PHARMACOGNOSY AND PHYTOCHEMISTRY

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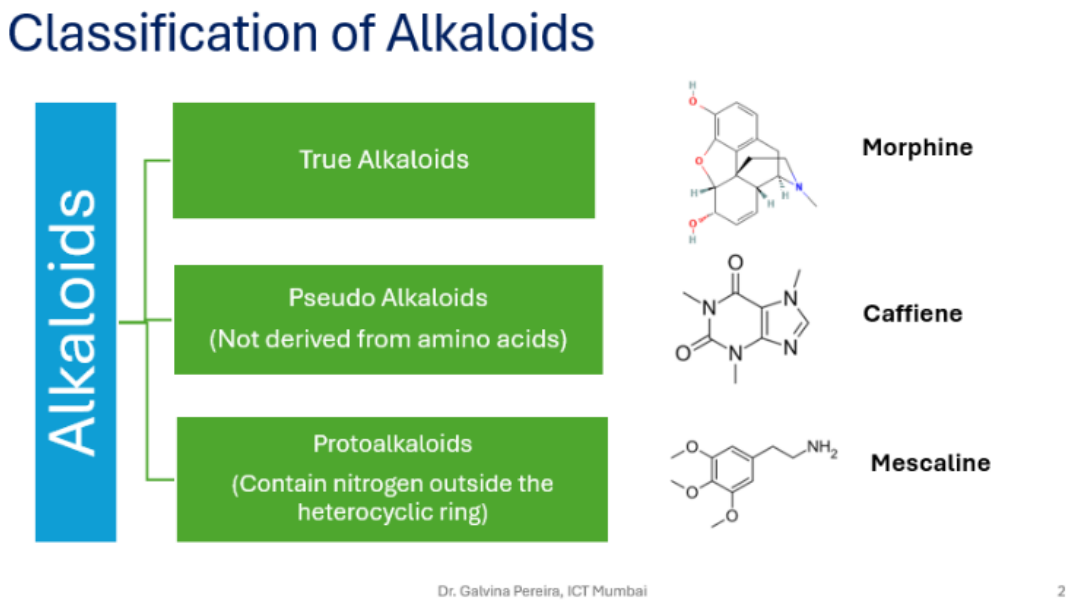
Week 5

Lecture 22

Classification of Alkaloids

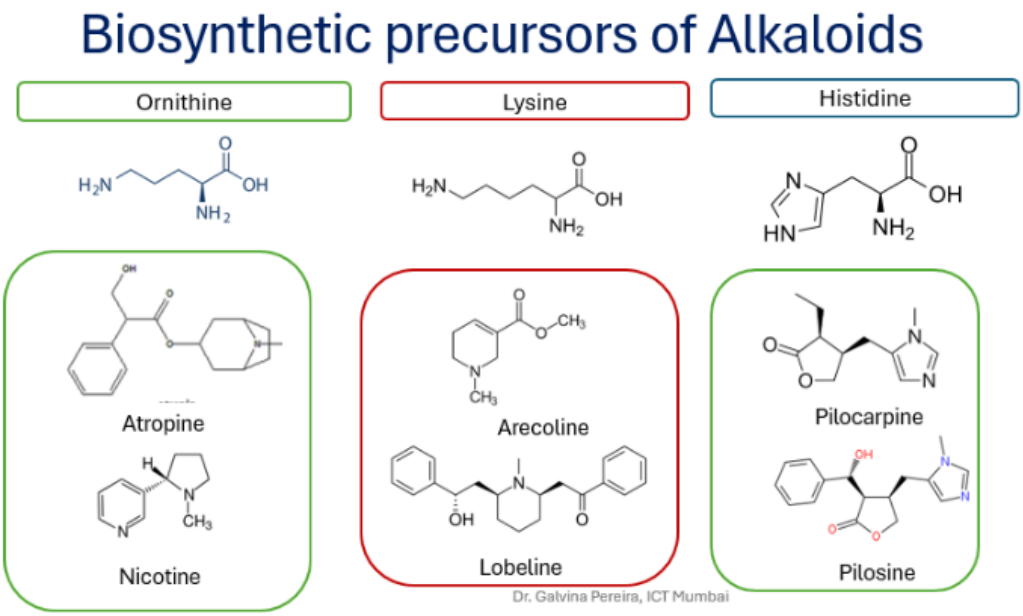
Hello everyone, and welcome to the NPTEL course on pharmacognosy and phytochemistry. This week, we are delving into a beautiful set of very potent compounds called alkaloids. In the previous session, we learned that alkaloids are nitrogen-containing compounds which are pharmacologically very active, meaning they have CNS effects, effects on our whole body, and they are very potent even in minute concentrations.



We learned that they are derived from amino acids and contain nitrogen. apart from nitrogen sometimes they also contain oxygen but that is not a mandate depending upon their biosynthesis and whether the nitrogen is present in the ring or not, we classified our

alkaloids as true alkaloids if the nitrogen is part of a heterocyclic ring and they derive from amino acids. We call them pseudo alkaloids if they are not derived from amino acids, and we call them proto alkaloids

if the nitrogen is outside the ring, meaning the nitrogen is no longer part of a heterocyclic ring. We learned a few examples wherein we took morphine as a case of a true alkaloid, caffeine as a case of a pseudo alkaloid, and mescaline as a case of a proto alkaloid. We classify alkaloids further based on their biosynthetic precursors. So, a few of the biosynthetic precursors of alkaloids are ornithine, lysine, histidine, phenylalanine, tryptophan, and so on.



So, let's learn them one by one and understand the genesis of alkaloids from this set of compounds. As we have defined alkaloids as nitrogen-containing compounds, many of them have their genesis from amino acids because naturally, amino acids contain nitrogen. So you will see that majority of precursors of alkaloids are your amino acids. Take case of ornithine.

Now, as you see here in ornithine, what happens during biosynthesis is you have a nitrogen and then you count the further number of carbons. Let me just put it as one. two,

three, four. Now what happens is if you just cut it off like this and cyclized it, so you should have four carbons, one, two, three, four.

Now one of the nitrogen is retained and one of the nitrogen is eliminated along with the carboxylic acid. The retained nitrogen is cyclised to form a 5-membered ring. Now examples of ornithine derived and colloids include atropine. Now where do you see this 5-membered ring in your atropine is just watch carefully.

So this is carbon number 1, carbon number 2, carbon number 3, carbon number 4, And here we go. So this is the five membered ring of your tropane alkaloids, especially atropine, which is being derived from ornithine. Another case is if we specifically take this ring in your nicotine, it's the same thing. So you can have four carbons: one, two,

three, and four. So, this five-membered nitrogen-containing ring, usually pyrrole or pyrrolidine, is generally derived from ornithine as an amino acid. Now, instead of five, if you are thinking of a six-membered ring, this six-membered ring can be brought in from here, but let's take fresh examples.

Take, for example, arecoline. Now here, instead of a five-membered ring, you have a six-membered ring. So how does that happen? In the same manner, a nitrogen then starts with carbons two, three, four, five. Break this off, cyclize it.

So I am just putting it as carbon number one, two, three, four, five, and I'm just putting a nitrogen at the center. So here you have a six-membered ring: five carbons and a nitrogen. Now this may vary in aromaticity; sometimes it might cyclize, sometimes it might remain aliphatic as such. A good example of a six-membered nitrogen-containing ring is your arecoline.

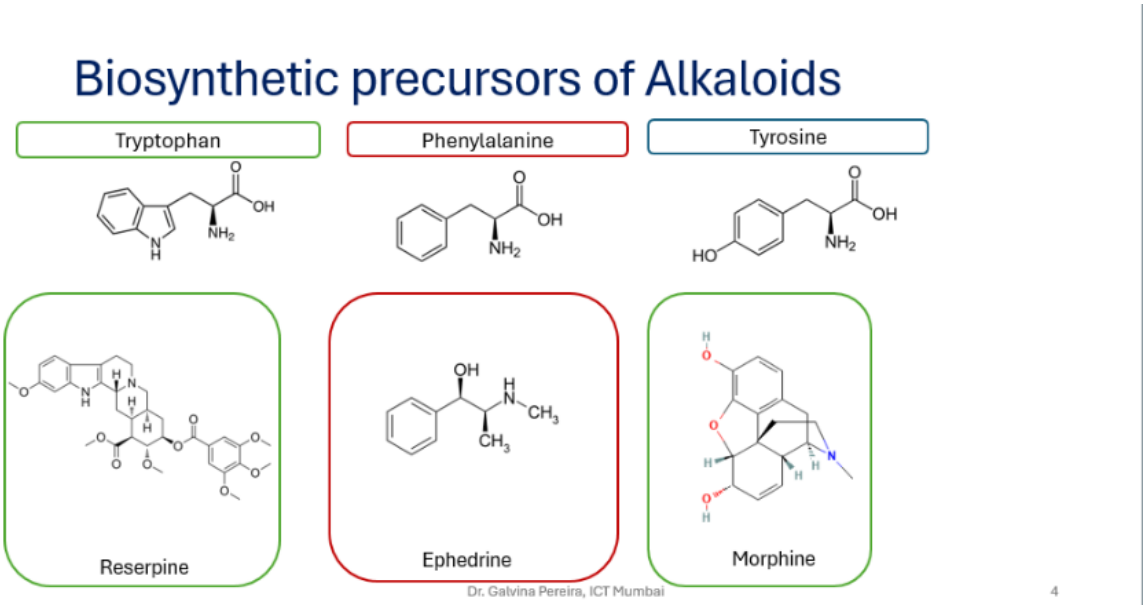
which occurs in arecoline and Lobeline. Now, the third case is derived from the amino acid histidine, generally imidazole types. So here, you see this kind of breaks off and the contribution of your imidazole moiety. is given by that. In many of the cases, you will also have observed that many of these nitrogens acquire amino acids.

They are all primary, but they methylate and become secondary amines. In addition to that, like in the previous lecture, we also discussed that owing to their alkaline nature,

they might also form salts with the acids present in plants. A few other biosynthetic precursors include tryptophan. Now, tryptophan is one of the amino acids derived from the shikimic acid pathway.

The other amino acids derived from the shikimic acid pathway are phenylalanine and tyrosine. So, all these three precursors come from one particular biosynthetic pathway, which is the shikimic acid pathway. Now, tryptophan mainly gives rise to a class of alkaloids called indole alkaloids. A good example of that is reserpine. Now, you can see a very complex structure, but let us find the indole in that.

So, this is your indole. If you were able to trace it before me, very nice. And if you see an additional, what you see here is 1, 2, and on the third carbon, on the third place, you have a nitrogen. So 1, 2, and on the third place, you have the nitrogen. So this part of the indole ring is retained as such.



So reserpine is an example of an alkaloid which is used in hypertension. to decrease blood pressure and another interesting indole alkaloid is your vinca If you have heard of the anti-cancer drug called vincristine or vinblastine, we also obtain it from tryptophan as a biogenetic source. Now, coming to alkaloids derived from your phenylalanine. This is an example we see even as a case of a protoalkaloid.

So here, the nitrogen is not a part of a heterocyclic ring. So we can call it a protoalkaloid as well. Now we retain the ratio. So it's phenyl. If you remember, phenylalanine is also a contributor to phenylpropanoids.

But what happens in this case is we are going to eliminate this carboxylic acid. And as a result, what happens is you have a phenyl, you have carbon number one, two, and a nitrogen at three. You have carbon number one, two, nitrogen at three. The subsequent methylation is done by other compounds with the help of enzymatic processes. So, ephedrine is one example of an alkaloid which is obtained from phenylalanine as a precursor.

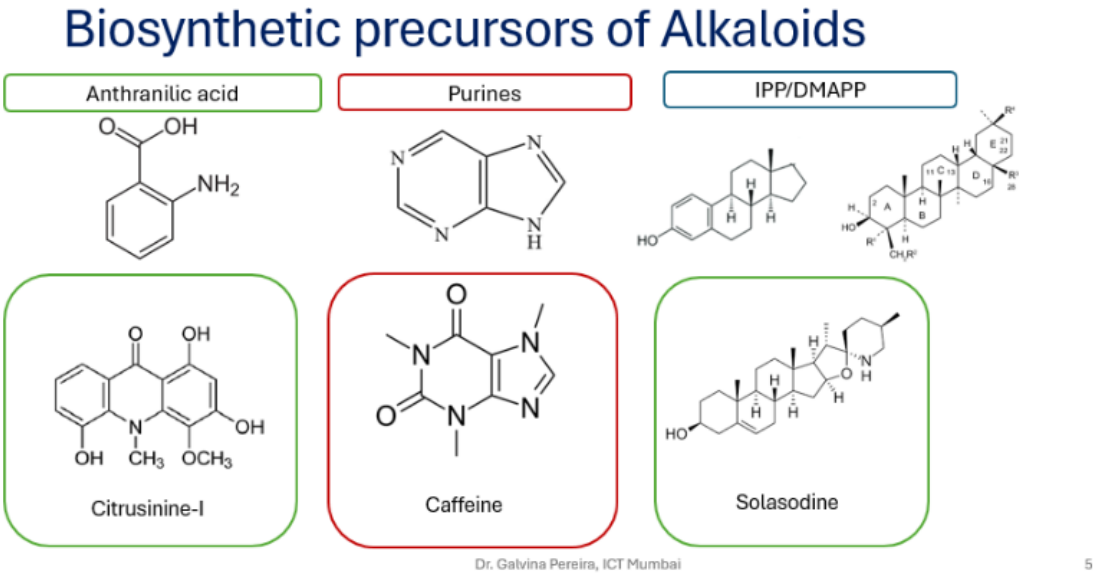
Now, we move to alkaloids derived from tyrosine. Tyrosine is very similar in structure to phenylalanine. In fact, it is called hydroxyphenylalanine. Now, what happens here is, apart from the carbon number 1, 2, and nitrogen, you will also have a hydroxy contribution happening over here.

Now, in some cases, because of biosynthetic arrangements, it may get slightly rearranged, but we can definitely trace the biosynthetic part of it. So, you can see one example I can quickly show you. So, this is your phenyl This is your hydroxy, and you can see here carbon number one.

Let me just trace that for you. Carbon number two. And this is your nitrogen. So, you have your phenylethylamine kind of contribution, which is given in the case of morphine. Now, there are numerous structural rearrangements possible.

So, we have just given you a very simplified version of the biosynthetic precursors. So, all these three biosynthetic precursors come from your shikimic acid pathway. Another biosynthetic precursor, which comes from the shikimic acid pathway, is anthranilic acid. In fact, it's a byproduct of the shikimic acid pathway. And, as you can see, there are some

alkaloids derived from anthranilic acid as well.



So, if you see here, your citrrusinine. Here, you have your phenyl group. This is the nitrogen part, and this is the carboxyl part. So they kind of fuse with other precursors or other biosynthetic parts joined together to give you citrusinine 1. Now, we come to the next contributions.

Next contributions, if you remember, we discussed one alkaloid as a pseudoalkaloid. And this pseudoalkaloid was caffeine. Caffeine is obtained from purine as a precursor, which are your DNA bases, if you remember. And you can see clearly what has been done is you have your ketone substitution. You have your methyl substitution, which is being done to purine.

And thereafter, you get your caffeine, theophylline, and theobromine depending upon the place of methylation. Now, the last set of precursors are the ones which are derived from what are called the terpenoidal pathway. If you remember your terpenoidal precursors, we have mainly two: isopentyl pyrophosphate and dimethyl allyl pyrophosphate. Now, they join to each other either in a head-to-tail fashion or in a tail-to-tail fashion to form long-chain compounds.

The next set of compounds are sterols. The sterols have four rings. The first three rings—A, B, C—are six-membered rings. Whereas the ring D is a five-membered ring. This is very typical of sterols, if you see your steroidal hormones.

If you see your plant steroids. Generally, they come from here. I will give you one example of a steroidal alkaloid, and that is your solasodine. So you can see here ring A. B, C are all six-membered rings, whereas your ring D is a five-membered ring.

Now what has happened is same like cholesterol you have a ring protrusion coming out of it and this protrusion is generally aliphatic and later on it is cyclized and this is one major compound which has been used for steroidal synthesis owing to its occurrence majorly nowadays diogenin or other compounds have become more popular when it comes to steroidal synthesis but this is one compound which can be also used for preparation of your steroidal hormones.

Apart from the sterol, you can see that your triterpenoids, triterpenoids basically are C30 structures. Your five-membered isopentyl pyrophosphate or dimethylallyl pyrophosphate cyclizes in a manner to form a five-ring system. Now, all these structures five rings are all six membered rings as compared to steroids where you see a ring D which was just a five membered ring here you have all as you know cyclohexane kind of structures it's very unlikely that they are aromatized

so you can see here and apart from that some of the alkaloids are also diterpenes a good example of diterpene alkaloid is your taxol So you can have your alkaloids having their genesis from terpenes, which can give rise to sterols, which can give like to diterpene or even triterpenoidal alkaloids. An example of steroidal alkaloid is your solasodine.

Now, you can also classify your alkaloids based on their bioactivity. We call it a pharmacological classification. A good example of that is alkaloids used to treat cancer. Majority taxol, vincristine, vinblastine have been used. They are called as anti-cancer compounds.

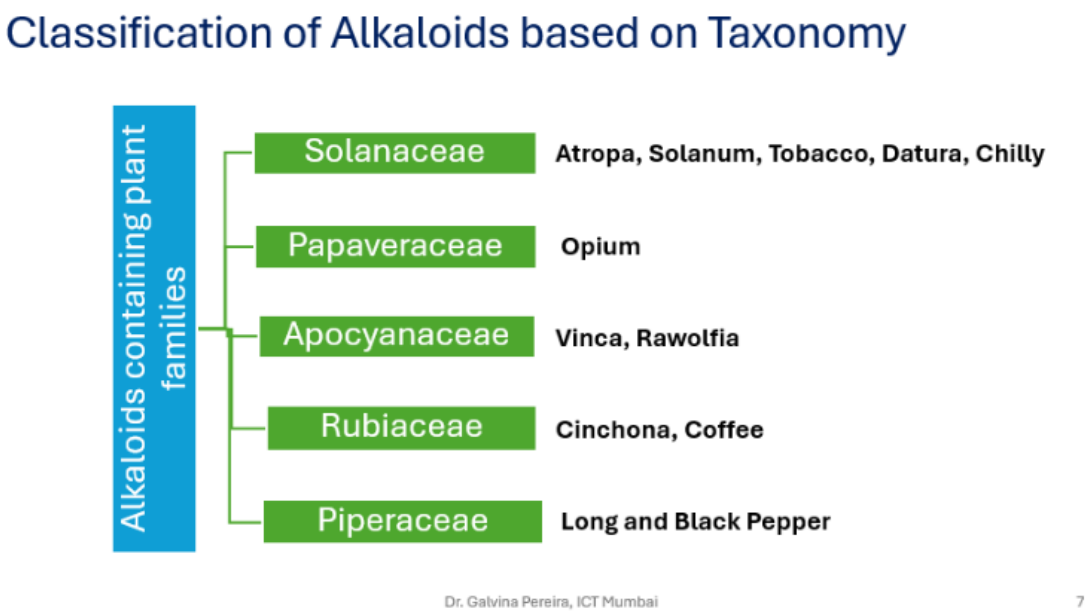
Alkaloids which are analgesic, mostly pain relievers. Morphine is a very potent pain reliever. And an analgesic, anti-malarial. Now this set of compounds, especially quinine, if you go to see, have their ability to kill the parasites which cause malaria. A good example of that is your plasmodium falciferum.

So it stops it from growing and multiplying. Then your antitussive alkaloids, the alkaloids which are used in management of coughs. You might have seen formulations containing codeine. You might have seen adulsa or vasaka formulation that contains an active called as vasicin. Now apart from that we have anticholinergic alkaloids.

Now this alkaloids are actually fighting with your acetylcholine to bind to the receptor and that is why they are called as anticholinergic. Now they have a good effect say for example increasing your heart rate. drying of mouth and you know relaxing your smooth muscles which can be used in cases of emergency or even in the cases of surgeries.

Now some of the alkaloids can kill parasites and worms. They are your quinine, emetin Some of the alkaloids can decrease your blood pressure. They include ralphia alkaloids such as reserpine, resinamine. Some alkaloids stimulate your brain, like having your tea or coffee in the early morning.

That's caffeine. And if you've seen people smoking, nicotine is the one responsible for CNS stimulant effects. Apart from that, there are alkaloids that give you a miotic effect, causing constriction of the pupil. A good example of that is your poppy plant. Now, this is not all.



The list is endless as more and more alkaloids are being discovered and their pharmacological activities are explored, which just gives you an idea of how diverse the effects of different alkaloids are. Now, alkaloids can also be classified based on taxonomy. Taxonomy is when you see the order or family in which these compounds occur. So just talking about family, there is one family that contains the most abundant alkaloids, and that's the Solanaceae family.

The Solanaceae family contains diverse alkaloids. This includes your Atropine which comes from atropa, solasodine which comes from solanum, tobacco, which contains nicotine; Datura, which was used in India for poisoning, especially Datura seeds; and chili or Capsicum, which contains a very pungent compound called capsaicin.

Now, apart from that, other families also contain alkaloids. This includes Papaveraceae. This is a narcotic alkaloid, opium. Then you have Apocynaceae, which contains your vinca and rauwolfia. Your vincristine and vinblastine are obtained from vinca roots, and your rauwolfia gives alkaloids

such as reserpine, resinamine, ajmalicine, and so on. Another family which contains alkaloids is your Rubiaceae. These are generally trees, such as your cinchona, which

gives us anti-malarial compounds such as quinine, and coffee, which gives us caffeine. Apart from that, you have Piperaceae, which is your long pepper and black pepper.

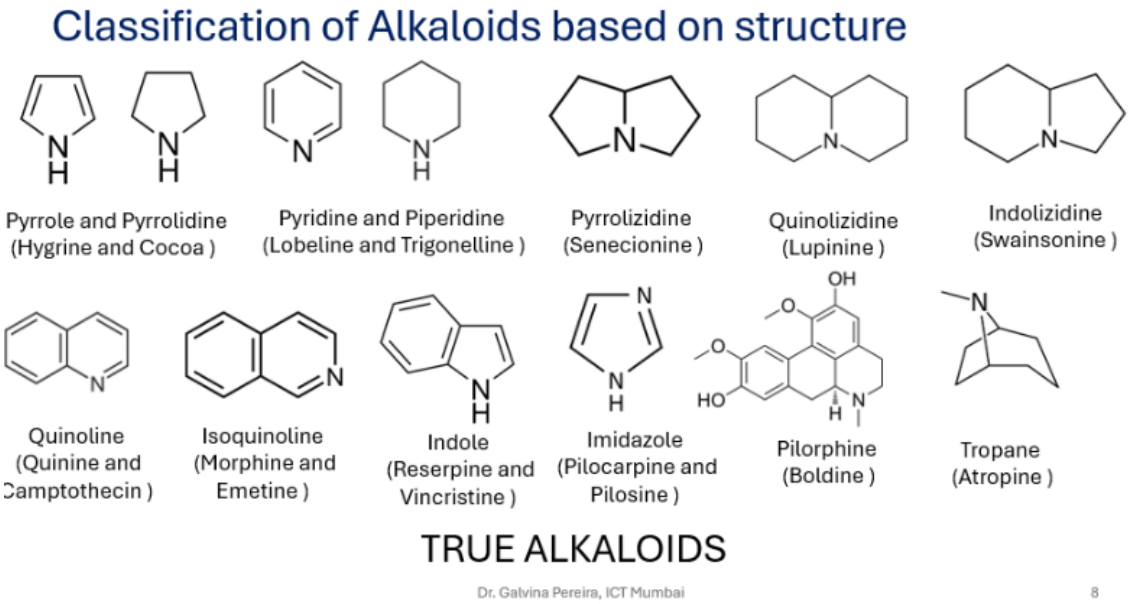
These are vines, basically, but if you eat the fruits of them, they are very pungent or what you call spicy, owing to an alkaloid called piperine. Now, alkaloids can also be classified based on their chemistry or structure into numerous classes. Talking about true alkaloids, where the nitrogen is part of your heterocyclic ring, and they have biosynthesis from amino acids.

There are a few examples. Take your pyrrole and pyrrolidine. We just saw the structures right now in your nicotine. Apart from that, it is present in your hygrine as well as in cocoa. Then you have pyridine and piperidine.

It's there in your lobeline. We saw the structure recently, and trigonelline, which is present in fenugreek seeds. Then we have pyrrolizidine. Pyrrolizidine—a good example of a structure supporting this is senecionine. Quinazolidine is a structure.

Basically, as you see, pyrrolizidine is when you have two five-membered rings fused together. Quinolizidine is when you have two six-membered rings fused together. So that's the difference, and there is a hybrid of the two. We call it indolizidine, where one ring is five-membered and one ring is six-membered. A good example of an alkaloid

containing this is swansonine.



Then you have quinoline, which is a structure present in quinine and an anticancer compound called camptothecin. Then you have isoquinoline, which is present in morphine and emetine. Indole, which you saw, is present in reserpine, vincristine, and vinblastine. Imidazole is present in pilocarpine and pilosine.

Then you have boldine. Boldine is a fused-ring structure. We call it as a pilorphine structure and a good example of pilorphine structure is boldine. An important set of alkaloids are your tropane alkaloids. So in this case also you will see a 5 membered and a 6 membered ring structure fused.

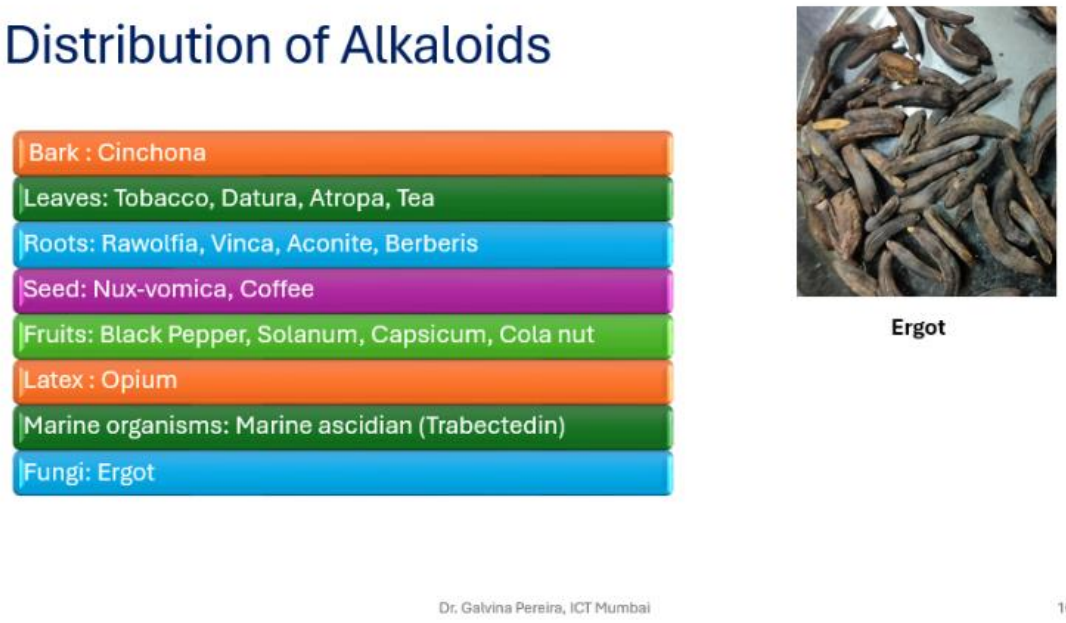
But the place or the position of the fusion is slightly different. It's not a joint at nitrogen. It in fact has an overlapping nitrogen, but it's actually joint at carbon. So if you see here, the difference between this and this is they just share this part in similarity and a nitrogen. Whereas if I have to do this.

What they share together is. This nitrogen containing methyl. So this part we call it as a 6 member and this part we call it as a 5 member. So these two are very similar but the sharing the carbon-carbon linkage is difference or is the point of difference between these two.

Now coming to your protoalkaloids, mostly we've seen right now in ephedrine and mescaline. In protoalkaloids, the amine is or the nitrogen is outside the ring. So good example of that is phenyl ethyl amine. And then you have pseudoalkaloids. They don't originate from amino acids.

A good example of that is the purine caffeine. Then you have steroidal compounds such as solasodine and terpenoidal compounds, which include taxol, a diterpene, and aconitine. Now, alkaloids are distributed in nature. They are found in plants.

They are found in microorganisms. They are found in fungi, and some have even been purified from animals. A good example of alkaloid location is their occurrence in bark, especially cinchona. They can be purified from leaves such as tobacco, datura, and atropa. Even tea leaves provide caffeine.



They are obtained from the roots such as Rauwolfia, Vinca, Echinite and Berberis. They have been purified from seeds. Coffee provides caffeine. Nux vomica yields strychnine and brucine, which are very potent bitter compounds. From the fruits, you have seen your black pepper, the solanum fruits, your chillies.

capsicum or your cola nut which was initially used to make your coca-cola is also a rich source of caffeine from the latexes such as opium alkaloids have been purified from

marine organisms such as marine ascidians and a good example of a very potent compound is trabectedin which is used in cancer therapy Another example of a very potent alkaloid is the one obtained from fungus. And that's your ergot.

I've just kept the image here. So that occurs in your serial, sickle serial. And this ergot is, you can see here, it's a fungus. It grows there. And from this, you can purify ergometrin, which is a powerful oxytocin agent.

So, these are few references you can look forward to for further reading and thank you everyone for your attention. Thank you. Thank you.