PHARMACOGNOSY AND PHYTOCHEMISTRY

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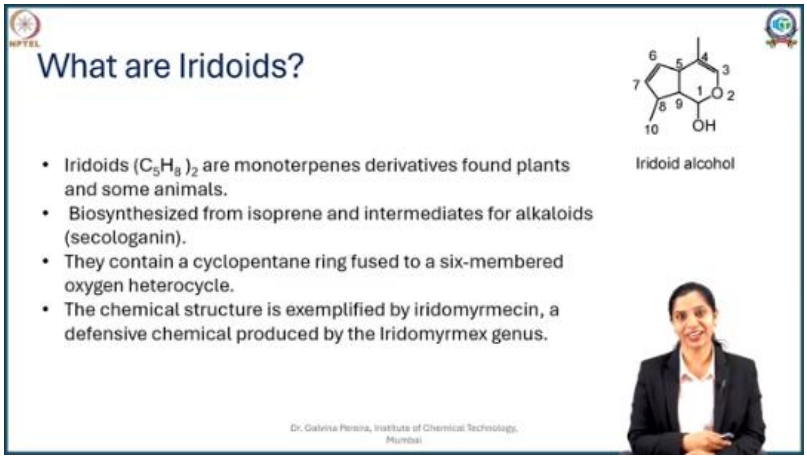
Week 8

Lecture40

Week 8: Lecture 40: Iridoids containing drugs

Hello everyone, and welcome to the NPTEL course in Pharmacognosy and Phytochemistry. In this session, which is session 5 of week 8, we are dealing with a compound or a set of compounds that are intensely bitter but derived from a very unique species—ants. So, welcome to the world of iridoids and iridoid-containing drugs. So, what are iridoids? Iridoids in nature are actually monoterpene derivatives.

Now, if they are monoterpene derivatives, why aren't they classified under monoterpenes? These monoterpene derivatives do get cyclized in a slightly different but definite manner. So, if you see this particular iridoid nucleus as represented by iridoid alcohol, if you carefully observe, you can still spot the monoterpene.



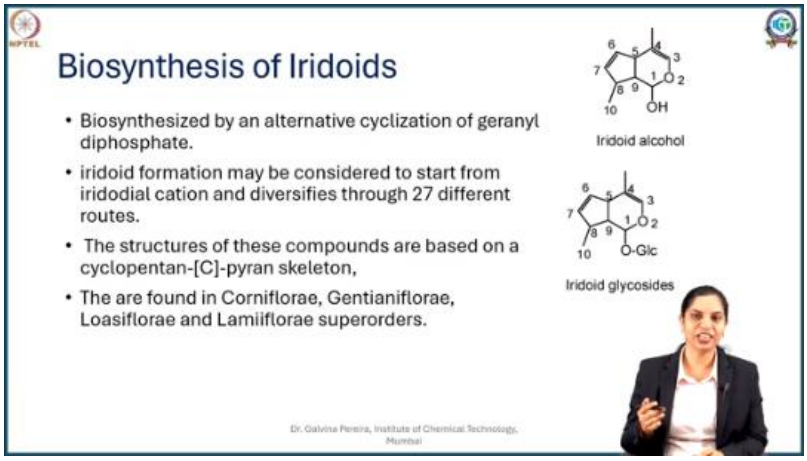
So, if you recall, monoterpenes are compounds that are dimers of C5. That is, you require two isoprene units. So, this is my first isoprene unit. And this is going to be my second isoprene unit. So, you have a proper C10 nucleus.

You have a proper isoprene joint in a head-to-tail manner. But they are not classified under terpenes because when they cyclize, they involve a heteromolecule. So you see that they have formed a six-membered pyran ring. And a five-membered cyclopentene ring, which are fused to each other and carry two methyl branchings. So we have this typical nucleus, which has a five-membered cyclopentene and a six-membered pyran.

Each of the rings, having a methyl group, is characterized as an iridoid nucleus. Now, the iridoid nucleus has this aspiration from a compound called iridomyrmicin. Now, iridomyrmicin was actually discovered in the Iridomyrmex genus, which is a genus of ants. Now, the Iridomyrmex genus is something that gives you a strong stinging effect. And there was a lot of inquisitive

There was a lot of research that has gone into finding out what this compound was, and eventually, the compound found was iridomyrmicin, and iridomyrmicin was found to be an iridoid compound, or that's where they get their compound name as iridoids. So anything that has this central aspiration of iridomyrmicin as a nucleus, or as we call it, a pharmacophore, belongs to the category of iridoids. So this particular pharmacophore or this particular nucleus contains a cyclopentanopyran nucleus or, more specifically, a dimethyl cyclopentanopyran nucleus. So where are these iridoids coming from?

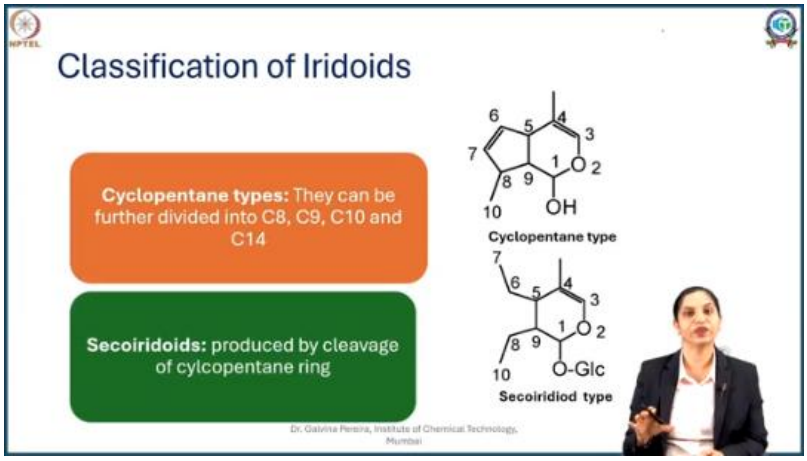
Now since we see a proper head to tail condensation needless to say they are prepared by cyclization of geranyl. Now this geranyl also involves an additional oxygen and that's where you get this pyrane oxygen from. Now, initially it is thought to be a geranyl derivative, but after the geranyl is produced in your acetate mevalonate pathway to prepare iridoids, you know, there are like 27 different branches or 27 different routes from which different set of iridoids can be prepared. Now this iridoid nucleus contain cyclopentanopyrin and they are located in different different families of plants. This include your corniflorae, your gentileflorae, lassiflorae and your lamiflorae superorders.



So they belong to your corniflorae genus. Gentian florae, Lassiflorae or Lamiflorae super orders and in those when you have your families or you have certain species of plants especially those growing in the temperate regions those you will find your iridoids occurring very commonly. Not only that amongst that you will find your iridoid glycosides also occurring more commonly where the glycosylation happens at the hydroxy group. Now, in terms of numbering of iridoids, the numbering of iridoid goes with your hydroxy taking the first position, the O of your pyrane taking the second position. This is represented by third, fourth.

The bridge carbon has the fifth one, sixth, seventh. Then you have your eighth, ninth. That's where your ring is over. And then you have your 10 okay now depending upon the different nucleus now you will ask that why not 11 you can give the name 11 but we are not giving it the reason being that we are putting it oxygen a number and in order to compensate for that we are giving one less number but in some cases where you want to substitute or when you want to add you can even denote or annotate this as 11 that's also perfectly all right

Now, if you go to see classification of iridoids, the classification of iridoid is that if the nucleus is kept as such, that is, if you have your cyclopentanopyrin kind of nucleus, that is the primordial or the prime one or that is the most common one. Now, in some cases, what happens is there is a demethylation happening. Now, when the demethylation happens, you get one less nucleus. So from C10, which is this, that is 10 carbon compounds, you get one carbon less, which is C9. You get second carbon less, which is C8.



And in some cases, what happens is a four carbon moiety gets stuck to it. And in that case, you call it as a C14 derivatives. But nonetheless, your cyclopentanopyrin nucleus still exists. Now in second case what happens is sometimes the bond between the 7th and 8th gets broken and what you can see as a result is if you just break this bond then you will find that your 10th And 8 are joined whereas 6 are joined to 7.

So you get what is called as an open ring. So your cyclopentane is no longer there. You just have the pyrane ring left with it. Such type of iridoids are called as seccoiridoids. Now in some cases it might also happen that this will cyclize with this maybe by a formation of acetate or esters.

OK, so that might be an ester linkage, and it might so happen that your 7th can cyclize with 4, what you saw as the 11th or the methyl substitution on 4. And that is also still classified as your seco-iridoid type. A good example of that is your seco-loganin, which is involved in the biosynthesis of certain alkaloids. So, let's see the physical properties. Like I said, these compounds are irritating.

When you consume them, these compounds are bitter. In nature, they are colorless. Some of them, because they have sugars attached, are soluble in water. But most of them are soluble in ethanol, acetone, as well as methanol. Some of them occur as glycosides.

Even in certain cases, the epoxides of your iridoid compounds are also found in plants. Now, if you see comparatively, like we discussed here, the compounds when they are in native form are very unstable and prone to rearrangement. But the moment they are converted into their glycoside derivatives, they are much, much more stable. The aglycons are more susceptible, and they are susceptible to acids as well as enzymes. Whereas, if you see derivatized or acetylated iridoids, they are more susceptible to alkali.

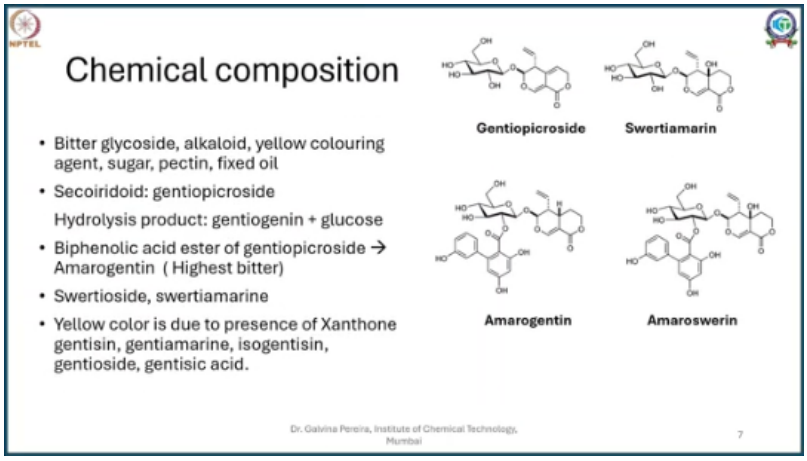
Now, also, one more thing is observed: iridoids as compounds are colorless, but when you treat them with acids or enzymes or in the presence of oxygen, they form complexes with acids, they form complexes with each other, and the end product is a bluish or violet-blue colored compound which is no longer soluble in water. If we Even if it is a glycoside, it still precipitates out, and that is a typical property of iridoidal compounds. And that's the reason you need to be very careful while dealing with iridoid compounds, ensuring that even during the extraction stages, you're not exposing them to harsh acids or alkalis. Now, I'm going to the first example of a drug containing iridoids.

The first example of a drug containing iridoids is gentian. Now, gentian has a lot of species in the Himalayan region. About 400 such species are known, and the most common medicinal plant in this category is yellow gentian, often referred to as *Gentiana lutea*. Now, what is done is you dig up these plants. The plant is generally cultivated or allowed to grow in the wild for a period of two to five years.

Once the plant is mature, the roots and rhizomes acquire a certain thickness and girth. In that case, you dig it up. And then it is dried, sliced, and used as gentian. They belong to the family Gentianaceae. Now, this plant is found in most of what are called the temperate regions.

This includes central and southern Europe, Turkey, Yugoslavia, France, Italy, and Germany. This is the image of a plant. Inflorescence of yellow gentian. The other species show differently colored inflorescences. Now, what does it contain?

It contains compounds that belong to secoiridoids. Now, if you recall secoiridoid compounds, here you can see you can still retain the pyran nucleus. But what has happened is your cyclopentane nucleus has vanished. So, in this case, our gentian contains secoiridoidal compounds wherein the 7 is protruding out. Now, this contains bitter glycosides, so most abundantly, you will see glycosides of secoiridoids. A good example is gentiopicroside. Now, this is the one which is more abundant in the plant, to the extent that it is almost 2 percent in the dry root,



or the rhizomes. Now, you will see the second one: Swertiamarin. Swertiamarin is nothing but a hydroxy derivative of gentiopicroside. So, gentiopicroside is major. Hydroxy gentiopicroside is what is called Swertiamarin.

Now, in some cases, what happens is their derivatives are referred to as bisphenolic derivatives. So, these are two phenols, often referred to as bisphenolic, and then there is an acid. So, you have bisphenolic acids being attached to this part of glucose, and if this attaches or a bisphenolic acid attaches to gentiopicroside, you get a compound called amarogenitin. Amarogenitin is considered to be the highest or most intensely bitter compound present in this plant. Now, if you take an example of swertiamarin and add bisphenolic acid to that, you get what is called amaroswerin.

So, these four compounds are secoiridoids. They are more specifically secoiridoidal glycosides. Now, you can take gentiopicroside and cut off the sugar. When you cut off or remove the sugar, you get an aglycone, and this aglycone is referred to as gentiogenin. For swertiamarin, you have hydroxygentiogenin. So, these are two aglycones which you get on hydrolysis after breaking the sugar.

Now, the color or slight yellow color of the underground parts, especially the roots and rhizomes, is attributed to the presence of xanthones. Different xanthones are present in gentian, and these include genticin, gentiamarin, isogenticin, gentioside, and genticic acid. They all contribute to the yellowness. Now, if you see or categorize flavones as well as xanthones, they show some color attributes, and specifically, this particular set of xanthones has a yellow color which is also seen in the roots and the rhizomes. Now, where do you use this?

Now, most of these plants, which are intensely bitter, are known to be stimulants, especially GI stimulants. So, these GI stimulants stimulate gastric secretions. These GI stimulants stimulate your bile acids, and that is how they act as bitter tonics. So, iridoid-containing drugs are very famous for their effect on your stomach as bitter tonics. Apart from that, they help you with the management of numerous digestive disorders. This includes loss of appetite—definitely, when the secretions increase, your appetite automatically increases. They help you deal with intestinal gas as well as diarrhea.

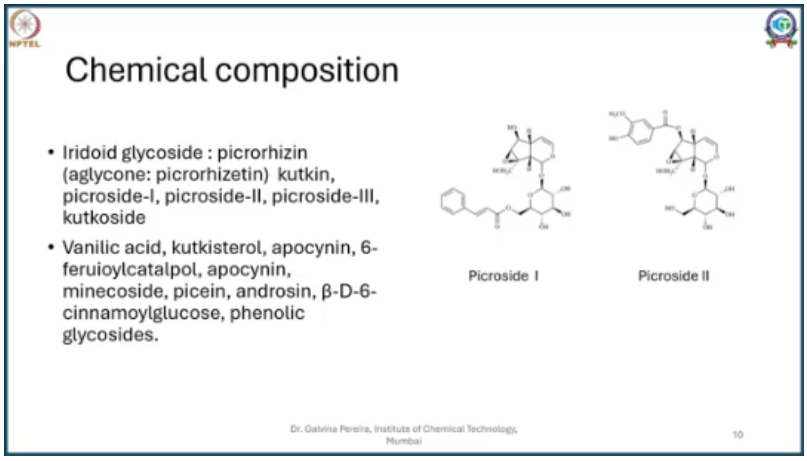
Now, apart from that, the compounds present in gentian also show anti-inflammatory and wound-healing activity. Like I said, because they are bitter tonics, they stimulate bile secretion. So, they are categorized as choleretic. They are antioxidants. Now, another advantage of iridoids is they have a very good protective action on the liver.

So, they are known as hepatoprotective. They prevent cirrhosis and necrosis and have a very beneficial healing effect on the liver. And that's the reason they are called hepatoprotectives. Apart from that, they show antifungal properties and help you in the management of anorexia. So, these are a few applications of gentian, and very similar uses you will find in another plant, which is more native to us—that's your picrorhiza.

Picrorhiza is commonly referred to as kutki. Kutki is obtained from dried roots and rhizomes. The roots are very tiny. More predominantly, what we take are the rhizomes of *Picrorhiza kurroa*, and it belongs to the Scrophulariaceae family. This is a plant that is very abundantly grown as well as cultivated in the Indian Himalayas.

You will find it growing right from the Kashmir region down to the Sikkim region. This plant is dug up, and the rhizomes, which are cylindrical—as you can see in the image—are irregularly curved. The interesting part is that in the rhizomes, wherever you see the nodes, rooting generally occurs, or the rootlets generally appear at the places where the nodes are located. So that's one way in which you can identify Picrorhiza rhizomes, or that is how they stand out. Now, what do they contain?

They also contain iridoids, but these iridoids are more of what you would call cyclopentanopyran. Previously, in gentian, we saw secoiridoids as the chief components. For Picrorhiza, we have cyclopentanopyran derivatives as the chief compounds. So you have picroside 1, 2, and 3. Picrosides generally have a cyclopentanopyran nucleus, but in addition to that, you can see here there is an epoxide present.



Again, making them slightly unstable. So you need to be very careful while dealing with this compound, especially when extracting it. You cannot use strong acids and bases as they may affect these linkages. Now, what happens here is, in some cases, it is attached to what is called vanillic acid. So picroside 2 has vanillic acid attached, whereas if you see picroside 1, both of them are glycosides, but you have cinnamic acid attached.

So this has cinnamic acid, whereas this has vanillic acid. So when they hydrolyze in your plant, your cinnamic acid and vanillic acid are present in their native state as well as in the hydrolyzed products. Apart from that, you have your kutkoside, which is also an iridoid compound. You have your kutkin and derivatives such as kutkisterol, apocynin, feruloylcatalpol, apocyanin, minecoside, picein, androsin, and cinnamoylglucose. Cinnamoylglucose chiefly comes from this breakdown.

So you have cinnamic acid plus glucose and your other phenolic glycosides. So all this contributes to the total effect of *Picrorhiza kurroa*, which is also used as a bitter tonic and is very famous in the Ayurvedic system of medicine for this particular action. So let's see where it is applied. So it is used as a bitter tonic. If you take it in slightly higher doses, it acts as a cathartic as well as a purgative.

So you have to be careful. It is a stomachache. And one thing about Ayurvedic medicines is that the medicines, mostly those which have a bitter note, have also been associated with antipyretic effects. So this drug, being bitter, shows antipyretic effects. It is reported to possess anti-periodic, cholagogic, febrifuge, as well as anti-malarial properties.

Not only that, it is used as a menagogue, emetic, and abortifacient. So you need to be very careful. And also, it is used in the treatment or as an antidote for dog bites so that the

infections don't spread. So these are two little examples of iridoid-containing drugs. But if you wish to read more about this set of compounds, you can refer to the following books.

Thank you, everyone, for your patient listening. Thank you.