PHARMACOGNOSY AND PHYTOCHEMISTRY

Dr. Galvina Pereira

Department of Pharmaceutical Sciences and Technology

Institute of Chemical Technology, Mumbai

Week 12

Lecture 60

W 12: L 60: Natural Product Databases for Studying Pharmacokinetic and Pharmacodynamic Properties

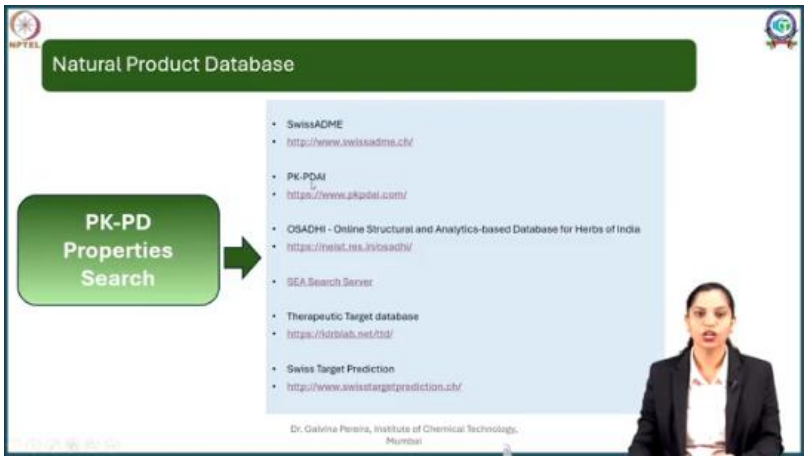
Thank you. Hello everyone, and welcome to session 5 of the NPTEL course in pharmacognosy and phytochemistry. This week, we are particularly learning computational and database techniques, as well as web-based server techniques, which can help us understand pharmacognosy and phytochemistry in much greater detail. So far, in the previous sessions, we have already studied plant-based databases. We have already studied databases pertaining to traditional applications as well as ethno-medicinal plants.

This included, if you remember, TKDL, IMPPAT, as well as the Indian Medicinal Plants Database. Thereafter, we went on to study what are called phytochemical searches. So once you have shortlisted the plants, these are the software tools that can help us identify what phytoconstituents these plants contain. Then, in the fourth session, we went on to understand a little more about phytochemical properties. Now, once you studied the phytochemical properties, it was through PubChem, Lotus, and Zinc natural products that all the properties, especially the physicochemical properties of your phytochemicals, were identified.

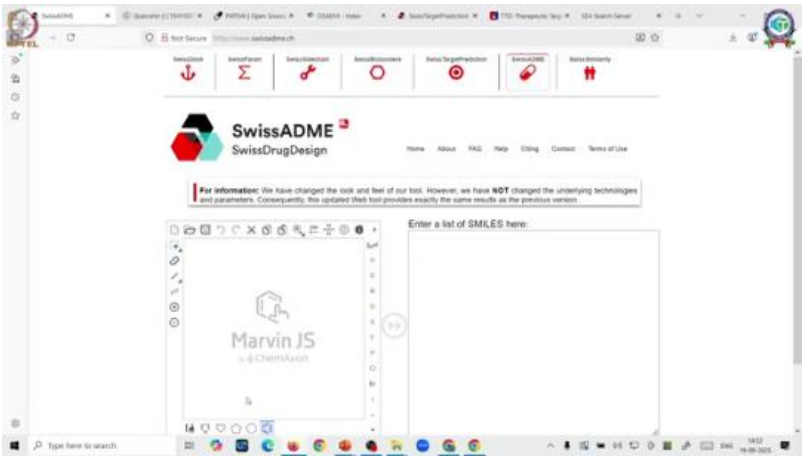
We also examined the natural product likeness of the compounds. In the last session, what we learned was How can we know whether what we have purified is actually the compound we are looking for? Is it the same one, or is it something different? This is spectroscopic analysis, and all these spectroscopic techniques provided us with values to compare.

Now in today's session we will move a step ahead and we will see what are the databases that can help us predict the pharmacokinetic as well as pharmacodynamic properties. there are certain softwares which are paid say for example gastro plus or simulation plus they're indeed a good softwares but those kind of require some initial registration as well as fees so in this session i will be particularly focusing on the freewares that we all can use and still get an idea about the adme that is the pharmacokinetic as well as the pharmacological properties or the therapeutic properties of your phytoconstituents. So here are a few softwares that helps us. One is the Swiss ADME and also there is what is called a Swiss target prediction.

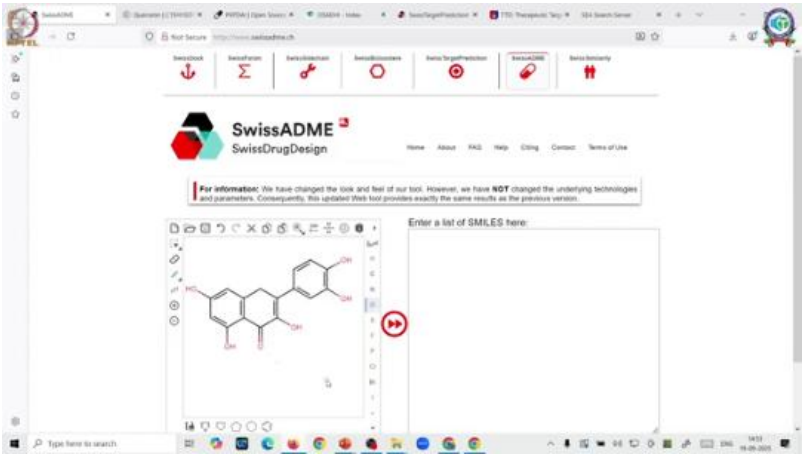
Swiss ADME is more about pharmacokinetic whereas Swiss target prediction is more about the pharmacodynamic effects which will tell us that what would possibly be the effects of consuming this drug. Not only that, you have few other software such as PKPD AI, which also gives you the pharmacokinetic properties. You have OCD databases. We have C server, which is a similarity based server that is going to help us determine the activity as well as the therapeutic target database. So let's see them one by one and analyze what each of them have to offer.



So starting with the Swiss ADME database, Swiss ADME database is a database which kind of predicts the pharmacokinetic properties. Now here are two ways in which you can enter in your query. You can put in the 2D format what is called as smiles or you can draw the structure. So if you want to draw the structure here. Again, let's go to our same query so that we know what each software can offer us.

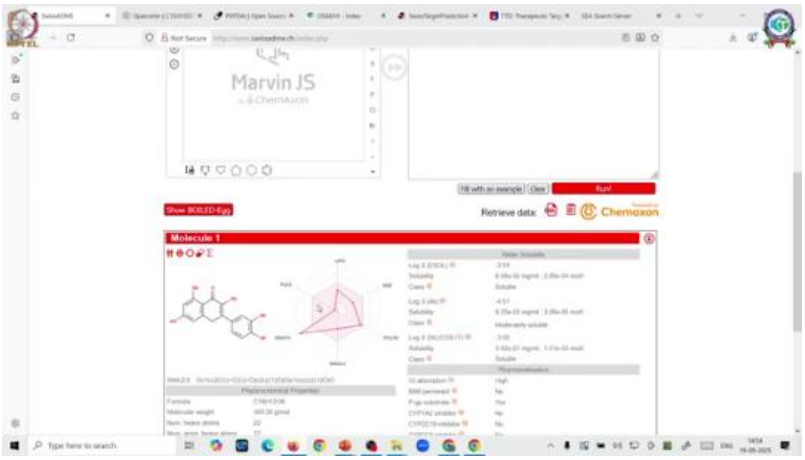


We'll go to our query, and that's our quercetin. Just kind of replacing this all with O. So here's our quercetin. Now, if I just click on this, it will convert a 3D structure into a 2D format. It's very simple. It's what is called the SMILES format.



So you can see here, this is what is called the SMILES notation. You can use this for predicting properties. I am just copying. Now, once you have this predicted, I will just click run. Now it is calculating.

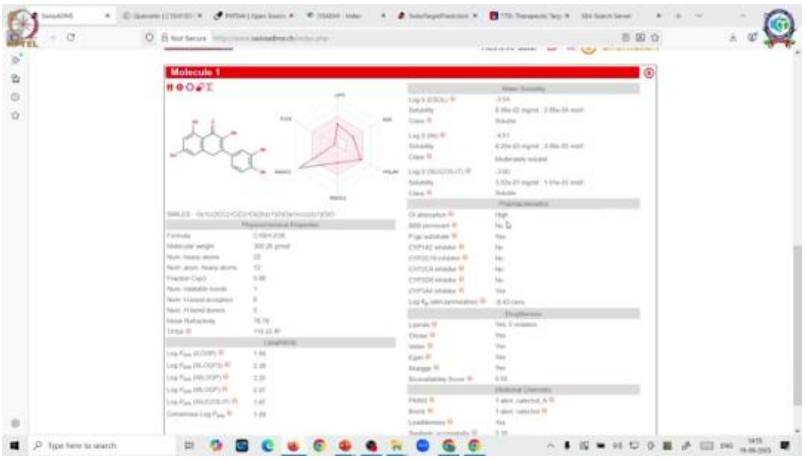
You can see a loading signal. Once that is done, you will see a few properties. Now, what is called this is the spider chart, and the spider chart will tell you the possibility of druggability. Now, for druggability, you see a little inner pink region. The properties such as flexibility, lipophilicity, size, polarity, insolubility, and saturation should all be within certain limits.



Now, what does this indicate? This indicates that the lipophilicity is optimum, the size is optimum, the polarity is optimum, and so is the insolubility. The unsaturation can be a little less than The flexibility can be even a little more, which is permitted, but it's almost reaching a perfect region. So then, going down, you can see certain things such as the molecular properties.

We also saw them in your other databases, which provided the physicochemical properties. This includes your molecular formula and molecular weight. Heavy atoms, the number of rotatable bonds, hydrogen bond donors, acceptors, and total polar surface area. The next gives you an idea about the lipophilicity. So comparatively, these ratings are low.

That means this molecule is less lipophilic. Now here, this next parameter is your water solubility, wherein it is almost water-soluble. That is moderately soluble. Then, GI absorption is high, and blood-brain permeability is low. What does that mean?



That means it's definitely when you're consuming it, you need not give it additional formulation methods or treatments to increase its GI absorption because naturally, its GI absorption is good. But if at all you have to make this drug or make this molecule reach your brain, what is going to happen here? The blood-brain permeability is zero. So in that case, you will require specific drug delivery systems to make or to deliver this molecule across your brain. So you have in your liver what are called cytochromes.

So these cytochromes are very vital for normal metabolism to happen. So is consuming your drug kind of now in this case? There's no oxygen, so I cannot call it quercetin, but let's call it a drug. So is this drug going to inhibit any of the cytochromes? So, if the answer is no, what does that mean? Whatever drugs are getting metabolized by this particular molecule, there will be no effect.

But if you see this last one, that is CYP3A4. So, CYP3A4 is also an activator. It is an active enzyme which is involved in the metabolism of many drugs. Now, if this is an inhibitor, what does that mean? This is going to inhibit this enzyme.

If it is inhibiting this enzyme, then whatever drugs were naturally metabolized by this enzyme will not happen. And you also have skin permeability values. You have your drug likeness. So, there are certain values we follow for a drug, Or for druggability, you have Lipinski's rule of five, which states that the molecular weight should not exceed 500.

And a lot of other rules are there. Depending on the scientists and their rules, the software automatically calculates. How many hydrogen bond donors are there? How many hydrogen bond acceptors are there? What is the molecular weight?

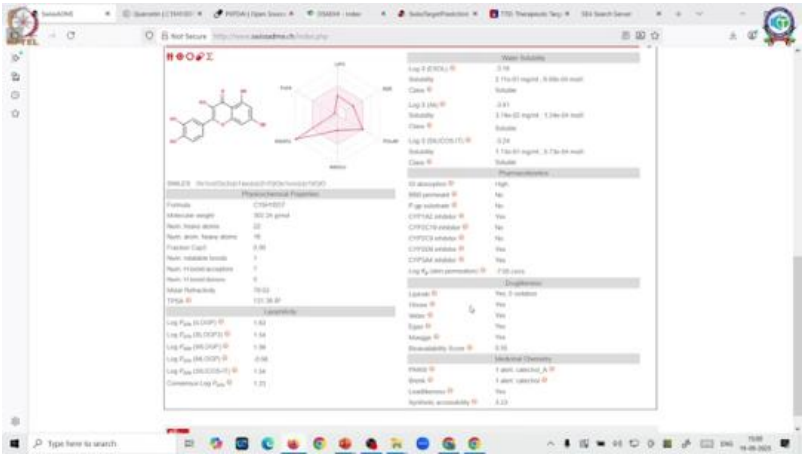
What is the molecular size? What is the total polar surface area of the molecule? Based on these rules, it tries to fit within them and determines whether it is compliant or not. So, it is mostly compliant. So, there is a good chance that this is a druggable moiety.

So pains are kind of false alerts. So yes, one alert is there, and that's catechol. So in terms of medicinal chemistry, you need to do this, and definitely, it is synthetically accessible. I will just modify this to a quercetin further, just to see if anything changes, or what we can do this time is we will just clear this off and We'll use the values taken from PubChem.

We can directly get it from PubChem, you remember. We saw it in the previous session. So you can just quickly raise a query for quercetin. From that, you pick up this region called the SMILES, which is essentially the 2D format. So what I'm doing now is I'm just copying this.

I'm putting it in my SwissADME. Pasting it here. So I have my quercetin as a query now. And then I hit run. So you can see here, it's kind of running the query.

And this time it is coming with oxygen. So yes, a little bit of the parameters have changed. If you see here now, this molecule is also a CYP1A2 inhibitor. Druggability is almost retained, and the pain is a catechol. So again, the solubility and lipophilicity have changed slightly if you have seen the values were earlier close to almost 3.



So now it is less lipophilic, that is, it is more polar. Now we move on to the next one, and that is your PKPD AI. Now PKPD AI is not a structure-based database. So it's not predicting based on calculation, but it's predicting based on searches. So what I can do is a quick literature search for my molecule.

So if I have to do a PKPD literature search, I will enter through this website. So again, I'll do my quercetin search and see what is happening. So ideally, earlier ones gave you properties based on calculation. This one will give you or come back with the articles. So you can see here the effect of quercetin on cytochromes, on P-glycoproteins, and the effect of quercetin on the pharmacokinetics of other drugs included.

So all of these articles that you are seeing will be based on the pharmacokinetics of your drugs. So if you want to research the PKPD properties of any molecule, you will search for it through this particular software. Now, moving on to the next one. The next one is the Oshadi software, which you have already seen. This time, we will go to the last tab, which is your cheminformatics.

Again, we will try to search. Let's click on the first molecule here. So your Oshadi software comes back. It tells you again about the chemical informatics. Or it tells us about the cheminformatics of a molecule.

In terms of its heavy atoms, rotatable bonds, hydrogen bond donors, aromaticity, solubility, and saturation. So you have your natural product likeness score, which is very high. More than 1. Then, as I said, there are a lot of rules pertaining to triggability. So you have Lipinski, which is accepted.

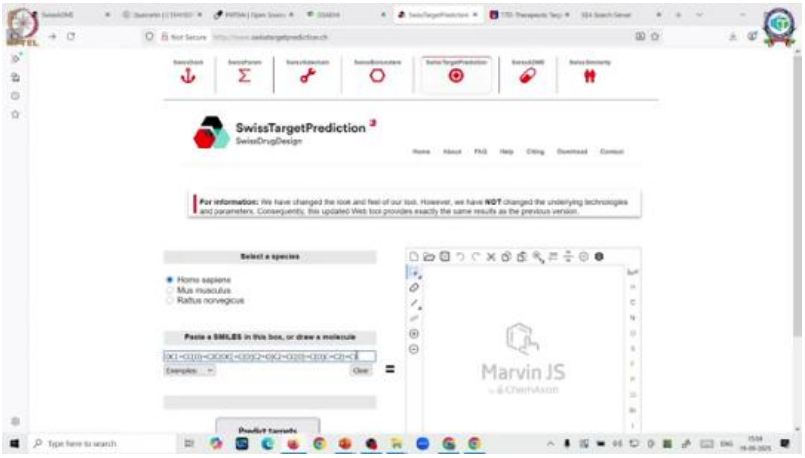
The ones which are set by Pfizer or GSK are rejected. The golden triangle rule is accepted. Absorption, P-glycoproteins, no. CACO, yes, but minimally, it is on the negative side. You have certain cell lines which are reported.

You see here the blood-brain barrier score is very low for this particular molecule. But yes, it is permeable. Then, how much is it able to? There, you just got yes or no as an answer. If you recall in your Swiss ADME database.

But even in your PKPD AI, you can see the literature. Here, it will bring you more curated values of cytochrome action or metabolism. These are kind of clearance values, toxicity values. You can see here you get good data. So, is it antiviral?

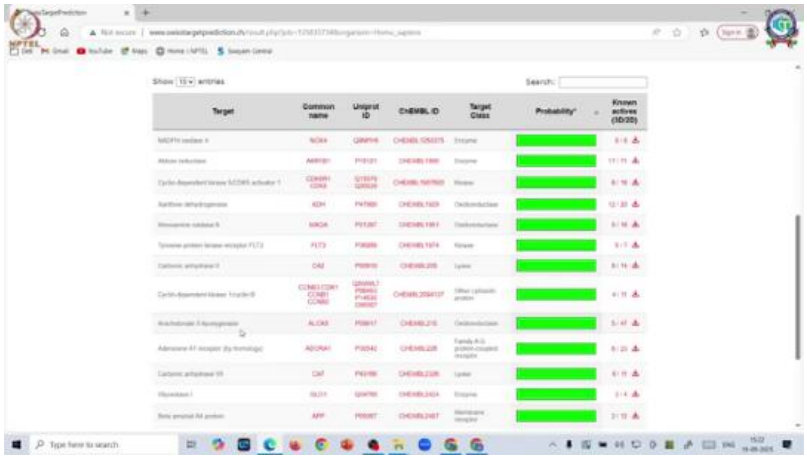
No. So, the Osadhi kind of database gives you readings about the physical attributes, chemical attributes, the drug likeness, absorption, distribution, metabolism, as well as excretion. Now, we move on to more pharmacodynamic databases. Now, pharmacodynamic databases, so far what we saw is what will happen to the drug in the body. So, once you consume it, is it going to get digested by your cytochromes?

What is going to happen to it? Now, how will or what will be the action of this molecule on our body? So, for this, we will first move to what is called the Swiss Target database. This is the same software wherein we saw the Swiss ADME, but this software or this particular web browser kind of helps us in bringing out what is called the pharmacodynamic properties.

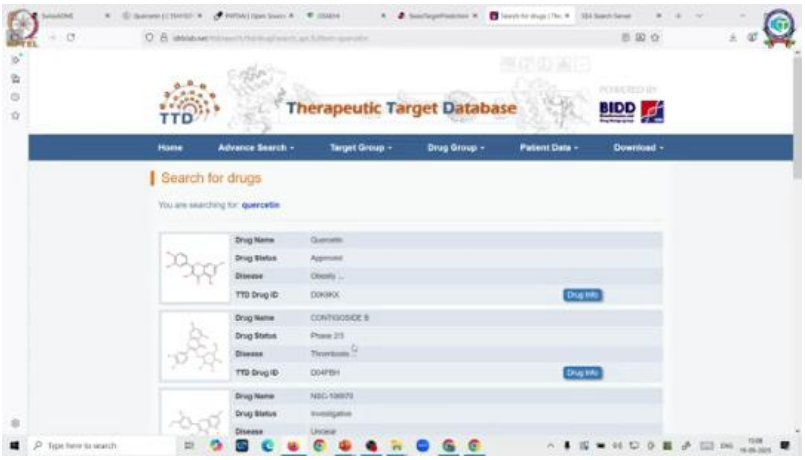


So again, I am just quickly deleting this and pasting my query, which is quercetin. So, I pick up my SMILES again and put it here so that we do not make any mistake. So, here you can see it has got the quercetin structure. Now, I am asking this software to predict targets for me. So, when we put in the query of quercetin in the Swiss Target database, here you can see the browser returns with certain results, and if you see it carefully, you can see it in terms of enzymes.

That is, these enzymes are demarcated by different colors, and you would see lyases, kinases, oxidoreductases, and so on. Now, many of these enzymes have been involved in disease conditions, and as a result, if you look carefully, the software gives you exactly that. So you will see that it is actively involved in interacting with NADPH4, oxidase, aldo reductase, cyclin-dependent kinase, xanthine dehydrogenase, and so on. So wherever this disease involves these kinds of enzymes, the interactions—because it is interacting with quercetin—there is a good possibility that this drug, especially quercetin, will interact with this enzyme and bring about the pharmacodynamic effect.

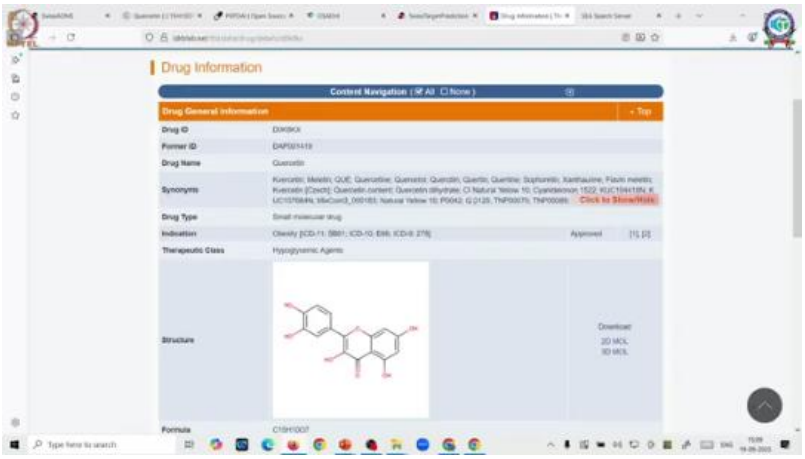


So you can see about 100 such interactions with different enzymes have been identified. The limitation of this is you can definitely predict the interaction, but the intensity, the dose, or the amount of interaction cannot be seen here. Now moving on to the next database, which is the Therapeutic Target Database. Here you enter your drug, say for example quercetin again, and then click search. So you can see quercetin is approved for obesity, and this is the TTDID.



So again, it is in phase 2 or 3. Basically, what is here is a quercetin glycoside called contigoside B, and it has almost reached phase 2 or 3. It is used for thrombosis. Another form, the methyl ester of quercetin, is again under investigation, and the mechanism is unclear. You will see numerous derivatives of quercetin that are under investigative research.

So rutin, quercetin, neohesperiocytes. So it will come across different things. Now just let's click on the first one and see the information. You can see here. These are all the names or synonyms it is known with.

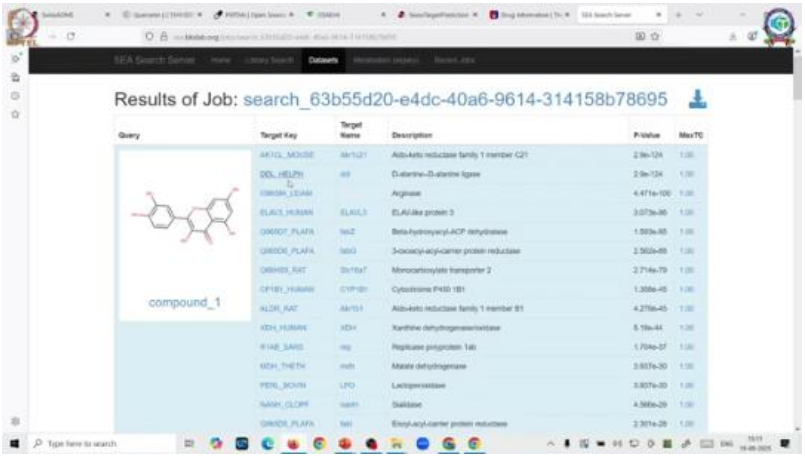


This is the target PCAT, and these are the references or literature from which the web-based server has predicted that it may show activity, especially as a hypoglycemic or anti-obesity agent. Now we move on to the last one, which is a SEA-based server. Now, the SEA-based server is what is called a similarity and ensemble-based approach. So, what the

server does is it curates a list of molecules. For example, based on the structure—not only the structure but also the structural similarity.

So, it will pick up a pharmacophore, and based on that pharmacophore, it will tell you what activity it has. For example, I am putting a query of quercetin again. Again, I will just pick up canonical SMILES or SMILES. I put it in my server and paste it. So, what does it tell you now?

So it can tell you that this molecule which is your query that is quercetin is active against all of these genes which are there or it can even call it different different receptors which are there now this receptors may be human based mouse based You can have it RAD based and so on. So it's very nonspecific. Then you have a typical abbreviation or target name and the description of the target where exactly this is found to be active.



Then you have what are called as P values. These are statistical value which tell us how much relevant or how much statistically significant is the activity. A value less than 0.05 is considered to be a good P value. The last table gives you what is called as the Tanimoto coefficient. Now what is this Tanimoto coefficient means?

The TC means the structural similarity. So if the TC value is 1 that means the structural similarity is 100% and this activity is of quercetin itself. But as you move down the table you will see that the TC values might go on decreasing. You can see here the values are less. Now these values are less the reason being the tanymoto coefficient the structure is not matching.

Maybe now imagine a molecule which doesn't have these two hydroxies. That means the percent similarity to quercetin will decrease. So how much percent similarity decrease if you consider 1 as 100. Now this is almost 76% structurally similar to quercetin. Whereas this is something or this is a molecule which is 60% structurally similar.

So something that is not one it has highlighted in other colors. So it will be easy for us to demarcate that this is not quercetin. These are other molecules which have a good structural similarity to that. Now imagine this. This has just kind of 39% structural similarity.

So in that case where the structural similarity goes below 70%, it is recommended that you do not pick up these values because less than 70% similar may indicate that it will no longer be a flavonoid nucleus. So today we saw different different databases. The Swiss ADME databases, the PKPD AI database, the OSHADI database, the C-server, TTD database as well as the Swiss prediction database. Some of these databases give us pharmacokinetic data like your Swiss ADME, PKPD as well as OSHADI whereas some of them also gave us the dynamic data which included the TTD as well as C server as well as your Swiss target prediction database.

So, with this, we end our course in pharmacognosy and phytochemistry. Through this course, we have been able to kind of learn what is pharmacognosy what is phytochemistry understand different different classes of compounds understand their methods of analysis as well as quality control and with this session we are also able to predict and compare computationally what spectral what physicochemical as well as what are the pharmacological properties of this so thank you everyone for being an avid learner At the end of this course, I would like to acknowledge my institute, the Institute of Chemical Technology Mumbai, for this tremendous opportunity of collaborating with NPTEL, my TAs Megha and Akansha, who have been very supportive in this role. As well as our laboratory staff, Mr. Kiran and Pooja Patil who have been helping us with the experiments.

I would also profusely extend my heartfelt thanks to the NPTEL IIT Mumbai team without which this would not have been a possible thing. So thank you everyone. Great learning and wish you all the best for your examinations. Thank you. Thank you.