Introduction to phytochemical pathways

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Plant Metabolism

– The biological reactions are essential to maintain life in living organisms and are known as primary metabolism.
– Plant convert sunlight energy to chemical energy, such as ATP,NADPH, by the mediation of chlorophyll in chloroplasts and synthesize sugars and starch from CO2 by using ATP and NADPH+.
– These carbohydrates are stored and used for differentiation and formation of plant tissues.

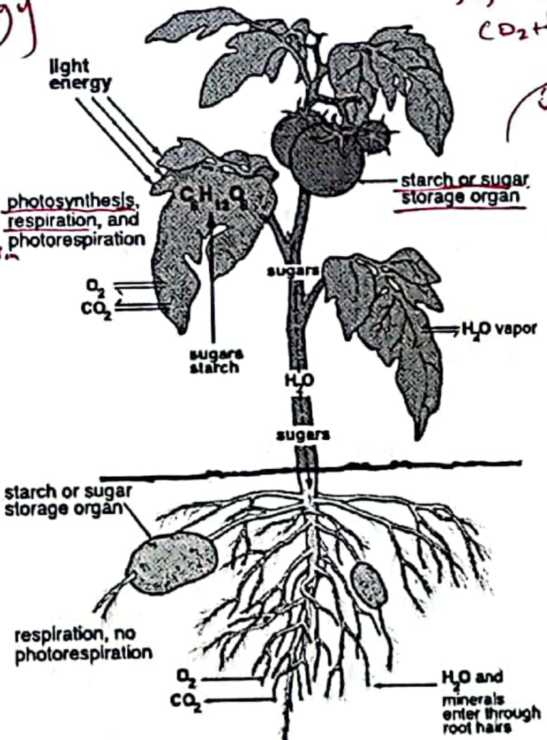
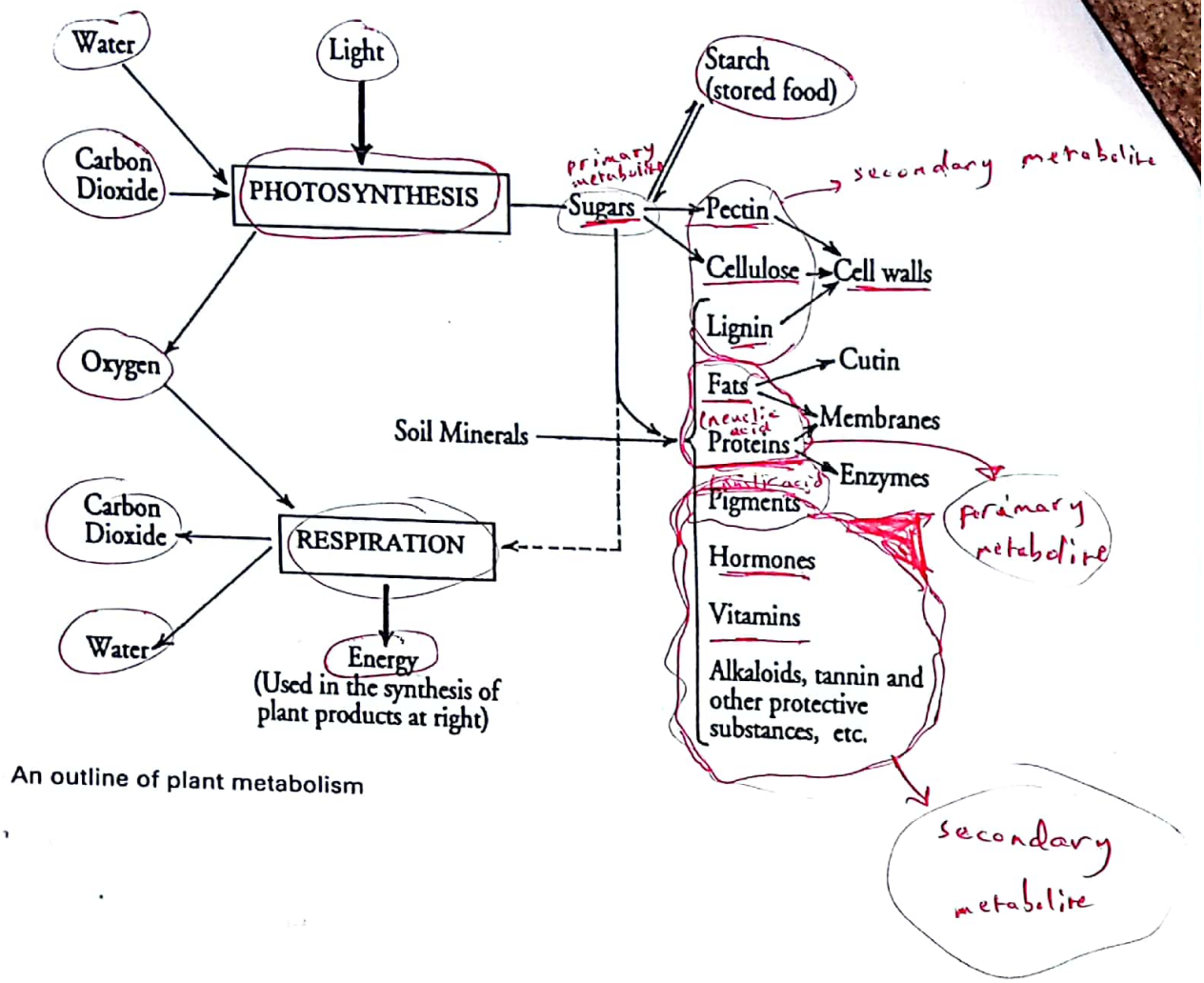


Figure 24. Photosynthesis, respiration, leaf water exchange, and translocation of sugar (photosynthate) in a plant.

$$\underset{\text{Carbon dioxide}}{6CO_2} + \underset{\text{Water}}{6H_2O} \xrightarrow{\text{Light}} \underset{\text{Sugar}}{C_6H_{12}O_6} + \underset{\text{Oxygen}}{6O_2}$$



An outline of plant metabolism

A* **All organisms** need to transform and interconvert a vast number of organic compounds to enable them to → live → grow → and reproduce. (primary metabolite)

B* They need to provide themselves with energy in the form of ATP. cellular respiration

C* They need a supply of building blocks to construct their own tissues.

D-An integrated network of **enzymes** mediated and carefully regulated chemical reactions is used for this purpose collectively referred to as→**intermediary metabolism** and the pathways involved are termed→ **metabolic pathways.**

E* Some of the important molecules of life are:

1-Carbohydrates, 2- Proteins, 3-Fats and 4-Nucleic acids. (primary metabolite)

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Primary Metabolites

- Primary metabolites are compounds produced by a living organism that are essential for its life and growth.

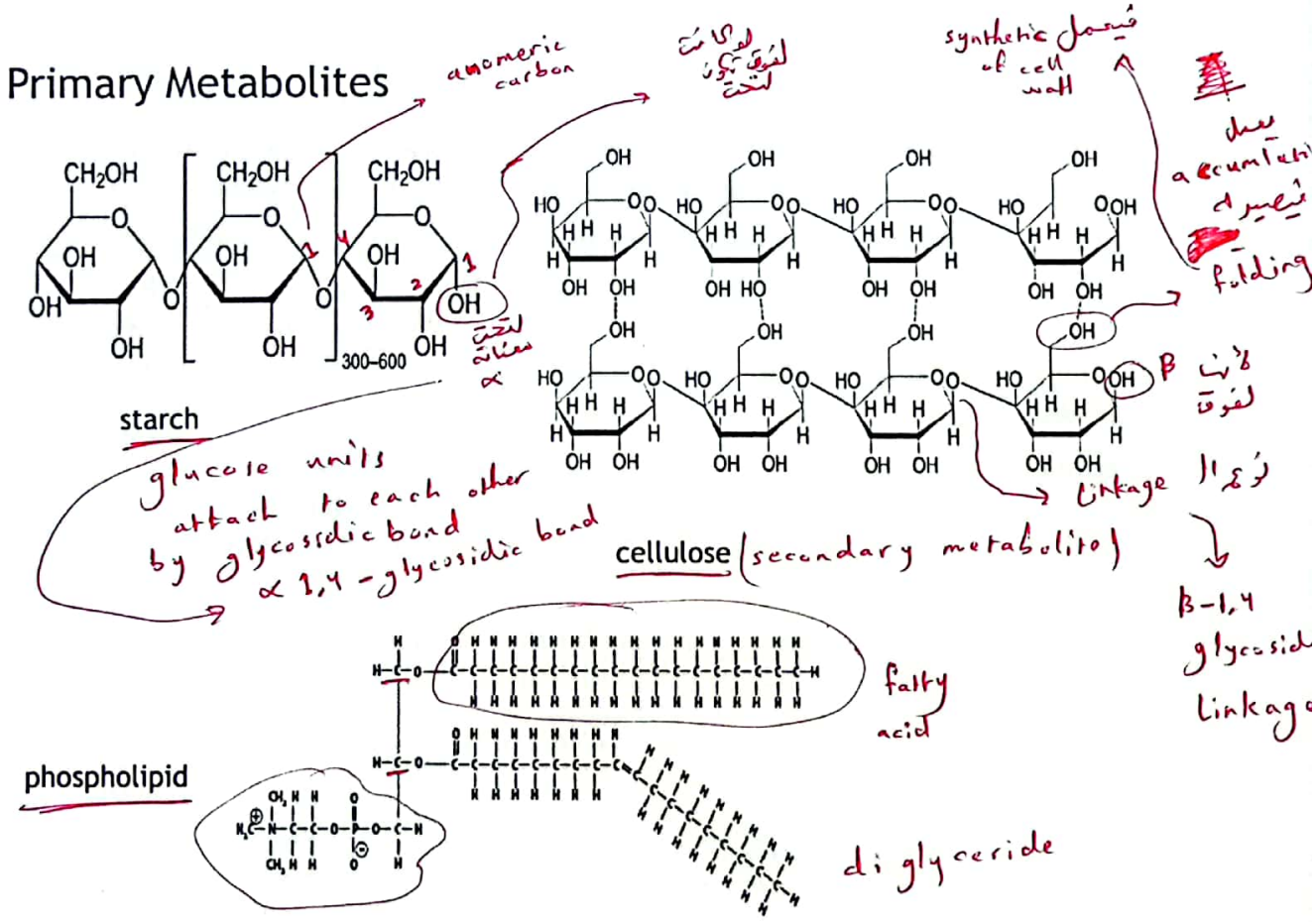
- The main primary metabolites are **carbohydrates, proteins, nucleic acids**, and **lipids**.
- They are occurring in all plants (in all green plants).

green part of plant

Apart from fats, these are polymeric materials.

يكونوا بشكل polymer ما عدا الـ fat

- * Carbohydrates(CHO): are composed of sugar units.
- * Proteins : are made up from amino acids
- * Nucleic acids:are based on nucleotides.



Plants and their metabolites

- **Primary metabolites**: Compounds produced during the fundamental pathways; essential for the plant life (H_2O, CO_2 → Photosynthesis): carbohydrates, fats, proteins, nucleic acids →primary activity of green plants

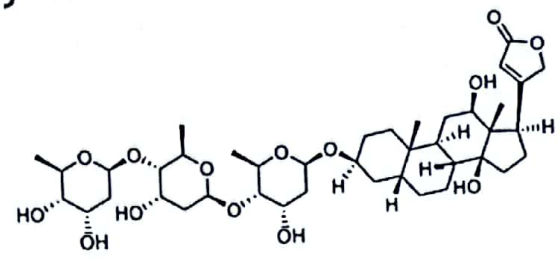
- **Secondary metabolites**: Not involved in the essential metabolism of the cell, but exert physiologic activity for the plant, its environment and human (phyto-hormons, plant-protection, plant-insect-, plant-animal interactions, source of drugs); produced through specific pathways with a limited distribution in nature; condition and species sensitive; most pharmacologically active natural products are 2ry metabolites

Relationship between primary and secondary metabolism:

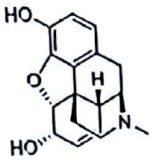
- The processes and products of primary metabolism are similar in most organisms, while those of secondary metabolism are more specific.

- In plants, primary metabolism is made up of photosynthesis, respiration, etc., using CO_2, H_2O, and NH_3 as starting materials, and forming products such as glucose, amino acids, nucleic acids. These are similar among different species.
- Secondary metabolites are low molecular weight compounds that are **not required for the growth of an organism**, but are produced for **adaptation** for its specific functions in nature and are considered a **phenotype** of the organism.
- They are derived **from primary metabolites** via secondary metabolic
  - Pathways
  - They are more important than primary metabolites as a **therapeutic agents.**

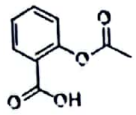
Secondary Metabolites



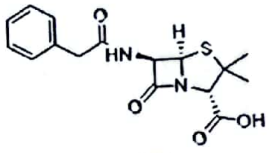
digoxin



morphine



aspirin



penicillin

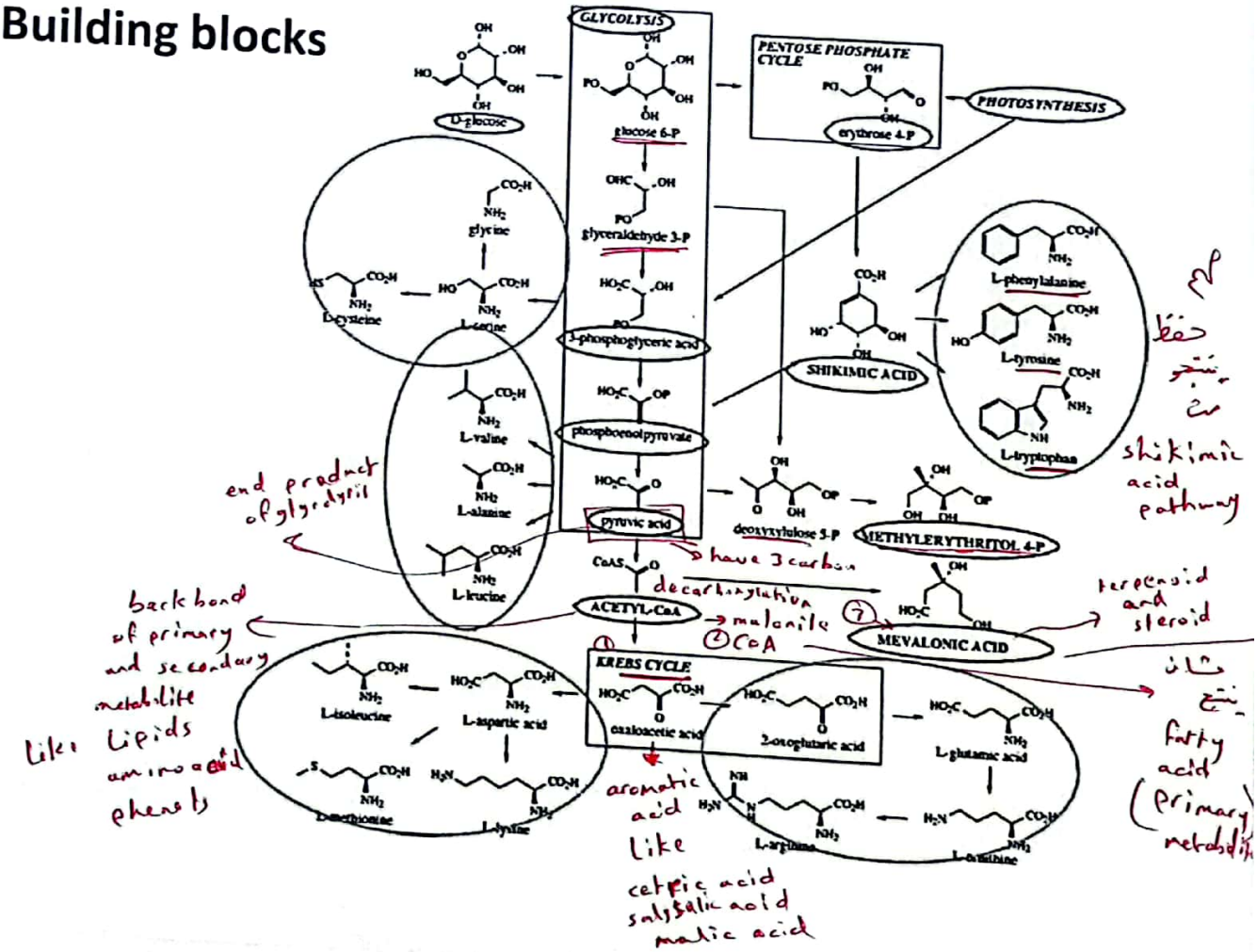
Secondary Metabolites

- Digoxin: cardiotonic, from foxglove (*Digitalis lanata*).
- Morphine: pain killer, from opium (*Papaver somniferum*). This is generally believed to be the first isolation of an active ingredient from a plant.
- Aspirin: painkiller and anti-infalmmatory, from willow (*Salix spp*).
- Penicillin: antibiotic, from (*Penicillium spp*).

Functions of Secondary Compounds

- The most common roles for secondary compounds in plants are ecological roles that govern interactions between plants and other organisms.
- Many secondary compounds are brightly colored pigments like anthocyanin that color flowers red and blue. These attract pollinators and fruit and seed dispersers.
- Nicotine and other toxic compounds may protect the plant from herbivores and microbes.
- Other secondary compounds like rubber and tetrahydrocannabinol (THC) from cannabis plants have no known function in plants.

Building blocks



GLYCOLYSIS

- Glycolysis: The final product is the pyruvuic acid (3 carbon) →Then the pyruvate has **2 options :**

- **A**→Further degradation to acetyl-CoA (2 carbon)
  → it is a backbone of many primary and secondary metabolites

- **B**→ Shicimic acid pathway:

  Pyruvic acid(phosphoenolpyruvate) combines with erythrose-4-P→ to form shikimic acid.

- * So to form shikimic acid we need:
  A-Calvin cycle
  B-Glycolysis

- Degradation of carbohydrates and sugars generally proceeds via the well characterized pathways, known as glycolysis and the kerbs / citric acid / tricarboxylic acid cycle, which release energy from the organic compounds by oxidative reactions.
- Oxidation of fatty acids from fats by the sequence called β-oxidation also provides energy

- **Acetyl-CoA can go to one of the following pathways:**
  1-Tricarboxylic acid cycle→ non aromatic plant acids(citric, succinic and malic acids)
- 2- To form primary metabolites as fatty acids depending on the enzymatic specificity:→ Acetyl- CoA + malonyl-CoA will start the formation of fatty acids
- 3- Can enter the secondary metabolites formation depending on enzyme availability by **two pathways**:

- *A*-**Mevalonic** acid pathway →terpenoids and steroids

- *B*-**Acetate-malonate pathway**→aromatic, monocyclic and polycyclic compounds(Anthraquinones,Prostaglandins, Fats,Marolide antibiotic(erythromycine), Tetracyclines

- * Krebs cycle= tricarboxylic acid cycle=citric acid cycle

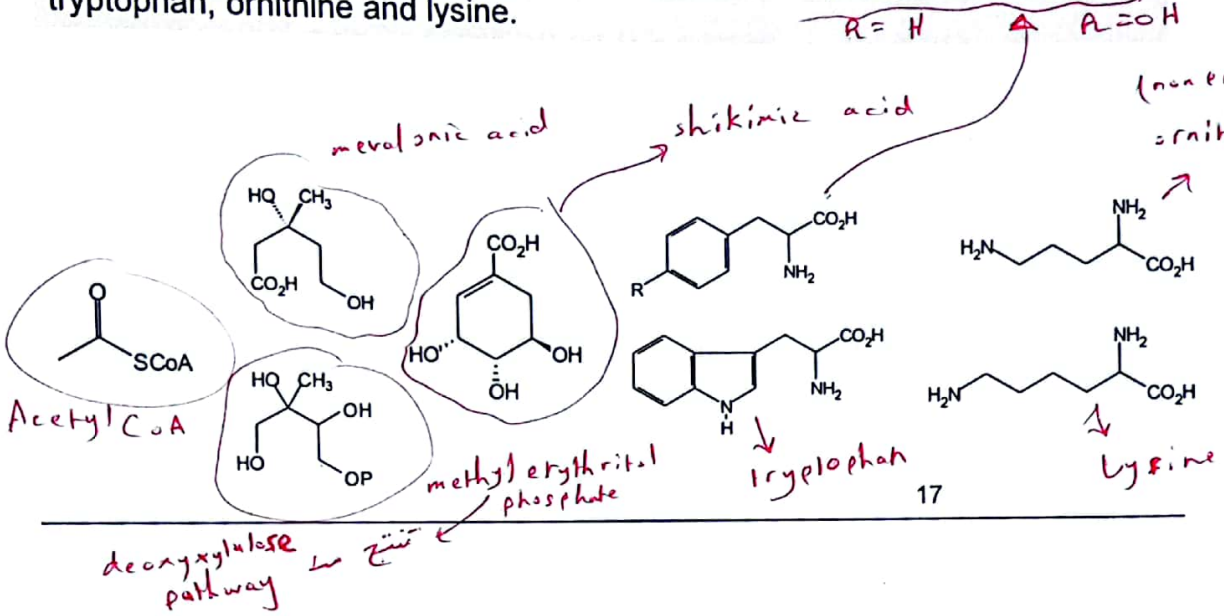
2 carbon

- # **AcetylCoA** is **formed by**
- 1→Oxidative decarboxylation of the **glycolytic** pathway product **pyruvic acid**. 3 carbon
- 2→It is **also** *produced* by →the β-oxidation of fatty acids, effectively reversing the process by which fatty acids are themselves synthesized from acetyl-CoA .

- ♦ **Mevalonic acid→mevalonate(Mevalonat- acetate)→**
- 1-Isoprene(Terpenoides)
- 2- Isoprene→ Squalene→steroids
- 6 carbon **Mevalonic acid** is itself formed →from **three** molecules of acetyl-CoA, but the mevalonate pathway channels acetate into a different series of compounds
- than does the acetate pathway.
- ♠ **Deoxyxylulose phosphate pathway:** → pathway عن طريق هذا ال terpenoid ينتج
- →arises from a combination of **two** glycolytic pathway intermediates, namely →pyruvic acid **and** →glyceraldehyde 3-phosphate.
- ♦**Shikimic acid** → shikimate pathway→ 1- Aromatic amino acids , 2- phenols, 3- Alkaloids, 4- lignans, 5- peptides and 6-antibiotics(penicillins)
- **Shikimic acid** is produced from a combination of →**phosphoenolpyruvate**,a glycolytic pathwayintermediate,**and** →**erythrose 4-phosphate** from the pentose phosphate.
- pathway (see figure of the building blocks).

Secondary metabolism: refers to the biosynthesis, utilization and breakdown of smaller organic compounds found in the cell. These compounds, called ***secondary metabolites***, arise from a set of intermediate building blocks : acetyl coenzyme A (acetyl-CoA), mevalonic acid (MVA) and methyl erythritol phosphate (MEP), shikimic acid, and the amino acids phenylalanine/tyrosine, tryptophan, ornithine and lysine.

because doesn't appear as a part from amino acid or protein



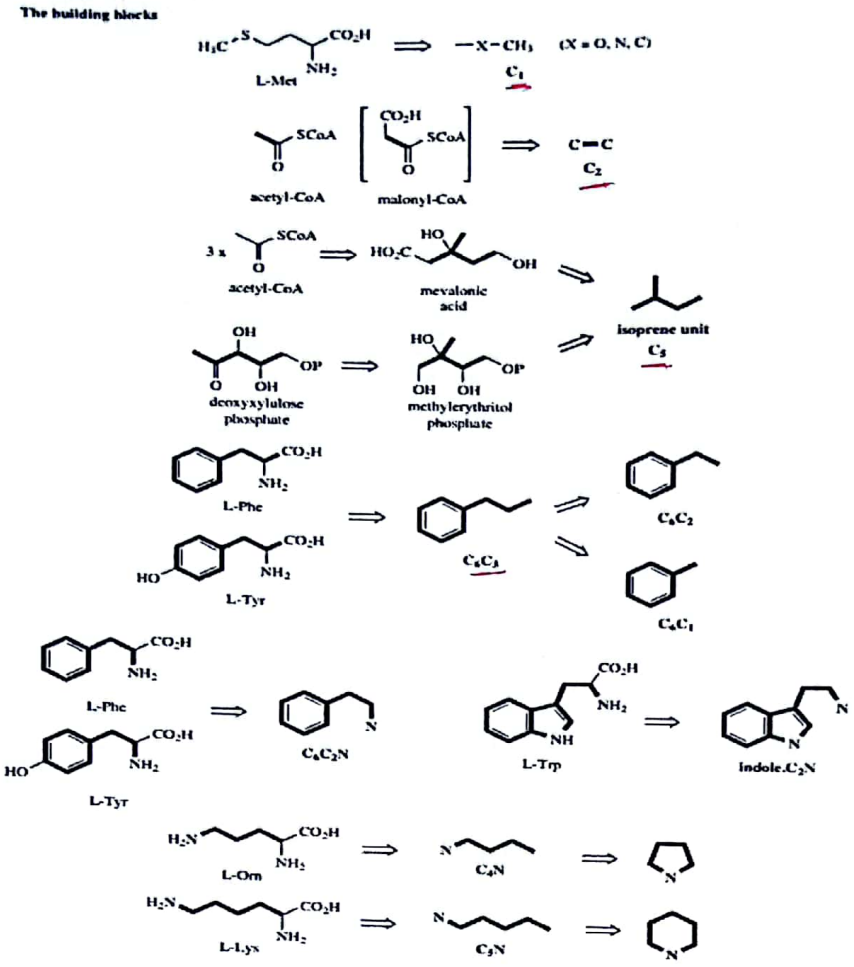
Constructing of natural products

* In addition to acetyl CoA ,shikimic acid, mevalonic acid and deoxyxylulose phosphate, **other** building blocks based on **amino acids** are frequently employed in **natural** products.

- **1**-Peptides, proteins, alkaloids, and many antibiotics are **derived**→ from **amino acids**, and the **origins** of the most important amino acid components of these are briefly indicated in.
- Figure
- **2**-Intermediates from the **glycolytic** pathway and the **Krebs cycle** are used in constructing many of them.
- **3**- Shikimate pathway → aromatic amino acids (phenyl alanine/ tyrosine /tryptophan) →**phenylalanine, tyrosine,** and **tryptophan**.
- **4**- Krebs cycle intermediates →**Ornithine,** a non-proteinamino acid, along with its homologue **lysine,** → are important **alkaloid** precursors.

because does not appear as any part of protein

from amino acid



C1:

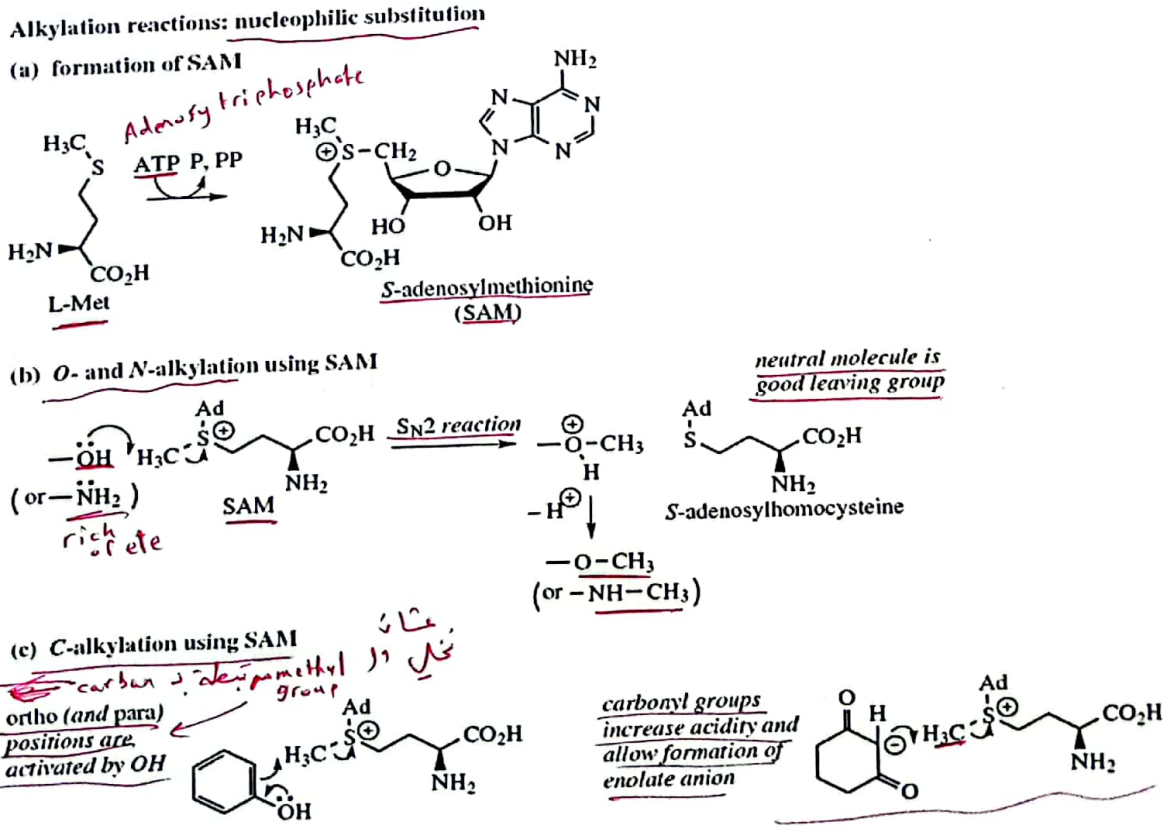
- ♣ The C1 methyl building unit is supplied from Lmethionine and is introduced by → a **nucleophilic** substitution reaction.

- →In nature, the leaving group is enhanced by converting L-methionine into ***S*-adenosylmethionine (SAM)**

→ C1: comment→ Formation of SAM

- 1- This gives a positively charged sulphur and facilitates
- → the nucleophilic substitution (SN2) type mechanism
- 2-Thus, *O*-methyl and *N*-methyl linkages **may** be obtained
- → using hydroxyl and amino functions as **nucleophiles**.
- 3- The methylenedioxy group (OCH2O)

C1:

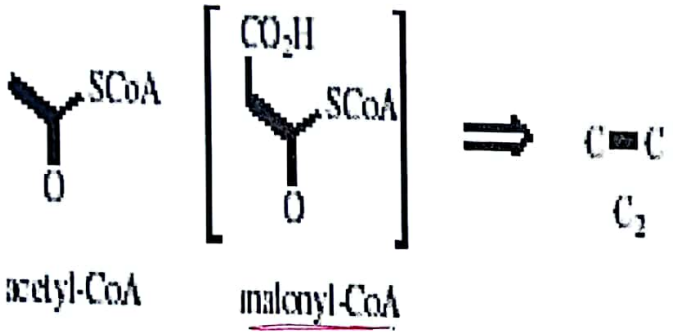


C2:

aromatic phenol or long fatty acid chain ← cleavage in C2 of acetate pathway

1- A two-carbon unit may be supplied by acetyl-CoA.
2- It forms part of a long alkyl chain (as in a fatty acid) or may be part of an aromatic system (e.g.phenols).
3- Of particular relevance is that in the latter examples, acetyl-CoA is first converted into the more reactive malonyl-CoA before its incorporation.

two carbon



acetyl-CoA malonyl-CoA

reactive form

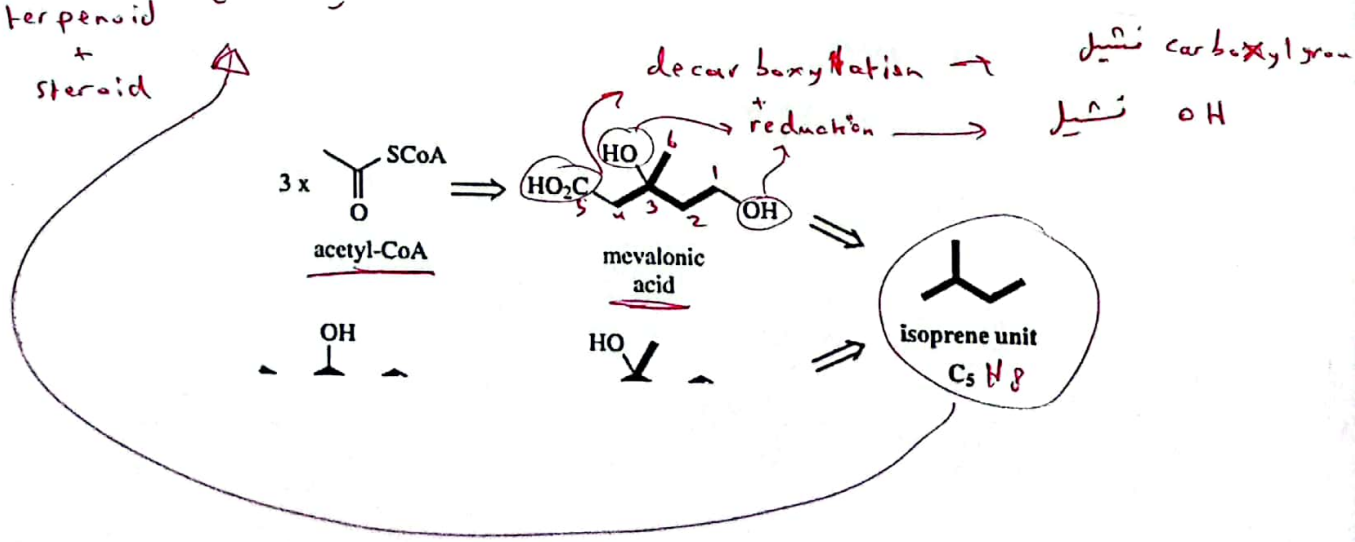
2 ← mono 10 C
3 unit of isoprene ← sesqeet 15 C
4 ← di 20 C
5 ← ses 25 C
tri 30 C

C_5H_8

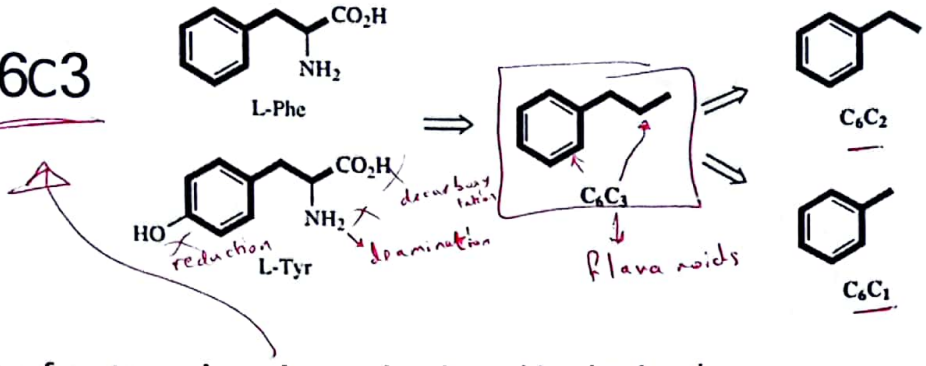
C5:

1-The branched-chain C5 'isoprene' unit is a feature of compounds formed→from mevalonate.
-Mevalonate itself is the product from three acetyl-CoA molecules, but only five of mevalonate's six carbons are used, the carboxyl group being lost.

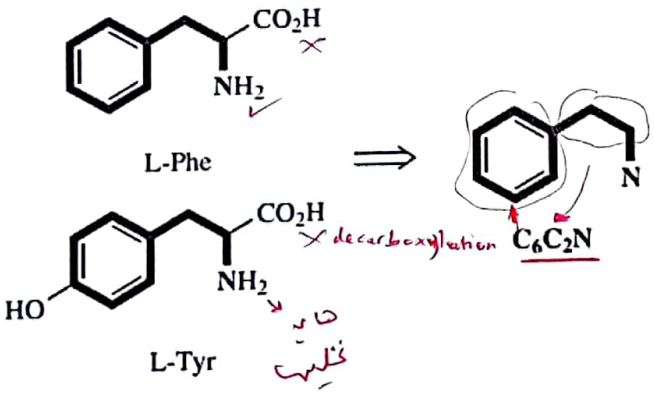
terpenoid + steroid



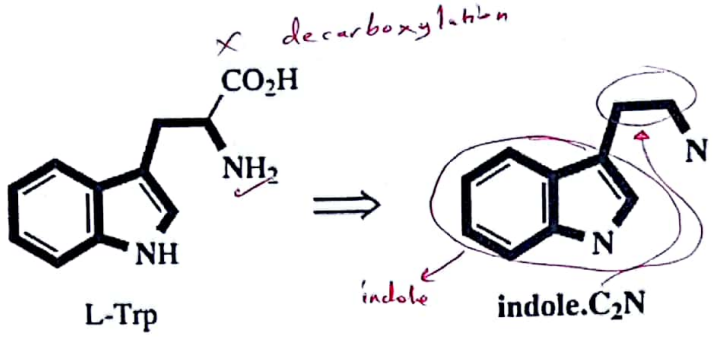
C6C3



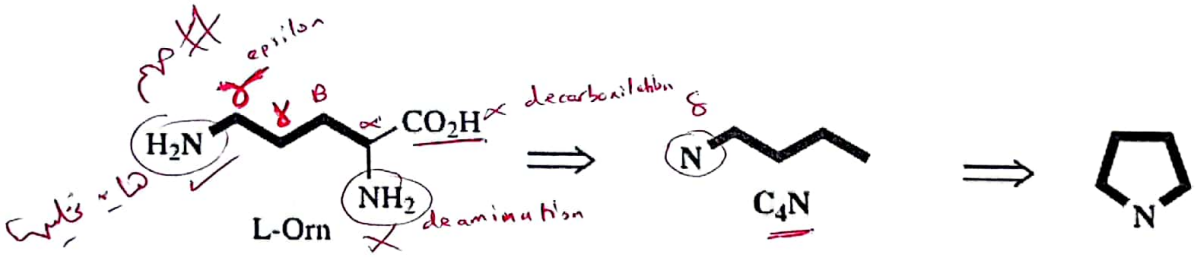
- 1-This refers to a **phenylpropyl** unit and is obtained
- →from the carbon skeleton of **either** L-**phenylalanine** or L-**tyrosine**, →two of the **shikim**ate-derived **arom**atic amino acids.
- 2-This,of course, requires loss of the amino group.
- 3-The C3 side-chain **may** be saturated or unsaturated, and may be oxygenated.
- 4- Sometimes the **side** chain is cleaved, removing **one** or **two** carbons.
- →Thus, **C6C2** and **C6C1** units **represent**
- →modified **shorten**ed **forms** of the **C6C3 system**.



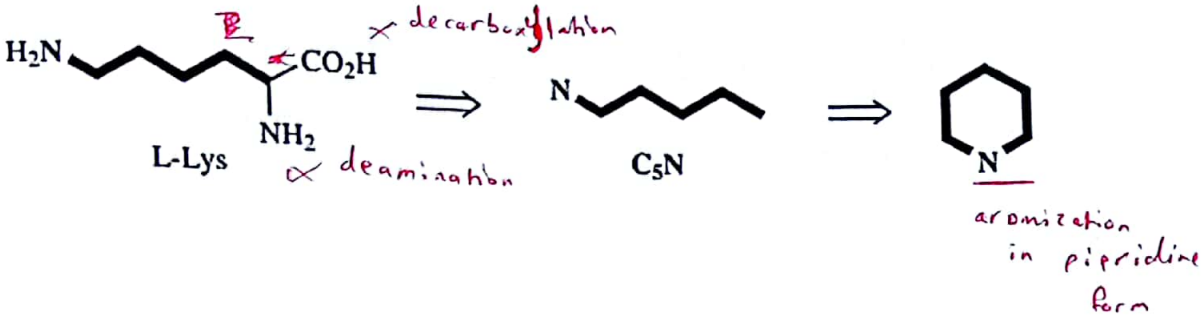
- **C6C2N:**
- 1-This building block is formed
  → from **either** L-**phenylalanine** or L-**tyrosine**,
  →Ltyrosine being by far the more common.
- 2-In the elaboration of this unit, the carboxyl carbon of the amino **acid** is **remove**d.



- **(Indole.C2N):**
- **1-It is formed** →from the aromatic amino acid L-**tryptophan**(Shik. acid p.w)
- **2**-This **indole**-containing system can undergo **decarboxyl**ation in a similar way to L- phenylalanine and L-tyrosine so **providing → the remainder** of the skeleton →as an indole.C2N unit.

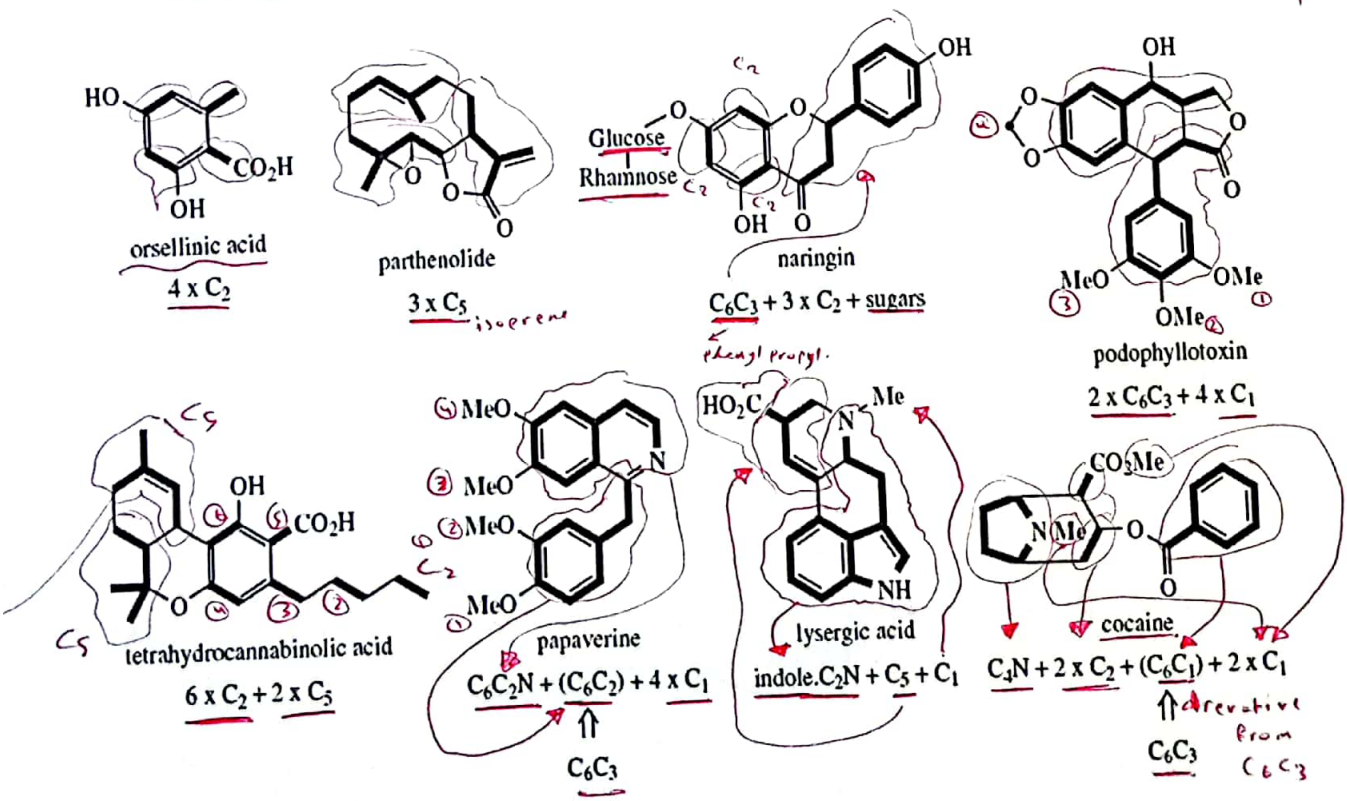


- **C4N:**
- **1**-The C4N unit is usually found →as a heteroceylic **pyrrolidine** system.
- **2**-It is produced from → the non-protein amino acid L-**ornithine**. (from Krebs cycle)
- **3**-In marked **contrast** to the C6C2N and indole.C2N units described above:
- →**ornithine** supplies **not** its α-amino nitrogen, **but** the δ-**amino** nitrogen.
- **4**-The carboxylic acid function and the α-amino nitrogen →are **both** lost.



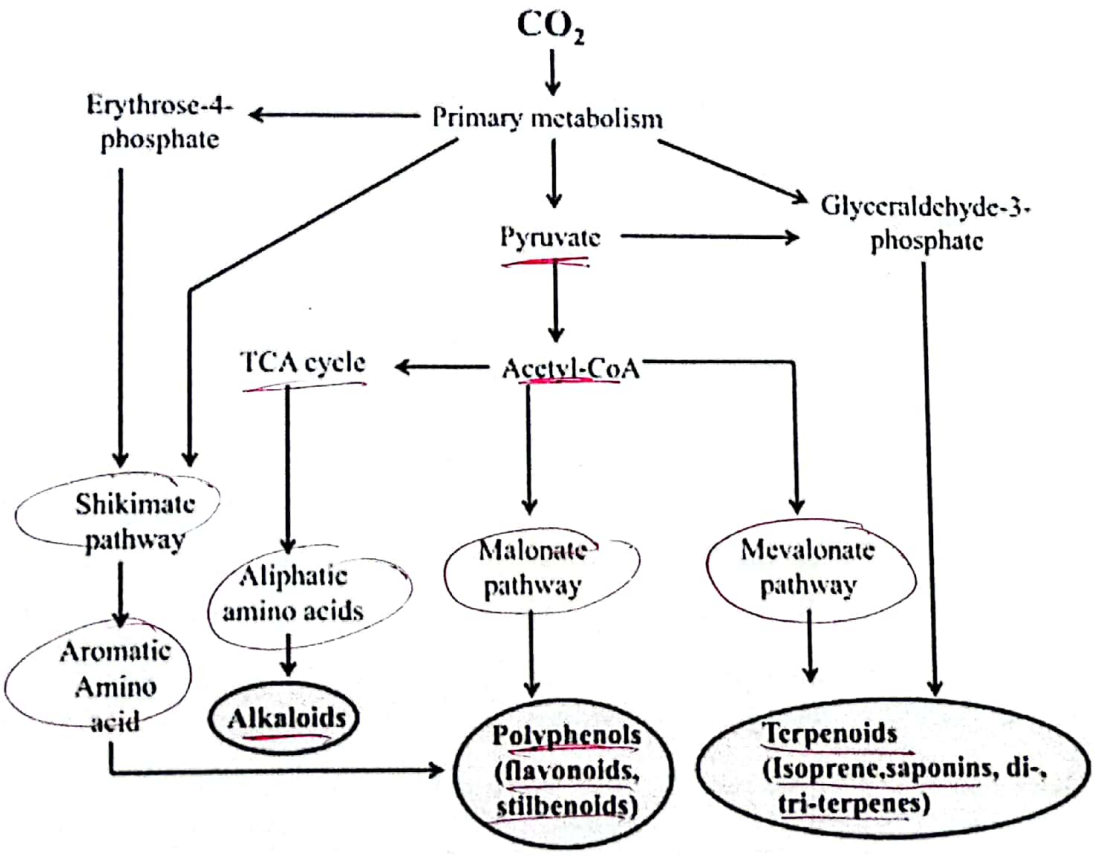
- **C5N:**
- 1-This is produced in **exact**ly the **same** way
- →as the C4N unit
- (piperidine)
- →**but** using L-**lysine** as **precu**rsor.

Examples of how compounds can be visualized as a combination of building blocks



The different secondary metabolites are biosynthesized using 3 different pathways.

- 1) Acetate – Malonate Pathway 2) Acetate – Mevalonate Pathway : **(terpenoids and steroids)**
- 3) Shikimic acid pathway (**aromatic amino acids and phenylpropanoids)**
- Each of them is responsible for the production of certain classes of secondary metabolites.



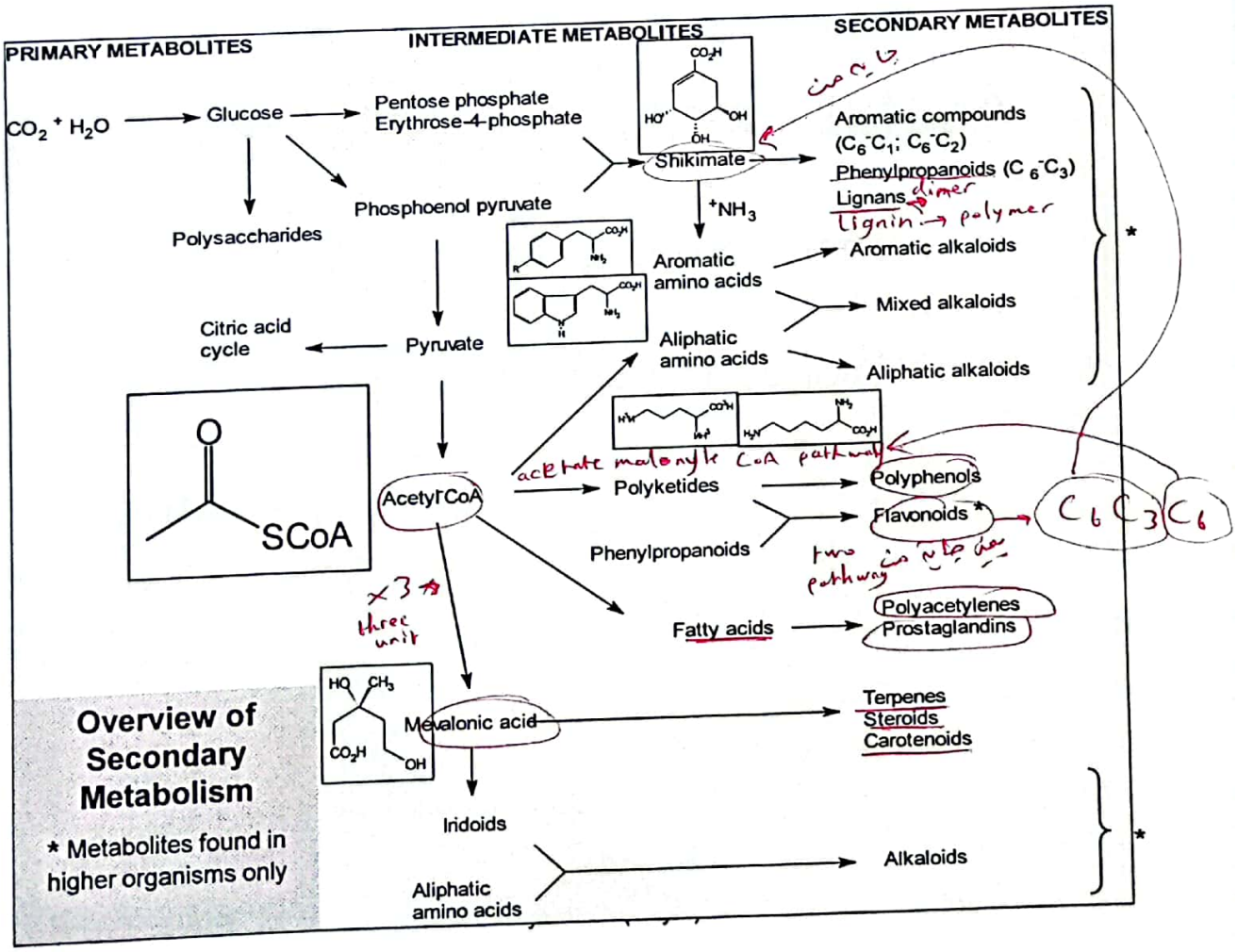
Important secondary metabolites formed from the acetate pathway include **phenols, prostaglandins, and macrolide antibiotics**, together with various **fatty acids** and derivatives at the primary/secondary metabolism interface.

Shikimic acid is produced from a combination of phosphoenolpyruvate, a glycolytic pathway intermediate, and erythrose 4-phosphate from the pentose phosphate pathway.

The shikimate pathway leads to a variety of **phenols, cinnamic acid derivatives, lignans, and alkaloids.**

Mevalonic acid is itself formed from three molecules of acetyl-CoA, but the mevalonate pathway channels acetate into a different series of compounds than does the acetate pathway.

Deoxyxylulose phosphate arises from a combination of two glycolytic pathway intermediates, namely pyruvic acid and glyceraldehyde 3-phosphate.



Plant Secondary Metabolites

- Secondary compounds are grouped into classes based on similar structures, biosynthetic pathways, or the kinds of plants that make them. The largest such classes are the alkaloids, terpenoids, and phenolics.

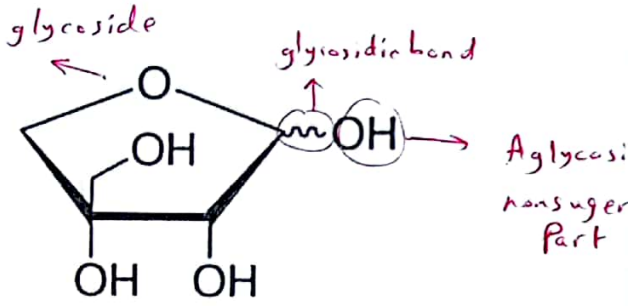
- Secondary compounds often occur in combination with one or more sugars. These combination molecules are known as glycosides. Usually the sugar is a glucose, galactose or rhamnose. But some plants have unique sugars. Apiose sugar is unique to parsley and its close relatives.

coriander البقدونس ، الكزبرة

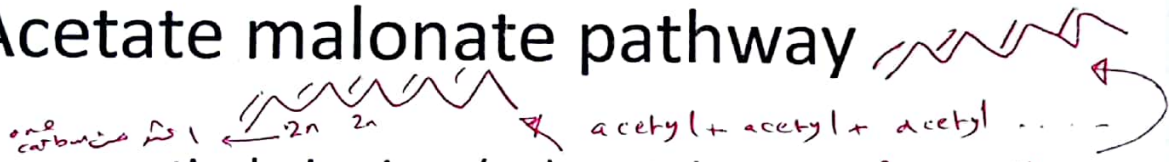
sugar بسكر ال link ال

compound ال

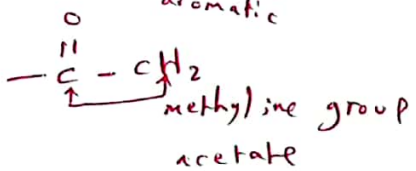
glycosidic linkage or bond



Acetate malonate pathway



- A-Non-aroamtic derivatives (polyacetylenes, polyynes) → = = = (double bond)
- B-Aromatic polyacetates (polyketides)



Acetate-derived Natural Products

Acetate formed from carbohydrate via pyruvic acid

Produce large no. of imp. natural products (flavonoids, anthraquinones, macrolides, terpenes & steroids)

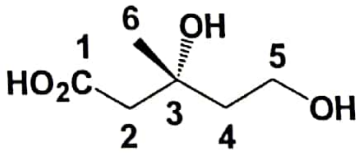
2 main routes originate with acetate pathway:

1. Acylpolymalonate pathway leading to FA & polyketides
2. Mevalonic acid pathway producing terpenes & steroids

Acetate mevalonate pathway

- Isoprenoid compounds
- Terpenes (mono-, sesqui-, di-, tri-, tetra-, poly-terpenes)
- Cardiac glycosides
- Saponin glycosides
- Steroids
- Vitamin D

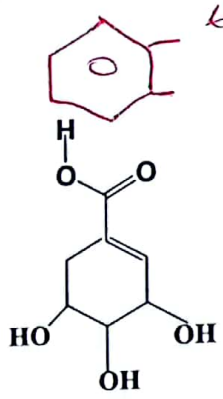
3 x Acetyl CoA



Mevalonic acid (MVA)

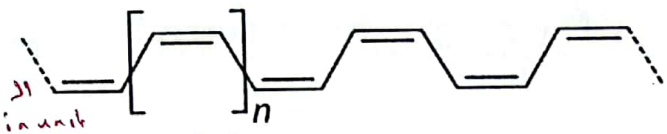
Shikimic acid pathway

- **Shikimic acid** is a very important building block of **phenolic** substances, because it contains a ring and it's also important for the formation of three important amino acids:
  Phenylalanine, Tyrosine and Tryptophan.
- Aromatic biosynthesis:
- Phenols
- Phenolic glycosides
- Phenyl-propane-derivatives
- Lignins
- Lignans
- Aromatic amino acids

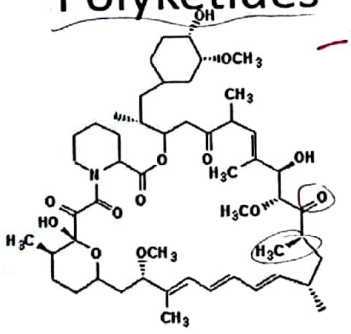


Shikimic Acid

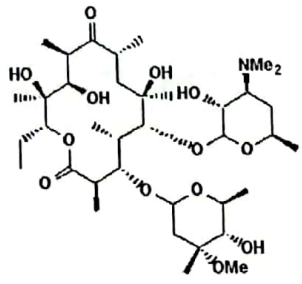
- Polyacetylene



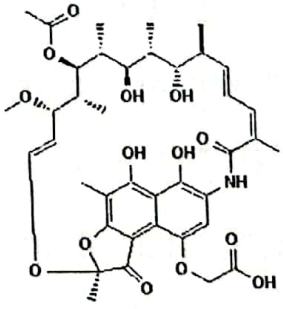
- Polyketides



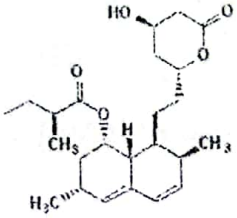
rapamycin
(immunosuppressant)



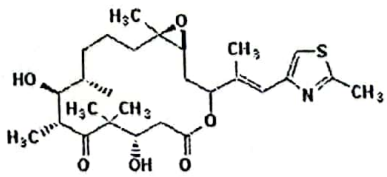
erythromycin A
(antibacterial)



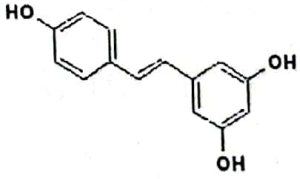
rifamycin B
(antituberculosis)



lovastatin
(anticholesterol)



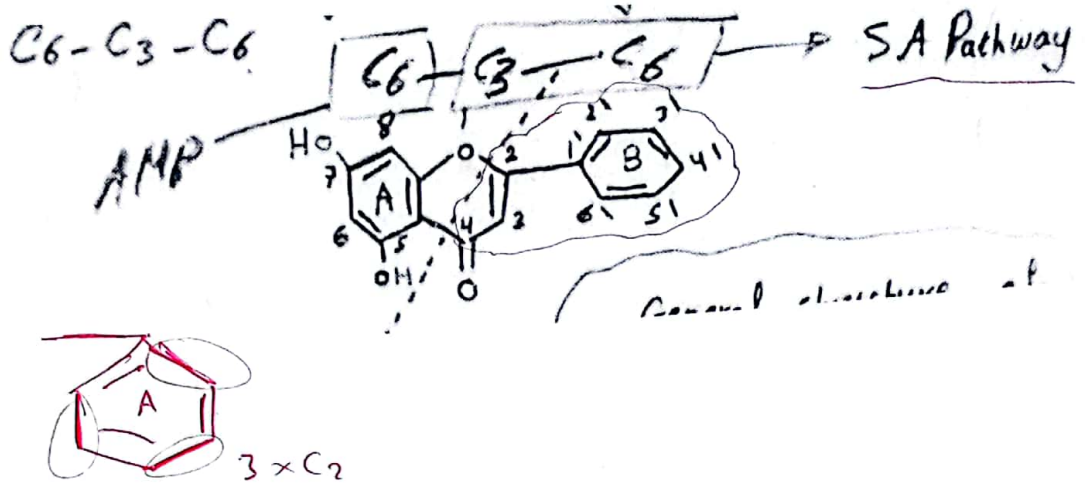
epothilone B
(anticancer)



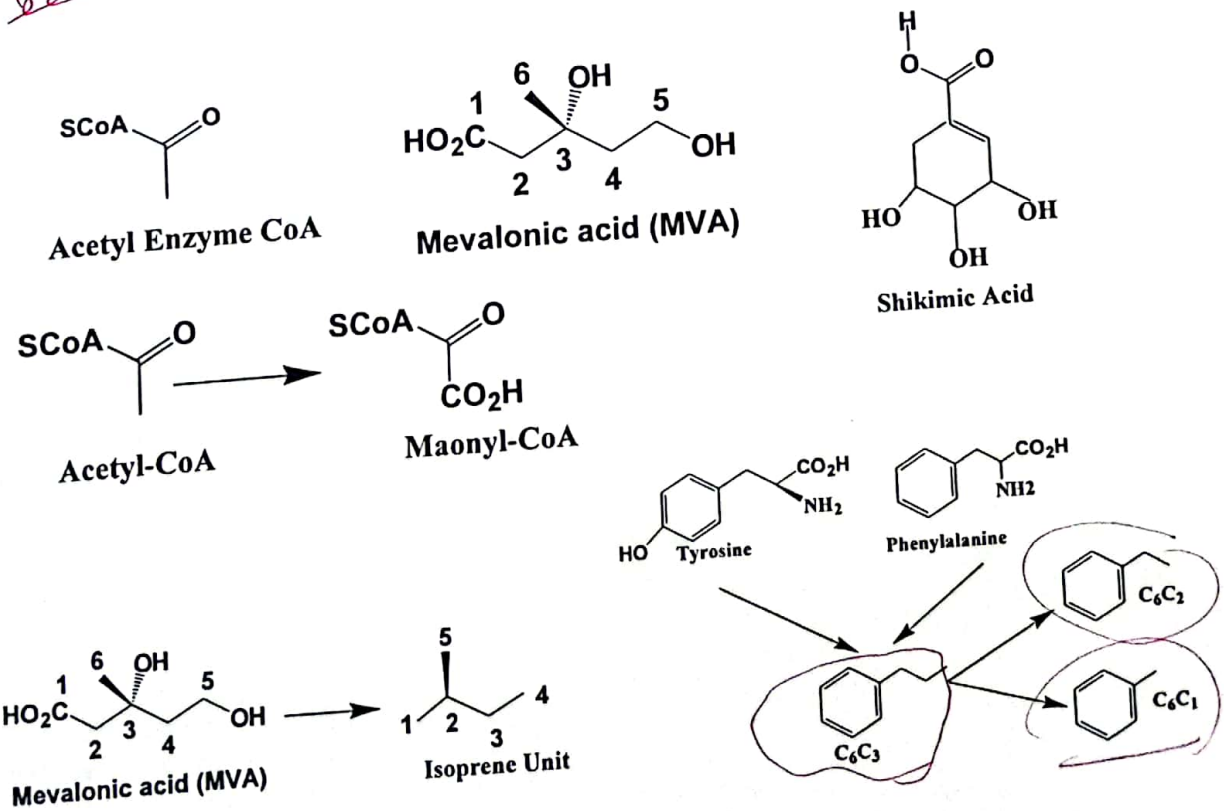
(E)-resveratrol
(chemopreventive)

Flavanoids from acetate malonate (C6)+ shikimic acid(C6C3)

**hint:in the record, the above sentences appear as " Flavanoids from mevalonic acid(C6)+ shikimic acid(C6C3)" and this is wrong sentence. The above is correct



Most important building blocks



"Amino acid" pathway

Includes all biogenetic drugs containing "N".:

-Alkaloids

-Cyanogenic glycosides

-Glucosinolates

-Alliines

-Antibiotics from amino acid metabolism

-Anticancer drugs from amino acid metabolism

29:10