Pharmacognosy Notes

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Tanins :- Large phenolic compounds, having more than one hydroxyl group that’s why they’re also called polyphenols

**Major Characteristics**

1. Tanins are large molecules, their MW reaches 30,000 dalton, they’re large biomolecules which are produced biologically not by synthetic chemistry because their synthesis by synthetic chemistry is not easy due to their stero-chemistry and multiple chiral centers. The enzymes that are responsible for their production they’re polyketide synthases also called “Cholcan synthases”.
2. Tanins contain Carbonyl and phenolic hydroxyl as well.
3. Most important property is that they precipitate proteins so they’re astringents, the functional group which is responsible for this property is the hydroxyl group mostly.

**Classification of Tanins**

1. Hydrolysable tanins – these contain ester linkage which is easily to be hydrolyzed in the presence of water and acid their basic unit is Gallic Acid Which is sometimes esterfied with sugar.
2. Non-Hydrolysable tanins (Condensed Tanins) – Difficult to be hydrolyzed, they’re formed by polymerization of Flavonoid.

**Extraction**

- Both types are soluble in H2O, the ideal solvent for the extraction of hydrolysable tanins is water, but Flavonoid only without polymerization is insoluble in H2O.
- When the linkage between flavonoids break down, you will get flavonoids which are water...
insoluble so the best solvent for the extraction of non hydrolysable tanins is H2O + Ether.

After extraction, a chromatography process should be done to get the pure compound, its difficult to separate them because they have similar stereo-chemistry and solubilities and physicochemical properties, Caution should be taken during separation because tanins can ppt protein that’s why Acetone is added to prevent the formation of the hydrogen bond between the tanins and protein and a high yield will be obtained.

**Medical Importance**

1- They have Antiviral + Antifungal + Anticancer + Antioxidant + Anti microbial Activities
2- Hypolipidimic agents
3- Anti-Aging
4- Protects the body from radiations + Chemicals + Free radicals

**The importance of the Astringency**

Patients with skin lesions, burns, Cold sores, Hemorrhoid and abrasion they have a damage on their external layer of the skin so the underlying tissues will be in direct contact with the environment and micro-organisms which may cause infections so adding any substances that can make precipitation like Tanins will form an isolated layer to protect the skin from the external environment and micro-organisms and aid in the process of healing and prevent the entry of micro-organisms that’s why Tanins have anti microbial activity, But their antimicrobial activity is effective only against the non resistant strains.

**Interactions**

1- Tanins should not be taken with Tea, Grapefruit, orange, pomegranate and anything that contain protein because they cause ppt of proteins.
2- They have a wide drug-interactions with many drugs for example anti hypertensive, sedatives, analgesics

**Epigallocatechin ( EPGC )**

Most important type of tanins, having anti-cancer and anti-oxidant activities, it’s a combination of gallic acid and flavonoids, mainly its found in Green tea but upon processing to black tea using Heat a cyclization will occur within EPGC leading to the formation of a new type of tanins called **Theaflavin** which have anti oxidant activity but lack the anti cancer activity.
Tanins Role in Nature

- The polyphenols are found in many fruits and plants but varies in concentration and location (Seeds, leaves, flowers tops ....... Etc) according to the plant they exist in
- Flavonoids - As long as they have a conjugated system they can absorb UV radiations and give a color which depends on the polymer concentration, the color ranges from Yellow, Orange, Blue, Green, Violet
- Flavonoids – are responsible for providing almost all the colors of the flowers/plants after the disappearance of chlorophyll, that’s why they’re called Plant Pigments, and usually the plants uses these pigments for insect attraction and as growth regulators.

Extra Informations

- Pomegranate have a high concentration of tanins, it has anti microbial, anti oxidant and anti aging activities (Every anti oxidant is anti aging because it will neutralize the free radicals which will lead to slowing down the aging process)
- Tanins should not be taken with proteins, at least there should be 2 hours between them according to gastic emptying
- Tanins are protectant against CVA (Cardiovascular accident), CVA occur when there’s extra lipids within the blood, these lipids undergoes beta oxidation where they will be oxidize and adhere to the lining of the blood vessels, day by day they will accumulate causing Atherosclerosis, so taking antioxidants will prevent this oxidation and prevent CVA occurrence
- Glutathione is an anti oxidant which is found in our bodies and can neutralize the free radicals but its capacity is limited that’s why anti oxidants should be taken like tanins
- Tanins are stronger anti oxidants than Vitamin E & C.

Flavonoids & Flavonolignans

Different from Tanins in biosynthetic pathway, chemical configuration and the electronic environment

Flavonoids & Flavonolignans As Anticancers

Flavonoids and Flavonolignans have an anti cancer activity due to their flat formula which able them to bind with the DNA strands and inhibit DNA gyrase thus interfering with the process of
transcription, later on they will interfere with the cell division, and since the cancer cells are highly proliferating so they will be highly affected by Flavonoids and Flavonolignans and undergoes Apoptosis.

**Flavonoids & Flavonolignans Used to treat Ulcers**

Due to the ability to precipitate proteins (Astringency), in Ulcers the epithelium tissue is damaged so the underlying layers will be in direct contact with the gastric acid giving the acids a chance for perforation, but precipitation will prevent perforation by forming an isolated layer.

**Side effects of Flavonoids & Flavonolignans**

- Rapid decrease in blood pressure
- Increase heart rate / Tachycardia
- Coma
- Major effect is inhibiting CYP450 isozymes which will lead to interfering with the metabolism of certain drugs resulting in prolonged half life and toxicity.

**Flavonolignans**

- Lignans comes from Para hydroxy cumaric acid pathway
- Lignans can be polymers
- Lignans are responsible for the hardness of the plant
- Lignans are found only in one species which is *Silybum marianum*

They are very useful for hepatic protection from hepatitis and cancer, they have a very potent anti oxidant activity, Silybins (Fam: *Silybum marianum*, usually concentrated in Seeds) which are a type of flavonolignans have a very potent anti oxidant activity even more potent than that of flavonoids.
- They’re one of the most abundant drugs in nature
- Their activity ranges from analgesics, narcotics, anti cancers and anti viral that’s why they have an important medicinal values
- They serves as models and upon modification new drugs are obtained
- They’re not produced by every plant unlike Tanins
- They’re produced by human, plant and a sort of micro-organisms like marine
- Endogenous neurotransmitters are sort of alkaloids
- They produced potent pharmacological activity with a very small concentration
- All types of alkaloids contain Nitrogen
- Opioids, anticancers and sedatives are alkaloids

So …… Alkaloids :- Are complex nitrogenous compounds, which are produced by biological system and aren’t produced synthetically, they excrete a potent pharmacological activity with a very small concentration and they’re derived from Amino acids.

**Why they’re important ?**
- Most of the receptors sites in the autonomic nervous system are designed to accept alkaloids, so micro grams of alkaloids can produce a huge change in biological system, so drugs like alkaloids which have similar structure to that of neurotransmitters will become in contact with the receptor sites either it will block the receptors site or activate it (Agonist).

**Give an example of an alkaloid which is produced by more than one species ?**
- Nicotine and Ergot alkaloids are produced by more than one species, usually a single alkaloid is produced by only one species.
**Physicochemical properties**

- They’re weak bases except the quaternary ammonium compounds which are weak acids.
- They contain an amine group which determine their biological activity, mostly the amine group is secondary and tertiary.
- They amine group usually contain unshared pair of electrons except in quaternary ammonium alkaloids in which the amine group doesn’t contain unshared pair of electrons.
- They’re insoluble in water except the quaternary ammonium compounds which are soluble.

**Extraction**

Their basicity is important for their extraction and the can be isolated during the extraction procedure.

Procedure: they’re soluble in organic solvents (chloroform, benzene... etc), so organic solvent must be used to extract them from the plant part, and during extraction the alkaloids and any lipid soluble compounds will move with organic solvent, and an extract of alkaloids + lipid substances will be obtained, so to get the alkaloids only, a change in the alkaloid phase should be done, meaning changing lipophilicity of the alkaloids and this is done by adding **weak acid** which will react with the alkaloids and from a salt and directly will be separated from the organic phase, now freeing the alkaloids from the salt is done by adding **weak base** ammonium chloride which will push the alkaloids from the salt and replace it and a pure crystals of alkaloids will be obtained. Quaternary ammonium compounds follows another procedure.

**True – Pseudo – Proto Alkaloids**

- True Alkaloids, derived from amino acids and have heterocyclic nitrogen within the structure (the nitrogen is within the cycle) like Quinine.
- Pseudo Alkaloids, not derived from amino acid, have a heterocyclic ring with a nitrogen like Caffeine.
- Proto Alkaloids, have a nitrogen which is not part of the cycle like Taxol.

![Quinine](image1.png)  ![Caffeine](image2.png)  ![Taxol](image3.png)
Classes of Alkaloids

- Mainly alkaloids are classified according to their nucleus (Mentioned in Lectures)
- Main Alkaloids are derived from the following amino acids:
  1. Quinoline, isoquinolone are derived from Phenylalanine
  2. Pyridine, Piperidine is derived from Lysine
  3. Pyrulidine is derived from Ornithine
  4. Tropane comes from Ornithine + Acetate (Acetyl CoA)
  5. Imidazole is derived from Alanine and Aspartic acids
  6. Purine is derived from Aspartic acid, Leucin and Alanine
  7. Indole is derived from Tryptophan

Areca

- An important alkaloid which resemble to acetylcholine so it acts on muscarinic receptors (M1, M2, M3) just like the acetylcholine, so its unspecific agonist of muscarinic receptors, it cause Euphoria, Relaxation and addiction.

Nicotine

- Like Acetylcholine, it acts on nicotinic receptors as an agonist
- Algae can produce nicotine beside some species (Mentioned in Lectures)
- All Solanaceae plants produce nicotine but in very small concentration
- Can reach the CNS within 3-7 Seconds and its highly addictive

Why some alkaloids are found in liquid form? give an Example

- Most alkaloids are found in solid form, rare types are found in liquid form like Nicotine and its liquid because it lacks Oxygen.
Tropane Alkaloids nucleus
- Mostly they are esterified with Tropic acid
- Tropic acid is derived from L-Phenylalanine
- There are many plants and species of Solanaceae family produces this type of alkaloids.

**History**
- They have been used as poisons by many ancient cultures like greeks, Egyptian and romans as well as remedy, females used to wash their eyes with these alkaloids for the purpose of beauty due to their mydriasis effect.

**Occurrence**
- They’re usually concentrated in leaves and flowering tops
- Some are found in seeds and stem
- They’re true alkaloids because they are derived from an amino acid (Ornithine) and the nitrogen is within the cycle

**Why They’re important?**
Their structure resemble to that of the acetylcholine so upon administration they will be bind to the muscarinic receptors as the acetylcholine and their effect will be generalized to the whole body, because of this there are many drugs which are derived from these alkaloids and act on CNS, GIT, Kidney, Eye, PNS and much more
The hydrophilic and hydrophobic interactions are to stabilize the drug molecules on the receptor site.

**Tropane Alkaloids effects on CNS**

Tropane alkaloids hinder the binding of the acetylcholine to the muscarinic receptors because they resemble the acetylcholine so they’re antagonists because they produce no action they just prevent the binding of acetylcholine to the the postsynaptic receptors.

Muscarinic receptors include five types which are classified according to their location:

1. M1 . Gq . Located in neuron area , exocrine glands, adrenal medulla
2. M2 . Gi,Gs . Located in the heart
4. M4 . Gi . CNS
5. M5 . Gq,Gs . CNS

M1 receptors are bound to phospholipase by Gq , so when acetylcholine binds to M1 receptor the phospholipase will be activated which will breakdown triglycerides to form triphosphate inositol IP3 that will act on the endoplasmic reticulum and increase the intracellular concentration of Calcium thus , inducing contraction, secretions and salivation.

Activating M2 receptors by acetylcholine will deactivate the second messenger cAMP , therefore the heart rate will decrease and so as the contraction rate of the SA node.
Activating M3 receptors by acetylcholine have the same cascade and mechanism as that of M1 receptors. Activated M3 receptors leads to Vasoconstriction, increase peristaltic movement, increase the contraction of smooth muscles, enhance defecation.

M4 and M5 are activated only at toxic level and high doses of the drug.

SO ........ Tropane alkaloids will prevent acetylcholine to bind to M receptors making the sympathetic autonomic system dominating and produce the following:

- Dryness of the mouth due to lackness in saliva secretion
- Decrease acid secretion and digesting enzymes
- Decrease peristaltic movement causing Constipation
- Urine retention
- Tachycardia

According to the previous effects we can use tropane alkaloids for Diarrhea, ulcers, abdominal cramps, flocculence and to provide relaxation for ureter and urinary bladder.

**Pharmacokinetics**

- Tropane alkaloids are soluble in organic solvents
- Protonated to quaternary ammonium compounds in physiological pH
- Can’t reach the CNS easily due to their hydrophobicity, they reach the CNS only at toxic levels
- Half-life 1-1:30 hr
- Metabolized by CYP450
- Excreted through urine

**Atropine**

- The five plants (Mentioned in Lecture) that produce atropine have a similar leaves shape and flowering top
- These plants can’t be used as an ornamented plant due to their high toxicity
- The five plants have a high concentration of Levo Hyoscyamine which is have very potent pharmacological activity, but upon extraction you will get a racemic mixture of dextro hyoscyamine and levo hyoscyamine which is called ATROPINE and its much less active than levo hyoscyamine
- Atropine over doses cause Dry mouth, blurred vision, constipation, tachycardia, increase risk for stroke, hypertension, nausea, vomiting, and may lead to death
Cocaine
- CNS stimulant, Local anesthetic, Narcotic and highly addictive substance
- Directly reaches the CNS without protonation nor acting on muscarinic receptors
- Dosage forms include orally, nasal insufflation, sprays, and IV
- Half life aprox 60-90 mins
- Excreted through urine
- Metabolized by CYP450

**How the cocaine cause addiction?**
Usually it acts on the dopaminergic pathway and increase the release of dopamine which is a catecholamine that’s not easily break down by enzymes unlike the acetylcholine which can be break down easily by acetylcholinesterase due to the weak ester bond, according to the mechanism of the dopamine release (Please read the full mechanism in Pharmacology Lecture 1 ) the dopamine in the last step will be reuptake by a transporter back to the neuron, the Cocaine will inhibit the transporter leading to increasing the concentration of dopamine in the synaptic cleft and causing desensitization and down regulation of the postsynaptic receptors and Euphoria, therefore the next dose should be larger than the one before it to have the same effect and reach euphoria level. that’s why its considered to be one of the most addictive substances and it can cause addiction from the very first dose.

**Cocaine Side effects**
- Tachycardia
- Anorexia
- Constipation
- Mydriasis and blurred vision
- Muscle weakness
- Osteoporosis
- Renal failure
- Hepatic failure
- Heart failure