PHARMACOGNOSY AND PHYTOCHEMISTRY

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Week 6

Lecture26

Week 6: Lecture 26: Glycosides

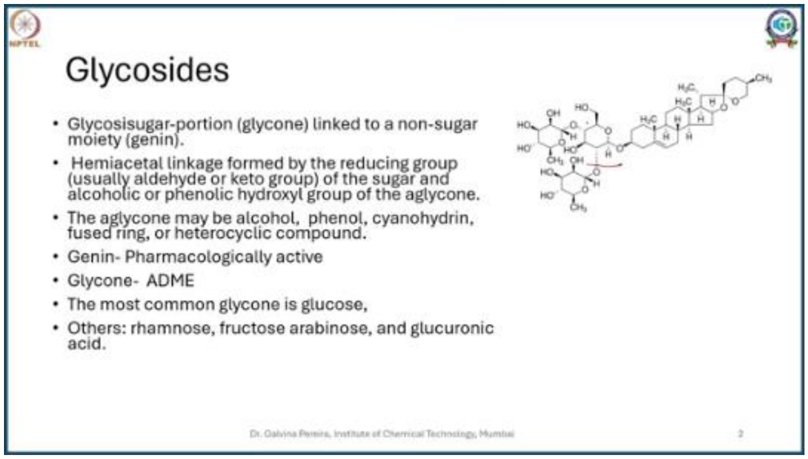
Thank you Hello everyone, and welcome to the NPTEL course on pharmacognosy and phytochemistry. This week, we are going to learn about a new set of compounds called glycosides. As the name indicates, glycosides are molecules that contain sugars. In that case, how do they differ from carbohydrates?

Let's see in this session. Glycosides are molecules essentially containing sugar as an integral part of their structure. But apart from sugar, they also contain a non-sugar moiety, often referred to as genins. So it is a sugar plus a non-sugar joined together by a linkage. Now, this linkage is generally a hemiacetal linkage.

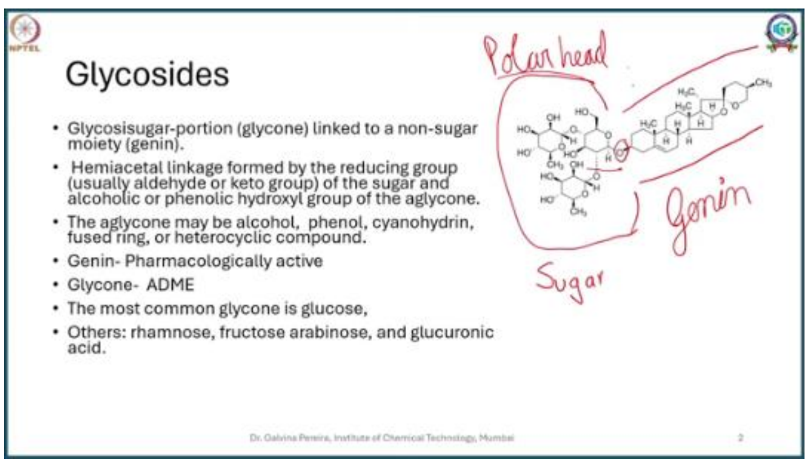
Hemiacetal linkages are actually linkages formed between the reducing group, generally an aldehyde or ketone group of the sugars, and the addition of a hydroxy or phenolic group or an alcoholic group of an aglycone. So this aldehyde or ketone group then adds to the hydroxy or phenolic group of an aglycone to form an ether-like compound. These ethers, or these ethereal linkages, are referred to as hemiacetal linkages, and these compounds are called sugar ethers.

Just to exemplify, here we have a molecule called dioxin. Dioxin is also a saponin in nature, which means it has the ability to form soap-like foam. So What happens here is, as you can see, you have a sugar moiety, and the sugars are also linked to each other. But let's just see this terminal sugar.

Now, this sugar part is linked to the genin part. Now, the point of linkage is this particular ether linkage. These are not esters. These are ether linkages, and that's why they are referred to as sugar ethers. So, sugar plus genin is basically what we call glycosides.



Now, interestingly, why these are called saponins, you can understand here. So, this behaves perfectly like a surfactant. So, I can put this part as a polar head, And this part is hydrophobic. So, this part is nonpolar.



So when you have a nonpolar group and a polar group, they have what is called a surfactant-like capacity, and hence diocin is a saponin. Apart from that, you will find that the aglycone group may not only be an alcohol; it might be a cyanohydrin. It might be something related to a sulfur-like compound or a heterocyclic compound. They join to form different types of linkages. Like in this case, it's an O linkage, but you can have an S linkage, N linkage, or even a C linkage as well.

Now, if you see carefully, sugars as such do not exhibit any pharmacological activity. We have seen in previous sessions that the main biological activity of most secondary metabolites is attributed to their structures, and the structural contribution in glycosides is the genin. So the genin is the pharmacologically active moiety of glycosides, whereas sugars have a role to play in their polarity. Now, what role does polarity play? Polarity helps in solubility, absorption, binding, distribution, metabolism, and so on.

So we say that the sugar part is responsible for the ADME. We also call it the pharmacokinetic parameters, whereas the genin part is responsible for the activity or pharmacodynamic parameters. Now, the sugars that get attached to the genins can be very diverse. It is not always the case that one particular sugar is found throughout the plant. If you see in terms of abundance, glucose is the most abundant sugar.

So as a result in glycosides also majoritally you will find glucose low. As the one linking with the genines but apart from that you might have other sugars also. This includes your rhamnose, fructose, arabinose. In some cases you might even have linkages with uronic acid derivatives such as glucuronic acid. Now properties chemically because they are sugar ethers they are in terms of their solubility somewhere in polar to mid polar range.

So they are soluble in water, they are soluble in alcohol but as you go on a lipophilic side you will see that their solubility decreases. And this also has a bearing on the number of sugars. So if it is less sugars, it might still dissolve to the extent of ethyl acetate butanol. But if you go on adding more and more sugars, the solubility increases in water and completely vanishes in organic solvent. Now the sugars, if they are reducing part.

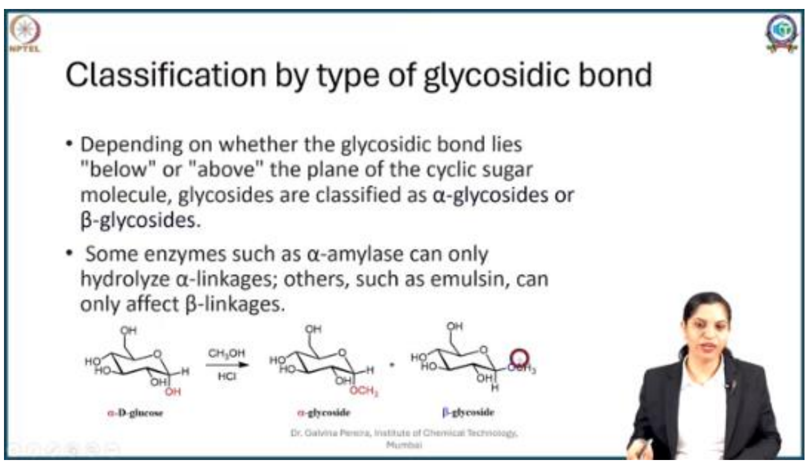
is involved in formation of hemiacetal linkages have no ability to reduce felling solution. So most of this glycosides when they are intact that is when the genin and the sugar is fused because their reducing end is occupied will not be able to reduce the felling solution. But if you are able to hydrolyze it in some cases you can do it by acids in some cases you can do it by enzymes. So after hydrolysis when the sugars are free in that case definitely they will have the ability to reduce the felling solution from blue color to a reddish precipitate. Now in terms of optical activity it is found that majority of these glycosides are levorotatory in nature.

Coming to the physical attributes such as their nature, very few glycosides occur in crystalline form. The presence of sugars, and as more sugars increase, renders them somewhat amorphous substances, which form sticky residues and are hygroscopic to a certain extent. In some cases, they are definitely free-flowing solids. Colorless and non-volatile in nature because the sugars reduce their volatility. Now, the sugar ethers can be hydrolyzed—this can be done by enzymes, acids, and also at elevated temperatures.

Now, it is observed that, compared to basic pH, acidic pH is much better for cleaving the ether linkage and releasing the component sugar. Now, in most natural glycosides, it is seen that the type of linkage is generally beta. The glycosides can be classified depending on their nature. As I said, in the majority, you will have a beta type, but in some cases, alpha is also possible. So how do you determine that?

What are these alpha and beta? So it all depends on whether the glycosidic bond lies above or below the plane. If you see a typical alpha glucose, you can observe the anomeric carbon—this is what is referred to as the anomeric carbon—and then check the hydroxyl group located on the anomeric carbon. If it is below the plane of the cyclic sugar, you call it an alpha linkage.

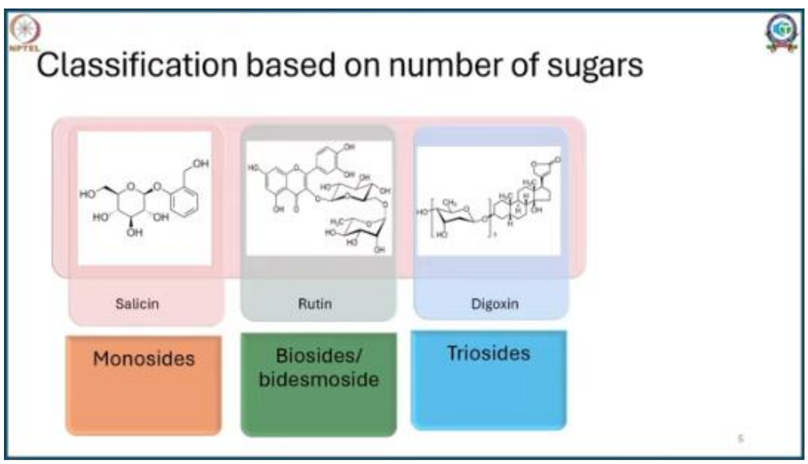
Now, in this case, let's say it etherifies with a So you get a methyl ester, but because this methyl ester is below the plane of the sugar, you call it an alpha glycoside or alpha methyl glycoside sugar. Now, in this case, what you see is this ether linkage with methanol is above the plane of the sugar, especially if you see it with respect to the anomeric carbon, and you call it a beta glycoside linkage. Now, why are these alpha and beta linkages important? You will see that depending on how the linkages are arranged, there are specific enzymes.



Not every enzyme can digest all types of linkages. Take, for example, in your saliva, you have alpha-amylase. In some cases, you have maltase, and alpha-amylases are predominantly known for hydrolyzing alpha linkages. That means if there are these kinds of linkages in your molecule—alpha linkages—then your alpha-amylase will be specifically able to digest it. But if your molecule has beta linkages, those will be resistant to your alpha-amylase.

Now, there are some enzymes, such as emulsin. They occur in plants, especially because, as you know, plants contain glycosides and have the mechanism to hydrolyze them. So these beta-emulsins are located in the vesicles, and the glycosides are located away. When the plant is consumed by an animal, it crushes these vesicles. As a result, these glycosides, especially emulsin, are released, and this glycosidase will cleave the beta-glucoside bond.

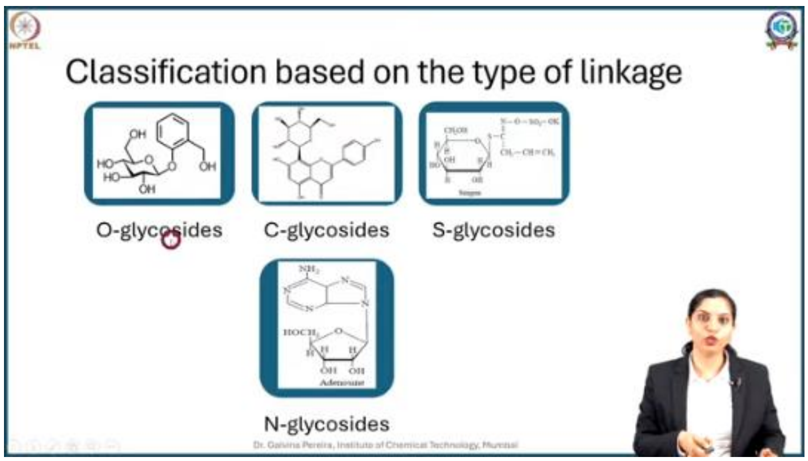
So in this case, you can release the aglycon moiety just by releasing the emulsin. So this is a kind of trick that plants use. When they want to defend themselves, this is seen mostly in bitter almonds or plants containing cyanogenetic glycosides. Now, based on the number of sugars, you can also classify your glycosides. Some glycosides just contain one sugar; they are referred to as monoglycosides. A good example is salicin. Salicin is an anti-inflammatory compound obtained from willow bark. And you can see here that hydroxy benzyl alcohol is attached to a sugar, and it's just one sugar because it's only one sugar. It's referred to as a monoglycoside.



Now, coming to the case where you have rutin. In the case of rutin, you can see that rutin is linked to a glucose, which is then linked to a rhamnose. So in this case, you have two sugars, and this is called a diglycoside or bidesmoside. Now, it is observed that whenever you carry out hydrolysis, the hemiacetal linkage is much more prone to hydrolysis compared to the second or inter-sugar linkages. As a result, when you do acid hydrolysis, predominantly this bond is the one that breaks first. So rutin will hydrolyze to quercetin, and you can get the aglycone on acid hydrolysis.

The third case you can see is triglycosides. Now, a triglycoside is when you have three sugars. Now, this is the case of digoxin, which is used in cardiac insufficiency. Taken from the digitalis plant, you see here the same repetition, but the three sugars are linked to each other, and these three sugars are digitoxoses. So three digitoxoses are linked to each other, and such compounds are called triglycosides. But these are not limiting; you might even have compounds with more than three sugar linkages.

Now you can also classify glycosides based on the type of linkages. So what is the molecule that is actually being attached to the sugar? Now let's take the case of salicin, which you saw right now, and you can see here in the case of salicin, you will see that your hydroxy benzyl alcohol is attached to glucose, and the point of linkage is an oxygen. In such cases, they are referred to as O-glycosides. Now coming to a second case, in the second case, you can see a sugar here that's again glucose, but this time there is no oxygen.



So this point of linkage is actually a carbon. So when our point of linkage is carbon, such kinds of glycosides are called C-glycosides. A good example of this is vitexin, which you see in your figure right now. Now, sometimes the sugars might be attached to compounds other than carbon and oxygen. And in this case, we have sulfur.

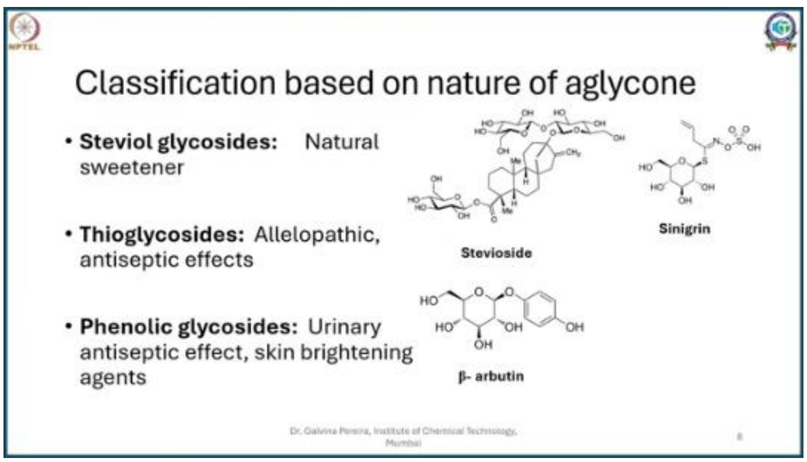
So in this case, you can see that to the glucose, what is attached here is a sulfur moiety, and that is why you call them S-glycosides. This is seen in your mustard sarsop. So the typical acrid aroma of your sulfur or sulfuraceous aroma of your mustard is because of sinigrin, which is an S-glycoside. And in your DNA, you have something called purine bases. Now, these purine bases are also attached to the sugar, but the point of attachment here is neither O, nor C, nor S, but it's an N.

In such cases, they are called N-glycosides. So, depending upon the type of linkages, we chiefly have four compounds, which are O-glycosides, C-glycosides, S-glycosides, and N-glycosides. Now, we can also divide the compounds or the glycosides based on the nature of a glycone. Now, this is the most widespread distribution because a glycone can be anything.

But I've just listed a few major classes of glycosides to explain how we can classify them depending upon a glycone. The first case is cardiac glycosides. As the name indicates, cardiac glycosides are actually a steroidal group referred to as cardenolides, and the steroidal group is attached to sugar. This class of glycosides has a very good effect on your CVS, and they've been used in congestive heart failure as well as in arrhythmias.

The next class is alcoholic glycosides. In this case, it's the alcoholic moiety that is used in the formation of sugars. A good example is salicin. Now, salicin is a precursor of aspirin. So, it is anti-inflammatory, antipyretic, and shows analgesic effects very similar to those of aspirin.

The next ones are actually sweet molecules. Now, if you see this, all of these molecules contain sugars, but in terms of their sweetness, not every glycoside is sweet. In fact, the majority of glycosides also have a slightly bitter taste as opposed to a sweet taste. But there are certain glycosides like stevia, which are known for imparting sweetness. And this sweetness is more than 100 times that of your normal sucrose.



So here you see in your structure is a diglycoside here. And a monoglycoside here. So here the sugars are linked at different positions, and they are responsible for imparting sweetness. Apart from stevia, they also have rubusoside, which imparts sweetness to stevia. Now we move to the next class, which are sulfur-containing S-glycoside compounds, thioglycosides.

Now, thioglycosides have an interesting property. We call it allelopathy. Allelopathy is a unique feature whereby a plant can... They retard the growth of adjacent shrubs, weeds, or grass, not allowing their metabolic processes to go smoothly. As a result, the plants growing in the vicinity suffer.

That is what we call it allelopathy or mutual suffering. So they suffer and they wither out eventually. A good example of this is synegrin. We just saw it. It's there in your black mustard.

Now, apart from that, we also have phenolic glycosides. Phenolic glycosides—I'll give you an example of beta-arbutin. Beta-arbutin is nowadays used in cosmetic industries for its skin-brightening effect. It also has antiseptic effects, and some of them are antimicrobial. And as a result, phenolics,

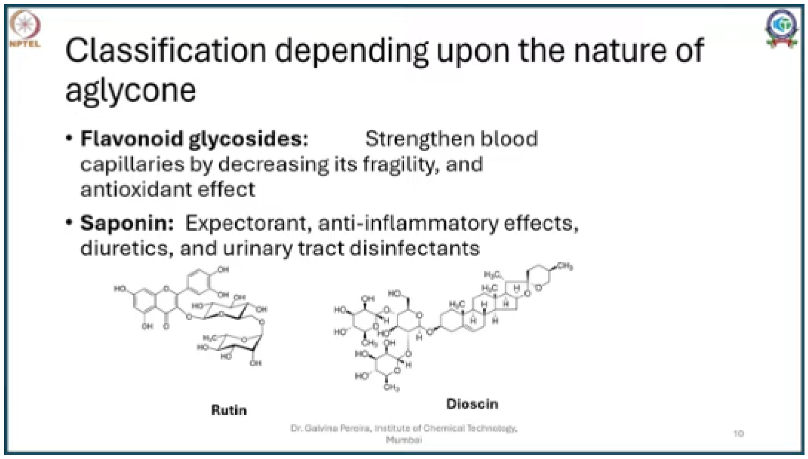
by their nature, are antimicrobial because phenolics have the ability to precipitate proteins. So they are used as urinary antiseptic agents or anti-infective agents. Now, apart from that, we also have cyanogenetic glycosides. Now, cyanogenetic glycosides are unique in a way—they are called biological warfare weapons. Now, what happens here is when we say the emulsion enzyme has the ability.

Now, in this case, the emulsion will break, and eventually, what happens from this glycoside is that it releases what is called hydrocyanic acid. Now, hydrocyanic acid is very toxic to predators, and as a result, animals that consume them are poisoned. So, cyanogenetic glycosides are actually defense chemicals produced by plants to prevent consumption. And definitely, hydrocyanic acid has a very unpleasant taste. So, that is also something we can take into account regarding its unpalatability.

Now, moving on to the next ones, the next ones are anthraquinones. Anthraquinone glycoside—a classic example is sennoside. In sennoside, what you will observe is a dianthrone moiety. Now, this dianthrone moiety can have a similar kind of structure—that is, a mirror structure.

In that case, you can call it sennoside A. Now, what happens here is that anthraquinones have the ability to irritate the gut, and this ability is responsible for their laxative as well as purgative effects. The next set of compounds are coumarin glycosides. Now, coumarin glycosides have very different activities. In fact, they dilate coronary arteries. They are known to block calcium channels, inhibit coagulation pathways, and also block.

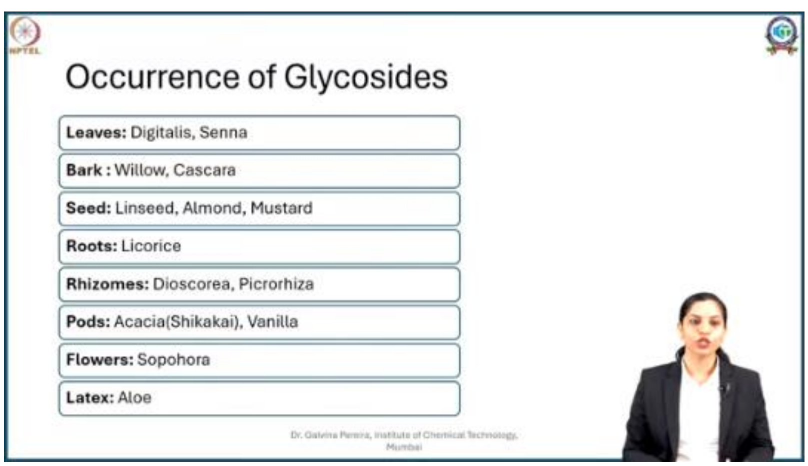
Known to act against microorganisms as anti-infective agents. A classic example is novobiocin, an antibiotic, and this is a typical coumarin nucleus located in novobiocin. We have two more classes. One is a flavonoid glycoside. Now, flavonoid glycosides, for example, rutin, are used in cases of varicose veins, wherein the walls of your arteries and veins become insufficient and lose their function.



They lose their structure and become more permeable. This is often referred to as vitamin P, which strengthens the blood capillaries, decreases their fragility, and exhibits antioxidant effects. Now, saponins—a good example is digoxin—which serves as a surfactant. It's used as an expectorant, anti-inflammatory, diuretic, and urinary tract disinfectant. And because of its steroidal structure, it is also used in the synthesis of steroidal hormones.

Where do these glycosides occur? I am just stating a few examples to show where these glycosides are found. They can be found in plants. They can be found in microorganisms. They can even be found in some animals.

So in terms of plants, you will find glycosides in leaves such as digitalis and senna. That is your digoxin and sennoside. You will find it in bark. such as willow, which is salicin, and cascara is cascaricide. You will see them occurring in seeds, mostly cyanogenetic and sulfur-containing glycosides, that is your thioglycosides.



In roots, such as your licorice, the glycyrrhizin. Rhizomes, you will find them in trichrorhiza and dioscorea. In certain pods, your surfactants like your shikakai, acacia, and vanilla. In flowers, Sophora is a very rich source of rutin. Sophora flowers contain almost like 20% rutin and in some cases latex such as aloe.

Aloe latex also shows anthraquinone glycosides like your senna, but they are monomeric in nature and they have a much stronger purgative effect. So Here are a few more references if you wish to read more about this set of compounds. And thank you everyone for your patient listening. Thank you.