PHARMACOGNOSY AND PHYTOCHEMISTRY

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Week 3

Lec 11

Week 3: Lecture 11: Carbohydrate based drugs

Thank you. Hello everyone, and welcome to the NPTEL course in pharmacognosy and phytochemistry. This week, we are going to focus on drugs that have their genesis from primary metabolites, and those are carbohydrate-based drugs. In your biochemistry course, you have already studied what carbohydrates are, but

let's revisit some basic concepts to understand these drugs better. Carbohydrates are often referred to as saccharides. They are the source of energy for plants and animals. In plants, they are stored in the form of starch, whereas in animals, you will find them in the form of glycogen. Structurally, they are referred to as polyhydroxy aldehydes or ketone derivatives, chiefly consisting of carbon, hydrogen, and oxygen, and that's the reason they are called carbohydrates, with the formula Cn H2n On. For example, take a simple molecule called alpha-D-glucose, where N is equal to 6, H2N means twice 6, which is 12, and O6. Most carbohydrates follow this formula.

Say, for example, alpha and beta in this formula: the alpha refers to the anomeric hydroxyl group. So, the hydroxyl group on the anomeric carbon, if it is below the plane, you call it alpha. Otherwise, it's called beta hydroxyl if it is above the plane. Now, these carbohydrates have been found abundantly in plants and are products of photosynthesis. So, from photosynthesis, you get water and carbon dioxide producing glucose,

and from glucose, you have a variety of pathways which lead to diverse sugars. Some of the sugars polymerize by forming ether linkages. And then they form what are called polysaccharides. So, if it is one, it is referred to as a monosaccharide. If it's two, you can refer to it as a disaccharide.

Trisaccharides and upwards are called polysaccharides. Now, animals are not photosynthetic. We don't carry out photosynthesis, but we have an ability or a unique pathway called gluconeogenesis, in which glucose or sugars can be synthesized from proteins or lipids, so they form a source of sugar in case we fast or if we have a diet lacking carbohydrates, our body

Will convert proteins and lipids into carbohydrates because carbohydrates are primarily the molecules. These are used to generate energy. Now, if you examine the physical and chemical properties of carbohydrates, if you have a single monomeric unit, what we call a monosaccharide group, take for example, glucose that we just saw. Monosaccharides generally occur in crystalline, free-flowing form. If you consume them, they are sweet to taste and easily soluble in water.

Simple examples include glucose, fructose, and so on. Now, when two such monosaccharides join by ether linkages, this linkage depends again on the nature of the hydroxy group. If this hydroxy group happens to be below the plane, we call it an alpha glycosidic linkage. If this group happens to be above the plane, you call it a beta group.

So, below the plane, you have an alpha group; above the plane, you have a beta group. So, depending upon that, the sugars or saccharides join to each other using either alpha or beta linkages. Now, why are these linkages important? If you examine your saliva, it contains numerous enzymes, and one enzyme is alpha-amylase.

So take, for example, your starch. Now, in starch, the glucose molecules are linked by alpha linkages. So an enzyme called alpha amylase can hydrolyze it, and hence your starch can be converted into glucose. But, for example, when you eat cellulose, something like a rope. Rope is made up of cellulose, or your cotton is made up of cellulose.

Now, when you consume cellulose—in cellulose, if you see here—the linkages are beta linkages. We have alpha amylase. So beta linkages cannot be hydrolyzed by us. And as a result, cellulose will remain undigested in our gut. So just a difference in the linkages here.

Changes the digestibility of the saccharides. Now, this can go on adding more sugars to form polysaccharides. When they form polysaccharides, they are no longer crystalline. So disaccharides are crystalline, sweet, soluble, and they can easily break down to give you energy. Say, for example, a disaccharide can be like sucrose, which will hydrolyze to give you glucose and fructose, both of which will give you energy.

But take, for example, polysaccharides. Now, this is a polymeric group. You will require a lot of enzymes to hydrolyze it. And hence, the digestion of polysaccharides is very slow. Hydration and solubility of polysaccharides are time-consuming phenomena, so they take time to hydrate, they take time to swell, and more time to dissolve.

So they are very resistant to dissolving in water, you can say. Now, depending upon what sugars are linked, if the same sugar is linked as a polymer—say, for example, the same glucose is linked as a polymer—you call it a homopolysaccharide. But if polysaccharides have a different sugar, say for example, one is glucose, one is fructose, one is arabinose. Different sugars are linked to each other. In that case, you call them heteropolysaccharides.

Examples of homopolysaccharides include starch and cellulose, whereas examples of heteropolysaccharides include agar and pectin. Now, what are the sources of carbohydrates? Carbohydrates are primary metabolites. They are found in

Most of the living organisms. But when you think of carbohydrate drugs, let me give you a few examples. Plants are the chief sources of carbohydrate drugs. So when you say acacia, dink, when you call it tragacanth, pectin, starch, inulin, all of them come from your plant sources.

From microbial sources, you get substances such as xanthan, gellan, welan, gum, and so on. From marine sources, you get carbohydrates which are transparent jelly-like, such as alginates, carrageenants which are used in your toothpaste, and agar, which is used in your microbial media. From animals, you can get carbohydrates such as honey, which is a product of bees. So once you have or break your honeycomb, you can get abundant saccharides, which are also an instant source of energy for us.

Now, coming to carbohydrates, carbohydrates are further derivatized to form a set of complex molecules and these complex molecules can be divided, classified, or called gums and mucilages. Now, what are gums and mucilages? Let us try to understand. Gums are molecules which are generally polymers or polysaccharides, as you call them.

Both of them are polysaccharides, but gums are polysaccharides that are generally the outcome of an injury given to a plant. So we can say that they are pathological products. So when you hit the plant, or when you cut the plant, or when you injure a plant, the plant tries to synthesize something to counteract the pain, and that process is called gummosis.

In this process, it will generate gum to close the wound and heal itself. Whereas mucilages are something you can see in chia seeds. Or you can see them in flaxseeds. When you consume them, or even in okra, which is ladyfinger, when you cut it, there is a slimy substance that comes out.

Those are naturally present. And physiologically, those polysaccharides that are present are called mucilages. So gums are pathological. They are generally protective in nature and form as a response to damage. Whereas mucilages are more physiological gums.

They are there to act as reserve food or stored food. Whereas, if you see gums, they easily dissolve in water. They might have an initial period which is required to hydrate. Mucilages swell. They clearly do not dissolve.

The reason being, they are located inside the cell. So when you see those chia seeds in your gums, sharbat, for example, you will see that the extra layer remains on top of the seed and does not disperse or dissolve in water. The reason is, it is located inside the membrane, and that doesn't allow it to flow freely. Examples of gums include acacia, tragacanth, karaya gum, whereas mucilages—you can see, you know, that jelly-like thing which is there inside the aloe vera leaf,

or isabgol, or even your flaxseed or chia seeds. Those are all examples of mucilages. In terms of chemical composition, there also lies some difference. Now, when we discussed polysaccharides, we said that these are sugar molecules which are attached to each other. Now imagine the sugars getting converted into acids, and we call them uronic acids.

So, for example, glucose will get converted into glucuronic acid. So, they are slightly acidic compared to your polysaccharides. So, gums are polymers of sugars and sugar uronic acids. Whereas, if you see mucilages, they contain sugar, sugar uronic acids, and some of them form esters with your sulfate molecules.

So, you have, in addition to your uronic acid, sulfate molecules being present, which makes them clearer and more transparent compared to your gums. Now, let's start with a gum-containing drug, and the simplest example I can give you is acacia. Acacia is an Indian gum, often referred to as gum arabic, gum acacia, or simply acacia. If you see the biological source in terms of USP as a reference, it is actually obtained from Acacia senegal, which is a plant more native to East African countries, mostly Sudan. And the Senegal region is where it is harvested from the widely grown plants, which are thorny trees. Whereas, in India, the plant more cultivated for this is your Acacia arabica. Both of them yield good-quality gum and belong to the family Leguminosae. A few other places from where you can obtain your gum are Morocco and also some African countries.

But if you look in terms of supply, the majority of the acacia supply still comes from Sudan. So you can see here, once the injury is done, the plant starts exuding and this exudate forms a tear-like appearance, and the tears are collected. So let's see the processing. So

What is done is this plant, generally from the wild or sometimes cultivated, is allowed to grow. You can take it from a young plant, but the gum quality is not so good. So ideally, it is allowed to grow for a period of six to eight years. And within the season, generally the dry season, as they say from November to February, what is done is small incisions are made in the bark.

Sometimes the bark is removed. Now here you have to be a little careful while removing the bark so that you do not expose the xylem. The reason for this is if you expose the xylem, then because it's a good supply, the ants and other insects find their way in. Once the ants and other insects find their way in, the tree doesn't yield gum. So even if in some cases during the cutting the xylem is exposed, it's covered again.

So that the ants and other insects don't infest it, and the gum exudation continues. So cuts are made, and the gum starts oozing out. Now it takes time. The process of gummosis takes time, and a good seasonal variation is seen in the process. So if you do it in the summer season, the process of gummosis is faster.

The reason they say is that the microbes are much more active. The infection happens fast, and as a result, to counteract the infection, the trees produce the gum quicker. So in the summer season, you will get the gum within three to four weeks. In the winter season, the infection runs very slowly.

And as a result, your gum will be produced in a much longer duration. That is six to eight weeks' time. Once the gum is produced, it is scraped off from the tree and dried in the sun. During the drying process, all the moisture present in the gum is evaporated, and from the translucent or clear tears, as we saw, the gum becomes harder and more opaque.

So it becomes brittle, it can be crushed, and on crushing, it appears like a cream-colored powder. So you can get acacia as tears in the market, or you can get it as crushed white powder, which is likely buff or brownish in color. It has absolutely no odor. It has a bland, slightly mucilaginous carbohydrate taste, but not a sweet one. And you might even come across small, tiny tears with varying concentrations or dimensions.

It is insoluble in alcohol, being a saccharide or a carbohydrate derivative, but is soluble in water. Now, what is it made up of? If you see gum arabic or acacia, it is said to be made up of arabin. Now, what is arabin? Arabin is basically salt.

You can say calcium, magnesium, or even potassium salts of arabic acid, and arabic acid is a polymer which is generally made up of galactose, rhamnose, or arabinose. So you will get that upon hydrolysis, but the chief backbone of it you will see is made up of D-galactopyranose, usually joined by 1,3 linkages. Now, where do you use acacia?

Acacia in India is generally used to make laddus, but pharmaceutically, it has great utility. It is used as a demulcent. It is used as a viscosity enhancer, and because it increases viscosity, it is used as a suspending agent. Because of its carbohydrate polar nature, it is used as an emulsifying binding agent as well as a stabilizer. Now, these polymers have also found uses.

In novel drug delivery systems, in the formation of microencapsulation. So, you can encapsulate a powder, a drug, or oil using gum arabic. It is also used in spray-dried powders. It is used in tablets. So, during the process of tableting, initially, the blend must be made.

That is a dough, and that dough is converted into granules. So, this is used for the granulation process. It is very compatible with other carbohydrates and proteins, and hence it is a good excipient, a highly compatible excipient. It is used to make candies and other food products.

Now, because of its viscosity-imparting property, it is used as an adhesive like glue, a binding agent for marbling colors. It's used in ink and in cosmetics. Acacia is also used in the making of eyeliners and mascara. Now, moving to another carbohydrate-based drug, and that's agar. This agar comes from marine sources.

It's also referred to as agar-agar for those from the food industry. It's also referred to as Japanese isinglass or vegetable gelatin—a vegan option. So, agar is called vegetable gelatin because it gives the same jelly-like consistency, a transparent jelly-like consistency, but it is obtained from plant sources, basically algal sources.

Now, what are these algal sources? You can obtain agar from numerous species. So, you can obtain it from Gelidium amansii. Now, this is an algal species or a red algal species cultivated in Japan.

Initially the art and craft of making agar was exclusive to Japan but with its widespread uses people started cultivating this red algae throughout and other algae were also explored. So in Australia if you go to see the agar comes from your Gracilaria species If you see New Zealand, it comes from Pterocladia species and other allied species. Other countries which also produce agar include your Korea, South Africa, US, Chile, Spain, Portugal.

So most of this who have a proximity to sea have started exploring this red algae and starting gaining agar from it. So how do you produce it? Preparation of agar or cultivation of agar has been done in Japan. I will show you. I mean this is the shallow sea where the sea depth is not greater than a meter.

So what is done is bamboos are kept with string and the sea kelps are planted. They are allowed to grow on the strings for a period of time and during the summer season they are taken out. Now once they are taken out they are dried. They are dried and beaten for the reason because you will see some shells or some sand will start infesting and growing.

Some sea creatures or marine creatures, barnacles like creatures will start growing on it and we don't want it. So they are shaken so that this extraneous debris which has accumulated on the sea kelp falls off. Now, once that is done, you can still get rid of it by washing it thoroughly. Now, this is washed with water so that all the other dirt, grime and other debris is removed out. And then this can be easily bleached by keeping it in sunlight.

It is seen that the pigments of this red algae are sensitive to sunlight. So the moment you expose it, a discoloration happens. So they are periodically rotated over a period of time in the sun and water is sprinkled continuously so that the pigment discolored.

Now, once that is done, you have a good clean red colour algae. Now this red algae is taken in a tank and about 50 times its weight of the algae you will take the water. Now this water generally is acidified water and it is acidified either with acetic acid or with sulfuric acid. to break the cell walls and to take the algal mass out of it so it's pulverized it's boiled well and the mass is dissolved

Now, once it is dissolved, you will see that it forms a viscous solution. This clear viscous solution is filtered when hot because on cooling, it will start to congeal and form a slimy mass, which is difficult to filter. So, while it is hot, it is filtered and then allowed to set in trays. Now, once it is allowed to set in trays, what happens is you get blocks like a tray block of it. This is again finely ground with the help of a knife or

coarsely ground. Then what is done is the surface area is increased. This is again kept for drying so every time it is ground and again kept for drying, you will get a size reduction and dehydration so more and more water loss happens. Now, in this case, if you take particular climatic advantage of Japan what happens is when you take this or set it in a tray and kind of grate it or grind it During the night when the temperature is cold, the water within the sea kelp crystallizes into ice and this ice later on during the daytime melts to form water and evaporates. So this freeze-thaw process for water continues, and eventually, you get a good grade of algae. This can further be dried to get a fine product which can be threads or which can be granulated to form powder. Now, we can do it industrially as well on a commercial scale.

You need to take this sea kelp the same way, get rid of all the dirt, debris, and barnacles by washing it for a day or so, keeping it exposed to water. And then heat it extensively with the help of a steam-heated digester. And expose it to acid, where it will hydrolyze and form a jelly. Now, this jelly is subjected to deep freezing, and it's made or converted into ice. What happens is this ice is then broken, heated, exposed, evaporated, and put into a rotary vacuum filter.

So that whatever moisture content it has will all vanish, and you get a nice powdered agar, which is then used in microbial media. So you can see here that once you do it, you will get a powder like this, which is a granulated agar, or sometimes it is extruded to form a string-like appearance. So this is how it is. So agar is yellowish or a little yellowish.

Yellow-white to gray. It has a mucilaginous taste and may occur as strips, flakes, sheets, or coarse powder. Now, when they are in the form of strips, you generally get a big, like 60-centimeter-long strip with just a small 4-millimeter diameter or width. When it is in the form of sheets, you get about a 50-centimeter big sheet with a 10-centimeter width.

Now, if you take agar in cold water, it doesn't dissolve. But if you boil it in hot water, it forms a clear jelly. So, 1% will form a clear jelly, and then it will set. And that's what you use as your microbial media.

So, analysis of it will tell you that agarose is made up of two polymers: the linear one being agarose and the branched one being agaropectin. Now, agarose is more of a neutral polymer, which is responsible for the gel or clear gel properties, and it is made up of agarose. D and L galactose units, whereas agaropectin is mucilaginous or what we call a sulfonated polysaccharide, which will yield galactose plus more uronic acid derivatives that have been esterified with sulfuric acid.

Now, agaropectin is responsible for the viscosity of agar solution. You can evaluate genuine agar by a few tests because it's mucilaginous and contains sulfate. If you take this agar, hydrolyze it by HCl, and then treat it with barium chloride. Barium chloride is a water-soluble salt, but it will react with the sulfates of agar to form barium sulfate. Now, barium sulfate is.

water insoluble, so barium sulfate precipitates down. So if you get a turbidity, a white color powder being formed which settles down, understand it's your genuine agar. Same way because of the sulfates, there is a dye called as ruthenium red which will bind to the sulfates and it will convert the mucilaginous matter into red color which is not going after washing or diluting with water. You will see chunks which are red in color and that test will tell you that definitely there are sulfates and your drug is mucilaginous.

You can also do the gelling test. Just take a 1% solution, heat it profusely to form a clear jelly and then cool it. If it sets, it's agar. And one more thing you can do is you can check it with iodine. Starch tends to form a blue color with iodine.

But if it's agar, it will give you a crimson red color. So this also distinguish it's from acacia as well as tragacanth. Now uses agar is chiefly used or extensively used in microbial medias. It is used as laxative because we cannot digest it. It's a suspending agent, emulsifier, and gelling agent for suppositories.

It's a surgical lubricant. It's also used as a tablet excipient, especially a disintegrating agent and an encapsulating agent like we saw in acacia. It is used in ointments and in some cases as a polymer in dental mold for an impression base. It is used as a nutrient media for the reason being your bacteria cannot consume or digest agar

and that's where it doesn't lose its consistency and it remains stiff throughout. It is initially used in making photographic plates, but now it is discontinued. It is used for making clear jellies in cosmetic industries and along with alginates, it might be used as a thickening agent in food, especially confectionaries and dairies where you want those clear jelly like consistency, but you don't want to use gelatin.

It is also used in sizing preparations for silk, paper, in dyeing, in printing industries. It is used for printing fabrics and textiles. And because of its adhesive properties, it is also used as a glue. So here's a few more references if you want to read more on this topic. And thank you everyone for your patient listening.

Thank you.