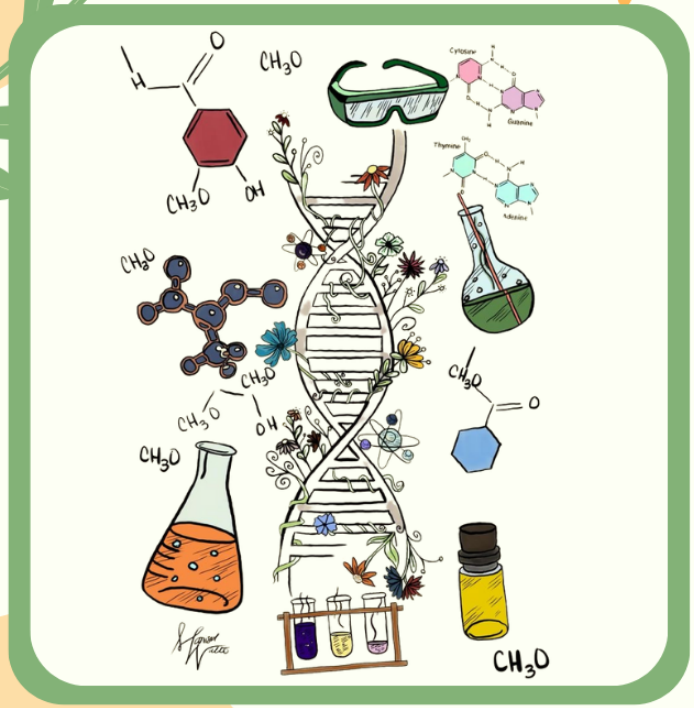
تفريغ عقاقير



اسم الموضوع: Chapter 9 Alkaloid

إعداد الصيدلاني/ـة: لؤي المجدلاوي

Soul Academy

لجان الدُّفعات

Alkaloids

Amino acid pathway

- None of the compounds we discuss until now is containing nitrogen, so what about nitrogen secondary metabolites ?
- in fact, all remaining nitrogenous substances have been pooled together in the amino acid pathway, this is not a strict pathway, it is just a pool to collect all nitrogenous substances under the same umbrella. So, it is not like the shikimate or mevalonate pathway that start with a common precursor.

Amino acid pathway include:

1- Cyanogenic glycosides : these compounds are liberating HCN upon hydrolysis and you will smell the odor of bitter almond when you hydrolyze these substances. رائحة سيئة مثل اللوز المُر

2- Thiocyanide glucosides or glucosinolates.

- There is a tiny difference between these two groups, glycosides means that we can have any sugar moiety, but glucosides have a constant sugar moiety which is glucose. There is another difference that thiocyanates, in addition to N, also they have sulfur in their skeleton.

S

3- Alliines :a very tiny class of the secondary metabolites which impart the characteristic smell to garlic(allicin) and onion in the family Amaryllidaceae. مجموعة صغيرة من خصائصها ان لها رائحة مثل الثوم و البصل

N

4- Alkaloids : the largest group of the nitrogenous compounds, so we will start with them and then discuss the remaining groups.

معظم الـ alkaloids غلب N جوا الـ ring وجاية من amino acid

Alkaloids

- Are the most heterogeneous class of secondary metabolites, they are widely distributed and almost 50 thousand of alkaloids are isolated until now. In this sheet we will talk about:
- Definition
- Classification
- Occurrence
- Forms of alkaloids
- Functions
- Nomenclature
- Physical properties

Alkaloids

- **Definition :** the name is derived from the Arabic word" alkali" meaning soda and "ids" meaning appearing, so alkaline appearing substances. The name indicate that they must be (1) ***basic***. In addition, they must (2) ***contain nitrogen*** in their structure. They are(3) ***found mainly in plants***, but also to a lesser extent in microorganisms and marine animals. Nowadays the greatest source for the synthesis and discovery of alkaloids are from marine organisms.
- All alkaloids are (4) ***physiologically active in low concentrations***. Like hallucinogenic alkaloids, they exert their hallucinogenic effect in nano-grams, so they are very potent active compounds.
- Alkaloids have certain(5) ***complexity*** in their structure. When we have an alkaloid which is simple in its structure, it will be found in many plant families (not specific). But something like atropine, it will be restricted into certain plant family or genus or species (very specific).
- So, the structure gives an indication if it could be widely distributed or limited in its occurrence, based on the complexity or simplicity of its structure.

Deviation from definition

بعض المفاهيم الخارجة عن القاعدة و التي تم اكتشافها مع التطور

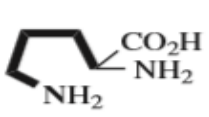
- Basicity: some alkaloids are not basic
- Nitrogen: the nitrogen in some alkaloids is not in a heterocyclic ring (it is in the side chain)
- plant origin: some alkaloids are derived from other sources such as marine
- **By this alkaloids were redefined as :**
- Cyclic organic compounds containing nitrogen in a negative state of oxidation, more or less basic, with limited distribution among living organisms.
- We say organic compounds so it is not necessarily of plant origin and we didn't insist that the nitrogen must be in the heterocycle. Limited distribution means that they are not found in all plant families and this is valid for all secondary metabolites.

Classification of alkaloids :

- Alkaloids can be classified according to many aspects :
- **1) Botanical source :** botanists classify alkaloids according to their family, e.g. solanaceae alkaloids, barabideaceae alkaloids, etc. or according to their genus.
- **2) Type of amines :** the nitrogen of alkaloids can occur as 1° amine, 2° amine,3° amine or quaternary ammonium compounds. So ,pseudochemically, we can classify them according to the degree of nitrogen, this will also determine the basicity of the compound.
- **3) Basic chemical structure :** the chemical nucleus of the compound with nitrogen incorporated form the basis of this classification. like tropane alkaloids, quinolone alkaloids, isoquinoline alkaloids and imidazole alkaloids.
- **4) Pharmacological effect :** pharmacologists classify alkaloids as :
- Alkaloids having oxytocin activity, alkaloids having analgesic activity, alkaloids having sympathomimetic activity, etc.

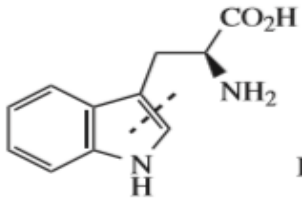
Classification of alkaloids :

5- Biogenetic origin : the origin of the nitrogen in alkaloids is the precursor amino acid. It has been found that 5 amino acids are incorporated in the **vast majority** of alkaloids, 2 of them are aliphatic : ornithine and lysine differing by the no. of C , and 3 are aromatic : phenylalanine, tyrosine (para-hydroxyphenylalanine) and tryptophan. Also we have **some** alkaloids derived from histidine.

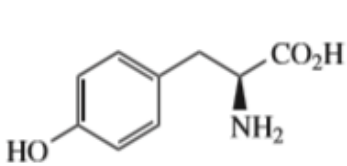


L-Orn

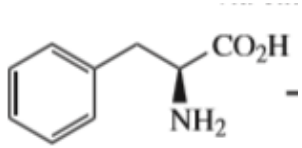
L-Lys



L-Trp



L-Tyr

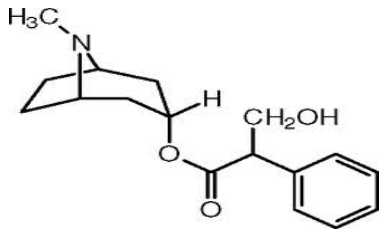


L-Phe

Classification of alkaloids :

6- According to biochemical origin alkaloids are subdivided into :

- 1-True, typical or real alkaloids : which are derived from the precursor amino acid and the N is incorporated in the heterocycle e.g. Atropine .

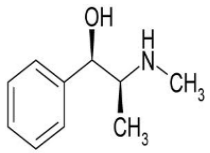


Classification of alkaloids :

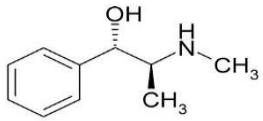
According to biochemical origin alkaloids are subdivided into :

بدائي

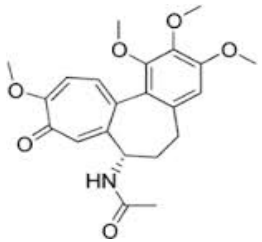
- 2-Proto alkaloids : originating from precursor amino acid but the nitrogen is not part of the heterocycle, it is located anywhere in the side chain e.g., ephedrine[1], pseudoephedrine[2]. Another example is colchicine[3] that is derived from two amino acids phenylalanine and tyrosine but the nitrogen is in the side chain, therefore colchicine despite the incorporation of 2 amino acids, it is not a true alkaloid it is a proto alkaloid.



Ephedrine



pseudoephedrine



colchicine

Classification of alkaloids :

According to biochemical origin alkaloids are subdivided into :

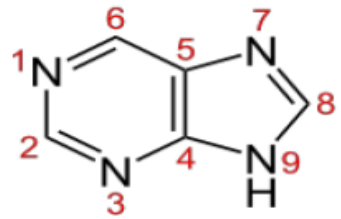
- 3-Pseudo alkaloids : where the nitrogen is incorporated in the heterocycle, but the source of the nitrogen is not an amino acid, it is from the transamination rxn. e.g : Pyrin
- 4-False alkaloids (non-alkaloids) : give false +ve test with the alkaloids reagents e.g., coumarins.

Identification tests

- Alkaloids give a precipitate with heavy metal iodides.
- Most alkaloids are precipitated from neutral or slightly acidic solution by Mayer's reagent (potassium- mercuric iodide solution). Cream colored precipitate.
- Dragendorff's reagent (solution of potassium bismuth iodide) gives orange colored precipitate with alkaloids.
- Caffeine, a purine derivative, does not precipitate like most alkaloids

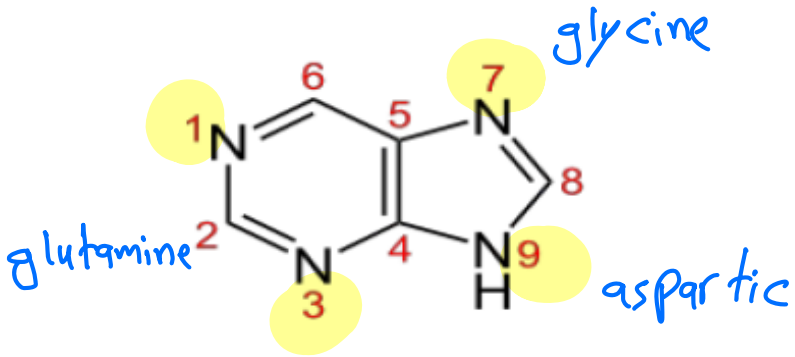
because Pseudo

Purine alkaloids



- A **purine** is a heterocyclic (bicyclic) aromatic orga[illegible]. It consists of a pyrimidine ring (a six-membered ring), fused to an imidazole ring (a five-membered ring). Each ring has two nitrogen atoms, nitrogen atoms in each ring are separated by one carbon atom so they are Meta to each other. The chemical formula of purine is highly unsaturated; purine alkaloids are formed through a biosynthetic pathway.

- Purine alkaloids are found in plant tissues, their existence depends on the presence of a certain group (Purine alkaloids have a very limited distribution). They are not distributed widely in the plants kingdom (**plantae**), they are only found in certain places or distinctive families.
- As we mentioned earlier, they are pseudo alkaloids (not synthesized from amino acids). They are known to be as water soluble molecules, even in free bases. For example, when we make a cup of cocoa or coffee or tea, we don't use alcohol or chloroform to make them soluble. However, purine alkaloids are much more soluble in hot water rather than cold water.



- **Notes:**
- nitrogen number 7 of the purine ring comes from **glycine**. Two of the other nitrogen atoms (number 1, 3) come from **glutamine** and the last one (nitrogen number 9) comes from **aspartic acid**.
- Purine ring formation doesn't originate from amino acids that we have discussed in our past lectures e.g., tyrosine, tryptophan, phenylalanine.
- In nomenclature, we start counting from the six-membered ring then move to the five-membered ring as shown above. Purine ring is found primarily in the DNA molecule and in other nucleic acids generally.

Purine alkaloids mechanism of action

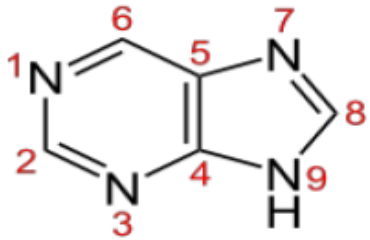
- they bind to phosphodiesterase, by inhibiting the cyclic AMP degradation to change the action potential. As a result, neurotransmitters will reach their site of action more effectively and in a faster way (increase in intracellular calcium, which causes vasodilation and smooth muscle relaxation).

- The effects of this group of alkaloids depend primarily on the central nervous system (CNS). Such as **caffeine** which is a major CNS stimulant or it's the most active CNS stimulant, while **theobromine and theophylline have** a more diuretic effect and a less CNS stimulant effect.
- **Theophylline** is used as a bronchodilator and a muscle relaxant (relaxation process of bronchial muscles). These are the general properties of compounds which have purine alkaloids

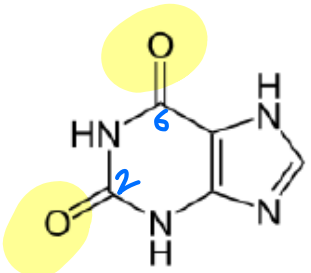
Purine alkaloids

xanthine

- pharmacologically active purine alkaloids belong to the oxygenated form of purine ring, which is called **xanthine**. The position of oxygen atoms is on carbon atoms number 6 and 2 in the form of ketonic functional group.
- First, oxidation process occurs on hydroxyl groups then another oxidation step takes place to produce the xanthine molecule.



Purin

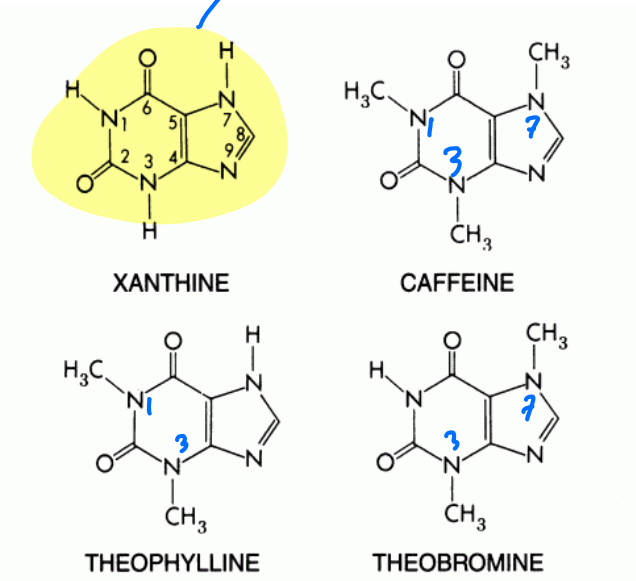


xanthine

Purine alkaloids

- The purine alkaloids **caffeine, theophylline and theobromine** depend on their structure on xanthine nucleus. Caffeine is the most active CNS stimulant, what makes it very distinctive is the presence of three methyl groups on a xanthine molecule on nitrogen atoms number 1,3, and 7, so caffeine is **1,3,7-trimethylxanthine**.
- The second derivative of xanthine is **theophylline**, it will lose one of the methyl groups that is found on nitrogen atom number 7 of the imidazole ring and will be named **1,3-dimethylxanthine**.

الأساسي للثلاث مركبات



*لتسهيل الحفظ

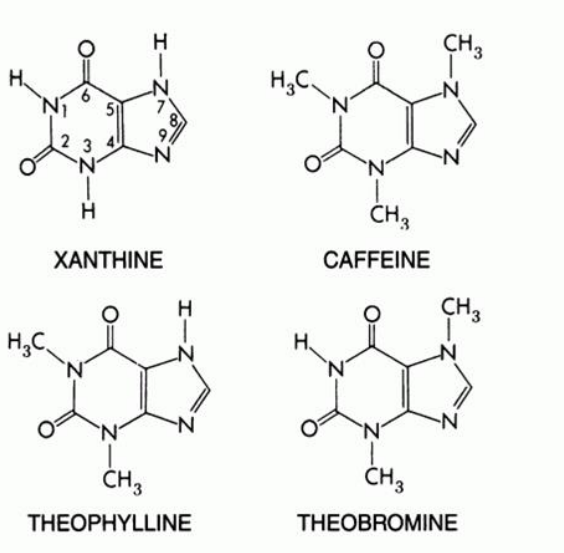
- الكافيين مثل القهوة أقوى مؤثر فضيع methyl 3

- Theophylline حرف الـ P نقطة خفيف فأرقامه صغيرة 1,3 أما حن تواجد الـ methyl

- Theobromine حرف الـ B نقطة ثقيل فأرقامه أكبر 3,7 أما حن تواجد الـ methyl

Purine alkaloids

- Theobromine, which is the least used compound of them medicinally; the only difference found is that the nitrogen atom number 1 loses its methyl group so it will be named **3,7-dimethylxanthine.** There is a resemblance in the biological structure between theobromine and theophylline but differs in the potency, in theobromine the nitrogen atom number 1 loses its methyl group while in theophylline nitrogen atom number 7 loses its methyl group



No wonder they go so well together.

Caffeine

Chocolate

Theobromine

They're just a methyl group apart.

Natural sources of Purine alkaloid

- natural sources that contain purine alkaloids include: coffee, tea, mate tea, and guarana
- Guarana plants grow in Latin America
- The percentage of caffeine, theobromine and theophylline differs between the different natural sources depending on their metabolism

Coffee

- consists of dried ripe seeds of ***Coffea arabica* (Rubiaceae)**
- This plants is a small evergreen tree, there is another species which is ***C. canephora*** , still arabica is more popular because people use it all around the world to drink coffee.
- Scientists called it arabica, because it was first discovered in Yemen
- Coffee has 1-2% of caffeine and traces (very low amounts) of theobromine and theophylline.
- Decaffeinated coffee, containing up to 0.08% caffeine, is obtained by Removing caffeine, usually by aqueous percolation prior to roasting. There is a second method of extracting caffeine using chloroform; it is very toxic even if it is washed with water several times.

قهوة منزوعة الكافيين

ولكن

Tea

- is prepared from the leaves of ***Camellia sinensis (Thea sinensis)*** **from Theaceae family**
- The plant is an evergreen short shrub.
- There are many kinds of tea; we have green tea, read tea, yellow tea, black tea…etc, they have different colors due to a fermentation process which differs from tea to tea and gives us at the end different colors.

Tea (Black/Green) الشاي

* Green tea and black tea, although derived from the leaves of the same plant, have different concentrations of the active constituents.
• Black tea: fully fermented leaves that are roasted (40mg caffeine/cup).
• Green tea: steamed, dried, non fermented leaves (20mg/cup).
* The immediate processing of harvested leaves used for green tea limits enzymatic changes, whereas leaves used for black tea are fermented before preparation, triggering the enzymatic process. Thus, green tea contains higher concentrations of the active catechin constituents compared to black tea.

* **Mate tea:**

- Most popular in Syria. Mate or Paraguay tea consists of the leaves of ***Ilex parguensis*** **(Aquifoliaceae)**, South American shrub.
- Mate tea contains 0.8-1.7% caffeine with smaller amounts of theobromine with little or no theophylline.
- Its caffeine content almost the same as that of tea.

* **Cocoa:**

- Taken from the dried ripe roasted seeds of ***Theobroma cacao*** **(Sterculiaceae)**, it's widely known for its ability to produce cacao butter or theobroma butter, which is one of the best and most expensive natural lipids used in pharmacy. The seeds of cocoa contain 35-50% of theobroma oil or butter.
- Cocoa contains 1-4% theobromine and 0.2-0.5% caffeine. اقل نسبة كافيين
- Its caffeine content is less than that of coffee and tea.

***Guarana:**

- it's a popular plant found in Brazil, obtained from the seeds of the plant ***Paullinia cupana*** **(Sapindaceae)** which are used to make a stimulant drink
- Has a very high caffeine content 3-5%
- Also, used in natural weight loss products.

Biological effects:

- Caffeine works mainly on the CNS and having so much of it can lead to insomnia and sleeping disorders, theophylline is a very good muscle relaxant which is used to treat asthma and is given via oral/intravenous route.
- Theobromine is a diuretic and a smooth muscle relaxant but not routinely (used less effective than theophylline).
- A lethal dose (جرعة خطيرة قاتلة) of caffeine is usually from 5 mg to 10 mg, this equals 45 bottles of soda drinks; which means consuming large amounts of fizzy drinks might lead to unhealthy life-style in addition to insomnia and other sleeping disorders.

5-10 g lethal

Occurrence

مصادر الظهور للalkaloid

di > Mono

- Primarily occur in plant kingdom and the dicotyledons are richer than monocotyledons, but they also occur in bacteria, Amphibians, animals and in marine organisms.

برمائيات

- Some claim that there are some plant families free of alkaloids (Labiatae for example) , but this statement is not completely true, as there are not enough studies that cover all the species or genera of these families that might be containing alkaloids, so we can't make a conclusion because there isn't to date any discovered alkaloid in a certain family.

لا يحتوي

sage مثل المرمية

- In animals, we also should highlight the origin of alkaloids. i.e., If it is originating from the plant diet or is a normal metabolic product. This need a lot of studies to show if it is a precursor existing in the plant.

اذا كان الحيوان يتغذى على نباتات تحتوي alkaloid قد يصبح
الحيوان يحتوي عليه كمثال بعض انواع الفراشات

Occurrence

- Within the plant, alkaloids has been isolated from all parts of the plant.
- Surprisingly, the site of biosynthesis of alkaloids in many plants differs from the site of deposition like in the tobacco plant, nicotine is not biosynthesized in the leaves of the plant *nicotiana tobaccom*, it is synthesized in the roots, then transported and deposited in the leaves.
- There are many interesting studies about this fact, one of these studies show that tomatoes plant grafted (تطعيم) with the roots of tobacco had nicotine in their leaves, and we can collect nicotine from the leaves.

قد يتم استخلاص ال alkaloid من اي مكان من النبتة لكن هذا لا يعني انه يتم انتاجه في كامل اجزاء النبتة ، بل له مكان محدد بالنبتة ينتج منه وينتشر الى باقي اجزاء النبات ، مثل النيكوتين في نبات الدخان يتم انتاجه في الجذور ثم ينتقل للاوراق ، او قد يتم انتقاله من نبات لآخر في حال تطعيم نوعين من النباتات احدها منتج لل alkaloid كمثال ال tomatoes مع ال tobacco

Forms of alkaloids :

اشكال التواجد لل alkaloid

1- Free bases like nicotine, less common than salts.

يوجد ✓

2- Salts with organic acids like oxalic acid or acetic acid.

لا يوجد ✗

3- Salts with inorganic acids like HCl or H_2SO_4

Example: atropine sulfate.

Forms of alkaloids

4- Salts with special acids like **opium meconate.** in fact, meconic acid was only identified and detected together with opium, therefore it is a very simple way to detect if a material is opium or not, instead of using complicated spectroscopy, we can make a very simple test using the meconic acid because meconic acid react with $FeCl_3$ (ferric chloride) and gives very intense **red** color, so if you put one drop and it turns red then this is opium, because when meconic acid identified, opium is identified. Another example is **cinchona** which contains quinine, quinidine, cinchonine and cinchodinine. they all occur as salts with **quinic acid**.

طريقة صعبة

طريقة سهلة

اللهم صل على سيدنا محمد

Forms of alkaloids

5- Few alkaloids occur in the form of glycosides, esters or amides.

This is important because if we want to isolate a compound when they are occurring as free base, free bases are soluble in organic solvents, so we can add diluted acids like HCl or H_2SO_4 to obtain the salt form that are soluble in water or hydroalchoholic solvents.

Non polar

Extraction of Free Bases

Process 1

powder

Water and lime (calcium oxide)

Extraction with organic solvent ether

Lime combines with acids, tannins and other phenolic substances

Organic extract

- concentration
- Aqueous acid

diluted acids like HCl or H_2SO_4 to obtain the salt form that are soluble in water or hydroalcoholic solvents.

Organic liquid

impurities

Aqueous liquid

Alkaloid salts

نريد استخراجه aqueous

Extraction of salt alkaloids

نفس الطريقة وكلن الخطوات بالعكس والمواد المستخدمة تختلف

Process 2

powder

- Water or aqueous alcohol containing dilute acid
- chloroform

organic

Pigments and other unwanted materials

aqueous

Alkaloid salts

- Sod. Bicarbonate or ammonia solution

Ppt. of alkaloid free base

Extract with organic solvent

conversion of salt to free bases by adding a base like ammonia, ammonium hydroxide, KOH or NaOH.

Functions of alkaloids

- For any secondary metabolite, including alkaloids, when a plant produces a specific secondary metabolite, the **first** thing we need to think about is the ecological balance or the interaction of the plant with its environment (other plants , insects, animals and human), so the most important role of alkaloids and many other secondary metabolites is the interaction of the plant with its environment, either for **survival** (in most cases) or **to adapt** living in dessert. Most of the plants that tolerate (تحمّل) the heat of dessert are alkaloid containing because they are bitter in taste and not used as a food for insects and herbivores.

طعمها سيء كي لا تتغذى عليها الحشرات

Functions of alkaloids

- Some of the alkaloids are involved in the growth either they promote growth or depress it , they may be responsible for the somnolence or the older process or autoaging, so alkaloids might be involved in determining the age of the plant.
- Alkaloids may be considered as **waste products** or as **energy source**.

اللهم صل على سيدنا محمد