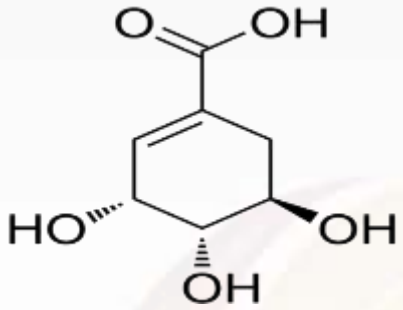
Shikimic Acid Pathway

DISCLAIMER

ALL THE CONTENT MATERIAL PROVIDED HERE IS ONLY FOR TEACHING PURPOSE.

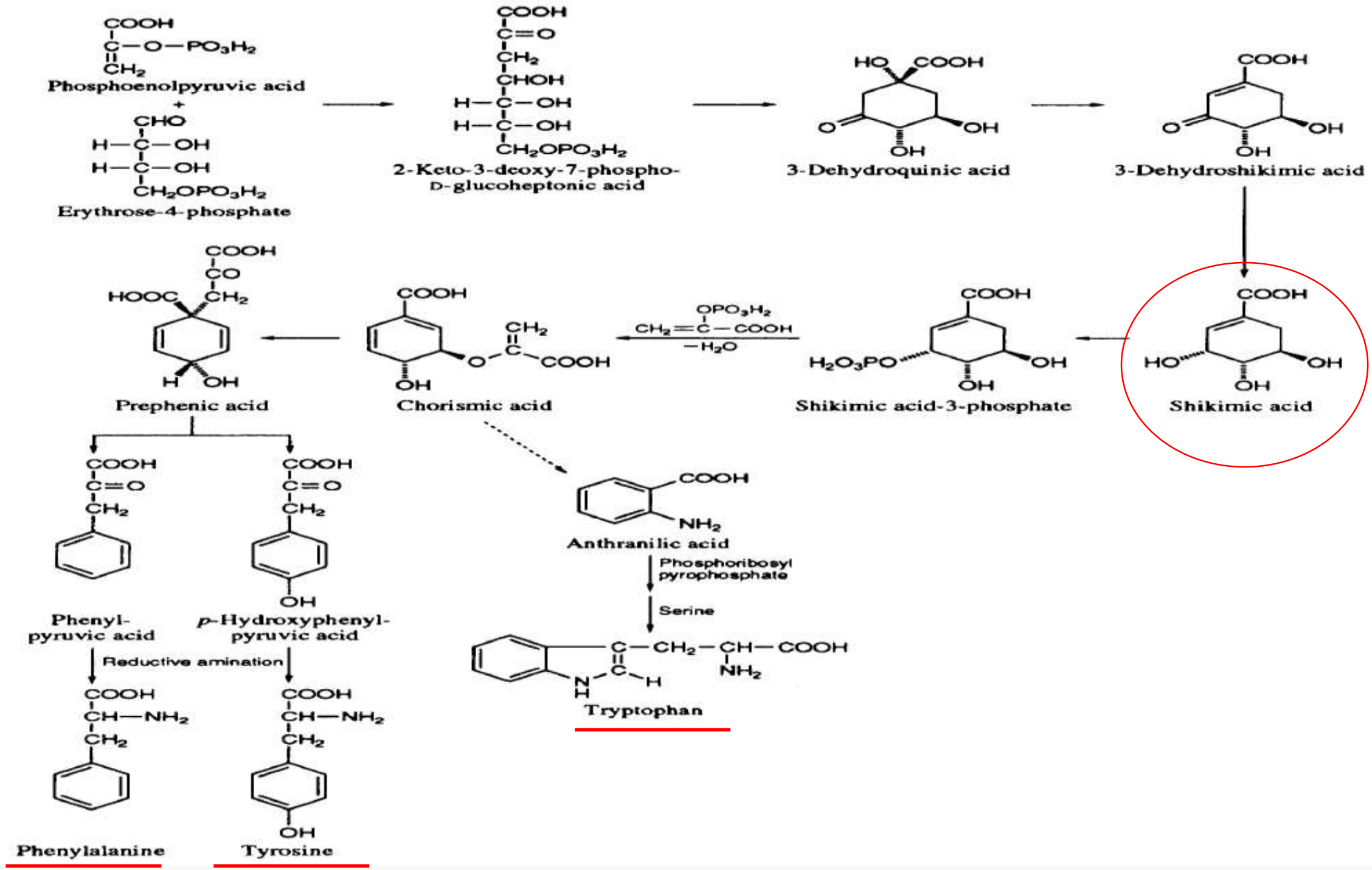
Shikimic acid



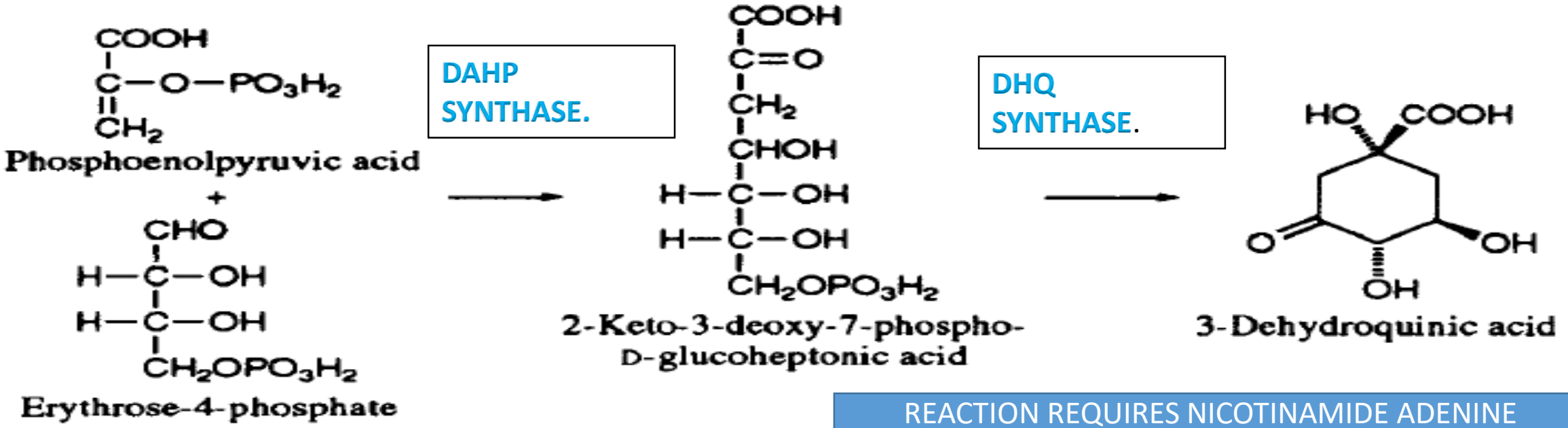
- Commonly known as its anionic form **shikimate**, is a cyclohexene, a cyclitol and a cyclohexanecarboxylic acid.
- It is an important biochemical metabolite in plants and microorganisms.
- Its name comes from the Japanese flower *shikimi* the Japanese star anise, *Illicium anisatum*), from which it 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).*

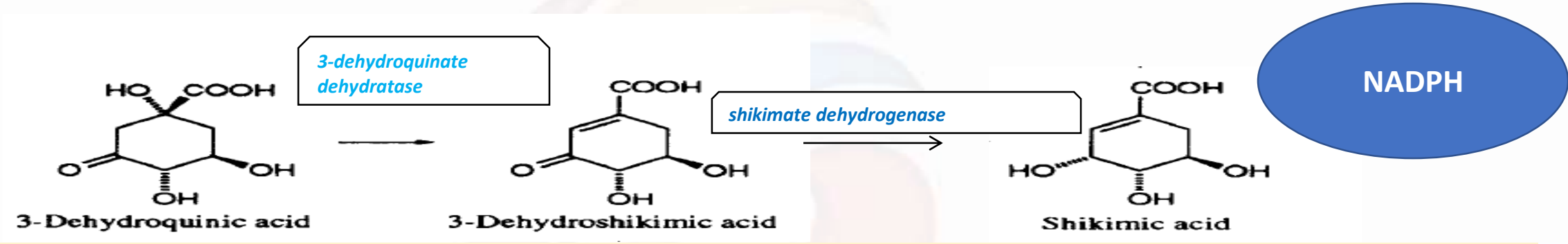

Phosphoenolpyruvic acid
Erythrose-4-phosphate
2-Keto-3-deoxy-7-phospho-D-glucoheptonic acid
3-Dehydroquinic acid
3-Dehydroshikimic acid
Shikimic acid
Shikimic acid-3-phosphate
Chorismic acid
Prephenic acid
Phenyl-pyruvic acid
p-Hydroxyphenyl-pyruvic acid
Reductive amination
Phenylalanine
Tyrosine
Anthranilic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

- *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.

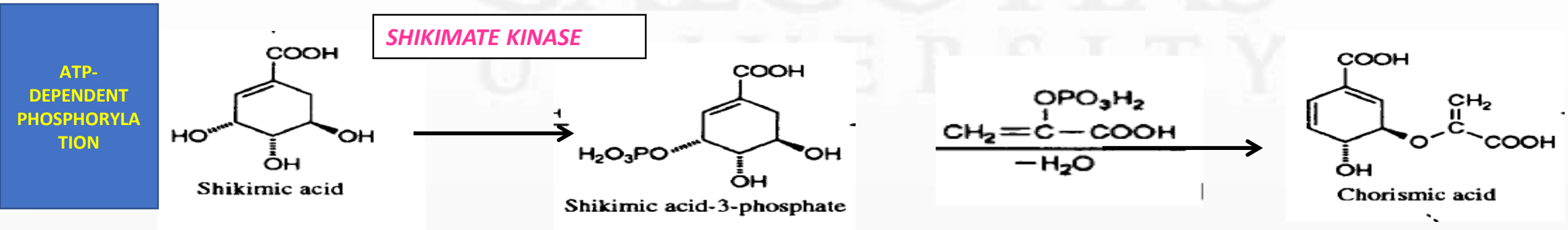


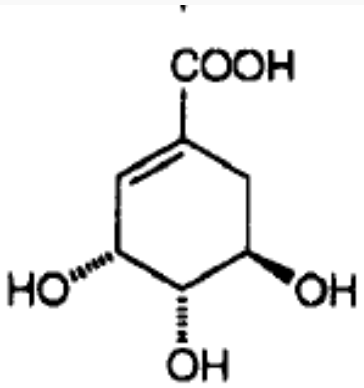
REACTION REQUIRES NICOTINAMIDE ADENINE DINUCLEOTIDE (NAD)

- 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.

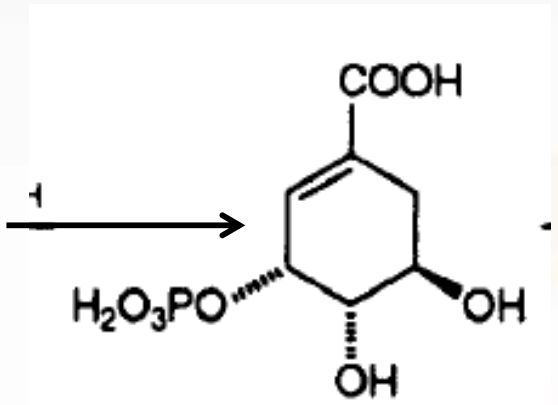


- The next enzyme involved is *shikimate kinase*, an enzyme that catalyzes the ATP-dependent phosphorylation of shikimate to form *shikimate 3-phosphate*. Shikimate 3-phosphate is then coupled with *phosphoenol pyruvate* to give *5-enolpyruvylshikimate-3-phosphate* via the enzyme *5-enolpyruvylshikimate-3-phosphate*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

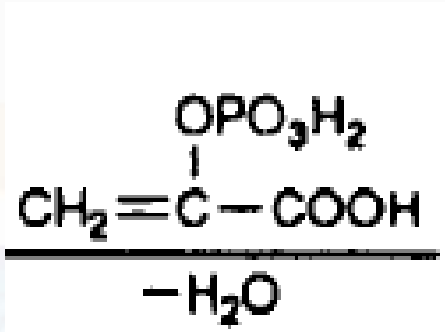


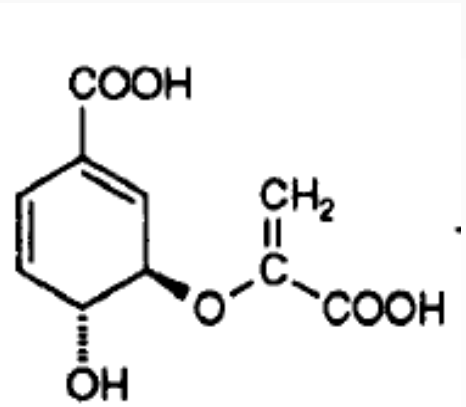


Shikimic acid



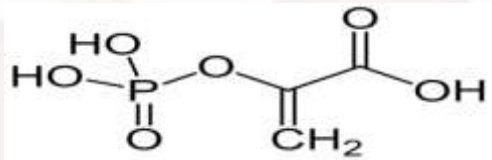
Shikimic acid-3-phosphate





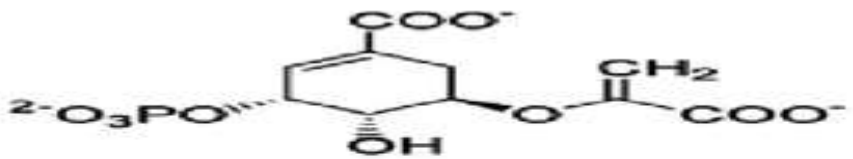
Chorismic acid

5-enolpyruvylshikimate-3-phosphate (EPSP) synthase.



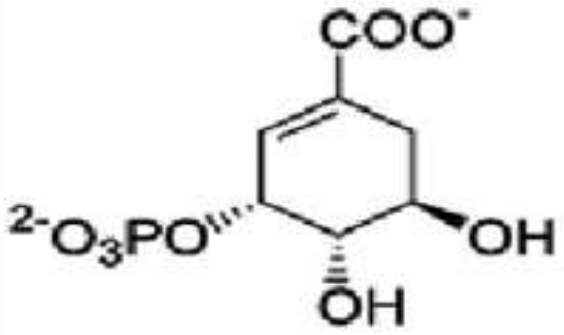
Shikimate 3-phosphate + *phosphoenol pyruvate*

chorismate synthase

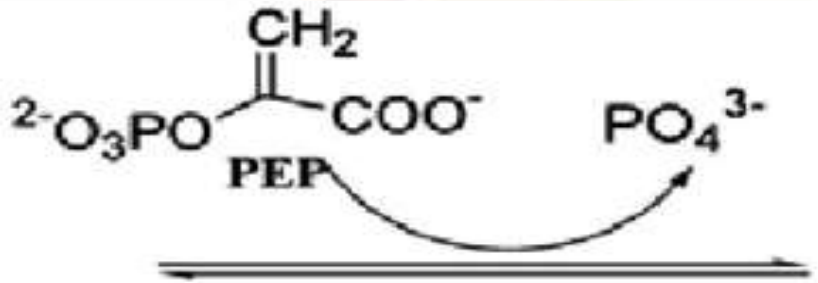


5-enolpyruvylshikimate-3-phosphate (EPSP)

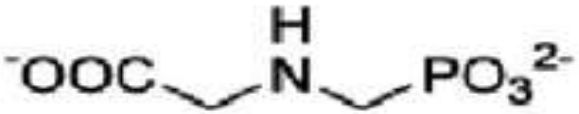
nolpyruvylshikimate-3-phosphate.



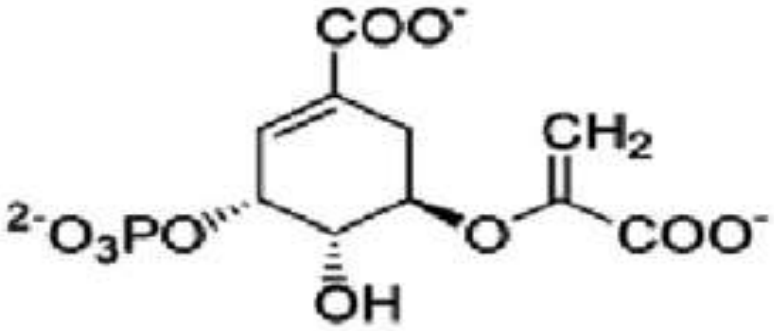
Shikimate-3-phosphate



Inhibtor

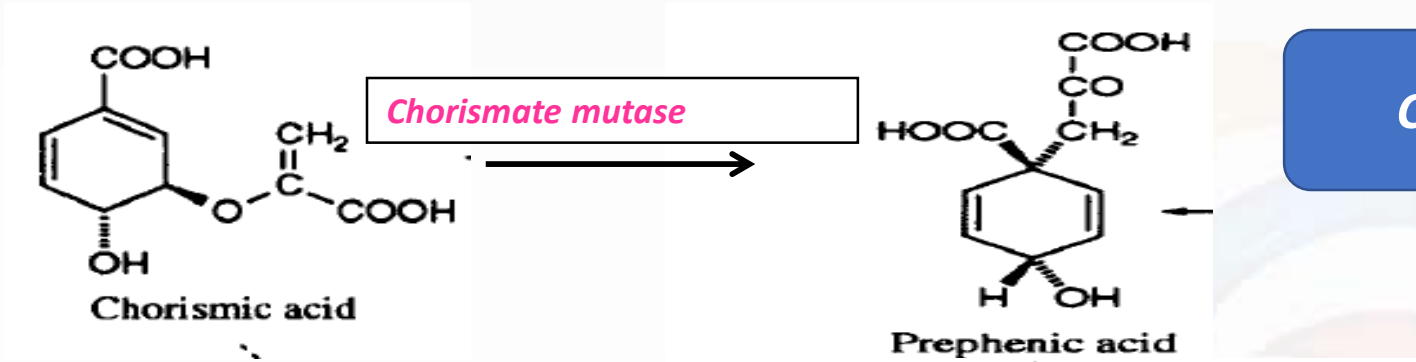


Glyfosate

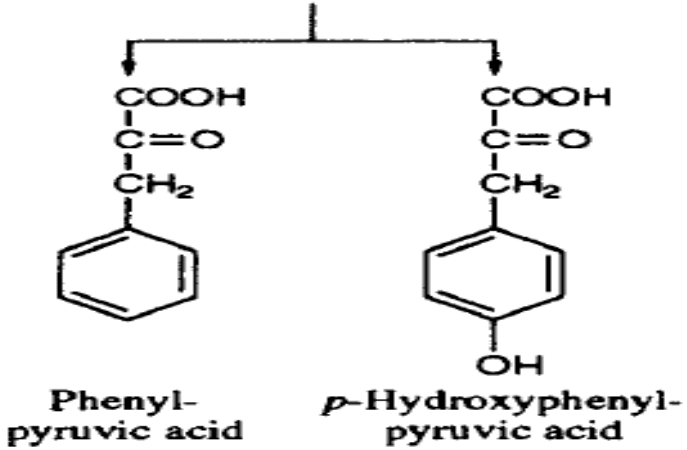


5-enolpyruvylshikimate-3-phosphate (EPSP)

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



Claisen rearrangement of chorismate



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.

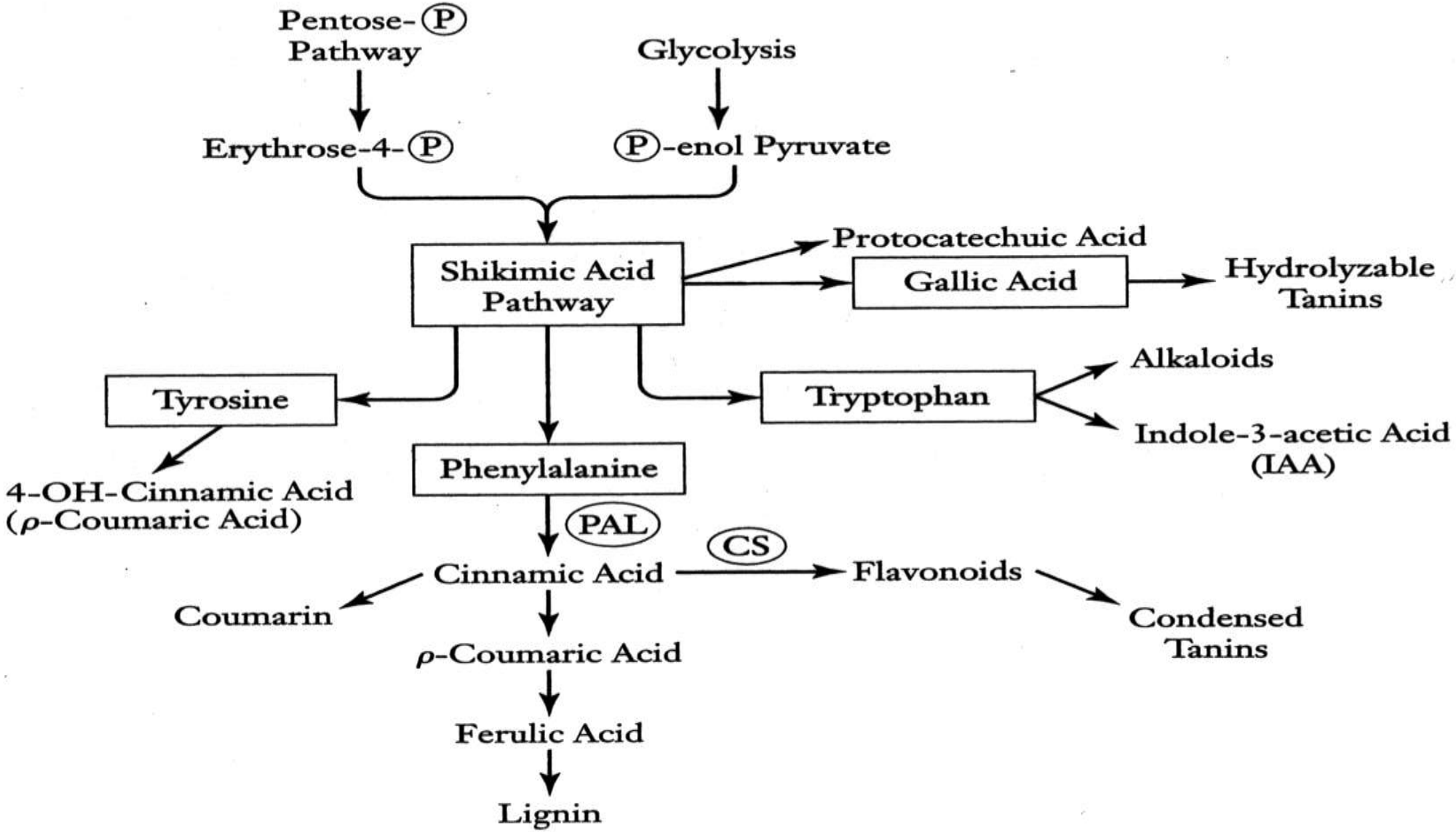
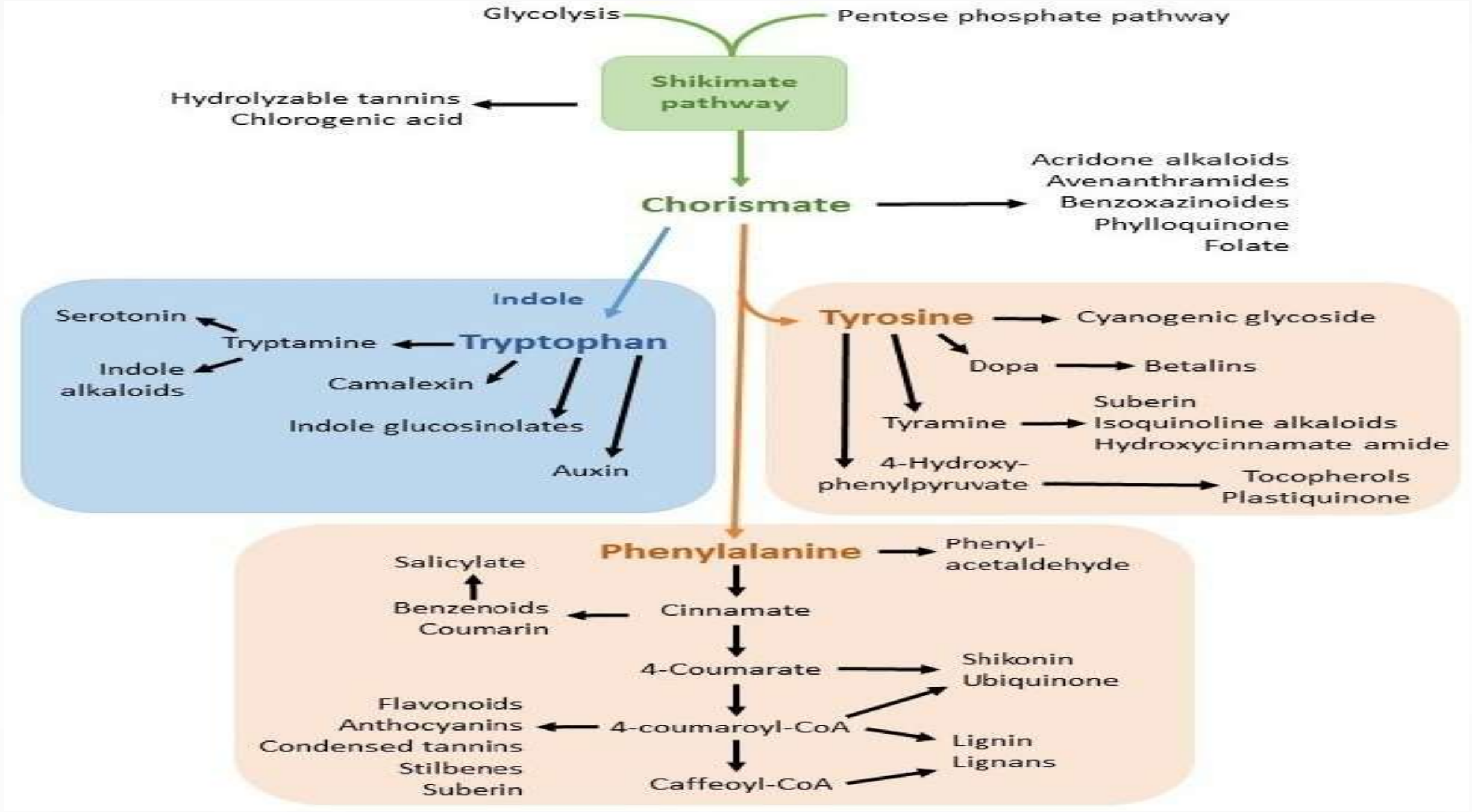


FIGURE 14.14 The central role of the shikimic acid pathway in the synthesis of various primary and secondary metabolites. PAL = phenylalanine ammonia lyase. CS = chalcone synthase.


Glycolysis
Pentose phosphate pathway
Shikimate pathway
Hydrolyzable tannins
Chlorogenic acid
Chorismate
Acridone alkaloids
Avenanthramides
Benzoxazinoides
Phylloquinone
Folate
Indole
Serotonin
Tryptamine
Tryptophan
Indole alkaloids
Camalexin
Indole glucosinolates
Auxin
Tyrosine
Cyanogenic glycoside
Dopa
Betalins
Tyramine
Suberin
Isoquinoline alkaloids
Hydroxycinnamate amide
4-Hydroxy-phenylpyruvate
Tocopherols
Plastiquinone
Phenylalanine
Phenyl-acetaldehyde
Salicylate
Benzenoids
Coumarin
Cinnamate
4-Coumarate
Shikonin
Ubiquinone
Flavonoids
Anthocyanins
Condensed tannins
Stilbenes
Suberin
4-coumaroyl-CoA
Lignin
Lignans
Caffeoyl-CoA

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.

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