

Biological sources of drugs

An examination of the list of drugs derived from natural sources , reveals the followings:

- 1.Plant** : The majority of plants are derived from Spermatophyta (the dominant seed bearing plants). Within the Spermatophyta the number of species & the number of useful medicinal plants are divided unevenly between the phyla Gymnospermae , which yields some useful oils, resins & the alkaloid ephedrine , & the Angiospermae , which is divided into monocotyledons & dicotyledons (both of these provide many useful drugs but especially the dicotyledons).
- 2.Fungi** : The fungi provide a number of useful drugs especially antibiotics, & are important in pharmacy in a number of other drugs.
- 3.Algae** : These are source of limited number of drugs ex: agar & alginic acid.
- 4.Lichens & mosses** : This group contribute little to medicine.
- 5.Ferns & lycopodium**
- 6.Land animals** : It provides traditional pharmaceutical materials ex: gelatin , wool fat , beeswax & are a source of hormones, vitamins & sera.
- 7.Bacteria** : Bacteriophyta is a source for the production of antibiotics , substrates & their employments in genetic engineering ex: in the production of human insulin.

Commerce & production

The crude drug which reaches the pharmaceutical manufacturing line will have passed through various stages , all can influence the nature & amount of active constituents. These headings are :

- 1- Environmental conditions: temperature, rainfall, day length & radiation, altitude.
- 2- Cultivated & wild plants.
- 3- Collection
- 4- Drying & grinding
- 5- Storage

1.Environmental conditions:

Plant growth , development & sometimes the nature & quantity of secondary metabolites are affected by temperature , rainfall , length of day & quality of light & altitude. Such effects have been studied by growing particular plant in different climatic areas & observing variations.

A-Temperature : It is a major factor controlling the development & metabolism of plants. Although each species has become adapted to its own natural environment , plants are frequently able to exist in a considerable range of temperature. Many tropical & subtropical plants will grow in temperate region during summer months , but lack frost resistance to withstand the winter. An example of the effect of temperature on plants is the formation of volatile oils appear to be enhanced at higher temperature , although very hot days may lead to physical loss of oil.

B-Rainfall : The important effects of rainfall on vegetation must be considered in relation to the annual rainfall , its distribution throughout the year , its effect on humidity & its effect coupled with the water-holding properties of the soil ex: different results have been reported for the production of volatile oils under different conditions of rainfall & sometimes it is coupled with the development of glandular hairs. Some times continuous rain can lead to loss of water soluble substances from leaves & roots by leaching , this gives the main reason for low yield of some active constituents in wet seasons from plants although its general condition is good..

C-Day-length & radiation characteristics : Plants differ in both the amount & intensity of the light they require. Wild plants will be found where its shade requirement is met & under cultivation similar shade must be provided. In certain cases research has shown that light is a factor which affect the amount of some substances produced ex : glycosides or alkaloids. It has been shown that under long day conditions peppermint leaves contain menthon , menthol & traces of menthofuran; while plants grown under short-day conditions contains menthofuran as a major component of the volatile oil.

Type of radiation had been studied in respect to morphological development of the plant , but little information had been reported concerning medicinal metabolites ex: many plants initiate flowers only in certain day length , therefor when flowering is essential this factor must be carefully considered before planting in a new region. Presence or absence of light , together with wave length range have a marked effect on the secondary metabolite production of some plants in tissue culture.

D-Altitude : Plants differ greatly in their altitude requirement ex: tea , coffee, cocoa , medicinal rhubarb , & cinchona require elevation , there fore changing or lowering the altitude with such plants will affect its metabolites production

ex: Cinchona succirubra the plant grows well at low levels but produce practically no alkaloids.

E-Atmospheric composition : Little informations are available about this factor but some reports indicated that changing atmospheric composition affect the amount & probably the type of some metabolites.

2.Cultivated & wild plants: Certain drugs are now obtained almost exclusively from cultivated plants ex: Cardamon , Ginger , Peppermint & Spearmint for oil production .Cultivation is essential in the case of drugs such as Indian hemp & Opium , which are subjected to government control & in many cases it is advisable because of the improved quality of the drug which is possible to produce. The improvement may be due to the following:

a-The ability to obtain collections of species , varieties , or hybrids which have the desired charecters ex: Cinnamon , Fennel , Cinchona.

b-The better development of the plants due to improved conditions of the soil , control of insects , pests , funji etc.

c-The better facilities for treatment after collection ex : drying at a correct temperature in cases of Digitalis , Belladona & the peeling of Cinnamon & Ginger.

For success in cultivation it is necessary to study the conditions under which the plant flourishes in the wild state & produce these conditions & / or improve them.

3.Collection :

Drugs may be collected from wild or cultivated plants & the task may be undertaken by unskilled or skilled workers depending on the plant to be collected. There are many points that should be taken in consideration during collection to have a good yield & quality of the plant , these are:

a-The season at which each drug is collected is usually important because the amount & sometimes the nature of the active constituents is not constant through out the year.

b-The age of the plant is also important & governs not only the total quantity of the active constituents produced but also the relative proportions of the components of the active mixture.

c-The time of collection whether it is day or night because there are avidence that the composition of a number of secondary metabolites varies through out the day & night.

d-Generally , leaves are collected as the flowers are beginning to open , flowers are collected just before they are fully expanded & underground organs as the aerial parts die down.

e-Leaves , flowers & fruits should not be collected when covered with dew or rain , barks are usually collected after a period of damp weather as they then separate more readily from the wood. For the gums , gum resins etc., dry weather is required & care should be taken to exclude vegetable debris as far as possible.

f-Any parts which are discoloured or attacked by insects or slugs should be rejected.

g- Under ground organs must be freed from soil . Shaking the drug before, during & after drying or beushing it may sufficient to separate a sandy soil, but in the case of a clay or other heavy soil washing is necessary.

4.Drying & grinding :

In most cases plant material is dried in the atmosphere prior to workup. It may be dried at room temperature or in the oven at no more than 30°C; it must be kept away from direct sunlight because ultraviolet radiation may produce chemical reactions giving rise to compound artifacts. Compact samples of fresh plant material with little air circulation may experience fungal infestation & elevated temperatures by fermentation if left to stand for several days, hence well-ventilated places & homogeneous distribution of the material should be ensured. Fresh plant material is sometimes specifically required for study & in these cases it should immediately extracted with solvent to prevent enzymatic processes or reactions that start after the plant is collected or during grinding. For instance, decomposition or rearrangements by pH changes may occur, leading to hydrolysis of constituents such as iridoid & flavonoid glycosides. These reactions may be prevented by denaturing the plant enzymes responsible by soaking the samples in methanol or ethanol soon after collection &/or by controlling the pH by adding a buffer.

If enzymic action is to be **encouraged** , **slow drying at moderate temperature** ex : Vanillapods is necessary , but if enzymic action is not desired, drying should take place as soon as possible after collection. Drugs containing volatile oils are liable to lose their aroma if not dried or if the oil is not distilled from them immediately , & all moist drugs are liable to develop mould. For these reasons drying apparatus should be situated as near to the growing plants as possible.

The duration of the drying process varies from a few hours to many weeks, & in case of open-air drying depends very largely on the weather. In suitable climates open-air drying is used for drugs such as Clove , Cardamon & Cinnamon. Even in warm & dry climates arrangements have to be made for getting the drug under the cover of sheds at night or during wet weather .

Drying in sheds the drugs (open-air drying) may be done by :

- 1- suspended in bundles from the roof
- 2- threaded on strings
- 3- placed on trays made of sacking or tinned wire-netting .
- 4- Paper spread on a wooden framework are also used especially for fruits from which it is required to collect the seeds.

In all drying sheds there must be a space of at least 15 Cm between super imposed trays , & air must circulate freely.

Note : Drying by artificial heat is more rapid than open-air drying & is often necessary in tropical countries where the humidity is very high.

Artificial drying is done by:

- 1- Belt driers which are used for large crops .
- 2-Alternatively heat may be applied by means of open fires.
- 3-stoves
- 4-hot- water pipes.

Rapid drying helps flowers & leaves to retain their colour & aromatic drugs their aroma , but the temperature used in each case must be governed by the constituents & the physical nature of the drug.

Generally leaves , herbs & flowers may be dried between 20-40 C & barks & roots between 30-65 C . If leaves & other delicate structures are overdried , they become very brittle & tend to break in transit , while drugs such as aloes & opium may require further drying after importation.

For the **grinding (comminution)** of plant material , several types of equipments can be used , from sophisticated mills & blenders , to simple axes, scissors , or knives. When the secondary metabolites to be extracted are thermolabile or volatile , the milling stage may be omitted to avoid losses by heat generated during comminution. The plant material may also be frozen with liquid nitrogen, & pound in a chilled mortar or thick polyethylene bag, even with fresh material. The grinding process assists the penetration of the solvent to the cellular structure of the plant tissues , thereby helping to dissolve the secondary metabolites & increase the yields of extraction. Generally , it has been found that the smaller the particle size of the plant material the more efficient the extraction.

5- Storage : Drugs stored in the usual containers ex: sacks , bales , wooden cases , cardboard boxes & paper bags , reabsorb about 10-12% or more of moisture. They are termed “**air dried**” . Plastic sacks will effectively seal the contents. The combined effects of moisture & temperature on humidity & the subsequent water condensation when the temperature falls , must be considered in drug storage.

Drugs such as Digitalis & Indian hemp should never be allowed to become air dried or they lose a considerable part of their activity . They may be kept in a sealed containers with a dehydrating agent . For large quantities the bottom of a case may be filled with quicklime & separated from the drug by a perforated grid or sacking. If the lime becomes moist , it should be renewed . Volatile oils should be stored in a sealed well filled containers in a cool , dark place. Similar remarks apply to fixed oils .

Air – dried drugs are always susceptible to the attack of insects & other pests , so they should be examined frequently during storage & any showing mould or worminess should be either rejected or treated, & sometimes to reduce undesirable microbial contamination & to prevent the development of other living organisms , materials may require sterilization before storage , but drugs so treated should comply with an acceptable limit for toxic residue.

Deterioration : The primary factors which must be considered in relation to drug deterioration are moisture content , temperature , light & presence of oxygen , when these conditions are suitable , living organisms ex : bacteria , mould , insects will rapidly multiply using drug as a source of nutrient.

- 1- **Humidity** : humidity in 10-12 % moisture may be sufficient to activate enzymes present in the leaves & bring about decomposition of the glycosides. Other drugs which contain mucilage quickly absorb moisture & become a sticky mass .
- 2- **Temperature** : an increase in temperature in combination with moisture may
 - a- accelerate enzyme activity .
 - b- large temperature rise will lead to a loss of volatile constituents ex: volatile oils.
 - c- In case of absorbent cotton wool cause a reorientation of the small amount of fatty material present leading to non or lower absorbency.
- 3- **Sun-light** : direct sunlight can cause :
 - a- Produce bleaching of leaves & flowers.
 - b- Decomposition of certain constituents ex: vitamins in cod-liver oil
- 4- **Oxygen** : this factor assists in the resinification of volatile oils & in the rancidification of fixed oils.

Methods of using plants:

- 1- Plants may be used as **isolated parts** e.g. dried leaves of plant as digitalis which contain glycosides as dogoxin which is used for the treatment of heart diseases & congestive heart failure.
- 2- **Whole plant** e.g. Catharanthus roseus & its active constituents vincristine & vinblastine which are used as anticancer.
- 3- **Extract of active constituents** e.g. extract of unripe fruit of plant as Papaver somniferum which contains morphine which is used as narcotic. The resultant extract is called **extractive** which refers to the principle constituents found in

natural substances & are separated or isolated from the natural substances by different means of extraction , these principles are responsible for the medicinal activities of the natural substances & these are found either single or mixtures.

Importance or value of of natural products drugs:

Natural drugs & their active constituents play many significant roles in modern medicine , as the followings:

- 1- Some medicinal plants & their drugs have a **high healing power** for some diseases specially cancer & heart diseases ,& till now these drugs are still in use in medicine e.g. digitalis & catharanthus (Vinca rosea).
- 2- Natural products provide a **good source for a number of useful drugs that are difficult in not possible to be produced commercially** by chemical or micro biological mean ; therefore , the only mean to produce these drugs is the plant e.g. digoxin , vincristine , vinblastine, morphine etc....
- 3- Natural products supply **basic compounds that can be modified structurally** to render them more active , less toxic , or change their activity e.g. production of codeine(cough suppressant) from morphine (narcotic & causes addiction).
- 4- Natural compounds can be used **as models for the synthesis** of some drugs that have the similar pharmacological activities e.g. salicin which is a glycoside having antirheumatic activity was used as a model for the synthesis of salicylic acid.
- 5- Some natural compounds which demonstrate little or no activity themselves can be **modified structurally by chemical or biological methods to produce potent drugs** not easily obtained by other methods e.g. using saponin glycosides as a source for the production of cortison & its derivatives & other hormones.

Commercial classification of medicinal plants:

In this system medicinal plants are classified according to their uses in the commercial market as follows:

- 1- **Medicinal plants:** these plants are sold for treating diseases.
- 2- **Condiments:** e.g. white & black pepper , cardamon , crocus etc...
- 3- **Aromatic plants:** these are medicinal because it contains volatile oils , but these drugs are employed as flavoring agents for food , cosmetics etc...
- 4- **Insectisides** :some plants & their active constituents are used for killing insects e.g. pyrethrum , or **as rodentiside** e.g. red squill or **fungiside** e.g. henna.
- 5- **Beverages** : some medicinal plants are used as beverages e.g. tea , coffee , cacao , cola etc...

Adultration of drugs:

Generally adultration means debasement of any crude drug. The crude drug adultration is whether intended or not , may arise from the following conditions:

- 1- **Inferiority** : any substance & drug regardless the cause e.g. Opium alkaloids which contain morphine should not contain less than 10% of anhydrous morphine , if the drug contain less than this percentages it is considered as inferior drug.
- 2- **Spoilage** : means any destruction in quality & value of crude drug by the action of bacteria , or fungi with the production of products unfit for human consumption.
- 3- **Deterioration** : e.g. Over roasted coffee bean leads to loss of caffeine.
- 4- **Admixture** : means crude drug contains inferior materials above the standard of official limit , this occur either by accident or ignorance , or due to carelessness.
- 5- **Substitution** : this type of adultration takes by completely different drug given instead of other one e.g. American saffron may be given instead of Spanish saffron.
- 6- **Sophistication** : in this type addition of inferior drug to another one intending to deception e.g. ginger which is yellow in color, pungent in taste & expensive can be replaced by a mixture of capsicum , wheat flour, & curcuma.

Therapeutic or pharmacological classification of medicinal plants:

In this system the medicinal plants are classified in groups according to their pharmacological activities or therapeutic uses, as follows:

- 1-**Cardiotonic** :e.g. Digitalis , red squill.
- 2-**Laxatives** :e.g. Senna , Castor , Aloe
- 3-**Anthelmintics**: e.g. Pomegranate
- 4-**Sedatives or narcotics**: e.g. Papaver , Datura

- 5-**Carminative**: e.g. Peppermint , Spearmint , Anise
6-**Antirhematics**: e.g. Salix , black mustard
7-**Nutrients**: e.g. Citrus , Allium , Garlic
8-**Anticancer**: e.g. vincristine , vinblastine (from vinca rosea)
9-**CNS stimulant**: e.g. caffeine , theophylline (from tea , coffee , cacao)
10-**Narcotic analgesic**: e.g. morphine (from opium)
11-**Cholinergic** : e.g. pilocarpine , muscarine
12-**Anti cholinergic**: e.g. atropine ,hyoscine (from Datura , Belladonna)
13-**Adrenergic** :e.g. ephedrine
14-**Anti arrhythmic**: e.g. quinidine (from Cinchona)
15-**Anti hypertensive**: e.g. reserpine
16-**Diuretics**: e.g. xanthine derivatives from tea & coffee
17-**Hypolipidimic**: e.g. garlic
18-**Astringent** :e.g. tannins (from gall or pomegranate)
19-**Antiseptics** : e.g. eucalyptus oil , thyme oil , eugenol
20-**Anti infectives**: e.g.
 a- Antibiotics : from moulds & streptomyces
 b- Antimalarial : quinine (from Cinchona)
 c- Amoebicides : emetine (from Ipecac)
 d- Anthelmintics : santonin (from Achilea)

Chemistry of natural products

Biological sources particularly plants are the main source for many organic compounds which are important pharmacologically & therapeutically. These compounds are synthesised & degraded to form another organic compounds by a series of chemical reactions . These chemical reactions are collectively called "**metabolism**", & so these chemical compounds are classified as **primary & secondary metabolites**.

Primary metabolites are biosynthesised through the photosynthesis , while secondary metabolites are biosynthetically derived from primary metabolites. The active constituents found in plants are:

1.Carbohydrates & related compounds: compounds composed of carbon , hydrogen , & oxygen as polyhydroxy aldehydes or ketone alcohols e.g. sucrose , lactose , starch , acacia , tragacanth , agar , pectin.

2.Glycosides : substances that on hydrolysis yield one or more sugar with another non sugar compound e.g. barbaloin , glycyrrhizin , vanillin etc...

3. Tannins : a group of complex phenolic compounds capable of combining with proteins e.g. gallotannins etc...

4. Lipids : compounds comprising fixed oils , fats , & waxes.

Fixed oils & fats are glyceryl esters of fatty acids that are saponified by alkalis e.g. olive oil , peanut oil , sesame oil , castor oil etc...

Waxes are esters of fatty acids with high-molecular weight , monohydric alcohols e.g. beeswax , carnauba wax.

5.Volatile oils: essential oils that represent the odoriferous principles of plants e.g. peppermint oil , clove oil , cinnamon oil , anise oil , rose oil .

6.Resins & resin combinations: compounds comprising resins , oleoresin , oleo-gum resins , & balsams.

Resins : solid or semisolid amorphous products of complex chemical nature: e.g. rosin , podophyllum resin , jalap resin.

Oleoresin : resins & volatile oils in homogeneous mixtures e.g. turpentine , copaiba .

Oleo-gum resins : oleoresins & gums in homogeneous mixtures e.g. asafetida , myrrh.

Balsama : resins with mixtures of aromatic substances such as benzoic acid , cinnamic acid or both e.g. benzoin , tolu balsam , Peru balsam , styrax.

7.Steroids : derivatives of cyclopenta phenanthrene e.g. estrogens , androgens, adrenal cortex hormones , cardioactive aglycones , bile acids , cholesterol , ergosterol.

8. Alkaloids : nitrogenous crystalline or oily compounds , usually basic in character e.g. atropine , morphine , quinine , cocaine , reserpine.

9. Peptide hormones: active principles secreted by certain endocrine glands e.g. glucagon , insulin , oxytocin , vasopressin , ACTH.

10. Enzymes & other proteins : organic catalysts produced by living organisms e.g. pepsin , pancreatin , rennin , trypsin. Proteins are nitrogenous organic substances composed of amino acid units e.g. gelatin , heparin , protamine.

11. Vitamins : chemical compounds necessary for normal growth & function e.g. thiamine , riboflavin , cyanocobolamin , ascorbic acid , tocopherol.

12. Antibiotics : chemical entities produced biosynthetically that are destructive or inhibitory to microorganisms e.g. penicillin , cephalosporin , polymyxin , tetracyclin , erythromycin , kanamycin , griseofulvin , gentamycin.

13. Biologics : products composed of antigenic matter or antibody preparations capable of developing a state of immunity in the patient e.g. adsorbed diphtheria toxoid , hepatitis B vaccine , poliomyelitis vaccines , immune globulins , diphtheria antitoxin ; also biologics related to human blood e.g. albumin human , antihemophilic factor.

14. Allergins: substances , usually proplasmic in origin that cause unusual responses in hypersensitive individuals e.g. pollen grains , mold spores , feathers , animal dander , poison ivy.

poisonous plants: Higher plants & fungi that produce toxic effects when introduced into the human body e.g. jimson weed , nightshade , amanita.

Herbs & "Health foods":

products of natural origin used by human in a self-treatment of disease states or less than optimal-health conditions. Many are without therapeutic effect , & some are toxic.