

# PHARMACOGNOSY AND PHYTOCHEMISTRY

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Week 8

Lecture 39

## Week 8: Lecture 39: Naphthoquinones containing drugs

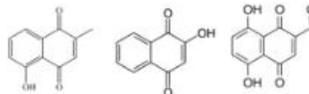
Thank you. Hello everyone, and welcome to the Week 8 Session 4 of the course on pharmacognosy and phytochemistry. Now, in the previous session, we started with a new set of pigments present in plants, which are called quinones. Quinones are diketone derivatives, and if you remember, depending on where they are substituted, you had benzoquinones, naphthoquinones, anthraquinones, and phenanthraquinones. If you recollect, you can even go to microbial families to find compounds such as tetracyclines, which are also quinoidal derivatives. Now, in this particular session, we will delve into one specific class of quinones: naphthoquinones.

So, naphthoquinones are based on a naphthalene nucleus. So, if you pick up naphthalene, which is a you know, dibenzene nucleus. And if you attach a diketone moiety to it, you get what are called naphthoquinones. Now, depending on where this diketone moiety is attached, you could have a 1,2-quinone or a 1,4-quinone.



### Naphthoquinones

- Naphthoquinones are based on the naphthalene molecule, with two ketone groups (C=O) attached.
- The isomeric forms include 1,2-naphthoquinone and 1,4-naphthoquinone.
- They are found in various natural sources, including plants, fungi, bacteria, and even some marine organisms.



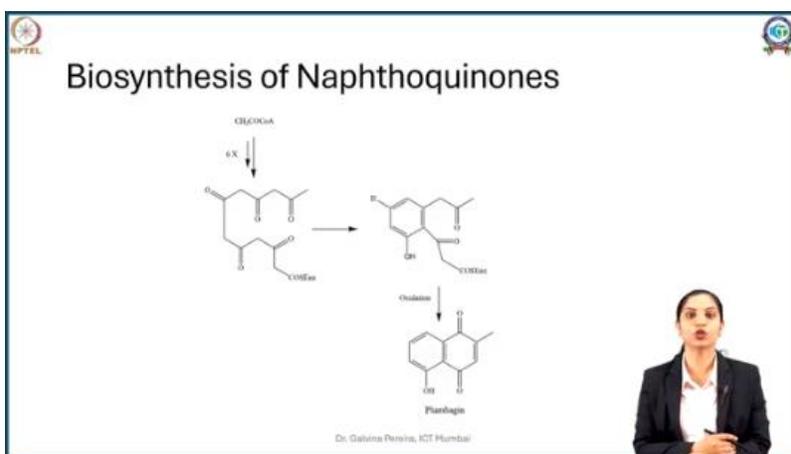
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Now, take a case, say, suppose if you have this particular type of functionality. This is called a 1,4-quinone. The reason is this is 1, this is 2, this is 3, this is 4. So, this is typically a 1,4-quinone.

But in some cases, what might happen is you might come across quinones that are ortho-substituted. So, in this case, they are called 1,2-naphthaquinone. So, if this is a naphthalene moiety, you can attach this. Complete the unsaturation, and you will find this is a typical example of 1,2-naphthaquinone, whereas this is an example of 1,4. So, all these three are examples of 1,4-quinones.

Now, depending upon that, you might have different quinones coming from different species. Now, quinones being oxidative-reductive pigments, are dispersed in plants, fungi, bacteria, and even in marine organisms, where they contribute to nice hues, colorations, and also help in electron transportation. So, these are examples of a few quinones: you have plumbagin, which comes from the plumbago plant; lawsone, which is in henna; and alkanin, which is in ratanjot. So, if you remember your quinones, the quinones are biosynthesized.

Coming to the example of naphthaquinone derivatives, again, the majority of naphthaquinones have been biosynthesized using acetyl-CoA precursors. So, these acetyl-CoA precursors require six such units of acetyl-CoA precursors. Just to be precise, this is 1, this is 2, this is 3, this is 4. This is 5, and this is 6. This is the carbonyl—the last one.



So you have six such acetyl CoA via malonyl CoA, and you remember they don't undergo reduction directly. So this is the first cyclization, as we saw in the previous session. The second cyclization is followed by oxidation as well as elimination. So this will get eliminated, and what you get as an outcome is what are called your NAFTO 1,4 quinone

derivatives. A good example of that is plumbagin because this methyl is retained in plumbagin.

So from plumbago, you get plumbagin. This is how it is biosynthesized. So few plants containing quinones or naphtha quinones that we are studying today are *Lawsonia inermis*, commonly referred to as henna; *Plumbago zeylanica*, commonly referred to as chitrak; and *Alkanna tinctoria*, commonly referred to in India as ratanjot. So let's start with a simple, humble plant: henna. So *Lawsonia*, or henna, is actually the drug, and what is used are the leaves.

So you can see here they are beautiful henna leaves. These henna leaves are plucked from the shrubs of *Lawsonia inermis*, which belongs to the Lythraceae family. Now these leaves can be plucked up to five times a year. So once you have fields containing henna plants, you can have multiple harvests, and it is said that of the harvest, the one collected in July, immediately after the summer season, is said to be loaded with pigments, whereas the harvest generally collected during the colder season, such as February, is said to have less pigment value. Now this plant is cultivated, and you will see the significance of henna in Middle Eastern culture.

In Southeast culture, it is cultivated there. It is cultivated in North Africa, Southeast Asia, India, as well as in Persia. It is also used extensively in those regions, as you know, as a beautiful ink that you can use on hands, called mehendi, and it is also used for coloring hair. It is also used as a hair colorant.

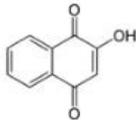
In all these regions, especially North Africa, Southeast Asia, and the Indian subcontinent, it is used for ornamental purposes as well as a hair colorant. So, this *Lawsonia*—what does it contain? Now, this *Lawsonia* contains quinone derivatives, more specifically a naphthoquinone derivative called Lawson. But if you observe something with your mehendi—if you use it directly, unstained or untreated—the stain is very faint. People often allow mehendi to mature. What happens is, apart from Lawson, henna also contains certain glycosides of naphthaquinones as well as Lawson.



## Chemical Composition



- Dried powdered leaves of henna contain about 0.5-1.5% lawsone
- Isoptumpagin, lawsoniaside, lalioside, lawsoniaside B, syringinoside, daphnorin, hennadiol
- (20S)-3β, 30-dihydroxylupane, lawnermis acid, laxanthonos I, II, III and lacoumarin etc
- Luteolin and its 7-O-glucoside, fats, resin and henna-tannin.



**Lawsone**

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During the process of maturing, where you soak the mehendi in water or keep it slightly acidic—you can squeeze lime or put it in tea, which is more acidic in nature— these acidic conditions create an optimal environment for hydrolysis of the sugars to yield free quinone derivatives. Now, these quinone derivatives, especially the naphthoquinone derivatives, are said to occur in three forms. This is your 1,4-quinone. Some postulates state that, in some cases, it is even found in a triene form, but it is very unstable there.

In some cases, it is found in the glucoside form. So, we eliminate this. Make this a single bond and just add a sugar out here. That is also the glycosidic form of Lawson in which it is present. So, if you want the glycosidic form to get converted into a glycone, that is the way it is done by soaking henna in water for a prolonged period of time and adding something acidic.

Some people even add tannins as a mixture to intensify the coloration attributed to Lawson. Now, what happens chemically here is Lawson is a quinone derivative. And this quinone derivative has a tendency to add to nucleophiles. And in your skin, there is keratin. Keratin carries positively charged atoms such as nitrogen and sulfur.

Now, in this case, what is going to happen is your Lawson will stick to keratin and it will form a kind of covalent bond. A covalent bond, once it forms, is difficult to remove, and as a result, it forms what is called a permanent stain. Now, when I say it gives a permanent stain, the question arises in your mind: when I apply mehendi or henna, it vanishes after a period of time. How is that a permanent stain? Now, this is explained by what is called skin turnover.

So your skin replenishes the cells and the older cells are kind of washed off during the cleaning when you do hand washing. So the older cells are discarded. Now imagine putting

mehendi on your hand. Now your loss zone has formed a permanent covalent bond with keratin. Now this cell is aging permanently.

And as it ages, it will get dislodged from your skin in a way to eliminate the older cells. So during the washing, during the scrubbing, the cells get eliminated and is replaced by new cells. But new cells are no longer bound to the law zone. And as a result, slowly, slowly your bhendi fades away. So the rate at which your mehendi fades away is actually the rate at which your skin produces new cells.

So when your mehendi diminishes at a very fast rate, we should be happy that our rate of skin regeneration goes very quickly. Same applies to hair. But what happens during repeated washes? The hair shades of certain cells and the cells are often in some cases bound to keratin. So that some loss in the pigmentation is there.

And as a result, the color becomes lighter over a period of time. Not only does Lawsonia henna contain isoplumbagin, which is a quinone derivative. You have a Lawsonia side. Now Lawsonia side is nothing but, you know, what is called diglucoside now. Imagine attaching this to your sugar.

So you have your all. You have your diglucoside, and that is what is called lawsone side. Then you have your laliocide, lawsone side B, then you have your syringoside, daphnorin, henna diol. All of these contribute in a way to give a good conducive environment for your henna or your lawsone to bind in. Now apart from that, there are different other classes of ingredients which include your lupine derivatives such as 20S,

3-beta-30-dihydroxy-lupine. Then you have your lonermis acid. Then you have xanthones. Xanthones are tricyclic analogs which also are in between your quinones and flavones. So those are your xanthone classes.

We have your lawsanthones 1, 2, 3. We also have coumarins present in henna, and that is your lacoumarin. Apart from that, a few flavonoids and their glycoside derivatives, which are present in henna, include luteolin, its glycoside, and some other compounds such as minute traces of fats, resins, and tannin derivatives, often referred to as henna tannins. Now, where do you use henna? Henna is used traditionally.

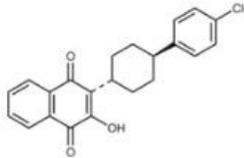
Also as a medicine in the treatment of jaundice. Now, henna is not something you can consume in large proportions, but a very dilute decoction of it is used or given to treat jaundice, ringworm infections, skin diseases, in certain cases, migraines, lepromatous patches, ulcers, smallpox, chickenpox, tumors. It is a mild anti-inflammatory and provides

a good amount of healing. And that's the reason even in cuts and bruises, some... Folklore medicine also prescribes that you can juice your henna and apply it there. It is used as a hair colorant, and it is also known that, apart from coloring, it prevents dandruff and, you know, kind of prevents hair fall as well. Now, it is also because of its anti-inflammatory effects given or is beneficial for patients suffering from what is called hand-foot syndrome.




Application

- Traditionally used in treatment of jaundice, treating ringworm infections and skin diseases, migraines, leprosy, ulcers, smallpox, chickenpox, tumours .
- Used as a hair colourant, prevents dandruff and hair fall
- Beneficial for patients suffering from hand foot syndrome owing to its anti-inflammatory, antipyretic, and analgesic actions.
- Lawsone is used as precursor for Atovaquone



**Atovaquone**



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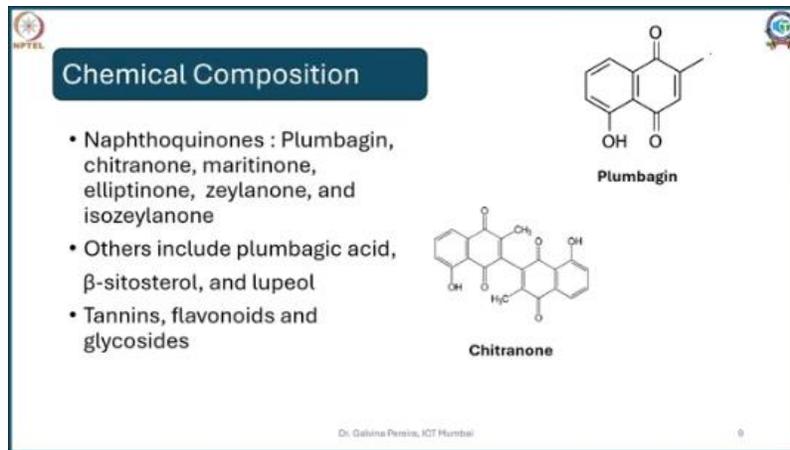
And it has, you know, like a painkiller, analgesic effects. Now, one interesting application of Lawson is if you see this structure carefully and I break it here. This is a compound called atova cone. Now, atova cone can be prepared easily from Lawson because it has the same kind of nucleus. So, two hydroxy Lawson nucleus, and to that, you need to specifically attach this group.

When you attach this group, you get a compound called autoacone, which is used in cases of pneumonia or in the treatment of pneumonia. Now we move on to our second drug. The second drug is referred to as Chitra or Plumbago. Now, Plumbago is actually roots which are used in Ayurveda, and these are obtained from *Plumbago zeylanica* plants. Now, this belongs to the Plumbaginaceae family.

Now, in Ayurveda, you have two types of Plumbago. The one with white flowers is referred to as Chitraka, which is your *Plumbago zeylanica*, and then there is a red-flower variety often referred to as Rakta Chitraka. Also referred to as *Plumbago rosea*. Now, in this case, what happens is Plumbago is cultivated in the Indian subcontinent, Asia, Australia, and even some places in Africa. This plant, especially the root part of it, is very potent because it contains a naphthoquinone derivative called plumbagin.

Now, compared to your Lawson, which had a hydroxy here. So, if you treat it as 1, 2, 3, 4, your Lawson has a 2-hydroxy. But in this case, especially in your plumbagin, it's 2-methyl-

2. 5-hydroxy-1,4-dione, that is a 1,4-naphthoquinone derivative. So, plumbagin is the one which is responsible for the potency, so much so that if you take an overdose of Plumbago, it is fatal.



So, plumbago in Ayurveda is kind of detoxified to get rid of quinones so that they are no longer fatal. Now, apart from plumbago, other quinones are also present. The other quinones are often dimers of plumbagin. Just to give you an example, you can see in this case what is happening here: one, two, three. I'm just putting here one.

Dash, 2 dash, 3 dash. So, you have your 3, 3-dash diplumbagin derivative, which is your chitranone. In a similar way, you have your marinone, elliptone, or elliptinone. Adhylanone and isodhylanone. All of these are dimers of plumbagin.

Apart from that, you have plumbagic acid, cytosterol, lupiol. You have tannins, flavonoids, and glycosides. Now, most of the effects or the good effects of plumbago are due to tannins, flavonoids, and glycosides. And most of the potent toxic effects are due to the naphthaquinones. And that is why it is mentioned in Ayurveda that whenever you are taking chitrat,

Especially the Rakta Chitra, the red variant, which also contains plumbagin, undergoes what is called Shodhan Prakriya or detoxification. What is done is quinones have a good ability to solubilize in alkaline pH. So in acidic to neutral pH, you can see the structure. They cannot be water-soluble. But imagine in an alkaline pH.

They tend to undergo what is called salt formation. Their salts, interestingly, have a very nice color. So plumbagin is a compound which is yellow in color. The sodium salt of plumbagin is deep pink in color or cherry pink in color. So they form deep-colored salts.

The salts are water-soluble. So what they do in Ayurveda is take the chitrak plant or, more specifically, the plumbago root, which is used. This plumbago root is soaked in lime. Now, lime being alkaline in nature will form salt and solubilize or remove plumbagin and other quinone derivatives. The other quinone derivatives are nothing but dimers of plumbago.

So it's going to remove that and in the process it is going to get rid of all the quinones. So soaking in lime will remove all the quinones and what are left are mostly these other compounds which will show the potency. So where all it is used in Ayurveda, it is used for treatment of rheumatic pain, dysmenorrhea, carbuncles, basically those pus-filled, you know, outgrowths which appear on the skin. Contusions are basically you know when you get wound or bruised you'll see a blackish coloration due to no blood being accumulated in the regions often resulting from a minute capillary burst. Those contusions of extremities even ulcers are something your plumbago extracts can easily treat. It is used in elimination of intestinal parasites. It's very common for most of the quinones to show this activity. It is also used in treatment of flatulence, dyspepsia, piles, intermittent fever because it's slightly bitter so that property somewhere helps in treatment and mitigation of fever, muscular rheumatism.

Now, apart from that, after purification using modern scientific methods, plumbagin is also reported and proven to show antimicrobial, antimalarial, anti-inflammatory, anti-cancer as well as anti-atherosclerotic activities. Now we move on to the third beautiful pigment-containing drug and that is your Alkana. Alkana is often referred to as Ratanjot. So if you see the color of your Lal Tel, especially your Dabar Lal Tel, that red color is attributed to Ratanjot. Not only that, if you have heard of a famous Kashmiri dish called as Rogan Ghosh, which is a

meat-based dish, it is said that the color for that dish is mainly derived from spices and in that spices one of the elements is your Alkana root which also contributes to the color of this curry. Now Alkana is a big genus and then it consists of many species. The chief one of it is your *Alkana Tinctoria* but other 17 such species are also counted and synonymously used as Alkana. All of them belong to Boraginaceae family member and are more indigenous to the Mediterranean region. So they grow mostly in your southern Europe to Mediterranean region and in some places in Iran. In India also you will find few species of Alkana growing there in Kashmir and that's the reason you put it in the gravy Rogan Josh which is more common in that part of the Indian geography.

So this plant bears beautiful, beautiful blue flowers. And if you dig the root, the roots are the ones responsible for the color. So if you see here, it's intensely blackish or blackish-bluish, you could say. But if you put it in oil or soak it in oil, they leach this red color pigment. Now, if you break this root completely, the internal side will reveal a whitish core, which is more of a starchy material.

Now, in terms of chemical composition, alkanna contains naphthazarine derivatives, which are also called hexenyl naphthazarine derivatives. Now, be careful: this is not isoprene; this is not 5; this is 1, 2, 3. This is 4, 5, 6. So it is called a hexenyl naphthazarine derivative. Naphthazarine is this particular nucleus.

**Chemical Composition**

Naphthoquinones: alkannin and shikonin are responsible for the colour of Alkanna and their esters such as acetylalkannin, propionylalkannin etc.

Flavonoid glycosides of quercetin, kaempferol, and luteolin.

Rosmarinic acid, lithospermic acid, and salvianolic acids, as well as rabdosiin

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The slide features two chemical structures: Alkannin (left) and Shikonin (right), both naphthoquinone derivatives with a hexenyl side chain. A small inset image of a woman is visible in the bottom right corner of the slide.

So you have your dione, and you have again your diol. And definitely, it can undergo what is called keto-enol tautomerism. And that's the reason it's beautifully colored. It gives what is called a deep magenta color. It also has a stereoisomer called shikonin, and alkanin and shikonin occur together in plants.

In some species, alkanin is more in percentage as compared to shikonin, whereas in certain alkanna species, it is found in the form of a racemic mixture. Now, apart from that, this hydroxy group is sometimes esterified with different compounds, the most common being acetyl, giving you acetylalkannin as well as propylalkannin. So you have esters, and you have polymers. In some cases, during the extraction steps of the pigments, it gets polymerized at this point itself. Now, apart from the pigments, your alkanna also contains flavonoid glycosides. This includes quercetin, camphorol, and luteolin, and acids such as rosmarinic acid, lithospermic acid, and savionic acid.

Now, it contains a small part of what is called rhabdozin as well. Now, knowing these pigments, there is an interesting phenomenon that is observed. So, I will show you with the

help of TLC. So, what happens here is I have just put a TLC image. The first TLC shows a standard of alkanin.

In a normal mobile phase made up of toluene, chloroform, acetone (50:51), using a silica plate, now because this pigment is a nice magenta in color, you can see the standard alkanin is pink, as well as the alkanin, as well as what goes on top, which are more of its ester derivatives. So, these are all ester derivatives which are there in the alkana extract. The moment you treat it with alkali, Like we discussed here, imagine a sodium or a potassium salt out here. It forms water-soluble beautiful salts. So now, these water-soluble beautiful salts are like your pH indicators. So, at an alkaline pH in the presence of alkali metals, it gets converted into a nice deep blue pigment.

So the alkali salt of Alcanna is a nice Prussian or day-blue coloration, and that is something which can be used to identify your naphthazerin pigments, especially Alkanin. Apart from that, as a color, *Alkana Tinctora* has been used as a natural red dye for textiles. It is used in foods as well as in cosmetics. The extracts of the plants have been taken and are used to prepare lipsticks or deep lipophilic stains. Now it is said that extracts of Alkana can also be used to maintain skin health because it's a very strong antioxidant, antiviral, and antibacterial agent.

Not only that, in terms of its skin benefits, it has also been proven to show anti-wrinkle and anti-aging activity. Traditionally, it is used for wound healing, and you might find a few literature sources wherein people have used Alkana extracts for wound healing. They have even incorporated those Alkana extracts in bandages wherein it can be applied to the wound, and the wound healing has happened at a significantly faster rate. Now, tincture Alkana is prepared basically by extracting Alkana in different solvents—that can be soaking in oil or it can be extracted in alcohol. Alcohol extract is often used as stains.

Now, this is used as stains for oils. So if I have a transverse section of plants and if there are oil droplets—now, oil droplets are transparent—it becomes difficult for me to understand whether they are water droplets or oil droplets. In such cases, the sections are often stained with a drop of tincture Alkana. So wherever the oil droplets are, they will imbibe this stain and they will become pink. Whereas wherever the water is, the pigment remains insoluble, and you will get a precipitate-like appearance, whereas in the oil globule, you will get a more homogeneous appearance.

Apart from that, because of its ability to show a nice color change from pink to blue, Alkana has also been used as a pH indicator. So, these are a few examples of quinone-containing

drugs. If you wish to read more on this topic, here are a few references. And thank you, everyone, for your patient listening. Thank you.