Introduction to phytochemical pathways

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إعداد الطالبة : آلاء العتوم

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.

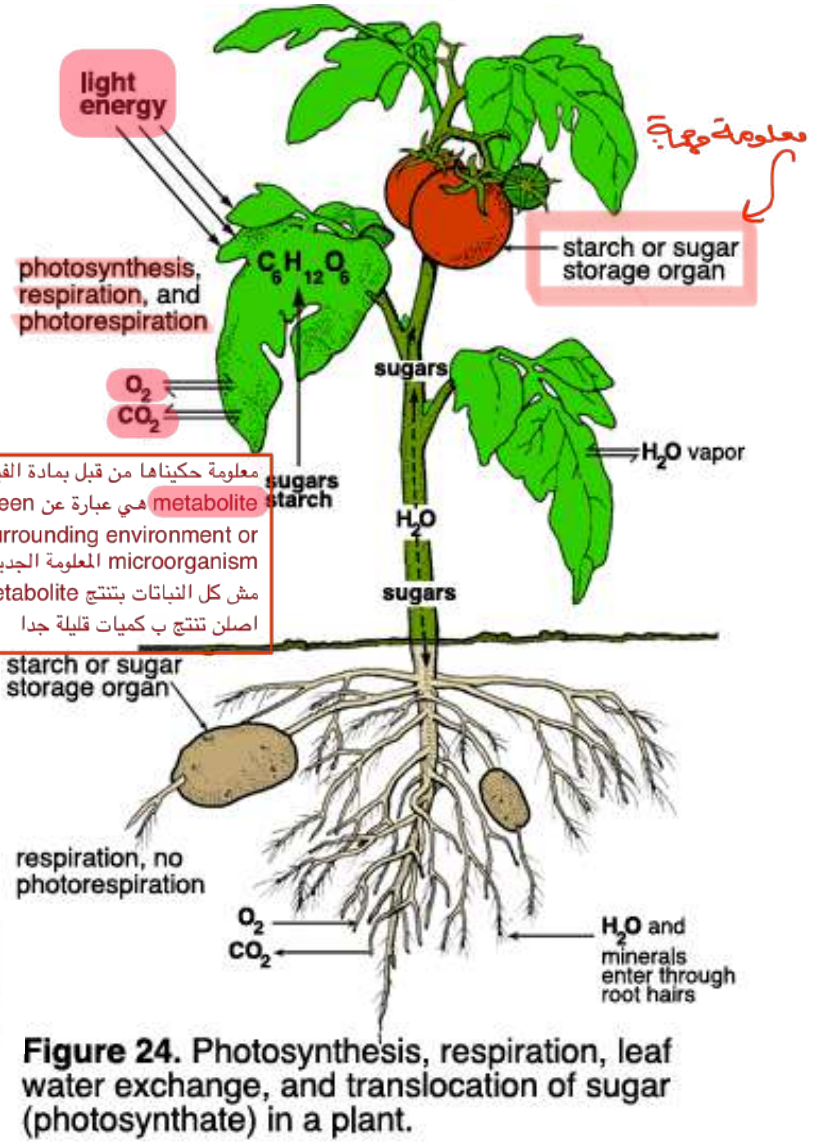
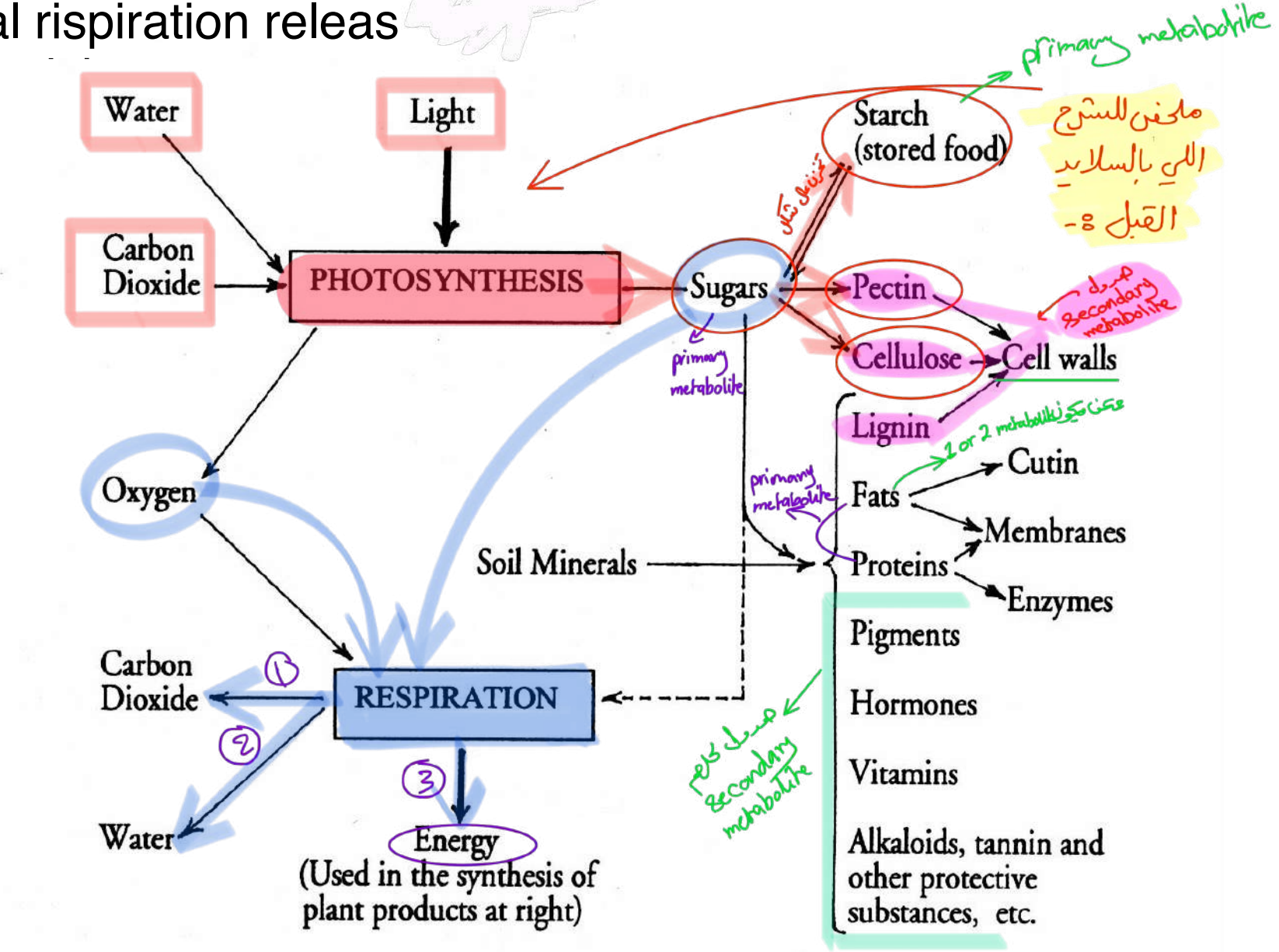


Figure 24. Photosynthesis, respiration, leaf water exchange, and translocation of sugar (photosynthate) in a plant.

$$6CO_2 + 6H_2O \xrightarrow{Light} C_6H_{12}O_6 + 6O_2$$

Carbon dioxide + Water → Sugar + starch + Oxygen

In serial rispiration releas



An outline of plant metabolism

يعني جميع النباتات بتنتج primary metabolite

حوني أنا عم بحكي عن الـ primary metabolite

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

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

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.

من أهم الأمثلة على الـ "primary metabolite"

Primary Metabolites

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

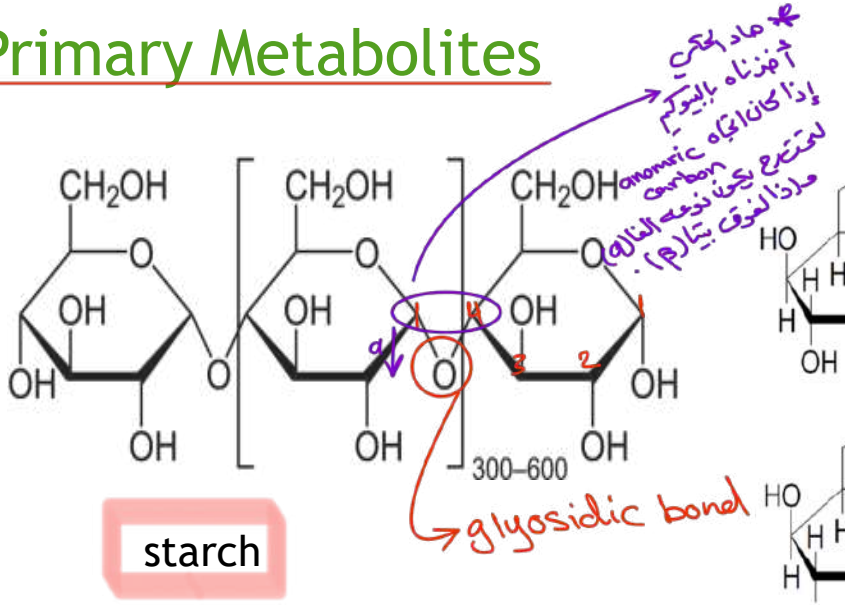
- The main primary metabolites are **carbohydrates, proteins, nucleic acids**, and **lipids**.
- They are occurring in all plants (in all green plants).

Apart from fats, these are polymeric materials.

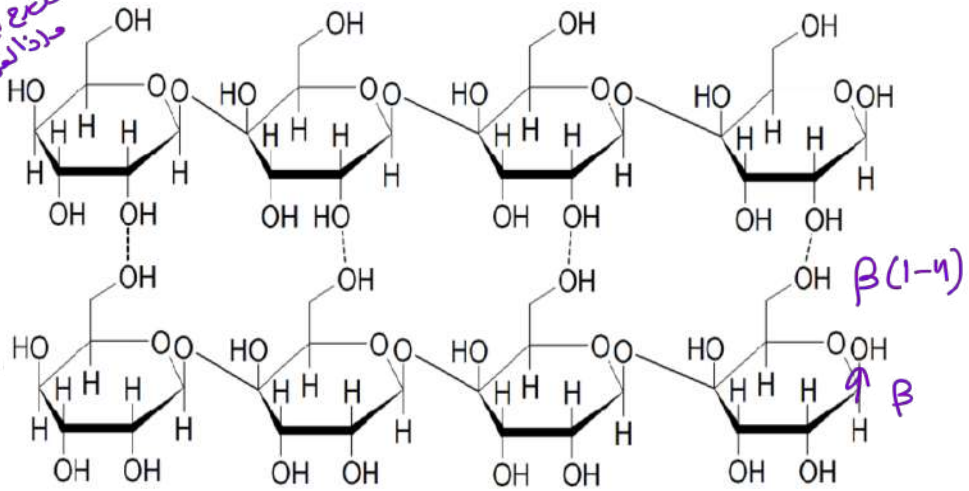
- * Carbohydrates(CHO): are composed of sugar units.
- * Proteins : are made up from amino acids
- * Nucleic acids:are based on nucleotides.

كل primary metabolite الـ جايين من polymeric materials ما عدا الـ "fat".

Primary Metabolites

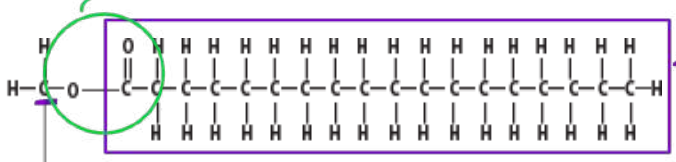


starch



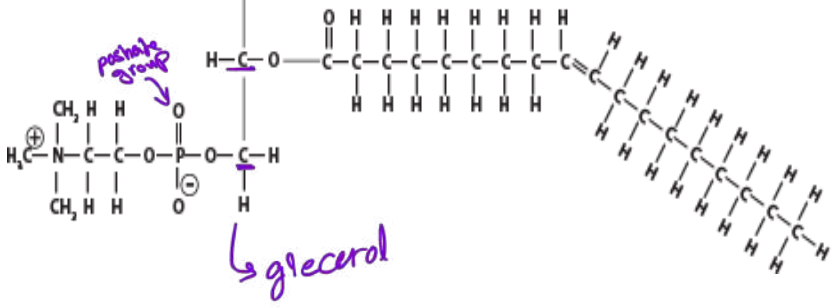
cellulose

secondary metabolite



phospholipid

in membrane



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

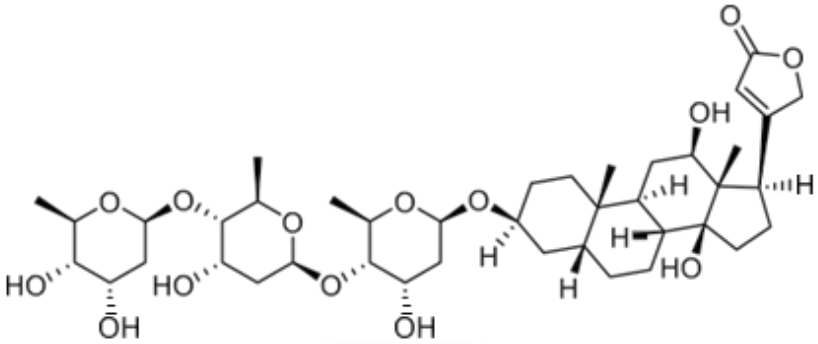
- **Secondary metabolites**: Not involved in the essential metabolism of the cell, but exert physiologic activity for the plant, its environment and human (phyto-hormons, plant-protection, plant-insect-, plant-animal interactions, source of drugs); produced through specific pathways with a limited distribution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

Relationship between primary and secondary metabolism:

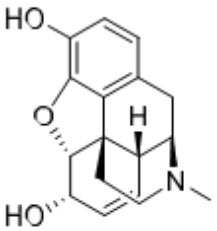
- The processes and products of primary metabolism are similar in most organisms, while those of secondary metabolism are more specific.

- 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.**

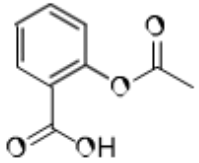
Secondary Metabolites



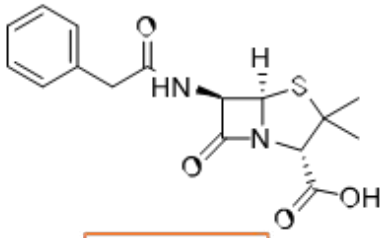
digoxin



morphine



aspirin



penicillin

Secondary Metabolites

معلومات أخذناها بمادة الفيرست

- 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.

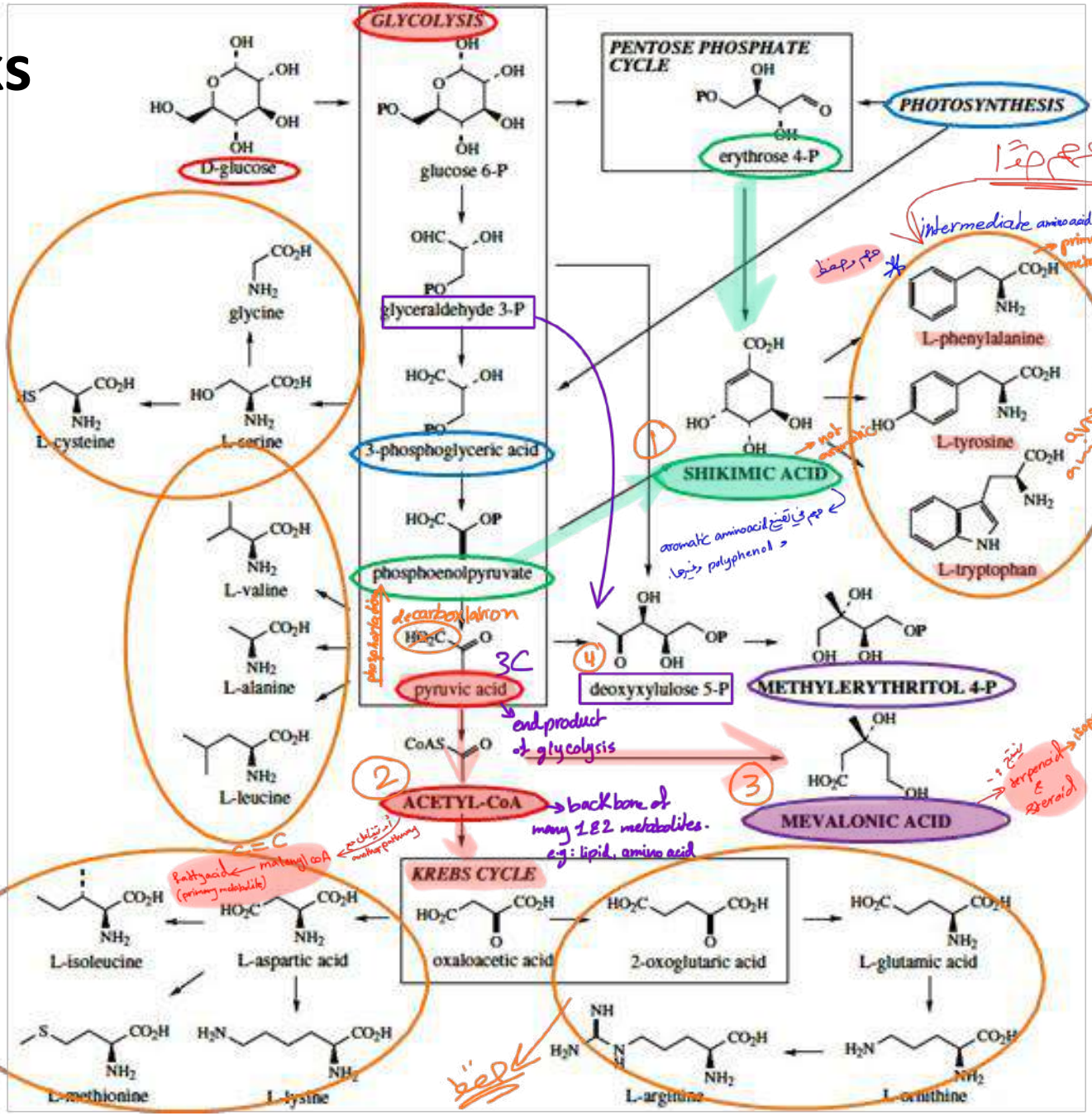
- Nicotine and other toxic compounds may protect the plant from herbivores and microbes.

مواد أكلة الأعشاب "حيوانات عاشبة"

- Other secondary compounds like rubber and tetrahydrocannabinol (THC) from cannabis plants have no known function in plants.

يستخدموها الناس للي عندهم Vomiting وبرضه تستخدم increase appetite

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:

  glycolysis →

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

  from krib-cycle

- * 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*- **Acet**ate-**malon**ate pathway→ aromatic, monocyclic and polycyclic compounds(Anthraquinones,Prostaglandins, Fats,Marolide antibiotic(erythromycine), Tetracyclines

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

- # **AcetylCoA** is **formed by**

هذه السلايد بشرح ال pathways بالعكس .

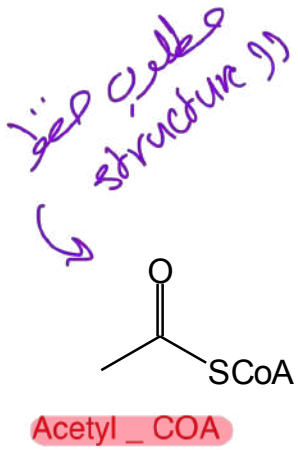
- 1→Oxidative decarboxylation of the **glycolytic** pathway product **pyruvic acid**.
- 2 →It is **also** *produced* by →the β-oxidation of fatty acids, effectively reversing the process by which fatty acids are themselves synthesized from acetyl-CoA .

- ♦ **Mevalonic acid→mevalonate(Mevalonat- acetate)→**
- 1-Isoprene(Terpenoides)
- 2- Isoprene→ Squalene→steroids
- **Mevalonic acid** is itself formed →from **three** molecules of acetyl-CoA, but the mevalonate pathway channels acetate into a different series of compounds

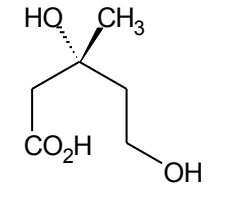
6C

- than does the acetate pathway.
- ♠ **Deoxyxylulose phosphate pathway:**
- →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).

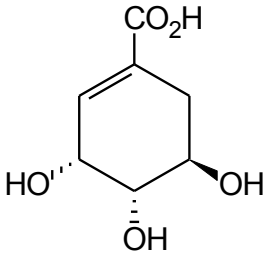
Secondary metabolism: refers to the biosynthesis, utilization and breakdown of smaller organic compounds found in the cell. These compounds, called ***secondary metabolites***, arise from a set of intermediate building blocks : acetyl coenzyme A (acetyl-CoA), mevalonic acid (MVA) and methyl erythritol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



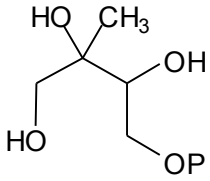
Acetyl _ COA



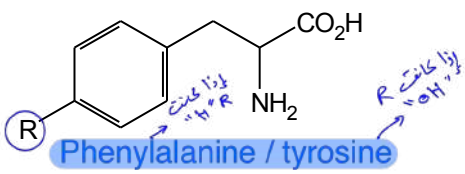
Mevalonic acid



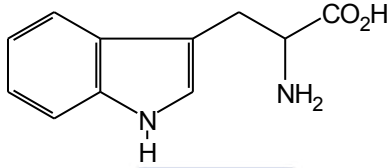
Shikimic acid



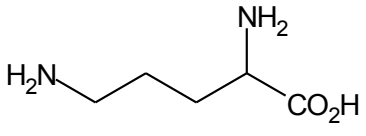
Methyl erythritol phosphate



Phenylalanine / tyrosine

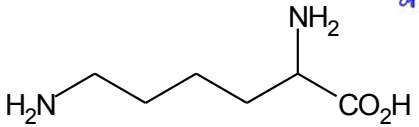


Tryptophan



Ornithine

dose not appear apart of protein



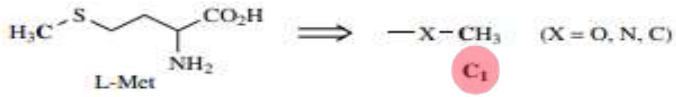
Lysine

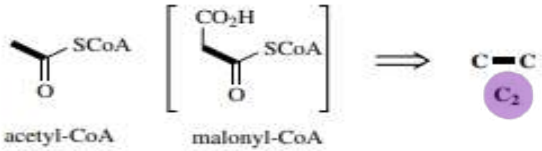
Constructing of natural products

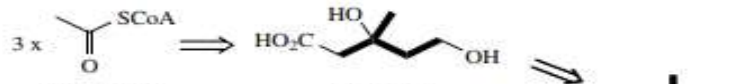
* In addition to acetyl CoA ,shikimic acid, mevalonic acid and deoxyxylulose phosphate, **othe**r building blocks based on **amino acids** are frequently employed in **natura**l products.

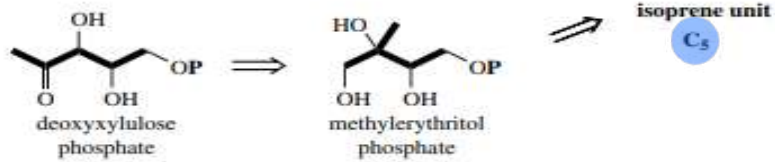
- **1-**Peptides, proteins, alkaloids, and many antibiotics are **derived**→ from **amino acids**, and the **origins** of the most important amino acid components of these are briefly indicated in.
- Figure
- **2** -Intermediates from the **glycolytic** pathway and the **Krebs cycle** are used in constructing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

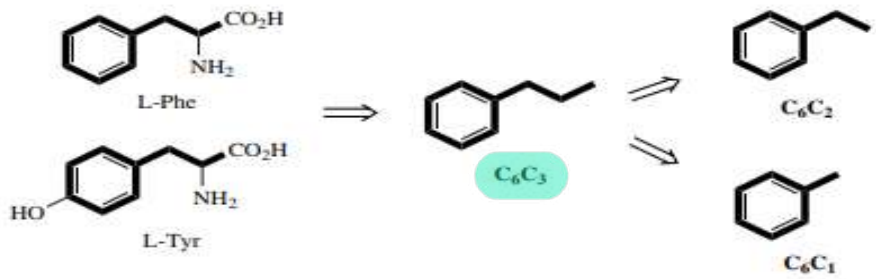
The building blocks

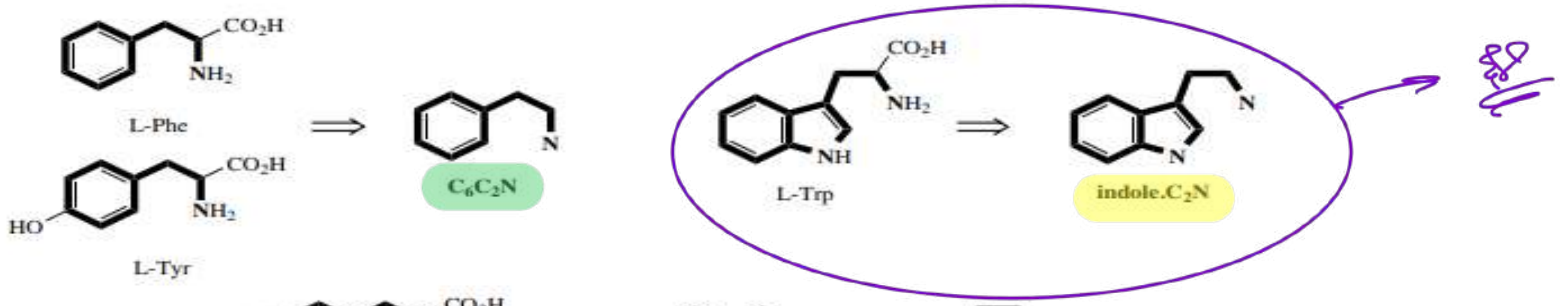


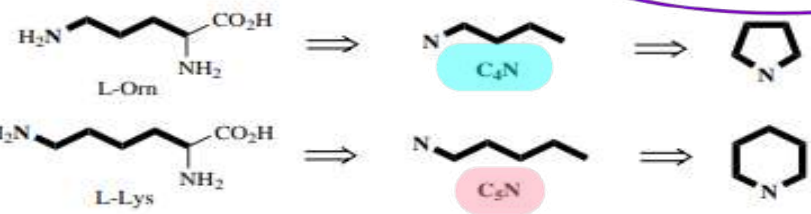












C1:

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

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

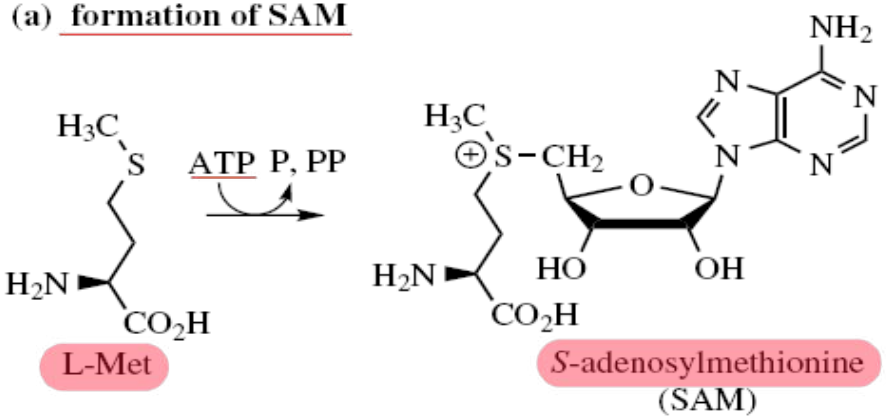
→ C1: comment→ Formation of SAM

- 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 **nucleop**hiles.
- 3- The methylenedioxy group (OCH2O)

C1:

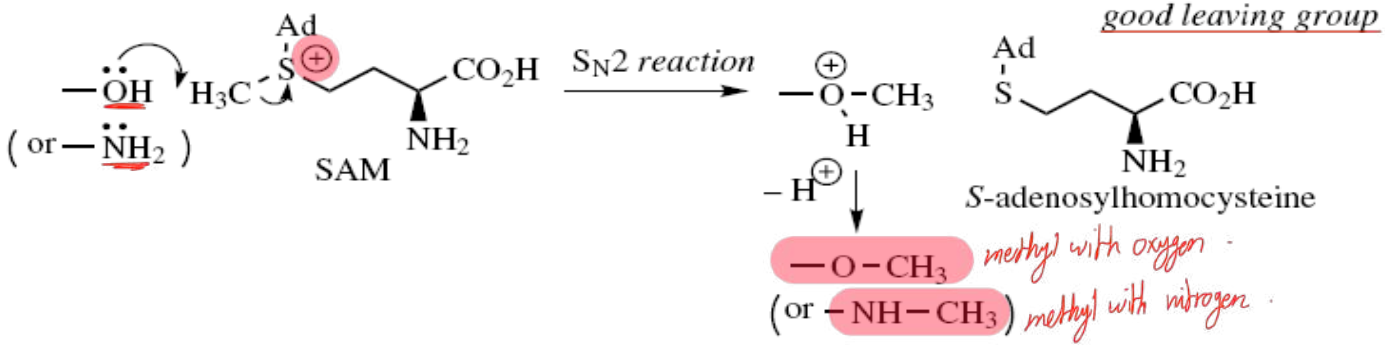
Alkylation reactions: nucleophilic substitution

(a) formation of SAM



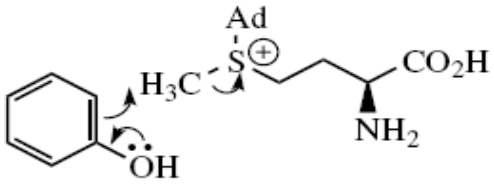
(b) *O*- and *N*-alkylation using SAM

neutral molecule is good leaving group

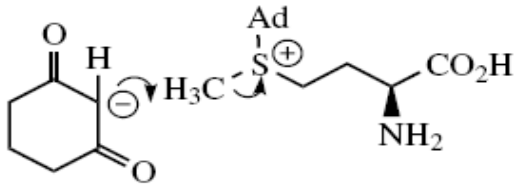


(c) *C*-alkylation using SAM

ortho *(and* para*)* *positions are activated by OH*

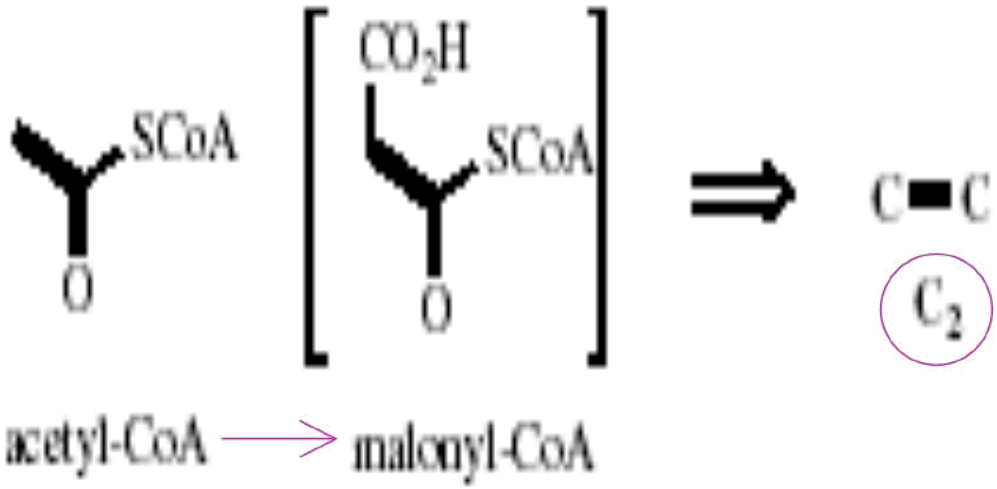


carbonyl groups increase acidity and allow formation of enolate anion



C2 :

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.



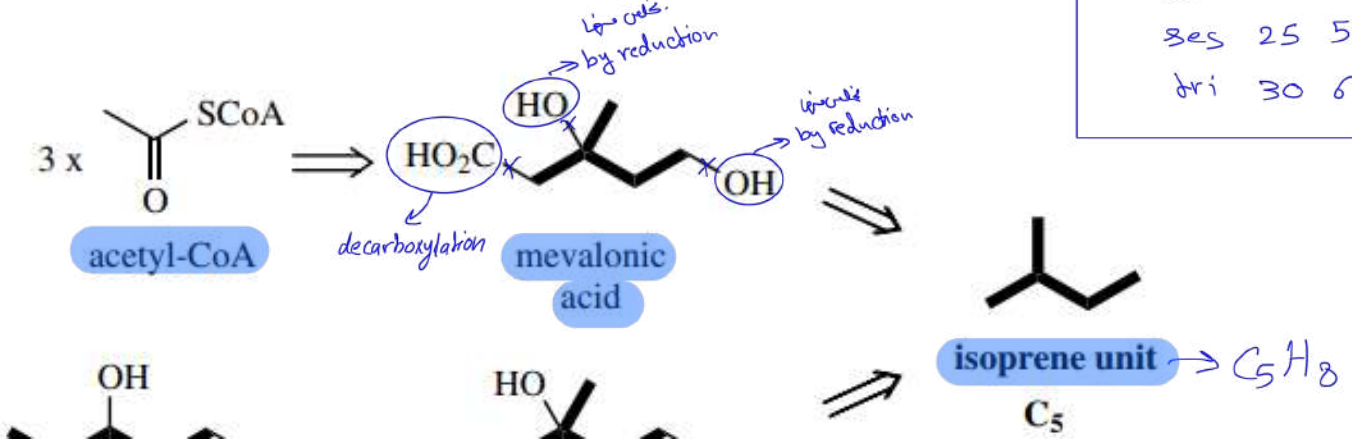
C5:

C_5H_8

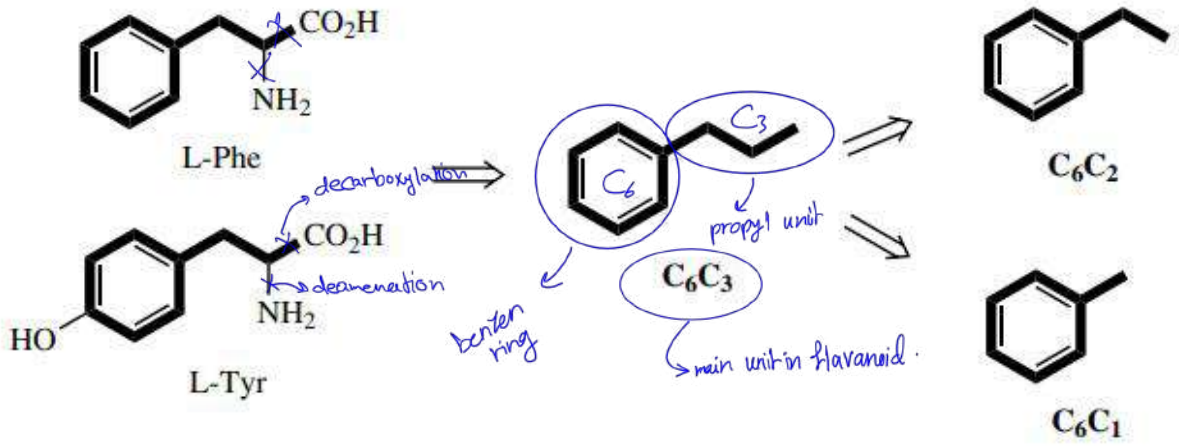
1-The branched-chain C5 '**isoprene**' unit is a feature of compounds formed→from **mevalonate.**

-**Mevalona**te itself is the product from **three** acetyl-CoA molecules, but only five of mevalonate's six carbons are used, the carboxyl group being lost.

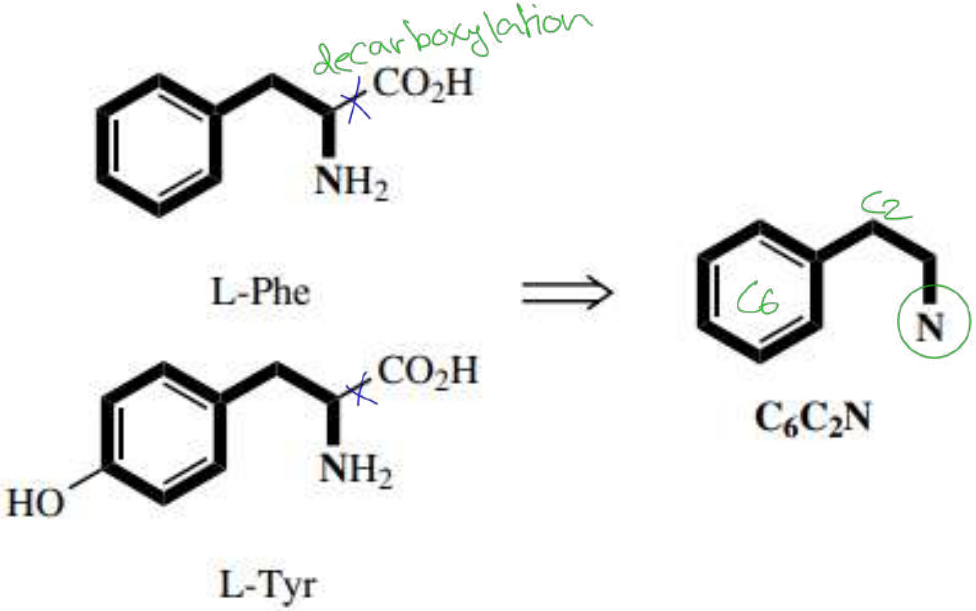
	number of C	isoprene units
mono	10	2
sesqui	15	3
di	20	4
ses	25	5
tri	30	6



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 **represen**t
- →modified **shorte**ned **forms** of the **C6C3 system**.



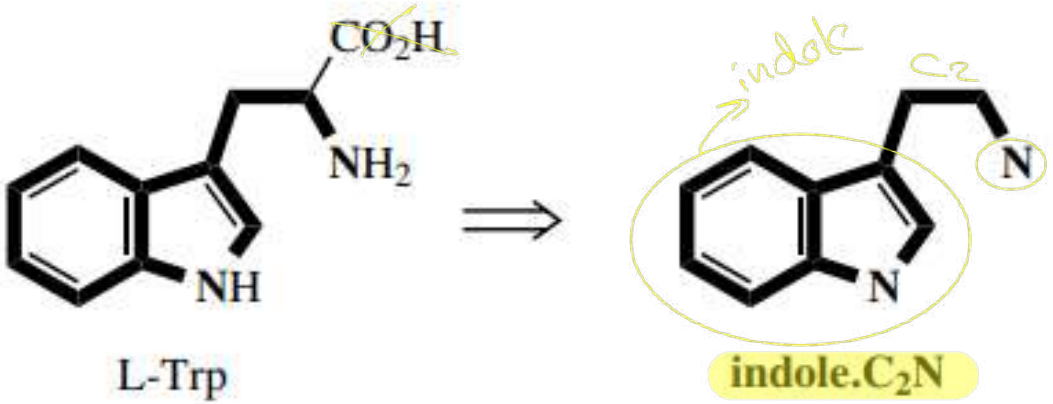
- **C6C2N:** الفرق بينها وبين اللي قبل إنه هون ما بيخلص في جزيء الـ amine

- 1-This building block is formed

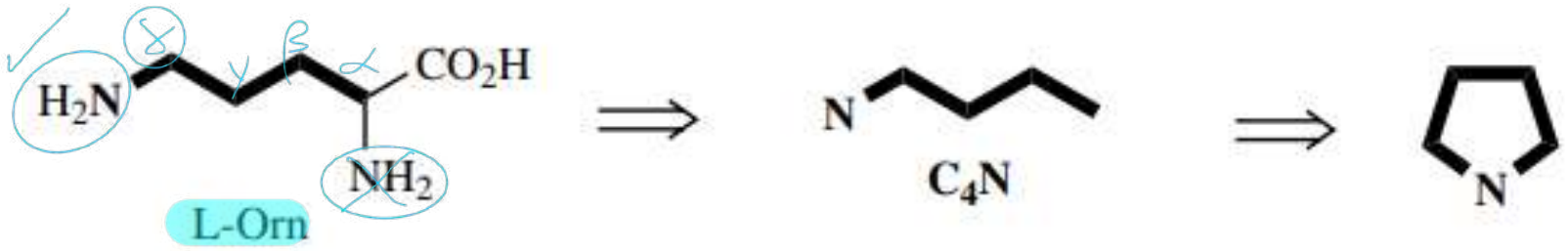
  → from **either** L-**phenylalanine** or L-**tyrosine**,

  →Ltyrosine being by far the more common.

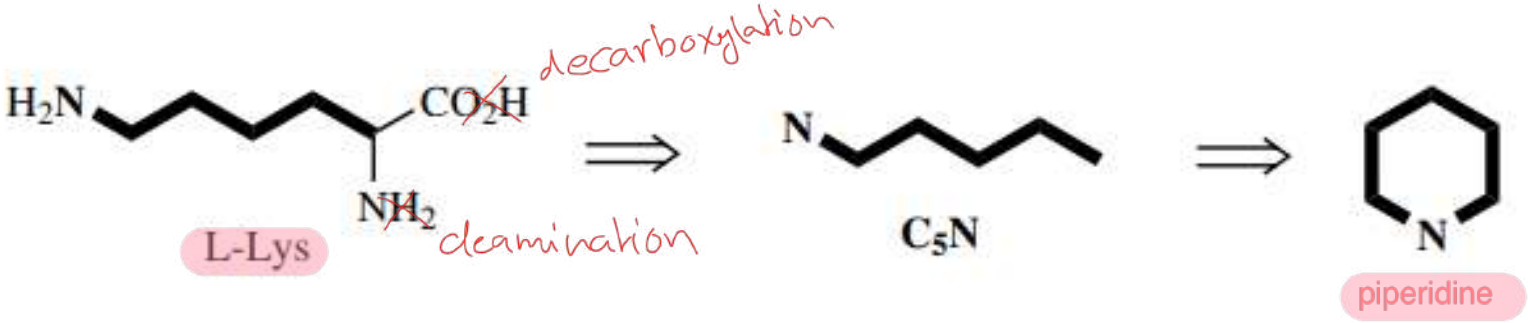
- 2-In the elaboration of this unit, the carboxyl carbon of the amino **acid** is **removed**.



- **(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.



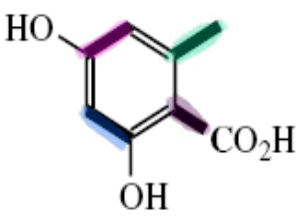
- **C4N:**
- **1-**The C4N unit is usually found
  →as a heteroceylic **pyrrolidine** system.
- **2**-It is produced from
  → the non-protein amino acid L-**ornithine**. → from Cribs cycle
  3-In marked **contrast** to the C6C2N and indole.C2N units described above:
- →**ornithine** supplies **not** 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 **exac**tly the **same** way
- →as the C4N unit
- (piperidine)
- →**but** using L-**lysine** as **precu**rsor.

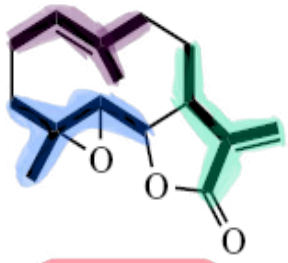
Examples of how compounds can be visualized as a combination of building blocks

دائما بيجي على سؤال



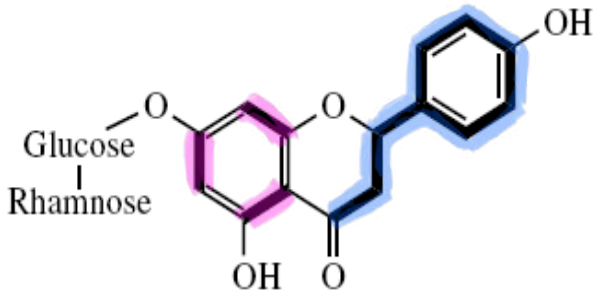
orsellinic acid

4 x C_2



parthenolide

3 x C_5



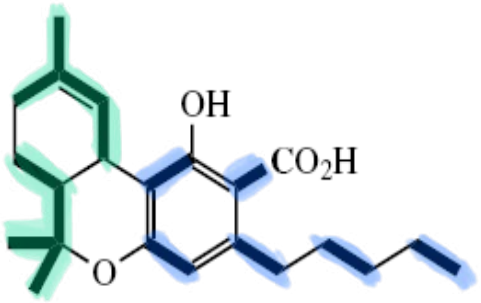
naringin

C_6C_3 + 3 x C_2 + sugars

podophyllotoxin

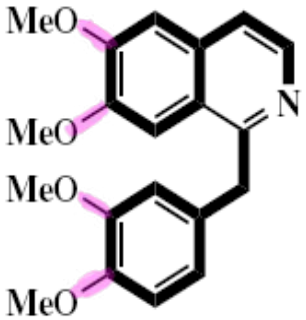
2 x C_6C_3 + 4 x C_1

↳ from shikimic



tetrahydrocannabinolic acid

6 x C_2 + 2 x C_5

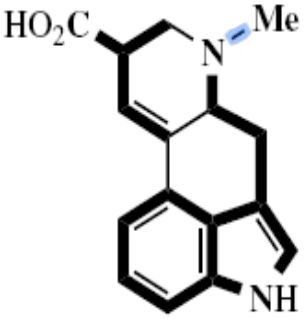


papaverine

C_6C_2N + (C_6C_2) + 4 x C_1

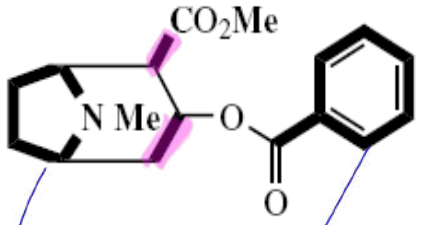
⇑

C_6C_3



lysergic acid

indole.C_2N + C_5 + C_1



cocaine

C_4N + 2 x C_2 + (C_6C_1) + 2 x C_1

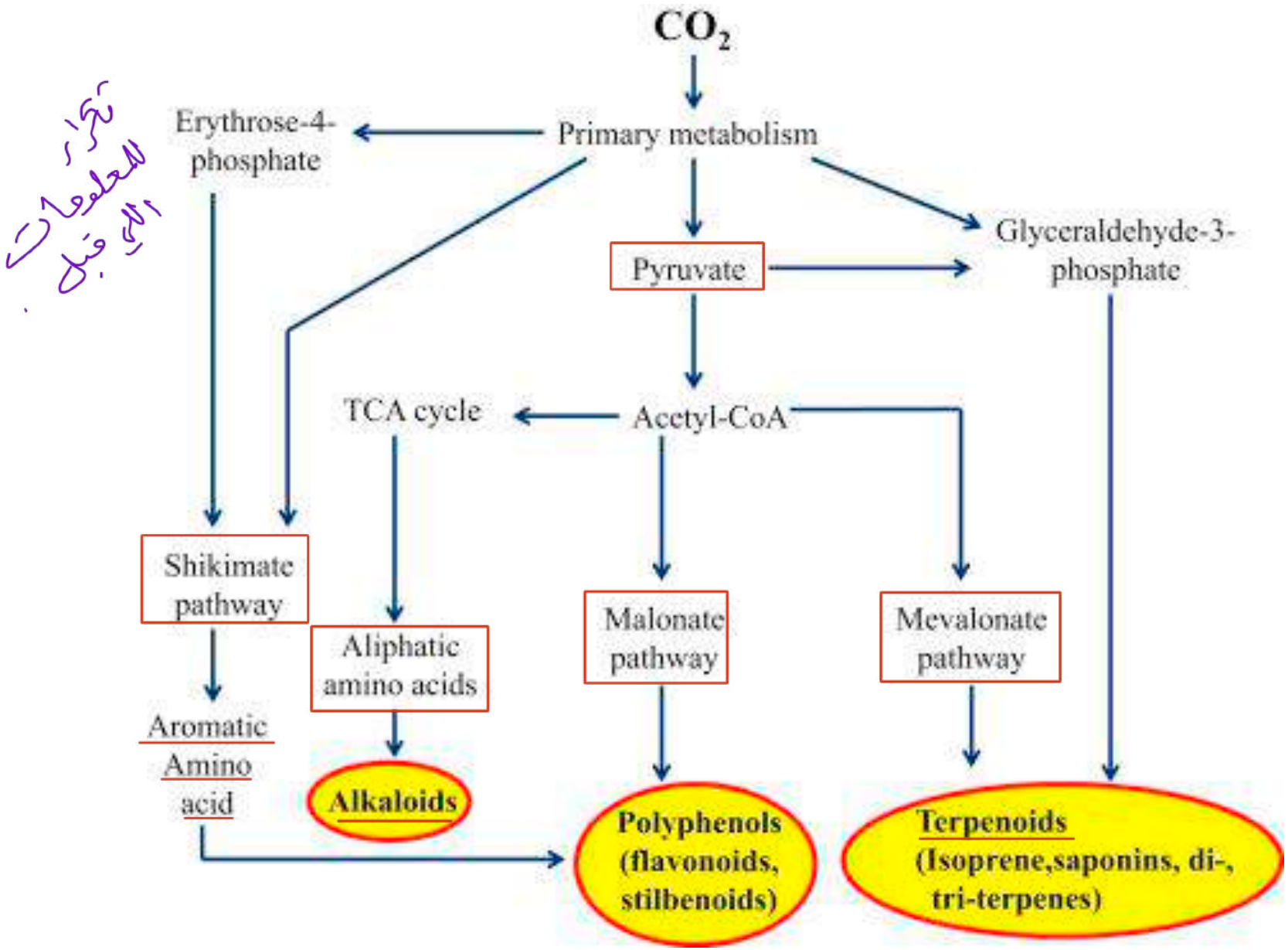
⇑

C_6C_3

The different secondary metabolites are biosynthesized using 3 different pathways.

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

4- amino acid pathway.


CO_2
Primary metabolism
Erythrose-4-phosphate
Pyruvate
Glyceraldehyde-3-phosphate
TCA cycle
Acetyl-CoA
Shikimate pathway
Aliphatic amino acids
Malonate pathway
Mevalonate pathway
Aromatic Amino acid
Alkaloids
Polyphenols (flavonoids, stilbenoids)
Terpenoids (Isoprene,saponins, di-, tri-terpenes)

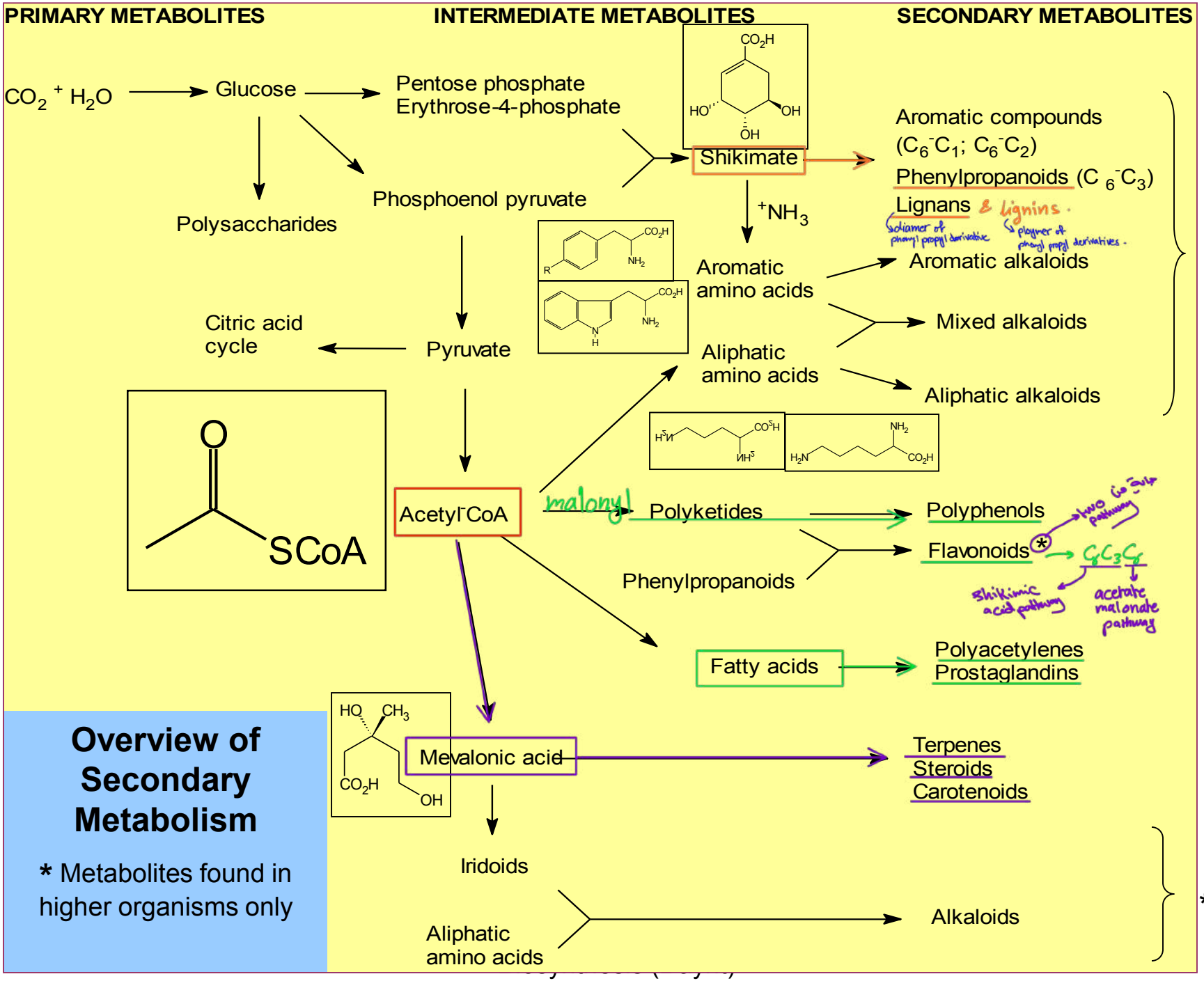
Important secondary metabolites formed from the acetate pathway include **phenols, prostaglandins, and macrolide antibiotics**, together with various **fatty acids** and derivatives at the primary/secondary metabolism interface.

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.


PRIMARY METABOLITES
INTERMEDIATE METABOLITES
SECONDARY METABOLITES
$CO_2 + H_2O$
Glucose
Pentose phosphate
Erythrose-4-phosphate
Shikimate
Aromatic compounds
(C_6-C_1; C_6-C_2)
Phenylpropanoids (C_6-C_3)
Lignans & Lignins
Polysaccharides
Phosphoenol pyruvate
$^+NH_3$
Aromatic amino acids
Aromatic alkaloids
Mixed alkaloids
Aliphatic amino acids
Aliphatic alkaloids
Citric acid cycle
Pyruvate
SCoA
Acetyl-CoA
malonyl
Polyketides
Polyphenols
Flavonoids
Phenylpropanoids
Fatty acids
Polyacetylenes
Prostaglandins
Mevalonic acid
Terpenes
Steroids
Carotenoids
Iridoids
Aliphatic amino acids
Alkaloids
*
Overview of Secondary Metabolism
* Metabolites found in higher organisms only

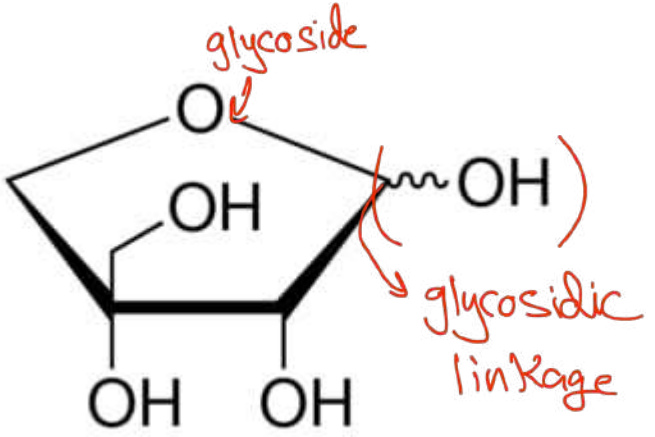
Plant Secondary Metabolites

- 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 (البقدونس) and its close relatives.

"glycoside" part sugar

"Aglycoside" part non sugar



Acetate malonate pathway

- A-Non-aroamtic derivatives (polyacetylenes, polyynes)
- 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)

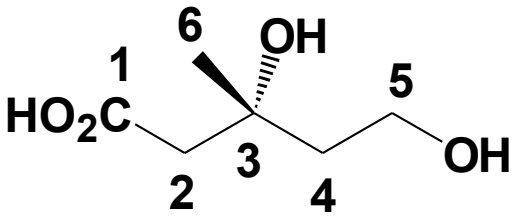
2 main routes originate with acetate pathway:

1. Acylpolymalonate pathway leading to FA & polyketides → aromatic acetyl unite
   ↳ non aromatic acetyl unite
2. Mevalonic acid pathway producing terpenes & steroids

Acetate mevalonate pathway

terpenoid يعني steroid.

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

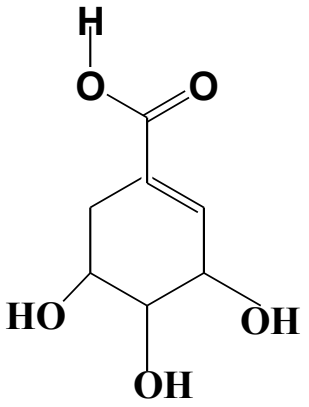


Mevalonic acid (MVA)

3 Acetyl-CoA

Shikimic acid pathway

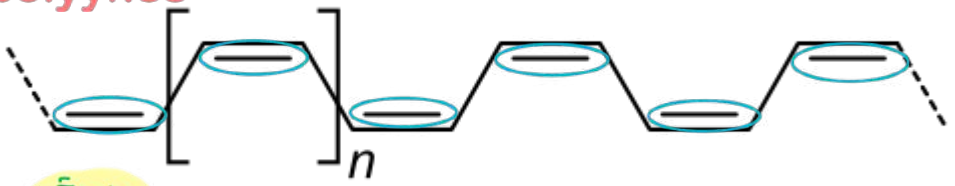
- **Shikimic acid** is a very important building block of **phenolic** substances, because it contains a ring and it's also important for the formation of three important amino acids: Phenylalanine, Tyrosine and Tryptophan.
- Aromatic biosynthesis:
- Phenols
- Phenolic glycosides
- Phenyl-propane-derivatives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



Shikimic Acid

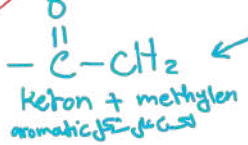
- Polyacetylene

polyynes

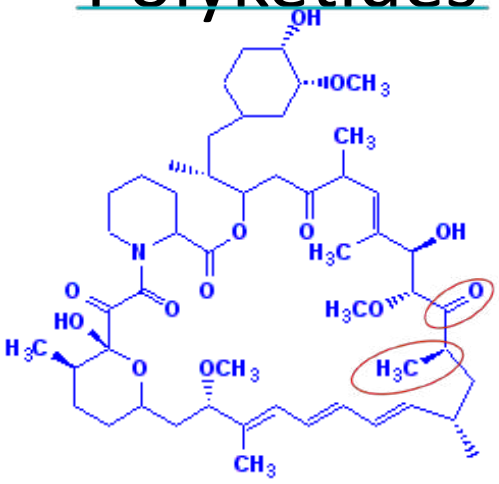


- Polyketides

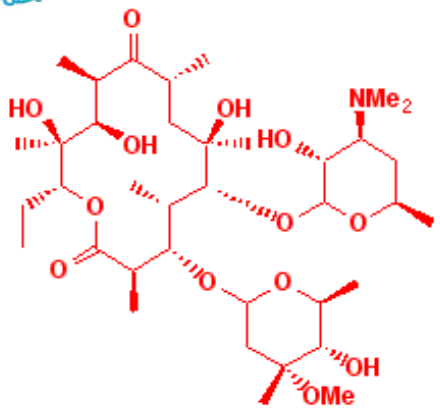
main unite



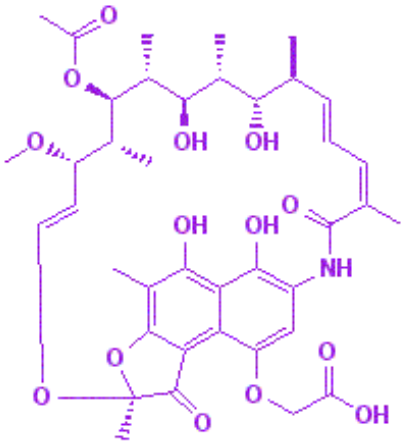
Keton + methylen aromatic



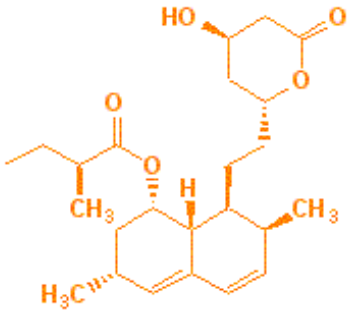
rapamycin
(immunosuppressant)



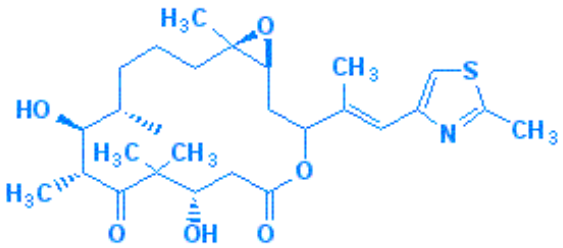
erythromycin A
(antibacterial)



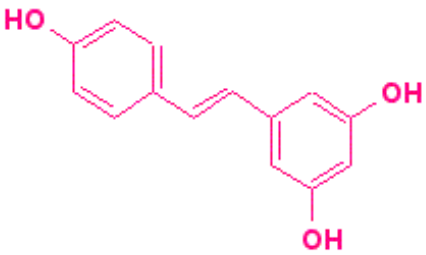
rifamycin B
(antituberculosis)



lovastatin
(anticholesterol)



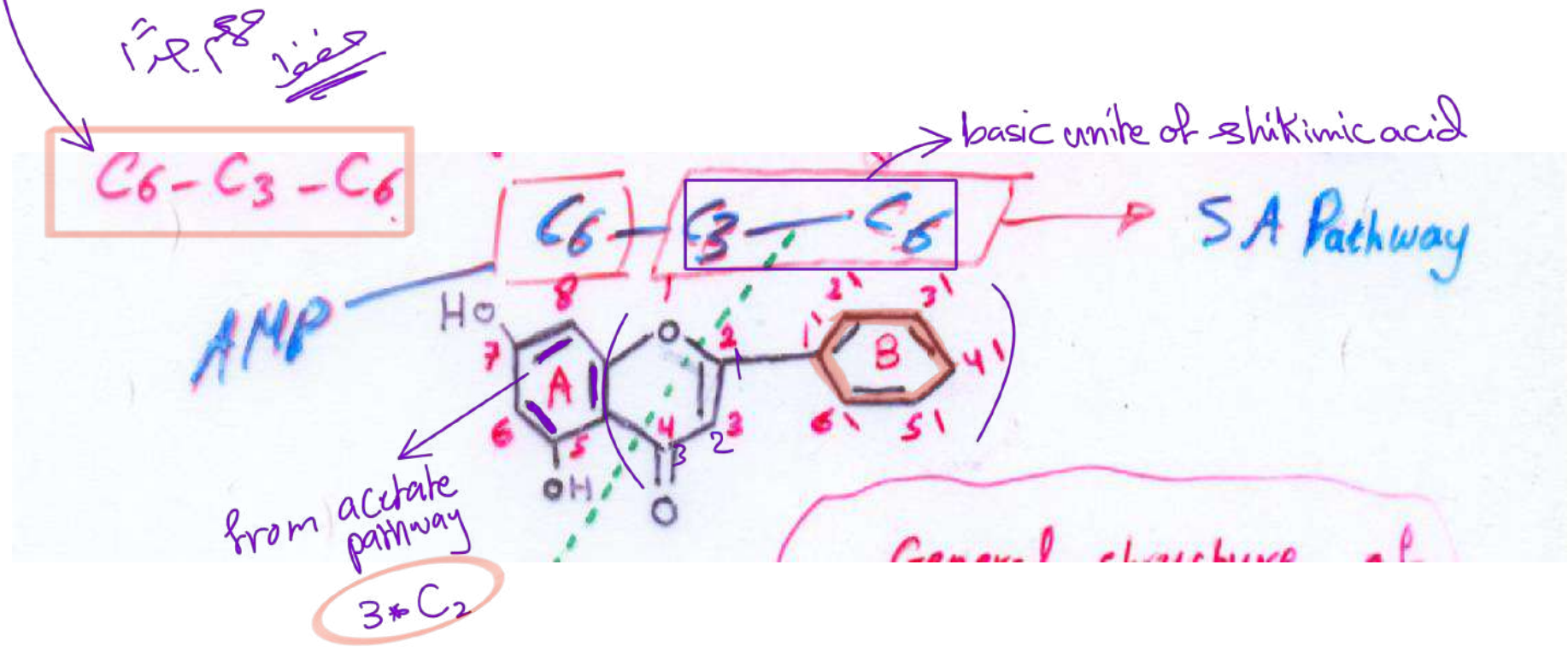
epothilone B
(anticancer)



(E)-resveratrol
(chemopreventive)

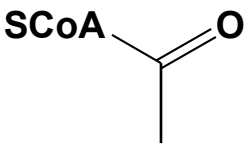
Flavanoids from acetate malonate (C6)+ shikimic acid(C6C3)

**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

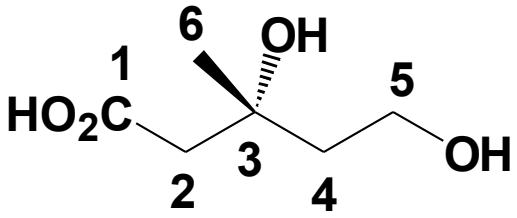


Flavanoids → 1 benzen ring & other benzen ring

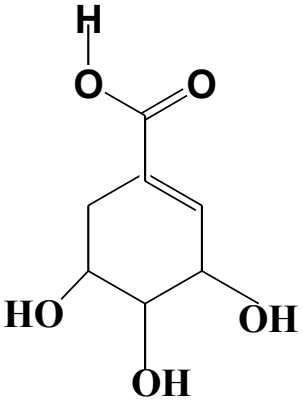
Most important building blocks



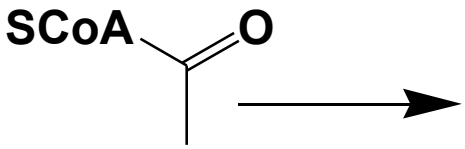
Acetyl Enzyme CoA



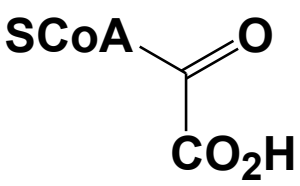
Mevalonic acid (MVA)



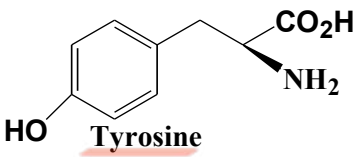
Shikimic Acid



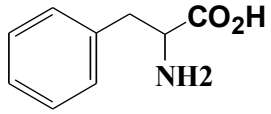
Acetyl-CoA



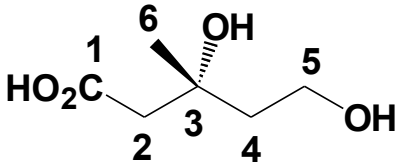
Maonyl-CoA



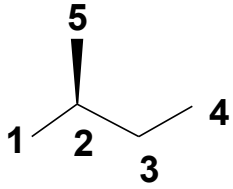
Tyrosine



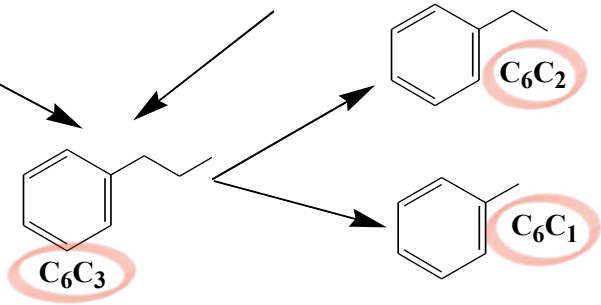
Phenylalanine



Mevalonic acid (MVA)



Isoprene Unit



“Amino acid” pathway

Includes all biogenetic drugs containing “N”.:

-Alkaloids

رح يتم شرحها بالتفصيل بالشابتر اللي بعده.

-Cyanogenic glycosides

-Glucosinolates

-Alliines

-Antibiotics from amino acid metabolism

-Anticancer drugs from amino acid metabolism