From textbook: ***(Pharmacognesy and Pharmacobiotechnology, 9th ed, Robbers JE, Speedie MK, Tyler VE.)***

(Introduction: General biosynthesis pathways of secondary metabolites)

- **The active constituents of a medicinal planet:** Are organic compounds of natural origin that are produced by living organisms (plants and micro-organism).

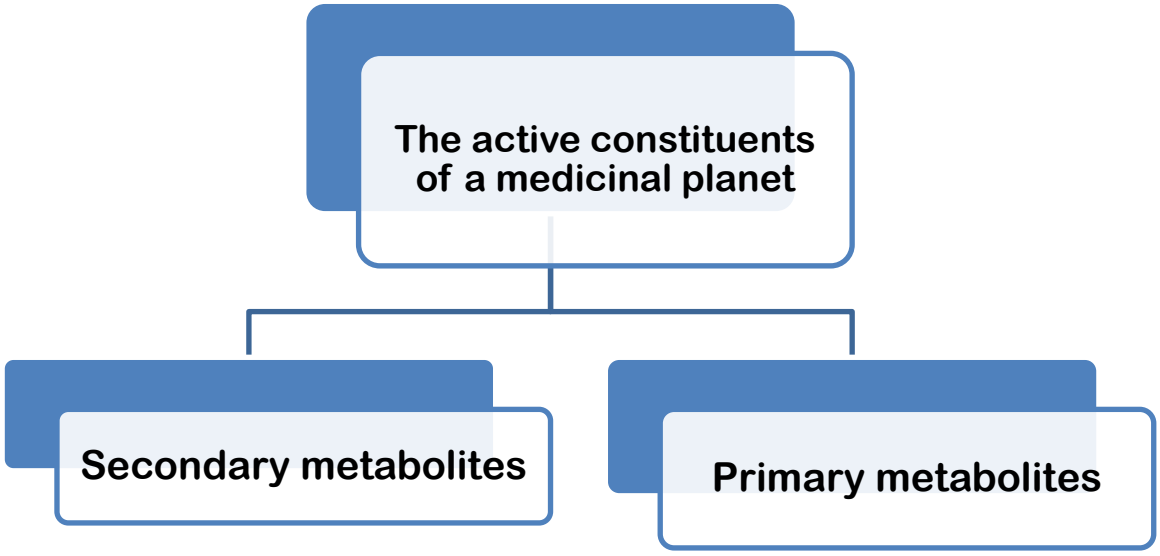

Figure 1: Classification of the active constituents of a medicinal planet

Definition of primary metabolites: Are Compounds that are involved in primary reactions of metabolism processes, these may include: carbohydrates, lipids, vitamins, amino acids, carboxylic acids, sugars, Fats, proteins, and nucleic acids.

Definition of secondary metabolites: Is a diverse group of plant compounds, which defends plants against a variety of herbivores and pathogenic microbes. Glycosides, resins, volatile oils, steroiods, alkaloids are considered secondary metabolites.

Importance of secondary metabolites:

1. Defends plants against a variety of herbivores and pathogenic microbes.
2. Providing structural support, as in the case of lignin, or acting as pigments, as in the case of the anthocyanins.

3. They serve as attractants (odor, color, taste) for pollinators and seed-dispersing animals.
4. Important as medicinal drugs, poisons, flavors, and industrial materials.
5. Absorbing harmful ultraviolet radiation, or in reducing the growth of nearby competing plants (phenolic compounds).

Divisions of Secondary metabolites :

Plant secondary metabolites can be divided into three chemically distinct groups: (**terpenes, phenolics, and nitrogen-containing compounds**).

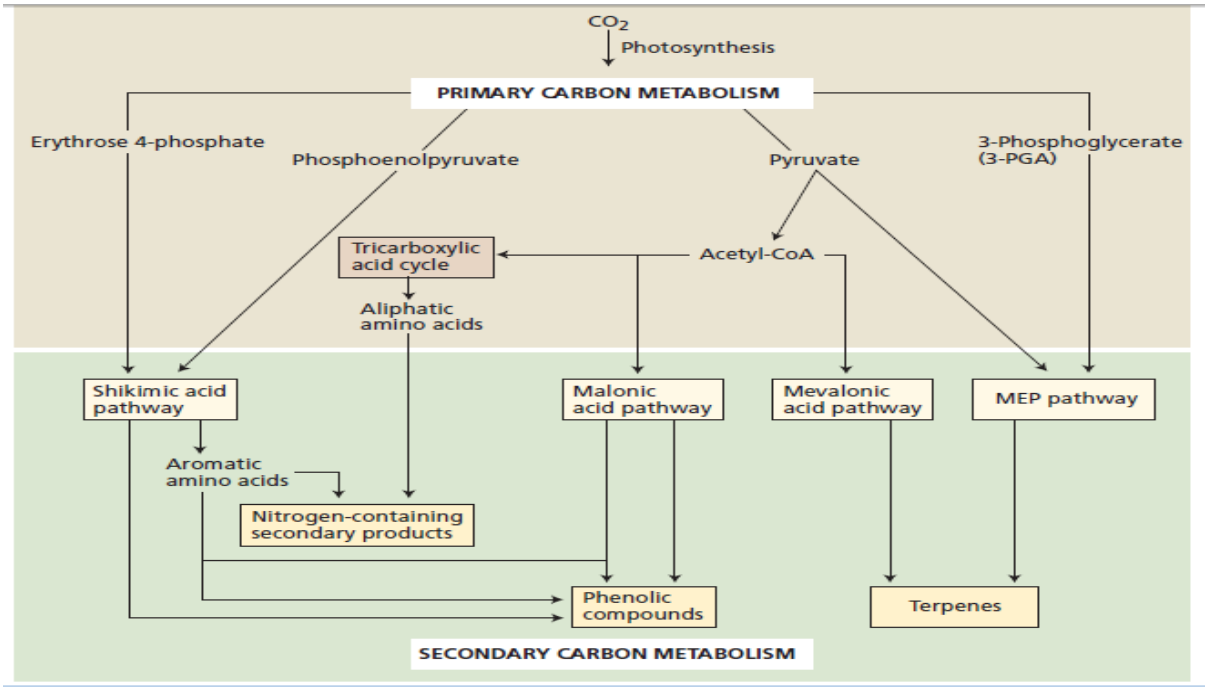

Figure.2: A simplified view of the major pathways of secondary-metabolite biosynthesis and their interrelationships with primary metabolism. (MEP) 2-*C*-methyl-d-erythritol 4-phosphate

Shikimic acid derived natural products:

Shikimic acid is the precursor for many aromatic amino acid and natural products.

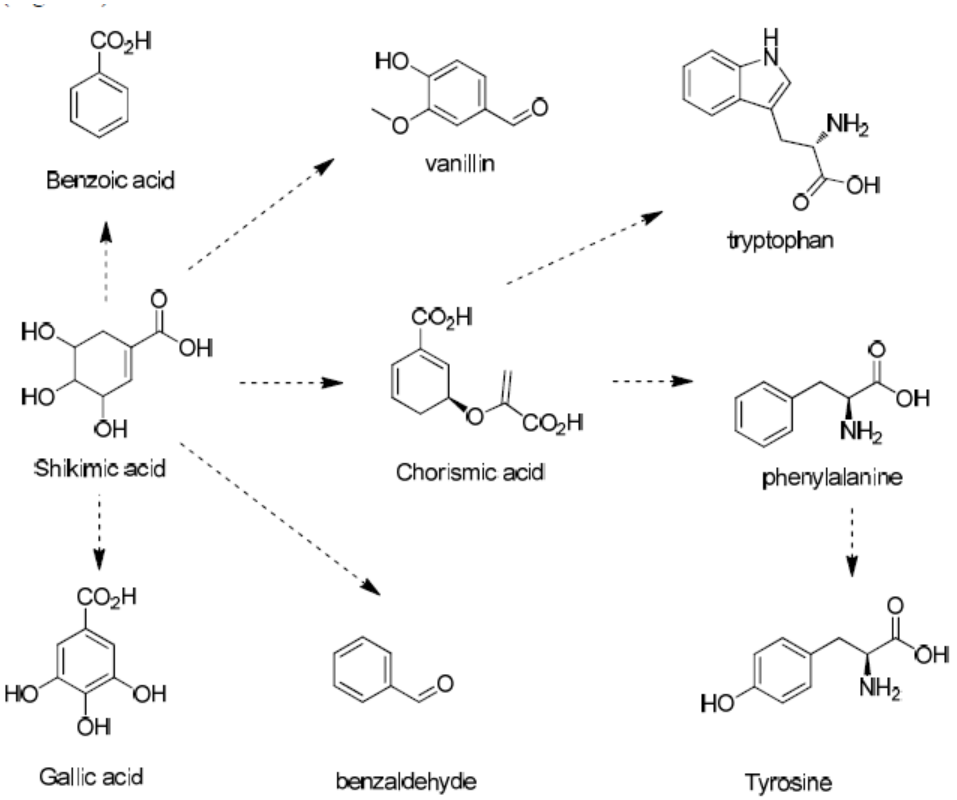

Figure3: Shikmic acid derived aromatic amino acid and natural products.

Secondary metabolites:

A) Terpenes (Terpenoids):

These are the largest class of secondary metabolites. Most of the diverse substances of this class are insoluble in water.

Terpenes are formed by the fusion of five-carbon isoprene units, terpenes are classified by the number of C5 units they contain. For example, 10-carbon terpenes, which contain two C5 units, are called monoterpenes .

Terpenes are synthesized from primary metabolites in at least two different ways.

1) **The cytosolic mevalonic acid pathway**, three molecules of acetyl-CoA are joined together stepwise to form mevalonic acid. This key six-carbon intermediate is then pyrophosphorylated, decarboxylated, and dehydrated to yield isopentenyl diphosphate (IPP). IPP is the activated five-carbon building block of terpenes.

Sesquiterpenes (three 5- C units) and **triterpenes** (six 5- C units) are synthesized through this pathway.

2) **The chloroplastic methylerythritol phosphate** (**MEP**) **pathway** that operates in chloroplasts. Glyceraldehyde 3-phosphate and two carbon atoms derived from pyruvate condense to form the five-carbon intermediate 1-deoxy-d-xylulose 5-phosphate. After this intermediate is rearranged and reduced to 2-*C*-methyl-d-erythritol 4-phosphate (MEP), it is eventually converted into IPP. **Mono- (two 5- C units), di- (four 5-C units),** and **tetraterpenes (eight 5- C units)** are derived from this pathway.

IPP and its isomer, dimethylallyl diphosphate (DMAPP), are the activated 5-carbon building blocks of terpene biosynthesis that join together to form larger molecules (IPP and DMAPP are the intermediates for terpens biosynthesis).

However, cross talk between these two pathways does occasionally occur, leading to terpenes that are "mixed" with regard to their biosynthetic origin.

B) Phenolic Compounds

Plants produce a large variety of secondary compounds that contain a phenol group: a hydroxyl functional group on an aromatic ring:

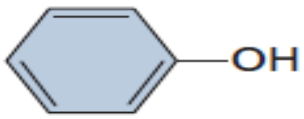

Figure4: Phenol group

Plant phenolics are a chemically heterogeneous group of nearly 10,000 individual compounds: Some are soluble only in organic solvents, some are water-soluble carboxylic acids and glycosides, and others are large, insoluble polymers. Phenylalanine is an intermediate in the biosynthesis of most plant phenolics.

Two basic pathways are involved for phenolic compounds biosynthesis:

1) **The shikimic acid pathway** converts simple carbohydrate precursors derived from glycolysis and the pentosphosphate pathway into the three aromatic amino acids: phenylalanine, tyrosine, and tryptophan. One of the pathway intermediates is shikimic acid, which has given its name to this

whole sequence of reactions. The shikimic acid pathway is present in plants, fungi, and bacteria but is not found in animals. Animals have no way to synthesize aromatic amino acids—phenylalanine, tyrosine, and tryptophan—which are therefore essential nutrients in animal diets.

The elimination of an ammonia molecule from phenyl alanine that is catalyzed by **phenylalanine ammonia lyase** (**PAL)** will form cinnamic acid. The activity of PAL is increased by environmental factors such as low nutrient levels, light (through its effect on phytochromes), and fungal infection.

2) Malonic acid pathway.

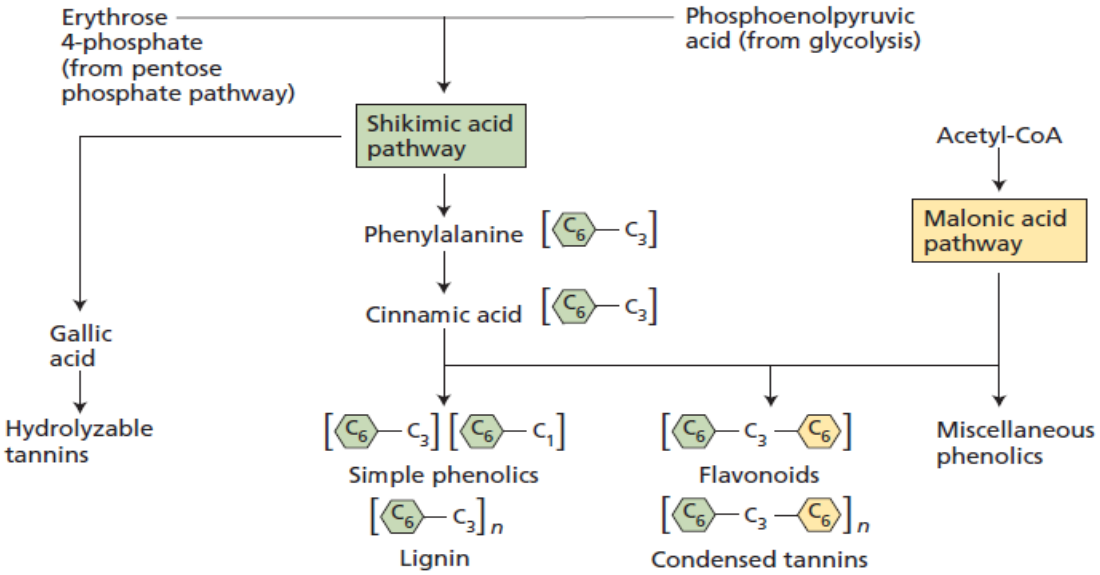

FIGURE 5: Plant phenolics are synthesized in several different ways. Formulas in brackets indicate the basic arrangement of carbon skeletons: C6 indicates a benzene ring, and C3 is a three-carbon chain.

3) **Nitrogen-Containing Compounds :** A large variety of plant secondary metabolites have nitrogen as part of their structure. Included in this category are such well-known antiherbivore defenses as alkaloids and cyanogenic glycosides, which are of considerable interest because of their toxicity to humans as well as their medicinal properties.

Most nitrogenous secondary metabolites are synthesized from common amino acids.

Among the Nitrogen- containing compounds are (the alkaloids) which are a large family of more than 15,000 nitrogen-containing secondary metabolites.
As a group, alkaloids are best known for their striking pharmacological effects on vertebrate animals.
The nitrogen atom is protonated; hence alkaloids are positively charged and are generally water soluble.
Alkaloids are usually synthesized from one of a few common amino acids—in particular, lysine, tyrosine, or tryptophan. However, the carbon skeleton of some alkaloids contains a component derived from the terpene pathway.

Several different types, including nicotine and its relatives are derived from ornithine, an intermediate in arginine biosynthesis.

Most alkaloids are now believed to function as defenses against herbivores, especially mammals, because plant defensive compounds and even use them in their own defense.