

PHARMACOGNOSY AND PHYTOCHEMISTRY

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Week 5

Lecture 23

Drugs Containing Alkaloids (Part 1)

Hello everyone, and welcome to the NPTEL course in Pharmacognosy and Phytochemistry. In the previous sessions, we saw what alkaloids are and the different classes of alkaloids, as well as where they occur. From this session onward, we will start discussing a few examples of drugs containing alkaloids. In this session, we will be looking at two drugs containing alkaloids. One is opium, and the other is belladonna.



Drugs containing Alkaloids

- Opium**
 - Morphine, Codeine, Papaverine
- Belladonna**
 - Atropine, Hyoscine, Scopolamine

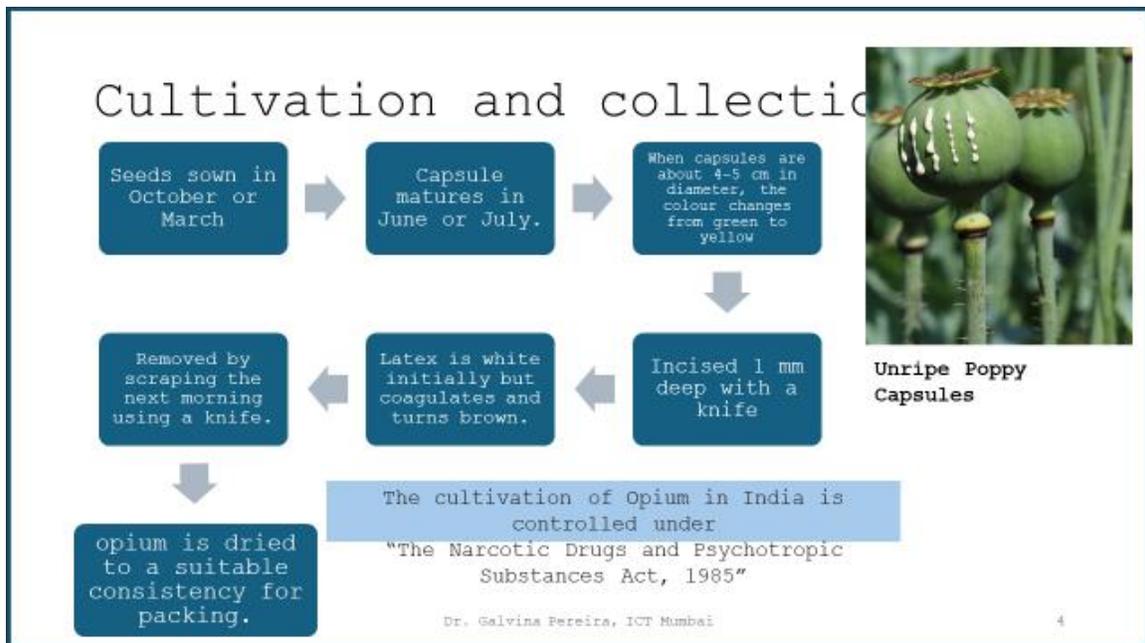


Opium is a narcotic drug chiefly known for containing compounds such as morphine, codeine, and papaverine. Whereas belladonna is a tropane alkaloid containing plant which is showing anticholinergic effect and this contains compounds such as atropine, hyoscine and scopolamine. So, let's learn their pharmacognosy. Opium is actually a latex.

So it is a dried latex obtained from a plant called *Papaver somniferum* latex is generally obtained by making tiny incisions on unripe capsules of *Papaver somniferum*, most commonly, or sometimes its variety *Papaver album*. Both of them belong to the family *Papaveraceae*. Now, going to the sources of opium, opium has been known as a narcotic substance for ages.

In fact, there were even wars over opium. It is cultivated chiefly in Asia, as well as a little in the African continent. If you go to see where all it occurs, it's chiefly cultivated in Turkey, Yugoslavia. India, in India it is cultivated in Madhya Pradesh, especially the Neemach region and in Uttar Pradesh. Apart from that, you will find cultivations of opium being done in Iran.

Afghanistan, China, Burma, Pakistan, nowadays in Thailand, Russia, Tasmania and Laos. If you see the opium of commerce now because this is narcotic and this is controlled substance the famous places or the places where opium is chiefly controlled and grown is India, Turkey, Persia, and Yugoslavia. So these are the main countries which are responsible for the trade of opium.



Now going to the cultivation and collection. How do we collect opium or how is it prepared? Now if you see opium we call it as the khus khus or the khus khus seeds. The seeds are very tiny or small. These are often mixed with sand or cultivated as such.

They are generally sown in October or March. Sometimes separated to protect the crops or sometimes sown all together. Now once that is done the crop matures subsequently in June or July. Now, during that stage, you will see flowers and some capsules coming from the plant. On average, a plant will have four to five capsules.

Now, these capsules, once they achieve a golf ball size diameter of about four to five centimeters, start maturing and turning or changing in color from greenish to yellow. So, during this time or just before this time, when they are greenish in coloration, what is done is special tool bearing a very tiny needle like spikes just less than a millimeter and this is called as nushtur can imagine it like a comb-like tool wherein the needles are placed a little apart from each other, and

then this is used to make incisions. You can see here in this diagram. The incisions are made, and the moment incisions are made, the latex starts flowing. Now, one care is to be taken that this capsule is slightly hollow internally. So, if these incisions go deep, the latex, instead of emanating outside the capsule, will go inside the capsule and get wasted. So, carefully, very tiny incisions are made, and the latex emanates out.

Now, the timing here is very crucial. This is generally done in the afternoon period, during which the latex exudes out and is subsequently collected. So now, this latex is slightly milky and slightly fluid. The subsequent morning, it almost dries up to a sticky residue. Initially, it will be white or milky in coloration.

But as it dries up, you will see it turning a little buff or brown. So next day when it is buff or brown, it's collected generally what is done is opium leaves are used and this knife which is used to scrape it kind of paste it on it, and all this opium latex is pooled together. Now, in some cases, this latex doesn't dry completely, so what is done is the vessel is slightly tilted so

whatever liquid is still there in that latex flows out, and you get a much drier latex as compared to just keeping it in the vessel. One more thing that is done is sometimes this latex is dried in shade or sometimes even artificial heat nowadays is used for drying this latex. Once dried, the latex is wrapped in butter paper or a grease-free paper and packed in a container weighed quantities why because this is a controlled substance so every step is being watched up by the narcotics department it is done in India. Then the packing and everything happens right in front of officials. So if you go to see in the Indian scenario, the cultivation of as well as the collection and processing of opium, is controlled under the Narcotics, Drugs and Psychotropic Substances Act of 1985. So apart from the capsules, nowadays, even the opium poppy straw has been used to get morphine.

Now, if you see in terms of alkaloidal content, the capsule entirely contains about 0.5% alkaloids. But if you see only the latex component, the dried latex component, the dried latex is much richer in alkaloids. It contains almost 25% of alkaloids by weight, and of which 10% is morphine alone. So let's see the chemical constituents. The most important compound which occurs in the latex is morphine now if you see in market you will get four forms of opium and you to be very careful in analyzing that analyzing that. One is raw opium—this is the one we discussed right now—that is, you take it from the plants. You weigh it and put it in a shield. So this is generally done for transportation purposes. And because it has been collected in the leaves, it contains vegetable debris, plant parts, and dirt.

And often, fine particles are present in that. To get a better version of it, what is done is this raw opium is re-dissolved or re-suspended in water in a way. made a clear solution this clear solution is filtered through sieve and then the filtrate is concentrated is concentrated. Now, because it is filtered through a sieve, all the vegetative debris is gone, and this form of opium is much purer. Later on, what is done is this filtrate is taken and evaporated to get a concentrated latex. This is what is called prepared opium.

Prepared opium is generally used for snuffing. Now, once that is done or once people smoke opium, whatever is left behind is called dross opium. So, dross opium is basically a waste product after smoking opium. The fourth category is important to us, and that is what

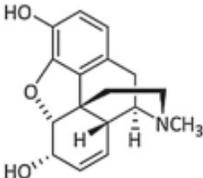
is called medicinal opium. To get medicinal opium, what we do is we take the prepared opium.

It is nicely made into a free-flowing powder or granules by diluting it a little bit with lactose. In the process, one care is to be taken that the morphine content should be between 9.5 to 10%. So, dilute it with lactose and keep the morphine content between 9.5 to 10%. You get what is called medicinal-grade opium. In some cases, this opium is also de-aromatized or made less narcotic by extracting it with petroleum ether.

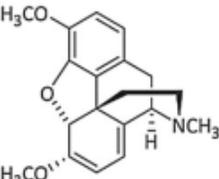
They say that once you do this, the aroma is lost, as well as some narcotic substances are also extracted in the process, and it is much richer in morphine. Now, opium contains more than about 35 alkaloids, which have been reported, and these alkaloids have been found in conjunction with meconic acid. In the previous sessions, we saw that alkaloids, owing to their alkaline nature, form associations or salts with acids.

Chemical Constituents

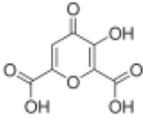
- Opium is available in four forms
- Raw Opium, Prepared Opium, Dross Opium, Medicinal Opium
- Opium contains about 35 alkaloids combined with meconic acid
- Morphine (10-16%) codeine (0.8-2.5%), narcotine, thebaine (0.5-2%), noscapine (4-8%), narceine and papaverine (0.5-2.5%).
- **Phenanthrene type/Isoquinoline alkaloids:** Morphine, codeine, oxymorphone, thebaine, and porphyroxine.



Morphine
Codeine



Thebaine



Meconic acid

Dr. Galvina Pereira, ICT Mumbai 5

Now, this meconic acid is a marker of the Papaveraceae family and is often found to be present in opium. So, people, if they want to check if it is genuine opium or not, they can either check for alkaloids or just check for the presence of meconic acid. In terms of appearance also, there's a slight difference between Indian and Persian opium, Indian being a little darker brown in color.

Now, if you see in terms of contents, the morphine content is— goes from 10 to 16 percent. Codeine, a little less, 0.8 to 2.5 percent. Then you have narcotine, thebaine, about 0.5 to 2 percent. Noscapine, 4 to 8 percent.

Narceine and papaverine go from 0.5 to 2.5 percent. On the basis of structure, you can divide alkaloids occurring in opium into different classes. The first one we saw is the isoquinoline class. If you remember, isoquinoline— So, you can typically see this ring plus this ring here—that's an isoquinoline ring.

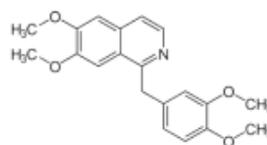
So this carbon here, you can find a match with this carbon here. So this is an isoquinoline ring, or sometimes it is also referred to as phenanthrene for this reason. You can see. A, B, C. If you take these three rings, they can also be called phenanthrene. So morphine, you will find them being called isoquinoline-type alkaloids or phenanthrene-type alkaloids.

So in this, we have morphine, codeine, thebaine—all are very similar in structure if you carefully see. morphine has hydroxy groups on both places when you see one of the hydroxy groups replaced by a methoxy you get codeine If both hydroxy groups are replaced by methoxy groups, you get thebaine . Apart from that, thebaine carries an additional unsaturation in this ring, so that's a little difference between morphine, codeine, and thebaine. This property makes morphine more acidic or less basic compared to thebaine, and this can be used as a way to extract morphine and separate it from other alkaloids. Moving to the next category, you have the phthalide type. Now you can see here there's a phthalide group, or you have a phthalide isoquinoline. This is a phthalide isoquinoline group.

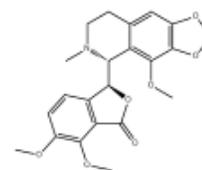
And a good example of that is narcotin. So you have narcotin, narcotoline, noscapin, oxynarcotin, narcin, as well as 5-odimethylnarcotin. as well as 5-odimethylnarcotin. So these are examples that have a phthalide group, which also has an isoquinoline group attached to it.

Chemical constituents

- **Phthalide Isoquinoline Type:** narcotoline, narcotine, noscapine, oxynarcotine, narceine, and 5'-O-demethyl-narcotine.

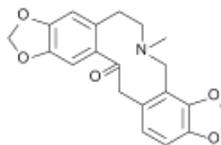


Papaverine



Narcotine

- **Benzyl Isoquinoline Type:** Papaverine, dl-laudanine, laudanidine, codamine and laudanosine.



Cryptopine

- **Cryptopine Type:** Protopine, cryptopine.
- **Miscellaneous:** Aporeine, diodeadine, meconidine, papaveramine and lanthopine

You can see there's an additional phthalide group as well. So you can call them phthalide isoquinoline moieties. Now you also have benzyl isoquinoline. So here again you have isoquinoline, and here you have a benzyl moiety. So you have phenanthrene.

Isoquinoline, you have your phthalide isoquinoline; now you have your benzyl isoquinoline. A good example of that is your papaverine, dl-papaverine, which includes both isomers of lordenine. You have laudanidine, you have codamine, and you have your laudanosine as examples of benzylisoquinoline type. Then there is something called a cryptopine type. So this is an example of cryptopine, and you can see here it's almost similar to isoquinoline, but this part is not joined.

For cryptopine, you have two examples: protopine and cryptopine. Apart from that, there are some miscellaneous classes such as aporanine, deodenine, meconidine, papaveramine, as well as lanthopine. So these are some of the alkaloids that occur in opium, and that makes it very potent. How do you check them? What you can do is quickly check them by doing a few chemical tests.

One thing you can check is for meconic acid. The next thing you can do is check for morphine. So for meconic acid, you just take the aqueous extract of opium with a little

amount of neutral ferric chloride solution. If it gives you a deep reddish purple coloration. Now, this reddish purple coloration is resistant to boiling.

So even after you boil it or you treat it with concentrated hydrochloric acid, the color shouldn't vanish. If the color doesn't vanish, that indicates that the meconic acid is present. For checking morphine what we can do is you can just take a little bit of latex and to that you add a little bit of concentrated H_2SO_4 that's sulfuric acid and formaldehyde. If you get a dark purplish coloration this indicates that your morphine is present.

Now opium despite being a narcotic drug and a control substance has numerous applications. So opium is used as a narcotic, analgesic and sedative. We have other mild non-narcotic or non-steroidal anti-inflammatory compounds. But in some cases when the pain is unbearable, take examples of cases when you have trauma, accidents or intense surgeries or in terminal cases of cancers when the pain is unbearable.

unbearable in that cases your morphine is prescribed. If giving morphine is not preferred a little milder virgin that's your codeine is also been given. So apart from that it is also been used to treat a little cases of diarrhea, dysentery and cough. Now codeine is little mild sedative and has made its way to cuff formulations. If you see noscapine, noscapine is a cough suppressant, but the good part is it's not narcotic.

So it acts as a central antitussive agent. Papaverine is a vasodilator. It is a smooth muscle relaxant, and it's often used to even cure muscle spasms. Now, one thing to note is that opium, especially morphine, is a controlled substance because it has a habit-forming tendency. So it causes addiction, and one derivative—

So just let me put it across. So if you see your morphine. If you acetylate it—you know, I am just converting it into acetyl. If you acetylate it, morphine gets converted into a narcotic substance called heroin, and heroin, you know, is a narcotic drug which has a very very high tendency to form dependence so it's controlled substance and and that's the reason acetylation reagents such as acetic anhydride are also controlled in the market.

Belladonna

- **Synonyms:** Deadly night shade, Death's herb, Poison black cherry
- **Biological Source:** dried leaves and flowering tops of *Atropa belladonna* Linn. (European Belladonna) and *Atropa acuminata* (Indian belladonna).
- **Family:** Solanaceae.
- It contains about 0.35% of total alkaloids calculated as hyoscyamine.
- **Geographical Source:** United States, Canada, UK, Germany and India

Now, moving on to the next example, we have Belladonna, meaning 'beautiful lady' but a poisonous one, so that's the reason it's called deadly nightshade, death's herb, or poison black cherry. The reason being, for people who are attracted to the fruits of this plant, it bears beautiful cherry-like but black-colored fruits; if consumed, they can prove fatal. Now this Belladonna, the drug chiefly, is dried leaves mostly and in some cases the flowering tops of *Atropa belladonna*, belladonna, the European one, or in some cases, the Indian belladonna, also referred to as *Atropa acuminata*. Both of them belong to the family Solanaceae.

Now, it contains somewhere between 0.3% to 0.6% alkaloids, but of that, it should contain 0.35% of total alkaloids calculated as hyoscyamine. Geographically, it's found in the US, Europe, as well as India and some parts of Canada as well. It's cultivated for its tropane alkaloids. This plant chiefly grows by sowing the seeds, and this is done in summer.

Cultivation and Collection

Seeds sown in nurseries

Seedlings are transplanted in April

leaves and flowering tops are cut at least three times a year for two months from one to three years old plants.

When the plant is four years old, the roots are dug out.

The collected drug is dried at 40-50°C.

Undried leaves deteriorate and give off ammonia.

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9

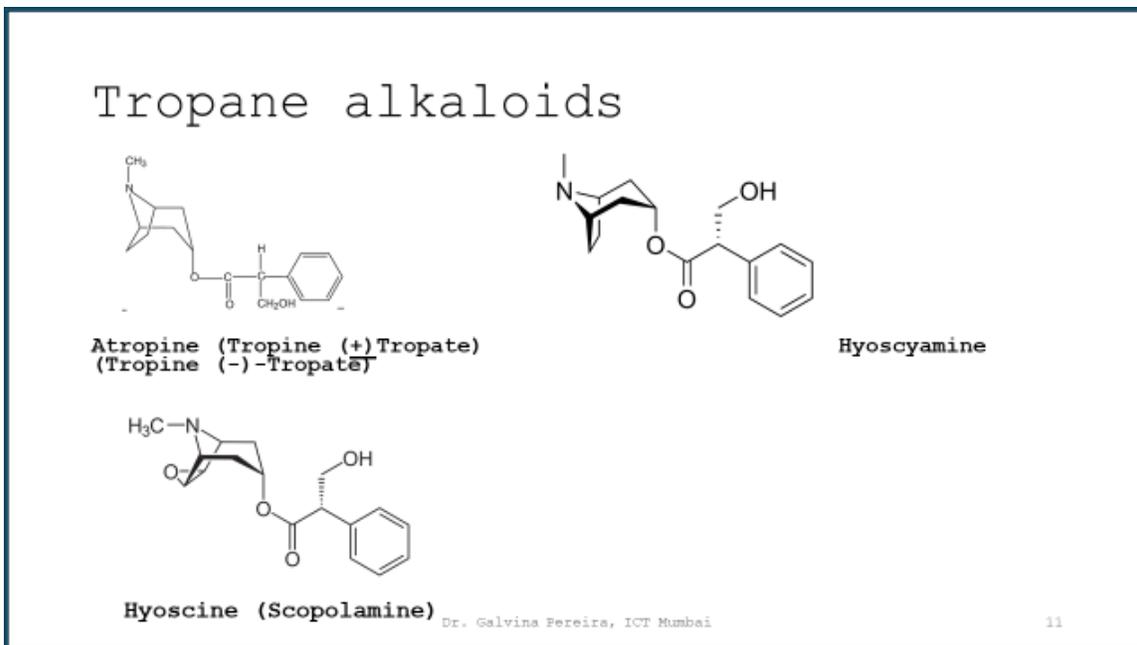
The reason this is done in summer is that it is said that the plants or the seedlings which grow in summer with vigor or with the heat have higher temperature. Colloidal content as compared to the plants grown in other seasons. Now, these plants are tiny; they adjust or achieve a maximum height of a meter or so and then bear beautiful purplish flowers generally facing downwards like a night lamp or a night shade and they bear cherry like black color fruits animals but, because of their poisonous nature, are proven to be fatal. Now, once the flowering season starts, what is done is the leaves as well as the flowering tops can be harvested from any age between 1 to 3-year-old plants. This is done maybe 2 to 3 times a year when the leaves are collected. Now, once the plant is 4 years or older, it is said that the alkaloid content decreases.

So, in those cases, it is then dug up and thrown away. Now, once the leaves are collected, they have to be carefully dried because if moisture is present, it starts deteriorating the drug. We will see why it deteriorates but once it deteriorates you can easily detect that by presence of amine or ammonia like odor. Now the reason for its deterioration has something to do with structure.

Now tropane alkaloids are actually esters. They are esters of alcohol called tropenol. We saw this when we classified our alkaloids as tropane alkaloids. So you have one 5-

membered ring, you have one 6-membered ring and what they have in common is these two carbons and a nitrogen.

So this tropenol is forms ester with your tropic acid. Let's add it in this manner to form an ester and this ester is called as atropine, okay Now, atropine is when it is generally racemic in nature, there is no assignment in terms of optical activity. In some cases, it's also referred to as, you know, 8-azobicyclo-octane nucleus which has been joined.

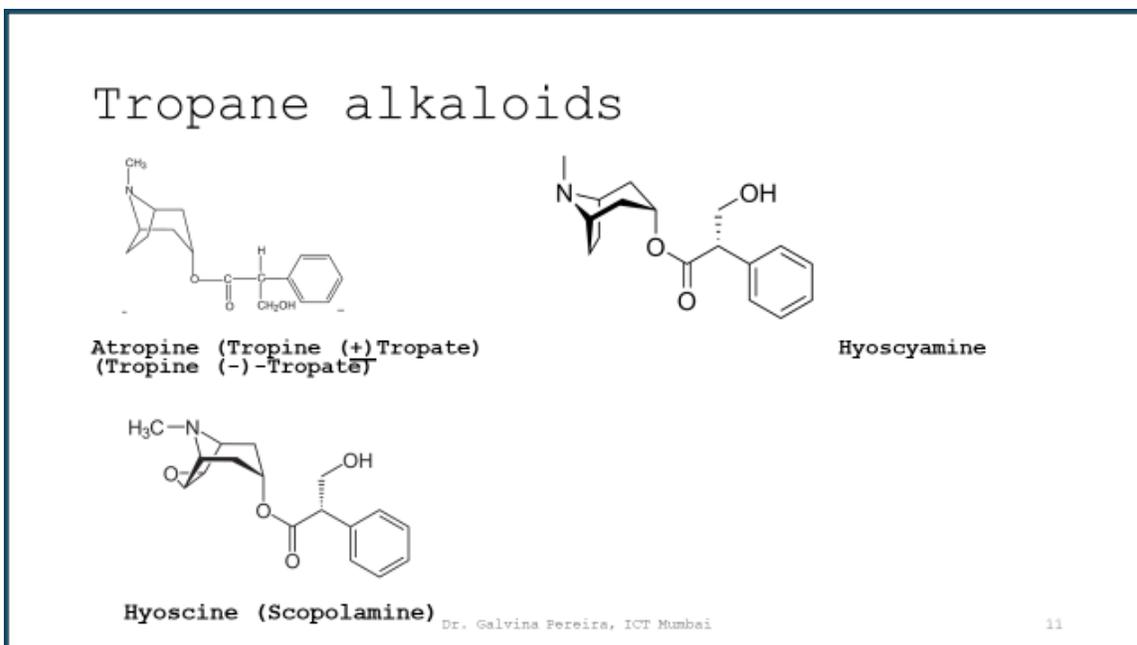


Now, depending upon it, like I said, atropine is a racemic mixture. So, you have your tropine, tropate in the both plus minus form referred to as Atropine. Hyoscyamine is specifically negative in terms of its optical activity. So, you can see here. Now, the plant, if you see the limits, contains 0.35% hyoscyamine.

It is said that the atropine is almost negligible in the plant at the initial stages. But as the plant dies and is extracted, racemization occurs, and more of this hyoscyamine is converted into atropine. And that's where your atropine is found. In addition to that, you have one more alkaloid, which is also predominant in this plant, and that is hyoscine. Hyoscine is generally the epoxide of hyoscyamine.

So at this position, if you attach an epoxide, you get what is called scopolamine. The interesting part about scopolamine is that it has the ability to permeate the blood-brain

barrier easily and, as a result, has more predominant CNS effects compared to atropine. So if you see the summary of alkaloids present, it contains 0.3 to 1% alkaloids, predominantly L-hyoscyamine and atropine.



You have apoatropine. Now, apoatropine is, instead of CH₂OH, When this hydroxyl is lost, you get a double bond out here. So that's your apoatropine. Belladonnine, you have cuscohygrine.

You have chrysotropic acid, atrosine, leucotropic acid. You have N-methylpyrrolone. You have homotropin. Apart from alkaloids, this plant is rich in flavonoids such as rutine and glycosides of kaempferol such as kaempferol-3-rhamnogalactoside and 7-glucoside. Then you have quercetin 7-glucoside.

Atropine, like I said, is generally formed by racemization during the extraction process. It's predominantly L-hyoscyamine which is present. Now you can check the presence of propane alkaloids by a very specific test which is called as Vitali morin test. Now if you take your propane alkaloids or extract enriched in propane alkaloids completely dried and if you treat it with fuming nitric acid completely evaporated by heating it and then whatever residue you get dissolve it in acetone.

To that, if you just add an alkali like an alcoholic potassium hydroxide solution, you will get a violet coloration. That's a very specific test for tropane alkaloids. Apart from that, if you have pure alkaloid, you could also perform a Gerrard's test, which is you can take the alkaloids and take a 2% solution of mercury chloride and ethanol. If it gives you a red color, it's mostly a tropine.

Chemical Test

- **Vitali-Morin's test:** Solid alkaloid + fuming HNO_3
→ Evaporate to dryness, dissolve residue in acetone, add methanolic solution of KOH → Violet colour.

- **Gerrard's test:** Alkaloid + 2% HgCl_2 in 50% Ethanol
→
→Red colour Atropine
→Red after warming Hyoscyamine
-->White ppt Hyoscine

- Addition of ammonia to the alcoholic solution of scopolamine shows blue fluorescence. This test is useful for detecting Belladonna poisoning.

Dr. Galvina Pereira, ICT Mumbai 13

If it gives you a red color, but only after much heating, it's good chance it's a Hyoscyamine. And if it is a white color precipitate that you're getting on reacting it, it's basically hyoscine. Now, one more test has been used to check. It was used earlier in patients to see if they've been poisoned by belladonna. How do you do that is...

You take the extract or the medicine or whatever you want to test, which you feel contains the alkaloids. You take alcohol or dissolve that solution in alcohol. Now, to this alcoholic solution, you add ammonia. In the presence of ammonia, if you see a blue color fluorescence, it's a good indicator of belladonna poisoning.

And that is specifically for the detection of scopolamine. In terms of applications, belladonna shows anticholinergic effects. So it blocks the muscarinic cholinergic receptors. And as a result, it gives you what is called narcotic, sedative, diuretic, and mydriatic effects. Now

It is used as an anodyne, a mild painkiller, and also it dries up the mucus. So if you want to check the secretion or dry the mucus, you can use atropine. Now it is used to relieve spasms because it's a smooth muscle relaxant of the gut as well as the respiratory tract. Now, as it dries up the secretion, it is also used to control excessive perspiration and In cases of tuberculosis, when people sweat a lot, if you want to control that, in some cases, atropine is given.

Now, it is also given as a drug in the treatment of peptic ulcers or digestive disorders, ulcerative colitis, or diarrhea, especially when your gut is inflamed and you need some gut relaxation. Apart from that, belladonna is also reported to a very good extent to act as a parasympathetic depressant. So these are a few applications of atropa. And even in its purest form, as you can see, atropine is also administered to the patient and is used in therapeutics.

Here are a few references to read more about this topic. And thank you, everyone, for your patient listening. Thank you.