Pharmacognosy

CHAPTERWISE NOTES

Biosynthetic Pathways

PHARMA

PHARMACOGNOSY

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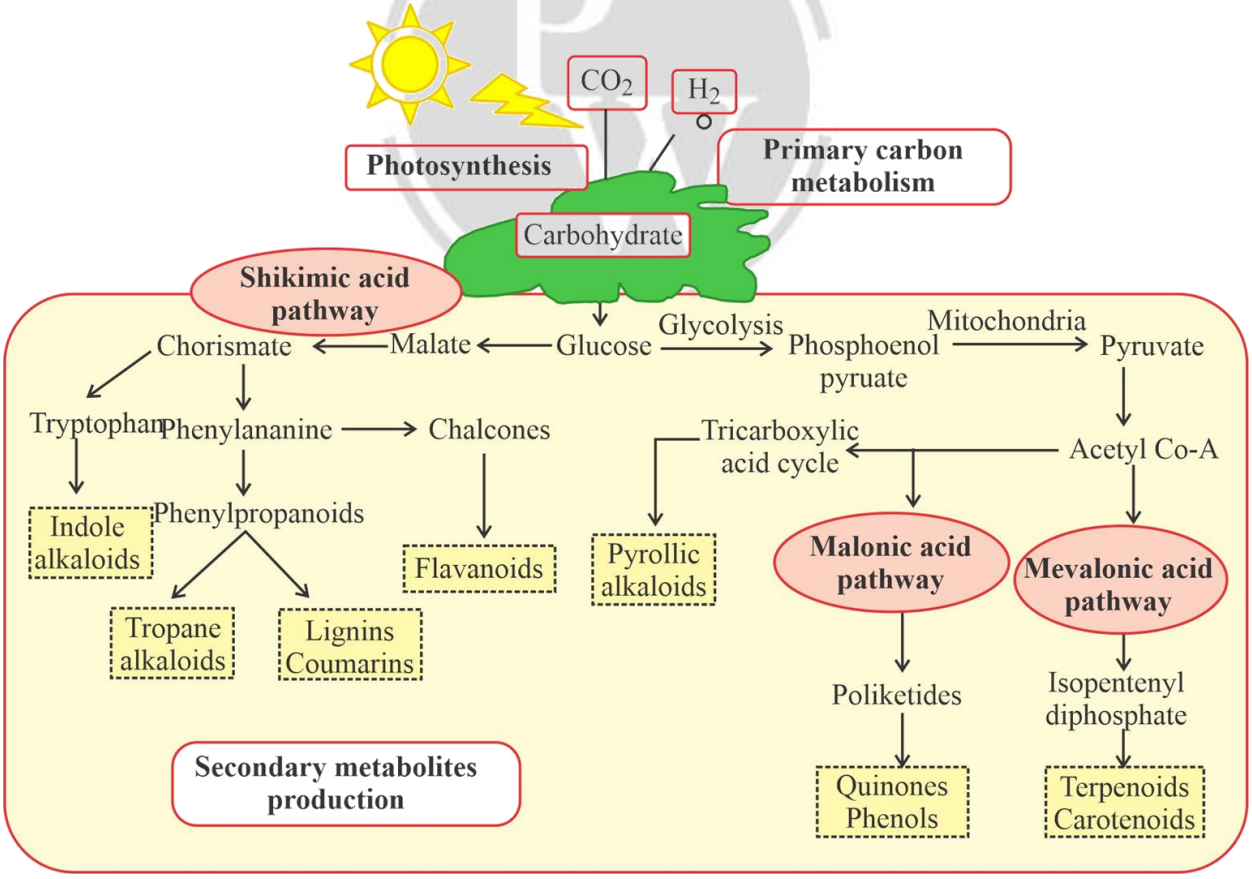
Biosynthetic Pathways:

Biosynthetic pathways in pharmacognosy are natural processes by which organisms produce **secondary metabolites-bioactive** compounds used in medicine. These pathways are essential for the formation of plant- and microbe-derived drugs.

Intermediary Metabolism:

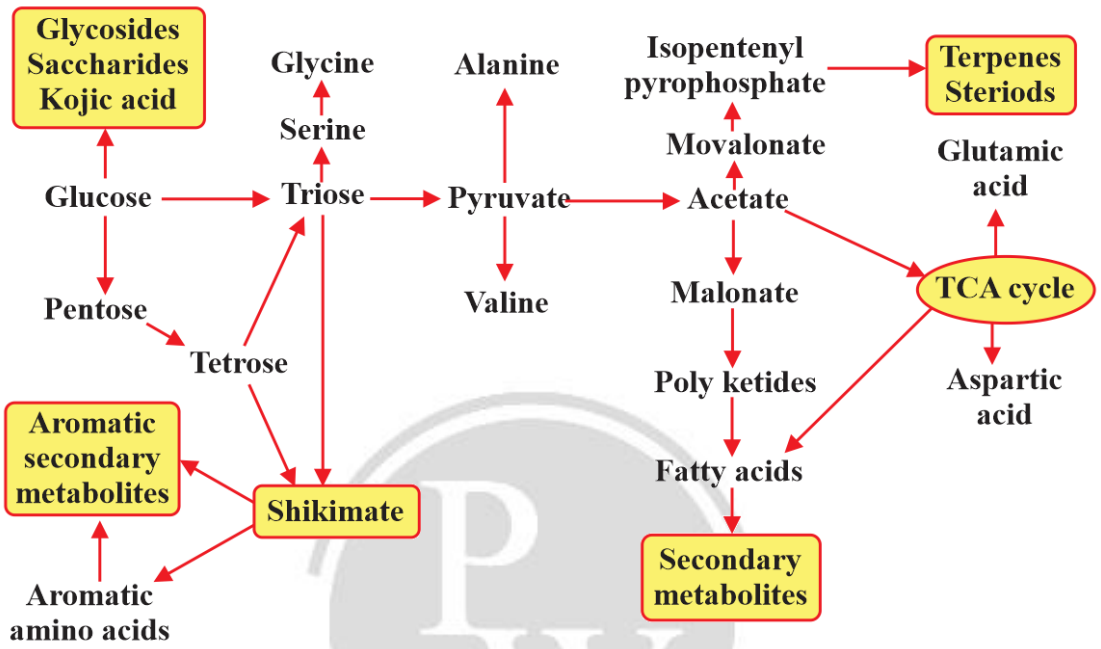
- Organisms rely on intermediary metabolism to transform organic compounds, enabling life functions like growth and reproduction.
- Metabolic pathways are enzyme-regulated chemical reactions that provide energy (ATP) and building blocks (e.g., carbohydrates, proteins, fats, nucleic acids).
- Primary metabolism is the essential network of pathways for synthesizing, degrading, and interconverting fundamental compounds in all organisms.



Primary vs. Secondary Metabolism:

- **Primary Metabolism:** Involves universal pathways for energy generation and basic compounds (e.g., glycolysis, Krebs cycle, *b*-oxidation).

- **Secondary Metabolism:** Focuses on compounds specific to certain organisms, often involved in defense or signaling (e.g., toxins, attractants, or colorants). Secondary metabolites have limited distribution and are often pharmacologically active.



Building Blocks for Secondary Metabolites:

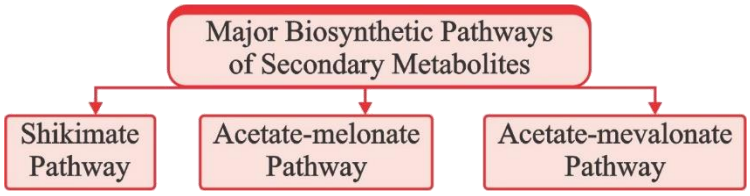
- Derived from primary metabolism, **key intermediates include acetyl-CoA, shikimic acid, mevalonic acid, and 1-deoxyxylulose 5-phosphate. These are used in acetate, shikimate, mevalonate, and deoxyxylulose phosphate pathways.**
- Amino acids also contribute to the synthesis of natural products (e.g., peptides, alkaloids, antibiotics).

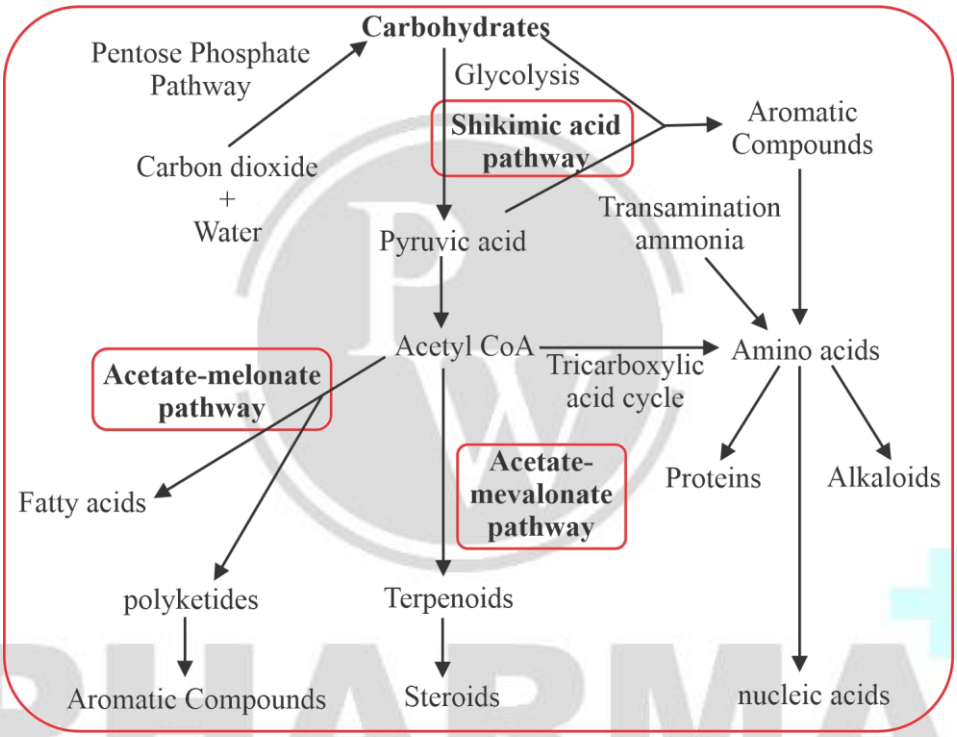
Key Building Blocks:

Skeleton	Description
Cl	A single carbon unit (e.g., methyl group) from L-methionine.
C2	A two-carbon unit from acetyl-CoA, forming part of fatty acids or aromatic systems.
CS (Isoprene)	Derived from mevalonate or deoxyxylulose phosphate, crucial for compounds like terpenoids.
C6-C3	Phenylpropyl units from L-phenylalanine or L-tyrosine, used Ill aromatic compounds.
C6-C2-N	Formed from L-tyrosine, often involved in alkaloids.
Indole-C2-N	Derived from L-tryptophan, it forms indole-containing systems.
C4-N (Pyrrolidine)	From L-omithine, found in alkaloids.
CS-N (Piperidine)	Derived from L-lysine, common in piperidine ring systems.

➤ Pathway s Involved:

✴ Secondary metabolites are synthesized via three main biosynthetic routes: **shikimate P,athway, acetate-malonate pathway, and acetate-mevalonate pathway.**





➤ Shikimic Acid Pathway

The shikimate pathway is a metabolic route used by plants and microorganisms (but not animals) to produce aromatic compounds, particularly the aromatic amino acids L-phenylalanine, L-tyrosine, and L-tryptophan, which are essential in the human diet.

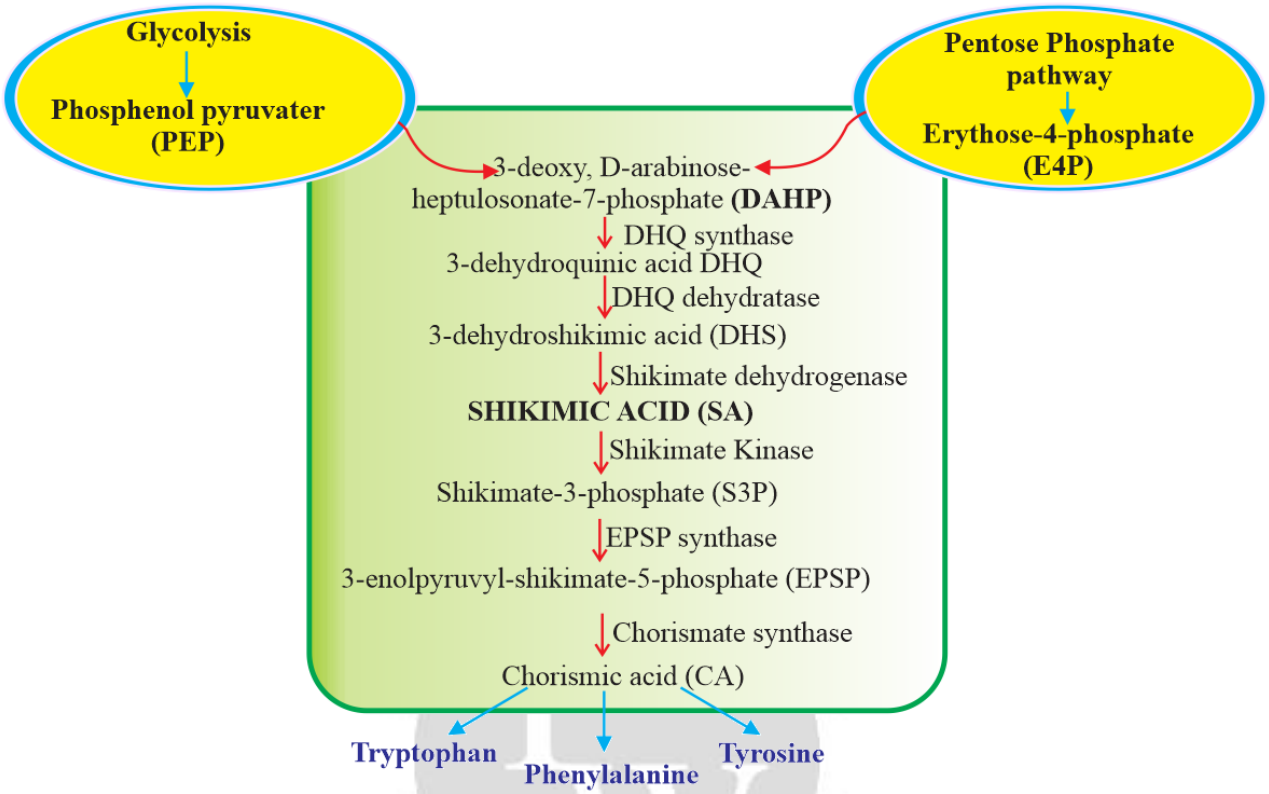
➤ Key Points:

1. **Pathway Overview:** The shikimate pathway involves the conversion of **phosphoenolpyruvate** (from glycolysis) and **D-erythrose 4-phosphate** (from the pentose phosphate cycle) to aromatic amino acids.
2. **Discovery and Study:** The pathway was characterized by studying *Escherichia coli* mutants, which helped identify the intermediates and enzymes involved.
3. **Shikimic Acid:** A central intermediate in the pathway, originally isolated from ***Illicium species*** (shikimi plant), is converted into various compounds through the pathway.
4. **Branch Points:**
   - ✴ **Dehydroquinic acid can be converted to shikimic acid or protocatechuic acid.**

- **Chorismic acid is a crucial branch point and can be converted into:**
  - **Anthranilic acid (for tryptophan biosynthesis).**
  - **Prephenic acid (for tyrosine and phenylalanine biosynthesis).**
  - **Aminobenzoic acid.**

5. **Key Enzymes and Reactions:**
   - **Phospho-2-oxo-3-deoxyheptonate aldolase** catalyzes the first step, forming **DAHP.**
   - **3-Dehydroquinate synthase** catalyzes the cyclization of **DAHP** to **3-dehydroquinic acid.**
   - **Shikimate kinase** adds a phosphate group to shikimic acid.
   - **Chorismate synthase** converts shikimic acid to **chorismic acid.**
6. **Conversion to Amino Acids:**
   - **Tryptophan:** From **anthranilic acid,** via intermediate steps, culminating in tryptophan synthase catalyzing the final reaction.
   - **Tyrosine:** Derived from **prephenic acid** through aromatization to **4-hydroxyphenylpyruvic acid,** followed by transamination.
   - **Phenylalanine:** Formed from **prephenic acid** by aromatization to **phenylpyruvic acid** and transamination.
7. **Cultural Significance:** The aromatic amino acids serve as precursors for various natural products like flavonoids, alkaloids, and lignans, and are involved in the production of benzoic acid derivatives like **gallic acid** and **p-aminobenzoic acid.**

This pathway is critical for the biosynthesis of a wide range of important compounds, including amino acids, alkaloids, and secondary metabolites.



➤ Acetate-Mevalonate Pathway

The Acetate-Mevalonate Pathway is a biosynthetic route that begins with acetyl-CoA and leads to the formation of mevalonic acid (mevalonate).

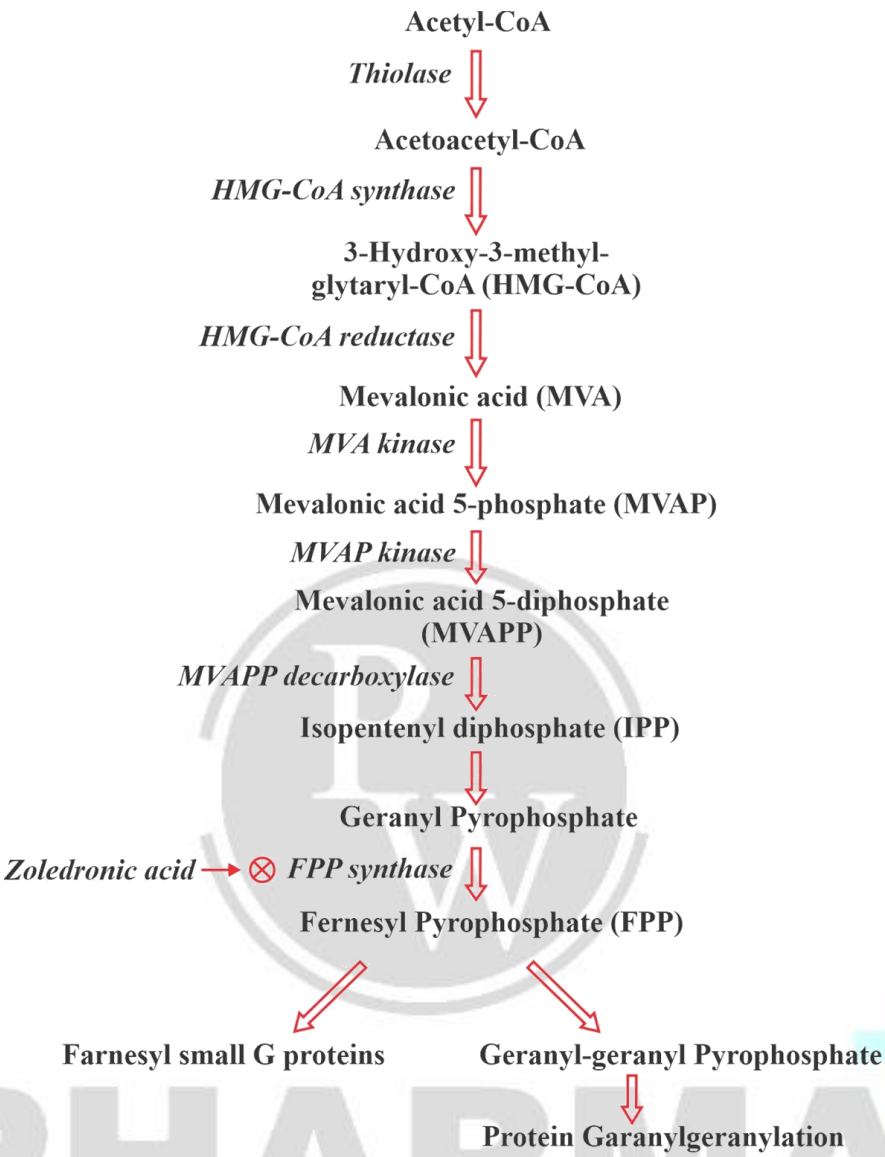
This pathway is crucial for the **synthesis of isoprenoid units (CS), such as isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP), which serve as the building blocks for terpenoids, steroids,** and other complex natural products.

The **Acetate-Mevalonate Pathway** is a key biosynthetic route involved in the production of many **secondary metabolites,** particularly **terpenoids** and **steroids.**

1. **Role of Acetate:** Acetic acid plays a crucial role in the biosynthesis of cholesterol, squalene, and rubber-like compounds. The discovery of **acetyl coenzyme A (acetyl-CoA),** also known as 'active acetate' in 1950, further supported its involvement in biogenetic pathways.
2. **Mevalonic Acid:** Acetyl-CoA is converted to **mevalonic acid,** which is an intermediate in the pathway.
3. **Isoprenoid Intermediates:**
   - ✶ Mevalonic acid is converted to **isopentenyl pyrophosphate (IPP)** and its isomer **dimethylallyl pyrophosphate (DMAPP).** These two compounds are the **active isoprene units,** key building blocks of isoprenoid compounds.
4. **Terpene Formation:**
   - ✶ **IPP** and **DMAPP** combine to form **geranyl pyrophosphate (GPP),** a **ClO-monoterpene.**
   - ✶ **GPP** can combine with another IPP to form **farnesyl pyrophosphate (FPP),** a **C15-sesquiterpene.**

- **FPP** can further combine with an additional IPP unit to form **geranylgeranyl pyrophosphate (GGPP),** a **C20-diterpene.**

5. **Squalene and Steroid Synthesis:**
   - **Farnesyl pyrophosphate (FPP),** through a series of steps, leads to the formation of **squalene.**
   - Squalene undergoes cyclization to form the **cyclopentanoperhydrophenanthrene** structure, which is the core of **steroidal compounds** like cholesterol.
6. **End Products:**
   - The pathway produces a variety of compounds, including:
     - **Steroids** (like cholesterol).
     - **Triterpenoids.**
     - **Monoterpenoids, ses uiterpenoids,** and **diterpenoids.**
     - **Carotenoids, :P-Olyprenols.**
     - **Glycosides** and **alkaloids** (in association with other Qathways).



➤ Acetate-Malonate Pathway

The Acetate-Malonate Pathway, also known as the Polyketide Pathway, is a biosynthetic route that starts with acetyl-CoA and malonyl-CoA as key precursors. It involves the repeated condensation of these two-carbon units to form polyketide chains, which can undergo various modifications such as cyclization, reduction, and oxidation.

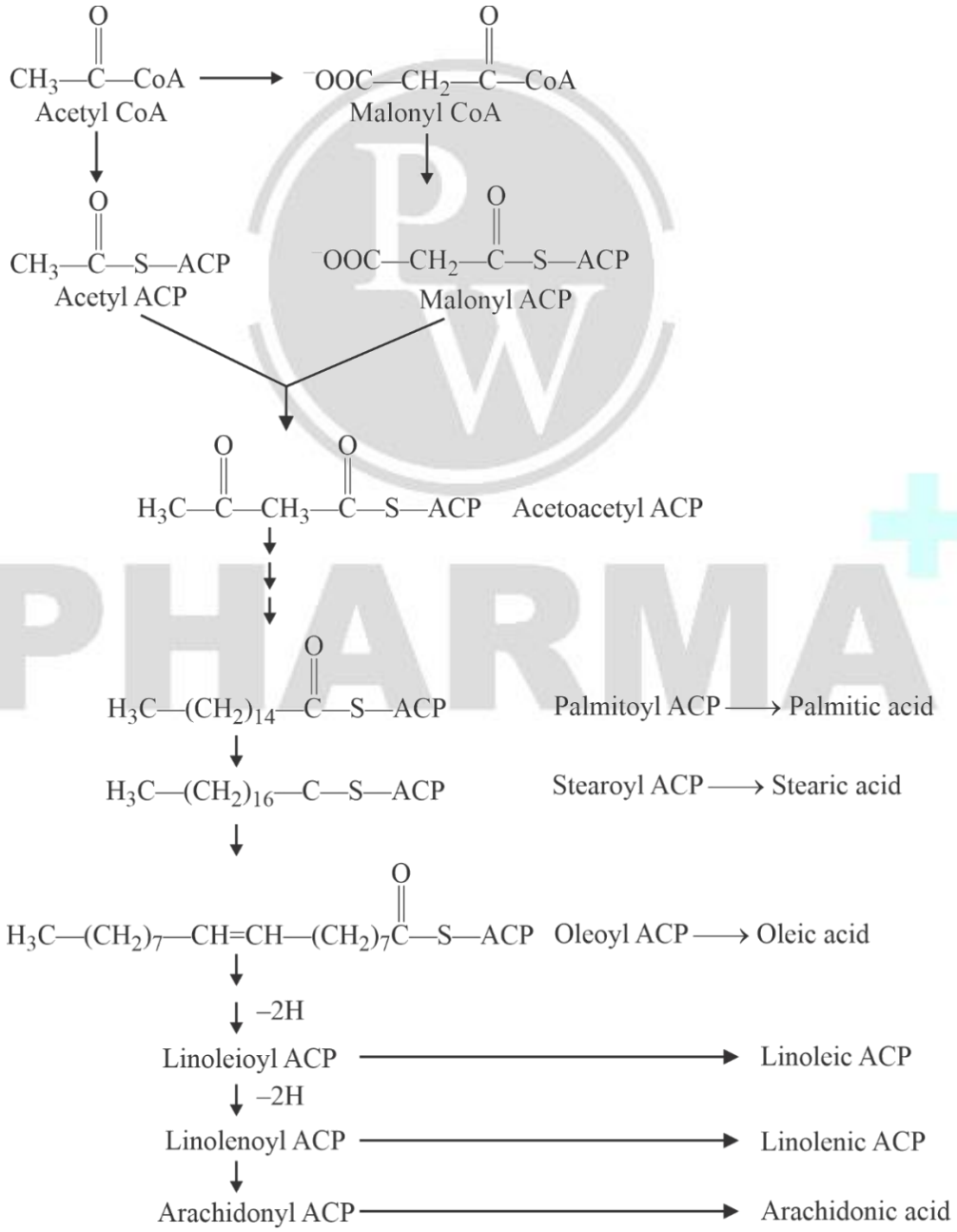
This pathway is primarily responsible for the **biosynthesis of secondary metabolites such as polyketide antibiotics (e.g., tetracycline, erythromycin), pigments (e.g., anthraquinones), mycotoxins, and other aromatic compounds.**

➤ Key Points:

1. **Acyl Carrier Protein (ACP):** The pathway involves **acyl carrier protein (ACP),** which facilitates the formation of **fatty acyl thioesters.** These intermediates are essential for fatty acid biosynthesis.
2. **Acetyl-CoA and Malonyl-CoA:** The pathway utilizes **acetyl-CoA** (C2 units) and **malonyl-CoA** (C3 units) as building blocks for fatty acid synthesis. The combination of these units results in the formation of **even-numbered fatty acids.**

3. **Fatty Acid Synthesis:** Through the **acetate-malonate pathway,** fatty acids are synthesized by the successive addition of **C2 (acetyl-CoA)** and **C3 (malonyl-CoA)** units. This process leads to fatty acids ranging from **n-tetranoic acid (butyric acid)** to **n-ecosanoic acid (arachidic acid).**
4. **Formation of Unsaturated Fatty Acids:** **Unsaturated fatty acids** are produced by **direct dehydrogenation** of the corresponding **saturated fatty acids.** This introduces double bonds into the fatty acid chain.
5. **Enzyme Role:** Specific enzymes play a key role in determining the **position of the double bonds** in the fatty acid chains during the formation of unsaturated fatty acids.

In summary, the acetate-malonate pathway is essential for the synthesis of fatty acids, involving **acetyl-CoA, malonyl-CoA,** and **ACP** as intermediates. The pathway leads to the production of both **saturated and unsaturated fatty acids** with enzyme-controlled placement of double bonds.



➤ Biosynthesis of Carbohydrates

Photosynthesis Overview: Photosynthesis is the process that converts light energy into chemical energy, producing carbohydrates (sugars) and oxygen. The general equation for photosynthesis is:

$$CO_2 + H_2O \xrightarrow[\text{Green plants}]{} \text{Sugar} + O_2$$

This process occurs in **green plants, algae,** and some bacteria.

1. **Key Compounds:**
   - **ATP (Adenosine Triphosphate) and NADPH (Nicotinamide Adenine Dinucleotide Phosphate) are the key molecules generated during photosynthesis.** These compounds mediate most biosynthetic reactions in plants.
2. **Primary Light Reactions:**
   - **Absorption of Light:** Light is absorbed by **chlorophyll** or transferred to chlorophyll by other pigments, producing **ATP** and **NADPH.**
   - **Photolysis of Water:** Water is split, releasing **oxygen** and **electrons.** These electrons are used to produce ATP and NADPH, which act as activating and reducing agents in the process.
3. **Blackmann Reaction (Dark Reaction):**
   - In the **dark reaction** (independent of light), **carbon dioxide** is reduced to form **four, five, six, and seven-carbon sugars.**
   - This process was first described by **Blackmann** and is referred to as the **Blackmann reaction.**
4. **Calvin Cycle:**
   - The **Calvin cycle,** first proposed by **Calvin,** describes the path of carbon during photosynthesis. In this cycle, **CO2** is fixed, and the carbon is incorporated into sugars.
5. **General Reaction in the Calvin Cycle:**

   $CO_2 + 2NADP + 2ATP$ ¾¾® $(CH_2O)_n + H_2O + 2\ ADP + 2\ NADPH$

   (Carbohydrate)
   - This results in the formation of **carbohydrates** (sugars) from **carbon dioxide,** powered by **ATP and NADPH.**

In summary, carbohydrates are synthesized through photosynthesis in green plants and certain microorganisms. The process involves the production of ATP and NADPH through light-dependent reactions and the fixation of carbon dioxide in the Calvin cycle during the dark reactions.

➤ Biosynthesis of Glycosides

1. **Glycosides Definition:** Glycosides are compounds formed by the condensation of a **sugar** and an **aglycone** (the acceptor unit).
2. **Two-Step Reaction Process:**
   - **Step 1:** **Sugar phosphates** bind with **uridine triphosphate (UTP)** to form a **sugar-uridine diphosphate (UDP) sugar complex.** This reaction is catalyzed by the enzyme **uridyl transf erase.**
   - **Step 2:** The **UDP-sugar complex** reacts with an **acceptor unit** (which could be an aglycone or another sugar), catalyzed by the enzyme **glycosyl transferase.**

$$UTP + Sugar\ 1-P \underset{\text{Uridyl transferase}}{\overset{(1)}{\rightleftharpoons}} UDP - Sugar + Ppi$$

$$UDP - Sugar + Acceptor \underset{\text{Glycosyl transferase}}{\overset{(2)}{\rightleftharpoons}} Acceptor - Sugar + UDP$$

3. **Formation of Higher Glycosides:** After the initial glycoside formation, other specific enzymes may transfer additional sugar units to the glycoside, leading to the formation of **di-glycosides, tri-glycosides, tetra-glycosides,** etc., through subsequent reactions.

In summary, glycosides are synthesized through the attachment of sugar units to an aglycone via **UDP-sugar intermediates.** These reactions are facilitated by **uridyl transferase** and **glycosyl transferase,** with the potential for further glycosylation in subsequent steps.

➤ Biosynthesis of Alkaloids

1. **General Overview:**
   - ✶ Alkaloids are nitrogen-containing compounds derived from amino acids.
   - ✶ Enzymatic pathways for alkaloid biosynthesis have been studied using radioactive precursors.
2. **Ornithine Derivatives:**
   - ✶ **L-Ornithine** is formed mainly from **L-glutamate** in plants and is a precursor for alkaloids like **nicotine** and **cocaine.**
   - ✶ Omithine forms **pyrrolidine rings** and is involved in tropane alkaloid biosynthesis (such as hyoscamine and cocaine).
3. **Lysine Derivatives:**
   - ✶ **L-Lysine** (a homologue of ornithine) forms **piperidine rings** in alkaloid biosynthesis.
   - ✶ Lysine derivatives are precursors for alkaloids like **lupinine, lupanine, anabasine,** and **pelletierine.**
   - ✶ **Lycopodium** alkaloids also belong to this group.
4. **Phenylalanine Derivatives:**
   - ✶ **L-Phenylalanine** contributes carbon atoms to alkaloids but not nitrogen.
   - ✶ **Ephedrine,** a nasal decongestant and bronchial dilator, is derived from phenylalanine in **Ephedra** species.
5. **Tyrosine Derivatives:**
   - ✶ **L-Tyrosine** is a precursor for a wide variety of alkaloids.
   - ✶ **Dopamine** is a key intermediate in the biosynthesis of **papaverine, berberine,** and **morphine.**
6. **Biosynthesis of Morphine:**
   - ✶ Morphine and related compounds like **thebaine** and **codeine** are derived from **dopamine.**
7. **Tryptophan Derivatives:**
   - ✶ **Tryptophan** and its decarboxylated form, **tryptamine,** are precursors for a **range of indole alkaloids.**
   - ✶ These include alkaloids from **Vinca, Rauwolfia,** and **Apocynaceae** families.
   - ✶ **D-Tubocurarine** (active component of curare) is a tryptophan derivative.

8. **Biosynthesis of Quinoline Alkaloids:**
   - The **Cinchona** genus produces quinoline alkaloids like **quinine** and **quinidine,** which have antimalarial properties.
   - These alkaloids are derived from modifications of indole, transforming into quinoline structures.
9. **Biosynthesis of Lysergic Acid:**

   Tryptophan (minus its carboxyl group) and an **isoprene unit** are the building blocks for **lysergic acid.**
   - **Dimethylallyl diphosphate** is alkylated onto tryptophan, forming intermediates like **chanoclavine-1** and **agroclavine.**
   - **Further oxidation and isomerizations lead to lysergic acid, a precursor for LSD.**

➤ **Key Points:**

- **Ornithine, lysine, phenylalanine, tyrosine,** and **tryptophan** serve as important precursors for various alkaloids.
- These amino acids undergo modifications (e.g., decarboxylation, methylation) to form alkaloid skeletons like **pyrrolidine, piperidine, indole,** and **quinoline.**
- Many medicinally valuable alkaloids, including **ephedrine, morphine, quinine,** and **lysergic acid,** are derived from these biosynthetic pathways.