

PHARMACOGNOSY AND PHYTOCHEMISTRY

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Week 7

Lecture34

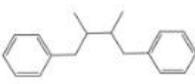
Week 7: Lecture 34: Lignan Containing drugs (Podophyllum, Linseed, Piper cubeba, Sesame)

Hello everyone, and welcome to the NPTEL course in pharmacognosy and phytochemistry. This week, we are learning about different phenylpropanoid derivatives. So far, we have finished studying flavonoid derivatives. This week, we will focus on two more classes of phenylpropanoid derivatives, and in this session, we are going to learn about lignans.

Now, what are lignans? So, lignans—maybe you have heard the terms lignins and lignans. Lignans are chemical derivatives. They are formed from the phenylpropanoid pathway and are biosynthetically derived from the shikimic acid pathway. We know that the shikimic acid pathway gives rise to different amino acids, the most common ones being phenylalanine and tyrosine.



What are lignans?



- Lignans are formed by the dimerization of two phenylpropanoid units, creating a diverse group of molecules.
- They are derived from **Shikimic acid pathway**
- They are often hydroxylated to possess phenolic groups
- The linkage is mostly via C-C but in some cases C-O linkages are also formed

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Phenylalanine and tyrosine contribute to C₆C₃, and if two such units join together, they are called lignans. So, lignans are essentially dimers of C₆C₃. We can just write it as C₆C₃ multiplied by two. Now, what happens is that sometimes during the biosynthetic pathway, instead of dimerizing, C₆C₃ may polymerize. So, when that happens—let me just put it as C₆C₃ multiplied by N—they are called lignins, and these are called lignans.

So, a little difference between the two: your lignans will be a little lighter in weight. They will be your C₉, Tusa, C₁₈ kind of compounds or their derivatives, whereas lignins would be very polymeric in nature. They'll be polymerizing, like we saw in your tannins, but more CC linkages are found here. If you remember, lignins are the ones which give rigidity to the plant tissue. So, you know, your plants when they are born are generally soft.

But if you check your wood, your wood is pretty stiff, and that stiffness comes from the lignin deposits. So, lignins are something which gives you more of a mesh network kind of structure that supports the cellulose and gives more strength to the trees. Whereas lignans are just dimers. They are a little low in molecular weight, just consisting of about 18 carbons or so around that range because they might be derivatives. They might form adducts with other compounds.

So, comparatively low in molecular weight, and they have a different role to play. Their basic role in plants is to carry out, you know, more of a defense function. So, very likely, these C₃, C₆ kind of compounds may join to each other. As you can see here, the linkage may be a CC linkage. But in some cases, you might also come across a CO linkage where there might be some oxygen-like compounds.

An atom located between two phenylpropanoid moieties. So the linkage, majority of the time, is a C-C linkage, but you might also come across a molecule which has a C-O linkage. Previously, when you saw a compound called a silymarin derivative, we called it a flavolignan, and in that flavolignan, the lignan moiety was attached by an O linkage. So yes, that is it.

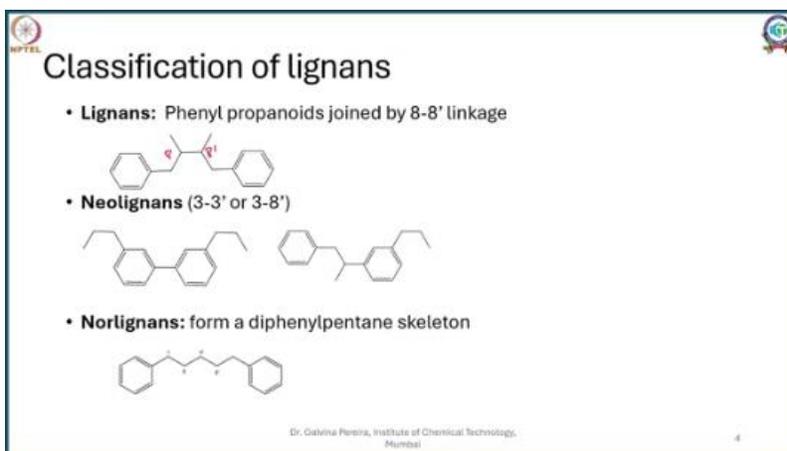
And in some cases, these lignan derivatives are hydroxylated. So they possess many hydroxyl groups. They also have phenol-like properties, such as antibacterial properties. So just to summarize, lignans are dimers of phenylpropanoids. They are often joined by C-C linkages, and in some cases, C-O linkages.

They are biosynthesized from the shikimic acid pathway and are known to possess many phenolic hydroxy groups. Now, regarding their occurrence, they are found in numerous

plants such as sesame, linseed, soy, and sunflower, especially in the seed regions. You can find them in cereals. They occur in cereals such as oats, rye, and barley. Some fruits, such as grapefruit, pear, or blackberries, are known to contain lignans, and in the case of vegetables, especially cucumber, cauliflower, and carrots, are some of the vegetables which are rich in lignans.

Now, what? What are lignans, and how do you classify them? As discussed, lignans are something which is C₃, C₆ into 2. Lignans can be classified based on their nature. So, phenylpropanoids, that is C₆, C₃, if they are joined by 8 linkages.

So, just showing here, you can see the 8 linkages are this. 8 and 8 dash. So, how do you come across these ones? There are a few examples herein. So, this is your 1, 2, 3, 4, 5, 6.



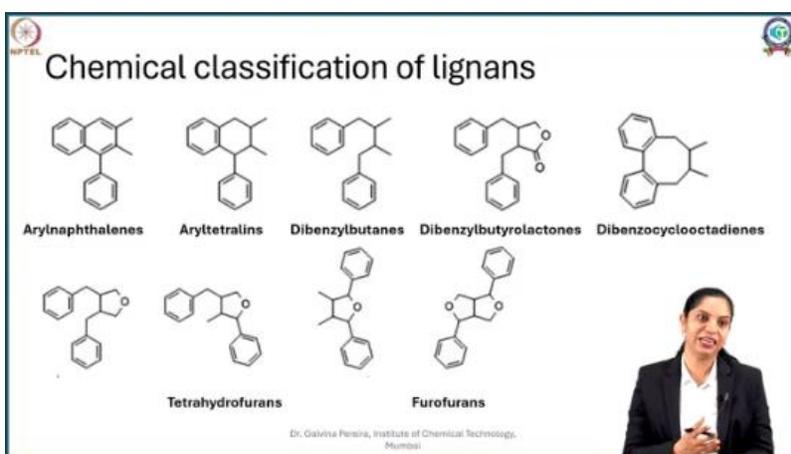
This is called a 7, this is 8, this is 9. So, this is 8, and this is 8 dash. Whereas, when you are seeing your neolignans, neolignans may be associated by 3, 3 dash. So, in this case, let's put it again: 1, 2, 3 with 1 dash. 2 dash, 3 dash.

So here there's what is called as a 3 3 linkage or in some cases there is a 3 8 linkage. So let's see here 1 2 3. So now this 3 is attached. So if you remember this is all 6 and then you go 7 dash 3. dash.

So, here the linkage is a 3, 8 dash. So, lignans are mostly 8, 8 linkages. Neolignans are 3, 3 dash linkages or 3, 8 dash linkages. Norlignans, what you principally observe is one of the methyl goes missing. or eliminated in the process and as a result so if you see this carefully ideally C₆ C₃ is C₉ so C₉ if I duplicate it or C₉ if I make it twice it should be C₁₈ but what happens here is you will just see one 9.

The other nine is missing. So typically nor lignans have what is called as diphenyl pentane kind of nucleus. So even in this case, imagine if a lignan were there missing this methyl group. you know, eliminate this methyl group. So, one methyl less wherein the formula of your lignans is not met.

So, they are not perfectly fitting the lignans, and that is the reason they are called norlignans. So, you have lignans, neolignans, as well as norlignans, based on the linkages. Another way of classifying them is based on their ring structure. So, the chemical classification of lignans classifies them as aryl naphthalene. So, whenever you have an aryl group attached to a naphthalene group.



So, these are your aryl naphthalenes. Then you have your aryl tetralenes. So, an aryl group attached to a tetralene group. Okay. So, you have aryl naphthalene, aryl tetralene.

Then you have dibenzyl butane. So, this is your benzyl group. So, one benzyl, second benzyl. I am just putting it like that. So, these are two benzyls, and here you have your 1, 2, 3, 4.

So, you have what is called a dibenzyl butane group. Now, this dibenzyl butane group may further cyclize and oxidize to form a lactone. In that case, you categorize this as a dibenzyl butyrolactone derivative. So, what has happened essentially is the same structure. What we are doing is adding a small lactone group here and a ring structure.

So, that is your dibenzyl butyrolactone. So, when we go to the next one, the next one is dibenzocyclooctadienes. Now, in dibenzocyclooctadienes, what happens is I can break this molecule symmetrically into two parts. Now, this is my one. This is my one dash.

This is my two. Two, and this is my two dash. So, this is a typical two two dash linkage, and what happens here is a two two dash linkage, but if you see in both cases, they are symmetrically balanced. So, your exact symmetric molecule, but when they join to each other, they give rise to an octadiene kind of structure, and this diene is contributed to this one two and one dash two dash linkages. Now, moving down, sometimes they condense and form what are called furan derivatives.

So depending upon that you have different different types of tetrahydrofurans. So you can see in three different ways you can have tetrahydrofurans derivatives and in some cases you can just carefully see you can split it exactly like this from the symmetry. Still you have your phenylpropane that is 1, 2, 3. In this case you can call it as As we define it as 7, 8, 9 and this is your 7, 8, 9.

So here what you see is again put it as a dash because it's a second group. And those are two phenyl propanoid joining to each other in a 8-8 dash manner. But because of the oxygen multisubstitution and double ring formation, you call them as furofuran derivatives. So chemically, your lignans can be classified as aryl naphthalenes, aryl tetralenes, dibenzyl butanes. And when they form lactone, you have dibenzylglutirrolactones.

Then you have dibenzocyclooctadiene. Then you have your furan derivatives, especially your tetrahydrofuran derivatives. And then you have your furanofuran derivatives. Now let's see some examples of drug containing lignans. Now lignans owing to their properties especially cytotoxic and antioxidant activities are known very effectively in cancers.

Now you can see drugs, and many of these drugs have been investigated for their potential as anti-cancer agents, and one of the good drugs in this case is podophyllum. Apart from podophyllum, we'll also discuss other drugs that contain lignans, such as linsid, cubeb (piper cubeba), and sesame. So let's discuss podophyllum. Podophyllum is a temperate plant that grows in the US and the Himalayan region of India. It's called American mandrake or mayapple because of its beautiful reddish-colored fruits.

The commercial drug is obtained from the underground parts, specifically the dried roots and rhizomes. Depending on the location, American podophyllum comes from *Podophyllum peltatum*. If you're talking about Indian or Asian podophyllum, it comes from two species: *Podophyllum hexandrium* and *Podophyllum emodi*. Now, both of these belong to the Berberidaceae family, and you will find them flowering during the seasons, especially autumn, when the rhizomes are taken, sliced, dried, and sold in the market. Commercially, American podophyllum is cultivated

in the regions of the US and Canada, whereas Indian podophyllum is found throughout the Himalayan belt. It is collected from regions such as Jammu, Kashmir, Himachal Pradesh, Uttarakhand, and even some parts of Sikkim. Now, there is a slight difference between American and Indian podophyllum. American podophyllum (*Podophyllum peltatum*) contains calcium oxalate clusters, which are slightly larger compared to Indian varieties. The smallest being the

30 micron in size or the largest being your 100 micron with an average size of calcium oxalate between 60 microns. Whereas if you see the Indian variant, the smallest size is about 20 micron, largest is 60 and the average size goes somewhere up to 30 micron. Your American one shows more of a simple solitary isolated starch grains, which are about 3 to 25 micron with an average of 15 micron in size. Whereas the Indian variant shows more stuck or what are called as compound starch grains. And they have a size little between 2 to 34.

But if you see the average, average is more on the lower side. So the average range is somewhere between 7 microns. Now, if you see the American variety, they are like about little bigger, 5 to 20 centimeter long and almost 5. 5 to 6 centimeter thick. So they are very thick and fat and very cylindrical whereas the Indian ones are very thin.

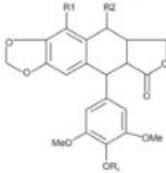
So they are just small 2 to 4 centimeter long and very tiny just 1 to 2 centimeter in their diameter. The American one shows a little longer internodes that is the distance between two internodes is very big whereas Indian The Indian variant shows a little shorter distance between the internodes. Now coming to a commerce, when you see the resin, the resin yields of the American variety is comparatively less. So it just gives you about 2 to 8% of resin as opposed to the Indian variant, which gives 6 to 12%.

But American variety is still considered as better variant because if you see the main lignan the podophyllotoxin content in the resin it is higher in the american variety and may go up to as high as 40 percent so imagine more than like half of the resin is made up of podophyllotoxin which we want whereas indian variety the podophyllotoxin content is found to be relatively less so despite giving more resin the yields of the podophyllotoxin remains still comparatively less So purchase or of commerce the American variety is considered to be more superior. Now what does it contain? Now this contains about like on an average 2 to 8 percent resin and this resin is called as podophyllin.



Chemical Constituents

- 2–8% resinous podophyllin.
- lignan derivatives podophyllotoxin, α- and β-peltatin in the form of glycosides and free aglycones.
- It also contains desmethyl podophyllotoxin, desoxypodophyllotoxin, podophyllotoxone, a flavonoid quercetin and starch




Compound	R1	R2	R3
Podophyllotoxin	H	OH	CH ₃
Desmethylpodophyllotoxin	H	OH	H
Desoxypodophyllotoxin	H	H	CH ₃
Podophyllotoxone	H	H	CH ₃
α-Peltatin	OH	H	H
β-Peltatin	OH	H	CH ₃

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Now this podophyllin is generally collected by extracting the roots in alcohol and So you will get most of the resin being dissolved in alcohol and then precipitating it by pouring the alcoholic extract in water. Now this compounds which are there, the resinous compounds which are there are insoluble in water and as a result they precipitate out. So whatever is precipitated out is collected and is used as resin. Now this resin is a very rich source of compounds called as podophyllotoxin.

peltatins and podophyllotoxin derivatives. So if you see your structure carefully again this is your main lignan moiety 1. So I will put here as my lignan 1. So this is the phenyl moiety of it and where does the propane go? So I am putting it as 7, 8, 9.

So now C6 is there. You have your 7, 8, 9, which is the bigger part of the ring. Now, the second part of the phenylpropanoid is this part. So again, once we carefully analyze, this is the C6 part of it. Let me put this as 7'.

So it's again an 8-8 linkage. And the ninth is something which is a carboxylic acid, which has been involved or formed or gets into what is called lactonization. Now, depending upon the substitution, you call different compounds. So, say, for example, in this case where your R1 is this, it's a hydrogen. Your R2 is a hydroxyl.

And your R3, that is here, it's a methyl. So you get what is called a trimethoxy derivative, and your R2 is a hydroxy derivative. In that case, you call the compound podophyllotoxin, and podophyllotoxin is the main lignan which is present in your podophyllum. Apart from that, if you remove the methyl group from here and just replace it by a hydroxy group, you get what is called desmethyl podophyllotoxin.

So, desmethyl means removal of a methyl group. At the same time, if you remove a hydroxy group from here, you get what is called desoxy. So here, it's normally hydroxy in

your podophyllotoxin. So if you remove that also, you will get what is called desoxypodophyllotoxin.

Now, apart from that, you also have podophyllotoxone in case it forms a ketone rather than an alcohol. Now, just shift the hydroxy group from R2 to R1. Earlier, what happened was this was H, and this was OH. So I'm just pointing out Earlier, this was H, and this was a hydroxy group.

I just interchange now—let this take H and let this take an OH. You get the compounds which are called peltatins. So, suppose if it is like podophyllotoxin but just missing or replacing the hydroxy group, you call it beta peltatin. But if you remove the methoxy, like your desmethylpodophyllotoxin, and then you replace the H, you call it alpha peltatin. So, these are all the lignan derivatives which are present in podophyllum, and they are used as cytotoxic agents.

Apart from that, your lignans will also contain quercetin and starch. So, let's see some applications. Like I said, it is cytotoxic in nature. So, it arrests what is called cell replication. So, your cancer cells cannot divide, and therefore, it's toxic to the cancer cells.

Now, because it is cytotoxic, it is also used in the treatment of venereal or other warts. So, you can easily get rid of those warts by applying a little bit of this podophyllum resin there in the form of an ointment or in the form of a little drop. Now, this podophyllotoxin causes a lot of gastric irritation. As a result, it is very effective as a purgative. But if you want the anti-cancer activity of it, we don't want GI irritation.

We want more absorption. So, as a result, what was done is, if you remember your podophyllotoxin, this was a hydroxy. So, if you attach sugar moieties out here, a little polar functionality to it, this compound is called etoposide. And etoposide is much, much better absorbed compared to your podophyllotoxin. Also, if you replace this with your thiophene moiety, you get what is called teniposide.

So etoposide is used for treatment of lung and testicular cancer, whereas your teniposide is more used for your lymphoblastic leukemia. Like I said, it's very, you know, strong irritant and a purgative but nowadays they are better and more safer drugs so it's replaced by senna it's replaced by isabgol and nowadays podophyllotoxin is no longer used as a purgative agent now moving on to the next drug is a beautiful uh Seed called as your linseed or flaxseed. We have it in our day to day kitchens.

It's also known as Alsi or Jivas. Now, it's actually a ripe seed obtained from *Linum catharticum*. It's a Linaceae family member. So it's a commonly grown crop in India. It's cultivated in America, Algeria, US, Canada, England, Russia.

You'll see it in the temperate regions also of grease, at least pain because of its vivid applications and good amount of compounds. So those who eat linseed or flax seeds very well know the advantages of it and they are attributed to a lot of compounds which are present in linseed. So let's see what's inside this beautiful seed. So linseed predominantly contains oil and this is one of the best oils when you have to see your omega-3 fatty acids. Linseed contains about 30 to 40% fixed oil of which majority is your linoleic acid which is 30 to 50%.

Chemical composition

- Linseed contains fixed oil (30–40%): linolenic acid (30–50%), linoleic acid (23–24%), oleic acid (10–18%)
- Mucilage (6–10%): Neutral: L-arabinose, D-xylose, and D-galactose; Acidic fraction includes L-rhamnose, L-fucose, L-galactose, and D-galacturonic acid.
- Protein (25%) (linin and colinin),
- Lignans: secoisolariciresinol diglucoside (SDG), Pinoresinol, lariciresinol, Matairesinol.
- linamarin which is a cyanogenetic glycoside
- Fibres

secoisolariciresinol diglucoside (SDG),

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So, the majority is omega-3 fatty acid, about 50%, then you have linoleic acid. Which is about 23 to 24%, and oleic acid, which is 10 to 18%. Now, if you see, all of them are unsaturated fatty acids. So, if you see the total percentage of PUFA, that is polyunsaturated fatty acid, it's much, much higher. Now, when you consume the seeds, you will come across mucilaginous matter, that is the sticky matter, and this mucilaginous matter is made up of uronic acids as well as sugars.

So, when you see the neutral fraction of the mucilage, it's made up of arabinose, xylose, galactose, whereas the acidic fractions include sugars such as rhamnose, fucose, galactose, and the galacturonic acid, which is the acidic moiety. The protein is a good fraction of it, almost 25%, containing your linin and colinin. Whereas, if you go to see lignans, the main part of it is a lignan called secoisolariciresinol diglucoside. Now, this is a secoisolariciresinol diglucoside.

is the main lignan component out here. Again, you can see the nature of linkages. So this is 7, this is 8. So again, this will be 7 dash, this will be 8 dash. So it is an 8-8 dash linkage.

Now, here to that, the ultimate, that is the 9 and 9-hydroxy groups, you have sugars attached to it and that makes it much, much more polar. Apart from SDG, that is your secoisolarisyrresinol diglucoside, you also have pinoresinol, larisyresinol and matioresinol. Apart from that, previously when we studied cyanogenetic glycosides, we know there's a cyanogenetic glycoside called as linamarin, which is also present in linseed. Now linseed is also cultivated for its fibers. So that is also something which is there in the seed coat also.

Now going to the applications. Now focusing on the lignan part of it, secoisolarisracinol, diglucosides and matieracinol, it is found that when you consume linseed are converted by the gut bacteria into compounds such as enterolignans or enterodiols or even enterolactones. Now this have a little phytoestrogen like activity. In some cases, they might show mimicking activity. In some cases, they might not mimic it, leading to inhibitory activity.

Now, mostly the mimicking activity is observed in case of SDG. And as a result, they act as mild phytoestrogens. They say that the other, you know, like phytoestrogen like activities or non steroid type estrogen like activities may be due to other effects of the lignans on the different systems of body. But moreover, all these effects are known to prevent or exhibit cancer protective activities. Your linseeds are very good sources of polyunsaturated fatty acids.

So they are good for your heart. The oil is also externally applied for gout and rheumatic swellings. They treat it well. Whereas, you know, linseed is given to children, especially the boiled mucilaginous infusion, because of its mucolytic activity. When chewed, it also gives a slight demulcent effect.

Which is good for colds, coughs, and bronchial affections. So these are a few applications of linseed. Now moving on to the next drug: Qubeb, also called Piper Qubeba or Kabab Chini. This is a herb, or rather a berry, used in Ayurveda as well as the Yunani system of medicine. What is done is, from the vines of Piper cubeba, these unripe berries are taken.

They are dried in a manner very similar to black pepper. And once dried, they are used as a source of Piper cubeba. This grows very abundantly in Southeast Asia, Indonesia, and

especially the Malaysian regions. So Indonesia, Malaysia, and Southeast Asia are the principal producers of Piper cubeba. Now, what does this contain in terms of lignans?

So if you see the chemical composition here, The chief lignan present, the earliest discovered lignan, is cubebin. So again, you can see here, this is 7, 8, I can put here as 8-dash, 9, 9-dash, 8. So it's again a linkage giving rise to a furan ring in between. And from cubebin, you have other cubebin derivatives such as cubebinolide, cubebinone, and cluzine.

Chemical Composition

- Lignans: cubebin, cubebinolide, cubebinone, clusin, hinokinin, yatein, and isoyatein, Kadsurin A and piperinone.
- Essential oil contains methyl eugenol and eugenol
- phenolic compounds like rutin, catechin, and gallic acid

Cubebin **Hinokinin**

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The slide features a list of chemical compositions and two chemical structures. The structure on the left is labeled 'Cubebin' and shows a furan ring system. The structure on the right is labeled 'Hinokinin' and shows a more complex structure with a lactone ring and a methoxy group. A small inset image of a woman, Dr. Gajvira Pereira, is visible in the bottom right corner of the slide.

Also, you get derivatives such as hinokinin. So hinokinin is again an 8-8 linkage. But rather than forming just a furan, it gives rise to a lactone kind of structure. Not only that, there is an additional methoxy substitution out here, which gives rise to an additional ring formation in both of these cases. Apart from that, you have kadsurin, kadsurin A, and piperinone.

Now, apart from that, you will see piper cubeba essential oil is also used. It is used in perfumery. It is also used in therapeutics. And from the fruits, you get phenolic compounds such as rutin, catechin, and gallic acid. So all in all, piper cubeba, traditionally in Ayurveda and Yunani systems of medicine, because of the lignans and flavonoid derivatives, has been very beneficial in the treatment of gonorrhoea, dysentery, syphilis, etc.

Abdominal pain, diarrhea, or, you know, the inflammation enteritis—even for asthmatic disease conditions—it is proven to be beneficial. Now, with more and more research going into the lignan derivatives, numerous lignans have been studied for their anti-cancer and antimicrobial effects. Of that, your cubebin was showing very promising or interesting activity against *Trypanosoma cruzi*, which is responsible for Chagas disease. Now, the other lignans also show anti-cancer effects, and that's the reason you will see numerous research reports wherein anti-cancer or even certain cancer-preventive activities have been

shown by the lignans present in your Piper cubebin. Traditionally, it also shows anti-inflammatory, hepatoprotective, and antibacterial activities.

Now, moving on to the last drug of this category: the sesame seeds. Now, sesame seeds—you already dealt with them when we studied lipids—that is, we studied the sesame oil. So, you get sesame seeds, and if you know, your sesame seeds are of two types: you have the white sesame seeds and black sesame seeds. They come from the same plant, that is, your *Sesamum indicum*, which belongs to the Pedaliaceae family. But black sesame seeds have their hull intact, whereas if you remove the hull, you get the internal pectin.

Sesame

- **Biological source:** Seeds of cultivated varieties of *Sesamum indicum* Linn., Family Pedaliaceae.
- Lignan sesamin (1%), the related sesamol
- During industrial refining, sesamol gets converted into antioxidant phenols, sesamol and sesamolol.

Sesamin

Sesamol

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Seed, and that's your white sesame seed. Now, if you press it, you get what is called sesame oil, which is rich in lignans. So, you know, like in oil, you get almost one percent sesame and their derivatives of lignans. If you carefully analyze, they are furofuran types, and here you can see it when we discussed it—this is seven, 8, 9. Here you have 7-dash, 8-dash, 9. So, again, you will see most of the linkages are 8, 8-dash type. But, interestingly, when you go to sesamol, it is not a continuous phenylpropanoid like here.

The bond has been interrupted here and that gives rise. So, if you break here, you get what is called as sesamol. So, sesamol is obtained from sesamol and you know like sesamol sesamolol is also another derivative which occurs in your sesame oil so sesame oil is used or it contains beneficial lignans if you know the ayurvedic preparations most of the ayurvedic preparations use sesame oil as a base oil for its stability and enhanced therapeutic effects Now, if you see the lignans, you can easily check for the presence of lignans, especially the sesamol or freeze alcohol, which comes after breaking the sesamol, that is your sesamol.

So the simple test is your Bowden's test. So Bowden's test is when you take the oil and shake it with about HCL containing 1% sucrose. On shaking gradually, you will see that it turns to pink color and that pink color is attributed to a reaction of sucrose. sesame oil with your sugars in presence of HCL. Now same test can be observed with furfural instead of sucrose.

So rather than adding sucrose if you add furfural this is called as your Villavacchia test. You studied this previously as a test to check the identity of sesame oil and this is basically attributed to your sesamol or free sesamol. Now coming to applications your sesamin is a very potent anti-inflammatory compound it shows antioxidant activities and like your categories of lignans it shows a potential anti-cancer properties it is said that if you have a diet which is rich in lignans it helps regulate your blood pressure your lipid profile and prevent cardiovascular disease condition Now, numerous research also shows wherein your sesamin is able to inhibit your cancer cell proliferation and induce apoptosis, especially in the cancerous cell.

So, it can be cytotoxic to cancerous cells and therefore shows beneficial activity in prevention as well as in the management of cancers. So, here are a few references if you wish to read more about this set of compounds, and thank you, everyone, for your patient listening. Thank you.