PHARMACOGNOSY AND PHYTOCHEMISTRY

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Week 8

Lecture 38

Quinones containing drugs

Hello everyone, and welcome to the Week 8 Session 3 of the NPTEL course in pharmacognosy and phytochemistry. In the previous two sessions, we saw a set of very beautiful pigments that are present in plants. We call them carotenoids, and those were tetraterpene derivatives, that is, C40 derivatives. In this session today, we will be studying quinones and quinone-containing drugs. So, what are these quinones and quinone-containing drugs?

Quinones are compounds that are widely distributed in nature. They are ketone dione moieties that are abundantly present in plants belonging to families such as Polygonaceae, Rubiaceae, Leguminosae, Rhamnaceae, as well as Liliaceae. If you recollect, in the previous sessions when we studied glycosides, we studied compounds such as sennosides and aloin, all of which are anthraquinone derivatives.

Sennosides belong to the family Leguminosae, whereas aloin belongs to the aloe vera plant, which is part of the family Liliaceae. Now, apart from plants, they are also found in lower plants like lichens or fungi. They possess numerous biological activities, the most striking one being their purgative effect. That is, their ability to irritate the GI mucosa.

So, if you remember your barbaloin or aloin, as well as if you remember your sennosides. Those were the anthraquinone derivatives, which had a strong purgative action. But apart from that, quinones also possess a very strong antibacterial effect. anti-tumor, in some cases cytotoxic, diuretic, as well as hemostatic effects. So, what are these different quinones, and how do we see them?

So, quinones, depending upon the nucleus in which they occur, are divided into different classes. So, if the nucleus is benzene and you apply a quinone—quinone is a diketone derivative. So, if to benzene you apply a diketone, you get what is called a benzoquinone derivative. To naphthalene, you apply a diketone, you get a naphthaquinone. To anthracene, if you apply a diketone, you get anthraquinones.

And to a phenanthrene nucleus, you get what are called phenanthraquinones. Now, these are not all. In addition to that, if you just extrapolate this to microbial sources, you might have encountered something like an antibiotic. Especially the antibiotic belonging to the tetracycline derivatives. Tetracycline derivatives are also examples of quinones, which have

a four-ring structure rather than the previously studied or now what we are studying—the three-ring structure. So, what role do quinones play in plants? Now quinones have a very good ability to undergo redox reactions. So they form what are called quinone and quinol, so this might just get converted to a dihydroxy

And you can have a benzene-like aromatization here. So that kind of interchange is very quick with quinones. And as a result, they form part of your redox systems, which are involved in the respiratory chain. So if you see the mitochondria, there is a respiratory chain called the electron transport chain. So quinones are part of the electron transport chain due to their ability to undergo redox reactions.

Now, apart from that, they play a very good role as plant pigments and also, as I said, they are defensive molecules. So they are antimicrobial, and for larger or higher animals, they cause GI irritation, thus preventing animals from consuming the plants. Now, moving on to biosynthesis. So how are they synthesized in nature?

The biosynthesis of quinones occurs via different pathways. Now, a majority or major pathway for the biosynthesis of quinones is the polyketide pathway. So what happens in the polyketide pathway is something very similar to your acetate-malonate pathway. So if you recollect your acetate malonate pathway, you had your acetyl-CoA pathway. Now, this acetyl-CoA, in the presence of an additional CO2—acetyl-CoA is a C2.

So in presence of additional carbon dioxide dioxide and factors such as biotin, in the presence of acetyl-CoA carboxylase, will add the CO2 to form what is called malonyl-CoA, and then subsequently it will go on adding more and more of this acetyl-CoA. Now, what happens is These structures then polymerize.

So, imagine this is a 2-unit; add one more acetyl-CoA to it, and you will form a 3, that is a C6 unit. So, this is C4; you will get C6, C8, C10, and so on. Now, imagine 8 such units joining. So, you can just count 8 very easily by counting the ketones out here. So, 1, 2, 3, 4, 5, 6, 7, 8.

So, 8 such kinds of acetyl-CoA getting converted to malonyl-CoA and being added up will give you what are called polyketides. Normally, when you went through your acetate malonate pathway via your fatty acid synthesis, what happened is this ketone group got converted into alcohols and thereafter got eliminated. So, eventually what we got was a hydrocarbon chain to give you fatty acids. But imagine a scenario where they don't get reduced completely.

Now, imagine if this reduction is partial and that leads to cyclization. So this cyclization will create what is called a typical anthracene nucleus. Now from this anthracene nucleus, imagine you have further oxidation. You get what are called anthraquinone derivatives. The steps proceed further to undergo reduction.

So you mostly have your plants containing anthracene, anthraquinone, or even hydroxy anthraquinone. So in plants, these remaining ketones get converted into hydroxy derivatives, and you have hydroxy anthraquinone derivatives. So in the end product, what comes out is a polyketide product. This polyketide product gets partially reduced to cyclize into a tricyclic system for the biosynthesis of anthraquinones. And this tricyclic system further undergoes reduction to form what are called hydroxy anthraquinones.

Not only that, it might undergo oxidation to form what are called 9-10 anthraquinone derivatives. So the biosynthesis of anthraquinones mostly happens via the acetate malonate pathway, but there are few quinones which have been synthesized from the isoprenoid pathway. There are few quinone derivatives which have also been synthesized via the shikimate pathway. Now, if you see naphthaquinones in a very similar manner, here again you can visualize: here you have your acetyl-CoA.

You can count how many acetyl-CoA units you are using by just counting the number of ketone moieties. So, 1, 2, 3, 4, 5, okay? And the sixth one is basically what is kind of involved in the joining reaction and this acetyl CoA like I said will first undergo a preliminary cyclization.

So you get an all or you get an phenol being formed. Then it will undergo a secondary cyclization. So you get two ring structures but in the process a subsequent oxidation converts it into a quinone. So it's basically a very simple process wherein your polyketides first reduce, join in cyclase to give you a cyclic structure.

Thereon it undergo oxidation to add a quinone moiety and some of this ketone moieties undergo reduction to develop hydroxy substituents on the quinones. So naturally most of the anthraquinones you will find hydroxy substituted. Now let's take a simple case or let's study today a class of quinones which is your benzoquinone. Benzoquinone as the name implies it is a quinone or a diketone substitution on a benzene ring.

Now you can see here as the case be with amylin. There is a 1,4 and even in thymoquinone, there is 1,4. But in nature, there are also quinones which are orthoquinones. Orthoquinones mean the second ketone will occur here at the ortho position. But compared to paraquinones, orthoquinones are thought to be comparatively unstable,

and their occurrence happens in a much less stable form. As far as the plant kingdom is concerned. So you will find the majority of the benzoquinones being paraquinones. That is your 1,4-quinones. Now, once they have formed quinones like we saw in biosynthesis.

They will undergo hydroxy substitution to change their polarity. Now as compared to embellin. If you see the second compound, thymoquinone. You can recollect this structure. If you recollect this structure, you will understand that this is typically a C10 that we did previously or

that we studied previously when we covered volatile oils. So this is one example. So thymoquinone is one example of a quinone derivative that has come from your isoprene synthesis. So, do you remember this? This is your 1, 2, 3, what we called it and said.

4, 5, cut it here, and then 1, 2, 3, 4, 5, cut it here. So, this is a typical isoprene derivative, whereas imbellin is more of a polyketide synthetic derivative. So like I said just put an emphasis majority of the quinones have been brought in by polyketide pathway polyketide pathway, but there are some which are derivatized from your isoprenyl pyrophosphate or what is called the acetate mevalonate pathway.

In some cases, they are also derived from the shikimate pathway. Now, depending upon that, you might have different substitutions occurring. In some cases, you will find long-chained ones. In some cases, you might have short-substituted quinones. Sometimes, in nature, you may also find compounds which are like your furanoquinones.

Now, quinones, especially your benzoquinones, are found in families such as Leguminosae, Asteraceae, Myrcinaceae, Comfreyaceae, or Araceae. Not only that, they also occur in some species of fungi. And these are very potent ones. So, they have what are called anti-inflammatory activities, but they also have the ability to ward off parasites.

So, they also show, to a certain extent, anthelmintic properties, especially if you look at quinones such as embelin. Now, let's take an example here. of drugs containing benzoquinones in today's session we will study two drugs containing benzoquinones and that is *Embelia ribes* and *Nigella sativa*. We'll first discuss *Embelia ribes,* that is your embelia. Now, embelia is a plant very indigenous to us; it is called false black pepper or wauding.

So traditionally, fruits of this plant have been boiled and given as a decoction to children, especially to ward off worms or for its anthelmintic effect. Now, this woading is actually a fruit or, more correctly, referred to as dried berries of the trees of *Embelia ribes.* Now, *Embelia ribes* is a deciduous tree which grows in somewhere down from Maharashtra to South India,

not only that, but down to Sri Lanka, Malaysia, or even in parts of South China it occurs. Now, this plant is also cultivated for woading, but the majority of its produce is still taken from wild sources. Now, once the plant is cultivated, within 2 to 3 years it starts fruiting. Now a good time to collect the fruit is generally during the summers and if you have to collect a very mature ripe fruit with the seeds, you can collect it in the early months when the fruits are very dark.

But if you want to use it for pharmaceutical purposes, mostly it's collected in May or summers when the fruits are reddish or they have this type of consistency. If you wait till late monsoon, they'll become blackish in color and then they are difficult to manage because they have a good content of tannins. So even the decoctions or the preparations containing them become very dark.

So what does this Embelia contain? Embelia contains chiefly a compound, especially a benzoquinone called embelin. So this is how the pure embelin looks like. It's a nice crystalline sticky flake. It's a little oleaginous because of the long chain or the aliphatic long chain.

So it's oily. It's a nicely flaky orange color. The interesting part is if you break the fruit. Okay, just see here. If you break this fruit open, you see the inner endosperm exposed.

The content of ambellin is so high, and it's located on the outer wall of the endosperm. So the moment you open this fruit in your hand, you will see some orange powder stuck to it. This orange powder is nothing but the ambellin. Now, apart from ambellin, it also contains a dimer of ambellin, which is your valangin. So this is nothing but a dimer.

So imagine your ambellin twice. You call it valangin, and it is often thought to be a byproduct or a deterioration product of ambellin. Now, in addition to that, Ambellin has a C11 chain. Suppose if you change it to a C13 chain, you get the third quinone compound, and that is your rapinone.

So your *Embelia ribes* contain chiefly embelin. It contains your dimer of embelin that's valangin and a little long chain that is a C13-substituted benzoquinone derivative, and that's your rapinone. Apart from that, it contains volatile oil. It also contains fixed oil, certain resinous substances,

tannins, alkaloidal compounds, cristambin, phenolic acids like caffeic acid, vanillic acid, and chlorogenic acid. Cinnamic acid and cumeric acid, and that is the reason when you tend to consume it or when you tend to eat it, it has a slightly sour odor as well as taste due to the presence of acidic substances. Now, where do you use embelin? Embelin is known in Ayurveda and has been used traditionally even in folklore medicine.

Like I said, the decoction of the fruits is given to eliminate intestinal worms as well as parasites. Not only that, consuming this water or the decoction of a melon has been reported o to give you relief from abdominal issues such as indigestion, constipation, flatulence, or even abdominal pain. Now, with little modern day investigation fruit extracts are known to cure tumors of certain types, help in dealing with ascites, which is

water accumulation, bronchitis, jaundice, and even certain mental disorders. Now, if you see embelin, embelin is one of our anti-fertility agents. So, it is used in spermicidal creams. It is even recommended in an Ayurvedic formulation called Pipliyadi Vati. Now, this formulation is actually a tablet or oral contraceptive tablet.

Now, this contains Embelia ribes as one of its ingredients. So yes, it has anti-fertility effects, and that is something we need to be cautious about when using it for other therapeutic purposes. The decoction of this fruit, apart from the above-mentioned uses, is also useful in the treatment of fevers. For diseases of the chest, respiratory disorders, as well as skin disorders.

The infusion of roots of *Ambela ripes* has been traditionally prescribed for the treatment of cough and diarrhea. Now, we move on to the next plant, which is cultivated in India on a large scale now because of its increased usage. This increase in usage has basically happened in the hair care industry, where Nigella seeds are also sold as onion seeds. So, onion seed oil is chiefly your Nigella seed oil.

That's another common name, or it is also referred to as your Kalonji oil. So, this is obtained from the seeds of *Nigella sativa*. Some people even call it black cumin, but it has nothing to do with cumin. It's not an Ambelifera family member. In fact, it is a Ranunculaceae family member.

Now, this is also a plant that grows and is generally harvested during the spring season. And what happens is, within 90 to 120 days, your crop is ready. These beautiful black seeds are located in the capsules of the plant. So, this plant after harvesting is threshed to break the capsules, and the breaking of the capsules releases the seeds. The seeds are collected, all the chaff is blown away, and then what you get is Nigella or the Kalonji seeds.

Now, these Kalonji seeds have an enhanced or increased therapeutic value. Because they contain a compound, especially a benzoquinone derivative called thymoquinone. Now, the seed mainly contains fixed oils, a little protein (about 16-19%), carbohydrates (which are almost equal to oil), fiber, and moisture. But thymoquinone is the one responsible for the majority of its effects.

So, as I said, it's an oxygenated terpene derivative, but you call it a benzoquinone. Now, that is present in the volatile oil. So, if you take the seeds, distill them, and collect the essential oil, you will see thymoquinone gets collected in the oil to the extent of almost 20 to 30%. Now, apart from that, the other essential components of the oil include

carvacrol, p-cymene, α-terpineol, longifolene, and trans-anethole. So, these are the other ones. And thymoquinone is a major part of the volatile oil, which is also responsible for a mild effect, what you call it as antioxidant, as well as the therapeutic effects of the oil. So, what are the therapeutic effects?

So, traditionally, especially in the Middle Eastern countries or Far East countries well as Kalonji extracts have been used to treat headaches, coughs, abdominal pain, diarrhea, asthma, and even rheumatism. headaches, coughs, abdominal pain, diarrhea, even asthma and rheumatism. Now, The increase in the utility of Kalonji has been due to its lipid-lowering effect and insulin-sensitizing

effect, which have been proven clinically. Now, not only that, it has also been used to address digestive disorders like a carminative, which includes indigestion, bloating, and even certain cases of diarrhea. Kalonji oil or black seed oil is nowadays included in hair care as onion seed oil, synonymously it is added, and it has good potential to promote hair growth.

So, one way is internal consumption for lipid-lowering and increasing insulin sensitivity, which is related to glycemic or diabetic effects or diabetes. Treatment of diabetic effects; on the other side, external application increases hair growth and enhances hair care properties, especially hair thickness. This has caused an increased market demand for the seed.

Apart from that, Kalonji is also part of numerous hepatoprotective formulations, and in animal models, it has been proven effective against carbon tetrachloride-induced liver fibrosis and cirrhosis. So these are two quinone examples. Let's move on to an anthraquinone example. Now, anthraquinones, unlike benzoquinones, have an anthracene moiety.

Anthracene is what you call it when you have three benzene rings stuck to each other. Now, previously, if you remember, we have studied a few anthraquinones. These anthraquinones include your senocytes. Your carminic acid is something we will discuss today. And if you remember your aloes, you had your aloin.

So we've already studied under the glycosides category, your sennosides and aloin, which are examples of anthraquinone glycoside derivatives. Now, anthraquinones mostly, like I said, are 9-10. So this is like 9-10 compounds. Anthraquinones mostly have para substitution preferred here because that is more, or that is considered to be more stable.

Now, because of biosynthesis, you see most of them have a hydroxy substitution. So mostly, your quinones will have some other hydroxy substitution due to your ketone of acetyl-CoA getting reduced and sometimes even the hydroxyl being added. Now, because of the hydroxyl being added, the majority of the quinones also add a sugar moiety and are converted into glucosides.

A good example of anthraquinone-containing drugs is your rhubarb. Senna, Cascara, Aloe. They are present in certain insects such as cochineal. They are present in certain fungi. They are also found in certain lichens.

In today's session, let's discuss one beautiful insect containing an anthraquinone derivative, and that's your cochineal. So cochineal is actually a pigment which is derived from an insect called Dactylopius coccus. Now, this Dactylopius coccus is a very tiny insect. As you can see here, it's covered. It's a very tiny insect.

It feeds on the sap of cacti and prefers the sap of a cactus called Opuntia. So, it is an Opuntia-loving insect, and it is found mostly in the American subcontinent, in Peru, Mexico, as well as the Canary Islands. That's where the cultivation of this insect is also done. So, actually, the insects have been cultivated and harvested.

The tiny larvae of this insect have been picked up and transported to cacti. Once they are transported to cacti, they stick to those cacti and start feeding on their sap. Now, these insects undergo fertilization. The males are generally tiny, whereas females grow to a slightly larger size, about three millimeters or so. They acquire pigment as part of their defense

system, which helps them ward off predators. As the female insects mature, the amount of pigment in them increases. Once that is done, this is actually a sessile parasite. They don't really move. Once they have attached to the Opuntia, they grow and dwell in the same place.

Even they lay their eggs there itself. Okay, so this insects when their harvesting time is there or when the harvesting time is due, the leaves are brushed. So all this insect kind of fall off. So you will see the process. So this female insects contain about 17 to 24 percent of their body weight of the carminic acid,

which is the reddish colored dye. So mostly they are brushed off. Then after they are brushed off, they are collected on a paper or on a plastic bags. They are dried in sun. So they are made crisp.

And this crisp insect is then kind of ground. This pounding or grinding creates a very fine powder. This powder as such is used for dyeing of textiles but for pharmaceutical and food application it needs extraction. So for textile applications, they just take the ground powder. For food and pharmaceutical application, this powder is extracted with solvent.

Now the pigment which is present here is carminic acid. So as you can see, it's an anthraquinone derivative, and it's an anthraquinone C-glucoside. So what happens is the sugar cannot be kicked out easily because it's a C-C linkage, and that sugar renders it little polarity. So I can extract this pigment in water. ethanol, acetone.

In some cases, I can heat it to get more of these pigments. Then it is filtered, wherein the insects stay back, and the filtrate contains your pigments. This is further concentrated, and you get a nice dye. Now, in some cases, what is done is this dye is further reacted with metals such as aluminium and converted into lakes. Lakes are the insoluble salts.

So they get converted from dyes to pigments. And in some cases, the pigments are also used. So if you see cochineal, cochineal is used as a natural food colorant. It is approved with an E number of E120. Carminic acid or carmine has a color index number 75470.

which gives a nice red tone and a good part of this red color is it's very stable to light and temperature otherwise, most natural colors are not, and that makes it a more ideal pharmaceutical or cosmetic-grade color because of its colorfastness, and in some cosmetics, you need to use temperature. So it is very conducive to use a stable pigment rather than a red color pigment such as anthocyanin, which will lead to deterioration.

Not only that, it shows a pH-dependent color change. It is said that carminic acid is more reddish at a slightly acidic pH, and then the color changes to a little purple as it goes to a neutral to near-alkaline pH. Now you can make different lakes mostly aluminium lakes are used in some cases even calcium lakes are prepared prepared. Apart from this, carminic acid is also used to stain bacteria, so it's used in bacteriological stains.

So these are a few examples of quinones. What we did were two examples of benzoquinones, that is, your embelin and thymoquinone, and one example of an anthraquinone compound, which was your carminic acid. But don't forget, we have already covered two more additional anthraquinone-containing drugs, and those are your senna and aloes.

They also belong to the anthraquinone class of compounds. So Here are a few more references if you wish to know more about this set of compounds. And thank you, everyone, for your patient listening. Thank you.