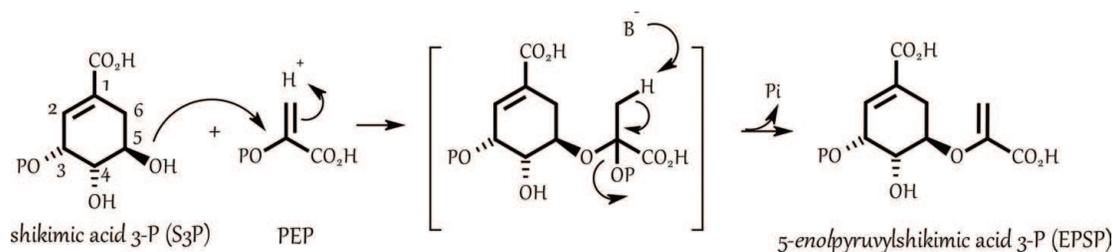
**Figure 8.** Phosphorylation of shikimic acid with ATP.

Shikimic acid is phosphorylated with ATP in the 5-hydroxyl group of shikimic acid. SK is an essential enzyme in several bacterial pathogens and is not present in the human cell; therefore the SK enzyme has been classified as a protein target for drug design, especially for chemotherapeutic development of antitubercular drugs [23, 24].

## 2.5 Synthesis of 5-enolpyruvylshikimate 3-phosphate (EPSP)

The 5-enolpyruvylshikimate 3-phosphate synthase, also called *aroA* enzyme (EPSPS; EC 2.5.1.19), catalyzes the condensation of PEP to the 5-hydroxyl group of S<sub>3</sub>P in the sixth reaction of the shikimate pathway to form 5-enolpyruvylshikimate 3-phosphate (EPSP). The reaction mechanism involves the protonation of PEP to subsequent nucleophilic attack of the hydroxyl at C-5 of S<sub>3</sub>P to form an intermediate that loses Pi to form EPSP, **Figure 9** [25].

EPSPS is the most studied enzyme of the shikimate pathway because it plays a crucial role in the penultimate step. If this enzyme is inhibited, there is an

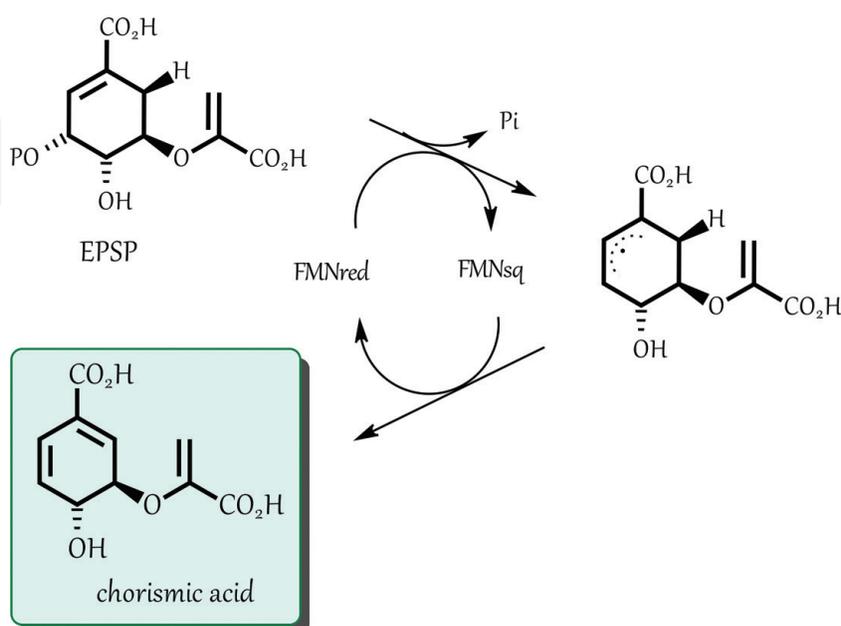


**Figure 9.**  
 Reaction mechanism of the condensation of S3P with PEP by EPSPS (EC 2.5.1.19) to form EPSP [25].

accumulation of shikimic acid [26], and the synthesis of aromatic amino acid is disabled, leading to the death of the plant [27]. Therefore, EPSPS is used as a target for pesticides, like glyphosate, **Figure 4**, the active ingredient in the herbicides RoundUp™, Monsanto Chemical Co., and Touchdown™, Syngenta. Glyphosate (*N*-(phosphonomethyl)glycine) inhibits EPSPS and is a potent nonselective herbicide that mimics the carbocation of PEP and binds EPSPS competitively [28]. Because the glyphosate is nonselective and kills food crops, there is interest in finding glyphosate-tolerant genes for genetically modified crops [29]. Two types of EPSPS enzymes have been identified: type I EPSPS (sensitive to glyphosate) identified mostly in plants and bacteria and type II EPSPS (nonsensitive to glyphosate and has a high affinity for PEP), found in some bacteria [27].

## 2.6 Synthesis of chorismic acid

The seventh and last reaction step of the shikimate pathway is the 1,4-*trans* elimination of the Pi group at C-3 from EPSPS to synthesize chorismic acid. This last step is catalyzed by chorismate synthase (CS; EC 4.2.3.5) that needs reduced flavin mononucleotide (FMN<sub>red</sub>) as a cofactor that is not consumed [2, 19]. The FMN<sub>red</sub> transfers an electron to the substrate reversibly [30]. Spectroscopic



**Figure 10.**  
 Reaction of mechanism to yield chorismic acid by chorismate synthase [30].

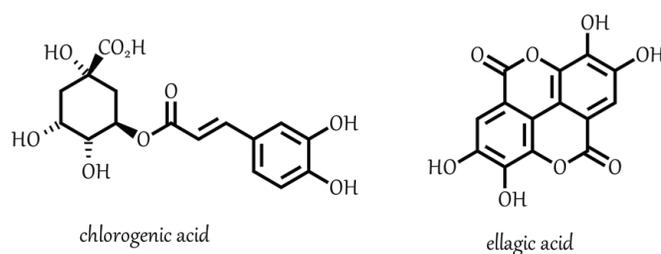
techniques and kinetic isotope effect studies suggest that a radical intermediate in a non-concerted mechanism is developed [30, 31], **Figure 10**. Chorismic acid, the final molecule of the shikimate pathway, is a key branch point to post-chorismic acid pathways, to obtain L-Phe, L-Tyr, and L-Trp, **Figure 2**. L-Phe is the substrate to phenylpropanoid and flavonoid pathways [13].

### 3. Factors that induce the synthesis of phenolic compounds in plants

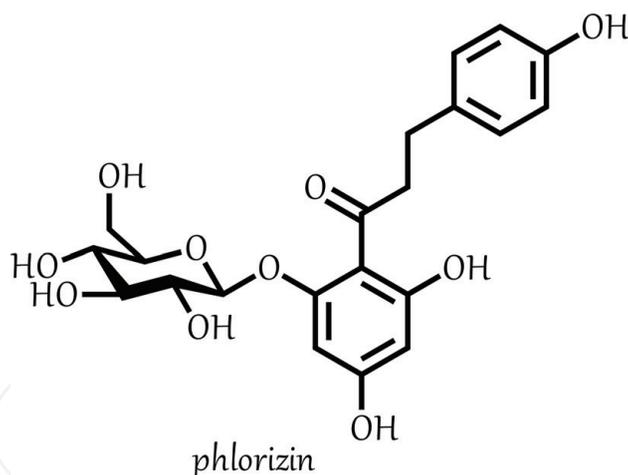
The expression of phenolic compounds is promoted by biotic and abiotic stresses (e.g., herbivores, pathogens, unfavorable temperature and pH, saline stress, heavy metal stress, and UVB and UVA radiation). UV radiation is divided into UVC ( $\leq 280$  nm), UVB (280–320 nm), and UVA (300–400 nm). UVA and UVB radiation are transmitted through the atmosphere; all UVC and some UVB radiation (highly energetic) are absorbed by the Earth's ozone layer. This accumulation is explained by the increase in enzymatic activity of the phenylalanine ammonia-lyase and chalcone synthase enzymes, among others [12]. Studies have been done about the increase of phenolic compounds, such as anthocyanins, in plants when they are exposed to UVB radiation [13]. Another study demonstrates that UVB exposure enhances anthocyanin biosynthesis in “Cripps pink” apples (*Malus x domestica* Borkh.) but not in “Forelle” pears (*Pyrus communis* L.) [32]. This effect may be due to UV radiation exposure and the cultivar of the plants studied. It is known that if plants are under stress, they accumulate phenolic compounds.

The increase in phenolic compounds in blueberry (*Vaccinium corymbosum*) plantlets cultivated in vitro exposed to aluminum (Al) and cadmium (Cd) has also been studied. These heavy metals cause high toxicity in plants, because they increase the oxidative stress by the production of reactive oxygen species (ROS). The authors of the study suggest that the phenolic compounds, specifically chlorogenic and ellagic acids, **Figure 11**, reduce the ROS in blueberry plants [33].

An interesting study was carried out in 2011 by Mody et al., where they studied the effect of the resistance response of apple tree seedlings (*Malus x domestica*) to a leaf-chewing insect (*Spodoptera littoralis*) [34]. The authors found a significant herbivore preference for undamaged plants (induced resistance) was first observed 3 days after herbivore damage in the most apical leaf. Also, the results showed higher concentrations of the flavonoid phlorizin, **Figure 12**, in damaged plants than undamaged plants. This indicates that insect preference for undamaged apple plants may be linked to phlorizin, which is the main secondary metabolite of the phenolic type in apple leaves.



**Figure 11.** Chemical structure of chlorogenic ( $C_6-C_3$ ) and ellagic ( $C_6-C_1$ ) acids.



**Figure 12.**  
Chemical structure of phlorizin ( $C_6-C_3$ ).

#### 4. Conclusions

Knowledge of the biosynthetic pathway of shikimic acid leads to understanding the reaction mechanisms of enzymes and thus discovering antimicrobials, pesticides, and antifungals. Studies with isotopic labeling of substrates, the use of X-ray diffraction, nuclear magnetic resonance (NMR), mass spectrometry (ES), biotechnology, as well as organic synthesis have contributed to explaining the shikimate pathway. Although the seven steps of the biosynthetic pathway are elucidated, these metabolites are the precursors of phenolic compounds, more complex molecules that are necessary for the adaptation of plants to the environment. So, the shikimate pathway is the basis for the subsequent biosynthesis of phenolic compounds. There is scientific interest in continuing to investigate the biosynthesis of phenolic compounds from several points of view: pharmaceuticals, agronomy, chemical and food industries, genetics, and health.

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#### Conflict of interest

The authors have no conflict of interest to declare and are responsible for the content and writing of the manuscript.

#### Ethical approval

This chapter does not contain any studies with human participants or animals performed by any of the authors.

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