

# PHARMACOGNOSY AND PHYTOCHEMISTRY

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Week 7

Lecture 32

## **Week 7: Lecture 32: Flavonoids Containing drugs (Part 1: Orange peel, Buckwheat, Strawberry)**

Thank you. Hello everyone, and welcome back to our session on flavonoids. We were learning about a class of beautiful natural pigments called flavonoids. Flavonoids are naturally yellow in color, but there are certain classes called anthocyanins, as we previously saw. Because of their charged nature, they have different colors.

You can see different flowers here, and these all contain anthocyanins. Nature converts flavonoids into anthocyanins. Plants store them carefully in the flower petals, and then they exhibit their beauty. Now, we will dwell a little bit more this week on some flavonoid-containing drugs. To start with, in this session, we will deal with three drugs. The first one is orange peel, the second one is buckwheat, and the third one is an interesting fruit: strawberry.

So let's see. The first drug we are dealing with here is orange peel. Now, you might be wondering what we consume in our day-to-day lives is actually orange pulp. But what is more important here is the orange peel. Surprisingly, orange peel has much more medicinal value than orange pulp.

And here's the reason why. To start with, oranges or citrus fruits are abundant. There are numerous species of citrus fruits, ranging from bergamot to Buddha's finger to lime kefir. You might come across different varieties of Malta. You might also come across different orange species in the market nowadays.

So, let's take one simple example of an orange peel containing a drug. That is the common fruit that you consume. That is your *Citrus aurantium*. Now, in *Citrus aurantium*, there is a sweet orange and a bitter orange. The sweet orange is *Citrus sinensis*.

The bitter orange is generally referred to as *Citrus aurantium*. They all belong to the family Rutaceae. Now, if you see this orange peel carefully, or you might have seen it while consuming your fruit, the outer part of the orange peel is orange, whereas the inner part is more whitish, porous, and slightly rough in nature, while the outer coating is more oleaginous. So, if you see your orange peel, you can divide it—I am just drawing it schematically—into two parts.

Let me call this the white part. Let me call this the orange part. So the orange part is generally called flavido. And the white part, because it's white, is called albedo. Now there is a little difference between the two.

So if you see the flavido part, that is the one which gives the flavor. So, you know, in culinary industries, they use the outer part. They kind of grate it and call it orange zest or lime zest. The reason being, in that outer part of the peel, you have numerous oil glands secreting volatile oil. So the volatile oil-containing glands, the pigment-storing organelles, are all located in the outermost layer called flavoduc.

Whereas if you see albedo, it's the lower whitish part. If you happen to consume orange peel at any time, you know that this whitish part is a little bitter to taste and it contains compounds called flavonoids. It contains pectins. It contains cellulose and hemicellulose. So the white part is rich in more fibrous derivatives.

Whereas if you see the flavonoid part, it is definitely cellulosic, but along with that cellulose are embedded numerous glands containing essential oils and also containing the pigments which are present in the Oranges. So oranges grow mostly in tropical and temperate regions. So you will find them growing in India, China, Spain, Medellin, Sicily, or Morocco.

They are the chief producers, but more or less you will find oranges growing everywhere in tropical or temperate regions. So it's a tree, and from this, the pulp is taken for juice, for food, and what is thrown out is the peel. And like I said, the peel is more medicinal. So these peels are either removed in the form of turnings or gratings, or they are chopped into tiny squares and dried to get what is called dried orange peel. Much of this dried orange peel goes into the extraction of orange oil or citrus oil, which is used in the perfume industry, and what is left is rich in pectin and flavonoids.

So you get pectin and flavonoids from the orange peel from which the oil has already been removed. So while removing the orange peel, some might have experienced a spurt of oil coming out as you bend the peel. So during processing, care has to be taken not to do it so that the oil is retained, and you can extract more oil from it. To prevent the evaporation of oil, it is always stored and dried in the shade.

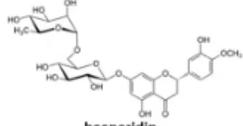
Now, what does this contain? So, focusing on our flavonoid derivatives, the chief flavonoid present in orange is hesperidin. Now, different citrus varieties or different orange varieties give you different yields of hesperidin. But if you go to see, all in all, you might come across approximately 1 to 2.5% of hesperidin. Now, if you see the structure of hesperidin, this is your rhamnose.



## Chemical Composition



- Flavonoids: hesperidin, iso hesperidin, Naringin, naringenin diosmin, diosmetin, rhoifoline, isorhoifoline,
- Polymethoxylated flavonoids: nobiletin, tangeritin
- Bitter orange peel contains of 1 to 2.5% volatile oil containing 90% limonene and small quantities of aldehydes citral, citronellal.
- vitamin C, and Pectin



**hesperidin**

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This is your glucose, and this is the main flavonoid derivative. Now, carefully, if you observe this flavonoid derivative, it is a flavanone. Flavanone—why? Because this is saturated; it is not unsaturated. So, this is a reduced part; there is no double bond here.

So, as a result, this is a flavanone derivative, and towards your 5 and 7, it's a hydroxy. If you remember, in the previous session while doing the biosynthesis, we saw that chiefly in most flavonoids, you will find substitution at 5, 7, 3' and 4'. So, the same applies here: you have hydroxy at 5, the 7 hydroxy is what is involved in the glucoside formation, and here you have hydroxy at 3' and a methoxy at 4'. So, this is the main flavonoid. Apart from that, you have your isohesperidin and your naringin.

Now, naringin differs in a way that I am just drawing the B ring. So, you will have just a hydroxy located at the four-dash position. The rest remains the same. So, that's your naringin. The erg-like one of that is your naringenin.

Now, the next flavonoid you have is your diosmin. Now, diosmin is slightly different. Diosmin is not a flavo- Diosmin is a flavo- That means when I'm going to draw diosmin, I kind of—sorry.

Double bond here. Now, it has become a flavonoid. So, when the double bond is there, I will call it diosmin. So, you have your diosmin and a glycone, diosmetin. Apart from that, you have what are called polymethoxylated flavones.

Now, what are polymethoxylated flavones? Now, just for your reference, I am drawing this for you. Ring A. I'm drawing your Ring A here. In polymethoxylated flavones, what happens is instead of a hydroxy group, you get a CH<sub>3</sub>. In polymethoxylated flavones, sometimes numerous substitutions happen, and you get a lot of derivatives here.

With a lot of other CH<sub>3</sub> derivatives also. So you have your nobiletin, tangeritin, which has a polymethoxylated AMOAT group present. Now, apart from that, the main flavonoid component, you will also have essential oil. The essential oil contains almost 90% pure hydrocarbon compound called limonene. And that is responsible for a beautiful aroma.

A little sweet note comes because of aldehydes such as citral and citronellal. So it has limonene, citral, and citronellal as its major components. These are very effective in their cleansing action. As a result, you will find numerous detergent bars using limonene as an

aroma agent as well as a cleansing agent. Apart from that, it's rich in vitamin C and also rich in the carbohydrate pectin.

So, industrially, much of your pectin is obtained from citrus peels. Why do you apply all this? So, because of the presence of flavonoids, you will see many of these citrus peels, like bitter or sweet orange peels. They all exhibit anti-inflammatory activity.

Now, this anti-inflammatory activity is also exhibited in the endothelial cells, which are called vascular cells. So, you see patients suffering from chronic venous insufficiency. So, what happens is my veins are no longer able to hold tightly. And as a result, they turn soft. The cells are not very strong in their binding, and as a result, the fluids tend to retain and seep out. All in all, these patients have swollen extremities, especially swollen limbs, because of the drainage of water that happens to them. Now, to treat this chronic venous insufficiency, another case of chronic venous insufficiency is when you develop varicose veins. So, to treat this chronic venous insufficiency, what is done is flavonoid derivatives, especially flavonoid glycosides, are taken. Now, these flavonoid glycosides are good.

They are anti-inflammatory. They help in blood circulation. They help in the endothelial health cell, especially of those cells. cells which are there in the veins and as a result they impart rigidity they impart structure and they kind of treat your varicose veins so if my you might have seen a tablet in market called as daflon daflon contains almost nine parts like a 450 is 250 so 450 parts is your diosmin And 50 part is your hesperidin.

So, these two glycosides which are present in orange peel are given in the form of daffodil or in the form of these tablets as a 500 mg tablets to treat varicose veins or chronic venous insufficiency. Now, apart from that, your pectin, which is obtained and flavonoids, especially the polyphenolic compounds, which are obtained from your orange peel, render a good antibacterial, antifungal effect. Even in certain cases, orange oil has been proven to show antimicrobial effects. The pectin present in it acts as a form of a soluble fiber and retards absorption of sugars and lipids by forming a thick mucilaginous substance in your gut. Now, because of this, you know, it's good for patients suffering from hypercholesterolemia.

So it acts as an anti-hypercholesterolemic agent. It also helps you decrease your blood glucose levels. Now because of limonene, because of the oil and because of its antimicrobial activity as well as the presence of cellulose also makes it a good exfoliant. So this is the reason you will see your orange peel powder being there in your numerous products. Orange peel extracts are there in your numerous products.

Now, diosamine we have seen diosmetin. Which is the aglycone of diosmin, is also reported and studied. And it is found to exhibit numerous activities because of its structure. This includes anti-cancer, antimicrobial, antioxidant, estrogenic, as well as anti-inflammatory. So next time you're consuming an orange, please see that you consume the peel too.

So with this, we move on to the next set of compounds, and the next compound is called buckwheat, often referred to as kuttu ka aata. We see in the market nowadays your buckwheat noodles, your buckwheat flour. Now, what is buckwheat? Buckwheat is made up of two common species of buckwheat that are there in the market.

One is the *Fagopyrum esculentum*, the common one. And then there is a tartary buckwheat, which is *Fagopyrum tataricum*. Now, both of them belong to the Polygonaceae family. They're not clearly Gramineae. They have a slightly different appearance, but all in all, the plant cycle is almost similar to them, like a 90-day cycle.

Now they are commonly grown in China, Russia, Brazil, Poland, and France. So if you see, as opposed to your other grains, the buckwheat kernel is slightly more, you know, like a heart shape or triangular shape. And you know, it's almost a little big, like half a centimeter to a centimeter, which is 4 to 9 mm in length. Now, this buckwheat contains flavonoids. Now, this flavonoid is your rutin.

As hesperidin, you have seen the substitution of the sugar was generally here. In rutin, the substitution happens at the third position. So again, you have your rhamnose here. You have your glucose here. Now, instead of a methoxy, you have a dihydroxy substitution at 3', 4' and a hydroxy substitution at 5 and 7.

**Chemical Composition**

- fatty acids, proteins, polysaccharides and dietary fiber, vitamins, as well as triterpenoid saponins,
- Flavonoids- rutin (1 -4 % in tartary buckwheat), quercetin, kaempferol, luteolin, vitexin, orientin, metabolites of quercetin and many others.
- Fagopyrins

**Rutin**

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So flavonoids are very easy to recollect because most of the time, you will find a very similar or close substitution here. Now, this is the main one. If you remove the sugar part of it, and convert it into an aglycone, this is called quercetin.

So quercetin is the aglycone of rutin. Apart from that, it also contains a flavonoid aglycone called kaempferol. It has lutein, vitexin, orientin, and other metabolites of quercetin. Apart from that, being a grain, it is rich in polysaccharides, proteins, and fatty acids. In fact, it is one of the drugs that is said to be gluten-free.

So if you eat kuttu or buckwheat flour, it is considered a gluten-free alternative for people with gluten intolerance. It is rich in vitamins and also contains, to a certain extent, triterpenoidal saponins. It also contains another interesting set of compounds called fagopyrins. Now, what are fagopyrins? Fagopyrins, if you see, are actually compounds that resemble sennosides. Now, what is the resemblance point? The resemblance point is a dianthrone moiety, but if you remember, in senna, the linkage was only at this point. So if you see phagopyrone, especially the photofagopyrins, you will see double linkages here. Now





## Phototoxicity of Buckwheat

- Buckwheat plants contain protofagopyrins, which are converted to fagopyrins when the plant extract is exposed to light
- protofagopyrins and fagopyrins belong to naphthodianthrone and act as photosensitizers (PS)
- Fagopyrin is a phototoxic substance .
- Symptoms include sunburn, sensitivity to hot and cold water, itching, and a fuzzy feeling in the face and hands.



These photofagopyrins in the presence of sunlight undergo what is called oxidative coupling and as a result become or get converted into fagopyrins. So, if you can see, an additional bond is formed out here. Mostly in these substitutions, you will find heterocyclic nitrogen-containing rings or other substitutions being attached. So the substitutions are add-ons, but just see the core part of it.

So, this reaction now you can see is a very resonance-stabilized structure. So, this structure that is phagopyrin has the ability to act like a photosensitizer. Now, what are photosensitizers? Photosensitizers are molecules. So, if we consume them and then we come into the presence of light,

photofagopyrin will get converted into phagopyrin. Fagopyrin will absorb light and start emitting fluorescence or start emitting radiation at a slightly higher wavelength. Now, because it starts emitting radiation at a slightly higher wavelength, what happens is they give rise to what is called phototoxicity. Now, this phototoxicity can be something like just mild itching or, in some cases, you know, it can give you sunburn or, you know, like a very fuzzy feeling or, you know, intense itching.

So this is again predominantly observed in animals, especially the white or albino animals that graze on this phagopyrum. The reason being, more than the grains, this fagopyrin or your photofagopyrins are found in the leaves as well as the inflorescence, especially the flowers. So if you consume that, the chances of you getting phototoxicity are much, much higher compared to grains, where these are minimal to almost non-existent. Now, comparatively, if you see your common buckwheat versus your tartary

buckwheat, the amount of flavonoids is much, much higher in your tartary buckwheat. So, where do you use this?

So, this buckwheat has nowadays become common. Because, as I said, it's rich in minerals and flavonoids, which have good antioxidant potential. And as a result, it is known to give you many good effects, especially, as we just saw previously, vitamin P-like effects. So rutin, being very close or similar in structure to hesperidin, also possesses very similar attributes. So it improves your blood vessel health.

It improves your vascularity. It improves strength. And as a result, it will help with your venous insufficiency. Rutin and quercetin, being polyphenolic in nature, will also show antioxidant effects. And as a result, they have anti-tumor, anti-mutagenic, cardioprotective, and to some extent, immunomodulatory effects.

Now, this is one of the grains, like I said, it's not clearly grainy, so it contains to a little extent improved blood sugar control. And as a result, it's used in numerous places. This includes your gluten-free food. Buckwheat noodles, which are there in the market nowadays. It's also used as a grain for preparing alcoholic beverages, preparing something like your buckwheat honey, which is made by fermenting buckwheat and your sauces.

Now we move on to the next drug. The next drug is not a drug. Actually, it's a fruit that you consume mostly during the winter season. You will see a lot of these occurring in the market here. And this is your simple, common strawberry.

So why is strawberry medicinal, or why is strawberry good, and why are we studying it here? So let's discuss strawberries in detail. So this is your common strawberry, also known as your *Fragaria ananassa*. Now it's actually the one which we consume in the market. It's a hybrid.

So whenever you see a notation like this, it indicates that the plant is a hybrid species. So It's a hybrid obtained from two wild species, *Phrygeria keolensis* and *Phrygeria virginia*. They belong to the Rosaceae family. Now, this fruit is actually a pseudocarp.

That means the fruit, as you see, is not a true fruit. What is there is, so what you see in red color is the receptacle of the flower. Whereas you see something like these tiny seeds, these tiny seeds or achenes or seed-like achenes are actually the fruits which are there on the surface. So it's not a true berry. It's a pseudocarp.

This is not a fruit. This is what you call the swollen receptacle. And these tiny seed-like things are the fruits which are there in the strawberry. So this strawberry is made up of beautiful pigments. In fact, people are advised to take pigmented foods for this reason.

Let's discuss it here. Strawberries contain mostly water. The sour taste is attributed to the presence of acids, including ascorbic acid. They also contain pigments which are intensely red in color. And because of the acidic pH, they appear more red.

**Chemical composition**

- Strawberries contain water ( about 91%), carbohydrates (around 7.7%), and Vitamin C
- Anthocyanins: pelargonidin 3-glucoside and cyanidin 3-glucoside
- Flavonoids: Quercetin, Kaempferol, Fisetin
- ellagitannins, and phenolic acids

**Pelargonidin-3-O-glucoside**

**Fisetin**

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The pigments which strawberries contain are pelargonidin, especially pelargonidin-3-O-glucoside. At the third position of this anthocyanin, you can clearly see it's an anthocyanin. Why? Because the flavylium ion is there. Due to the flavylium ion, the oxygen carries a charge, giving rise to the typical red coloration as opposed to the pale yellow of flavonoids.

They also contain a little bit of cyanidin-3-glucoside. Both of these pigments account for the red coloration of strawberries. The more sunlight there is, the more pigment the plant will produce. We know that flavonoid derivatives are produced in response to stress and UV exposure. The more UV exposure they receive, the more pigment they will produce.

Now an interesting part of these anthocyanin derivatives is that anthocyanins act as pH indicators. So if you see this carefully, this is acidic pH. What happens? And as you go toward a more neutral pH, you will get what is called quinoid formation.

So what happens is this will go. This will kind of stabilize, and you might get a quinoid formation here. This quinoid formation later on in alkaline pH leads to a link, what is called the ring C cleavage, and as a result, a lot of color changes happen. And that's the reason anthocyanins are natural pH indicators as well. So at acidic pH, you have the flavylium ion.

At neutral pH, you have a little quinoid moiety minus this. And at near alkaline pH, if you keep it for a longer duration of time, you will see that the ring will open up. Not only that, the coloration of anthocyanin pigments also depends on the nature of substitution. So what you see here is a single hydroxy. Now in this case, if I make a triple hydroxy instead of pelargonidin, you get derivatives like delphinidin.

Now, delphinidin is more intense red to pink in color. Now, I can have this OH substituted by CH<sub>3</sub>. So, I'll get peonidin and malvidin. So, peonidin and malvidin are more bluish-purplish color pigments. So, going from a single hydroxy, which is red, to more hydroxy substitutions, which are more pink.

Two methoxy substitutions are more blue to purple. So, depending upon what is present on this typical ring B, you can get different colors. Depending upon the pH, you will also get different colors of your pigments. So, that is why anthocyanins are very important as well as interesting. Apart from that, it also contains a flavonoid derivative, especially a flavonol derivative, and that's fisetin.

Fisetin is a very important supplement in the market nowadays, which is also used as an anti-aging supplement. You will have quercetin, kaempferol, ellagitannins, and other phenolic acids, which are also present. Now, let's see the uses. So, what advantages do I get when I consume strawberries? Definitely, you have advantages when consuming

phenolic acids, you have advantages of consuming your vitamin C. So you have anti-inflammatory and depending upon anthocyanins and flavonoids, which are also

polyphenolic and antioxidant in nature, you get numerous advantages. So it has been reported to support your brain health, heart health and also in cancer prevention. Now, the reason fisetin is becoming more popular in the market nowadays is it has antioxidant anti-inflammatory effect, but it has what is called a senolytic. Now, senolytic is the ability to kill what are called as zombie cells so remember you have aging cells and aging cells have a phenomenon called as apoptosis so they should naturally die but in some cases these cells just sustain so that leads to what are called as age related disorders or aging disorders so imagine if somehow you are able to cause apoptosis in such cells and get rid of the cells

This is how senolytic agents work. So wherein the apoptosis process is stalled, it's not working properly. Senolytic do their way of clearing the cells. They kind of re-emphasize this mechanism and get rid of the age cells. As a result, leaving scope for the new cells to grow and divide and more healthy generation of newer cells, especially your brain cells, especially your skin.

And as a result, that's where your senolytic agents feature in. Nowadays, senolytic agents have also been studied for cancer prevention. So with this, we discussed three drugs today. We had your buckwheat. We had your orange and we had your strawberries.

So if you wish to read more about it, here are a few references. And thank you, everyone, for your patient listening. Thank you.