# Shikimic Acid Pathway

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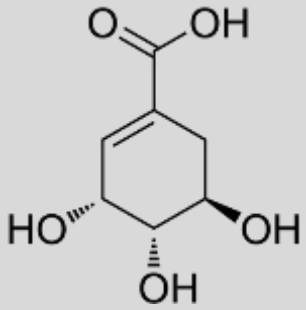
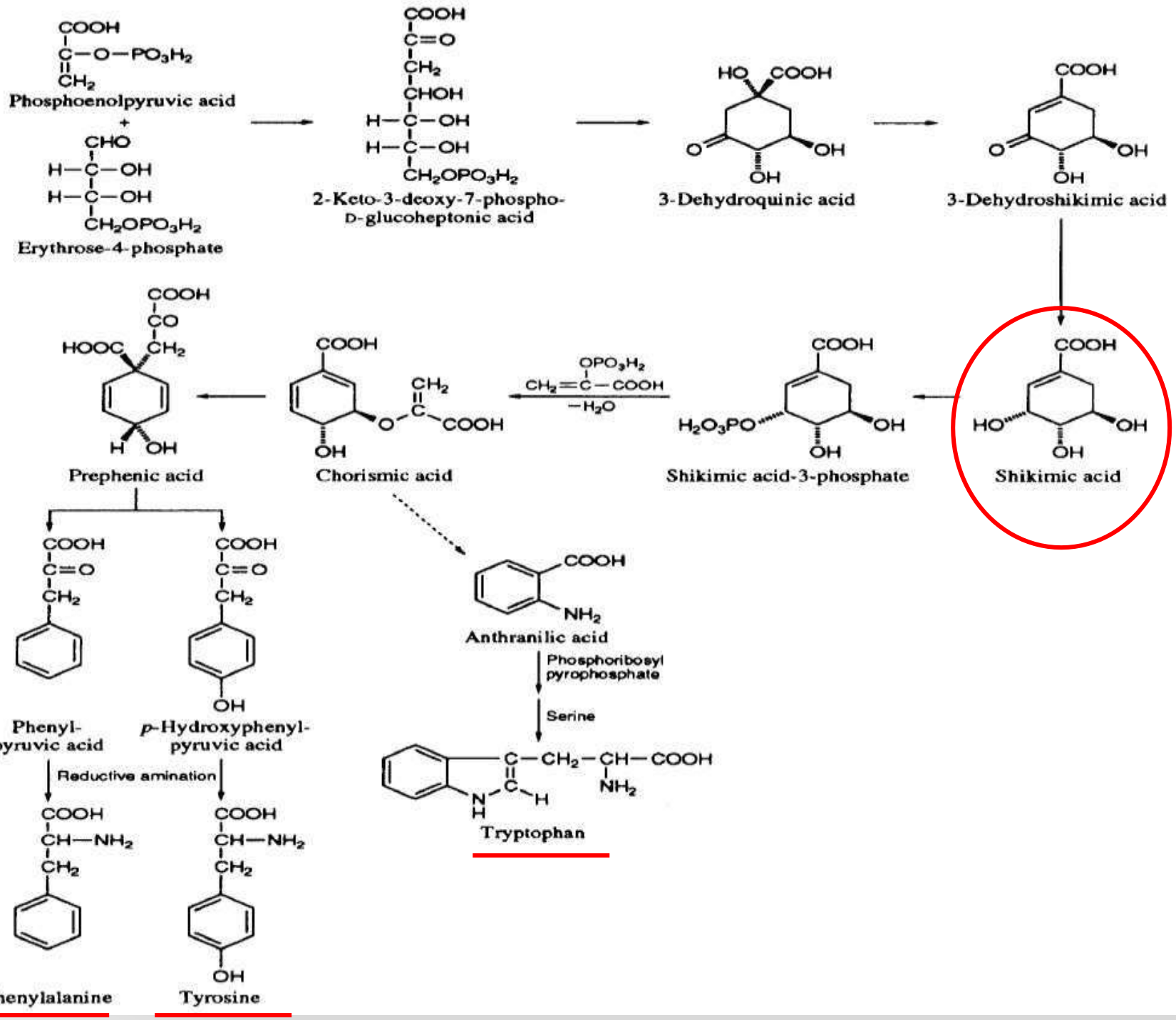
# Shikimic acid




- Commonly known as its anionic form **shikimate**, is a cyclohexene, a cyclitol and a cyclohexanecarboxylic acid.
- It is an important biochemical metabolite in plants and microorganisms.
- Its name comes from the Japanese flower *shikimi* the Japanese star anise, *Illicium anisatum*), from which it was first isolated in 1885 by Johan Fredrik Eykman.
- The elucidation of its structure was made nearly 50 years later.
- Shikimic acid is also the glycoside part of some hydrolysable tannins.

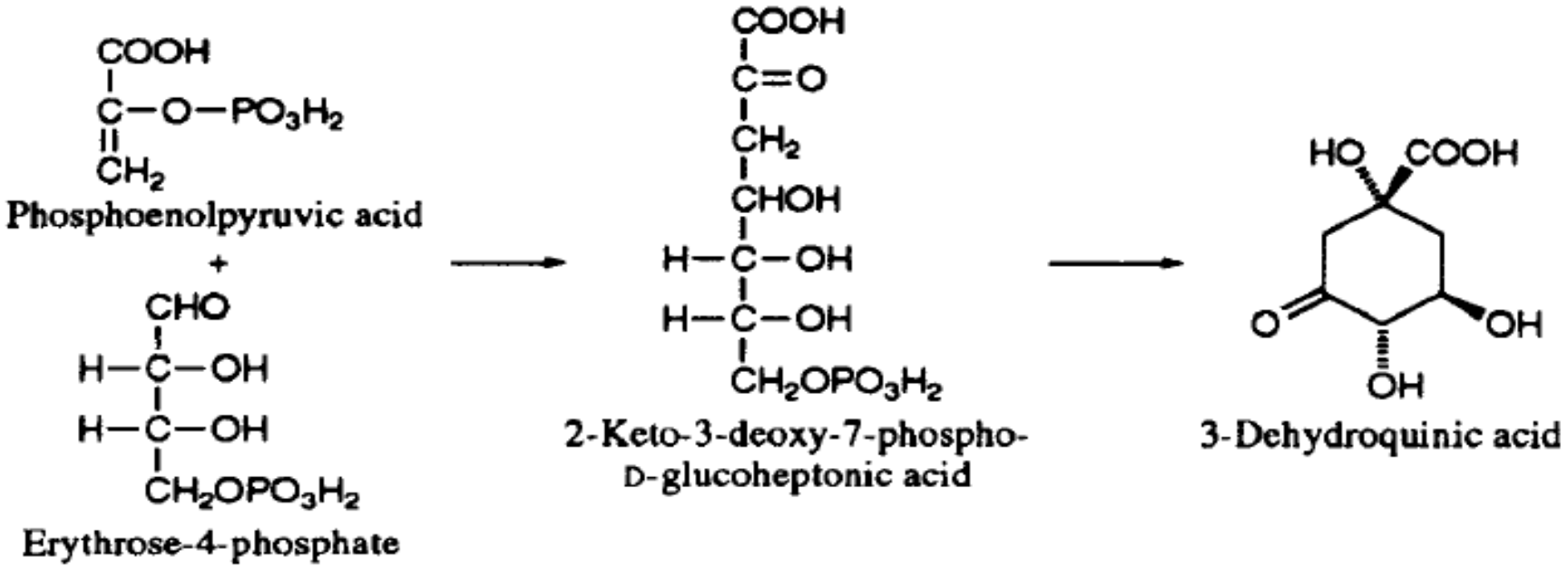
- The shikimate pathway is a seven step metabolic route used by *bacteria, fungi, algae, parasites, and plants* for the biosynthesis of aromatic amino acids (*phenylalanine, tyrosine, and tryptophan*).
  - This pathway is not found in animals; therefore, phenylalanine and tryptophan represent *essential amino acids* that must be obtained from the animal's diet

  - Animals can synthesize tyrosine from phenylalanine, and therefore is not an essential amino acid except for *individuals unable to hydroxylate phenylalanine to tyrosine).*

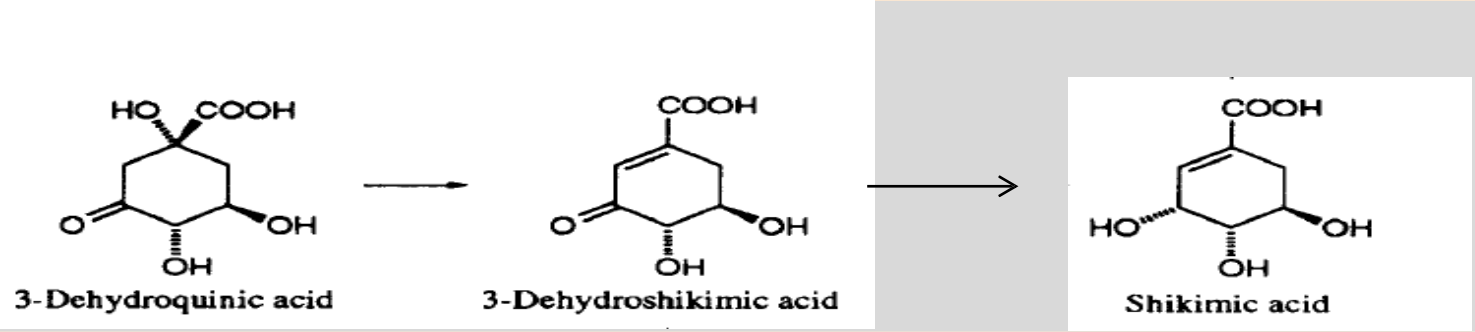

Phosphoenolpyruvic acid
Erythrose-4-phosphate
2-Keto-3-deoxy-7-phospho-D-glucoheptonic acid
3-Dehydroquinic acid
3-Dehydroshikimic acid
Shikimic acid
Shikimic acid-3-phosphate
Chorismic acid
Prephenic acid
Anthranilic acid
Phosphoribosyl pyrophosphate
Serine
Tryptophan
Phenyl-pyruvic acid
p-Hydroxyphenyl-pyruvic acid
Reductive amination
Phenylalanine
Tyrosine

- *Phosphoenolpyruvate* and *erythrose-4-phosphate* react to form *2-keto3-deoxy7phosphoglucoheptonic acid*, in a reaction catalyzed by the enzyme **DAHP synthase.**
- *2-keto3-deoxy7phosphoglucoheptonic acid* is then transformed to *3-dehydroquinate (DHQ)*, in a reaction catalyzed by **DHQ synthase.**
- Although this reaction requires nicotinamide adenine dinucleotide (NAD) as a cofactor,

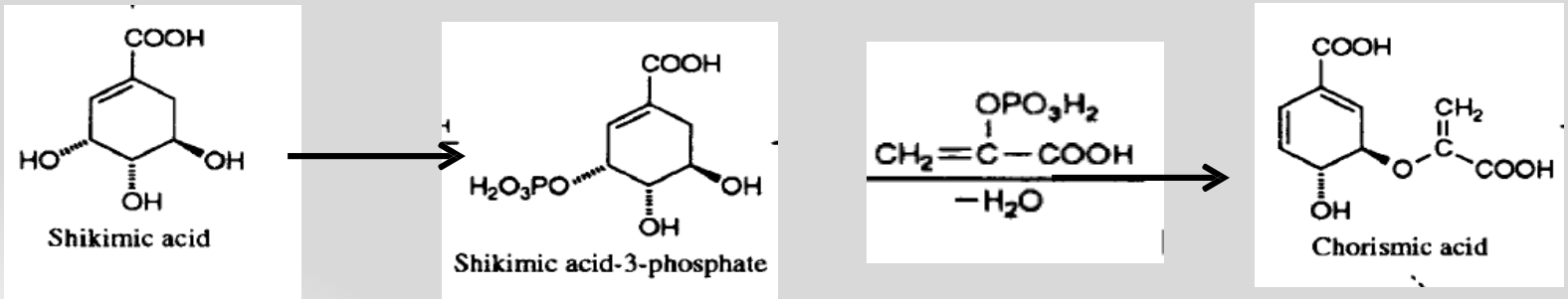
the enzymic mechanism regenerates it, resulting in the net use of no NAD.



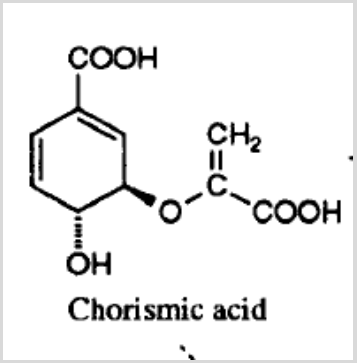
- DHQ is dehydrated to *3-dehydroshikimic acid* by the enzyme *3-dehydroquinate dehydratase*, which is reduced to *shikimic acid* by the enzyme *shikimate dehydrogenase*, which uses nicotinamide adenine dinucleotide phosphate (NADPH) as a cofactor.



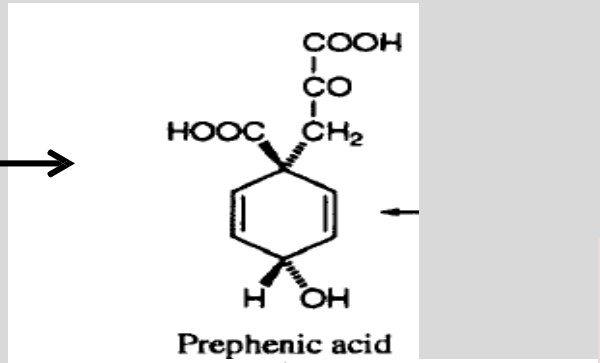

- The next enzyme involved is *shikimate kinase*, an enzyme that catalyzes the ATP-dependent phosphorylation of shikimate to form *shikimate 3-phosphate*. Shikimate 3-phosphate is then coupled with *phosphoenol pyruvate* to give *5-enolpyruvylshikimate-3-phosphate* via the enzyme *5-enolpyruvylshikimate-3-phosphate* ***(EPSP) synthase***.
- Then 5-enolpyruvylshikimate-3-phosphate is transformed into chorismate by a ***chorismate synthase.***



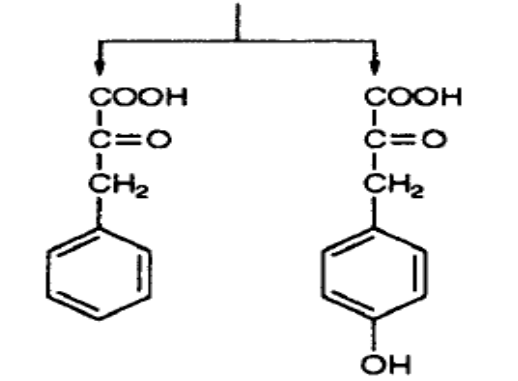
- *Prephenic acid* is then synthesized by a *Claisen rearrangement* of chorismate by ***Chorismate mutase***.



Chorismic acid



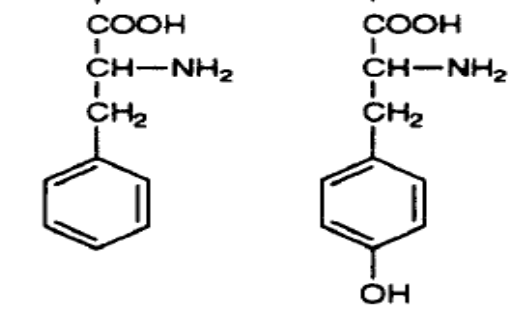
Prephenic acid



Phenyl-pyruvic acid

*p*-Hydroxyphenyl-pyruvic acid

Reductive amination



Phenylalanine

Tyrosine

*Prephenate* is *oxidatively decarboxylated* with retention of the hydroxyl group by **Prephenate dehydrogenase** to give *p-hydroxyphenylpyruvate*, which is transaminated using glutamate as the nitrogen source to give *tyrosine and α-ketoglutarate*.

**Role of Shikimic Acid Pathway:**

•Starting Point in The Biosynthesis of Some Phenolics

*Phenyl alanine and tyrosine are the precursors* used in the biosynthesis of phenylpropanoids. The phenylpropanoids are then used to produce the *flavonoids, coumarins, tannins and lignin.*

•Gallic acid biosynthesis

Gallic acid is formed from *3-dehydroshikimate* by the action of the *enzyme shikimate dehydrogenase* to produce *3,5-didehydroshikimate*. The latter compound spontaneously rearranges to gallic acid.

- **Other compounds**
  - •Shikimic acid is a precursor for:
    - ➢ indole, indole derivatives and aromatic amino acid tryptophan and tryptophan derivatives such as the psychedelic compound dimethyltryptamine.
    - ➢ many alkaloids and other aromatic metabolites.

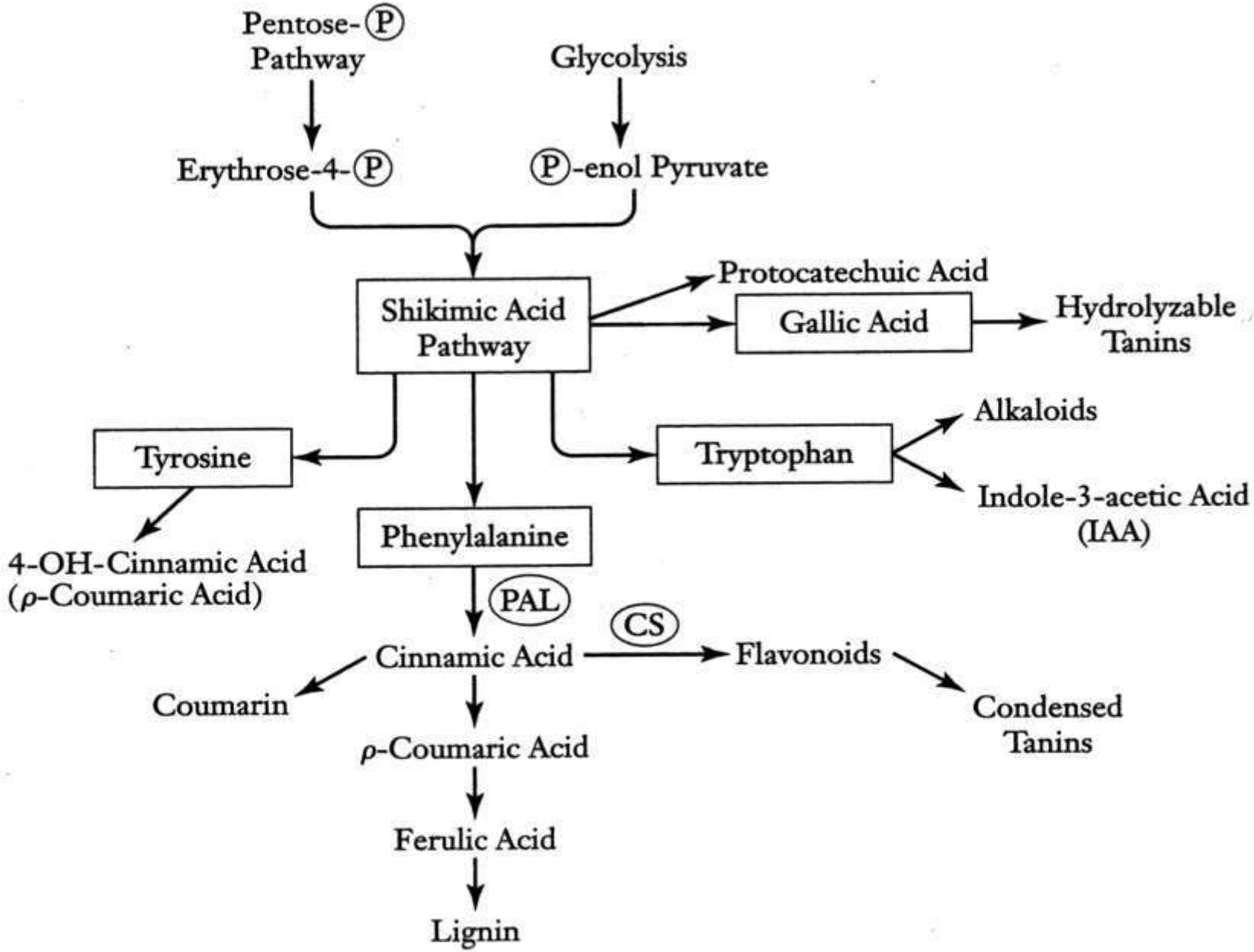



**FIGURE 14.14 The central role of the shikimic acid pathway in the synthesis of various primary and secondary metabolites. PAL = phenylalanine ammonia lyase. CS = chalcone synthase.**

**Uses:**

- In the pharmaceutical industry, shikimic acid from the Chinese star anise (*Illicium verum*) is used as a base material for production of *oseltamivir (Tamiflu)*.

**Target for drugs**

- Shikimate can be used to synthesize *(6S)-6-Fluoroshikimic acid*, an antibiotic which inhibits the aromatic biosynthetic pathway.
- **Glyphosate**, the active ingredient in the **herbicide Roundup**, kills plants by interfering with the shikimate pathway in plants. More specifically, glyphosate inhibits the enzyme 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS). "Roundup Ready" genetically modified crops overcome that inhibition.

# Bibliography: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